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HIGHLIGHTS OF THE

5th Belgian Multidisciplinary Meeting on Urological Cancers (BMUC)

BMUC

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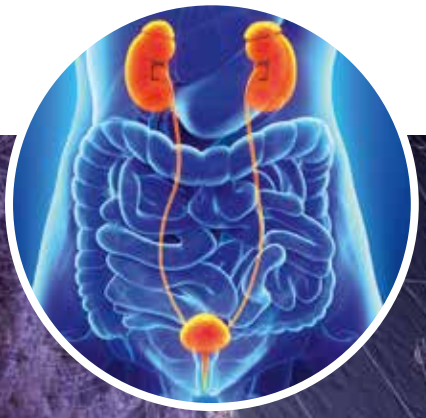

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OPDIVO® (nivolumab)

OPDIVO is reimbursed for the treatment of advanced RCC and Urothelial Cancer after prior therapy[1]

OPDIVO as monotherapy is indicated for the treatment of:[1]

Advanced renal cell carcinoma after prior therapy in adults

Locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy

Bristol-Myers Squibb

RCC – renal cell carcinoma

Reference: 1. OPDIVO Summary of Product Characteristics.

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COLOPHON

This publication is a special edition from the publisher of the Belgian Journal of Medical Oncology, Ariez International Publishers BV. The aim of this special is to inform clinicians, active in the field of Oncology, on important Highlights of leading international and national medical symposia & congresses. In addition other new developments, opinions and insights of relevance to daily clinical practice, are discussed with the aim of supporting daily clinical decision making and management of patients with oncologic diseases or adherent symptoms and medical needs.

Special editions are distributed amongst medical specialists in Belgium, such as oncologists, surgeons and radiotherapists.

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5th Belgian Multidisciplinary Meeting on Urological Cancers (BMUC)

OPDIVO® (nivolumab)

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions. **NAME OF THE MEDICINAL PRODUCT OPDIVO** 10 mg/mL concentrate for solution for infusion. **QUALITATIVE AND QUANTITATIVE COMPOSITION** Each mL of concentrate contains 10 mg of nivolumab. One vial of 4 mL contains 40 mg of nivolumab. One vial of 10 mL contains 100 mg of nivolumab. Nivolumab is produced in Chinese hamster ovary cells by recombinant DNA technology. Excipient with known effect Each mL of concentrate contains 0.1 mmol (or 2.5 mg) sodium. For the full list of excipients, see section 6.1. **PHARMACEUTICAL FORM** Concentrate for solution for infusion (sterile concentrate). Clear to opalescent, colourless to pale yellow liquid that may contain few light particles. The solution has a pH of approximately 6.0 and an osmolality of approximately 340 mOsm/kg. **CLINICAL PARTICULARS 4.1 Therapeutic indications** Melanoma OPDIVO as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. Relative to nivolumab monotherapy, an increase in progression-free survival (PFS) and overall survival (OS) for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression (see sections 4.4 and 5.1). Non-Small Cell Lung Cancer (NSCLC) OPDIVO as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults. Renal Cell Carcinoma (RCC) OPDIVO as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults. Classical Hodgkin Lymphoma (cHL) OPDIVO as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin. Squamous Cell Cancer of the Head and Neck (SCCHN) OPDIVO as monotherapy is indicated for the treatment of squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy (see section 5.1). Urothelial Carcinoma OPDIVO as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy. **4.2 Posology and method of administration** Treatment must be initiated and supervised by physicians experienced in the treatment of cancer. *Posology OPDIVO as monotherapy* The recommended dose of OPDIVO is either nivolumab 240 mg every 2 weeks **or** 480 mg every 4 weeks (see section 5.1) depending on the indication, as presented in Table 1 . Table 1: Recommended dose and infusion time for intravenous administration of nivolumab monotherapy Recommended dose and infusion time per indication*: Melanoma: 240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes; Renal Cell Carcinoma: 240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes; Non-Small Cell Lung Cancer: 240 mg every 2 weeks over 30 minutes; Classical Hodgkin lymphoma: 240 mg every 2 weeks over 30 minutes; Squamous Cell Cancer of the Head and Neck: 240 mg every 2 weeks over 30 minutes; Urothelial Carcinoma: 240 mg every 2 weeks over 30 minutes *As per monotherapy indication in section 4.1. If melanoma or RCC patients need to be switched from the 240 mg every 2 weeks schedule to the 480 mg every 4 weeks schedule, the first 480 mg dose should be administered two weeks after the last 240 mg dose. Conversely, if patients need to be switched from the 480 mg every 4 weeks schedule to the 240 mg every 2 weeks schedule, the first 240 mg dose should be administered four weeks after the last 480 mg dose. *OPDIVO in combination with ipilimumab Melanoma* The recommended dose is 1 mg/kg nivolumab in combination with 3 mg/kg ipilimumab administered intravenously every 3 weeks for the first 4 doses. This is then followed by a second phase in which nivolumab monotherapy is administered intravenously at either 240 mg every 2 weeks **or** at 480 mg every 4 weeks, as presented in Table 2. For the monotherapy phase, the first dose of nivolumab should be administered; 3 weeks after the last dose of the combination of nivolumab and ipilimumab if using 240 mg every 2 weeks; or 6 weeks after the last dose of the combination of nivolumab and ipilimumab if using 480 mg every 4 weeks. Table 2: Recommended doses and infusion times for intravenous administration of nivolumab in combination with ipilimumab *Nivolumab*: Combination phase, every 3 weeks for 4 dosing cycles: 1 mg/kg over 30 minutes / Monotherapy phase: 240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes; *Ipilimumab:* Combination phase, every 3 weeks for 4 dosing cycles: 3 mg/kg over 90 minutes Treatment with OPDIVO, either as a monotherapy or in combination with ipilimumab, should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment with nivolumab for clinically stable patients with initial evidence of disease progression until disease progression is confirmed. Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability. Guidelines for permanent discontinuation or withholding of doses are described in Table 3. Detailed guidelines for the management of immune-related adverse reactions are described in section 4.4. Table 3: Recommended treatment modifications for OPDIVO or OPDIVO in combination with ipilimumab Immune-related adverse reaction: *Immune-related pneumonitis: Severity:* Grade 2 pneumonitis; *Treatment modification:* Withhold dose(s) until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete; *Severity:* Grade 3 or 4 pneumonitis; *Treatment modification:* Permanently discontinue treatment; *Immune-related colitis: Severity:* Grade 2 diarrhoea or colitis; *Treatment modification:* Withhold dose(s) until symptoms resolve and management with corticosteroids, if needed, is complete; *Severity:* Grade 3 diarrhoea or colitis - OPDIVO monotherapy; *Treatment modification:* Withhold dose(s) until symptoms resolve and management with corticosteroids is complete; *Severity:* Grade 3 diarrhoea or colitis - OPDIVO+ipilimumab; *Treatment modification:* Permanently discontinue treatment; *Severity:* Grade 4 diarrhoea or colitis; *Treatment modification:* Permanently discontinue treatment; *Immune-related hepatitis: Severity:* Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin; *Treatment modification:* Withhold dose(s) until laboratory values return to baseline and management with corticosteroids, if needed, is complete; *Severity:* Grade 3 or 4 elevation in AST, ALT, or total bilirubin; *Treatment modification:* Permanently discontinue treatment; *Immune-related nephritis and renal dysfunction: Severity:* Grade 2 or 3 creatinine elevation; *Treatment modification:* Withhold dose(s) until creatinine returns to baseline and management with corticosteroids is complete; *Severity:* Grade 4 creatinine elevation; *Treatment modification:* Permanently discontinue treatment; *Immune-related endocrinopathies: Severity:* Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis, Grade 2 adrenal insufficiency, Grade 3 diabetes; *Treatment modification:* Withhold dose(s) until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete. Treatment should be continued in the presence of hormone replacement therapy[a] as long as no symptoms are present; *Severity:* Grade 4 hypothyroidism, Grade 4 hyperthyroidism, Grade 4 hypophysitis, Grade 3 or 4 adrenal insufficiency, Grade 4 diabetes; *Treatment modification:* Permanently discontinue treatment; *Immune-related skin adverse reactions: Severity:* Grade 3 rash; *Treatment modification:* Withhold dose(s) until symptoms resolve and management with corticosteroids is complete; *Severity:* Grade 4 rash; *Treatment modification:* Permanently discontinue treatment; *Severity:* Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN); *Treatment modification:* Permanently discontinue treatment (see section 4.4); *Other immune-related adverse reactions: Severity:* Grade 3 (first occurrence); *Treatment modification:* Withhold dose(s); *Severity:* Grade 3 myocarditis; *Treatment modification:* Permanently discontinue treatment; *Severity:* Grade 4 or recurrent Grade 3 ; persistent Grade 2 or 3 despite treatment modification ; inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day; *Treatment modification:* Permanently discontinue treatment Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4). [a] Recommendation for the use of hormone replacement therapy is provided in section 4.4. OPDIVO or OPDIVO in combination with ipilimumab should be permanently discontinued for: Grade 4 or recurrent Grade 3 adverse reactions; Persistent Grade 2 or 3 adverse reactions despite management. Patients treated with OPDIVO must be given the patient alert card and be informed about the risks of OPDIVO (see also package leaflet). When OPDIVO is administered in combination with ipilimumab, if either agent is withheld, the other agent should also be withheld. If dosing is resumed after a delay, either the combination treatment or OPDIVO monotherapy could be resumed based on the evaluation of the individual patient. *Special populations Paediatric population* The safety and efficacy of OPDIVO in children below 18 years of age have not been established. No data are available. *Elderly* No dose adjustment is required for elderly patients (≥ 65 years) (see sections 5.1 and 5.2). Data from NSCLC and SCCHN patients 75 years of age or older are too limited to draw conclusions on this population. *Renal impairment* Based on the population pharmacokinetic (PK) results, no dose adjustment is required in patients with mild or moderate renal impairment (see section 5.2). Data from patients with severe renal impairment are too limited to draw conclusions on this population. *Hepatic impairment* Based on the population PK results, no dose adjustment is required in patients with mild hepatic impairment (see section 5.2). Data from patients with moderate or severe hepatic impairment are too limited to draw conclusions on these populations. OPDIVO must be administered with caution in patients with moderate (total bilirubin > 1.5 × to 3 × the upper limit of normal [ULN] and any AST) or severe (total bilirubin > 3 × ULN and any AST) hepatic impairment. Method of administration OPDIVO is for intravenous use only. It is to be administered as an intravenous infusion over a period of 30 or 60 minutes depending on the dose (see Tables 1 and 2). The infusion must be administered through a sterile, non-pyrogenic, low protein binding in-line filter with a pore size of 0.2-1.2 µm. OPDIVO must not be administered as an intravenous push or bolus injection. The total dose of OPDIVO required can be infused directly as a 10 mg/mL solution or can be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for injection (see section 6.6). When administered in combination with ipilimumab, OPDIVO should be given first followed by ipilimumab on the same day. Use separate infusion bags and filters for each infusion. For instructions on the preparation and handling of the medicinal product before administration, see section 6.6. **4.3 Contraindications** Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. **4.8 Undesirable effects** Summary of the safety profile In the pooled dataset of nivolumab 3 mg/kg as monotherapy across tumour types (n = 2578) with minimum follow-up ranging from 2.3 to 28 months, the most frequent adverse reactions (≥ 10%) were fatigue (30%), rash (17%), pruritus (13%), diarrhoea (13%), and nausea (12%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). With a minimum of 24 months follow-up in NSCLC, no new safety signals were identified. In the pooled dataset of nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma (n = 448) with minimum follow-up ranging from 6 to 28 months, the most frequent adverse reactions (≥ 10%) were rash (52%), fatigue (46%), diarrhoea (43%), pruritus (36%), nausea (26%), pyrexia (19%), decreased appetite (16%), hypothyroidism (16%), colitis (15%), vomiting (14%), arthralgia (13%), abdominal pain (13%), headache (11%), and dyspnoea (10%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). Among the patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in CA209067, 154/313 (49%) had the first onset of Grade 3 or 4 adverse reactions during the initial combination phase. Among the 147 patients in this group who continued treatment in the single-agent phase, 47 (32%) experienced at least one Grade 3 or 4 adverse reaction during the single-agent phase. Tabulated summary of adverse reactions Adverse reactions reported in the pooled dataset for patients treated with nivolumab monotherapy (n = 2578) and for patients treated with nivolumab in combination with ipilimumab (n = 448) are presented in Table 4. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from available post-marketing data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness. Table 4: Adverse reactions *Infections and infestations: Nivolumab monotherapy:* Common: upper respiratory tract infection; Uncommon: pneumonia[a], bronchitis; *Nivolumab in combination with ipilimumab:* Common: pneumonia, upper respiratory tract infection; Uncommon: bronchitis; *Neoplasms benign, malignant and unspecified (including cysts and polyps): Nivolumab monotherapy:* Rare: histiocytic necrotising lymphadenitis (Kikuchi lymphadenitis); *Blood and lymphatic system disorders: Nivolumab monotherapy:* Very common: neutropaenia[a,b]; Uncommon: eosinophilia; *Nivolumab in combination with ipilimumab:* Common: eosinophilia; *Immune system disorders: Nivolumab monotherapy:* Common: infusion related reaction[c], hypersensitivity[c]; Rare: anaphylactic reaction[c]; Not known: solid organ transplant rejection; *Nivolumab in combination with ipilimumab:* Common: infusion related reaction, hypersensitivity; Uncommon: sarcoidosis; Not known: solid organ transplant rejection; *Endocrine disorders: Nivolumab monotherapy:* Common: hypothyroidism, hyperthyroidism; Uncommon: adrenal insufficiency, hypopituitarism, hypophysitis, thyroiditis, diabetes mellitus; Rare: diabetic ketoacidosis; *Nivolumab in combination with ipilimumab:* Very common: hypothyroidism; Common: adrenal insufficiency, hypopituitarism, hypophysitis, hyperthyroidism, thyroiditis; Uncommon: diabetic ketoacidosis[c], diabetes mellitus[c]; *Metabolism and nutrition disorders: Nivolumab monotherapy:* Common: decreased appetite; Uncommon: dehydration, metabolic acidosis; Not known: tumour lysis syndrome[c]; *Nivolumab in combination with ipilimumab:* Very common: decreased appetite; Common: dehydration; Not known: tumour lysis syndrome[c]; *Hepatobiliary disorders: Nivolumab monotherapy:* Uncommon: hepatitis[c]; Rare: cholestasis; *Nivolumab in combination with ipilimumab:* Common: hepatitis[c]; *Nervous system disorders: Nivolumab monotherapy:* Common: peripheral neuropathy, headache, dizziness; Uncommon: polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis); Rare: Guillain-Barré syndrome, demyelination, myasthenic syndrome, encephalitis[a,c]; *Nivolumab in combination with ipilimumab:* Very common: headache; Common: peripheral neuropathy, dizziness; Uncommon: Guillain-Barré syndrome, polyneuropathy, neuritis, peroneal nerve palsy, autoimmune neuropathy (including facial and abducens nerve paresis), encephalitis[c]; *Eye disorders:* Uncommon: uveitis, blurred vision, dry eye; Not known: Vogt-Koyanagi-Harada syndrome[h]; *Nivolumab in combination with ipilimumab:* Common: uveitis, blurred vision; Not known: Vogt-Koyanagi-Harada syndrome[h]; *Cardiac disorders: Nivolumab monotherapy:* Uncommon: tachycardia; Rare: arrhythmia (including ventricular arrhythmia)[d], atrial fibrillation, myocarditis[a,c]; *Nivolumab in combination with ipilimumab:* Common: tachycardia; Uncommon: arrhythmia (including ventricular arrhythmia)[a,d], atrial fibrillation, myocarditis[a,c]; *Vascular disorders: Nivolumab monotherapy:* Common: hypertension; Rare: vasculitis; *Nivolumab in combination with ipilimumab:* Common: hypertension; *Respiratory, thoracic and mediastinal disorders: Nivolumab monotherapy:* Common: pneumonitis[a,c], dyspnoea[a], cough; Uncommon: pleural effusion; Rare: lung infiltration; *Nivolumab in combination with ipilimumab:* Very common: dyspnoea; Common: pneumonitis[a,c], pulmonary embolism[a], cough; Uncommon: pleural effusion; *Gastrointestinal disorders:* Very common: diarrhoea, nausea; Common: colitis[a], stomatitis, vomiting, abdominal pain, constipation, dry mouth; Uncommon: pancreatitis, gastritis; Rare: duodenal ulcer; *Nivolumab in combination with ipilimumab:* Very common: colitis[a], diarrhoea, vomiting, nausea, abdominal pain; Common: stomatitis, pancreatitis, constipation, dry mouth; Uncommon: intestinal perforation[a], gastritis, duodenitis; *Skin and subcutaneous tissue disorders: Nivolumab monotherapy:* Very common: rash[e], pruritus; Common: vitiligo, dry skin, erythema, alopecia; Uncommon: erythema multiforme, psoriasis, rosacea, urticaria; Rare: toxic epidermal necrolysis[a,f], Stevens-Johnson syndrome[a,f]; *Nivolumab in combination with ipilimumab:* Very common: rash[e], pruritus; Common: vitiligo, dry skin, erythema, alopecia, urticaria; Uncommon: psoriasis; Rare: toxic epidermal necrolysis[a,f], Stevens-Johnson syndrome[f]; *Musculoskeletal and connective tissue disorders: Nivolumab monotherapy:* Common: musculoskeletal pain[g], arthralgia; Uncommon: polymyalgia rheumatica, arthritis; Rare: Sjogren's syndrome, myopathy, myositis (including polymyositis)[a,f], rhabdomyolysis[a,f]; *Nivolumab in combination with ipilimumab:* Very common: arthralgia; Common: musculoskeletal pain[g]; Uncommon: spondyloarthropathy, Sjogren's syndrome, arthritis, myopathy, myositis (including polymyositis)[a,f], rhabdomyolysis[a,f]; *Renal and urinary disorders: Nivolumab monotherapy:* Uncommon: tubulointerstitial nephritis, renal failure (including acute kidney injury)[a,c]; *Nivolumab in combination with ipilimumab:* Common: renal failure (including acute kidney injury)[a,c]; Uncommon: tubulointerstitial nephritis; *General disorders and administration site conditions: Nivolumab monotherapy:* Very common: fatigue; Common: pyrexia, oedema (including peripheral oedema), pain; Uncommon: chest pain; *Investigations*[b]*: Nivolumab monotherapy:* Very common: increased AST, increased ALT, increased alkaline phosphatase, increased lipase, increased amylase, hypocalcaemia, increased creatinine, hyperglycaemia[c], lymphopaenia, leucopoenia, thrombocytopaenia, anaemia, hypercalcaemia, hyperkalaemia, hypokalaemia, hypomagnesaemia, hyponatraemia; Common: increased total bilirubin, hypoglycaemia, hypermagnesaemia, hypernatraemia, weight decreased; *Nivolumab in combination with ipilimumab:* Very common: increased AST, increased ALT, increased total bilirubin, increased alkaline phosphatase, increased lipase, increased amylase, increased creatinine, hyperglycaemia[c], hypoglycaemia, lymphopaenia, leucopoenia, neutropaenia, thrombocytopaenia, anaemia, hypocalcaemia, hyperkalaemia, hypokalaemia, hypomagnesaemia, hyponatraemia; Common: hypercalcaemia, hypermagnesaemia, hypernatraemia, weight decreased.

[a] Fatal cases have been reported in completed or ongoing clinical studies [b] Frequencies of laboratory terms reflect the proportion of patients who experienced a worsening from baseline in laboratory measurements. See "Description of selected adverse reactions; laboratory abnormalities" below. [c] Life-threatening cases have been reported in completed or ongoing clinical studies. [d] The frequency of adverse events in the cardiac disorders system organ class regardless of causality was higher in the nivolumab group than in the chemotherapy group in post-CTLA4/BRAF inhibitor metastatic melanoma population. Incidence rates per 100 person-years of exposure were 9.3 vs. 0; serious cardiac events were reported by 4.9% patients in the nivolumab group vs. 0 in the investigator´s choice group. The frequency of cardiac adverse events was lower in the nivolumab group than in the dacarbazine group in the metastatic melanoma without prior treatment population. All were considered not related to nivolumab by investigators except arrhythmia (atrial fibrillation, tachycardia and ventricular arrhythmia). [e] Rash is a composite term which includes maculopapular rash, rash erythematous, rash pruritic, rash follicular, rash macular, rash morbilliform, rash papular, rash pustular, rash papulosquamous, rash vesicular, rash generalised, exfoliative rash, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis exfoliative, dermatitis psoriasiform, drug eruption and pemphigoid. [f] Reported also in studies outside the pooled dataset. The frequency is based on the program-wide exposure. [g] Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, and spinal pain. [h] Post-marketing event (also see section 4.4). [i] Reported in clinical studies and in the post-marketing setting.

Description of selected adverse reactions Nivolumab or nivolumab in combination with ipilimumab is associated with immune-related adverse reactions. With appropriate medical therapy, immune-related adverse reactions resolved in most cases. Permanent discontinuation of treatment was required in a greater proportion of patients receiving nivolumab in combination with ipilimumab than in those receiving nivolumab monotherapy for immune-related colitis (16% and 0.8%, respectively), immune-related hepatitis (9% and 1%), and immune-related endocrinopathies (2.7% and 0.1%). Among patients who experienced an event, high-dose corticosteroids (at least 40 mg prednisone equivalents) were required in a greater proportion of patients receiving the combination regimen than in patients receiving nivolumab monotherapy for the management of immune-related colitis (46% and 15%, respectively), immune-related hepatitis (46% and 21%), immune-related endocrinopathies (27% and 7%, respectively), and immune-related skin adverse reaction (7% and 4%, respectively). The management guidelines for these adverse reactions are described in section 4.4. *Immune-related pneumonitis* In patients treated with nivolumab monotherapy, the incidence of pneumonitis, including interstitial lung disease and lung infiltration, was 3.4% (87/2578). The majority of cases were Grade 1 or 2 in severity reported in 0.8% (21/2578) and 1.7% (44/2578) of patients respectively. Grade 3 and 4 cases were reported in 0.7% (19/2578) and <0.1% (1/2578) of patients respectively. Grade 5 cases were reported in < 0.1% (2/2578) of patients in these studies. Median time to onset was 3.6 months (range: 0.2-19.6). Resolution occurred in 63 patients (72.4%) with a median time to resolution of 6.1 weeks (range: 0.1+-96.7+). + denotes a censored observation. In patients treated with nivolumab in combination with ipilimumab, the incidence of pneumonitis including interstitial lung disease, was 7.8% (35/448). Grade 2, Grade 3, and Grade 4 cases were reported in 4.7% (21/448), 1.1% (5/448), and 0.2% (1/448) of patients, respectively. One of the Grade 3 pneumonitis cases worsened over 11 days with a fatal outcome. Median time to onset was 2.6 months (range: 0.7-12.6). Resolution occurred in 33 patients (94.3%) with a median time to resolution of 6.1 weeks (range: 0.3-35.1). *Immune-related colitis* In patients treated with nivolumab monotherapy, the incidence of diarrhoea, colitis, or frequent bowel movements was 13.1% (339/2578). The majority of cases were Grade 1 or 2 in severity reported in 8.5% (220/2578) and 3.0% (78/2578) of patients respectively. Grade 3 cases were reported in 1.6% (41/2578) of patients. No Grade 4 or 5 cases were reported in these studies. Median time to onset was 1.8 months (range: 0.0-26.6). Resolution occurred in 296 patients (88.1%) with a median time to resolution of 2.1 weeks (range: 0.1-124.4+). In patients treated with nivolumab in combination with ipilimumab, the incidence of diarrhoea or colitis was 46.7% (209/448). Grade 2, Grade 3, and Grade 4 cases were reported in 13.6% (61/448), 15.8% (71/448), and 0.4% (2/448) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 1.2 months (range: 0.0-22.6). Resolution occurred in 186 patients (89.4%) with a median time to resolution of 3.0 weeks (range: 0.1-159.4+). *Immune-related hepatitis* In patients treated with nivolumab monotherapy, the incidence of liver function test abnormalities was 6.7% (173/2578). The majority of cases were Grade 1 or 2 in severity reported in 3.5% (91/2578) and 1.2% (32/2578) of patients respectively. Grade 3 and 4 cases were reported in 1.6% (41/2578) and 0.3% (9/2578) of patients, respectively. No Grade 5 cases were reported in these studies. Median time to onset was 2.1 months (range: 0.0-27.6). Resolution occurred in 132 patients (76.7%) with a median time to resolution of 5.9 weeks (range: 0.1-82.6+). In patients treated with nivolumab in combination with ipilimumab, the incidence of liver function test abnormalities was 29.5% (132/448). Grade 2, Grade 3, and Grade 4 cases were reported in 6.7% (30/448), 15.4% (69/448), and 1.8% (8/448) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 1.5 months (range: 0.0-30.1). Resolution occurred in 124 patients (93.9%) with a median time to resolution of 5.1 weeks (range: 0.1-106.9). *Immune-related nephritis and renal dysfunction* In patients treated with nivolumab monotherapy, the incidence of nephritis or renal dysfunction was 2.8% (71/2578). The majority of cases were Grade 1 or 2 in severity reported in 1.6% (41/2578) and 0.7% (18/2578) of patients respectively. Grade 3 and 4 cases were reported in 0.4% (11/2578) and <0.1% (1/2578) of patients, respectively. No Grade 5 nephritis or renal dysfunction was reported in these studies. Median time to onset was 2.3 months (range: 0.0-18.2). Resolution occurred in 42 patients (61.8%) with a median time to resolution of 12.1 weeks (range: 0.3-79.1+). In patients treated with nivolumab in combination with ipilimumab, the incidence of nephritis or renal dysfunction was 5.1% (23/448). Grade 2, Grade 3, and Grade 4 cases were reported in 1.6% (7/448), 0.9% (4/448), and 0.7% (3/448) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 2.6 months (range: 0.5-21.8). Resolution occurred in 21 patients (91.3%) with a median time to resolution of 2.1 weeks (range: 0.1- 125.1+). *Immune-related endocrinopathies* In patients treated with nivolumab monotherapy, the incidence of thyroid disorders, including hypothyroidism or hyperthyroidism, was 9.6% (248/2578). The majority of cases were Grade 1 or 2 in severity reported in 4.2% (107/2578) and 5.4% (139/2578) of patients, respectively. Grade 3 thyroid disorders were reported in < 0.1% (2/2578) of patients. Hypophysitis (1 Grade 1, 2 Grade 2, 5 Grade 3, and 1 Grade 4), hypopituitarism (4 Grade 2 and 1 Grade 3), adrenal insufficiency (including secondary adrenocortical insufficiency) (1 Grade 1, 9 Grade 2, and 5 Grade 3), diabetes mellitus (including Type 1 diabetes mellitus) (3 Grade 2 and 1 Grade 3), and diabetic ketoacidosis (2 Grade 3) were reported. No Grade 5 cases were reported in these studies. Median time to onset of these endocrinopathies was 2.8 months (range: 0.3-29.1). Resolution occurred in 117 patients (42.9%). Time to resolution ranged from 0.4 to 144.1+ weeks. In patients treated with nivolumab in combination with ipilimumab, the incidence of thyroid disorders was 25.2% (113/448). Grade 2 and Grade 3 thyroid disorders were reported in 14.5% (65/448) and 1.3% (6/448) of patients, respectively. Grade 2 and Grade 3 hypophysitis (including lymphocytic hypophysitis) occurred in 5.8% (26/448) and 2.0% (9/448) of patients, respectively. Grade 2 and Grade 3 hypopituitarism occurred in 0.4% (2/448) and 0.7% (3/448) of patients, respectively. Grade 2, Grade 3, and Grade 4 adrenal insufficiency (including secondary adrenocortical insufficiency) occurred in 1.6% (7/448), 1.3% (6/448) and 0.2% (1/448) of patients, respectively. Grade 1, Grade 2, Grade 3, and Grade 4 diabetes mellitus and Grade 4 diabetic ketoacidosis were each reported in 0.2% (1/448) of patients. No Grade 5 endocrinopathy was reported. Median time to onset of these endocrinopathies was 1.9 months (range: 0.0-28.1). Resolution occurred in 64 patients (45.4%). Time to resolution ranged from 0.4 to 155.4+ weeks. *Immune-related skin adverse reactions* In patients treated with nivolumab monotherapy, the incidence of rash was 26.4% (680/2578). The majority of cases were Grade 1 in severity reported in 20.1% (518/2578) of patients. Grade 2 and Grade 3 cases were reported in 5.1% (131/2578) and 1.2% (31/2578) of patients respectively. No Grade 4 or 5 cases were reported in these studies. Median time to onset was 1.4 months (range: 0.0-27.9). Resolution occurred in 428 patients (63.8%) with a median time to resolution of 17.1 weeks (0.1-150.0+). In patients treated with nivolumab in combination with ipilimumab, the incidence of rash was 65.0% (291/448). Grade 2 and Grade 3 cases were reported in 20.3% (91/448) and 7.6% (34/448) of patients, respectively. No Grade 4 or 5 cases were reported. Median time to onset was 0.5 months (range: 0.0-19.4). Resolution occurred in 191 patients (65.9%) with a median time to resolution of 11.4 weeks (range: 0.1-150.1+). Rare cases of SJS and TEN some of them with fatal outcome have been observed (see sections 4.2 and 4.4). *Infusion reactions* In patients treated with nivolumab monotherapy, the incidence of hypersensitivity/infusion reactions was 4.7% (121/2578), including 6 Grade 3 and 2 Grade 4 cases. In patients treated with nivolumab in combination with ipilimumab, the incidence of hypersensitivity/infusion reactions was 3.8% (17/448); all were Grade 1 or 2 in severity. Grade 2 cases were reported in 2.2% (10/448) of patients. No Grade 3-5 cases were reported. *Complications of allogeneic HSCT in classical Hodgkin Lymphoma* In 49 evaluated patients from two cHL studies who underwent allogeneic HSCT after discontinuing nivolumab monotherapy, Grade 3 or 4 acute GVHD was reported in 13/49 patients (26.5%). Hyperacute GVHD, defined as acute GVHD occurring within 14 days after stem cell infusion, was reported in three patients (6%). A steroid-requiring febrile syndrome, without an identified infectious cause, was reported in six patients (12%) within the first 6 weeks post-transplantation, with three patients responding to steroids. Hepatic veno-occlusive disease occurred in one patient, who died of GVHD and multi-organ failure. Nine of 49 patients (18.4%) died from complications of allogeneic HSCT after nivolumab. The 49 patients had a median follow-up from subsequent allogeneic HSCT of 5.6 months (range: 0-19 months). *Laboratory abnormalities* In patients treated with nivolumab monotherapy, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 5.2% for anaemia (all Grade 3), 1.0% for thrombocytopaenia, 1.0% for leucopoenia, 10.0% for lymphopaenia, 1.1% for neutropaenia, 2.1% for increased alkaline phosphatase, 2.7% for increased AST, 2.2% for increased ALT, 1.2% for increased total bilirubin, 0.9% for increased creatinine, 3.8% for hyperglycaemia, 1.0% for hypoglycaemia, 3.5% for increased amylase, 7.9% for increased lipase, 6.4% for hyponatraemia, 1.8% for hyperkalaemia, 1.5% for hypokalaemia, 1.2% for hypercalcaemia, 0.7% for hypermagnesaemia, 0.5% for hypomagnesaemia, 0.7% for hypocalcaemia, and 0.1% for hypernatraemia. In patients treated with nivolumab in combination with ipilimumab, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 2.8% for anaemia (all Grade 3), 1.2% for thrombocytopaenia, 0.5% for leucopoenia, 6.7% for lymphopaenia, 0.7% for neutropaenia, 4.3% for increased alkaline phosphatase, 12.4% for increased AST, 15.3% for increased ALT, 1.2% for increased total bilirubin, 2.4% for increased creatinine, 5.3% for hyperglycaemia, 8.7% for increased amylase, 19.5% for increased lipase, 1.2% for hypocalcaemia, 0.2% each for hypernatraemia and hypercalcaemia, 0.5% for hyperkalemia, 0.3% for hypermagnesaemia, 4.8% for hypokalaemia, and 9.5% for hyponatraemia. *Immunogenicity* Of the 2022 patients who were treated with nivolumab monotherapy 3 mg/kg every 2 weeks and evaluable for the presence of anti-product-antibodies, 231 patients (11.4%) tested positive for treatment-emergent anti-product-antibodies with fifteen patients (0.7 %) testing positive for neutralising antibodies. Of 394 patients who were treated with nivolumab in combination with ipilimumab and evaluable for the presence of anti-nivolumab antibodies, 149 patients (37.8%) tested positive for treatment-emergent anti-nivolumab antibodies with 18 patients (4.6%) testing positive for neutralising antibodies. Although the clearance of nivolumab was increased by 24% when anti-nivolumab-antibodies were present, there was no evidence of loss of efficacy or altered toxicity profile in the presence of nivolumab antibodies based on the pharmacokinetic and exposure-response analyses for both monotherapy and combination. Elderly No overall differences in safety were reported between elderly (≥ 65 years) and younger patients (< 65 years). Data from NSCLC and SCCHN patients 75 years of age or older are too limited to draw conclusions on this population (see section 5.1). Data from cHL patients 65 years of age or older are too limited to draw conclusions on this population (see section 5.1). Hepatic or renal impairment In the non-squamous NSCLC study (CA209057), the safety profile in patients with baseline renal or hepatic impairment was comparable to that in the overall population. These results should be interpreted with caution due to the small sample size within the subgroups. Reporting of suspected adverse reactions Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V. **MARKETING AUTHORISATION HOLDER** Bristol-Myers Squibb Pharma EEIG Uxbridge Business Park Sanderson Road Uxbridge UB8 1DH United Kingdom **MARKETING AUTHORISATION NUMBER(S)** EU/1/15/1014/001-002 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION** Date of first authorisation: 19 June 2015 **DATE OF REVISION OF THE TEXT** Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1506BE18PRO2452-01 date of preparation 05/2018

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT KEYTRUDA® 50 mg powder for concentrate for solution for infusion, KEYTRUDA® 25 mg/mL concentrate for solution for infusion. **2. QUALITATIVE AND QUANTITATIVE COMPOSITION** • ***50 mg*** One vial of powder contains 50 mg of pembrolizumab. After reconstitution, 1 mL of concentrate contains 25 mg of pembrolizumab. • ***25 mg/mL*** One vial of 4 mL of concentrate contains 100 mg of pembrolizumab. Each mL of concentrate contains 25 mg of pembrolizumab. Pembrolizumab is a humanised monoclonal anti-programmed cell death-1 (PD-1) antibody (IgG4/kappa isotype with a stabilising sequence alteration in the Fc region) produced in Chinese hamster ovary cells by recombinant DNA technology. For the full list of excipients, see section 6.1. **3. PHARMACEUTICAL FORM** • ***50 mg*** Powder for concentrate for solution for infusion. White to off-white lyophilised powder. • ***25 mg/mL*** Concentrate for solution for infusion. Clear to slightly opalescent, colourless to slightly yellow solution, pH 5.2 – 5.8. **4. CLINICAL PARTICULARS 4.1 Therapeutic indications** KEYTRUDA as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations. KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA. KEYTRUDA as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV. KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy (see section 5.1). KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy. **4.2 Posology and method of administration** Therapy must be initiated and supervised by specialist physicians experienced in the treatment of cancer. PD-L1 testing for patients with NSCLC Patients with NSCLC should be selected for treatment based on the tumour expression of PD-L1 confirmed by a validated test (see section 5.1). Posology KEYTRUDA should be administered as an intravenous infusion over 30 minutes every 3 weeks. The recommended dose of KEYTRUDA is: • 200 mg for NSCLC that has not been previously treated with chemotherapy, cHL or for urothelial carcinoma; • 2 mg/kg for NSCLC that has been previously treated with chemotherapy or for melanoma. Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity. Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed. ***Dose delay or discontinuation (see also section 4.4)*** *Table 1: Recommended treatment modifications for KEYTRUDA* ***Immune-related adverse reactions/Severity (Treatment modification)*** Pneumonitis: Grade 2 (Withhold until adverse reactions recover to Grade 0-1*), Grade 3 or 4, or recurrent Grade 2 (Permanently discontinue); Colitis: Grade 2 or 3 (Withhold until adverse reactions recover to Grade 0-1*), Grade 4 or recurrent Grade 3 (Permanently discontinue); Nephritis: Grade 2 with creatinine > 1.5 to ≤ 3 times upper limit of normal (ULN) (Withhold until adverse reactions recover to Grade 0-1*), Grade ≥ 3 with creatinine > 3 times ULN (Permanently discontinue); Endocrinopathies: Symptomatic hypophysitis, Type 1 diabetes associated with Grade > 3 hyperglycaemia (glucose > 250 mg/dL or > 13.9 mmol/L) or associated with ketoacidosis, Hyperthyroidism Grade ≥ 3 (Withhold until adverse reactions recover to Grade 0-1* For patients with Grade 3 or Grade 4 endocrinopathy that improved to Grade 2 or lower and is controlled with hormone replacement, if indicated, continuation of pembrolizumab may be considered after corticosteroid taper, if needed. Otherwise treatment should be discontinued. Hypothyroidism may be managed with replacement therapy without treatment interruption.); Hepatitis: Grade 2 with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 to 5 times ULN or total bilirubin > 1.5 to 3 times ULN (Withhold until adverse reactions recover to Grade 0-1*), Grade ≥ 3 with AST or ALT > 5 times ULN or total bilirubin > 3 times ULN (Permanently discontinue), In case of liver metastasis with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases ≥ 50% and lasts ≥ 1 week (Permanently discontinue); Skin reactions: Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) (Withhold until adverse reactions recover to Grade 0-1*), Grade 4 or confirmed SJS or TEN (Permanently discontinue); Other immune-related adverse reactions: Based on severity and type of reaction (Grade 2 or Grade 3) (Withhold until adverse reactions recover to Grade 0-1*), Grade 3 or 4 myocarditis (Permanently discontinue), Grade 4 or recurrent Grade 3 (Permanently discontinue). ***Infusion-related reactions:*** Grade 3 or 4 (Permanently discontinue). Note: toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI - CTCAE v.4). * If treatment-related toxicity does not resolve to Grade 0-1 within 12 weeks after last dose of KEYTRUDA, or if corticosteroid dosing cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks, KEYTRUDA should be permanently discontinued. The safety of re-initiating pembrolizumab therapy in patients previously experiencing immune-related myocarditis is not known. KEYTRUDA should be permanently discontinued for Grade 4 or recurrent Grade 3 adverse reactions, unless otherwise specified in Table 1. For Grade 4 haematological toxicity, only in patients with cHL, KEYTRUDA should be withheld until adverse reactions recover to Grade 0-1. Patients treated with KEYTRUDA must be given the Patient Alert Card and be informed about the risks of KEYTRUDA (see also package leaflet). ***Special populations*** ***Elderly*** No overall differences in safety or efficacy were reported between elderly patients (≥ 65 years) and younger patients (< 65 years). No dose adjustment is necessary in this population. Data from patients ≥ 65 years are too limited to draw conclusions on cHL population (see section 5.1). ***Renal impairment*** No dose adjustment is needed for patients with mild or moderate renal impairment. KEYTRUDA has not been studied in patients with severe renal impairment (see sections 4.4 and 5.2). ***Hepatic impairment*** No dose adjustment is needed for patients with mild hepatic impairment. KEYTRUDA has not been studied in patients with moderate or severe hepatic impairment (see sections 4.4 and 5.2). ***Ocular melanoma*** There are limited data on the safety and efficacy of KEYTRUDA in patients with ocular melanoma (see section 5.1). ***Eastern Cooperative Oncology Group (ECOG) performance status score ≥ 2*** Patients with ECOG performance status score ≥ 2 were excluded from the clinical trials of melanoma, NSCLC and cHL (see sections 4.4 and 5.1). ***Paediatric population*** The safety and efficacy of KEYTRUDA in children below 18 years of age have not yet been established. No data are available. Method of administration KEYTRUDA must be administered by intravenous infusion over 30 minutes. KEYTRUDA must not be administered as an intravenous push or bolus injection. • ***50 mg*** For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6. • ***25 mg/mL*** For instructions on dilution of the medicinal product before administration, see section 6.6. **4.3 Contraindications** Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. **4.8 Undesirable effects** ***Summary of the safety profile*** Pembrolizumab is most commonly associated with immune-related adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of pembrolizumab (see "Description of selected adverse reactions" below). The safety of pembrolizumab has been evaluated in 3,830 patients with advanced melanoma, NSCLC, cHL or urothelial carcinoma across four doses (2 mg/kg every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg every 2 or 3 weeks) in clinical studies. In this patient population, the most common adverse reactions (> 10%) with pembrolizumab were fatigue (21%), pruritus (16%), rash (13%), diarrhoea (12%) and nausea (10%). The majority of adverse reactions reported were of Grade 1 or 2 severity. The most serious adverse reactions were immune-related adverse reactions and severe infusion-related reactions (see section 4.4). ***Tabulated list of adverse reactions*** Adverse reactions observed in clinical studies and reported from post-marketing use of pembrolizumab are listed in Table 2. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness. *Table 2: Adverse reactions in patients treated with pembrolizumab:* Infections and infestations Uncommon: pneumonia. Blood and lymphatic system disorders Common: anaemia; Uncommon: neutropenia, thrombocytopenia, leukopenia, lymphopenia, eosinophilia; Rare: immune thrombocytopenic purpura, haemolytic anaemia. Immune system disorders Common: infusion related reaction[a]; Rare: sarcoidosis; Not known: solid organ transplant rejection. Endocrine disorders Common: hyperthyroidism, hypothyroidism[b]; Uncommon: hypophysitis[c], adrenal insufficiency, thyroiditis. Metabolism and nutrition disorders Common: decreased appetite; Uncommon: type 1 diabetes mellitus[d], hyponatraemia, hypokalaemia, hypocalcaemia. Psychiatric disorders Uncommon: insomnia. Nervous system disorders Common: headache, dizziness, dysgeusia; Uncommon: epilepsy, lethargy, neuropathy peripheral; Rare: Guillain-Barré syndrome, myasthenic syndrome. Eye disorders Uncommon: uveitis[e], dry eye. Cardiac disorders Uncommon: myocarditis. Vascular disorders Uncommon: hypertension. Respiratory, thoracic and mediastinal disorders Common: pneumonitis[f], dyspnoea, cough. Gastrointestinal disorders Very common: diarrhoea, nausea; Common: colitis[g], vomiting, abdominal pain[h], constipation, dry mouth; Uncommon: pancreatitis[i]; Rare: small intestine perforation. Hepatobiliary disorders Uncommon: hepatitis[j]. Skin and subcutaneous tissue disorders Very common: rash[k], pruritus[l]; Common: severe skin reactions[m], vitiligo[n], dry skin, erythema; Uncommon: lichenoid keratosis[o], psoriasis, alopecia, dermatitis, dermatitis acneiform, eczema, hair colour changes, papule; Rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema nodosum. Musculoskeletal and connective tissue disorders Common: arthralgia, myositis[p], musculoskeletal pain[q], arthritis[r], pain in extremity; Uncommon: tenosynovitis[s]. Renal and urinary disorders Uncommon: nephritis[t]. General disorders and administration site conditions Very common: fatigue; Common: asthenia, oedema[u], pyrexia, influenza like illness, chills. Investigations Common: alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatinine increased; Uncommon: blood bilirubin increased, amylase increased, hypercalcaemia. The following terms represent a group of related events that describe a medical condition rather than a single event: a. infusion-related reactions (drug hypersensitivity, anaphylactic reaction, hypersensitivity and cytokine release syndrome); b. hypothyroidism (myxoedema); c. hypophysitis (hypopituitarism); d. type 1 diabetes mellitus (diabetic ketoacidosis); e. uveitis (iritis and iridocyclitis); f. pneumonitis (interstitial lung disease); g. colitis (colitis microscopic and enterocolitis); h. abdominal pain (abdominal discomfort, abdominal pain upper and abdominal pain lower); i. pancreatitis (autoimmune pancreatitis and pancreatitis acute); j. hepatitis (autoimmune hepatitis and drug induced liver injury); k. rash (rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular and genital rash); l. pruritus (urticaria, urticaria papular, pruritus generalized and pruritus genital); m. severe skin reactions (dermatitis exfoliative, erythema multiforme, exfoliative rash, pemphigoid and Grade ≥ 3 of the following: pruritus, rash, rash generalised and rash maculo-papular, dermatitis psoriasiform, pruritus generalised); n. vitiligo (skin depigmentation, skin hypopigmentation and hypopigmentation of the eyelid); o. lichenoid keratosis (lichen planus and lichen sclerosus); p. myositis (myalgia, myopathy, polymyalgia rheumatica and rhabdomyolysis); q. musculoskeletal pain (musculoskeletal discomfort, back pain, musculoskeletal stiffness, musculoskeletal chest pain and torticollis); r. arthritis (joint swelling, polyarthritis and joint effusion); s. tenosynovitis (tendonitis, synovitis and tendon pain); t. nephritis (nephritis autoimmune, tubulointerstitial nephritis and renal failure or renal failure acute with evidence of nephritis, nephrotic syndrome); u. oedema (oedema peripheral, generalised oedema, fluid overload, fluid retention, eyelid oedema and lip oedema, face oedema, localized oedema and periorbital oedema). ***Description of selected adverse reactions*** Data for the following immune-related adverse reactions are based on patients who received pembrolizumab across three doses (2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks) in clinical studies (see section 5.1). The management guidelines for these adverse reactions are described in section 4.4. ***Immune-related adverse reactions (see section 4.4)*** Immune-related pneumonitis Pneumonitis occurred in 139 (3.6%) patients, including Grade 2, 3, 4 or 5 cases in 56 (1.5%), 38 (1.0%), 9 (0.2%) and 5 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of pneumonitis was 3.7 months (range 2 days to 21.3 months). The median duration was 2.1 months (range 1 day to 17.2+ months). Pneumonitis led to discontinuation of pembrolizumab in 60 (1.6%) patients. Pneumonitis resolved in 81 patients, 1 with sequelae. Immune-related colitis Colitis occurred in 71 (1.9%) patients, including Grade 2, 3 or 4 cases in 15 (0.4%), 44 (1.1%) and 3 (<0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of colitis was 3.6 months (range 7 days to 16.2 months). The median duration was 1.3 months (range 1 day to 8.7+ months). Colitis led to discontinuation of pembrolizumab in 18 (0.5%) patients. Colitis resolved in 61 patients. Immune-related hepatitis Hepatitis occurred in 23 (0.6%) patients, including Grade 2, 3 or 4 cases in 4 (0.1%), 16 (0.4%) and 2 (<0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hepatitis was 1.3 months (range 8 days to 21.4 months). The median duration was 1.5 months (range 8 days to 20.9+ months). Hepatitis led to discontinuation of pembrolizumab in 7 (0.2%) patients. Hepatitis resolved in 19 patients. Immune-related nephritis Nephritis occurred in 15 (0.4%) patients, including Grade 2, 3 or 4 cases in 3 (0.1%), 10 (0.3%) and 1 (<0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of nephritis was 4.9 months (range 12 days to 12.8 months). The median duration was 1.8 months (range 10 days to 10.5+ months). Nephritis led to discontinuation of pembrolizumab in 7 (0.2%) patients. Nephritis resolved in 9 patients. Immune-related endocrinopathies Hypophysitis occurred in 21 (0.5%) patients, including Grade 2, 3 or 4 cases in 6 (0.2%), 12 (0.3%) and 1 (<0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hypophysitis was 3.7 months (range 1 day to 17.7 months). The median duration was 3.3 months (range 4 days to 12.7+ months). Hypophysitis led to discontinuation of pembrolizumab in 6 (0.2%) patients. Hypophysitis resolved in 10 patients, 2 with sequelae. Hyperthyroidism occurred in 135 (3.5%) patients, including Grade 2 or 3 cases in 32 (0.8%) and 4 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hyperthyroidism was 1.4 months (range 1 day to 21.9 months). The median duration was 2.1 months (range 10 days to 15.5+ months). Hyperthyroidism led to discontinuation of pembrolizumab in 2 (0.1%) patients. Hyperthyroidism resolved in 104 (77%) patients, 1 with sequelae. Hypothyroidism occurred in 345 (9.0%) patients, including Grade 2 or 3 cases in 251 (6.6%) and 4 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hypothyroidism was 3.5 months (range 1 day to 18.9 months). The median duration was not reached (range 2 days to 29.9+ months). One patient (< 0.1%) discontinued pembrolizumab due to hypothyroidism. Hypothyroidism resolved in 81 (23%) patients, 6 with sequelae. In patients with cHL (n=241) the incidence of hypothyroidism was 14.1% (all Grades) with 0.4% Grade 3. Immune-related skin adverse reactions Immune-related severe skin reactions occurred in 63 (1.6%) patients, including Grade 2 or 3 cases in 4 (0.1%) and 52 (1.4%) patients, respectively, receiving pembrolizumab. The median time to onset of severe skin reactions was 2.5 months (range 4 days to 21.5 months). The median duration was 2.0 months (range 3 days to 17.8+ months). Severe skin reactions led to discontinuation of pembrolizumab in 6 (0.2%) patients. Severe skin reactions resolved in 41 patients. Rare cases of SJS and TEN, some of them with fatal outcome, have been observed (see sections 4.2 and 4.4). Complications of allogeneic HSCT in classical Hodgkin lymphoma Of 23 patients with cHL who proceeded to allogeneic HSCT after treatment with pembrolizumab, 6 patients (26%) developed GVHD, one of which was fatal, and 2 patients (9%) developed severe hepatic VOD after reduced-intensity conditioning, one of which was fatal. The 23 patients had a median follow-up from subsequent allogeneic HSCT of 5.1 months (range: 0-26.2 months). ***Immunogenicity*** In clinical studies in patients treated with pembrolizumab 2 mg/kg every three weeks, 200 mg every three weeks, or 10 mg/kg every two or three weeks, 36 (1.8%) of 2,034 evaluable patients tested positive for treatment-emergent antibodies to pembrolizumab, of which 9 (0.4%) patients had neutralising antibodies against pembrolizumab. There was no evidence of an altered pharmacokinetic or safety profile with anti-pembrolizumab binding or neutralising antibody development. ***Reporting of suspected adverse reactions*** Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system: **in Belgium:** Agence Fédérale des Médicaments et des Produits de Santé. Division Vigilance. EUROSTATION II. Place Victor Horta, 40/40. B-1060 Bruxelles. (Website: www.afmps.be, e-mail: adversedrugreactions@fagg-afmps.be), **in Luxembourg:** Direction de la Santé – Division de la Pharmacie et des Médicaments. Villa Louvigny – Allée Marconi. L-2120 Luxembourg. (Website: http://www.ms.public.lu/fr/activites/pharmacie-medicament/index.html). **7. MARKETING AUTHORISATION HOLDER** Merck Sharp & Dohme Limited. Hertford Road. Hoddesdon. Hertfordshire EN11 9BU. United Kingdom **8. MARKETING AUTHORISATION NUMBER(S)** EU/1/15/1024/001, EU/1/15/1024/002 **9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION** Date of first authorisation: 17 July 2015. **10. DATE OF REVISION OF THE TEXT** 12/2017. Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu. **DELIVERY**: only on prescription.

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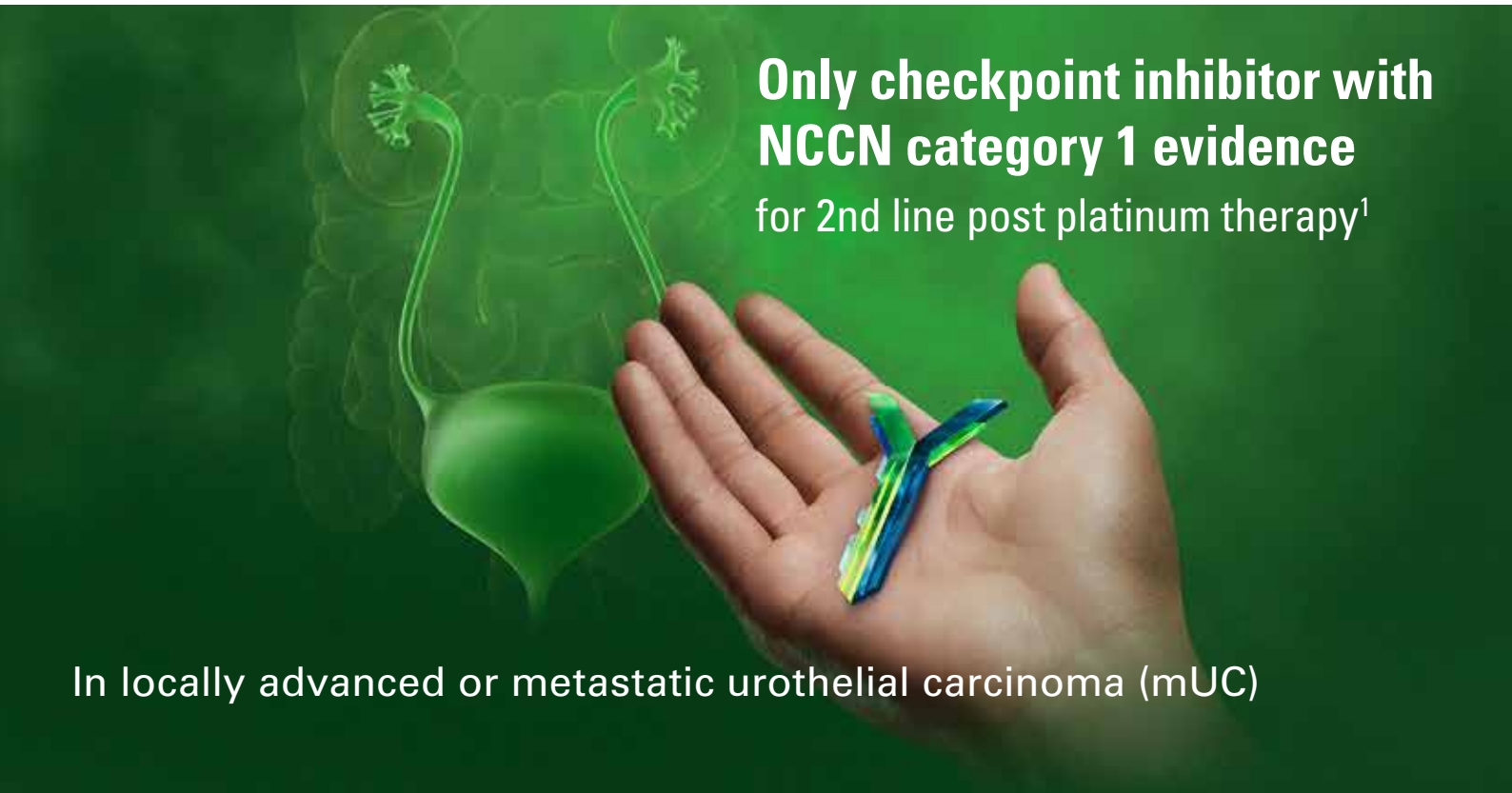

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1. National comprehensive Cancer Network (NCCN): NCCN Guidelines, Bladder Cancer (https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf, accessed 03/2018).
2. SmPC KEYTRUDA®, 12/2017

mUC = metastatic urothelial carcinoma; PD-1 = programmed death receptor-1; NCCN = National Comprehensive Cancer Network.

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Interview with Professor Sylvie Rottey
(BMUC President)

2018 Marked the 5th edition of the Belgian Multidisciplinary Meeting on Urological Cancers (BMUC). This meeting is a collaboration between the BSMO, BVU/SBU, and BVRO/ABRO and took place on 9 and 10 March 2018. We invited Prof. Sylvie Rottey *(BMUC President)* to share her thoughts on the achievements of BMUC and of the future plans with the organization.

FOR THOSE NOT FAMILIAR WITH HOW THE SOCIETY WAS FOUNDED, CAN YOU SHARE THE INSPIRATION FOR AND FOUNDING OF THE SOCIETY?

About 5 years ago the idea was raised at the BSMO to organise a meeting bringing together urologists, radiation oncologists and medical oncologists involved in the management of urological cancers. All these specialties are very much involved in the care for urological cancer patients, especially in prostate cancer. We set up a scientific committee consisting of 3 medical oncologists, 3 urologists and 3 radiation oncologists coming from the three established organisations/societies in their field of expertise. We had some meetings to discuss the content and formula of such a meeting and that's how we started.

The main goal of BMUC was to combine the different multidisciplinary specialties. This multidisciplinarity is key for BMUC as we strive to have a platform allowing for in depth discussions and brainstorms on new data and emerging clinical insights in the field of urological cancer.

WHAT IS THE ADDED VALUE OF MULTIDISCIPLINARITY IN MANAGING UROLOGICAL CANCERS?

Especially for patients with prostate cancer, but also for patients with other urological cancers, there are often different treatment options, all supported by level 1 evidence. In these cases it is important to discuss the patient file and the patient comorbidities with the entire medical team. If there are different options, the patient has the right to hear the

different possibilities and should be able to visit the different specialists. That way he, or she can obtain a clear picture of the different possibilities: what about radiation?, is surgery an option?, would systemic treatment be better? In addition to this, it is important for us to think out of the box, especially for rare urological tumours. In this light, multidisciplinary brainstorming can really help to establish the best treatment path for the patient.

WHAT WERE THE KEY MOMENTS AND ACHIEVEMENTS IN THE BRIEF HISTORY OF BMUC?

First of all, the 5 meetings we had so far. These meetings are always hosted in March and we had the pleasure to welcome some very important speakers over the years. In my opinion, the most important speaker we had was Prof Emmanuel Antonarakis *from the John Hopkins cancer centre in Baltimore. In his presentation he discussed the different mutations seen in prostate cancer patients and explained how we should cope with them in the treatment of these patients. Also the congress highlights session during the meeting is always well appreciated. We also try to have 1 "pro and con" session during each congress. These sessions help you to think out of the box and force you to look at the available scientific literature in a critical way. Finally, at the end of 2017, we became an official organisation with our own statutes. This is an important milestone because it will add significantly to our 'critical weight' as an organization. We will now be able to set up other symposia apart from our annual meeting and set-up in-depth co-operations with the industry. We are now also able to submit articles under the name of BMUC and even start BMUC supported clinical trials.*

> Multidisciplinarity is key for BMUC as we strive to have a platform allowing for in-depth discussions and brainstorms on new data and emerging clinical insights in urological cancer.

WHAT PROJECTS ARE CURRENTLY RUNNING?

First of all we have our annual conference in La Hulpe and we will continue this meeting with the same formula. Apart from that we are planning to organize some smaller, more regional preceptorships that will be more accessible for everybody. In these sessions we will mainly focus on case discussions with a small group of physicians. We would like to have these meetings as interactive as possible, which is easier to do with a group of 20-30 people as compared to an audience of 150 as is the case for the annual BMUC meeting. There are also other plans, like writing Belgian treatment guidelines on different topics.

WHAT DO YOU BELIEVE TO BE THE GREATEST STRENGTHS OF BMUC?

Surely, the multidisciplinarity. In addition to this, we try to focus on items that are relevant for the clinicians: emerging treatment options, practical tools, practical discussions. Every year we have some discussions on whether we would also include some more translational topics in our meeting, but for now we will stick to topics that directly impact the daily practice of clinicians. Of course, researchers are also participating, since translational research also requires a good understanding of recent clinical literature and daily practice.

Active surveillance in prostate cancer

Presented by: A. de la Taille
(CHU Henri Mondor, assistance publique des hôpitaux de Paris, Paris, France)

Data regarding the natural history of prostate cancer (PCa) disease confirm the clinical insignificance of low-grade prostate cancer, which is associated with scant or no metastatic dissemination. Active surveillance (AS) is a conservative management approach, conducted for patients with "low-" or "favorable-risk" disease, which avoids long-term adverse effects on the patient's quality of life. In a lecture during BMUC 2018, **Prof. de la Taille** explained why he thinks that AS is an option that we need to consider and why we should discuss this with the patient before the biopsy is taken.

INTRODUCTION

Prospective trials evaluating the effect of prostate-specific-antigen (PSA) screening indicate that this approach decreases the incidence of metastatic disease with 41% and reduces the mortality rate by 20%. However, the number needed to treat to prevent 1 PCa death is 48. This indicates that there is a significant over diagnosis with this PSA approach.[1] The vast majority of men diagnosed with localized PCa in the US opt for active treatment, indicating the significant over-treatment in PCa. This is not surprising as it is not always easy to convince your patients to opt for AS if something abnormal is seen on his biopsy. Therefore it is important for physicians to come up with strong arguments in support of AS. The main objective of AS is reducing the overtreatment of clinically insignificant disease and reserve treatment for patients whose disease is reclassified as higher risk after a period of observation within the window of curability. This raises three main questions:

1) Can we determine who has insignificant disease?
2) What constitutes reclassification and need for intervention?
3) How do we avoid that the window of curability is missed?

WHO HAS INSIGNIFICANT DISEASE?

To determine who has insignificant disease we must first take a closer look at the inclusion and exclusion criteria of the clinical trials evaluating AS in PCa. A systematic review of these studies indicates that the inclusion criteria differ between the trials. There are differences in the maximum Gleason score (up to 6, or 7), the maximum number of positive cores (2 to 3), the PSA level (ranges from below 10 to below 20), the percentage of cancer involvement per core, etc...[2] Based on the different studies, nine criteria for AS eligibility were established:

1. Histologically proven adenocarcinoma of the prostate
2. Men should be fit for curative treatment
3. PSA level at diagnosis ≤ 10 ng/mL
4. PSA density less than 0.2
5. Clinical stage T1C or T2
6. Adequate biopsy sampling
7. Gleason score 3+3= 6
8. <2 positive biopsy cores
9. Participants must be willing to attend the follow-up visits

With respect to pathology, the following exclusion criteria for AS were set: predominant ductal carcinoma (including pure intraductal carcinoma), sarcomatoïd carcinoma, small cell carcinoma, EPE or LVI in needle biopsy and perineural invasion.

What about follow-up? The different studies included in the systematic review of *Thomson et al.* have a median

time from entry to discontinuation of AS ranging from 2.2 to 5.4 years. In the studies with sufficient follow-up, about half of the patients stopped AS after 10 years.[2]
If the criteria above are fulfilled, the results obtained with AS are good. In fact, the risk of PCa-related death at 10 years was only 2% at 8 years in a study of the Royal Marsden institute and 3% at 30 years in a Canadian study.[3,4] However, despite these stringent criteria, there is still a small proportion of patients who do have an aggressive PCa. In fact, in the study by *Klotz et al.* the 10-year PCa-specific survival was 98.5%, indicating that a small proportion of patients would have died from PCa. How can we find these patients? Data reported by *Suardi et al.* show that 3.3 to 7.1% of patients who were deemed eligible for AS using the strictest criteria harbored unfavorable prostate cancer characteristics.[5]

> The main objective of AS is reducing the overtreatment of clinically insignificant disease.

WHEN DO WE NEED TO STOP AS AND INTERVENE?

In the guidelines of the EAU, the following triggers to stop AS are listed: a change in PSA kinetics (i.e. a PSA doubling time <3 years), a progression on follow-up biopsy consisting of an in increase in Gleason grade, or tumor volume (i.e. increase in absolute cores involved with cancer, percentage of positive cores >33%, absolute tumor length, or an increase in the percentage of tumor tissue >50% within single core), patient preference, or clinical/radiographic evidence of local/distant progression.[6] It is to be expected that mutiparameteric MRI will also play its role in this decision in the near future.

Several issues remain when dealing with AS.[7] First of all, non-compliance with AS is important. For example, in a small study in Veterans Affair patients on AS only half of the patients complied with the protocol-mandated biopsy at 1 year.[8] Also repeat biopsies come with some risk. First of all, there is the cost issue and biopsies can also be painful. In addition prostate biopsies are associated with potential complications. In a large SEER analysis, including more than 17,000 prostate biopsies, it was shown that the risk of hospitalization

within 30 days of prostate biopsy was significantly higher than in a control population. Moreover, infectious complications after prostate biopsy have increased in recent years.[9] Serial prostate biopsies in AS also appear to have an adverse effect on erectile function.[10] Recent data indicate an improved recovery of erectile function after a radical prostatectomy when patients are younger.[11] However, *de la Taille* underlines that, in his opinion, this should not be a reason to avoid AS in younger patients. Despite these potential complications, re-biopsy represents a key requirement with AS. Also the EAU guidelines indicate that a repeat biopsy within 6 to 12 months is mandatory to exclude sampling errors.[6] In his center, *de la Taille* uses the following protocol for AS: PSA every 6 months, re-biopsy at 6 months and every 2 years thereafter and MRI every 2 years.

Whether AS is also an option for patients with Gleason 7 is subject to debate. One should be careful in this setting as these patients are more likely to develop metastatic PCa. This is illustrated by results of the Sunnybook experience indicating a 15-year metastasis-free survival rate of 94% for Gleason 6 patients as compared to 84% in patients with a Gleason 3+4 (PSA 10-20 ng/ml) and of only 63% in patients with a Gleason 4+3 (PSA less than 20 ng/ml).[12] The EAU guidelines indicate that AS is possible for Gleason 7 patients, but only for patients with Gleason 3+4 and less than 10% pattern 4.[6]

> Whether AS is also an option for patients with Gleason 7 is subject to debate.

However, recent findings suggest that any grade 4 pattern is associated with a three-fold increased risk of metastases compared to Gleason 6.

BIOMARKERS AND MUTIPARAMETERIC MRI

PSA and PCA3 proved to be unreliable triggers for intervention in AS. In fact, *Ross et al.* showed that PSA velocity (AUC 0.61) and PSA doubling time (AUC 0.59) are not sensitive/specific for the identification of reclassification.[13] As a result, the NCCN guidelines now say that PSA doubling time appears to be unreliable for the identification of progressive disease that remains curable. Similarly, *Tosoian et al.* showed that there is no difference in PCA3 between progressors and non-progressors (p= 0.13; AUC: 0.58).[14] As such, serum and urinary biomarkers are unreliable triggers for intervention. Biological markers, including transmembrane protease, serine 2-TMPRSS2-ERG fusion, or PSA isoforms appear promising, as does genomics on the tissue sample itself. However, more data will be needed before such markers can be used in clinical practice.

> Data indicate that the functional outcomes of AS are excellent with very good oncological results.

Finally, multiparametric MRI (mpMRI) can be useful in identifying patients who are suitable for AS.[15] For example, in a patient with a low Gleason score, a negative mpMRI can be reassuring to go for AS. In contrast, a patient with Gleason 7 and a larger tumor diameter on mpMRI should preferably not be selected for AS.

CONCLUSIONS

PSA screening saves lives but also leads to overtreatment. AS reduces overtreatment of low-risk PCa and as such, solves the main issue with PSA screening. Data indicate that the functional outcomes of AS are excellent with very good oncological results. However, some issues remain: what should be the trigger for changing the approach; How to deal with anxiety & non-compliance?; What about biopsy-related complications?; etc.. In the (near) future innovative imaging and new biomarkers should address some of these issues.

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Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4). **Concomitant medicinal products** Concomitant medicinal products that are strong inhibitors of CYP3A4 should be used with caution, and chronic use of concomitant medicinal products that are strong inducers of CYP3A4 should be avoided (see sections **4.4** and 4.5). Selection of an alternative concomitant medicinal product with no or minimal potential to induce or inhibit CYP3A4 should be considered. **Special populations** Elderly patients No specific dose adjustment for the use of cabozantinib in older people (≥ 65 years) is recommended. Race There is little experience with cabozantinib in non-White patients. Patients with renal impairment Cabozantinib should be used with caution in patients with mild or moderate renal impairment. 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Patients should be instructed to not eat anything for at least 2 hours before through 1 hour after taking CABOMETYX®. **Contraindications** hypersensitivity to the active substance or to any of the excipients listed in section 6.1. **Undesirable effects** Summary of safety profile The most common serious adverse reactions associated with cabozantinib are abdominal pain (3%), pleural effusion (3%), diarrhoea (2%), and nausea (2%). The most frequent adverse reactions of any grade (experienced by at least 25% of patients) included diarrhoea (74%), fatigue (56%), Nausea (50%), decreased appetite (46%), palmar-plantar erythrodysaesthesia syndrome (PPES) (42%), hypertension (37%), vomiting (32%), weight decreased (31%), and constipation (25%). Tabulated list of adverse reactions Adverse reactions are listed in Table 2 according to MedDRA system organ class and frequency categories. Frequencies are based on all grades and defined as: very common (≥1/10), common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Table 2: Adverse reactions reported with cabozantinib Infections and infestations: Common, abscess. Blood and lymphatic disorders: Very Common, anaemia. Endocrine disorders: very common, hypothyroidism. Metabolism and nutrition disorders : very common, decreased appetite, hypophosphataemia, hypoalbuminaemia, hypomagnesaemia, hyponatraemia, hypokalaemia, hyperkalaemia, hypocalcaemia, hyperbilirubinemia. Common, dehydration. Nervous system disorders : very common, dysgeusia, headache, dizziness. Uncommon, convulsion. Ear and labyrinth disorders common, tinnitus. Vascular disorders: very common hypertension. Common, pulmonary embolism. Respiratory, thoracic, and mediastinal disorders : very common, dysphonia, dyspnoea, cough. Gastrointestinal disorders: very common, diarrhoea, nausea, vomiting, stomatitis, constipation, abdominal pain, dyspepsia. Common, abdominal pain upper, gastrooesophageal reflux disease, haemorrhoids. Uncommon, anal fistula, pancreatitis. Hepatobiliary disorders: uncommon, hepatitis cholestatic. Hepatobiliary disorders: Uncommon, hepatitis cholestatic. Skin and subcutaneous tissue disorders: very common, palmar-plantar erythrodysaesthesia syndrome, rash, dry skin. Common, pruritus, alopecia. Musculoskeletal and connective tissue disorders: very common, pain in extremity, muscle spasms, arthralgia. Uncommon, osteonecrosis of the jaw. Renal and urinary disorders : very common, proteinuria. General disorders and administration site conditions: very common, fatigue, mucosal inflammation, asthenia. Common, peripheral oedema. Investigations: very common, weight decreased, serum ALT, AST, and ALP increased, creatinine increased, triglycerides increased, hyperglycaemia, hypoglycaemia, lymphopenia, neutropenia, thrombocytopenia, GGT increased, amylase increased, blood cholesterol increased, lipase increased. Description of selected adverse reactions Data for the following reactions are based on patients who received CABOMETYX® 60 mg qd po in the pivotal RCC study (section 5.1). Gastrointestinal (GI) perforation GI perforations were reported in 0.9% of cabozantinib-treated RCC patients (3/331). Events were Grade 2 or 3. Median time to onset was 10.0 weeks. Fatal perforations have occurred in the cabozantinib clinical program. Fistulas Fistulas were reported in 1.2% (4/331) of cabozantinib-treated patients, and included anal fistulas in 0.6% (2/331) cabozantinib-treated patients. One event was Grade 3; the remainder was Grade 2. Median time to onset was 30.3 weeks. Haemorrhage The incidence of severe haemorrhagic events (Grade ≥ 3) was 2.1% in cabozantinib-treated RCC patients (7/331). Median time to onset was 20.9 weeks. Fatal haemorrhages have occurred in the cabozantinib clinical program. Reversible Posterior Leukoencephalopathy Syndrome (RPLS) No case of RPLS was reported in this study, but RPLS has been reported in other clinical studies. Reporting of suspected adverse reactions Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system. For Belgium : EUROSTATION II, Place Victor Horta 40/40, B-1060 Bruxelles. Website: www.afmps.be. 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Abbreviations : OS: Overal Survival. PFS Progression Free Survival. ORR: Objective Response Rate. RCC: Renal Cell Carcinoma.

Reference: 1. Summary of Product Characteristics (SmPC). - **2.** Choueiri TK, et al. N Engl J Med 2015;373:1814-23. - **3.** Choueiri TK, et al. Lancet Oncol 2016;17:917–272. **4.** Choueiri TK, et al. Lancet oncology 2016: S1470-2045(16)30107-3.

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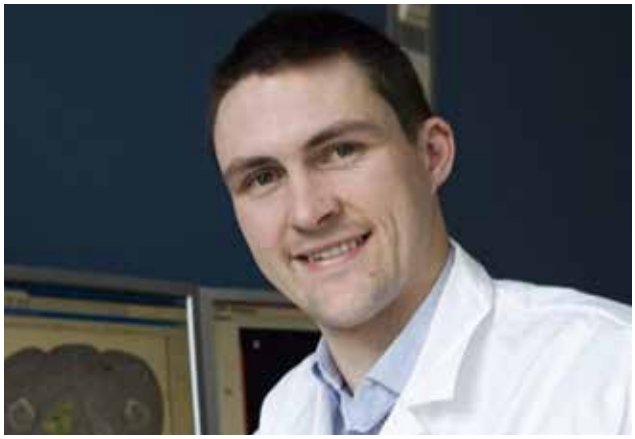
What about oligometastatic therapy in prostate cancer?

Presented by: Prof. P. Ost, MD, PhD *(University Hospital Ghent)* and Prof. B. Tombal, MD, PhD *(Cliniques Universitaires St-Luc, Brussels)*



In a pro and con debate, **Prof. Piet Ost** and **Prof. Betrand Tombal** discussed the potential of metastasis-directed therapy for patients with oligorecurrent prostate cancer.

CASE PRESENTATION

To set the scene for the discussion, *Prof. Ost* started with the presentation of a typical clinical case. A 61 year old male presents with a PSA of 5.3 ng/ml. An MRI and biopsy reveal a Gleason 3+4=7 in 6/21 cores. The patient underwent a robot-assisted radical prostatectomy (RARP) with negative margins and the tumor was staged as pT3a 4+3=7, N0. Unfortunately, the patient relapses and receives salvage radiotherapy, but after some time his PSA starts to rise again. This is what happens in about 30% of all localized prostate cancer patients. What we used to do in these patients was conventional imaging. However, if the PSA is below 10 and you perform a bone scan, you will most likely end up with a negative result. The question now is: *"How do you treat this guy?"*. The majority of the BMUC attendees deemed it best to 'wait and see' in this patient (observation and ADT at time of progression). Nowadays, conventional imaging has largely been replaced by more modern imaging tools, like PET PSMA. This patient also underwent PSMA imaging and he turned out to have a solitary nodal lesion. When asked how to treat this patient now, a shift was seen in the audience. In fact, 66% of the audience indicated that local, metastasis-directed therapy (MDT) would be the best option in this case. *Prof. Ost* build further on the case and asked if the treatment would change if the patient had a solitary bone metastasis instead of a single node lesion? In this scenario, 60% of attendees still opted for MDT.

> The current EAU guidelines state that it is not recommended to routinely offer ADT to asymptomatic prostate cancer patients with a biochemical recurrence.

CLINICAL DATA IN SUPPORT OF MDT

The current EAU guidelines state that it is not recommended to routinely offer an androgen-deprivation therapy (ADT) to asymptomatic prostate cancer patients with a biochemical recurrence. They also argue against the use of ADT in patients with a PSA doubling time above 12 months.[1] These 'wait and see' recommendations are backed by the results of a recent Australian trial (TOAD) demonstrating that there is no advantage of immediate ADT over delayed ADT in prostate cancer patients with biochemical recurrence.[2]

The potential of MDT in these patients was evaluated in the STOMP trial.[3] In this multicenter, randomized, phase II study, patients with asymptomatic prostate cancer were eligible if they had a biochemical recurrence after primary treatment with curative intent, three or fewer extracranial metastatic lesions on PET-CT and serum testosterone levels >50 ng/mL. In total, 62 patients were randomly assigned (1:1) to either surveillance or MDT of all detected lesions (surgery or stereotactic body radiotherapy). Surveillance was performed with PSA follow-up every 3 months and repeated imaging at PSA progression or clinical suspicion for progression.[3] Looking at biochemical progression, 35% of patients in the surveillance group had a PSA decline vs. 75% in the MDT group. As such, 25% did have a PSA increase, despite MDT indicating that new metastases are developing. On the other hand in the surveillance group we also see some impressive spontaneous PSA regression, sometimes to undetectable levels (i.e. regressions of the metastatic lesions). The biochemical recurrence free survival was significantly longer with MDT than with surveillance (HR[95%CI]: 0.30-0.94]; p= 0.03).[4] At a median follow-up time of 3 years, the median ADT-free survival (primary endpoint) was 13 months for the surveillance group and 21 months for the MDT group (HR[80%CI]:0.60[0.40, 0.90]; log-rank p= 0.11). A closer look at the indication for starting ADT learns that in 55-60% of cases polymetastatic progression was the reason to start ADT. According to *Prof. Ost*, *"this indicates that these patients were not truly oligometastatic, but that we only saw the tip of the iceberg on imaging. This underlines the need for a better patient selection."* Subgroup analyses of the STOMP data in function of the PSA doubling time and the location of the metastasis (nodal or not) did not reveal any significant differences. However, there seemed to be a signal that patients with a PSA doubling time of less than 3 months benefited more from MDT.

The first evidence for local therapy in oligometastatic prostate cancer patients is positive.

In summary, the first evidence for local therapy in oligometastatic prostate cancer patients is positive. *Prof. Ost* underlined that this does not mean that everybody needs to change their practice. *"This is only a phase II trial, which is unable to show a difference on survival, or any other hard endpoint."* To gain some insight on the effect of MDT on survival, *Steuber et al.* compared the data from the STOMP trial with data from a large surgical center (which is rather skeptical to MDT) where the standard of care for these patients is delayed or immediate ADT. This retrospective, matched-case comparison suggests that MDT is associated with a 3% gain in cancer specific survival at 5 years, increasing to 10% at 10 years.[5] *"Again, these are not hard, randomized data, but they do give a strong positive signal to invest in larger, prospective trials in this setting."*

For *Prof. Tombal* the main question is not whether we should irradiate patients with oligometastatic disease, but rather when to order modern imaging for a patient.

SOME CRITICAL REFLECTIONS

Prof. Tombal started off by saying that he agrees with *Prof. Ost* on the fact that imaging is not perfect and that there is emerging evidence that MDT can be of help in the oligometastatic setting. For him, the main question is not whether we should irradiate patients with oligometastatic disease, but rather when to order modern imaging for a patient.

A crucial paper from *Pound et al.*, published almost 2 decades ago, learned that there are three main risk factors in patients with a rising PSA: the Gleason score, the time to recurrence and the PSA doubling time.[6] According to *Prof. Tombal*, these three factors need to be kept in mind. To illustrate this, three scenarios were described. In a patient with Gleason 7, a time to PSA recurrence of more than 2 years and a PSA doubling time of more than 10 months, the likelihood of remaining metastasis-free at 7 years is 82%. On the other end of the spectrum is a patient with Gleason 7, a PSA recurrence of less than 2 year and a PSA doubling time of 6 months, his chance of being metastasis-free at 7 years is only 15%. As such, before talking about ADT, or before we are considering PET-PSMA screening we should consider the actual metastasis risk of the patient. *"Unfortunately"*, *Prof. Tombal* continues, *"many physicians have decided that PET-PSMA should overrule risk classification. In fact, a positive PET-PSMA scan turns a patients with a long PSA doubling time and a long time*

to biochemical recurrence into a high risk patient. This is not in line with the reality." In low grade patients with low PSA kinetics there is space for monitoring. These patients there have a major risk of overtreatment due to the 'excessive diagnostic accuracy'. Moreover, surgical studies indicate that not everything you see on imaging turns out to be cancerous.[7]

> Prof. Tombal: *"Yes there is a role for MDT in oligometastatic prostate cancer and MDT is there to stay. However, MDT is not the answer for everybody and we need to make different patient subgroups."*

On the other hand, as indicated by *professor Ost*, it may also be that the oligometastatic lesion you see is only the tip of the iceberg. According to *professor Tombal*, the standard of care for high-grade patients with high PSA kinetics should remain to be ADT. This might be in contrast with the data discussed by *professor Ost*, indicating no difference in outcome for delayed and immediate ADT, but these studies are not focused on the subgroup of high-risk patients. If you look at this high-risk group in detail, you do see an advantage of immediate ADT. This was demonstrated by *Moul et al.* who showed that early hormonal therapy was associated with delayed clinical metastasis in patients with a pathological Gleason sum greater than 7 or a PSA doubling time of 12 months or less (HR: 2.12; p= 0.01).[8] *Professor Tombal* concluded: *"yes there is a role for MDT in oligometastatic prostate cancer and MDT is there to stay. However, MDT is not the answer for everybody and we need to make different patient subgroups. For patients with a short PSA doubling time and a Gleason 8 for whom there are no local options left you have two choices: use MDT to delay the start of ADT, or combine a short course of hormonal therapy with MDT to impact a hard clinical endpoint (i.e. survival). For patients with a long PSA doubling time and a Gleason score below 8, we need to be more careful. These patients have a very good prognosis and are very prone to overtreatment."*

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Therapeutic sequencing in prostate cancer

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Over the last 10 years we have witnessed a revolution in the treatment of metastatic castration-resistant prostate cancer (mCRPC). The introduction of several new therapeutic modalities had a significant impact on the overall survival (OS) of these patients. Whereas the median OS for patients with mCRPC was only 24.2 months back in 1997, this has increased to 39.4 months in a patient cohort from 2007 to 2013. This represents an increase in the median OS with 1.5 years.[1] Currently, patients with mCRPC have 6 different drugs at their disposal. The question now is: "how to best sequence these different options?"

mCRPC: FIRST-LINE CHOICES

A first question that needs to be answered in the light of first-line therapy for mCRPC is *"when to start therapy?"* Is it best to wait with the treatment, or do patients benefit from early treatment? Blood prostatic-specific antigen (PSA) testing allows the identification of CRPC before clinical metastases or symptoms occur, providing a long diagnostic lead time in many patients. Several hormonal manipulations are directed towards lowering the PSA in patients. For example, adding bicalutamide was shown to be associated with a PSA response in 20% of patients, but did not impact the overall survival (OS). Also, the PSA decrease obtained with this approach is usually short lived.[2] Changing the LHRH agonist can also lead to a PSA response, but also has no impact on progression-free survival (PFS) or OS. A recent study looking into early treatment initiation of mCRPC is of the TERRAIN trial. In this study, 375 asymptomatic or mildly symptomatic mCRPC patients who did not receive prior chemotherapy were randomized to receive either enzalutamide, or bicalutamide.[4] In this study, enzalutamide was associated with a 10 month improvement in PFS compared to bicalutamide (median PFS 15.7 *vs.* 5.8 months; HR[95CI]: 0.44 [0.34-0.57]; p< 0.0001).[5] Similar results were obtained in the phase II STRIVE trial, where enzalutamide significantly reduced the risk of prostate cancer progression or death compared with bicalutamide in patients with non-metastatic or metastatic CRPC.[5] Now what do the guidelines say? The French national guidelines state that there is level 1 evidence that hormonal manipulations are not recommended. Second, it is advised to stop anti-androgen if prescribed and not to wait for potential withdrawal syndrome before changing therapy (go directly for newer agents).[6] The EAU guidelines recommend a similar approach in this setting.[7]

> The introduction of several new therapeutic modalities had a significant impact on the OS of mCRPC patients.

A second question that was raised is *"do we need to use chemotherapy, or prefer novel hormonal therapy?"* The 2018 EAU guidelines for mCRPC indicate that the first parameter to assess is the ECOG performance status

(PS) of patients. If the patient has an ECOG PS of 2 or more, you can opt for active monitoring, or anti-androgens if the patient is asymptomatic. Every mCRPC patient should be given the possibility to maximise the number of treatment lines. In a healthy patient (ECOG 0-1) you need to assess whether he has symptoms. In patients with asymptomatic, or mildly symptomatic disease abiraterone acetate (AA), enzalutamide, or docetaxel are recommended in 1st line. In contrast, if the patient has symptoms, docetaxel is the treatment of choice.[7] The French guidelines are largely similar and stipulate that new hormonal therapies should be used in patients with few or no symptoms and without organ metastases. Chemotherapy on the other hand is preferred in the event of an undifferentiated neuro-endocrine tumour, highly symptomatic organ or bone metastases, or rapid tachyphylaxis after initial hormone therapy (if the patient's age and general condition permit).[6]

> Unfortunately, for the moment there is no formal or informal evidence to support the use of enzalutamide or AA in a specific sequence.

If you sit in front of a patient with asymptomatic, or mildly symptomatic disease, *do you opt for enzalutamide or AA?* Unfortunately, for the moment there is no formal or informal evidence to support the use of these new therapies in a specific sequence. It seems logical to use the most active and least toxic treatment upfront, but how can we identify that treatment? There are currently no prospective data available on sequence, but there are data from three retrospective trials.[8-10] These trials indicate that the rate of >50% PSA response is higher when you first use enzalutamide, compared to the AA first approach. However, when looking at the time to PSA progression, these trials indicate superiority of the AA-enzalutamide sequence (median PSA PFS: 18.4 months *vs.* 12.8 months with enzalutamide-AA; HR[95%CI]: 0.44[0.37-0.81]; p= 0.0091). Unfortunately, the signals on PSA response and PFS seen in these analysis do not translate into a superior OS for one of the two sequences.[8-10] As such, we only have retrospective data on a small number of patients, showing no difference in OS and we cannot conclude on the best sequence for the moment. We will have to wait for the presentation of the first prospective trial comparing both sequences.[11]

Currently, a randomised study is ongoing comparing both sequences in 200 treatment naïve mCRPC patients. For the moment we don't have the results after two lines of treatment, but at ASCO 2017, the results after 1 line of therapy were presented. At that time, enzalutamide was associated with a higher rate of PSA reduction, but no difference in OS was seen (median 14.9 months with enzalutamide *vs.* 10.2 months with AA; HR[95%CI]: 0.83[0.55-1.25]; p= 0.372).[12] Another reason to opt for one of the two treatments in first-line could be the different toxicity profile of the agents. For example, enzalutamide should be avoided in patients with epilepsy, while AA (which is given in combination with prednisone) should not be used in patients with a contra-indication for corticosteroids. However, this only affects a minority of patients and will not be very helpful in clinical practice. Perhaps quality of life (QoL) could help us? In the Aquarius trial, enzalutamide was shown to be associated with more depression, a decreased cognitive function and more fatigue than AA.[12] In another analysis, it was shown that the rate of hospital admissions was lower in patients treated with enzalutamide compared to those treated with AA and prednisone. In addition to this, there are several theranostic factors under evaluation that could help in making the decision (e.g. AR-V7, circulating tumour cells, DNA MMR defects, etc...), but these are not yet ready for clinical practice.

> Currently, a randomised study is ongoing comparing the ezalutamide-AA and AA-enzalutamide sequence in 200 treatment-naive mCRPC patients.

A fourth question that needs answering in the first-line management of mCRPC patients is: *"go for docetaxel, or prefer cabazitaxel?"* This question was addressed in the phase III FIRSTANA study comparing two cabazitaxel-based regimens to docetaxel. Among the 1,168 mCRPC patients who did not previously receive chemotherapy enrolled in the trial, a similar OS was demonstrated for docetaxel and cabazitaxel.[13] As such, docetaxel should be the chemotherapy of choice, given the fact that it is less toxic than cabazitaxel.

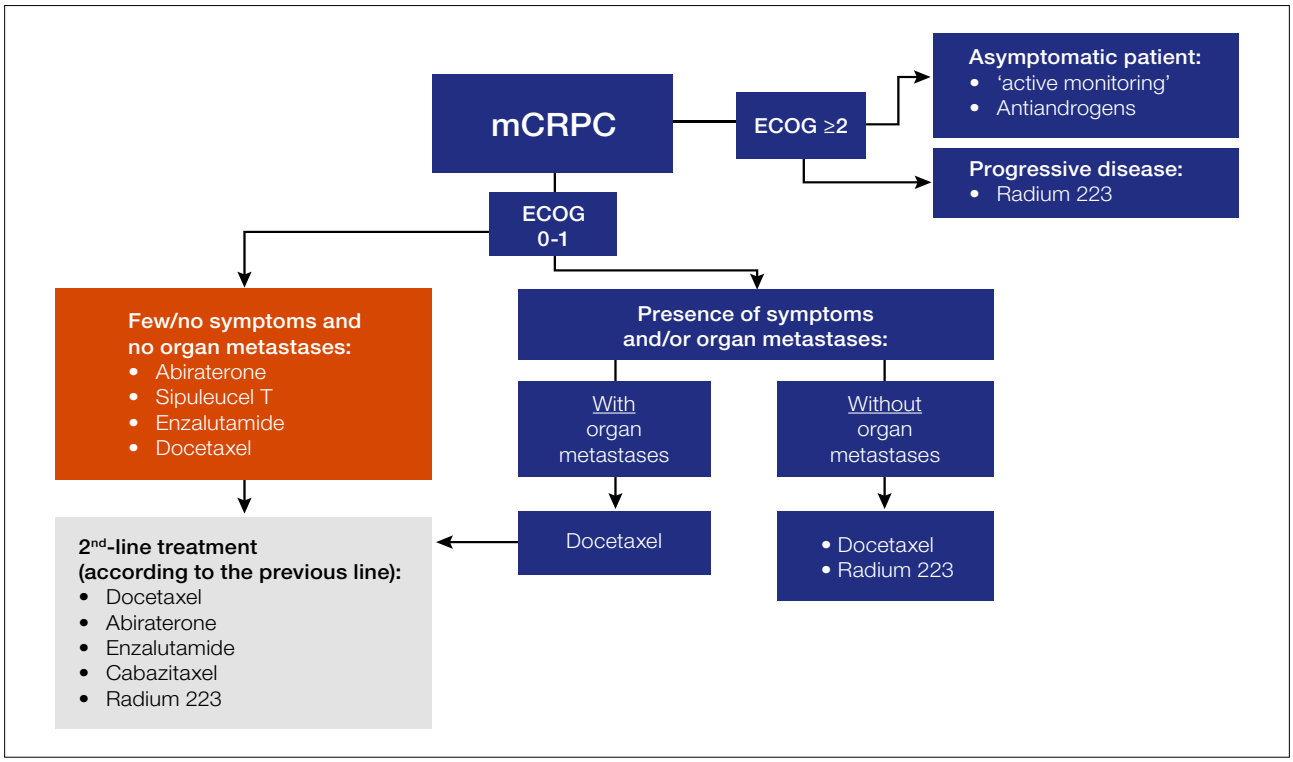

FIGURE 1. 2018 EAU guidelines for the treatment of mCRPC.[7]

A last question that can be raised relates to the *use of treatment combinations in first-line*. In this light, the phase IV PLATO trial is evaluating the safety and efficacy of continued enzalutamide + AA/prednisone versus placebo + AA/prednisone after PSA progression on enzalutamide. The trial did not meet its primary endpoint, as the PSA PFS was not statistically different between both study arms (median PSA PFS 5.7 for enzalutamide + AA/prednisone and 5.6 months with placebo + AA/prednisone).[14] As such, this combination strategy does not seem to be the way forward, especially given the high cost of this approach.

In summary, the first-line treatment of mCRPC is an evolving field that is becoming ever-more complex. This complexity will likely increase further in the near future, with the publications of enzalutamide studies and the impact of the CHAARTED, STAMPEDE and LATITUDE data on clinical practice. For now, we should stick to the 2018 EAU guidelines as depicted in *Figure 1*.

WHAT ABOUT METASTATIC HORMONE SENSITIVE PROSTATE CANCER?

It is known that *de novo* M1 hormone sensitive prostate cancer (HSPC) is associated with a poor prognosis. In the control arm of STAMPEDE trial, androgen deprivation therapy (ADT) alone is associated with a median OS of 42 months from diagnosis.[15] A couple of years ago, both the CHAARTED and the STAMPEDE trial demonstrated that adding docetaxel to ADT in mHSPC patients leads to a significant improvement in OS. In CHAARTED the median OS was 44 months with ADT and increased to 57.6 months when docetaxel was added (HR[95%CI]: 0.61[0.47-0.80]; p< 0.001), while in STAMPEDE the median OS with docetaxel + ADT was 81 months, which was 10 months longer than what was seen with ADT alone (HR[95%CI]: 0.78[0.66-0.93]; p= 0.006) (*Figure 2*).[16,17] In contrast, in the GETUG-15 study including M1 HSPC patients, ADT + docetaxel did not lead to a significant OS improvement compared to ADT alone (median OS: 62.1 *vs.* 48.6 months; HR[95%CI]: 0.88[0.68-1.14]; p= 0.3).[18] The most likely explanation for this is that 85% of patients in the ADT alone arm received docetaxel at progression (*vs.* 41-48% in CHAARTED and STAMPEDE).[19] As such, this trial is rather comparing immediate versus delayed docetaxel than docetaxel *vs* no docetaxel. In a meta-analysis taking together the data for all M1 HSPC patients in CHAARTED, STAMPEDE and GETUG-15, the addition of docetaxel to ADT was shown to be associated with a 23% reduction in the risk of death (HR[95%CI]: 0.77[0.68-0.87]; p< 0.0001).

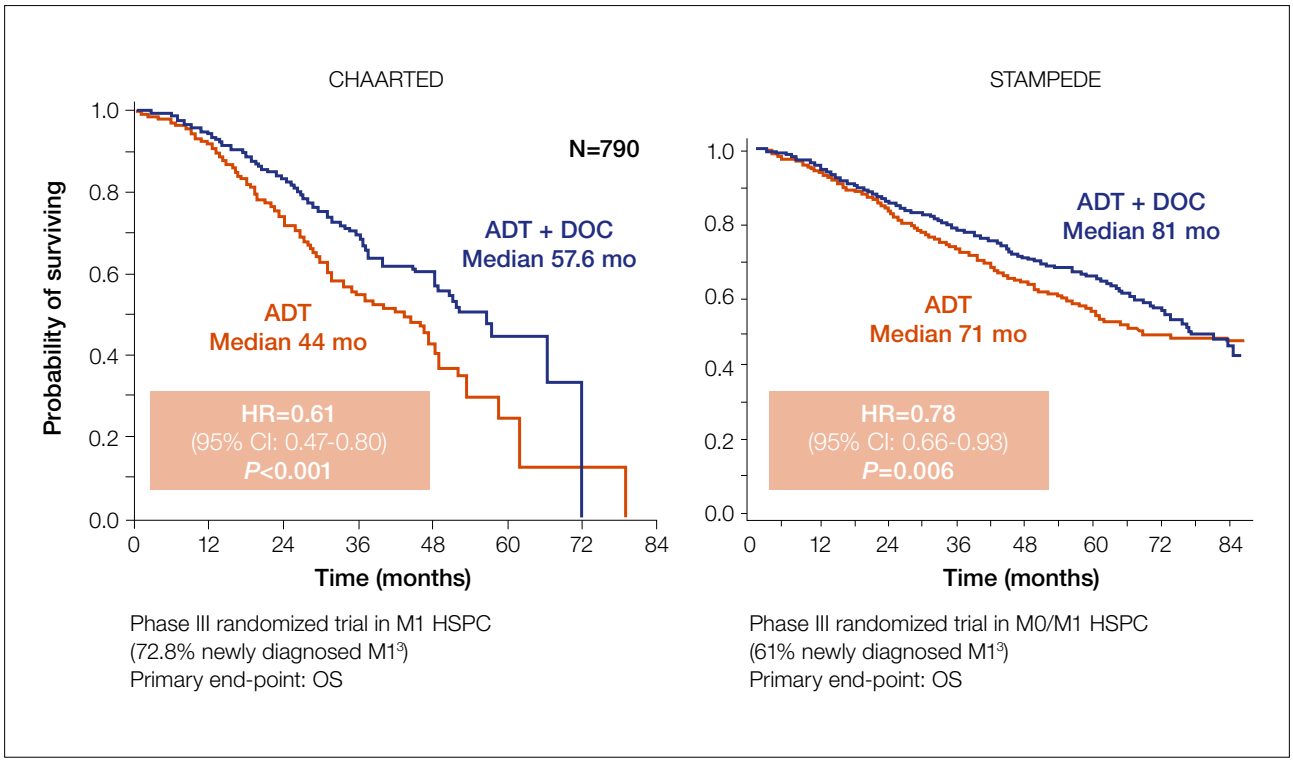

FIGURE 2. Overall survival in M0, or M1 patients enrolled in the phase III CHAARTED and STAMPEDE trial.[16,17]

This translates into a 10% absolute difference in OS at 4 years.[20] As a result, the EAU guidelines have endorsed ADT plus docetaxel as the preferred treatment for all HSPC patients whose first presentation is M1 disease.[7] A couple of months later, results of the LATITUDE (M1) study and data from another arm of STAMPEDE (M0/M1) were presented related to the effect of adding AA to ADT. Also with this approach, the OS was significantly improved (LATITUDE HR[95%CI]: 0.62[0.51-0.76]; p< 0.001; STAMPEDE: HR[95%CI]: 0.63[0.52-0.76]; p< 0.001).[21,22] A meta-analysis of these two studies (N=2201) indicates that adding AA plus prednisone to ADT leads to a 14% absolute improvement in OS at 3 years.[23]

The question will now be: what is best: adding AA, or adding docetaxel to ADT? This question can partly be answered by results of STAMPEDE. A head to head comparison of these two options in STAMPEDE indicates that there is no difference in OS between both. However, looking at PFS and failure-free survival (FFS), there is a signal for superiority of AA.[24] Also the toxicity could play a role in the decision. With docetaxel, you have a short term treatment that is associated with a higher rate of (febrile) neutropenia, while with AA you have a treatment that takes several years and which is associated with cardiovascular disorders. These different aspects need to be discussed with the patient.

Another unanswered question is how to treat patients who progressed and who received docetaxel or AA as first-line therapy. A recently published analysis of GETUG-15 indicates that rechallenging docetaxel at castration-resistance was active only in a limited number of patients who were treated upfront with chemo-hormonal therapy for metastatic castration-naïve prostate cancer. Anticancer activity was suggested with AA or enzalutamide in this setting, suggesting that this is the better option for these patients.[25] A second issue that needs to be considered relates to primary resistance to androgen-receptor targeted agents in mCRPC. This was the case in 1 out of 3 with AA in COU-AA-301 and 1 out of 4 with enzalutamide in AFFIRM.[26,27] It is important that these patients are identified early on to allow a timely treatment change (i.e. close monitoring during first 3 months).

The question for phusicians treating M1 HSPC patients is: "*what is best: adding AA, or docetaxel to ADT?*"

HOW TO DEAL WITH M0 CRPC?

Several studies are ongoing in high-risk M0 CRPC patients with a PSA doubling time of 10 months or less. In the SPARTAN trial, patients are randomly assigned to apalutamide or placebo with metastasis free survival as primary endpoint. The first results of this trial were presented at ASCO GU 2018 indicating a 72% reduction in the risk for metastasis in patients receiving apalutamide (median 40.5 *vs.* 16.2 months; HR[95%CI]: 0.28[0.23-0.35]; p< 0.0001). Also the OS was reduced by 30% in the apalutamide arm, but this difference was not statistically significant (HR[95%CI]: 0.70[0.47-1.04]; p= 0.07).[28] Also at ASCO GU 2018, the first results of the PROSPER trial were presented, comparing enzalutamide with placebo in 1,560 M0 CRPC patients. Similarly, the metastasis free survival was significantly better with enzalutamide (HR[95%CI]: 0.29 [0.24-0.35]; p< 0.0001), but this was not translated into an OS advantage (HR[95%CI]: 0.80[0.58-1.09]; p= 0.1519).[29] Longer follow-up of these studies is needed before any conclusions can be drawn.

Both SPARTAN and PROSPER demonstrated a longer metastasis-free survival when patients with high-risk M0 CRPC are treated with apalutamide, or enzalutamide. However, this did not lead to a better OS.

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NAAM VAN HET GENEESMIDDEL: ZYTIGA 500 mg filmomhulde tabletten. **KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING:** Elke filmomhulde tablet bevat 500 mg abirateronacetaat Hulpstoffen met bekend effect: Elke filmomhulde tablet bevat 253,2 mg lactose en 13,5 mg natrium. **FARMACEUTISCHE VORM:** Filmomhulde tablet. Paarse, ovale, filmomhulde tabletten (20 mm lang en 10 mm breed), waarop aan één kant "AA" en aan de andere kant "500" werd aangebracht. **Therapeutische indicaties:** ZYTIGA is met prednison of prednisolon geïndiceerd voor: – de behandeling van nieuw gediagnosticeerde hoog-risico gemetastaseerde hormoongevoelige prostaatkanker (mHSPC) bij volwassen mannen, in combinatie met androgeendeprivatietherapie (ADT) – de behandeling van gemetastaseerde castratieresistente prostaatkanker (mCRPC) bij volwassen mannen die asymptomatisch of licht symptomatisch zijn na falen van androgeendeprivatietherapie en voor wie behandeling met chemotherapie nog niet klinisch geïndiceerd is ; – de behandeling van mCRPC bij volwassen mannen bij wie de ziekte progressief was tijdens of na een chemotherapieschema op basis van docetaxel. **Dosering en wijze van toediening:** Dit geneesmiddel dient te worden voorgeschreven door een bevoegde beroepsbeoefenaar in de gezondheidszorg. Dosering: De aanbevolen dosis is 1.000 mg (twee tabletten van 500 mg) als eenmalige dagelijkse dosis, niet met voedsel in te nemen (zie 'Wijze van toediening' hieronder). Als de tabletten met voedsel worden ingenomen, verhoogt dat de blootstelling aan abirateron. *Dosering van prednison of prednisolon* Voor mHSPC wordt ZYTIGA gebruikt met 5 mg prednison of prednisolon per dag. Voor mCRPC wordt ZYTIGA gebruikt met 10 mg prednison of prednisolon per dag. Bij patiënten die niet chirurgisch zijn gecastreerd, moet chemische castratie met een *luteïnising hormone-releasing hormone* (LHRH)-analoog tijdens de behandeling worden voortgezet. *Aanbevolen monitoring* Serumtransaminases moeten worden bepaald voordat de behandeling wordt gestart, elke twee weken in de eerste drie maanden van de behandeling en daarna maandelijks. De bloeddruk, het serumkalium en de vochtretentie moeten maandelijks worden gemeten.
Patiënten met een aanzienlijk risico op congestief hartfalen dienen echter gedurende de eerste drie maanden van de behandeling elke twee weken gecontroleerd te worden en daarna maandelijks. Bij patiënten met reeds bestaande hypokaliëmie of degenen die hypokaliëmie ontwikkelen terwijl ze met ZYTIGA worden behandeld, dient overwogen te worden de kaliumconcentratie bij de patiënt op ≥ 4,0 mM te houden. Voor patiënten die ≥ graad 3 toxiciteiten ontwikkelen, waaronder hypertensie, hypokaliëmie, oedeem en andere, non-mineralocorticoïde toxiciteiten, dient de behandeling te worden onderbroken en geschikte medische behandeling te worden ingesteld. Behandeling met ZYTIGA mag niet eerder worden hervat dan nadat de symptomen van de toxiciteit zijn afgenomen tot graad 1 of tot baseline. In geval van een gemiste dagdosis van ZYTIGA, prednison of prednisolon, moet de behandeling de volgende dag worden hervat met de gebruikelijke dagdosis. *Levertoxiciteit:* Voor patiënten die tijdens de behandeling levertoxiciteit ontwikkelen (alanineaminotransferase [ALAT] verhoogd of aspartaataminotransferase [ASAT] verhoogd tot meer dan 5 maal de bovengrens van de normaalwaarde [ULN]), moet de behandeling onmiddellijk worden onderbroken (zie rubriek 4.4). Nadat de leverfunctietestwaarden weer op baseline van de patiënt zijn, kan de behandeling worden hervat in een verlaagde dosis van 500 mg (één tablet) eenmaal per dag. Bij patiënten bij wie de behandeling is hervat, moeten serumtransaminases minimaal elke twee weken gedurende drie maanden gecontroleerd worden en daarna maandelijks. Als de levertoxiciteit bij de verlaagde dosis van 500 mg per dag opnieuw optreedt, moet de behandeling worden beëindigd. Als patiënten op enig moment tijdens de behandeling ernstige levertoxiciteit ontwikkelen (ALAT of ASAT 20 maal de ULN), moet de behandeling worden stopgezet en mogen patiënten niet opnieuw worden behandeld. *Leverinsufficiëntie:* Er is geen dosisaanpassing nodig voor patiënten met reeds bestaande milde leverinsufficiëntie, Child-Pugh Klasse A. Aangetoond is dat matige leverinsufficiëntie (Child-Pugh Klasse B) de systemische blootstelling aan abirateron met ongeveer een factor 4 verhoogt na eenmalige orale doses van 1.000 mg abirateronacetaat (zie rubriek 5.2). Er zijn geen gegevens over de klinische veiligheid en werkzaamheid van meervoudige doses abirateronacetaat, toegediend aan patiënten met matige of ernstige leverinsufficiëntie (Child-Pugh Klasse B of C). Een dosisaanpassing kan niet voorspeld worden. Het gebruik van ZYTIGA moet zorgvuldig worden geëvalueerd bij patiënten met matige leverinsufficiëntie, bij wie het voordeel duidelijk moet opwegen tegen de mogelijke risico's. ZYTIGA mag niet worden gebruikt bij patiënten met ernstige leverinsufficiënte. *Nierinsufficiëntie:* Bij patiënten met nierinsufficiëntie is geen dosisaanpassing noodzakelijk Er is echter geen klinische ervaring bij patiënten met prostaatkanker en ernstige nierinsufficiëntie. Bij deze patiënten is voorzichtigheid geboden. *Pediatrische patiënten:* Er is geen relevante toepassing van ZYTIGA bij pediatrische patiënten. Wijze van toediening: ZYTIGA is voor oraal gebruik. De tabletten moeten minstens twee uur na het eten worden ingenomen en na het innemen van de tabletten mag men minstens één uur niet eten. Deze tabletten moeten in hun geheel worden doorgeslikt met water. **Contra-indicaties:** – Overgevoeligheid voor de werkzame stof of voor een van de vermelde hulpstoffen. – Vrouwen die zwanger zijn of die zwanger zouden kunnen zijn. – Ernstige leverinsufficiëntie [Child-Pugh-klasse C]. **Bijwerkingen:** In een analyse van bijwerkingen van samengevoegde fase 3-studies met ZYTIGA waren de bijwerkingen die bij 1-10% van de patiënten werden waargenomen perifeer oedeem, hypokaliëmie, hypertensie, urineweginfectie en alanineaminotransferase verhoogd en/of aspartaataminotransferase verhoogd. Andere belangrijke bijwerkingen zijn onder andere hartaandoeningen, levertoxiciteit, breuken en allergische longblaasjesontsteking. ZYTIGA kan hypertensie, hypokaliëmie en vochtretentie veroorzaken als farmacodynamisch gevolg van het werkingsmechanisme. In fase 3-studies werden verwachte mineralocorticoïde bijwerkingen vaker gezien bij patiënten die werden behandeld met abirateronacetaat dan bij patiënten die werden behandeld met placebo: hypokaliëmie bij 18% vs. 8%, hypertensie bij 22% vs. 16% en vochtretentie (perifeer oedeem) bij 23% vs. 17%. Bij patiënten die werden behandeld met abirateronacetaat werden CTCAE (versie 4.0)-graad 3 en 4 hypokaliëmie gezien bij respectievelijk 6% en 2% van de patiënten, CTCAE (versie 4.0)-graad 3 en 4 hypertensie bij respectievelijk 8% en 5% van de patiënten en vochtretentie (perifeer oedeem) graad 3 en 4 bij respectievelijk 1% en 1% van de patiënten. Mineralocorticoïde reacties konden in het algemeen succesvol medisch worden behandeld. Gelijktijdig gebruik van een corticosteroïd verlaagt de incidentie en de ernst van deze bijwerkingen. Lijst van bijwerkingen in tabelvorm: In studies bij patiënten met gemetastaseerde gevorderde prostaatkanker die een LHRH-analoog gebruikten of eerder een orchidectomie ondergingen, werd ZYTIGA toegediend in een dosis van 1.000 mg per dag in combinatie met een lage dosis prednison of prednisolon (ofwel 5 ofwel 10 mg per dag, afhankelijk van de indicatie). Bijwerkingen die tijdens klinische studies en postmarketingervaring zijn waargenomen, staan hieronder vermeld naar frequentiecategorie. De frequentiecategorieën zijn als volgt gedefinieerd: zeer vaak (≥ 1/10), vaak (≥ 1/100 tot < 1/10), soms (≥ 1/1.000 tot < 1/100), zelden (≥ 1/10.000 tot < 1/1.000), zeer zelden (<1/10.000) en niet bekend (frequentie kan met de beschikbare gegevens niet worden bepaald). Binnen elke frequentiecategorie zijn de bijwerkingen weergegeven in afnemende mate van ernst. **Tabel 1: Bijwerkingen vastgesteld in klinische studies en postmarketing: Systeem/orgaanklasse:** Bijwerking en frequentie. **Infecties en parasitaire aandoeningen:** zeer vaak: urineweginfectie; vaak: sepsis. **Endocriene aandoeningen:** soms: bijnierinsufficiëntie. **Voedings- en stofwisselingsstoornissen:** zeer vaak: hypokaliëmie; vaak: hypertriglyceridemie. **Hartaandoeningen:** vaak: hartfalen*, angina pectoris, atriale fibrillatie, tachycardie; soms: andere aritmieën; niet bekend: myocardinfarct, QT-verlenging (zie de rubrieken 4.4 en 4.5) **Bloedvataandoeningen:** zeer vaak: hypertensie. **Ademhalingsstelsel-, borstkas- en mediastinumaandoeningen:** zelden: allergische longblaasjesontsteking[a]. **Maagdarmstelselaandoeningen:** zeer vaak: diarree; vaak: dyspepsie. **Lever- en galaandoeningen:** zeer vaak: alanineaminotransferase verhoogd en/of aspartaataminotransferase verhoogd[b]; zelden: hepatitis fulminant, acuut leverfalen. **Huid- en onderhuidaandoeningen:** vaak: rash. **Skeletspierstelsel- en bindweefselaandoeningen:** soms: myopathie, rabdomyolyse. **Nier- en urinewegaandoeningen:** vaak: hematurie. **Algemene aandoeningen en toedieningsplaatsstoornissen:** zeer vaak: oedeem perifeer. **Letsels, intoxicaties en verrichtingscomplicaties:** vaak: breuken**. * Hartfalen omvat ook congestief hartfalen, linkerventrikeldisfunctie en ejectiefractie verlaagd. ** Breuken omvat osteoporose en alle breuken met uitzondering van pathologische breuken. [a]Spontane rapportage uit postmarketingervaring. [b] Alanineaminotransferase verhoogd en/of aspartaataminotransferase verhoogd omvat ALAT verhoogd, ASAT verhoogd en leverfunctie afwijkend. De volgende CTCAE (versie 4.0)-graad 3 bijwerkingen traden op bij patiënten die met abirateronacetaat werden behandeld: hypokaliëmie 5%, urineweginfectie 2%, alanineaminotransferase verhoogd en/of aspartaataminotransferase verhoogd 4%, hypertensie 6%; breuken 2%; perifeer oedeem, hartfalen en atriale fibrillatie elk 1%. CTCAE (versie 4.0)-graad 3 hypertriglyceridemie en angina pectoris kwamen voor bij <1% van de patiënten. CTCAE (versie 4.0)-graad 4 urineweginfectie, alanineaminotransferase verhoogd en/of aspartaataminotransferase verhoogd, hypokaliëmie, hartfalen, atriale fibrillatie en breuken kwamen voor bij < 1% van de patiënten. Een hogere incidentie van hypertensie en hypokaliëmie werd gezien bij de hormoongevoelige populatie (studie 3011). Hypertensie werd gemeld bij 36,7% van de patiënten in de hormoongevoelige populatie (studie 3011), tegenover 11,8% en 20,2% in respectievelijk studie 301 en 302. Hypokaliëmie werd gezien bij 20,4% van de patiënten in de hormoongevoelige populatie (studie 3011), tegenover 19,2% en 14,9% in respectievelijk studie 301 en 302. De incidentie en ernst van de bijwerkingen was hoger in de subgroep van patiënten met een ECOG2 performance status-score op baseline en eveneens bij oudere patiënten (≥75 jaar). Beschrijving van bepaalde bijwerkingen: *Cardiovasculaire reacties* De drie fase 3-studies sloten patiënten uit met ongecontroleerde hypertensie, klinisch relevante hartziekte blijkens een myocardinfarct of een manifestatie van arteriële trombose in de afgelopen 6 maanden, ernstige of onstabiele angina of hartfalen met NYHA klasse III of IV (studie 3011 en 302) of een gemeten cardiale ejectiefractie van < 50%. Alle ingesloten patiënten (zowel behandeld met medicatie als met placebo) werden gelijktijdig behandeld met androgeendeprivatietherapie, voornamelijk door middel van LHRH-analogen, hetgeen geassocieerd is met diabetes, myocardinfarct, cerebrovasculair accident en plotse hartdood. De incidentie van cardiovasculaire bijwerkingen in de fase 3-studies bij patiënten die abirateronacetaat gebruikten, ten opzichte van patiënten die placebo innamen, waren als volgt: atriale fibrillatie 2,6% vs. 2,0%, tachycardie 1,9% vs. 1,0%, angina pectoris 1,7% vs. 0,8%, hartfalen 0,7% vs. 0,2% en aritmie 0,7% vs. 0,5%. *Levertoxiciteit:* Levertoxiciteit met verhoogd ALAT, ASAT en totaal bilirubine, is gemeld bij patiënten die met abirateronacetaat werden behandeld. In klinische fase 3-studies werd levertoxiciteit graad 3 en 4 (bijvoorbeeld ALAT- of ASAT-verhoging > 5 x ULN (upper limit of normal) of bilirubineverhoging > 1,5 x ULN) gemeld bij ongeveer 6% van de patiënten die abirateronacetaat ontvingen, doorgaans tijdens de eerste 3 maanden na het starten van de behandeling. In Studie 3011 werd levertoxiciteit graad 3 of 4 gezien bij 8,4% van de met ZYTIGA behandelde patiënten. Bij tien patiënten die ZYTIGA ontvingen, werd de medicatie beëindigd vanwege levertoxiciteit; twee hadden graad 2-levertoxiciteit, zes hadden graad 3-levertoxiciteit, en twee hadden graad 4-levertoxiciteit. Geen enkele patiënt overleed aan levertoxiciteit in studie 3011. Patiënten met verhoogde ALAT- of ASAT-waarden op baseline hadden in de fase 3-studies een grotere kans op verhoogde leverfunctietestwaarden dan degenen met normale waarden op baseline. Wanneer verhogingen van ALAT of ASAT > 5 x ULN of verhogingen van bilirubine > 3 x ULN werden gezien, werd abirateronacetaat onderbroken of stopgezet. In twee gevallen trad er een aanzienlijke verhoging op van de leverfunctietestwaarden (zie rubriek 4.4). Deze twee patiënten, met normale leverfunctie op baseline, kregen ALAT- of ASAT-verhogingen van 15 tot 40 x ULN en bilirubineverhogingen van 2 tot 6 x ULN. Na beëindiging van de behandeling normaliseerden bij beide patiënten de leverfunctietestwaarden en één patiënt werd opnieuw behandeld zonder dat de verhoogde waarden terugkeerden. In studie 302 werden verhogingen van ALAT of ASAT van graad 3 of 4 waargenomen bij 35 (6,5%) patiënten die met abirateronacetaat werden behandeld. De verhogingen van aminotransferases verdwenen bij alle patiënten op 3 na (2 met nieuwe multipele levermetastases en 1 met ASAT-verhoging ongeveer 3 weken na de laatste dosis van abirateronacetaat). In fase 3-klinische studies werd staken van de behandeling wegens verhoging van ALAT en ASAT of een afwijkende leverfunctie gemeld bij 1,1% van de patiënten behandeld met abirateronacetaat en bij 0,6% van de patiënten behandeld met placebo; er werden geen overlijdensgevallen gemeld als gevolg van levertoxiciteit. In klinische studies werd het risico voor levertoxiciteit beperkt door uitsluiting van patiënten met hepatitis of significante afwijkingen van de leverfunctietesten op baseline. In de 3011-studie werden patiënten met op baseline ALAT en ASAT > 2,5 x ULN, bilirubine > 1,5 x ULN of degenen met actieve of symptomatische virale hepatitis of chronische leverziekte, ascites of stollingsstoornissen secundair aan leverdisfunctie van deelname uitgesloten. In studie 301 werden patiënten met ALAT en ASAT ≥ 2,5 x ULN op baseline in afwezigheid van levermetastases en > 5 x ULN indien er wel levermetastases aanwezig waren uitgesloten van deelname. In studie 302 konden patiënten met levermetastasen niet worden geïncludeerd en werden patiënten met ALAT en ASAT ≤2,5 x ULN op baseline uitgesloten. Als zich bij patiënten die deelnamen aan klinische studies abnormale leverfunctietestwaarden ontwikkelden, werden deze op doortastende wijze behandeld door middel van een verplichte onderbreking van de behandeling en hernieuwde behandeling alleen toe te staan nadat de leverfunctietestwaarden gedaald tot de waarden zoals gemeten bij de patiënt op baseline (zie rubriek 4.2). Patiënten met verhogingen van ALAT of ASAT > 20 x ULN werden niet opnieuw behandeld. De veiligheid van hervatting van de behandeling bij dergelijke patiënten is onbekend. Het mechanisme dat tot levertoxiciteit leidt, is niet duidelijk. Melding van vermoedelijke bijwerkingen Het is belangrijk om na toelating van het geneesmiddel vermoedelijke bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden via: **België:** Federaal agentschap voor geneesmiddelen en gezondheidsproducten (www.fagg.be). **Nederland:** Nederlands Bijwerkingen Centrum Lareb, Website: www.lareb.nl **Aard en inhoud van de verpakking:** PVdC/PE/PVC/aluminium blisterverpakking met 14 filmomhulde tabletten in een kartonnen wallet. Elke kartonnen doos bevat (56 filmomhulde tabletten) 4 wallets. PvdC/PE/PVC/aluminium blisterverpakking met 12 filmomhulde tabletten in een kartonnen wallet. Elke kartonnen doos bevat (60 filmomhulde tabletten) 5 wallets. **HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN:** Janssen-Cilag International NV, Turnhoutseweg 30, B-2340 Beerse, België. **AFLEVERINGSWIJZE**: Geneesmiddel op medisch voorschrift. **DATUM VAN HERZIENING VAN DE TEKST:** 15/11/2017. *Meer informatie is beschikbaar op verzoek.*

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1. Zytiga®, (abirateroneacetaat), samenvatting van de productkenmerken, Janssen-Cilag International NV Turnhoutseweg 30,B-2340 Beerse,België **2.** http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002639/WC500144999.pdf **3.** Fizazi K et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomized, double-blind, placebo-controlled phase 3 study, Lancet Oncol 2012 **4.** Harland S et al. Effect of abiraterone acetate treatment on the quality of life of patients with metastatic castration-resistant prostate cancer after failure of docetaxel chemotherapy, Data presented in part at the European Multidisciplinary Cancer Congress, 2011 **5.** Ryan CJ et al; Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302):final overall survival analysis of a randomised, double-blind,placebo-controlled phase 3 study, The Lancet Oncol 2015 **6.** Rathkopf DE, et al. Updated Interim Efficacy Analysis and Long-term Safety of Abiraterone Acetate in Metastatic Castration-resistant Prostate Cancer Patients Without Prior Chemotherapy (COU-AA-302). Eur Urol (2014), **7.** Fizazi K et al. Abiraterone acetate plus Prednisone in Metastatic Castration Sensitive Prostate Cancer, N Engl J Med,2017 **8.** Chi KN et al. Benefits of Abiraterone acetate plus prednisone when added to androgen deprivation therapy in Latitude on patient-reported outcomes, Presented at ESMO Congress, Madrid 2017

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Congress highlights 2018

Presented by: Dr. D. De Maeseneer *(University Hospital Ghent)*, Dr. F-X. Otte *(Institut Jules Bordet, ULB Brussels)* and Dr. S. Albisinni *(Hôpital Erasme, ULB Brussels)*

ASCO GU represents one of the yearly highlights in the field of genitourinary cancer. During BMUC 2018 the key data presented at this meeting were summarized.

THE UROLOGIST

Dr. Simone Albisinni gave an overview of the ASCO GU highlights from an urologist point of view. He selected three studies: POUT, SPARTAN and PROSPER.[1-3]

The POUT study enrolled 26,261 patients with histologically confirmed stage pT2–T4, N0–N3 upper tract urothelial cancer following radical nephroureterectomy and removal of any obvious nodal disease and with a negative postoperative CT scan. Within 90 days postsurgery, patients were randomized (1:1) to receive 4 cycles of gemcitabine-based chemotherapy or surveillance. The choice of chemotherapy partner (cisplatin or carboplatin) depended on glomerular filtration rate alone: patients with a glomerular filtration rate >50 mL/min were given cisplatin, and if the glomerular filtration rate was 30 to 49 mL/min, they were given carboplatin. Patients who were deemed unfit for cisplatin based on other comorbidities were not allowed to enter the trial. All patients received supportive care. In total, 261 patients were recruited in the trial with a mean age of 69 years. Twenty-nine percent of patients had pT2 disease, 71% had pT3-4 disease and 91% was N0. Two thirds of patients were eligible for cisplatin and the remaining third was treated with carboplatin.

The two blockbuster studies presented at ASCO GU 2018 were SPARTAN and PROSPER.

Overall, 64% received the four planned chemotherapy doses.

For the primary endpoint of 3-year disease-free survival (DFS), chemotherapy had a strong benefit: 71% in the chemotherapy group *vs.* 54% in the surveillance group (HR[95%CI]: 0.49[0.31-0.76]; p= 0.001). Chemotherapy was significantly superior to surveillance in subgroups of nodal involvement, planned type of chemotherapy, microscopic margin, and disease stage (with a similar hazard ratio for benefit seen across all subgroups). The Metastasis-free survival at 2 years also favored adjuvant chemotherapy (74% *vs.* 60%; p< 0.001). With respect to overall survival (OS), a trend towards superiority of chemotherapy was seen (HR: 0.55), but these data were still immature. Grade 3 or higher toxicities were reported in 53.2% of the chemotherapy recipients and in 13.5% in the surveillance group. The most frequent grade 3/4 toxicities with chemotherapy were neutropenia (24.3% with gemcitabine/cisplatin and 37.3% with gemcitabine/carboplatin); nausea (2.9% and 7.8%, respectively); vomiting (1.4% and 9.8%); and febrile neutropenia in 5.7% and 7.8%.[1]

The two blockbuster studies presented at ASCO GU 2018 were PROSPER and SPARTAN. The SPARTAN study enrolled 1,207 men with non-metastatic castration-resistant prostate cancer (CRPC) who stopped responding to androgen-deprivation therapy and were at high risk of metastasis, with a PSA doubling time of 10 months or less, and randomized them in a 2:1 ratio to receive oral apalutamide *vs* placebo added to ongoing

androgen-deprivation therapy. When metastases developed, second therapies were added, and patients could opt to receive on-study abiraterone plus placebo, a standard of care. At study entry, median PSA doubling time was 4.5 months in both arms. Apalutamide reduced the risk of metastasis and death by 72% compared with placebo and significantly prolonged the median metastasis-free survival by 2 years (40.5 *vs.* 16.2 months; HR[95%CI]: 0.28[0.23-0.35]; p< 0.0001). Apalutamide also significantly improved the time to metastasis, progression-free survival, and symptom progression compared with placebo. In fact, there was a 55% risk reduction in the time to symptomatic disease progression (p< 0.001). A consistent benefit of apalutamide was observed in all subgroups. Apalutamide was well tolerated, and quality-of-life scores were maintained when the drug was added to androgen-deprivation therapy. The most common adverse events in the apalutamide group were fatigue, hypertension, rash, and diarrhea.[2]

It remains to be seen what the data of SPARTAN and PROSPER will mean for the rapidly evolving landscape of M0 CRPC. Also the reimbursement issues in European countries will play their part.

The PROSPER trial enrolled a similar patient population as the SPARTAN trial: 1,401 men with non-metastatic CRPC and a rapidly rising PSA (PSA doubling time of 10 months or less). Men continued on androgen-deprivation therapy and were randomized 2:1 to receive enzalutamide or placebo. The primary endpoint of median metastasis-free survival was 36.6 months for enzalutamide *vs.* 14.7 months for placebo, representing a 71% relative risk reduction (HR[95%CI]: 0.29[0.24-0.35]; p< 0.0001). Also the median time to use of new antineoplastic therapy was significantly longer with enzalutamide: (39.6 *vs.* 17.7 months, p< 0.0001) as was the PSA progression (37.2 *vs.* 3.9 months; p< 0.0001). As expected, adverse events of any grade were higher in the enzalutamide-treated group: 87% *vs.* 77% for placebo. Grade 3 or higher adverse events were reported in 31% *vs.* 23%, respectively. Deaths due to adverse events were reported in 3% and 1%, respectively. Adverse events of special interest (any grade) that were higher in the enzalutamide group were as follows hypertension in 12% (*vs.* 5%), major cardiovascular disease in 5% (*vs.* 3%), and mental impairment in 5% (*vs.* 2%).[3] As such, SPARTAN and PROSPER are two largely positive trials, and both drugs are highly effective in delaying the onset of metastases in m0 CRPC. However, the clinical benefit of treating m0 CRPC is still to be determined as we don't know yet if the advantage in metastasis-free survival will translate into a significant OS benefit. Furthermore, we still need to see what the impact of delaying metastases will be on quality of life (for now there was no deterioration in QoL, but also no improvement…). In addition, there are some concerns regarding falls and fractures with apalutamide and regarding other causes of mortality with enzalutamide. It remains to be seen what these data will mean for the rapidly evolving landscape of M0 CRPC (e.g. new imaging modalities, what to do after this treatment line?). In addition to this, the reimbursement issues in European countries will also play their part.

THE RADIATION ONCOLOGIST

The use of adjuvant treatment for patients with high risk or node-positive prostate cancer remains controversial despite retrospective data demonstrating a benefit.[4] The controversy revolves around the risk of overtreatment in addition to the lack of evidence demonstrating the superiority of adjuvant over early salvage therapy. During ASCO GU 2018, *Dr. Alberto Briganti* presented the available data supporting the use of adjuvant radiation therapy and systemic therapy for patients with nodal disease. The use of radiation therapy on patients with N1 disease has been underutilized and understudied due to the association of nodal involvement with a systemic state rather than a local state. As a result, most data available on the added value of radiation therapy in N1 patients is in combination with hormonal therapy and mainly come from retrospective single center and multicenter retrospective trials. The best data in the use of adjuvant therapy for patients with N1 disease come from a retrospective multicenter trial which included 1,300 patients showing that combination therapy with ADT is associated with a better OS compared to ADT and placebo. Smaller single-center trials have echoed similar results, but selection bias remains a significant limitation due to the retrospective nature of these publications. Currently, there are no planned clinical trials on the matter, which is likely related to the overall feeling that these patients are likely to be overtreated. Unfortunately, patients with nodal involvement were excluded from the prospective randomized adjuvant *vs.* early salvage trials,

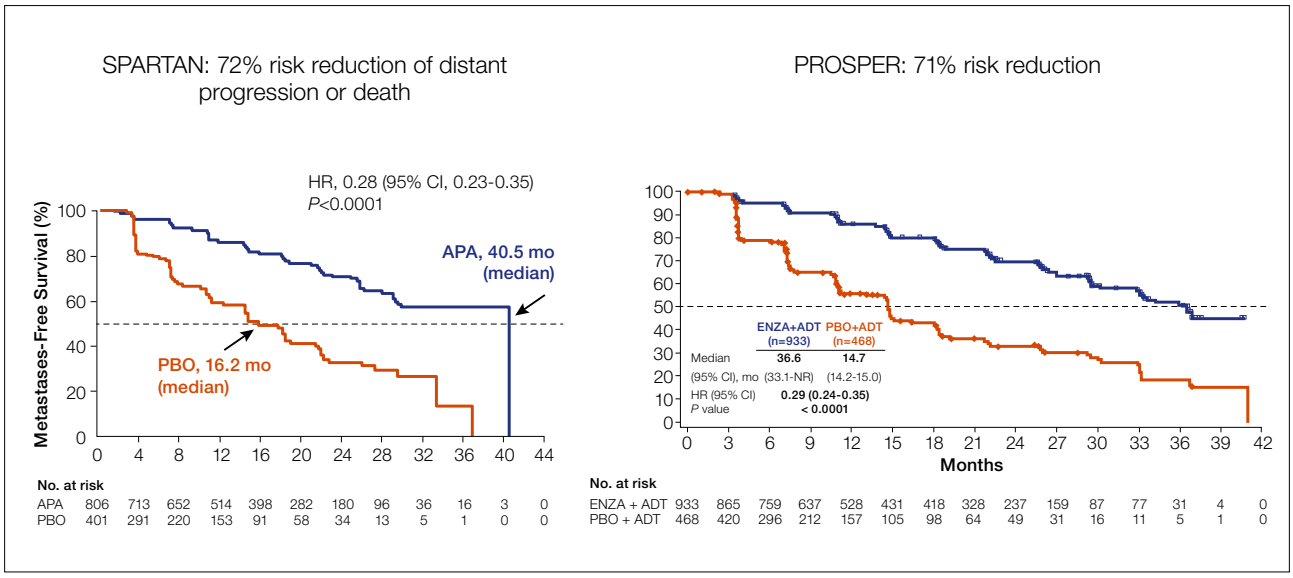

FIGURE 1. Metastasis free survival in PROPSER and SPARTAN.[2,3]

limiting the conclusion we can draw from these trials. In summary, a significant number (20%) of patients undergoing radical prostatectomy with lymph node dissection are noted to have nodal involvement. There is weak evidence on the added benefit of adjuvant radiation therapy in the setting of nodal disease, based on retrospective analyses. The data in favor of adjuvant systemic therapy is stronger but more robust prediction markers are needed to better select patients who would benefit from the added therapy.

There is weak evidence on the added benefit of adjuvant radiation therapy in the setting of nodal disease, based on retrospective analyses. Data for adjuvant systemic therapy are nore robust, but better prediction markers are needed.

While radical cystectomy has historically been the standard of care for patients with muscle-invasive urothelial carcinoma of the bladder, there is increasing interest in evaluating bladder-sparing treatment modalities. In the phase II, multi-center NRG/RTOG 0712 study, patients with muscle-invasive urothelial carcinoma of the bladder who elected to pursue bladder-sparing treatment were randomized to one of two treatment groups.[5] The first group received cisplatin/5-FU as well as twice-daily radiotherapy, while the second group received low-dose gemcitabine and daily radiotherapy. In total, 70 patients with cT2-cT4aN0 disease were included in the trial. The primary endpoint of the study was the rate of distant metastases (DM) at 3 years, with acute and late toxicities, tumor response, and 3-year bladder-intact distant metastasis free survival as key secondary objectives. The median follow-up in the study was 5.1 years. Patients in the cisplatin/5-FU group with twice-daily radiation were noted to have a 77.8% (21/28) rate of DM-free survival at 3 years as compared to 84% in the low-dose gemcitabine and daily radiation cohort. Furthermore, there were impressive complete response (CR) rates at 3 years, with 87.9% of patients in the cisplatin/5/FU twice-daily radiation group showing a CR, *vs.* 75% in the low-dose gemcitabine and daily radiation group. Overall, both bladder-sparing regimens were well tolerated. As such, the DM rate at 3 years was similar in both arms of the trial and were comparable to that of previously published surgical series. Concurrent gemcitabine is a reasonable alternative to CDDP, especially in patients with poor renal function, or hearing loss. Also, daily radiation was found to be a good alternative for the BID radiation, which may allow a wider adoption of selective preservation by trimodal therapy.[5]

Also in prostate cancer, de *Crevoisier et al.* presented the results of a phase III randomized trial comparing daily versus weekly image-guided radiotherapy.[6] The optimal frequency of prostate cancer image-guided radiation therapy (IGRT) has not yet been clearly identified. The presented trial recruited 470 patients with N0 localized

prostate cancer and randomly assigned them (1:1) to two prostate IGRT control frequency groups: daily or weekly (Days 1, 2, and 3, then weekly). The primary outcome was 5-year recurrence-free survival (RFS), with OS and toxicity as secondary endpoints. After a median follow-up of 4.1 years there was no statistically-significant difference in RFS between the groups (HR95%CI]: 0.81[0.52, 1.25]; p= 0.330), while the OS was significantly worse in the daily control group (HR[95%CI]: 2.12[1.03, 4.37]; p= 0.042). On the other hand, the incidence of late rectal toxicity (Grade ≥1) was significantly lower in the daily control group (HR[95%CI]: 0.71[0.53, 0.96]; p= 0.027) as was the incidence of acute rectal bleeding (6% *vs.* 11%). The investigators also reported that the biochemical recurrence rate was significantly lower in the daily control group compared to the weekly control cohort (HR[95%-CI]: 0.45[0.25, 0.80]; p= 0.007). Finally, the incidence of secondary cancer was significantly higher with the daily control (HR[95%CI]: 2.21[1.10-4.44]; p= 0.026). In summary, compared to weekly control, daily IGRT control in prostate cancer significantly decreases the risk of biochemical recurrence and late rectal toxicity but is associated with an increased risk of second cancer (be vigilant). Longer follow-up is needed to gain more insight in the strange observation of a longer OS in the weekly control cohort (related to risk of second cancer on the daily control group?).[6]

A final presentation mentioned by *Dr. Otte* looked at the role of immunotherapy in patients undergoing radiation therapy for bladder cancer (*Solanki et al.*). Classic radiation therapy mechanisms include direct effects (i.e. DNA double strand breaks leading to mitotic and apoptotic cell death), but also indirect effects, like the generation of free radicals leading to DNA double strand breaks and ultimately apoptotic cell death. In this process, radiation leads to the release of tumor antigens and damage-associated molecular patterns, which subsequently leads to antigen presenting cell activation,

Compared to weekly IGRT, daily IGRT control in prostate cancer significantly decreases the risk of biochemical recurrence and late rectal toxicity, but is associated with an increased risk of second cancer.

migration to lymph nodes and T-cell activation. This 'abscopal effect' is considered to be the "radiation oncologist's holy grail". With this effect, a response can be yielded to distant sites due to an immune response created by radiotherapy on a primary tumor. This hypothesis forms the rationale to combine radiotherapy with immunotherapy. The idea, is that this combination will improve the control of the primary tumor secondary to radio-sensitization, allow for a systemic response, and ultimately result in immune memory. However, there are several practical questions that need answering before we can move forward with radiotherapy and immunotherapy for bladder cancer:

1. *What is the optimal sequence of immunotherapy and radiotherapy?* Data from a colorectal mouse model suggests that immunotherapy is better one day after radiotherapy *vs.* 7 days prior to radiotherapy. As such it appears that increased PD-L1 expression from radiotherapy appears to be limited to a few days. However, secondary analysis of KEYNOTE-001 and the PACIFIC trial in NSCLC showed an improved PFS with delivering anti-PD1/PD-L1 after chemo-radiation.[7,8]
2. *What is the optimal radiotherapy dose and fractionation?* In vivo studies of breast cancer mice suggest that high dose per fraction appears to be more immune stimulating, whereas patients in the PACIFIC trial received 54-66 Gy in conventional fraction sizes.[7,9]
3. *What is the optimal radiotherapy field size to treat?*
4. *What sites should we irradiate?* For definitive radiotherapy, it likely makes sense to treat the primary tumor, but the question remains whether we have to treat the whole tumor? For palliative radiotherapy, can we choose lesions that are more likely to elicit an immune response?
5. *What about concurrent chemotherapy?*
6. *What is the best immunotherapy combination?*

There are several ongoing bladder cancer trials combining radiotherapy and immunotherapy to assess the concurrent and best immunotherapy combination. Hopefully, these trials will help to elucidate how radiotherapy and immunotherapy are best combined in bladder cancer.

THE MEDICAL ONCOLOGIST

RENAL CELL CARCINOMA

In the treatment of advanced renal cell carcinoma (RCC) lots is expected from combination therapy. This concept proved to be successful in the Checkmate 214 study, showing an OS benefit of nivolumab + ipilimumab over sunitinib monotherapy in the first-line treatment of metastatic RCC.[10] During ASCO GU 2018, updated safety data of this trial were presented indicating a low rate of high-grade (3-4) adverse events. Moreover, these adverse events rapidly resolved (except for thyroid problems).[11] Also at ASCO GU, the first results of the phase III IMmotion 151 study were presented, comparing the combination of the VEGF targeting agent bevacizumab with the PD-L1 inhibitor atezolizumab versus sunitinib as first-line treatment for metastatic RCC.[12] In total 915 treatment-naïve metastatic RCC patients were randomized to atezolizumab (1200mg IV q 3 weeks + bevacizumab 15 mg/kg IV q3 weeks), or sunitinib (50 mg PO daily 4 week on/2 week off). In PD-L1 positive patients (40% of total study population), the median PFS was 11.2 months with the combination therapy *vs.* 7.7 months with sunitinib (HR[95%CI]: 0.74[0.57,0.96]; p=0.02). In the intention to treat analysis, this HR was 0.83 (95%CI: 0.70, 0.97) with a median PFS of 11.2 months for atezolizumab + bevacizumab compared to 8.4 months for sunitinib. In the PD-L1+ group, the confirmed ORR was 43% and 35% for atezolizumab + bevacizumab and sunitinib, respectively. OS was immature at this first interim analysis. The safety profile demonstrates acceptable tolerability with only 40% of atezolizumab + bevacizumab treated patients having grade 3-4 treatment-related adverse events (*vs.* 54% with sunitinib). Additionally, discontinuation rate was lower with atezolizumab + bevacizumab compared to sunitinib. The only grade 3-4 adverse events that were more common with atezolizumab + bevacizumab compared to sunitinib was proteinuria.[12]

A third noteworthy combination trial (phase I) in RCC that was presented evaluated the first-line combination of axitinib and pembrolizumab. Eleven advanced RCC patients were enrolled in the dose finding phase with an additional 41 patients in the dose expansion cohort. The first data of this study indicate that this combination is tolerable and that it is associated with a high ORR (+70%). Moreover, the duration of these responses proved to be long (median 18.6 months).[13]

BLADDER CANCER

A retrospective, international study looked at the impact of the number of cycles of platinum-based 1st-line chemotherapy for advanced urothelial carcinoma. The authors examined the association of the number of cycles of chemotherapy with OS after controlling for previously recognized prognostic factors used in a nomogram. Effectively they compared 3-5 cycles *vs.* 6-9 cycles of chemotherapy. The study included 472 patients (338 treated with cisplatin, 134 with carboplatin). A total of 157 patients received 3-5 cycles (median 4) and 315 received 6-9 cycles (median 6). Interestingly, there was no significant difference in OS between 3-5 *vs.* 6-9 cycles of platinum-based chemotherapy (HR[95%CI]: 1.02[0.77-1.33]; p= 0.91). No significant interactions were observed with type of platinum (p = 0.09) and "completed planned CT" (p = 0.56). A comparison of 4 *vs.* 6 cycles (p = 0.57) and < 6 *vs.* 6 *vs.* 7-9 (p= 0.9) also yielded no signifi-

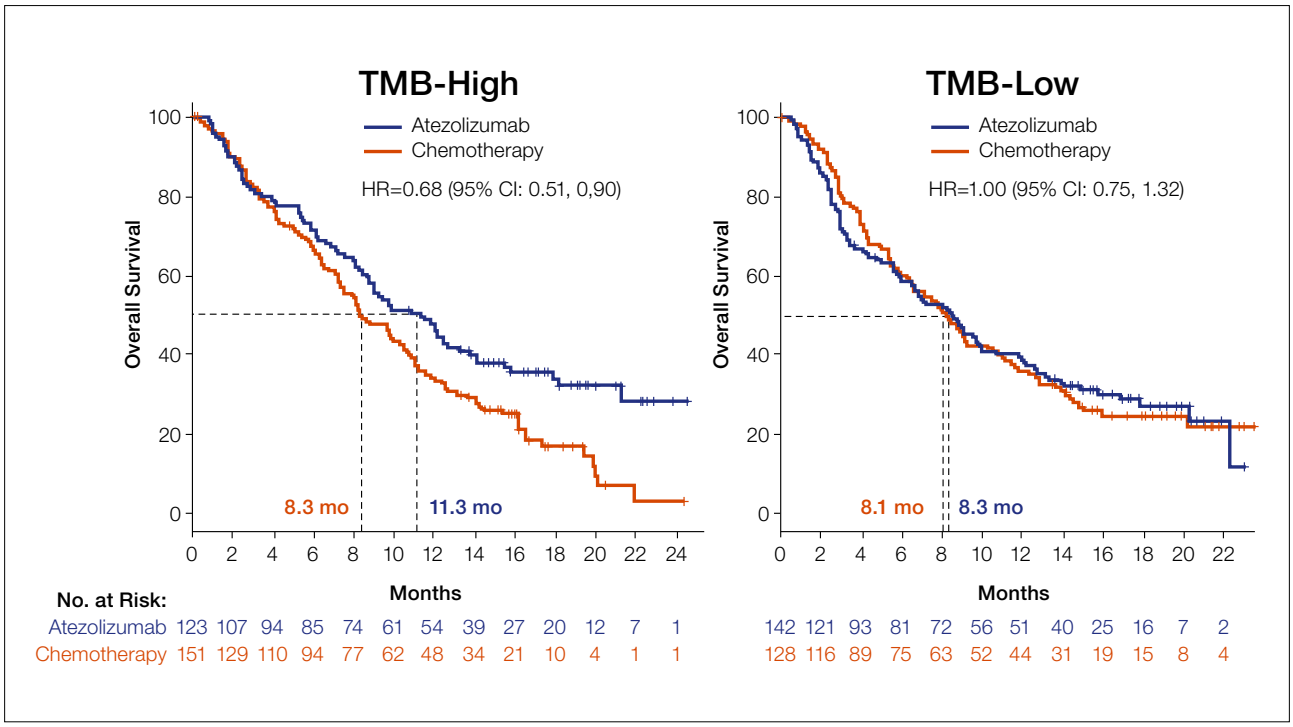

FIGURE 2. OS by TMB in the phase III IMvigor 211 study.[15]

cant differences for association with OS.[14] At this time, these are the best data we have to say that maybe reducing the number of cycles of chemotherapy may not impair oncologic outcomes. The reduction in toxicity itself may make this worthwhile. Obviously, the limitations of a hypothesis-generating retrospective analysis apply here. Only a prospective analysis can remove any unknown confounders from the analysis. However, as this is a relatively rare condition, a large prospective study will be difficult to set up.

Overall, the phase III IMvigor 211 study failed to show an OS advantage for atezolizumab compared to chemotherapy in platinum-treated patients with advanced urothelial carcinoma. During ASCO GU, an analysis of the OS in this study in function of the tumor mutational burden (TMB) was presented. In TMB high patients, atezolizumab was associated with a median OS of 11.3 months, which significantly better than the 8.3 months seen with chemotherapy (HR[95%CI]: 0.68[0.51, 0.90]) (*Figure 2*). In TMB low patients, no OS benefit was seen with atezolizumab over chemotherapy (HR[95%CI]: 1.00[0.75-1.32]). Nevertheless, complete and partial responses as well as prolonged OS were also observed in patients with TMB-low tumors in both arms.[15]

Two year follow-up data of the Keynote-045 study, comparing pembrolizumab with chemotherapy in platinum-treated advanced urothelial carcinoma, confirm the significantly superior OS with pembrolizumab. After a median follow-up of 27.7 months, the HR for OS was 0.70 (95%CI: 0.57-0.85; p= 0.00017). The median OS with pembrolizumab was 10.3 months as compared to 7.3 months with chemotherapy. After two years, almost twice as much patients treated with pembrolizumab was still alive, compared to chemotherapy (27% *vs.* 14.3%).[16]

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XTANDI™ is indicated for the treatment of adult men with metastatic castration-resistant prostate cancer:

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2. whose disease has progressed on or after docetaxel therapy.[1]

astellas ONCOLOGY

1. XTANDI™, SmPC.
mCRPC (metastatic Castration Resistant Prostate Cancer).
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RÉSUMÉ DES CARACTÉRISTIQUES DU PRODUIT 1. DÉNOMINATION DU MÉDICAMENT Xtandi 40 mg, capsule molle **2. COMPOSITION QUALITATIVE ET QUANTITATIVE** Chaque capsule molle contient 40 mg d'enzalutamide. Excipient à effet notoire Chaque capsule molle contient 57,8 mg de sorbitol. Pour la liste complète des excipients, voir rubrique 6.1. **3. FORME PHARMACEUTIQUE** Capsule molle. Capsules molles, de forme oblongue (environ 20 mm x 9 mm), de couleur blanche à blanc cassé, avec la mention « ENZ » imprimée à l'encre noire sur une face. **4. DONNÉES CLINIQUES 4.1 Indications thérapeutiques** Xtandi est indiqué dans : le traitement du cancer métastatique de la prostate résistant à la castration (CPRC métastatique) chez les hommes adultes asymptomatiques ou peu symptomatiques, après échec d'un traitement par suppression androgénique et pour lesquels la chimiothérapie n'est pas encore cliniquement indiquée (voir rubrique 5.1) le traitement du CPRC métastatique chez les hommes adultes dont la maladie a progressé pendant ou après une chimiothérapie à base de docétaxel. **4.2 Posologie et mode d'administration** Un traitement par enzalutamide doit être initié et supervisé par un médecin spécialiste expérimenté dans le traitement médical du cancer de la prostate. Posologie La dose recommandée est de 160 mg d'enzalutamide (quatre capsules molles de 40 mg) en une seule prise quotidienne par voie orale. La castration médicale par un analogue de l'hormone de libération de la lutéinostimuline (LHRH) doit être maintenue pendant la durée du traitement pour les patients n'ayant pas subi de castration chirurgicale. Si le patient oublie de prendre la dose prescrite de Xtandi à l'heure habituelle, elle doit être administrée aussi près que possible de l'heure habituelle de prise. Si le patient oublie de prendre la dose prescrite de Xtandi pendant toute une journée, il convient de reprendre le traitement le lendemain à la dose quotidienne habituelle. En cas de toxicité de grade supérieur ou égal à 3 ou d'effet indésirable intolérable, il convient de suspendre le traitement pendant une semaine ou jusqu'à ce que les symptômes reviennent à un grade inférieur ou égal à 2, puis de reprendre le traitement à la même dose ou à une dose réduite si nécessaire (120 mg ou 80 mg). *Utilisation concomitante avec des inhibiteurs puissants du CYP2C8* L'utilisation concomitante d'inhibiteurs puissants du CYP2C8 doit être évitée autant que possible. Si le patient doit recevoir un inhibiteur puissant du CYP2C8 de façon concomitante, la dose d'enzalutamide doit être réduite à 80 mg en une prise quotidienne. En cas d'arrêt de l'administration concomitante de l'inhibiteur puissant du CYP2C8, l'enzalutamide doit être repris à la dose utilisée avant l'instauration de l'inhibiteur puissant du CYP2C8 (voir rubrique 4.5). *Patients âgés* Aucune adaptation posologique n'est nécessaire chez les patients âgés (voir rubriques 5.1 et 5.2). *Insuffisance hépatique* Aucune adaptation posologique n'est nécessaire chez les patients présentant une insuffisance hépatique légère, modérée ou sévère (respectivement classes A, B et C de Child-Pugh). Un allongement de la demi-vie de l'enzalutamide a toutefois été observé chez les patients présentant une insuffisance hépatique sévère (voir rubriques 4.4 et 5.2). *Insuffisance rénale* Aucune adaptation posologique n'est nécessaire chez les patients présentant une insuffisance rénale légère à modérée (voir rubrique 5.2). La prudence est recommandée chez les patients présentant une insuffisance rénale sévère ou de stade terminal (voir rubrique 4.4). *Population pédiatrique* Il n'y a pas d'utilisation justifiée de l'enzalutamide dans la population pédiatrique dans l'indication du traitement du CPRC métastatique chez les hommes adultes. Mode d'administration Xtandi est à utiliser par voie orale. Les capsules molles ne doivent pas être mâchées, dissoutes ni ouvertes mais doivent être avalées entières avec de l'eau, et peuvent être prises avec ou sans nourriture. **4.3 Contre-indications** Hypersensibilité au principe actif ou à l'un des excipients mentionnés à la rubrique 6.1. Femmes enceintes ou susceptibles de l'être (voir rubrique 4.6). **4.4 Mises en garde spéciales et précautions d'emploi** Risque de convulsions La prudence est recommandée lorsque Xtandi est administré à des patients présentant des antécédents de convulsions ou d'autres facteurs de prédisposition, parmi lesquels, entre autres, lésion cérébrale sous-jacente, accident vasculaire cérébral, tumeurs cérébrales primitives ou métastases cérébrales, ou alcoolisme. En outre, le risque de convulsions peut être accru en cas d'administration concomitante de médicaments abaissant le seuil épileptogène. La décision de poursuivre le traitement chez les patients qui présentent des convulsions doit être évaluée au cas par cas. Syndrome d'encéphalopathie postérieure réversible De rares cas de Syndrome d'Encéphalopathie Postérieure Réversible (SEPR) ont été rapportés chez des patients traités par Xtandi (voir rubrique 4.8). Le SEPR est un trouble neurologique rare, réversible, pouvant se manifester par la survenue rapide des symptômes suivants : convulsions, céphalées, confusion, cécité et autres troubles de la vision ou troubles neurologiques, avec ou sans hypertension associée. Le diagnostic de SEPR requiert une confirmation par imagerie cérébrale, de préférence par imagerie par résonance magnétique (IRM). Chez les patients qui développent un SEPR, l'arrêt du traitement par Xtandi est recommandé. Utilisation concomitante d'autres médicaments L'enzalutamide est un inducteur enzymatique puissant et peut entraîner une diminution de l'efficacité de nombreux médicaments couramment utilisés (voir les exemples en rubrique 4.5). Une réévaluation des traitements concomitants doit être conduite à l'initiation du traitement par l'enzalutamide. L'utilisation concomitante de l'enzalutamide et de médicaments qui sont des substrats cibles de nombreuses enzymes du métabolisme ou de transporteurs (voir rubrique 4.5) doit généralement être évitée si leurs effets thérapeutiques sur le patient sont importants et si leur posologie ne peut pas être facilement ajustable sur la base du suivi de l'efficacité ou des concentrations plasmatiques. L'administration concomitante de warfarine ou d'anticoagulants coumariniques doit être évitée. Si Xtandi est administré en même temps qu'un anticoagulant métabolisé par le CYP2C9 (tel que la warfarine ou l'acénocoumarol), une surveillance additionnelle du rapport normalisé international (INR) doit être conduite (voir rubrique 4.5). Insuffisance rénale La prudence est recommandée en cas d'utilisation chez des patients présentant une insuffisance rénale sévère, l'enzalutamide n'ayant pas été étudié dans cette population de patients. Insuffisance hépatique sévère Un allongement de la demi-vie de l'enzalutamide a été observé chez les patients présentant une insuffisance hépatique sévère, peut-être lié à une augmentation de la distribution tissulaire. La pertinence clinique de cette observation reste inconnue. Un allongement du temps nécessaire pour atteindre l'état d'équilibre des concentrations est toutefois prévisible ; de même, il pourrait être constaté un allongement du temps nécessaire pour atteindre l'effet pharmacologique maximal ainsi que du temps jusqu'à l'apparition et jusqu'au déclin de l'induction enzymatique (voir rubrique 4.5). Antécédents récents de maladies cardiovasculaires Les patients présentant des antécédents récents d'infarctus du myocarde (au cours des 6 mois précédents) ou d'angor instable (au cours des 3 mois précédents), une insuffisance cardiaque de classe III ou IV selon la classification de la New York Heart Association (NYHA) sauf en cas de fraction d'éjection ventriculaire gauche (FEVG) supérieure ou égale à 45 %, une bradycardie ou une hypertension non contrôlée ont été exclus des études de phase III. Il convient d'en tenir compte lorsque Xtandi est prescrit à des patients présentant ces caractéristiques. Un traitement par suppression androgénique peut allonger l'intervalle QT Chez les patients présentant des antécédents ou des facteurs de risques de l'allongement de l'intervalle QT, et chez les patients recevant de manière concomitante des médicaments susceptibles d'allonger l'intervalle QT (voir rubrique 4.5), les médecins doivent évaluer le rapport bénéfice / risque en prenant en compte le risque potentiel de torsades de pointes avant l'initiation du traitement par Xtandi. Chimiothérapie concomitante La sécurité d'emploi et l'efficacité de l'utilisation concomitante de Xtandi et d'une chimiothérapie cytotoxique n'ont pas été établies. L'administration concomitante d'enzalutamide n'a pas d'effet cliniquement significatif sur la pharmacocinétique du docétaxel administré par voie intraveineuse (voir rubrique 4.5) ; cependant, une hausse de la fréquence de neutropénie induite par le docétaxel ne peut être exclue. Excipients Xtandi contient du sorbitol (E420). Les patients présentant une intolérance héréditaire rare au fructose ne doivent pas prendre ce médicament. Réactions d'hypersensibilité Des réactions d'hypersensibilité ont été observées avec enzalutamide, se manifestant par des symptômes incluant, mais pas uniquement, un œdème de la langue, un œdème labial et un œdème pharyngé (voir rubrique 4.8). **4.8 Effets indésirables** Résumé du profil de sécurité Les effets indésirables les plus fréquents sont l'asthénie/fatigue, les bouffées de chaleur, les céphalées et l'hypertension. Les autres effets indésirables importants comprennent les chutes, les fractures non pathologiques, les troubles cognitifs et la neutropénie. Des cas de convulsions ont été rapportés chez 0,5 % des patients traités par enzalutamide, chez 0,1 % des patients sous placebo et chez 0,3 % des patients traités par bicalutamide. De rares cas de Syndrome d'Encéphalopathie Postérieure Réversible ont été rapportés chez des patients traités par enzalutamide (voir rubrique 4.4). Liste tabulée des effets indésirables Les effets indésirables observés au cours des études cliniques sont listés ci-dessous par catégorie de fréquence. Les catégories sont définies comme suit : très fréquent (≥ 1/10) ; fréquent (≥ 1/100, < 1/10) ; peu fréquent (≥ 1/1 000, < 1/100) ; rare (≥ 1/10 000, < 1/1 000) ; très rare (< 1/10 000), fréquence indéterminée (ne peut être estimée sur la base des données disponibles). Les effets indésirables sont classés par ordre de gravité décroissant dans chaque catégorie de fréquence.

Tableau 1 : Effets indésirables observés au cours des études cliniques comparatives et post- commercialisation

Classes de systèmes d'organes selon MedDRA	Effet indésirable et fréquence
Affections hématologiques et du système lymphatique	Peu fréquent : leucopénie, neutropénie Fréquence indéterminée * : thrombopénie
Affections du système immunitaire	Fréquence indéterminée * : œdème de la langue, œdème labial, œdème pharyngé
Affections psychiatriques	Fréquent : anxiété Peu fréquent : hallucinations visuelles
Affections du système nerveux	Très fréquent : céphalées Fréquent : trouble de la mémoire, amnésie, troubles de l'attention, syndrome des jambes sans repos Peu fréquent : troubles cognitifs, convulsions Fréquence indéterminée * : syndrome d'encéphalopathie postérieure réversible
Affections cardiaques	Fréquence indéterminée * : allongement de l'intervalle QT (voir rubriques 4.4 et 4.5)
Affections vasculaires	Très fréquent : bouffées de chaleur, hypertension
Affections gastro-intestinales	Fréquence indéterminée * : nausées, vomissements, diarrhée
Affections de la peau et du tissu sous-cutané	Fréquent : sécheresse cutanée, prurit Fréquence indéterminée * : rash
Affections musculo-squelettiques et systémiques	Fréquent : fractures** Fréquence indéterminée * : myalgie, spasmes musculaires, faiblesse musculaire, dorsalgie
Affections des organes de reproduction et du sein	Fréquent : gynécomastie
Troubles généraux et anomalies au site d'administration	Très fréquent : asthénie/fatigue
Lésions, intoxications et complications liées aux procédures	Fréquent : chutes

* Notifications spontanées issues de l'expérience post-commercialisation ** Inclut toutes les fractures à l'exception des fractures pathologiques Description d'une sélection d'effets indésirables *Convulsions* Dans les études cliniques comparatives, 11 (0,5 %) des 2051 patients traités à la dose quotidienne de 160 mg d'enzalutamide ont présenté des convulsions, alors que un patient (< 0,1 %) parmi ceux ayant reçu le placebo et un patient (0,3 %) parmi ceux ayant reçu du bicalutamide ont présenté des convulsions. La dose semble être un facteur prédictif important du risque de convulsions, comme l'indiquent des données précliniques et les données obtenues lors d'une étude de recherche de dose. Dans les deux études cliniques comparatives, les patients présentant des antécédents de convulsions ou des facteurs de risque de convulsions ont été exclus. Au cours de l'étude AFFIRM, sept (0,9%) des 800 patients traités à la dose quotidienne de 160 mg d'enzalutamide après chimiothérapie ont présenté des convulsions ; aucune convulsion n'a été observée chez les patients ayant reçu le placebo. Plusieurs de ces patients présentaient des facteurs de risque potentiels susceptibles d'avoir augmenté le risque de convulsions de façon indépendante. Au cours de l'étude PREVAIL, un (0,1 %) des 871 patients n'ayant pas reçu de chimiothérapie et traités à la dose quotidienne de 160 mg d'enzalutamide, et un patient (0,1 %) recevant le placebo ont présenté des convulsions. Dans l'étude clinique comparative avec le bicalutamide, 3 patients (0,8 %) sur les 380 patients naïfs de chimiothérapie traités par enzalutamide et 1 patient (0,3 %) sur les 387 ayant reçu du bicalutamide ont présenté des convulsions. Dans un essai simple-bras évaluant l'incidence des convulsions chez les patients présentant des facteurs de prédisposition aux convulsions (dont 1,6% avaient des antécédents de convulsions), 8 (2,2%) des 366 patients traités par enzalutamide ont présenté des convulsions. La durée moyenne de traitement était de 9,3 mois. Le mécanisme par lequel l'enzalutamide pourrait abaisser le seuil épileptogène est inconnu, mais pourrait être mis en rapport avec les données des études *in vitro* qui montrent que l'enzalutamide et son métabolite actif se lient au canal chlore du récepteur GABA et peuvent en inhiber l'activité. Déclaration des effets indésirables suspectés La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration. Belgique Agence Fédérale des Médicaments et des Produits de Santé Division Vigilance, Eurostation II, Place Victor Horta, 40/40 B-1060 Bruxelles website : www.afmps.be e-mail: adversedrugreactions@fagg-afmps.be Luxembourg Direction de la Santé Division de la Pharmacie et des Médicaments Villa Louvigny – Allée Marconi L-2120 Luxemburg website : http://www.ms.public.lu/fr/activites/pharmacie-medicament/index.html **6. DONNÉES PHARMACEUTIQUES 6.1 Liste des excipients** Contenu de la capsule Macrogol-8 glycérides caprylocapriques Butylhydroxyanisole (E320) Butylhydroxytoluène (E321) Enveloppe de la capsule Gélatine Solution de sorbitol sorbitan Glycérol Dioxyde de titane (E171) Eau purifiée Encre de marquage Oxyde de fer noir (E172) Acétophtalate de polyvinyle **6.5 Nature et contenu de l'emballage extérieur** Pochette en carton contenant 28 capsules molles sous plaquettes thermoformées (PVC/PCTFE/aluminium). Chaque boîte contient 4 pochettes (112 capsules molles). **7. TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHÉ** Astellas Pharma Europe B.V. Sylviusweg 62 2333 BE Leiden PAYS-BAS **8. NUMÉRO(S) D'AUTORISATION DE MISE SUR LE MARCHÉ** EU/1/13/846/001 **9. MODE DE DELIVRANCE Médicament sur prescription médicale 10. DATE DE MISE À JOUR DU TEXTE 02/2018** Des informations détaillées sur ce médicament sont disponibles sur le site internet de l'Agence européenne des médicaments http://www.ema.europa.eu.

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mCRPC (metastatic Castration Resistant Prostate Cancer).
ADT (Androgen Deprivation Therapy).

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SAMENVATTING VAN DE PRODUCTKENMERKEN 1. NAAM VAN HET GENEESMIDDEL Xtandi 40 mg zachte capsules **2. KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING** Elke zachte capsule bevat 40 mg enzalutamide. Hulpstof met bekend effect Elke zachte capsule bevat 57,8 mg sorbitol. Voor de volledige lijst van hulpstoffen, zie rubriek 6.1. **3. FARMACEUTISCHE VORM** Zachte capsule. Witte tot gebroken witte, langwerpige, zachte capsules (van ongeveer 20 mm x 9 mm) gemarkeerd met "ENZ" in zwarte inkt op één zijde. **4. KLINISCHE GEGEVENS 4.1 Therapeutische indicaties** Xtandi is geïndiceerd voor: de behandeling van volwassen mannen met gemetastaseerde castratieresistente prostaatkanker (CRPC) die asymptomatisch of licht symptomatisch zijn na falen van androgeendeprivatietherapie voor wie behandeling met chemotherapie nog niet klinisch geïndiceerd is (zie rubriek 5.1); de behandeling van volwassen mannen met gemetastaseerde CRPC bij wie de ziekte progressief was tijdens of na behandeling met docetaxel. **4.2 Dosering en wijze van toediening** Behandeling met enzalutamide moet worden gestart en gemonitord door gespecialiseerde artsen die ervaring hebben met de medische behandeling van prostaatkanker. Dosering De aanbevolen dosis is 160 mg enzalutamide (vier zachte capsules van 40 mg) als eenmaal daagse orale dosis. *Bij patiënten die niet operatief zijn gecastreerd dient chemische castratie met een 'Luteinising Hormone Releasing Hormone' (LHRH)-analoog tijdens de behandeling te worden voortgezet.* Als een patiënt Xtandi niet op het gebruikelijke tijdstip inneemt, dient de voorgeschreven dosis zo dicht mogelijk op het gebruikelijke tijdstip te worden ingenomen. Als een patiënt een dosis van een hele dag mist, dient de behandeling de volgende dag met de gebruikelijke dagelijkse dosis te worden hervat. Als een patiënt last krijgt van een ≥ graad 3 toxiciteit of een onverdraaglijke bijwerking, dient de behandeling gestopt te worden gedurende één week of tot de symptomen verbeteren tot ≤ graad 2. Vervolgens dient de behandeling, indien gerechtvaardigd, hervat te worden op dezelfde of een verlaagde dosis (120 mg of 80 mg). *Gelijktijdig gebruik met sterke CYP2C8-remmers* Het gelijktijdig gebruik van sterke CYP2C8-remmers dient, indien mogelijk, te worden vermeden. Als aan patiënten ook een sterke CYP2C8-remmer dient te worden toegediend, dient de dosis enzalutamide verlaagd te worden naar 80 mg eenmaal daags. Als het gelijktijdig toedienen van de sterke CYP2C8-remmer wordt stopgezet, dient de dosis enzalutamide weer teruggebracht te worden naar de dosis zoals deze was voorafgaand aan het toedienen van de sterke CYP2C8-remmer (zie rubriek 4.5). *Ouderen* Er is geen dosisaanpassing noodzakelijk voor oudere patiënten (zie rubriek 5.1 en 5.2). *Leverinsufficiëntie* Er is geen dosisaanpassing noodzakelijk voor patiënten met lichte, matige of ernstige leverinsufficiëntie (respectievelijk Child-Pugh-klasse A, B of C). Een toegenomen halfwaardetijd van enzalutamide is echter waargenomen bij patiënten met ernstige leverinsufficiëntie (zie rubriek 4.4 en 5.2). *Nierinsufficiëntie* Er is geen dosisaanpassing noodzakelijk voor patiënten met lichte tot matige nierinsufficiëntie (zie rubriek 5.2). Voorzichtigheid is geboden bij patiënten met ernstige nierinsufficiëntie of terminale nierziekte (zie rubriek 4.4). *Pediatrische patiënten Er is geen relevante toepassing van enzalutamide bij pediatrische patiënten voor de indicatie behandeling van volwassen mannen met gemetastaseerde CRPC.* Wijze van toediening Xtandi is voor oraal gebruik. De zachte capsules Xtandi mogen niet worden gekauwd, opgelost of geopend, maar moeten in hun geheel worden doorgeslikt met water en kunnen met of zonder voedsel worden ingenomen. **4.3 Contra-indicaties** Overgevoeligheid voor de werkzame stof of voor één van de in rubriek 6.1 vermelde hulpstoffen. Vrouwen die zwanger zijn of kunnen worden (zie rubriek 4.6). **4.4 Bijzondere waarschuwingen en voorzorgen bij gebruik** Risico op insulten Voorzichtigheid is geboden wanneer Xtandi wordt toegediend aan patiënten met een voorgeschiedenis van insulten of andere predisponerende factoren waaronder, maar niet beperkt tot, onderliggend hersenletsel, beroerte, primaire hersentumoren of -metastasen of alcoholisme. Daarnaast kan het risico op insulten hoger zijn bij patiënten die gelijktijdig geneesmiddelen krijgen die de insultdrempel verlagen. De beslissing over voortzetting van de behandeling bij patiënten die een insult ontwikkelen, dient per geval te worden genomen. Posterieur reversibel encefalopathiesyndroom Bij patiënten die Xtandi kregen zijn zeldzame gevallen van het posterieure reversibele encefalopathiesyndroom (PRES) gemeld (zie rubriek 4.8). PRES is een zeldzame, reversibele, neurologische aandoening, die zich kan presenteren met snel ontwikkelende symptomen waaronder insulten, hoofdpijn, verwardheid, blindheid en andere visuele en neurologische stoornissen, met of zonder geassocieerde hypertensie. Een diagnose van PRES vereist een bevestiging door middel van beeldvorming van de hersenen, bij voorkeur door magnetic resonance imaging (MRI). Het wordt aanbevolen om de behandeling met Xtandi te stoppen bij patiënten bij wie zich PRES ontwikkelt. Gelijktijdig gebruik met andere geneesmiddelen Enzalutamide is een krachtige enzyminductor en kan leiden tot het verlies van werkzaamheid van veel vaak gebruikte geneesmiddelen (zie voorbeelden in rubriek 4.5). Daarom dient een evaluatie van gelijktijdig gebruikte geneesmiddelen uitgevoerd te worden bij het starten van de enzalutamidebehandeling. Gelijktijdig gebruik van enzalutamide met geneesmiddelen die gevoelige substraten zijn van vele metaboliserende enzymen of transporters (zie rubriek 4.5) dienen over het algemeen vermeden te worden als het therapeutische effect van deze geneesmiddelen van groot belang is voor de patiënt en dosisaanpassingen niet makkelijk uitgevoerd kunnen worden op basis van monitoring van werkzaamheid of plasmaconcentraties. Gelijktijdige toediening met warfarine en coumarine-achtige anticoagulantia dient te worden vermeden. Wanneer Xtandi gelijktijdig wordt toegediend met een anticoagulans dat wordt gemetaboliseerd door CYP2C9 (zoals warfarine of acenocoumarol) dient extra International Normalised Ratio (INR) monitoring te worden uitgevoerd (zie rubriek 4.5). Nierinsufficiëntie Voorzichtigheid is geboden bij patiënten met ernstige nierinsufficiëntie, omdat enzalutamide niet is onderzocht bij deze patiëntenpopulatie. Ernstige leverinsufficiëntie Een toegenomen halfwaardetijd van enzalutamide is waargenomen bij patiënten met een ernstige leverinsufficiëntie, waarschijnlijk gerelateerd aan een toegenomen weefseldistributie. De klinische relevantie van deze observatie blijft onbekend. Een langere tijd om de steady-state plasmaconcentraties te bereiken wordt echter verwacht, en zowel de tijd tot maximaal farmacologisch effect als de tijd tot start en afname van de enzyminductie (zie rubriek 4.5) kan worden verlengd. Recente hartaandoeningen In de fase 3-studies werden patiënten uitgesloten met een recent myocardinfarct (in de voorgaande 6 maanden) of onstabiele angina (in de voorgaande 3 maanden), hartfalen klasse III of IV van de New York Heart Association (NYHA) behalve bij een linkerventrikelejectiefractie (LVEF) ≥ 45%, bradycardie of ongecontroleerde hypertensie. Hier dient rekening mee gehouden te worden wanneer Xtandi bij deze patiënten wordt voorgeschreven. Androgeendeprivatietherapie kan het QT-interval verlengen Bij patiënten met een voorgeschiedenis van of risico op QT-verlenging en bij patiënten die gelijktijdig geneesmiddelen gebruiken die mogelijk het QT-interval kunnen verlengen (zie rubriek 4.5), dient de arts de baten/risicoverhouding, inclusief de kans op torsade de pointes, te beoordelen voorafgaand aan de start van Xtandi. Gebruik in combinatie met chemotherapie De veiligheid en werkzaamheid van gelijktijdig gebruik van Xtandi met cytotoxische chemotherapie zijn niet vastgesteld. Gelijktijdige toediening van enzalutamide heeft geen klinisch relevant effect op de farmacokinetiek van intraveneuze docetaxel (zie rubriek 4.5); een toename in het optreden van docetaxel-geïnduceerde neutropenie kan echter niet worden uitgesloten. Hulpstoffen Xtandi bevat sorbitol (E420). Patiënten met een zeldzame erfelijke fructose-intolerantie dienen dit geneesmiddel niet te gebruiken. Overgevoeligheidsreacties Overgevoeligheidsreacties zijn waargenomen met enzalutamide, zich manifesterend met symptomen als, maar niet beperkt tot, tongoedeem, lipoedeem en farynxoedeem (zie rubriek 4.8). **4.8 Bijwerkingen** Samenvatting van het veiligheidsprofiel De meest voorkomende bijwerkingen zijn asthenie/vermoeidheid, opvliegers, hoofdpijn en hypertensie. Andere belangrijke bijwerkingen zijn vallen, niet-pathologische fracturen, cognitieve stoornis en neutropenie. Insulten traden op bij 0,5% van de met enzalutamide behandelde patiënten, bij 0,1% van de met placebo behandelde patiënten en bij 0,3% van de met bicalutamide behandelde patiënten. Zeldzame gevallen van het posterieure reversibele encefalopathiesyndroom zijn gerapporteerd bij patiënten die zijn behandeld met enzalutamide (zie rubriek 4.4). Lijst met bijwerkingen in tabelvorm De bijwerkingen waargenomen tijdens klinische studies worden hieronder per frequentiecategorie opgesomd. De frequentiecategorieën van bijwerkingen worden als volgt gedefinieerd: zeer vaak (≥1/10), vaak (≥1/100, <1/10), soms (≥1/1.000, <1/100), zelden (≥1/10.000, <1/1.000), zeer zelden (<1/10.000) en niet bekend (kan met de beschikbare gegevens niet worden bepaald). Binnen elke frequentiegroep zijn de bijwerkingen gerangschikt op afnemende ernst.

Tabel 1: Bijwerkingen die zijn vastgesteld in de gecontroleerde klinische studies en post-marketing

MedDRA Systeem/orgaanklasse	Bijwerking en frequentie
Bloed- en lymfestelselaandoeningen	Soms: leukopenie, neutropenie niet bekend*: trombocytopenie
Immuunsysteemaandoeningen	Niet bekend*: tongoedeem, lipoedeem, farynxoedeem
Psychische stoornissen	Vaak: angst soms: visuele hallucinaties
Zenuwstelselaandoeningen	Zeer vaak: hoofdpijn vaak: geheugenstoornis, amnesie, aandachtsstoornis, restless legs syndroom soms: cognitieve aandoening, insult niet bekend*: posterieur reversibel encefalopathiesyndroom
Hartaandoeningen	Niet bekend*: QT-verlenging (zie rubriek 4.4 en 4.5)
Bloedvataandoeningen	Zeer vaak: opvlieger, hypertensie
Maagdarmstelselaandoeningen	Niet bekend*: misselijkheid, braken, diarree
Huid- en onderhuidaandoeningen	Vaak: droge huid, pruritus niet bekend*: huiduitslag
Skeletspierstelsel- en bindweefselaandoeningen	Vaak: fracturen** niet bekend*: myalgie, spierspasmen, spierzwakte, rugpijn
Voortplantingsstelsel- en borstaandoeningen	Vaak: gynaecomastie
Algemene aandoeningen en toedieningsplaatsstoornissen	Zeer vaak: asthenie/vermoeidheid
Letsels, intoxicaties en verrichtingscomplicaties	Vaak: vallen

* Spontane meldingen afkomstig van post-marketingervaring ** Dit omvat alle fracturen met uitzondering van pathologische fracturen Beschrijving van geselecteerde bijwerkingen *Insult* In gecontroleerde klinische studies kregen 11 patiënten (0,5%) van de 2051 patiënten die behandeld werden met een dagelijkse dosis van 160 mg enzalutamide een insult, terwijl één patiënt (< 0,1%) die behandeld werd met placebo en één patiënt (< 0,3%) die behandeld werd met bicalutamide een insult kregen. De dosis lijkt een belangrijke voorspeller van het risico op insult te zijn, zoals weergegeven in preklinische gegevens en gegevens uit een dosisescalatiestudie. In de gecontroleerde klinische studies werden patiënten met een eerder insult of risicofactoren voor het krijgen van een insult uitgesloten. In de AFFIRM-studie kregen zeven (0,9%) van de 800 patiënten die na chemotherapie behandeld werden met een dagelijkse dosis van 160 mg enzalutamide een insult, terwijl geen insulten voorkwamen bij patiënten die placebo kregen. Bij een aantal van deze patiënten waren potentieel bijdragende factoren aanwezig die elk op zich het risico op een insult kunnen hebben verhoogd. In de PREVAIL-studie trad bij één (0,1%) van de 871 chemotherapienaïeve patiënten die werden behandeld met een dagelijkse dosis van 160 mg enzalutamide en bij één patiënt (0,1%) die placebo kreeg, een insult op. In gecontroleerde studies met bicalutamide hadden 3 patiënten (0,8%) van de 380 chemotherapienaïeve patiënten die behandeld werden met enzalutamide en 1 patiënt (0,3%) van de 387 bicalutamide gebruikers een insult ervaren. In een single-armstudie om de incidentie van insulten te beoordelen bij patiënten met predisponerende factoren voor een insult (waarbij 1,6% een voorgeschiedenis van insulten had), kregen 8 (2,2%) van de 366 patiënten die met enzalutamide behandeld werden, een insult. De mediane duur van de behandeling was 9,3 maanden. Het mechanisme waardoor enzalutamide de insultdrempel kan verlagen is niet bekend, maar kan te maken hebben met gegevens uit *in-vitro*-onderzoeken waaruit blijkt dat enzalutamide en de actieve metaboliet ervan zich binden aan en de activiteit kunnen remmen van het GABA-gereguleerde chloridekanaal. Melding van vermoedelijke bijwerkingen Het is belangrijk om na toelating van het geneesmiddel vermoedelijke bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. Beroepsbeoefenaren in de gezondheidszorg worden verzocht alle vermoedelijke bijwerkingen te melden via het nationale meldsysteem. België Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten Afdeling Vigilantie, Eurostation II Victor Hortaplein, 40/40 B-1060 Brussel website : www.fagg.be e-mail: adversedrugreactions@fagg-afmps.be Luxemburg Direction de la Santé Division de la Pharmacie et des Médicaments Villa Louvigny – Allée Marconi L-2120 Luxemburg website : http://www.ms.public.lu/fr/activites/pharmacie-medicament/index.html **6. FARMACEUTISCHE GEGEVENS 6.1 Lijst van hulpstoffen** Capsule-inhoud Caprylocaproylmacrogol-8 glyceriden Butylhydroxyanisol (E320) Butylhydroxytolueen (E321) Capsule-omhulsel Gelatine Sorbitol-sorbitanoplossing Glycerol Titaniumdioxide (E171) Gezuiverd water Drukinkt Zwart ijzeroxide (E172) Polyvinylacetaatftalaat **6.5 Aard en inhoud van de verpakking** Een kartonnen etui met daarin blisterverpakkingen van PVC/PCTFE/aluminium met 28 zachte capsules. Elke doos bevat 4 etuis (112 zachte capsules). **7. HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN** Astellas Pharma Europe B.V. Sylviusweg 62 2333 BE Leiden Nederland **8. NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN** EU/1/13/846/001 **9. AFLEVERINGSWIJZE** Geneesmiddel op medisch voorschrift **10. DATUM VAN HERZIENING VAN DE TEKST 02/2018** Gedetailleerde informatie over dit geneesmiddel is beschikbaar op de website van het Europees Geneesmiddelenbureau (http://www.ema.europa.eu).

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A new treatment paradigm in metastatic bladder cancer: chemotherapy and immune checkpoint inhibition in 2018

Presented by: Ronald de Wit; MD, PhD
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The positive outcome of several randomized clinical trials evaluating immune checkpoint inhibitors in patients with metastatic bladder cancer dramatically changed the treatment paradigm in this setting. In his presentation, **Prof. de Wit** summarized the clinical data generated with PD-1/PD-L1 inhibitors in this setting, but he kicked off by summarizing the historical results obtained with chemotherapy in patients with metastatic urothelial cancer.

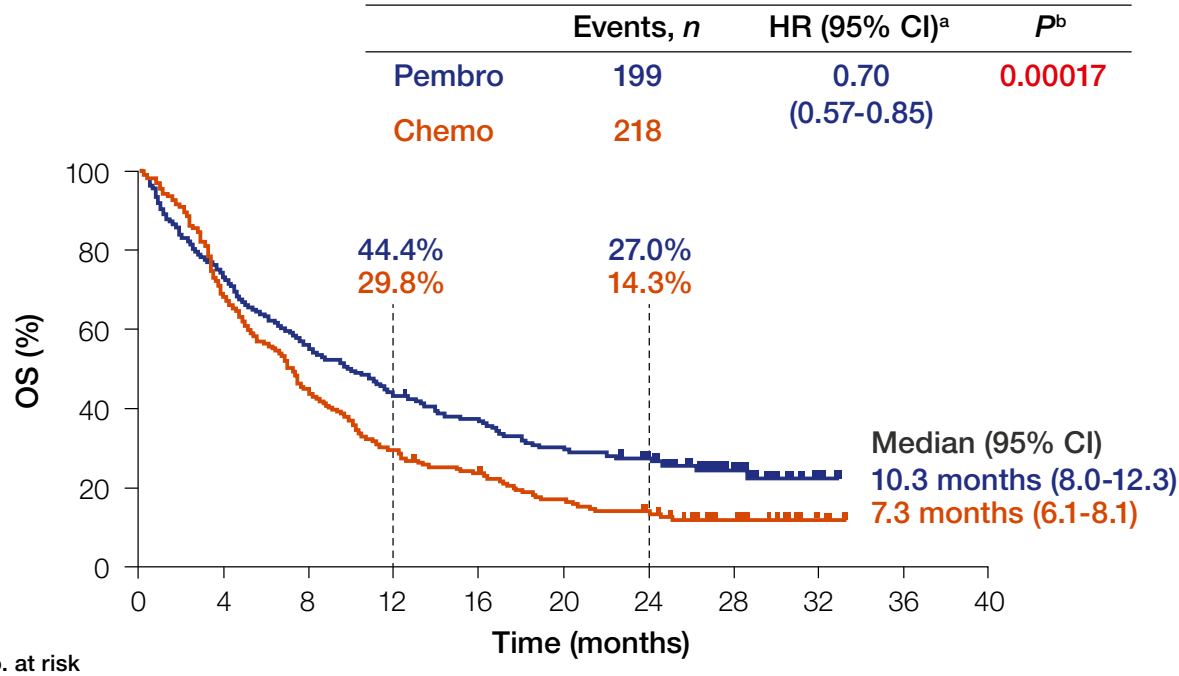
CHEMOTHERAPY IN METASTATIC UROTHELIAL CANCER

Cisplatin-based combination chemotherapy has long been the standard of care for patients with metastatic bladder cancer. The landmark of systemic chemotherapy in advanced urothelial cancer was the development of the combination of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) at the Memorial Sloan-Kettering Cancer Center (MSKCC) in 1983.[1] Its activity against urothelial cancer has been considerable with response rates of >50%, 3-year survival of 20-25% and a median survival of >1 year.[1-3] Furthermore, MVAC was shown to be superior to single-agent cisplatin in a randomized trial establishing the role of combination chemotherapy in advanced bladder cancer.[4] In 2000, *von der Maase et al*. established gemcitabine-cisplatin as an alternative for MVAC, yielding a comparable overall survival (OS) with a more favorable safety profile.[5] Several studies have evaluated the substitution of cisplatin by carboplatin, but carboplatin-based chemotherapy has generally produced inferior results (both in RR and median OS) to cisplatin-containing combinations. Two randomized phase II studies showed inferior RR with carboplatin as opposed to cisplatin-based chemotherapy indicating the inferiority of carboplatin-based chemotherapy.[6,7] In the EORTC 30986 study, gemcitabine-cisplatin was compared to M-CAVI. In this trial, both regimens were effective, but it became clear that for both regimens the response rate dropped with rising toxicity in patients with more adverse factors (e.g. visceral metastasis, poor performance status, renal impairment, etc.).[8] This finding set the treatment paradigm for cisplatin-unfit urothelial cancer patients. For elderly patients that are basically healthy, gemcitabine-cisplatin was the preferred option. In unfit patients (comorbidities, GFR rate 30-60 ml/min, unfit performance status [PS]), gemcitabine-carboplatin was the treatment of choice. The third group consists of unfit patients with additional adverse prognostic factors. For them, it is unlikely that chemotherapy will have any benefit.[8]

The clinical efficacy of chemotherapy in the second-line therapy of metastatic bladder cancer is limited (overall response rate [ORR] of only 12%). In the US the use of docetaxel in second-line is widespread, while in the EU vinflunine is used in some countries.

IMMUNE CHECKPOINT INHIBITION IN METASTATIC UROTHELIAL CARCINOMA

Keynote-045 is an open-label, international, phase 3 trial including 542 patients with advanced urothelial cancer with an ECOG PS of 0-2, that had recurred



[a]Based on Cox regression model with treatment as covariate stratified by ECOG performance status (0/1 vs 2).
Liver metastases (yes vs no), hemoglobin (<10 vs ≥ 10 g/dL). And time from completion of chemotherapy (<3 vs ≥3 months).
[b]One-sided *P* value based on stratified log-rank test.
Data cutoff date: October 26, 2017.

FIGURE 1. Overall survival in the Keynote-045 study.[9]

or progressed after platinum-based chemotherapy. Patients were randomly assigned to receive either pembrolizumab (200 mg IV Q3W) or investigator's choice of chemotherapy (paclitaxel [175 mg/m^2 Q3W], docetaxel [75 mg/m^2 Q3W], or vinflunine [320 mg/m^2 Q3W]).[9] The final results of this trial were reported at ASCO-GU 2018.[9] The study revealed an OS benefit with pembrolizumab (primary endpoint), with a median OS of 10.3 months as compared to 7.3 months with chemotherapy (HR[95%CI]: 0.73[0.59-0.91]; p= 0.0022) (*Figure 1*). At 2 years, 27% of patients in the pembrolizumab arm was still alive, which was twice as much as the 14% seen in the chemotherapy arm. The subgroup analysis of this trial indicated that the OS benefit of pembrolizumab was seen in all investigated subgroups, irrespective of the presence of visceral disease, the hemoglobin level, the ECOG PS and the number of risk factors.[9] One possible observation of the subgroup analysis could be that patients with liver metastasis do somewhat worse on pembrolizumab than the rest. Specifically looking at the combined positive score (CPS) for PD-L1 expression, it becomes clear that both in patients with a CPS <10% (HR[95%CI: 0.75[0.59-0.95]; p= 0.00859) and in patients with a CPS ≥10% (HR[95%CI]: 0.56[0.38-0.82]; p= 0.00153) pembrolizumab is associated with a significantly better OS than chemotherapy. Also the ORR was significantly higher

In addition to the better efficacy, pembrolizumab was also associated with a more favorable toxicity profile than chemotherapy in patients with cisplatin pretreated advanced urothelial cancer.

with pembrolizumab than with chemotherapy (21.1% *vs.* 11%; CR: 9.3% *vs* 2.9%). Importantly, responses with pembrolizumab were more durable than what was seen with chemotherapy (median not reached *vs.* 4.4 months). Looking at the response rate in function of CPS, it becomes clear that pembrolizumab yields an ORR of approximately 20% in patients with a CPS ≥10% and in patients with a CPS <10%. Interestingly, the ORR with chemotherapy in patients with a CPS ≥10% was remarkably low at only 6.7% (*vs.* 13% in CPS <10%). In addition to the better efficacy, pembrolizumab was also associated with a more favorable toxicity profile than chemotherapy, with a lower incidence of bothersome adverse events (AEs) like fatigue, nausea, decreased appetite and diarrhea. AEs of interest with pembrolizumab were hypothyroidism, pneumonitis, hyperthyroidism and colitis. In addition to this, one must also remain vigilant for other immune-related AEs, typical for immune checkpoint inhibitors. Pembrolizumab was shown to be associated with consistently better health-related quality of life (HRQoL) than the investigator's choice of chemotherapy. Pembrolizumab also prolonged the time to deterioration in HRQoL compared with chemotherapy.

Chronologically, atezolizumab was the first ICI approved for the treatment of bladder cancer. IMvigor 210 was a phase II clinical trial that evaluated the efficacy of atezolizumab in 310 patients after the failure of platinum-based chemotherapy, with no restrictions on the number of prior lines of therapy.[10] Some of these patients had received up to 5 lines of prior chemotherapy. The primary endpoint was ORR. At baseline, 36% of patients in the study had renal impairment (creatinine clearance below 60mL/min) and 78% had visceral metastatic sites. One fifth of patients received 2 previous metastatic treatment lines and another fifth even received 3 or more prior lines of treatment for their metastatic disease. In total, 73% of patients previously received cisplatin-based therapy. Patients were classified according to PD-L1 expression on their immune cells, with IC2/3 representing strong expression, IC1 representing moderate expression, and IC0 representing zero expression. Overall, the treatment with atezolizumab resulted in an ORR of 16% with 7% of complete responses (CRs). The higher the PD-L1 expression level on immune cells, the better the ORR, reaching up to 28% with 15% CRs in IC2/3 patients. Nevertheless, responses were also seen in patients with low levels of PD-L1 expression (ORR 9% in IC0 and 11% in IC1 patients). The atezolizumab treatment was associated with a median OS of 7.9 months (11.9 months in IC2/3 patients; 6.7 months in IC0/1 patients, with a 12 month OS rate of 37% (50% in IC2/3 patients; 31% in IC0/1 patients).[10] Following these positive results, the phase 3 IMvigor 211 study was designed including 931 patients with locally advanced or metastatic bladder cancer after failure of platinum-based chemotherapy, who were randomized to receive either atezolizumab or investigator's choice of chemotherapy.[11] The median OS (primary endpoint) in PD-L1 positive patients treated with atezolizumab was reported to be 11 months compared to a median OS of 10.6 months in PD-L1 positive patients treated with chemotherapy (HR[95%CI]: 0.87[0.63-1.21]; p= 0.41). As such, the primary endpoint of the study was unfortunately not met. The ORR with atezolizumab was 23% compared to 22%.

Immune checkpoint inhibition was also successfully evaluated as first-line therapy for patients who are ineligible for cisplatin-based chemotherapy.

Checkmate 275 assessed the safety and activity of nivolumab in 270 patients with metastatic or surgically unresectable bladder cancer, whose disease had progressed or recurred despite previous treatment with at least one platinum-based chemotherapy regimen.[12] A confirmed objective response (primary endpoint) was achieved in 19.6% of 265 patients. Once again, a higher PD-L1 expression was associated with a better ORR (PD-L1 in ≥25%: 28.4%; PD-L1 ≥1%: 23.8%; PD-L1 <1%: 16.1%). However, similar to what was seen with atezolizumab, a considerable proportion of PD-L1-negative patients also responded to this therapy. Importantly, the responses to nivolumab were found to be durable, with 77% of ongoing responses after 15 months of therapy. In all patients, the median OS was 9 months, increasing to 12 months in high PD-L1 expressing patients.[12]

Immune checkpoint inhibition was not only explored as a treatment option in second-line, after failure of cisplatin-based chemotherapy, it was also evaluated as first-line therapy for patients who are ineligible for cisplatin. In cohort 1 of IMvigor 210 study, atezolizumab was used to treat 119 patients with metastatic bladder cancer, who were considered cisplatin-ineligible due to

renal impairment, hearing loss, peripheral neuropathy, or an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2. At baseline, 21% of patients in this study were aged 80 years or older. In total, 92% had metastatic disease and 66% presented with visceral metastases. 70% of the patients presented with renal impairment, while 20% were assessed as having an ECOG PS 2.[12] Promisingly, the median OS (primary endpoint) was reported to be 15.9 months, with an ORR of 24% in all patients. No difference was seen between patients with high or low PD-L1 expression. The median PFS in this cohort was 2.7 months and 57% of patients reached the 1-year survival mark.[12]
As a historical control: carboplatin plus gemcitabine induces a response in 36% but is associated with a median OS of only 9.3 months. With this therapy 37% of patients reach the 1-year survival mark.[13]
In Keynote-052, pembrolizumab was tested as first-line therapy for cisplatin ineligible patients. In total, 370 patients with advanced bladder cancer who received no prior chemotherapy for metastatic disease, and who were considered ineligible for cisplatin were treated with pembrolizumab for 24 months. The protocol defined criteria for cisplatin ineligibility included a creatinine clearance rate of less than 60 mL per minute, an ECOG PS of 2, grade ≥2 neuropathy, or NYHA class III heart failure. The ORR (primary endpoint) was 29%, with a CR achieved in 7% of patients. Interestingly, the regimen also performed very well in older and frail patients. For example, in patients older than 75 years with an ECOG PS of 2 the ORR was 32%, with a CR in 6%. Overall, the median OS in this trial was found to be 11.5 months.[7] Interestingly, in contrast to what was seen in second-line, CPS seemed to be associated with response in first-line. In fact, among patients with a CPS <10% in Keynote-052, the ORR was 17%, while this reached 37% in patients with a CPS ≥10%.
To put the results of Keynote-052 in context, *prof de Wit* was so brave to make an indirect comparison with the results of the previously mentioned EORTC 30986 study. With gemcitabine-carboplatin, the median PFS was 5.8 months while this was only 2 months in keynote-052. In this respect it is important to note that the keynote study included patients with a worse prognosis than the EORTC trial (e.g. 85% *vs*. 50% visceral metastases). The median OS with gemcitabine-carboplatin in EORTC 30986 was 9.3 months, while the median was not reached in keynote 052 (to be presented at ASCO 2018). At 6 months, the OS rate was 67% with pembrolizumab in Keynote-052.

CONCLUSIONS

In summary, the introduction of immune checkpoint inhibitors (atezolizumab, pembrolizumab, nivolumab) dramatically changed the treatment landscape of advanced urothelial cancer patients. Looking at the future, Keynote-361 and phase 3 studies with atezolizumab in 1st line will provide randomized data of platinum-based chemotherapy *vs*. chemotherapy + checkpoint inhibition *vs*. immune checkpoint inhibition alone.

When dealing with immune checkpoint inhibition one must always remain vigilant for specific immune related AEs. These AEs can occur in any organ and at any time during (or even after) the treatment. When a patient encounters immune related side effects it is important to define the clinical symptoms so that the side effects can be graded. Subsequently, the aetiology should be explored and handling of the side effects should be performed in close collaboration with a dedicated organ specialist. As such, managing immune related side effects requires a multidisciplinary approach. There are a lot of guidelines on how to act on immunotherapy related side effects. Recently, the immunomanager webtool was launched by the Belgian Society of Medical Oncology (BSMO). This is an electronic document which provides comprehensive guidelines on the incidence, symptoms, diagnostic algorithm and treatment for the different types of immune related adverse events (*www.bsmo.be/immunomanager*). During BMUC 2018, *Prof Sandrine Aspeslagh (Institut Jules Bordet, Brussels)* gave a case-based overview of the different functionalities of this novel webtool.

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Biomarkers in the era of immunotherapy: lessons learned from lung, bladder and kidney cancer

Presented by: M. Kockx, MD, PhD *(HistoGeneX)*

Immune checkpoint inhibition has rapidly changed the treatment paradigm of several cancer types, including non-small cell lung cancer (NSCLC), melanoma, urothelial cancer and renal cell carcinoma (RCC). Lots of research is currently focused on the search for biomarkers that can predict whether a patients will respond to immunotherapy or not. During his lecture at BMUC 2018, **Dr. Mark Kockx**, pathologist and founder of HistoGeneX shared his views on this matter.

WHAT CAN PATHOLOGY TELL US?

Tumors are developing ecosystems with clinical interactions between cancer cells and the microenvironment. When looking at tumor samples as a pathologist you notice that some tumors have inflamed characteristics, while in other tumors, there is hardly any inflammation in the stroma. A good way to visualize this is a dual staining for pancytokeratin (staining a marker for epithelial differentiation) and CD8. In doing so you can see whether the immune cells have penetrated the tumor or not. If this is the case you have an indication that the immune system is still capable to move into the tumor strands and attack the tumor cells. The presence of these CD8+ cytotoxic T cells in the tumor is essential given their central role in the anti-tumor immune response. In many cancers, this CD8 infiltration is suboptimal. What is the reason for this? Let us go back to basics: the tumor microenvironment is a pathologically active niche that shapes tumor evolution. The immune system naturally identifies and eliminates cancerous cells. However, the tumor exploits a number of molecular pathways to proliferate and evade the immune system. Chen and Mellman brought all this information together in a rational map of the cancer-immunology interface. The result of this effort was a seminal article that continues to provide an intellectual framework for cancer immunotherapy research around the world.[1]

> The presence of CD8-positive cytotoxic T-cells in the tumor is essential given their central role in the anti-tumor immune response.

Chen and Mellman demonstrated that the generation of an anti-cancer immune response is a cyclic process that can be self-propagating, leading to an accumulation of immune-stimulatory factors that in principle should amplify and broaden T cell responses.[1] First, neo-antigens created by oncogenesis are released and captured by antigen presenting cells (APCs) for processing (*step 1*). For this step to yield an anticancer T cell response, it must be accompanied by immunogenic signals (e.g. pro-inflammatory cytokines, factors released by dying tumor cells). In the second step, APCs present the tumor-associated antigens to T-cells via MHC molecules (*step 2*). When a T cell encounters an antigen-presenting cell to which it can bind, it will initiate an activation program (*step 3*, priming and activation). This activation requires three sets of signals: a cascade generated by the T-Cell Receptor (TCR), a cascade generated through the costimulatory molecules (B7:CD28) and cytokines. This T-cell activation is regulated by immune checkpoints: costimulatory and inhibitory interactions that protect against auto-immunity and exces-

TABLE 1. Overview of available PD-L1 IHC kits

Clone/Assay	Evaluation	Pharma	Therapy
28-8 (Rb) PharmDX-DAKO	TC	FDA Complementary Dx (BMS)	Nivolumab (Opdivo®)
22C3 (Ms) PharmDX-DAKO	TC	FDA Companion Dx (MSD)	Pembrolizumab (Keytruda®)
SP142 (Rb) Ventana	TC & IC	FDA Complementary Dx (Roche)	Atezolizumab (Tecentriq®)
SP263 (Rb) Ventana	TC & IC	FDA Complementary Dx (Roche)	Durvalumab Nivolumab (Opdivo®)

sive immune responses. Finally, the activated effector T-cells enter the bloodstream and traffic to the site of the tumor (*step 4*), migrating across the endothelial barrier into the tumor bed (*step 5*). There, T-cells specifically recognize and bind to cancer cells through the interaction between its TCR and its cognate antigen bound to MHCI (*step 6*), and kill their target cancer cell (*step 7*). Killing of the cancer cell releases additional tumor-associated antigens (step 1 again) to increase the breadth and depth of the response in subsequent revolutions of the cycle. In cancer patients, the Cancer-Immunity Cycle does not perform optimally. For example, tumor antigens may not be detected, APCs and T cells may treat antigens as self rather than foreign, T cells may not properly home to tumors, T-cells can be inhibited from infiltrating the tumor, or factors in the tumor microenvironment might suppress those effector cells that are produced.[1]

Building on this foundational framework, three different immune phenotypes were identified that describe the level of T-cell presence and activity within the tumor microenvironment. These immune phenotypes identify the T-cell activities that are required to reinitiate the cancer immunity cycle.[2,3] In the *immune desert* phenotype, T-cells are absent from the tumor and the tumor microenvironment. In this case, it is necessary to generate active, tumor-directed T-cells (generate antigens, enhance antigen presentation, etc.).[2-4] The *immune excluded* phenotype is characterized by the fact that T-cells have accumulated, but are not efficiently infiltrating the tumor microenvironment. Therapeutic strategies for this phenotype are the recruitment of T-cells to the tumor, address the stromal barrier, or to redirect and engage T-cells.[3-5] In the *immune inflamed* phenotype, T-cells do infiltrate, but are not functioning properly. To address this phenotype, T-cells should be activated to kill the tumor cells.[2-4]

BIOMARKER STRATEGIES FOR IMMUNE CHECKPOINT INHIBITORS

PD-1/PD-L1 inhibitors are among the first immune checkpoint inhibitors that have been introduced in the treatment of several tumor types. Given their mechanism of action, the first potential biomarker that was elaborately studied was PD-L1. Unfortunately, conflicting results came out of the different studies and PD-L1 expression proved not to be a prerequisite for a response to PD-1/PD-L1 inhibition. To find an explanation for this, one must look back to the immune response process in which PD1 and PD-L1 are involved. In fact, PD1 and PD-L1 are indicators of the presence of immune cells, rather than an indicator of true immunosuppressive activity (their expression is a reaction to immune activation).[2] There is one exception to this rule: constitutive PD-L1 expression. This can be the result of an amplification of the PD-L1 gene at locus 9p24.1 (well known in Hodgkin lymphoma), or by oncogenic pathway activation (via STAT3, AKT). This process differs fundamentally from the adaptive, or inducible resistance normally seen in tumors.[5] When talking about PD-L1 expression, one cannot avoid to talk about the available immunohistochemistry (IHC) kits. In fact, each drug was developed with their own PD-L1 assay (*Table 1*). The use of these different assays results in significant complexity in clinical practice.

LESSONS LEARNED FROM NSCLC

The different PD-L1 assays turned out to be a major challenge in NSCLC. Every assay has its own typical staining pattern making it very difficult to use the same assay for all checkpoint inhibitors. To counter this, the blueprint initiative was launched. This was an industrial-academic collaborative partnership to provide information on the analytical and clinical comparability of the four PD-L1 IHC assays used in clinical trials.

To this end, 39 NSCLC tumors were stained with the four PD-L1 IHC assays: 22C3, 28-8, SP142, and SP263.[6] This study showed that scores in tumor cells (TCs) were similar for 22C3, 28-8 and SP263, but lower when using SP142. Also SP263 and SP142 stained immune cells (ICs) more intensely than the other assays. Furthermore, higher agreement was seen when TCs were scored compared to ICs.[6] In addition to this, the Blueprint 2 study demonstrated that digital pathology review was equivalent to glass slides.

In the clinical studies evaluating atezolizumab in NSCLC, a higher expression of PD-L1 was associated with a higher response rate.[7] Similarly, other markers of a T-effector cell signature, like a high level of IFN-gamma or granzyme B expression also correlate with a higher response rate to atezolizumab. Also in POPLAR, it was shown that particularly among patients with high levels of T-effector cell in the tumor, the overall survival (OS) was significantly better with atezolizumab than with docetaxel (HR[95%CI]: 0.43[024-0.77]). In contrast, patients with low levels of T-effector cells did not have an OS benefit with atezolizumab over docetaxel.[7]

LESSONS LEARNED FROM BLADDER CANCER

A first observation with respect to PD-L1 staining in bladder cancer is the fact that these tumor cells show less PD-L1 staining and that most of the PD-L1 staining is seen on immune cells. For the moment, there is no real explanation for this. In the IMvigor 210 study, assessing atezolizumab in advanced urothelial cancer patients who progress after cisplatin-based chemotherapy, the objective response rate (ORR) increased with an increasing PD-L1 expression on immune cells. Also the OS was longer in patients with a high IC PD-L1 score (median 11.4 months in IC2/3 *vs.* 6.6 months in IC0/1).[8] However, in the IMvigor 211 trial, a phase III study in the same setting of post platinum therapy for advanced urothelial cancer, the picture was different. In this trial the HR for OS of atezolizumab *vs.* chemotherapy was similar for IC2/3 and IC0/1 patients (0.81 and 0.84, respectively).[9] Surprisingly, in this study,

> In bladder cancer, PD-L1 staining typically stains tumor cells to a lesser extent and most staining can be found on immune cells.

PD-L1 expression turned out to act like a prognostic factor, with PD-L1 overexpression resulting in a more favorable outcome in both arms.[9] Further biomarker analyses in this trial looked at tumor mutational burden (TMB). In the subgroup of patients with high TMB, atezolizumab was associated with a statistically significant OS benefit compared to chemotherapy (95%CI): 0.68[0.51-0.90]). When combining TMB with PD-L1 expression, a subgroup of patients with an even more pronounced OS benefit of atezolizumab was identified. In fact, in patients with a high TMB and PD-L1 IC2/3 had a 50% reduction in the risk of death if they received atezolizumab compared to chemotherapy (HR[95%CI]: 0.50[0.29-0.86]).[9]

LESSONS LEARNED FROM RCC

In this tumor type it has been shown that blocking PD-L1 unleashes an immune response. In fact, in some RCC cases with low PD-L1 expression, the PD-L1 expression increases after treatment with atezolizumab.[10]

In the phase II IMmotion150 study, the combination of atezolizumab with bevacizumab is assessed in treatment-naïve, advanced RCC.[11] In patients with PD-L1 expression in at least 1% of IC, the combination of atezolizumab and bevacizumab was associated with a non-significant improvement in PFS compared to sunitinib (median PFS 14.7 *vs.* 7.8 months; HR[95%CI]: 0.64[0.38-1.08]; p= 0.095). Interestingly, an exploratory endpoint examined the association between outcome and tumor microenvironment gene signatures. Three different gene signatures are seen in RCC: angiogenesis, preexisting immunity (T-effector signature), or myeloid inflammation. In the subgroup of patients with High T-effector and high myeloid gene expression, it was shown that the addition of bevacizumab to atezolizumab led to a significant improvement in PFS. This reduced atezolizumab monotherapy activity in the T-effector-high and myeloid inflammatory-high patients suggests a potential mechanism of immune escape, which may be rescued by the addition of bevacizumab.

CONCLUSIONS

Neoplastic cells constantly interact with host cells, the extracellular matrix and bioactive molecules which constitute the tumor microenvironment. Tumoral molecular features influence the tumor microenvironment and in turn the tumor microenvironment can also influence gene expression. Host immune cells have essential roles in regulating tumor growth in the tumor microenvironment. NSCLC cells frequently express PD-L1 on the surface of tumor cells as well as infiltrating immune cells. Bladder and RCC express PD-L1 almost exclusively on tumor infiltrating immune cells and only rarely on tumor cells. With respect to biomarkers, Kockx concluded that effective immunotherapy biomarkers will likely require multiple analyses leveraging advanced morphological techniques combined with gene expression data and mutational load. It is also likely that predictive biomarkers for non-responders will become more important.

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What do we still need to know about the treatment of RCC?

Presented by: L. Albiges, MD, PhD
(Institut Gustave Roussy, Paris, France)

The introduction of immune checkpoint inhibitors dramatically changed the treatment paradigm of patients with advanced RCC. In her lecture, **Dr. Laurence Albiges** gave an overview of real-life data with nivolumab and gave her insights on how the first-line treatment landscape of patients with advanced RCC will evolve in the years to come.

MAKING THE MOST OF THE AVAILABLE OPTIONS

The real-world GETUG-AFU 26 NIVOREN study evaluates the performance of nivolumab in daily clinical practice. In this prospective, single arm, French multicenter study, 729 metastatic clear-cell RCC patients were treated with 3 mg/kg Q2W. All patients in the study failed at least 1 line of VEGF inhibition. The primary endpoint of the study was the incidence of high-grade (3-5) adverse events, but the study also evaluated overall survival (OS), progression-free survival (PFS) and overall response rate (ORR) as secondary objectives. The presented analysis is based on the data from the first 528 patients enrolled in the study (median follow-up 12 months).[1] In total, 15% of these patients had an ECOG PS 2 and 26.5% had poor IMDC prognosis features. About half of patients received one prior line of treatment, but 25% of patients received nivolumab in 4th line, or beyond. Furthermore, 14% had brain metastases, one quarter received prior everolimus and one third had a GFR of less than 60 ml/min. After a median follow-up of 13.3 months, 71.2% of patients had discontinued treatment: 50.4% due to progression, 9.7% due to toxicity and 6.6% due to death. The median duration of therapy was 4.2 months (median of about 10 infusions). Treatment-related grade 3-4 adverse events were seen in 14.6% of patients and 4 patients had a (suspected) treatment-related death. The confirmed ORR was 18.5% (18.1% partial responses), but 47.2% of patients had upfront progressive disease. The median PFS was 4.0 months, while the median OS was 18.6 months. After 1 year, two thirds of patients were still alive (66.3%). Looking at specific subgroups, it is not surprising to see that PS 2 patients do worse with a median OS of 10.8 months *vs.* 18.6 months in PS 0/1 patients ($p < 0.0001$). More surprisingly, the number of previous therapy lines did not seem to have an impact on the OS with nivolumab: median OS in patients with 2 or less previous treatment lines 18.6 months *vs.* 16.2 months for patients with more than 2 previous treatment lines. In patients who previously received everolimus, the outcome on nivolumab was worse than on patients who did not (median OS 15.9 *vs.* 18.6 months; $p = 0.0442$). Importantly, patients with a poor kidney function derived the same benefit of nivolumab than patients with an adequate renal function ($p = 0.8560$). In *Table 1*. The results of this real-world study are compared to the results obtained in the pivotal Checkmate 025 study.[1,2] This comparison shows that in real-life, a shorter OS is obtained, with a lower response rate and a higher risk of upfront disease progression. Of note, about 40% of patients in the real-life study received nivolumab beyond progression, indicating that they also received some degree of benefit from the treatment.

> Real-life data with nivolumab in RCC show a shorter OS than in clinical trials, with a lower response rate and a higher risk of upfront disease progression.

Several open questions on the routine use of nivolumab remain to be answered. First of all, when should we use nivolumab? Is it best to use it in second-line, or third line? To address this question, the GETUG AFU

TABLE 1. Summary of results of checkmate 025 and GETUG-AFU 26 NIVOREN.[1,2]

	Checkmate 025	GETUG-AFU 26 NIVOREN
N	406	528 (overall 729)
Median follow-up (months)	14	13.3
Median PFS (months)	4.6	4.0
Median OS (Months)	25.0	18.6
ORR	25%	18.5%
Stable disease	34%	34.3%
Progressive disease	35%	47.2%
Tx beyond progression	44%	39.6%
Grade 3-5 treatment related AEs	19%	15.4% (14.6% grade 3-4; <1% grade 5)

32 – SEUQUAN study is launched comparing nivolumab as second line followed by axitinib in third line to the reverse sequence. A second important question is how we can save refractory, or progressive patients? TITAN is a trial in which advanced RCC patients are initially treated with nivolumab. In function of their response their treatment can be 'boosted': for patients with a complete or partial response, the nivolumab treatment is continued, while in patients with stable or progressive disease, ipilimumab is added to nivolumab (of note: this trial is being conducted in first and second line). As a third open question, *dr Albiges* addressed the issue of brain metastases. In patients with brain metastases who receive nivolumab, you sometimes see a response in the metastatic lesions, but progressive disease in the brain. This is something we should keep in mind. In this light it could be of use to treat the brain metastases before starting nivolumab.

The most recent EAU guidelines indicate sunitinib, or pazopanib as the preferred 1st line treatment for IMDC favorable risk patients, while in poor and intermediate risk patients, ipilimumab plus nivolumab is recommended upfront.

WHAT WILL BE THE BEST TREATMENT OPTION IN 1st LINE?

The phase III Checkmate 214 study showed a superior OS of ipilimumab plus nivolumab compared to sunitinib in the 1st-line treatment of advanced, or metastatic clear-cell RCC (median OS in intermediate/poor risk IMDC patients not reached *vs.* 26 months; HR[99.8%-CI]: 0.63[0.44-0.89]; p< 0.0001).[3] In addition to this, the combination of ipilimumab and nivolumab was associated with a CR rate of 9% (*vs.* 1% with sunitinib) (ORR: 42% *vs.* 27%). Overall the combination therapy was associated with a lower rate of grade 3-5 adverse events. Nevertheless, treatment discontinuation due to adverse events was seen in 15% of patients treated with ipilimumab-nivolumab as compared to 7% with sunitinib. This illustrates that physicians are more familiar with sunitinib than with the toxicities seen with ipilimumab-nivolumab and that there will likely be a learning curve in clinical practice. Interestingly, an exploratory analysis of this trial showed that in favorable risk patients, sunitinib outperformed ipilimumab-nivolumab, both in terms of ORR (52% with sunitinib *vs.* 29% with the ipi-nivo combination; p= 0.0002) and PFS (median PFS with ipi-nivo 15.3 months *vs.* 25.1 months with sunitinib; HR[99.1%CI]: 2.18[1.29-3.68]; p< 0.0001). In line with these findings, the most recent EAU treatment guidelines sunitinib or pazopanib is still the preferred 1st line treatment option for IMDC favorable risk patients, while in poor and intermediate

patients, ipilimumab-nivolumab is recommended.[4]
In addition to the combination of two immune checkpoint inhibitors, clinical studies are also assessing the combination of an immune checkpoint inhibitor with a VEGF targeted agent in advanced RCC. The first of these phase III studies to report data was IMmotion 151 comparing atezolizumab plus bevacizumab to sunitinib as first-line treatment in 915 advanced or metastatic RCC patients.[5] In this trial, the combination therapy was associated with a median PFS of 11.2 months, which was significantly longer than the 7.7 months seen with sunitinib (HR[95%CI]: 0.74[0.57-0.96]; p= 0.02). This benefit was seen across all investigated subgroups, including patients with a favorable IMDC or MSKCC risk score. PD-L1 expression is not a pre-requisite for a response to the atezolizumab-bevacizumab combination, but an incremental effect in PFS was seen with an increasing PD-L1 expression (the higher the PD-L1 expression, the better the HR for PFS). At the time of the analysis, the OS data were still immature (30% maturity) but showed a trend towards a better OS with the combination (median not reached *vs.* 23.3 months; HR[95%CI]: 0.68[0.46-1.00]). Interestingly, the safety profile of atezolizumab-bevacizumab compared favorably to that of sunitinib, with less diarrhea, less nausea, less decreased appetite, etc. The only adverse event of interest that was seen more frequently with the combination was proteinuria.[5]
Several other combinations are also under evaluation in advanced RCC. For example, pembrolizumab is being tested in combination with axitinib or lenvatinib, while nivolumab and avelumab are assessed in combination with tivozanib and axitinib, respectively. The first results with these combinations are very promising, with ORRs ranging from 60 to 70%.

> In addition to the combination of two immune checkpoint inhibitors, several studies are also evaluating the combination of an immune checkpoint inhibitor and a VEGF targeted agent. The first results of these trials are very promising.

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The continuously evolving treatment landscape in renal cell carcinoma

Presented by: Viktor Grünwald, MD, PhD
(Hannover medical School, Hannover, Germany)

As a result of intensive fundamental and clinical research the treatment of localized and advanced renal cell carcinoma is constantly changing and improving. At the 2018 annual BMUC meeting, **Prof. Viktor Grünwald** gave an overview of the recent findings in clinical research and of the approaches that are expected to change the management of renal cell carcinoma (RCC) in the future.

ADJUVANT THERAPY FOR RCC

A number of clinical studies recently evaluated whether adjuvant therapy could improve the treatment of patients with locoregional RCC. This includes three randomized phase 3 studies on adjuvant treatment with tyrosine kinase inhibitors (TKIs) in patients with resected high-risk RCC (ASSURE, PROTECT, S-TRAC).[1-4] Unfortunately, only S-TRAC had a positive outcome in terms of its primary endpoint of disease-free survival (DFS; HR[95%CI]: 0.76[0.59-0.98]; p= 0.03).[1] Moreover, since S-TRAC failed to show an overall survival (OS) benefit of its investigational drug sunitinib versus placebo (HR[95%CI]: 1.01[0.72-1.44]) one can argue about the added value of adjuvant TKIs in mRCC. As a result, the Committee for Medicinal Products for Human Use of the European Medicines Agency refused to recommend sunitinib as adjuvant treatment in high-risk RCC.

> It seems unlikely that one fixed TKI dose accomodates the needs of all RCC patients. Individual dosing according to the tolerability of the patients rather seems the key to success.

Adjuvant treatment with immune checkpoint inhibitors has shown positive results in melanoma, where the outcome of these inhibitors has been investigated for more than a decade.[5] Currently, adjuvant immunotherapy is also being tested in RCC. For instance, the randomized phase 3 CheckMate 914-study compares the efficacy and safety of CTLA-4 inhibitor ipilimumab plus PD-1 inhibitor nivolumab with placebo in patients with resected high-risk, localized RCC. The primary outcome of the study is DFS, and secondary outcomes include OS and toxicity. A second example is the randomized phase 3 IMmotion 010-study evaluating the outcome of adjuvant treatment with PD-L1-inhibitor atezolizumab or placebo.

MULTIPLE OPTIONS FOR THE TREATMENT OF METASTATIC RCC

The availability of TKIs has clearly improved the survival of RCC patients. Grünwald: *"However, it took us a long time to realize that the outcome of many TKIs is similar. For instance, the efficacy of sunitinib and pazopanib has been shown to be virtually equal.[6] Furthermore, in my view we have been reluctant to learn how to optimally use TKIs. For instance, it seems unlikely that one fixed dose of TKIs accommodates the needs of all patients. Individual dosing according to the tolerability of the patient rather seems to be the key to success."*[7]

At present, over ten different drugs are available for the treatment of metastatic RCC (mRCC). This includes first, second and third generation TKIs, as well as the PD-1 inhibitor nivolumab, the VEGF inhibitor bevaci-

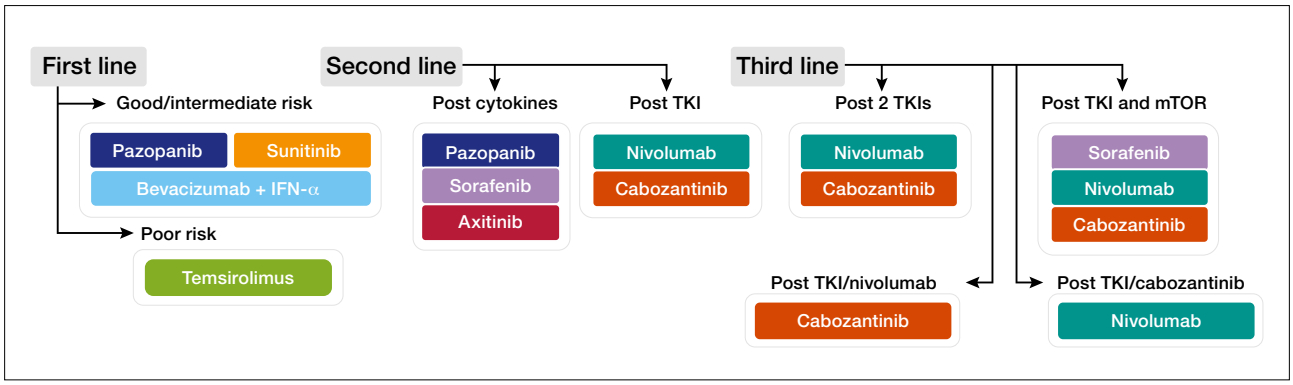

FIGURE 1. Treatment options for mRCC as recommended by the ESMO guidelines.[7]

zumab and the mTOR pathway inhibitors everolimus and temsirolimus. When talking about the treatment of RCC one should acknowledge that RCC is not a single disease, but a group of cancers that differ in many aspects, including prognosis.[8] Therefore, risk-assessment has been included in the guidelines on RCC, and the ESMO recommendations for the first-line treatment of mRCC have been adapted accordingly (*Figure 1*).[9] A second ground rule in these guidelines is that further line treatment is influenced by exposure in previous lines. *"In view of the above, it came as a surprise that cabozantinib compared to sunitinib significantly improved the progression-free survival (PFS) of patients with newly diagnosed intermediate- or poor-risk mRCC, especially those with bone metastases"*, says Grünwald.[10] Also in second line cabozantinib shows a clear benefit for patients with bone metastases, as indicated by the results of the phase 3-METEOR-trial.[11]

In addition to the novel drugs used as monotherapy, multiple combination treatments are currently being tested in clinical research. For instance the combination of ipilimumab and nivolumab is under evaluation in the randomized phase 3 CheckMate 214-study. Although the recent interim analysis of this study was designed to evaluate PFS, the results already revealed a striking improvement in OS of mRCC patients treated with the combination as compared to sunitinib (HR [99.8%CI]: 0.63[0.44-0.89]; p< 0.0001).[12] Moreover, treatment with ipilimumab plus nivolumab was associated with a complete response (CR) rate of 9% *vs.* 1% following sunitinib. This is a very encouraging finding, since we hardly ever observed a CR rate above 1% in mRCC, irrespective of the type of treatment. Clearly the results do not account for all patients, as demonstrated by the results in favorable-risk patients (N= 249), where the efficacy of sunitinib outperforms the combination treatment (median PFS: 15.3 *vs.* 25.1 months; HR[99.1%CI]: 2.18[1.29-3.68]; p< 0.0001).[12]

More recently, the results of the randomized phase 3 IMmotion151-study showed that atezolizumab plus bevacizumab significantly improved the median PFS as compared to sunitinib in patients with newly diagnosed PD-L1-positive (≥1%) mRCC (median PFS: 11.2 *vs.* 7.7 months; HR[95%CI]: 0.74[0.57-0.96]; p= 0.02).[13] Furthermore, the combination treatment was associated with an objective response rate (ORR) and CR-rate of 43% and 9%, respectively, as compared to 35% and 4% for sunitinib. Interestingly, the median duration of response (DoR) with the atezolizumab-bevacizumab combination was not reached after a median follow-up of 15 months (*vs.* 12.9 months with sunitinib). Most likely, these positive results will have an impact on future guidelines.

Recently, the results of clinical studies in mRCC showed that a number of combination treatments, including atezolizumab plus bevacizumab and axitinib plus avelumab, are associated with higher ORR and CR rates than sunitinib monotherapy.

Recently the results of clinical studies in mRCC showed that a number of combination treatments, including atezolizumab plus bevacizumab, and axitinib plus avelumab, are associated with higher ORR and CR rates than sunitinib monotherapy.[8,12,14,15] *"In my view especially the latter is an important result, since patients with a CR have a high chance to be cured by the therapy.*

However, since there are so many possibilities, the question is which combination treatment is optimal for each individual patient. For instance, one can combine immunotherapy with chemotherapy, radiotherapy or targeted therapy. Possibly, biomarkers like PD-L1 can help to select those patients that have the highest change of response, particularly in first line treatment.[16] *However, there is a high chance that this approach is still too simple, and that we must strive towards clinical prognostication, and molecular and immune profiling of individual patients."*

ONGOING IMMUNOTHERAPY STUDIES IN mRCC

One of the current studies comparing immunotherapy-based combination treatments with the standard of care in newly diagnosed mRCC is SUNNIFORECAST. This is a European, randomized phase 2-trial comparing the combination of ipilimumab and nivolumab with sunitinib as first line treatment in patients with non-clear cell mRCC. The primary endpoint is OS at twelve months. Secondary endpoints include ORR, PFS and safety. Furthermore, several studies evaluate the outcome of tailor-made immunotherapy in mRCC. For instance, NIVOSWITCH is a randomized phase 2-study in TKI-treated mRCC patients (clear cell) which compares nivolumab with TKI continuation. The primary endpoint of this study is OS at two years. In addition, TITAN-RCC is an 'immune titrated' study in which newly diagnosed as well as previously treated mRCC patients (clear cell) are first treated with nivolumab. Subsequently, patients with a complete or partial response continue nivolumab, while patients with stable or progressive disease will be treated with nivolumab plus ipilimumab. Hopefully, this trial will give us insight in which patients respond sufficiently on monotherapy and which patients benefit more from a combination approach."

CONCLUSIONS

Recent clinical studies have further improved the treatment of localized and advanced RCC and resulted in multiple novel treatment strategies for newly diagnosed and previously treated disease. Now it is time to determine from which strategies individual patients benefit the most. In addition to the currently used risk-stratification, biomarkers and molecular profiling are anticipated to contribute to the rational selection of these patients in the (near) future.

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Penile cancer

Presented by: M. Albersen, MD, PhD
(University hospital Leuven, Belgium)

It has become of yearly tradition of BMUC to put a tumor type in the spotlight that is often overlooked at (inter)national symposia. This year, **Prof. Maarten Albersen** gave an overview of the current treatment landscape of penile cancer.

INTRODUCTION

Penile cancer is a rare cancer type that is associated with considerable patient morbidity. It represents less than 1% of all male cancers and most commonly has a squamous histology. Known risk factors for the development of penile cancer include no childhood circumcision, HPV and HIV infections, smoking and a low socio-economic status.[1] Overall, the incidence of penile cancer is 8/million/year, corresponding to 45 new cases of penile cancer per year in Belgium. With approximately 500 physicians licensed in urology, this would mean that, on average, an urologist sees one case of penile cancer per 5.6 years. This low patient number, in combination with the specialized and complex management that these patients need, make a strong case for a centralized care of penile cancer. Data from the cancer registry indicate that between 2001 and 2010, 406 cases of penile cancer were diagnosed in Flanders, with a 5-year overall survival (OS) rate of 69.8%.[2]

TREATMENT OF THE PRIMARY TUMOR

Recently the TNM staging for penile cancer was updated. This was necessary, as the previous TNM classification had several shortcomings in terms of usability in clinical staging and prognostic value. In *Table 1*, an overview of the current TNM staging is provided.[3]
When there is a suspicion for a penile carcinoma in situ (PeIN), it is important to always take a biopsy. In fact, about 20% of these cases actually turn out to have

TABLE 1. 2017 TNM staging for penile cancer.[3]

Stage	Criteria
pTis	Carcinoma in situ (PeIN)
pTa	Non-invasive localized squamous cell carcinoma
pT1	Invades lamina propria
pT1a	No lymphovascular or perineural invasion, or G3 tumor
pT1b	With lymphovascular and/or perineural invasion, and/or G3 tumor
pT2	Invades corpus spongiosum with/without urethra invasion
pT3	Invades corpora cavernosa (including tunica albuginea) with/without urethra invasion
pT4	Invades into adjacent structures (scrotum, bone, prostate)

an invasive component.[4] The recommended treatment for these patients consists of circumcision, imiquimod (12 weeks), 5-FU (4-6 weeks), or laser treatment. Of note, the latter comes with a higher retreatment rate and a higher risk of progression than the other treatment modalities. In refractory cases, a glans resurfacing can be performed.[4]

> In patients where nodes are not palpable (high or intermediate risk cN0 disease), the EAU and ESMO guidelines argue against the use of surveillance and underline the need for surgical staging.

For T1-2-3 primary tumors, both the EUA and ESMO stipulate that organ-sparing surgery should be preferred whenever possible.[4,5] With radiotherapy, or brachytherapy, local control can be obtained in 70-90% of the cases. However, in up to 40% meatal stenosis is seen. In T1-2-3 cases, a radical circumcision should always be performed plus a wide local excision (WLE) with/without foreskin plasty or primary closure, a hemiglansectomy, or a glansectomy. Split thickness skin grafts are increasingly used to recreate the appearance of a glans and improve the aesthetic outcome of these procedures. In guidelines, a margin of 5 mm is advocated, but there does not seem to be a significant difference in outcome with a margin of 1-5 mm. However, when the margins are below 1 mm there is a higher risk for local recurrence.[4,5]

CONTEMPORARY LYMPH NODE MANAGEMENT

In patients where nodes are not palpable (high/intermediate risk cN0 disease), the EAU and ESMO guidelines argue against the use of surveillance and underline the need for surgical staging.[4,5] In fact, early detection of lymph node metastases by dynamic sentinel node biopsy (DSNB) and subsequent resection in clinically node negative T2-3 penile cancer improves survival compared with a policy of surveillance.[6] Another option in these patients consists of modified/superficial inguinal lymph node dissection (mILND).[7] With this technique, a shorter incision is needed (6-8 cm) and the vena saphena magna and the lateral area to the arteria femoralis can be preserved. mILND has a low false negative rate (0.5-5%) but the complication rate is significant, ranging from 10-36%.[7] With DSNB, far less complications are seen. Initially, the sensitivity of DLNB was inferior to that of mILND, but this has changed with the addition of ultrasound (US).[8] In a meta-analysis, a pooled detection rate of 88.3% was reported with a sentinel lymph node biopsy (sensitivity 88%). When a radiotracer and blue dye for sentinel lymph node mapping is used, the detection rate increases to 90.1 (sensitivity 92%).[9] Of note, this low rate of false negative results can only be obtained in centralized healthcare.

For patients with palpable nodes (cN1-N2) there is no role for prophylactic antibiotics before evaluation. In these patients there is a very high likelihood of metastatic disease and antibiotics could delay the treatment. For cN1-N2 patients, staging for systemic dissemination (CT or PET-CT) is indicated, followed by radical ILND after a confirmatory biopsy. Unfortunately, this technique comes with a high complication rate (42-57%). The following measures can help to avoid complications: prophylactic antibiotics until the drain is removed, drains removed if < 30ml, debridement of nonviable skin edges, early ambulation and prophylactic thrombo-embolic prophylaxis, and the use of compression stockings. With respect to the adjuvant radiotherapy in this setting, the literature is of poor quality with heterogeneous inclusion in the different studies. The current EAU guidelines do not indicate it.[3] In contrast, the use of adjuvant chemo-therapy is recommended, in particular when the administration of triple combination chemotherapy (5-FU, paclitaxel/docetaxel, cisplatin [TPF]) is feasible and when the treatment has curative intent. There are no data for the adjuvant chemotherapeutic treatment of penile carcinoma in stage pN1. As such, the administration of adjuvant chemotherapy to these patients is only advised in a clinical trial.[3,4,10] Whether there is a role for prophylactic pelvic lymph node dissection (PLND) is

> For cN1-N2 patients, staging for systemic dissemination (CT or PET-CT) is indicated, followed by radical ILND after a confirmatory biopsy. Unfortunately, this technique comes with a high complication rate and appropriate measures should be taken to avoid complications.

subject to debate as there are no strong data supporting it. These and other issues will be addressed in the InPACT phase III trial.

> It is important to never perform incisional biopsies in patients with bulky, or fixed nodes (cN3) as this can result in significant morbidity and mutilation.

What to do in patients with bulky, or fixed nodes (cN3)? For these patients, the EAU and the NCCN recommend neo-adjuvant chemotherapy. The preferred regimen for this seems to be a taxane with cisplatin and a taxane whenever feasible.[3,4,11] In his lecture, *dr Albersen* underlined that it is important to never perform incisional biopsies in these patients as this can result in significant morbidity and mutilation.

FUTURE PERSPECTIVES

Translational research indicates that EGFR is involved in penile carcinogenesis. This could open the door for targeted therapy in this setting.[12] In addition to this, *Udager et al.* recently reported frequent PD-L1 expression in primary and metastatic penile squamous cell carcinoma. (62.2% PD-L1 positivity). Moreover, PD-L1 expression seemed to be associated with high-risk clinicopathological features and a poor clinical outcome.[13] These data provide a rational basis for further investigation of anti-PD-1/PD-L1 immunotherapy in patients with advanced penile cancer.

Another evolution in the field of penile cancer consists of the establishment of the European reference network in rare urogenital tumors (eUROGEN). Initiatives like this are important given the fact that centralized care is important in penile cancer: the more patients are treated in the same center, the better the outcome.

Several challenges still remain in penile cancer: there is a lack of models for translational; research and preclinical phase II trials, the comprehension of penile tumor biology is suboptimal and there is uncertainty on the role of radiotherapy and on the poor performance of systemic therapy. We hope that these issues will be addressed in future years, ultimately leading to a better outcome and quality of life for patients with penile cancer.

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Pembrolizumab survival benefit sustained in 2-Year Urothelial Cancer Data Results presented at ASCO GU 2018

Two-year follow-up data showed sustained improvements in overall survival (OS) with pembrolizumab (Keytruda®) over chemotherapy in pretreated patients with locally advanced or recurrent urothelial cancer, according to updated findings from the phase III KEYNOTE-045 trial presented by Prof. Bellmunt at the 2018 Genitourinary Cancers Symposium.

The most important observation of these follow-up data is that 27% of patients that received pembrolizumab are still alive, compared with 14% of patients in the group assigned to receive chemotherapy.

At the 2-year follow-up, the hazard ratio has improved over the initial results, increasing from 0.73 to 0.70 (P =.00017), showing that there is a 30% reduction in the risk of death in patients receiving pembrolizumab, Bellmunt says.

The initial results of the trial showed pembrolizumab had a superior response rate over chemotherapy, at 21% versus 11%. Investigators have now seen additional responses with subsequent follow-up, and the responses are durable. In the pembrolizumab arm, the median duration of response has not yet been reached, but is close to 50%. In the chemotherapy arm, the median duration of response is 4.5 months.

"Level 1 evidence supports the use of pembrolizumab as a standard of care for this patient population," said lead investigator Joaquim Bellmunt, MD, PhD, director of the Bladder Cancer Center, Dana-Farber Cancer Institute, Boston. *"Pembrolizumab is the first immuno-therapy to demonstrate superior survival over chemotherapy in patients with advanced urothelial carcinoma after failing platinum-based therapy."*

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IMmotion 151 supports atezolizumab plus bevacizumab as first-line treatment for patients with PD-L1 positive advanced renal cell carcinoma

During the 2018 genitourinary cancer symposium (ASCO GU), results were presented of the phase III IMmotion 151 study, evaluating the combination of atezolizumab plus bevacizumab (atezo + bev) in 915 treatment-naïve patients with advanced or metastatic renal cell carcinoma (RCC). People in the atezo + bev arm received atezolizumab at a fixed dose of 1200 mg and bevacizumab at a dose of 15 mg/kg via intravenous (IV) infusion every 3 weeks until loss of clinical benefit or unacceptable toxicity, while patients in the sunitinib arm received sunitinib 50 mg orally, once daily in a 4 weeks on, 2 weeks off schedule, until loss of clinical benefit or unacceptable toxicity.

The study met its co-primary endpoint of investigator-assessed progression-free survival (PFS) in patients with PD-L1 expression (⩾1%). In this cohort, atezo + bev was associated with a 26% reduced risk of disease progression or death compared to people treated with sunitinib (median PFS: 11.2 vs. 7.7 months; HR[95%CI]: 0.74[0.57-0.96]; p=0.02). This benefit in PFS was seen in all investigated subgroups, irrespective of the presence of liver metastases, tumor histology (sarcomatoid or not) and whether or not patients underwent a nephrectomy. Importantly, in the PD-L1 positive cohort, a numerical difference in PFS favoring atezo + bev was seen across all patient risk factor groups (favorable, intermediate and poor) compared to sunitinib. The data

for the co-primary endpoint of overall survival (OS) in the intent-to-treat (ITT) population were immature at the time of the presented analysis, but show an encouraging trend (medians not reached in both arms; HR[95%CI]: 0.81[0.63-1.03]; p= 0.09). Atezo + bev also outperformed sunitinib with respect to the response rate: in the PD-L1 positive cohort, atezo + bev induced an objective response in 43% as compared to 35% with sunitinib. Interestingly, atezo + bev induced a complete response (CR) in 9% of PD-L1 positive patients (vs. 4% with sunitinib). The latter is impressive given the fact that CRs are historically rare in patients with advanced RCC. The responses with atezo + bev also seem to be more durable than the responses seen with sunitinib (median duration of response [DoR]: not reached vs. 12.9 months).

The safety profile of the combination therapy was consistent with the known safety profile of the individual medicines. Importantly, the rate of treatment-related grade 3/4 adverse events was lower with the atezo + bev combination (40%) than with sunitinib alone (54%) in the ITT population. In addition, a pre-defined analysis of patient-reported outcomes (PRO) revealed that the combination of atezo + bev markedly delayed the time to a worsening of disease symptoms that interfere with day-to-day life compared to sunitinib, (median time to deterioration: 11.3 vs. 4.3 months; HR[95%CI]: 0.56[0.46-0.68]) in the ITT population.

In summary, the first results of IMmotion 151 supports atezolizumab plus bevacizumab as first-line treatment for patients with PD-L1 positive advanced renal cell carcinoma.

Ipilimumab + nivolumab: a new standard in first-line renal cell carcinoma?

As reported in The New England Journal of Medicine by earlier this year, the phase III CheckMate 214 trial has shown an overall survival (OS) advantage with nivolumab plus ipilimumab over sunitinib in patients with previously untreated advanced renal cell carcinoma (RCC). In this study, 1,096 patients with advanced clear cell RCC were randomized to receive nivolumab (3 mg/kg) plus ipilimumab (1 mg/kg) every 3 weeks for 4 doses followed by nivolumab (3 mg/kg every 2 weeks), or oral sunitinib (50 mg once daily for 4 weeks in 6-week cycles). The co-primary endpoints were OS, objective response rate (ORR) and progression-free survival (PFS) among patients with intermediate or poor prognostic risk.[1]

After a median follow-up of 25.2 months, the median OS in the intermediate and poor risk patients treated with nivolumab/ipilimumab was not yet reached as compared to 26 months in patients who received sunitinib (HR: 0.63; p< 0.001). At 18 months, 75% of patients in the combination arm were still alive versus 60% in the sunitinib-treated patients. In this cohort, the ORR was 42% (9% complete response [CR]) with ipilimumab/nivolumab vs. 27% (1% CR) with sunitinib. Finally, ipilimumab plus nivolumab was also associated with a PFS advantage over sunitinib in the intermediate/poor risk patients (median PFS: 11.6 vs. 8.4 months), but this difference did not meet the prespecified threshold for significance of 0.009 (p= .003).

In the overall patient population (also including the 249 patients with a favorable risk profile), the median OS was not reached with the combination and reached 32.9 months with sunitinib (HR: 0.68; p< 0.001). At 18 months the OS rates were 78% and 68% with ipilimumab + nivolumab and sunitinib, respectively. Among favorable-risk patients alone, the OS was 94% vs. 96% at 12 months and 88% vs. 93% at 18 months, with the HR non-significantly favoring sunitinib (HR: 1.45, p= 0.27).

Interestingly, the incidence of grade 3 or 4 adverse events (AEs) was 46% in the nivolumab/ipilimumab group as compared to 63% in the sunitinib group. The most common AEs in the nivolumab/ipilimumab group were increased lipase (10%), diarrhea (4%), and fatigue (4%), and the most common in the sunitinib group were hypertension (16%), palmar-plantar erythrodysesthesia (9%), and increased lipase (7%). Treatment-related immune-related adverse events of any grade occurred in 80% of patients in the nivolumab/ipilimumab group; among these patients, 35% received high-dose corticosteroids. Treatment-related AEs led to discontinuation of treatment in 22% of the nivolumab/ipilimumab group and 12% of the sunitinib group.

In summary, the OS and ORR were significantly higher with nivolumab plus ipilimumab than with sunitinib among intermediate- and poor-risk patients with previously untreated advanced renal cell carcinoma. In line with these findings, the most recent EAU treatment guidelines recommend the combination of ipilimumab and nivolumab as the preferred 1st line treatment of patients with poor and intermediate risk metastatic RCC. For patients with a favorable IMDC risk profile, sunitinib or pazopanib is recommended.[2]

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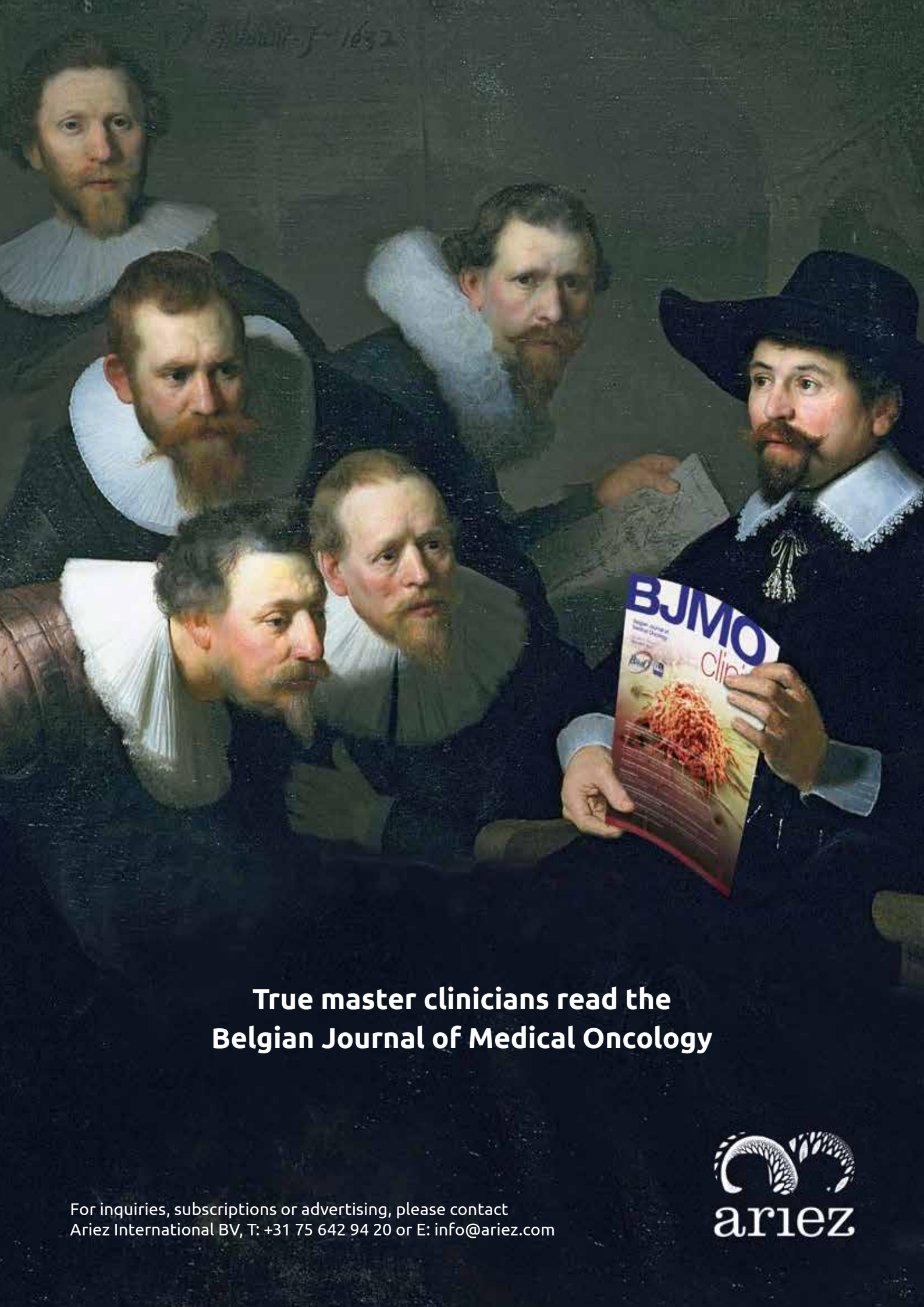

True master clinicians read the Belgian Journal of Medical Oncology

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NAME OF THE MEDICINAL PRODUCT Tecentriq 1,200 mg concentrate for solution for infusion. QUALITATIVE AND QUATANTITATIVE COMPOSITION Each 20 mL vial of concentrate contains 1,200 mg atezolizumab*. After dilution (see section 6.6 of SmPC), one mL of solution contains approximately 4.4 mg of atezolizumab. *Atezolizumab is an Fc-engineered, humanised IgG1 antiprogrammed deathligand 1 (PDL1) monoclonal antibody produced in Chinese hamster ovary cells by recombinant DNA technology. For the full list of excipients, see section 6.1 of SmPC. PHARMACEUTICAL FORM Concentrate for solution for infusion. Clear, colourless to slightly yellowish liquid. THERAPEUTIC INDICATIONS Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) after prior platinumcontaining chemotherapy or who are considered cisplatin ineligible (see section 5.1 of SmPC). Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic nonsmall cell lung cancer (NSCLC) after prior chemotherapy. Patients with EGFR activating mutations or ALKpositive tumour mutations should also have received targeted therapy before receiving Tecentriq (see section 5.1 of SmPC). POSOLOGY AND METHOD OF ADMINISTRATION Tecentriq must be initiated and supervised by physicians experienced in the treatment of cancer. Posology. The recommended dose of Tecentriq is 1,200 mg administered intravenously every three weeks. Duration of treatment. It is recommended that patients are treated with Tecentriq until loss of clinical benefit (see section 5.1 of the SmPC) or unmanageable toxicity. Delayed or missed doses. If a planned dose of Tecentriq is missed, it should be administered as soon as possible; it is recommended not to wait until the next planned dose. The schedule of administration must be adjusted to maintain a 3week interval between doses. Dose modifications during treatment. Dose reductions of Tecentriq are not recommended. Dose delay or discontinuation. (see also sections 4.4 and 4.8 of the SmPC) **Table 1: Dose modification advice for Tecentriq.** [Immune related adverse reaction→Severity→Treatment modification]: **Pneumonitis**→grade 2→Withhold Tecentriq. Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤10mg prednisone or equivalent per day. Pneumonitis→grade 3 or 4→Permanently discontinue Tecentriq. **Hepatitis**→Grade 2: (ALT or AST > 3 to 5 x upper limit of normal [ULN] or blood bilirubin > 1.5 to 3 x ULN)→Withhold Tecentriq. Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Hepatitis→Grade 3 or 4: (ALT or AST > 5 x ULN or blood bilirubin > 3 x ULN)→Permanently discontinue Tecentriq. **Colitis**→Grade 2 or 3 Diarrhoea (increase of ≥ 4 stools/day over baseline) or Symptomatic Colitis→Withhold Tecentriq. Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone equivalent per day. Colitis→Grade 4 Diarrhoea or Colitis (life threatening; urgent intervention indicated)→Permanently discontinue Tecentriq. **Hypothyroidism or hyperthyroidism**→Symptomatic→Withhold Tecentriq. Hypothyroidism: Treatment may be resumed when symptoms are controlled by thyroid replacement therapy and TSH levels are decreasing. Hyperthyroidism: Treatment may be resumed when symptoms are controlled by antithyroid medicinal product and thyroid function is improving. **Adrenal insufficiency**→Symptomatic→Withhold Tecentriq. Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and patient is stable on replacement therapy. **Hypophysitis**→Grade 2 or 3→Withhold Tecentriq. Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and patient is stable on replacement therapy. Hypophysitis→Grade 4→Permanently discontinue Tecentriq. **Type 1 diabetes mellitus**→Grade 3 or 4 hyperglycaemia (fasting glucose > 250 mg/dL or 13.9 mmol/L)→Withhold Tecentriq. Treatment may be resumed when metabolic control is achieved on insulin replacement therapy. **Infusion-related reactions**→Grade 1 or 2→Reduce infusion rate or interrupt. Treatment may be resumed when the event is resolved. Infusion-related reactions→Grade 3 or 4→Permanently discontinue Tecentriq. **Rash**→Grade 3→Withhold Tecentriq. Treatment may be resumed when rash is resolved and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Rash→Grade 4→Permanently discontinue Tecentriq. **Myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome and Meningoencephalitis**→All Grades→Permanently discontinue Tecentriq. **Pancreatitis**→Grade 3 or 4 serum amylase or lipase levels increased (> 2 x ULN) or Grade 2 or 3 pancreatitis→Withhold Tecentriq. Treatment may be resumed when serum amylase and lipase levels improve to Grade 0 or Grade 1 within 12 weeks, or symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Pancreatitis→Grade 4 or any grade of recurrent pancreatitis→Permanently discontinue Tecentriq. **Myocarditis**→Grade 2→Withhold Tecentriq. Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Grade 3 and 4→Permanently discontinue Tecentriq. **Other immune-related adverse reactions**→Grade 2 or Grade 3→Withhold until adverse reactions recovers to Grade 0-1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Grade 4 or recurrent Grade 3→Permanently discontinue Tecentriq (except endocrinopathies controlled with replacement hormones. Patients treated with Tecentriq must be given the Patient Alert Card and be informed about the risks of Tecentriq (see also package leaflet). Special populations. *Paediatric population.* The safety and efficacy of Tecentriq in children and adolescents aged below 18 years have not been established. No data are available. *Elderly.* Based on a population pharmacokinetic analysis, no dose adjustment of Tecentriq is required in patients ≥ 65 years of age. *Renal impairment.* Based on a population pharmacokinetic analysis, no dose adjustment is required in patients with mild or moderate renal impairment (see section 5.2 of SmPC). Data from patients with severe renal impairment are too limited to draw conclusions on this population. *Hepatic impairment.* Based on a population pharmacokinetic analysis, no dose adjustment is required for patients with mild hepatic impairment. Tecentriq has not been studied in patients with moderate or severe hepatic impairment (see section 5.2 of SmPC). *Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2.* Patients with ECOG performance status ≥ 2 were excluded from the clinical trials in NSCLC and 2nd line UC (see sections 4.4 and 5.1 of SmPC). Method of administration. Tecentriq is for intravenous use. The infusions must not be administered as an intravenous push or bolus. The initial dose of Tecentriq must be administered over 60 minutes. If the first infusion is well tolerated, all subsequent infusions may be administered over 30 minutes. For instructions on dilution and handling of the medicinal product before administration, see section 6.6 of SmPC. CONTRAINDICATIONS Hypersensitivity to atezolizumab or to any of the excipients listed in section 6.1 of SmPC. UNDESIRABLE EFFECTS *Summary of the safety profile.* The safety of Tecentriq is based on pooled data in 2,160 patients with metastatic UC and NSCLC. The most common adverse reactions were fatigue (35.4%), decreased appetite (25.5%), nausea (22.9%), dyspnoea (21.8%), diarrhoea (18.6%), rash (18.6%), pyrexia (18.3%), vomiting (15.0%), arthralgia (14.2%), asthenia (13.8%) and pruritus (11.3%). *Tabulated list of adverse reactions.* The Adverse Drug Reactions (ADRs) are listed below by MedDRA system organ class (SOC) and categories of frequency. The following categories of frequency have been used: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness. **Table 2: Summary of adverse reactions occurring in patients treated with Tecentriq in clinical trials. Blood and lymphatic system disorders**: Common, thrombocytopenia. **Immune system disorders**: Common, hypersensitivity. **Endocrine disorders:** Common, hypothyroidism[a], hyperthyroidism[b] - Uncommon, diabetes mellitus[c], adrenal insufficiency[d] – Rare, hypophysitis. **Metabolism and nutrition disorders:** Very common, decreased appetite – Common, hypokalaemia, hyponatremia. **Nervous system disorders:** Uncommon, Guillain-Barré syndrome[e], noninfective meningitis[f] – Rare, noninfective encephalitis[g], myasthenic syndrome[h]. **Cardiac disorders:** rare, myocarditis[h]. **Vascular disorders**: Common, hypotension. **Respiratory, thoracic, and mediastinal disorders:** Very Common, dyspnoea – Common, pneumonitis[i], hypoxia, nasal congestion. **Gastrointestinal disorders:** Very common, nausea, vomiting, diarrhoea - Common, abdominal pain, colitis[j], dysphagia - Uncommon, pancreatitis[k], lipase increased - Rare, amylase increase. **Hepatobiliary disorders**: Common, AST increased, ALT increased - Uncommon, hepatitis[l]. **Skin and subcutaneous tissue disorders**: Very Common rash[m], pruritus. **Musculoskeletal and connective tissue disorders**: Very common, arthralgia - Common, musculoskeletal pain. **General disorders and administration site conditions:** Very Common pyrexia, fatigue, asthenia – Common, infusion related reaction, influenza like illness, chills. [a] Includes reports of hypothyroidism, blood thyroid stimulating hormone increased, thyroiditis, blood thyroid stimulating hormone decreased, myxoedema, thyroid function test abnormal, thyroiditis acute, thyroxine decreased. [b] Includes reports of hyperthyroidism, blood thyroid stimulating hormone increased, thyroiditis, blood thyroid stimulating hormone decreased, endocrine ophthalmopathy, exophthalmus, thyroid function test abnormal, thyroiditis acute, thyroxine decreased. [c] Includes reports of diabetes mellitus and type 1 diabetes mellitus. [d] Includes reports of adrenal insufficiency, primary adrenal insufficiency, and Addison's disease. [e] Includes reports of GuillainBarré syndrome and demyelinating polyneuropathy. [f] Includes reports of meningitis. [g] Includes reports of encephalitis. [h] Reported in studies other than those in metastatic UC and NSCLC patients. The frequency is based on the exposure in 8,000 patients across all atezolizumab clinical trials. [i] Includes reports of pneumonitis, lung infiltration, bronchiolitis, interstitial lung disease, radiation pneumonitis. [j] Includes reports of colitis, autoimmune colitis, colitis ischaemic, colitis microscopic. [k] Includes reports of pancreatitis and pancreatitis acute. [l] Includes reports of autoimmune hepatitis, hepatitis, hepatitis acute. [m] Includes reports of acne, eczema, erythema, erythema of eyelid, erythema multiforme, exfoliative rash, eyelid rash, folliculitis, furuncle, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, dermatitis exfoliative, drug eruption, palmarplantar erythrodysaesthesia syndrome, rash, rash erythematous, rash generalised, rash macular, rash maculopapular, rash papular, rash papulosquamous, rash pruritic, rash pustular, seborrhoeic dermatitis, skin exfoliation, skin toxicity, skin ulcer, toxic skin eruption. Description of selected adverse reactions. The data below reflect exposure to atezolizumab for clinically significant adverse reactions in clinical studies (see section 5.1 of SmPC). The management guidelines for these adverse reactions are described in sections 4.2 and 4.4 of SmPC. *Immunerelated pneumonitis.* Pneumonitis occurred in 3.1% (68/2,160) of patients who received atezolizumab for metastatic UC and NSCLC. Of the 68 patients, one experienced a fatal event. The median time to onset was 3.5 months (range 3 days to 20.5 months). The median duration was 1.5 months (range 0 days to 15.1 + months; + denotes a censored value). Pneumonitis led to discontinuation of atezolizumab in 10 (0.5 %) patients. Pneumonitis requiring the use of corticosteroids occurred in 1.6% (34/2,160) of patients receiving atezolizumab. *Immunerelated hepatitis.* Hepatitis occurred in 0.3% (7/2,160) of patients who received atezolizumab for metastatic UC and NSCLC. The median time to onset was 1.1 months (range 9 days to 7.9 months). The median duration was 1 month (range 9 days to 1.9+ months; + denotes a censored value). Hepatitis led to discontinuation of atezolizumab in 2 (< 0.1%) patients. Hepatitis requiring the use of corticosteroids occurred in 0.2% (5/2,160) of patients receiving atezolizumab. *Immunerelated colitis.* Colitis occurred in 1.1% (23/2,160) of patients who received atezolizumab for metastatic UC and NSCLC. The median time to onset was 4 months (range 15 days to 15.2 months). The median duration was 1.4 months (range 3 days to 17.8+ months; + denotes a censored value). Colitis led to discontinuation of atezolizumab in 5 (0.2%) patients. Colitis requiring the use of corticosteroids occurred in 0.5% (10/2,160) of patients receiving atezolizumab. *Immunerelated endocrinopathies.* Hypothyroidism occurred in 4.7% (101/2,160) of patients who received atezolizumab for metastatic UC and NSCLC. The median time to onset was 5.5 months (range 21 days to 31.3 months). Hyperthyroidism occurred in 1.7% (36/2,160) of patients who received atezolizumab for metastatic UC and NSCLC. The median time to onset was 3.5 months (range 21 days to 31.3 months). Adrenal insufficiency occurred in 0.3% (7/2,160) of patients who received atezolizumab for metastatic UC and NSCLC. The median time to onset was 5.7 months (range: 3 days to 19 months). Adrenal insufficiency requiring the use of corticosteroids occurred in 0.3% (6/2,160) of patients receiving atezolizumab. Hypophysitis occurred in < 0.1% (1/2,160) of patients who received atezolizumab for metastatic UC and NSCLC. The time to onset for this patient was 13.7 months. Diabetes mellitus occurred in 0.3% (6/2,160) of patients who received atezolizumab for metastatic UC and NSCLC. The time to onset ranged from 3 days to 6.5 months. Diabetes mellitus led to the discontinuation of atezolizumab in 1 (< 0.1%) patient. *Immunerelated meningoencephalitis.* Meningitis occurred in 0.1% (3/2,160) of patients who received atezolizumab for metastatic UC and NSCLC. The time to onset ranged from 15 to 16 days. All three patients required the use of corticosteroids and discontinued atezolizumab. Encephalitis occurred in < 0.1% (2/2,160) of patients who received atezolizumab for metastatic UC and NSCLC. The time to onset was 14 and 16 days. Encephalitis led to discontinuation of atezolizumab in 1 (< 0.1%) patient. Encephalitis requiring the use of corticosteroids occurred in < 0.1% (1/2,160) of patients receiving atezolizumab. *Immunerelated neuropathies.* GuillainBarré syndrome and demyelinating polyneuropathy occurred in 0.2% (5/2,160) of patients who received atezolizumab for metastatic UC and NSCLC. The median time to onset was 7 months (range: 18 days to 8.1 months). The median duration was 4.6 months (0+ day to 8.3+ months; + denotes a censored value). GuillainBarré syndrome led to discontinuation of atezolizumab in 1 patient (< 0.1%). GuillainBarré syndrome requiring the use of corticosteroids occurred in < 0.1% (2/2,160) of patients receiving atezolizumab. *Myasthenic syndrome.* Myasthenia gravis occurred in < 0.1% (4/6,000) of patients across all atezolizumab clinical trials in multiple tumour types. The time to onset ranged from 20 days to 4 months. All four patients discontinued atezolizumab. Myasthenic syndrome/myasthenia gravis requiring the use of corticosteroids occurred in < 0.1% (3/6,000) of patients receiving atezolizumab. *Immunerelated pancreatitis.* Pancreatitis, including amylase increased and lipase increased, occurred in 0.5% (10/2,160) of patients who received atezolizumab for metastatic UC and NSCLC. The median time to onset was 5.5 months (range: 9 days to 16.9 months). The median duration was 19 days (range 3 days to 11.2+ months; + denotes a censored value). Pancreatitis requiring the use of corticosteroids occurred in < 0.1% (2/2,160) of patients receiving atezolizumab. *Immune-related myocarditis.* Myocarditis occurred in < 0.1% (2/8,000) of patients across all atezolizumab clinical trials in multiple tumour types. The time to onset was 18 and 33 days. Both patients required corticosteroids and discontinued atezolizumab. *Immunogenicity.* In study IMvigor210, 43.9% of patients tested positive for antiatezolizumab antibodies (ATAs) at one or more postdose time points. In study OAK (GO28915), the treatmentemergent ATA rate was 30.4%. Overall, ATA positivity appeared to have no clinically relevant impact on pharmacokinetics, efficacy or safety. No data are available to allow conclusions to be drawn on any possible effect of neutralising antibodies. Reporting of suspected adverse reactions. Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system. *België/Belgique* : Federaal agentschap voor geneesmiddelen en gezondheidsproducten /Agence fédérale des médicaments et des produits de santé - Afdeling Vigilantie / Division Vigilance -EUROSTATION II, Place Victor Hortaplein, 40/ 40 - B-1060 Brussel/ Bruxelles - Website: www.fagg.be / Site internet: www.afmps.be - e-mail: adversedrugreactions@fagg-afmps.be – *Luxembourg* : Direction de la Santé – Division de la Pharmacie et des Médicaments, Villa Louvigny – Allée Marconi, L-2120 Luxembourg, Site internet: http://www.ms.public.lu/fr/activites/pharmacie-medicament/index.html MARKETING AUTHORISATION HOLDER Roche Registration GmbH, Emil-Barell-Strasse 1, 79639 Grenzach-Wyhlen, Germany MARKETING AUTHORISATION NUMBER EU/1/17/1220/001 MODE OF DELIVERY on medical prescription DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION 21 September 2017 DATE OF REVISION OF TEXT. 04/04/2018 Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu . R.E. Dr. Chr. Lenaerts - BE/TCN/0418/0013 – 10/04/2018

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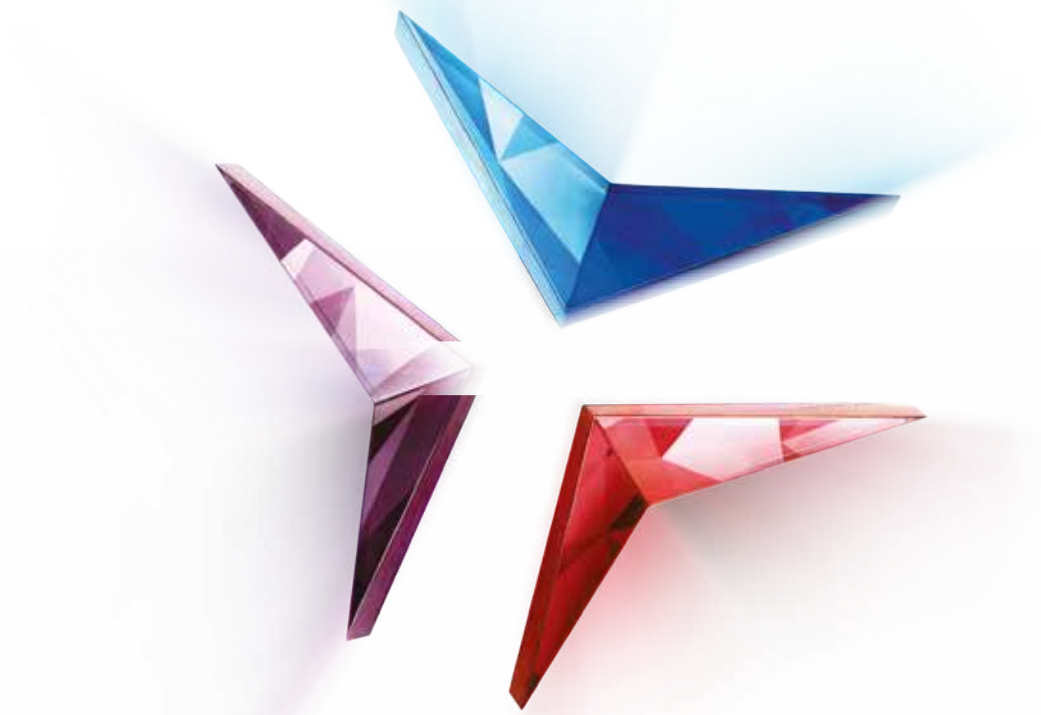

TECENTRIQ (ATEZOLIZUMAB) AS MONOTHERAPY IS REIMBURSED FOR THE TREATMENT OF ADULT PATIENTS WITH

locally advanced or metastatic urothelial carcinoma (UC)
after prior platinum-containing chemotherapy or who are considered cisplatin ineligible.[1]

locally advanced or metastatic non-small cell lung cancer (NSCLC)
after prior chemotherapy.[1]

1. Tecentriq Summary of Product Characteristics

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section "Reporting of suspected adverse reactions" for details on how to report.

R. E.: Dr. Chr. Lenaerts - BE/ TCN /0817/0008a(2)a - 06/03/2018