

2021 Radiotherapy highlights

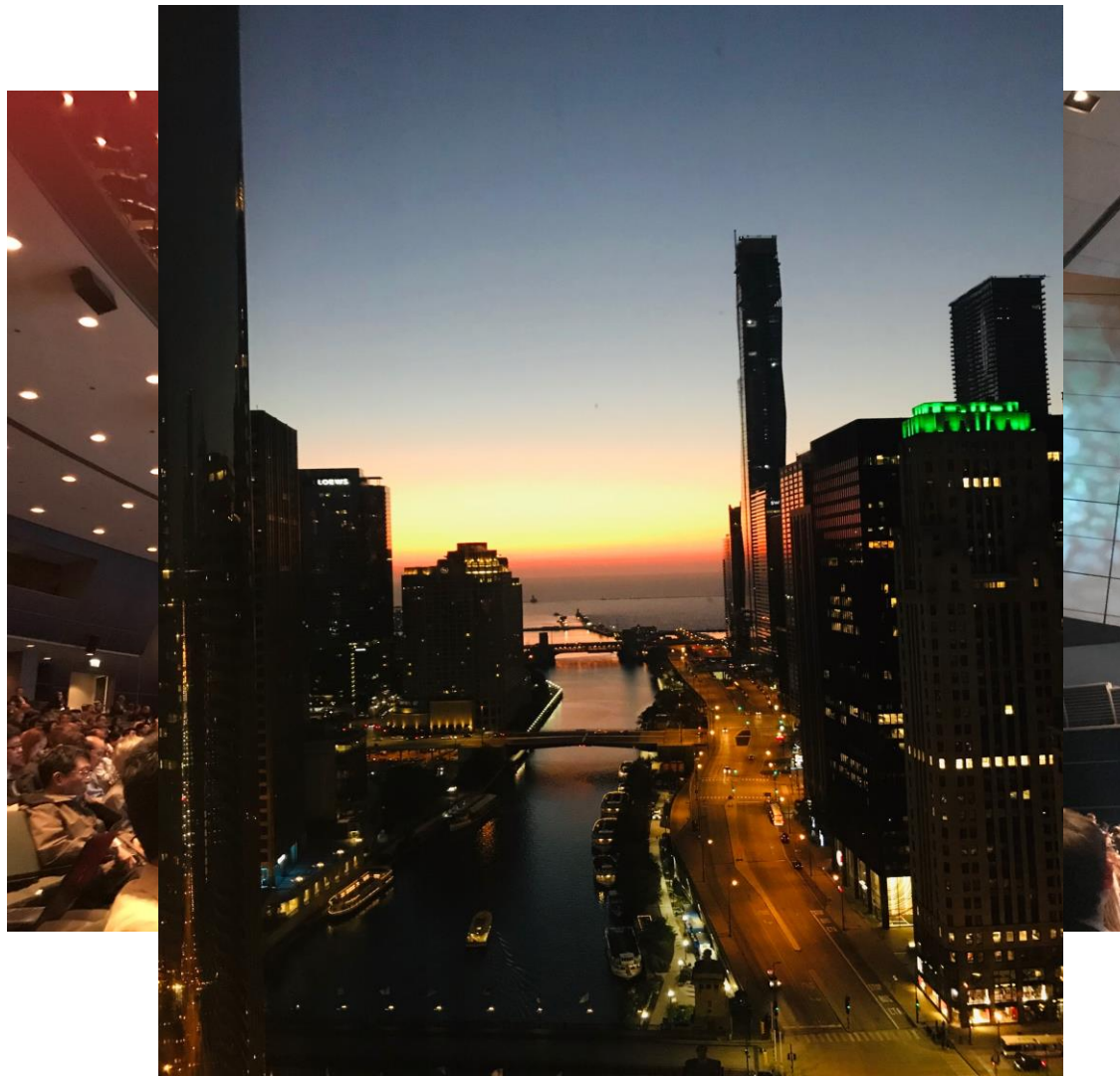
Prof. dr. Benedikt Engels

UZ Brussel, Vrije Universiteit Brussel

Conflicts of interest

- I have no potential conflict of interest to report

Pre vs Post-COVID



Overview



- Prostate cancer
 - Primary setting
 - SBRT
 - High-risk N0-1M0
 - Salvage setting
 - Dose/ADT/pelvic RT
 - Early salvage vs adjuvant
 - Metastatic setting
 - Local RT
- Bladder and renal cancer
 - Hypofractionation and bladder preserving treatments
 - SBRT + immunotherapy

Overview



- **Prostate cancer**

- **Primary setting**

- **SBRT**

- High-risk N0-1M0

- Salvage setting

- Dose/ADT/pelvic RT

- Early salvage vs adjuvant

- Metastatic setting

- Local RT

- **Bladder and renal cancer**

- Hypofractionation and bladder preserving treatments

- SBRT + immunotherapy

Late toxicity of SBRT vs standard RT



The ROYAL MARSDEN
NHS Foundation Trust

ICR The Institute of
Cancer Research

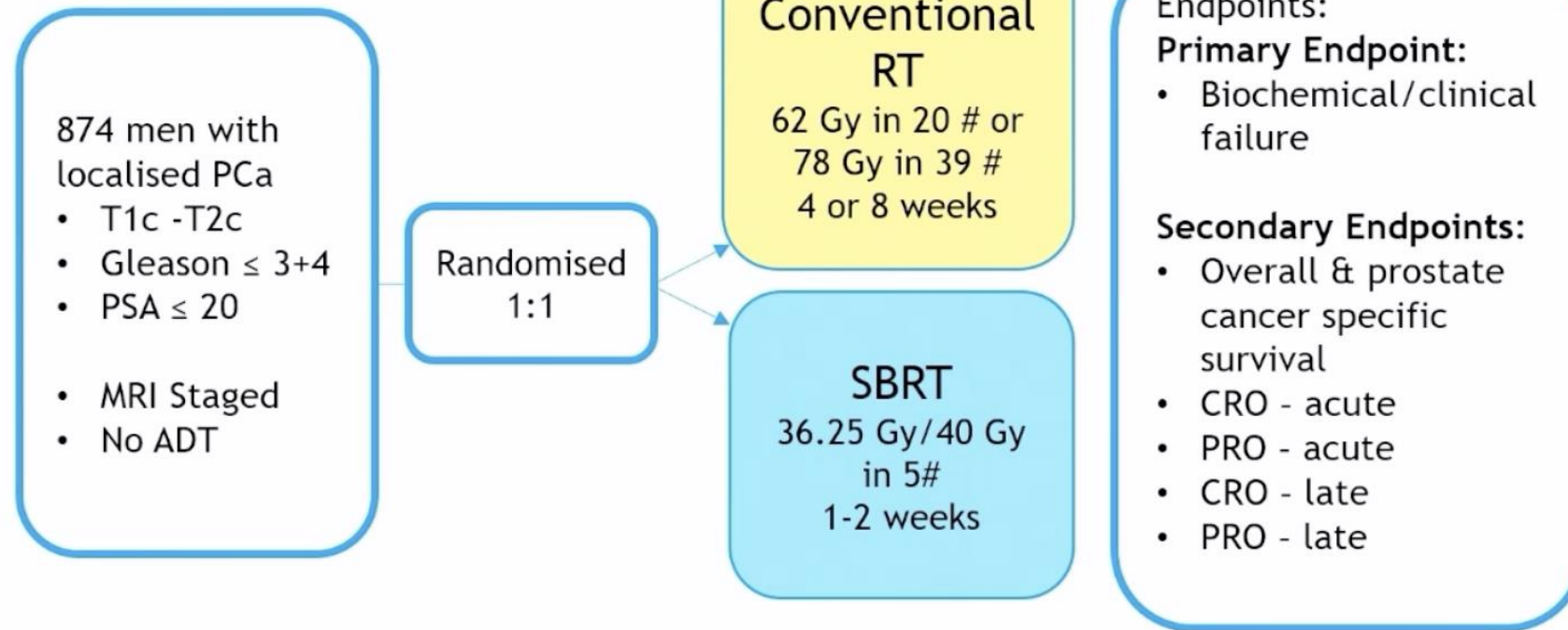
ESTRO2021

Comparison of side effects at 2 years in the randomised PACE-B trial (SBRT vs standard radiotherapy for prostate cancer)

Alison C Tree , Emma Hall, Peter Ostler, Hans van der Voet, Andrew Loblaw, William Chu,
Daniel Ford, Shaun Tolan, Suneil Jain, Alexander Martin, John Staffurth, Philip Camilleri,
Kiran Kancharla, John Frew, Douglas H Brand, Andrew Chan, Ian S Dayes, Stephanie Brown,
Julia Pugh, Stephanie Burnett, Aileen Dufton, Clare Griffin, Muneeb Mahmud, Olivia
Naismith, Nicholas van As on behalf of the PACE Trial Investigators



PACE B trial schema

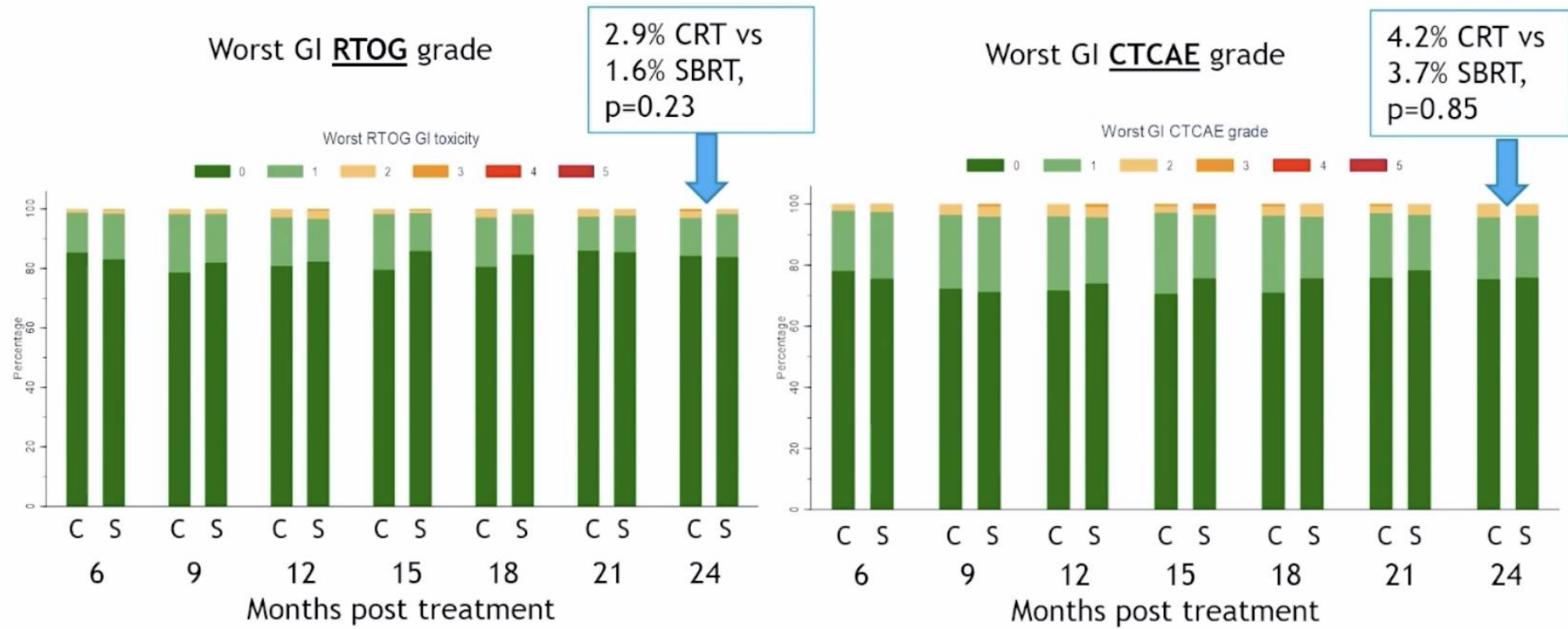


ESTRO2021



No difference in Gastrointestinal G2+ toxicity at 2 years

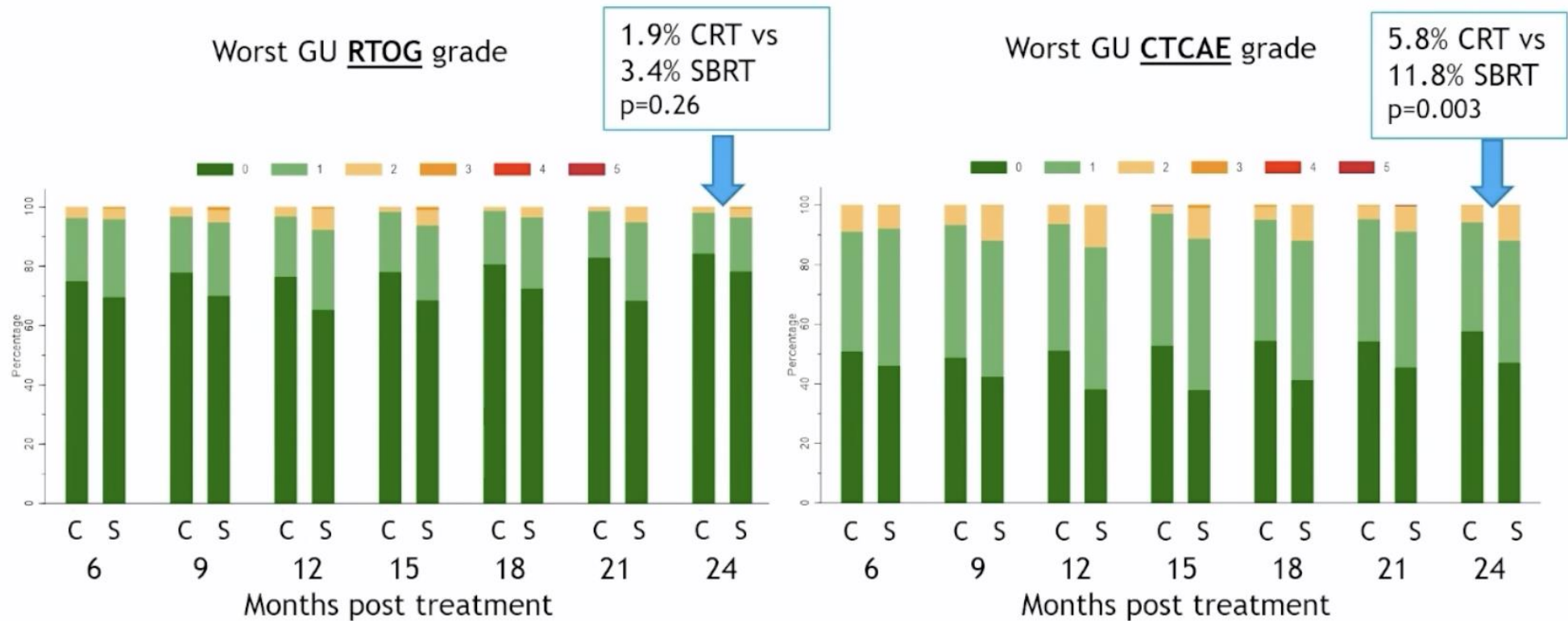
ESTRO 2021

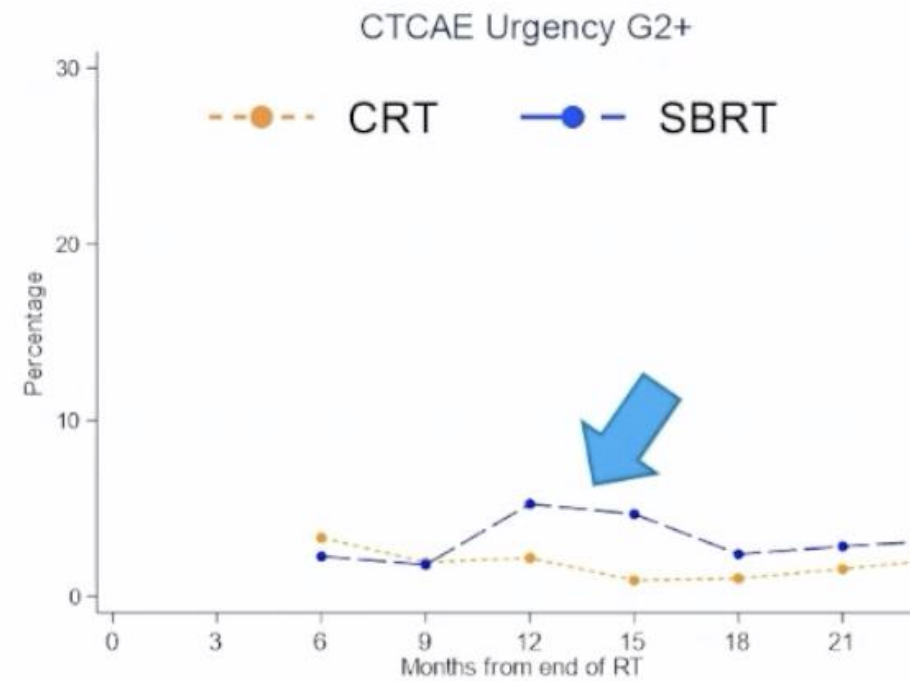
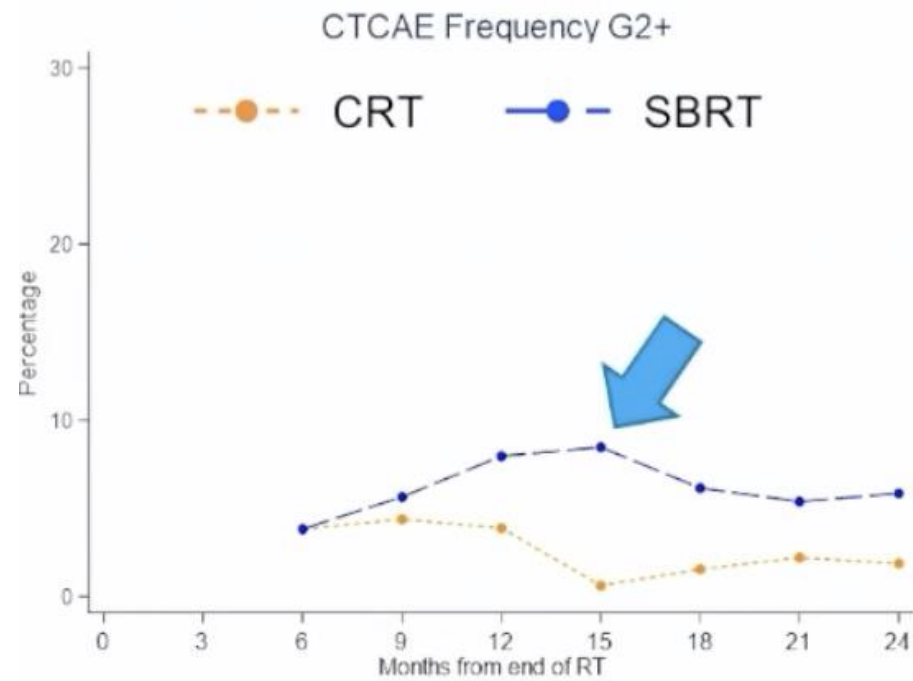




Higher CTCAE Genitourinary G2+ toxicity at 2 years after SBRT

ESTRO 2021

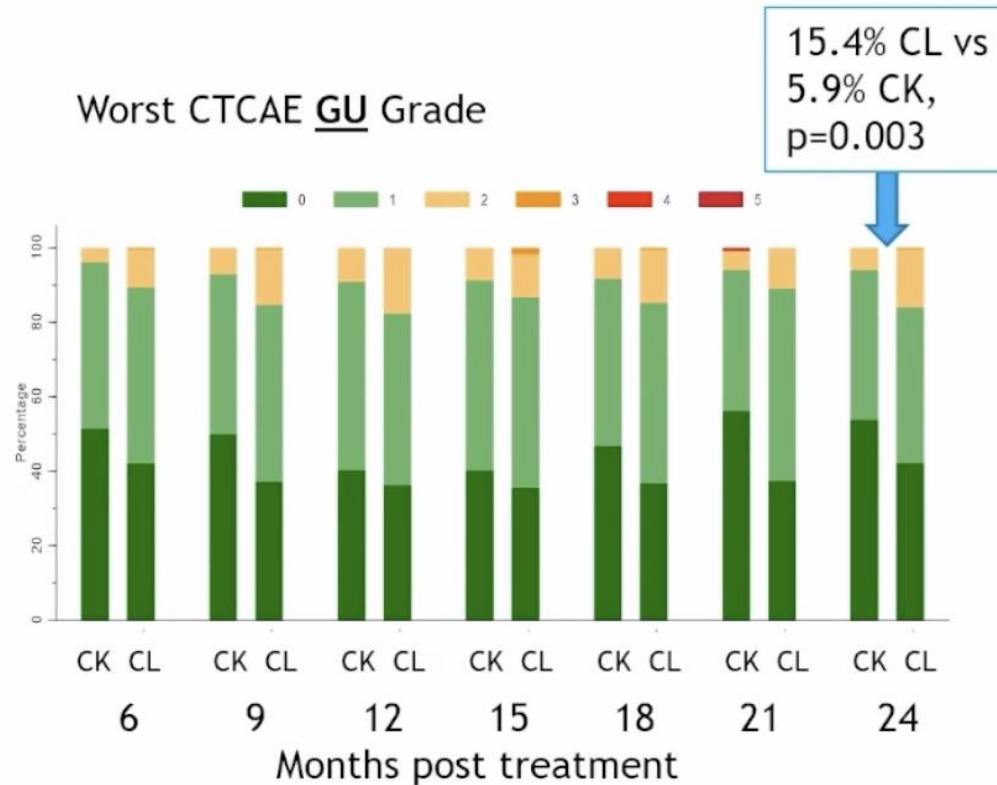
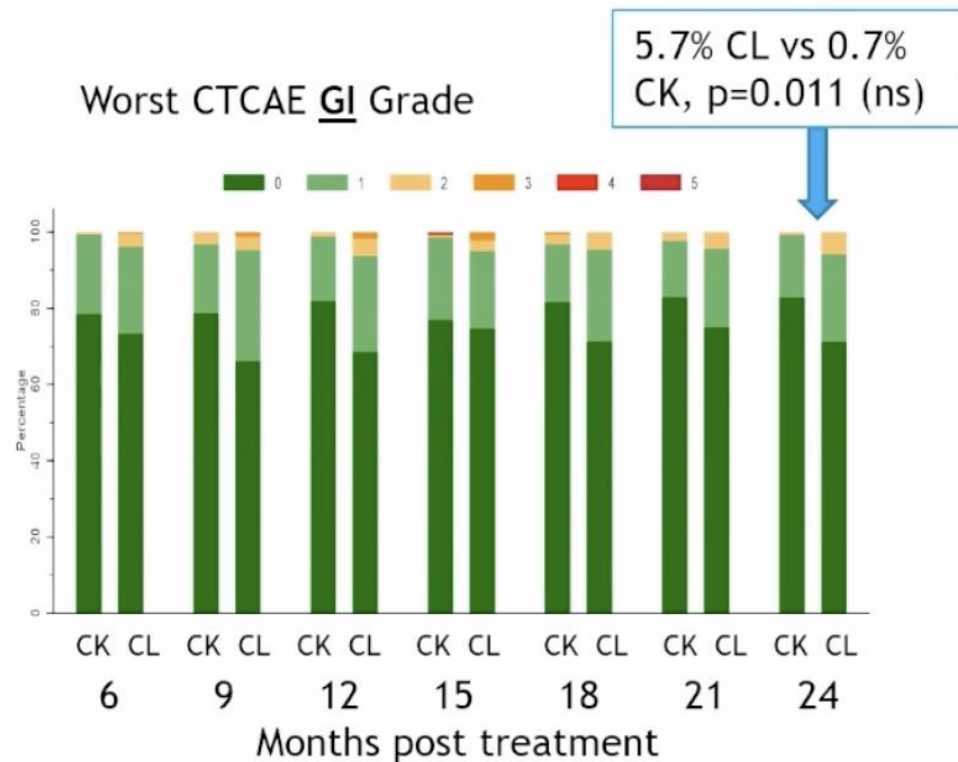






Is there a difference between Cyberknife (CK) and conventional linac (CL) SBRT?

ESTRO2021



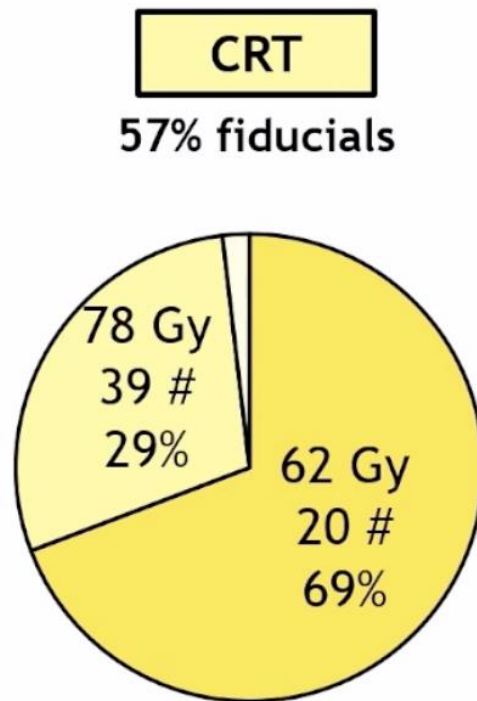
Reflections



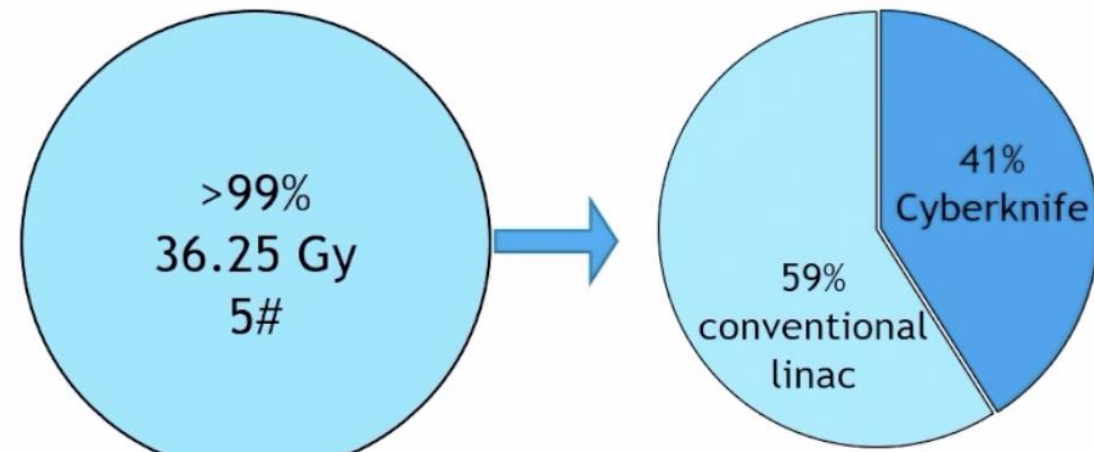
- The difference in GI and GU toxicity between Cyberknife and linac-based SBRT is hypothesis-generating and further exploration in multivariate analysis is warranted
- Factors which may influence toxicity positively:
 - smaller *prostatic volumes* and more favourable *baseline GU symptoms*
 - more *bladder neck* ($V_{37\text{Gy}} < 5 - 10\text{cc}$) and *rectal wall dose* reduction
 - lower *max urethral dose* ($V_{42\text{Gy}} < 50\%$, not mandatory)
 - longer *overall treatment time* (EOD vs 1 week)
 - long *beam-on time*
 - *MRI for planning*
 - *fiducials* and *intra-fraction motion control*, but this was always the case in linac based SBRT?

Prostate plus 1cm seminal vesicles treated
Daily IGRT to prostate mandatory

ESTRO 2021



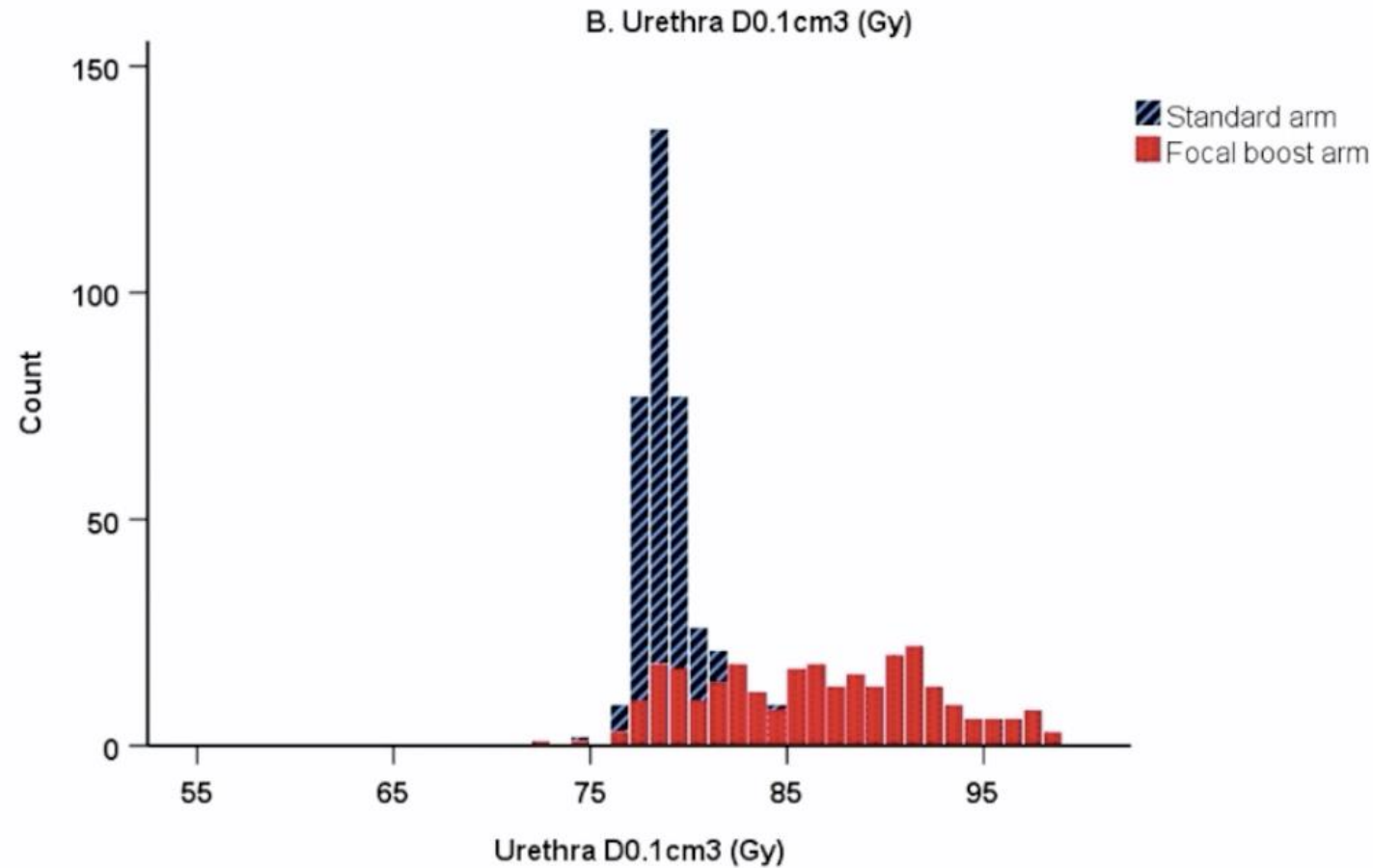
SBRT
73% fiducials
Prescribed as ICRU 91



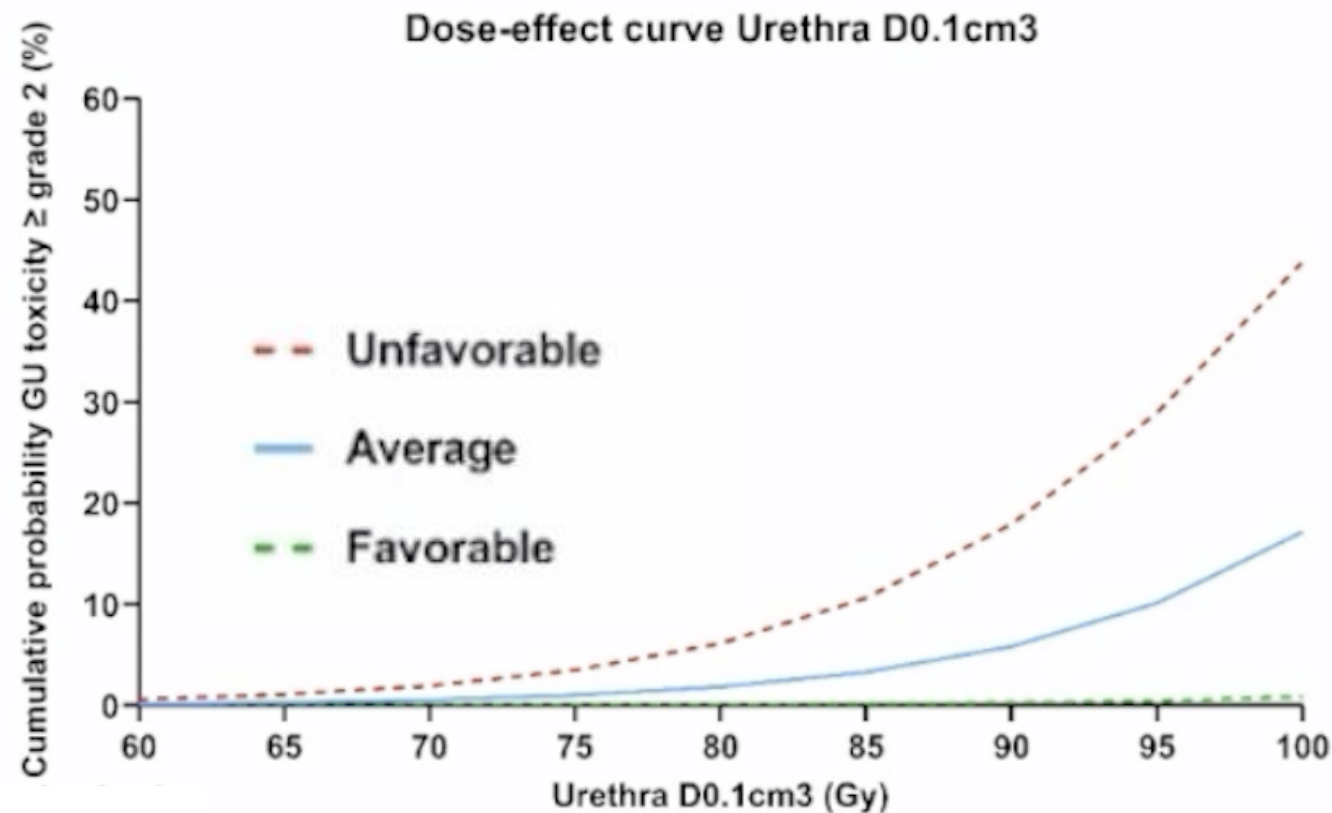
28% fiducials + cone-beam CT

27% no fiducials + cone-beam CT

Urethra dose-effect relation for GU toxicity



Urethra dose-effect relation for GU toxicity



Unfavorable risk group

- Higher T-stage (T3b or T4)
- Diabetes mellitus
- Baseline GU toxicity grade ≥ 1

Overview



- **Prostate cancer**

- **Primary setting**

- SBRT

- **High-risk N0-1M0**

- Salvage setting

- Dose/ADT/pelvic RT

- Early salvage vs adjuvant

- Metastatic setting

- Local RT

- **Bladder and renal cancer**

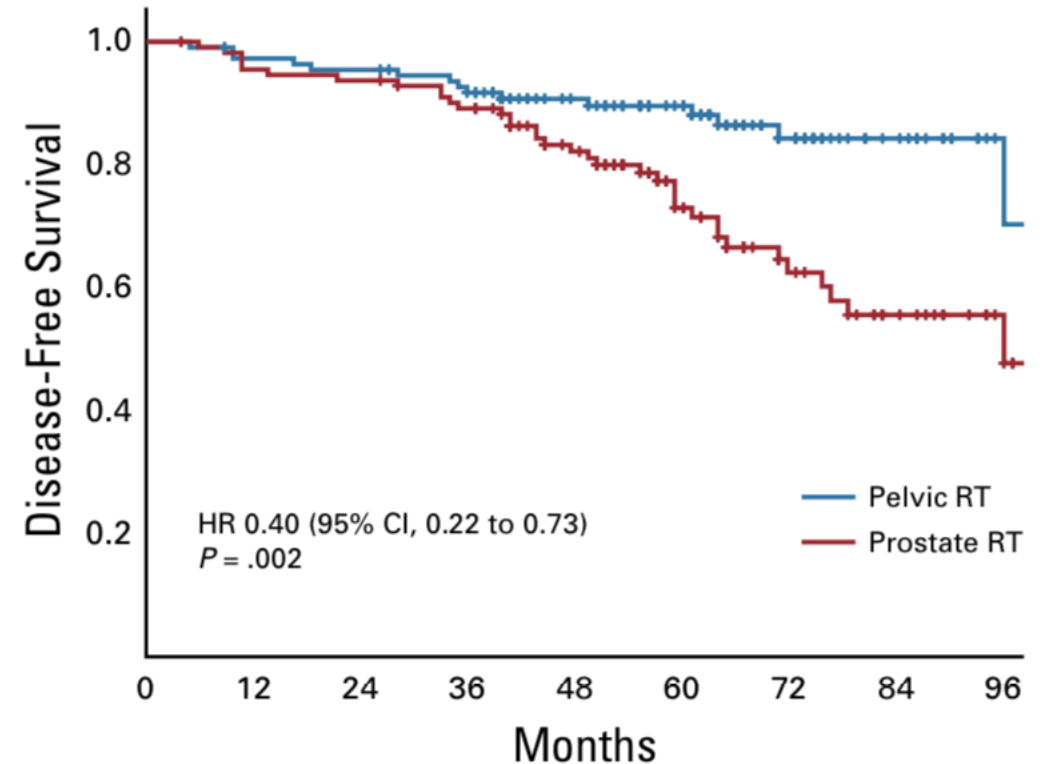
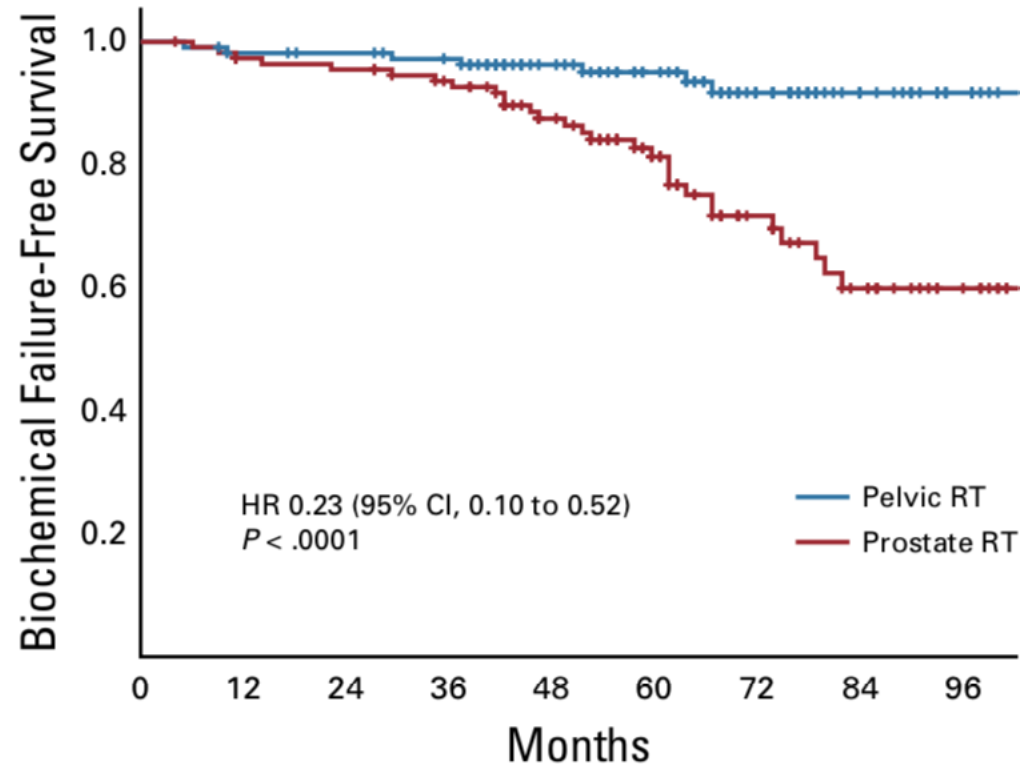
- Hypofractionation and bladder preserving treatments

- SBRT + immunotherapy

Prostate RT +/- pelvic RT in (very-)high N0M0



- 68 Gy/25fr vs 68/25fr + 50Gy/25fr to pelvic nodes **including common iliac**
- 80% staged by PSMA-PET/CT, median estimated Roach nodal risk 38%



Patterns of disease recurrence

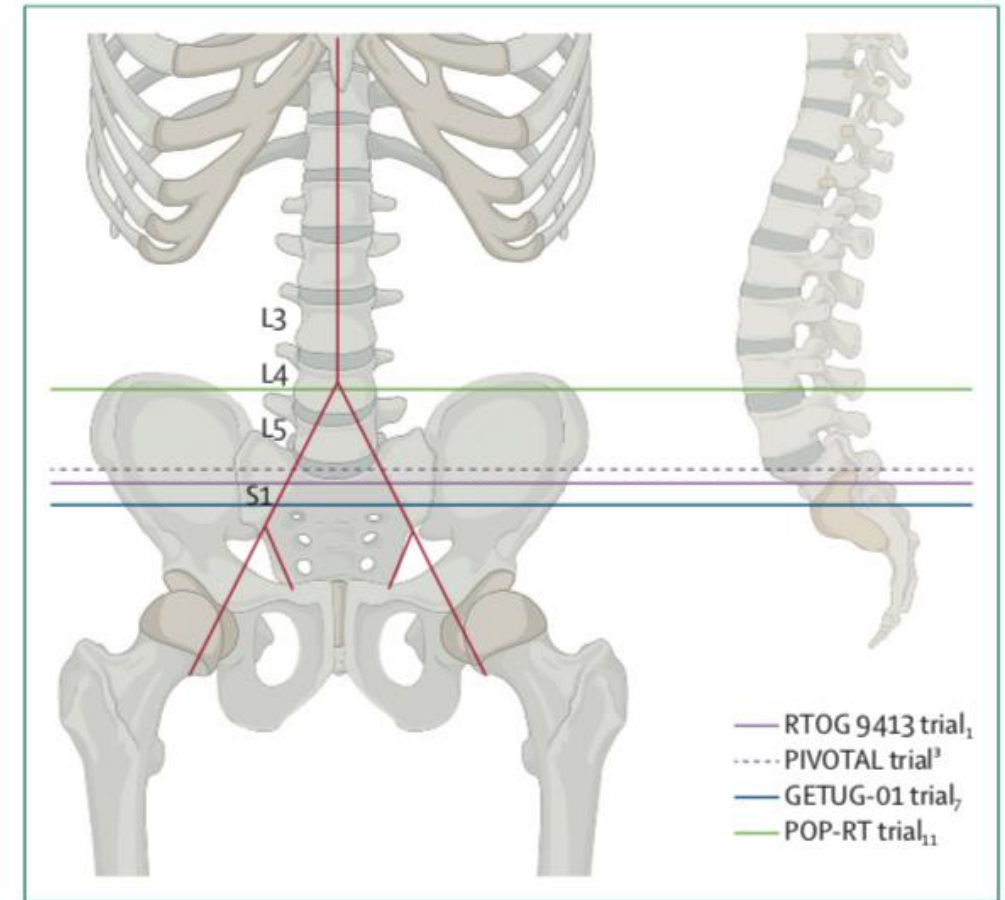


Site of recurrence	Whole pelvic radiotherapy	Prostate-only radiotherapy
Regional pelvic nodes (Total)	1	15
• Regional only	0	3
• Regional with distant metastases	1	11
• Regional with local recurrence	0	1
Distant metastases		
• Distant metastases only	4	5
• With local recurrence	1	2
Local recurrence only	0	1
No radiological disease (only biochemical failure)	0	2
Pattern unknown	2	4
Total	8*	29

Elective nodal RT in prostate cancer

Conclusion

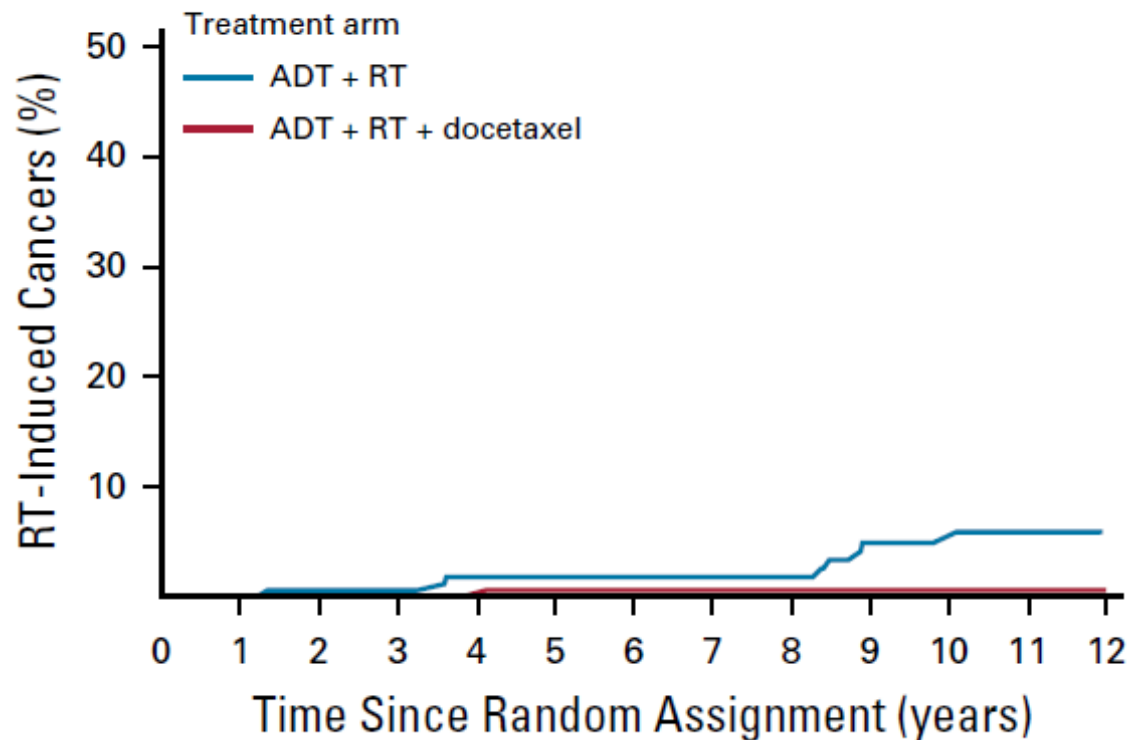
New data suggest a substantial benefit for elective nodal radiotherapy in patients with high risk of pathologically positive pelvic lymph nodes. Although a clear cutoff is still not decided, we propose that a risk of lymph node invasion more than 35%, using the Roach formula, should lead to elective nodal radiotherapy. The biological dose to the prostate and seminal vesicles should be at least 78 Gy. A biological dose of 50 Gy should be considered for the pelvic nodal areas. The upper border of the pelvic field should encompass the bifurcation of the abdominal aorta



RT + ADT +/- docetaxel in NOMO



- No effect on OS
 - Less RT-induced cancers
 - Reduced prostate cancer-specific mortality in subgroup with PSA < 4ng/mL

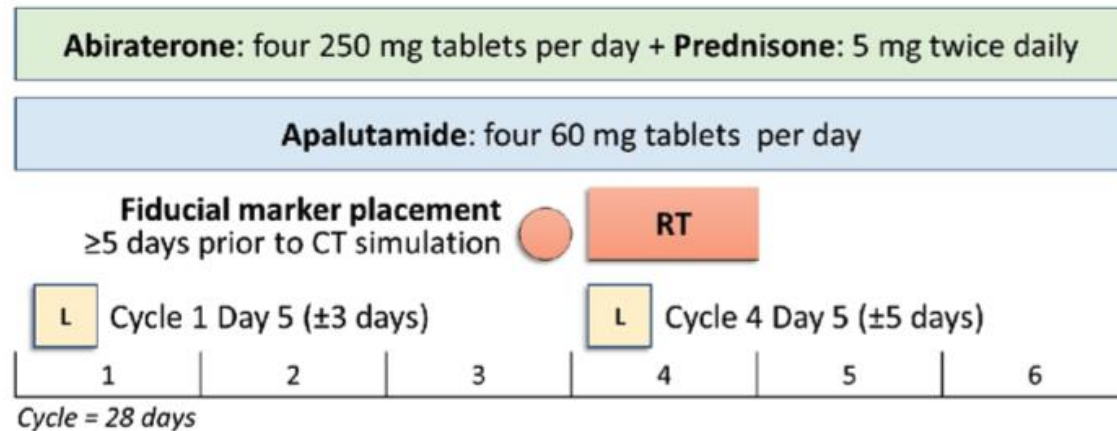


PSA Subgroup	< 4 ng/mL	
Randomized Treatment Arm	ADT + RT	ADT + RT + Docetaxel
Total No. of patients	14	13
Total No. of deaths	6	2
Cause of death, No. (%)		
Prostate cancer	4 (28.57)	0 (0.00)

RT + ADT + apa/abi in very high risk NOMO

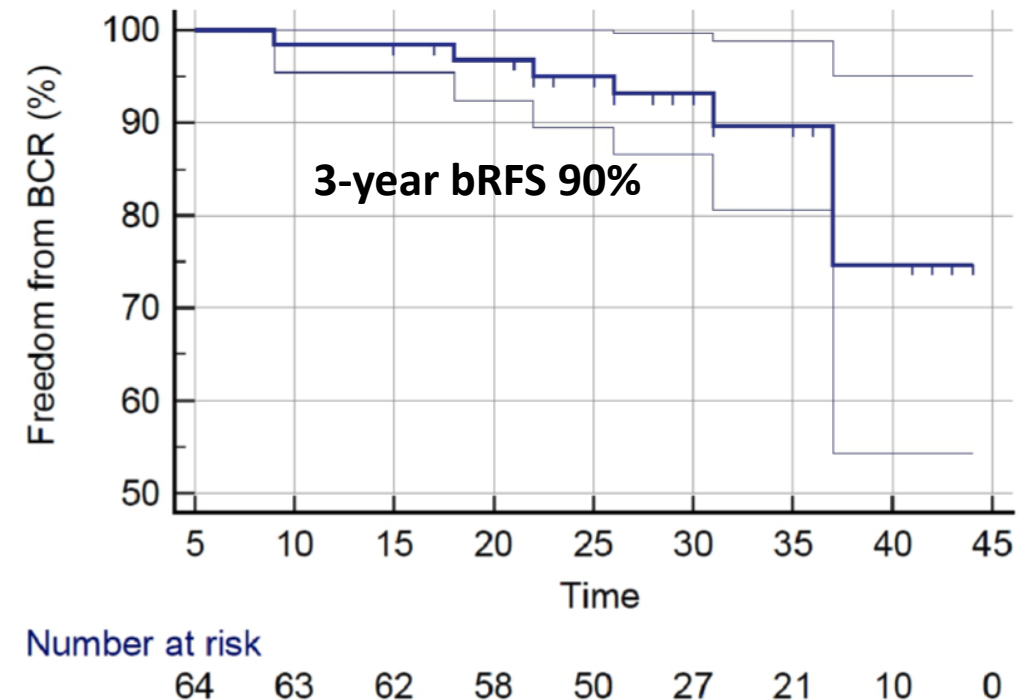


- 70% Gleason 9-10
- Early multi-drug approach



L = Leuprolide: 22.5 mg 3-month depot intramuscular injection

RT = Ultra-hypofractionated radiation therapy: 7.5-8 Gy x 5 fractions to prostate and seminal vesicles every other day for five total treatments.



- Reduction of ADT exposure and duration/volume of RT (SBRT, no elective nodal RT)

RT + ADT + 2 years abi in high risk NO-1M0



Abiraterone acetate plus prednisolone with or without enzalutamide added to androgen deprivation therapy compared to ADT alone for men with high-risk nonmetastatic prostate cancer: primary combined analysis from two comparisons in the STAMPEDE platform protocol

Gerhardt Attard, Louise Brown, Noel Clarke, Laura Murphy, William Cross, Rob Jones, Silke Gillessen, J.Martin Russell, Adrian Cook, Jo Bowen, Anna Lydon, Ian Pedley, Omi Parikh, Simon Chowdhury, Zafar Malik, David Matheson, Chris Parker, Matthew Sydes, Mahesh Parmar, Nicholas James **on behalf of the STAMPEDE investigators***

Conducted by Medical Research Council Trials Unit at University College London, U.K.

ClinicalTrials.gov number, NCT00268476 & Current Controlled Trials number, ISRCTN78818544

*113 U.K. and Swiss sites: list of investigators and collaborators at www.stampetrial.org

www.stampetrial.org

Attard et al, ESMO 2021

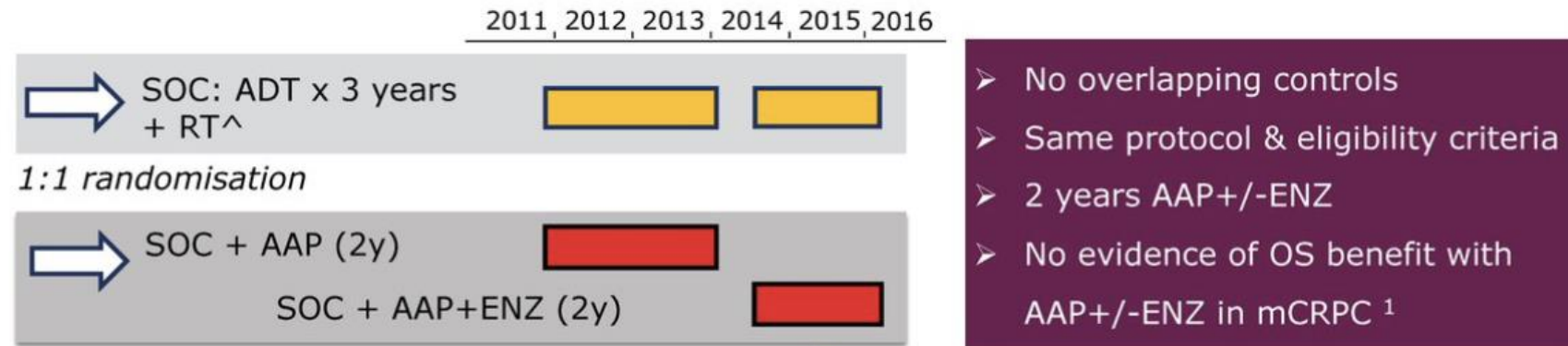


RT + ADT + 2 years abi in high risk N0-1M0



Study design

- M0 pts in AAP comparison: continued FU with **no further** efficacy inspections
- 2019 - amended the reporting plan* to split M1 & M0, power the 1^{ary} end-point on MFS, meta-analyse with new data from AAP+ENZ comparison



*published as a pre-specified declaration of our intentions: Attard G, et al. Eur Urol. Epub 2021 Jul 14



Gerhardt Attard MD FRCP PhD

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

SOC, standard of care
^when indicated

¹Morris MJ, et al. J Clin Oncol 2019;37:5008

RT + ADT + 2 years abi in high risk N0-1M0



Patient population

M0

No evidence of metastases on bone and CT scan of pelvis, abdo, chest
(pre-defined stratification criterion)

Newly-diagnosed

Any of:

- Node-Positive
- ≥ 2 of: Stage T3 or T4
PSA ≥ 40 ng/ml
Gleason 8, 9 or 10

Relapsing after previous RP or RT

Any of:

- Node-positive
- PSA ≥ 4 ng/ml, rising & doubling time < 6 m
- PSA ≥ 20 ng/ml

All patients

Written informed consent
Fit for all protocol treatment
Fit for follow-up

Full criteria: www.stampededtrial.org

RT + ADT + 2 years abi in high risk N0-1M0



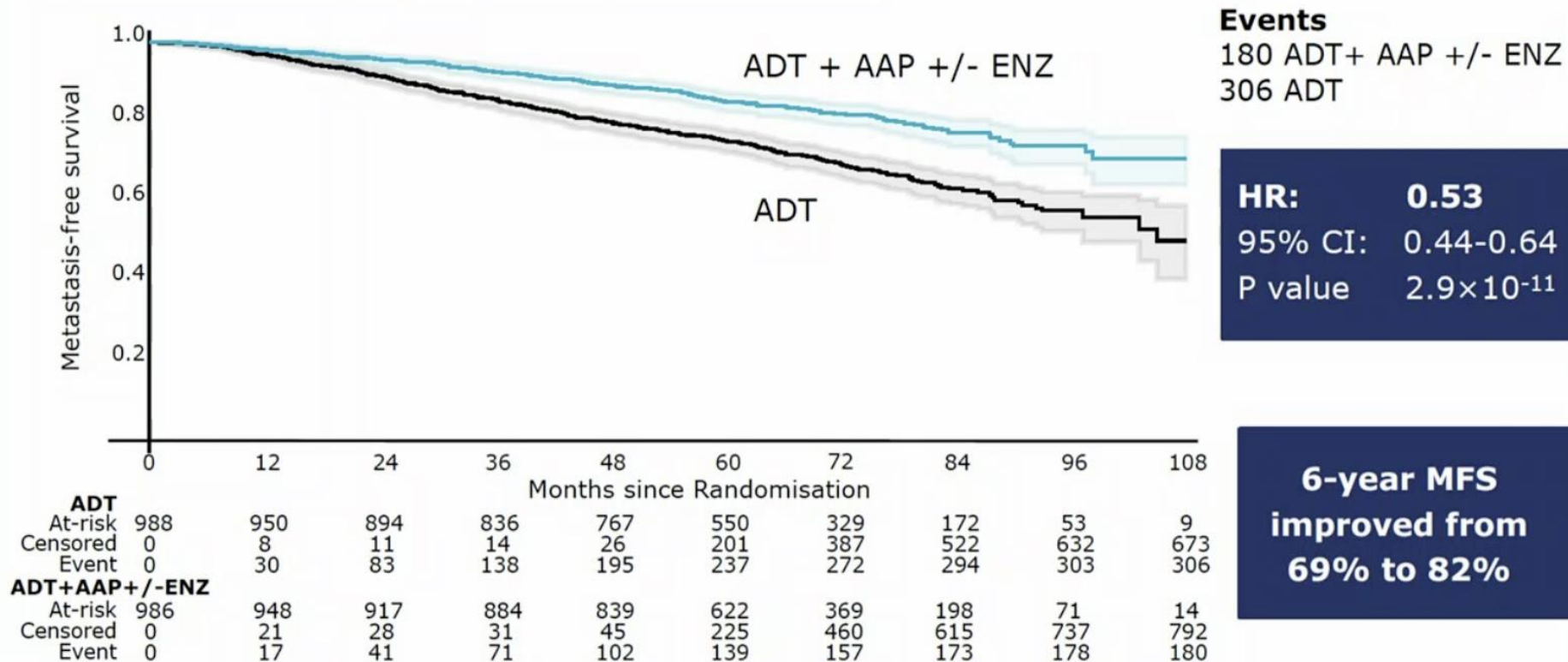
Patient characteristics

- Randomised groups were well balanced (**N=1974**)
- Median age = 68 years
- Median PSA = 34 ng/ml
- N1 = 39%
- 3% relapsing after prior treatment
- Planned for local radiotherapy: - 99% newly-diagnosed, N0
- 71% newly-diagnosed, N1
- 7% previously-treated patients
- Median follow-up = 72 months
(85 months AAP comparison & 60 months AAP+ENZ comparison)

RT + ADT + 2 years abi in high risk NO-1M0



Metastasis-free survival



Kaplan-Meier estimates with 95% CI in lighter shade



Gerhardt Attard MD FRCP PhD

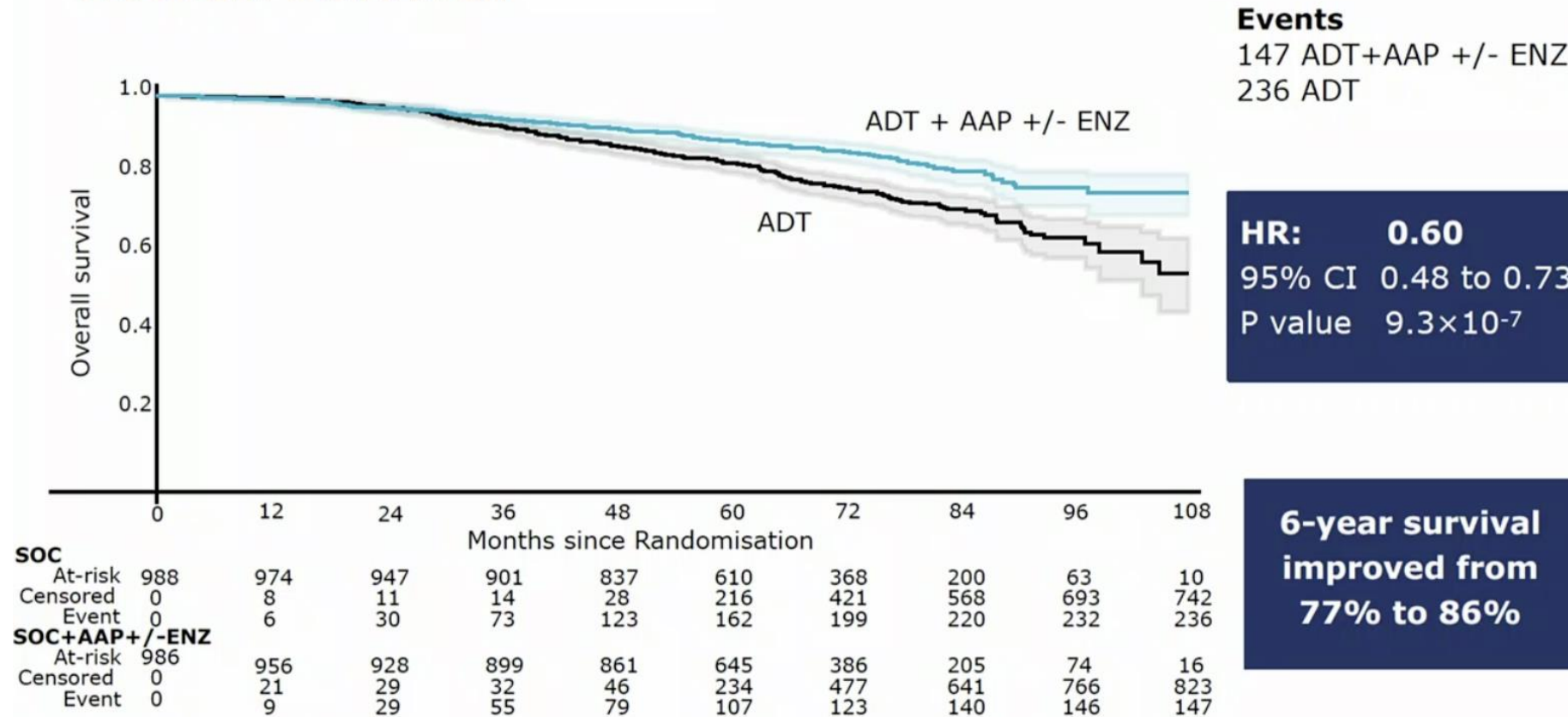
Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

Non-proportional hazards $P=0.46$

RT + ADT + 2 years abi in high risk NO-1M0



Overall survival



Kaplan-Meier estimates with 95% CI in lighter shade



Gerhardt Attard MD FRCP PhD

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

Non-proportional hazards $P=0.1$

RT + ADT + 2 years abi in high risk N0-1M0



Conclusions

- **2 years** of AAP-based therapy significantly improves MFS & overall survival of high-risk M0 PCa starting ADT and should be considered **a new standard of care**
- Adding ENZ to AAP increases toxicity but has no discernible effect on efficacy

Overview



- **Prostate cancer**

- Primary setting
 - SBRT
 - High-risk N0-1M0
- **Salvage setting**
 - **Dose**/ADT/pelvic RT
 - Early salvage vs adjuvant
- Metastatic setting
 - Local RT

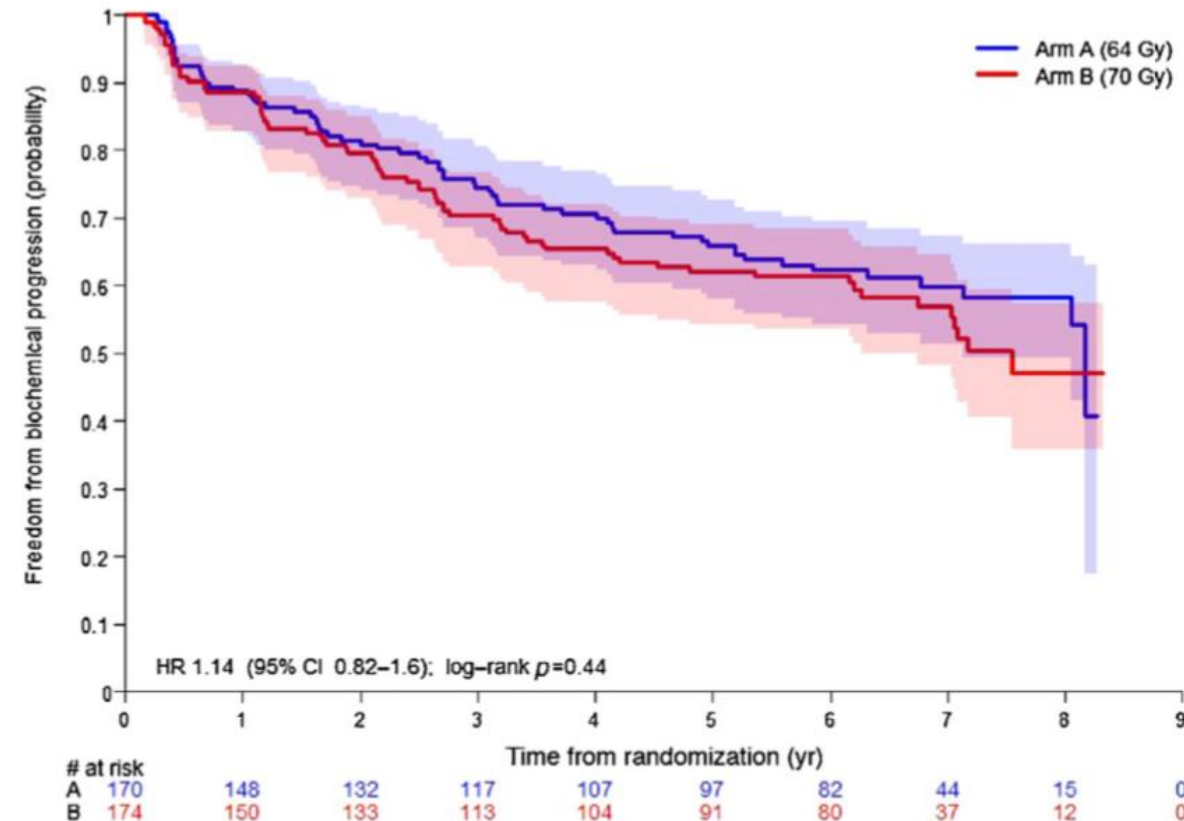
- **Bladder and renal cancer**

- Hypofractionation and bladder preserving treatments
- SBRT + immunotherapy

70Gy vs 64Gy: SAKK 09/10 randomized trial



- 350 patients
- No evidence of macroscopic disease
- No ADT, No pelvic RT



Increase in grade 2 or more late GI toxicity with 70Gy

Overview



- **Prostate cancer**

- Primary setting
 - SBRT
 - High-risk N0-1M0
- **Salvage setting**
 - Dose/**ADT/pelvic RT**
 - Early salvage vs adjuvant
- Metastatic setting
 - Local RT

- **Bladder and renal cancer**

- Hypofractionation and bladder preserving treatments
- SBRT + immunotherapy



Short Term Androgen Deprivation Therapy Without or With Pelvic Lymph Node Treatment Added to Prostate Bed Only Salvage Radiotherapy: The NRG Oncology/RTOG 0534 SUPPORT Trial

A Pollack, TG Karrison, AG Balogh, D Low, DW Bruner, JS Wefel, LG Gomella, E Vigneault, JM Michalski, S Angyal, H Lukka, SL Faria, G Rodrigues, MC Beauchemin, SA Seaward, AM Allen, DC Monitto, W Seiferheld, and HM Sandler

ASTRO 2018

NRG/RTOG 0534/SPPORT Trial Design

A Phase III Trial of Short Term Androgen Deprivation with Pelvic Lymph Node or Prostate Bed Only Radiotherapy (SPPORT) in Prostate Cancer Patients with a Rising PSA after Radical Prostatectomy

S T R A T I F Y	SV Involvement 1. No 2. Yes	R A N D O M I Z E	Arm 1: PBRT Alone PBRT 64.8-70.2 Gy Arm 2: PBRT + STAD PBRT 64.8-70.2 Gy + STAD for 4-6 months beginning 2 months before RT Arm 3: PLNRT + PBRT + STAD PLNRT to 45 Gy and PBRT to 64.8-70.2 Gy, + STAD for 4-6 months beginning 2 months before RT
	Prostatectomy Gleason Score 1. Gleason ≤ 7 2. Gleason 8-9		
	Pre-Radiotherapy PSA 1. PSA ≥ 0.1 and ≤ 1.0 ng/mL 2. PSA > 1.0 and < 2.0 ng/mL		
	Pathology Stage 1. pT2 and margin negative 2. All others		

Primary endpoint FFP at 5 years:

- PSA $\geq$ nadir + 2 ng/mL
- clinical progression (local, regional, distant)
- death due to any cause

PBRT +/- ADT +/- PLNRT



SPPORT: Patient Characteristics

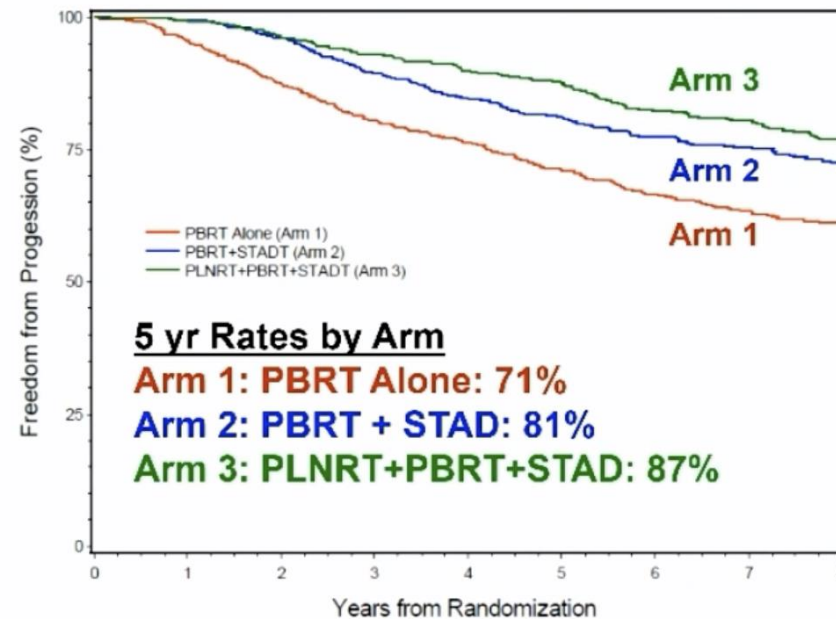
Assessable: 1716 pts
Median FU: 8.2 yr
Median age: 64 yr
Median entry PSA: 0.35 ng/mL
PSADT (n=471): 43% >12 mo
Median time from surgery: 2.1 yr
Seminal Vesical Invasion: 15%
pT3: 47%
GLSC 7: 68%; GLSC 9-8: 17%
Margin+: 50%
Pelvic LND: 65%; Median #LNs: 6

PBRT +/- ADT +/- PLNRT



FFP: Primary Endpoint

Per Protocol Criteria: Arm 3 was Superior to the other arms



No. at Risk									
PBRT Alone	564	506	449	403	371	333	290	234	180
PBRT+STADT	578	555	524	480	440	401	341	273	193
PLNRT+PBRT+STADT	574	559	536	511	484	459	396	324	250

Median FU 8.2 yr

5 yr Rate Comparison

Arm 3 vs Arm 1: $p < 0.001$

Arm 2 vs Arm 1: $p < 0.001$

Arm 3 vs Arm 2: $p = 0.003$

Adjusted HRs & 97.5% CIs

3 vs 1: 0.5 (0.39-0.64)

2 vs 1: 0.62 (0.47-0.77)

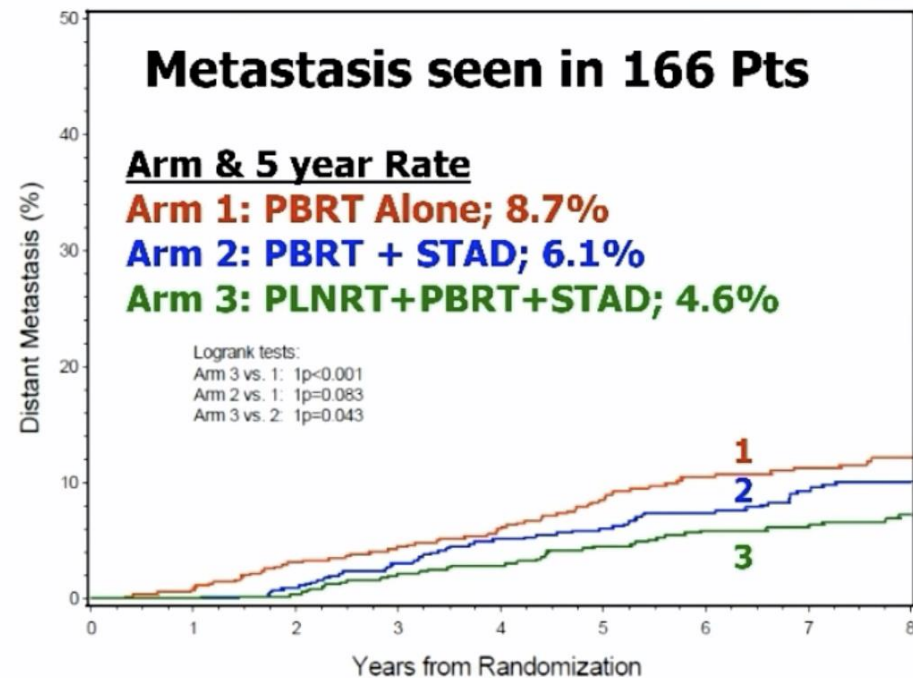
3 vs 2: 0.71 (0.63-1.07)

Lancet, in press

PBRT +/- ADT +/- PLNRT



Distant Metastasis



Logrank tests
Arm 3 vs Arm 1: $p < 0.001$
Arm 2 vs Arm 1: $p = 0.083$
Arm 3 vs Arm 2: $p = 0.043$

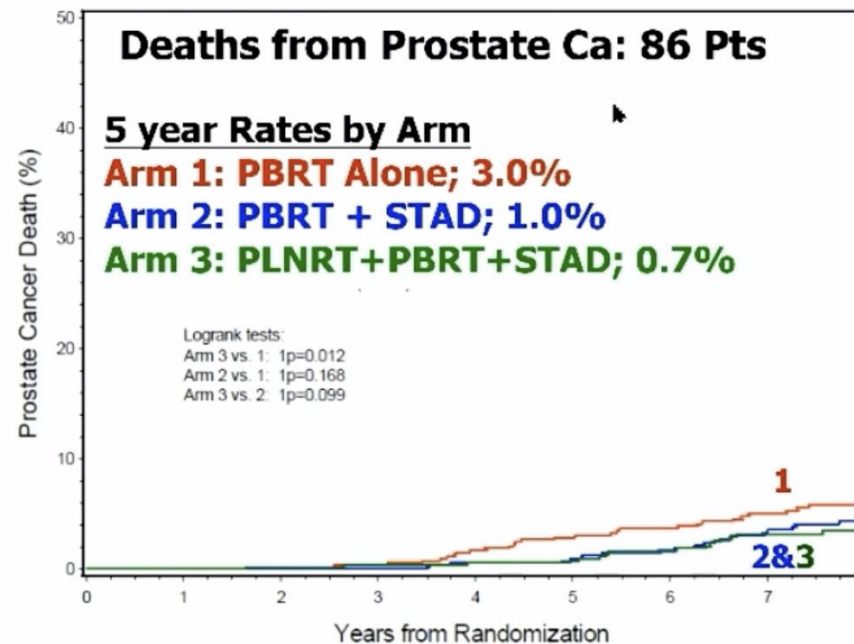
No. at Risk

PBRT Alone	564	535	513	494	470	441	404	337	268
PBRT+STADT	578	558	543	521	498	474	415	335	244
PLNRT+PBRT+STADT	574	561	550	531	513	491	436	354	275

PBRT +/- ADT +/- PLNRT



Death Due to Prostate Cancer



Logrank tests
Arm 3 vs Arm 1: $p<0.012$
Arm 2 vs Arm 1: $p=0.168$
Arm 3 vs Arm 2: $p=0.099$

**No statistically
significant
differences in OS**

No. at Risk

PBRT Alone	564	540	529	516	495	472	441	360	286
PBRT+STADT	578	558	548	538	523	500	444	360	264
PLNRT+PBRT+STADT	574	561	552	543	527	512	455	368	287

Overview



- **Prostate cancer**

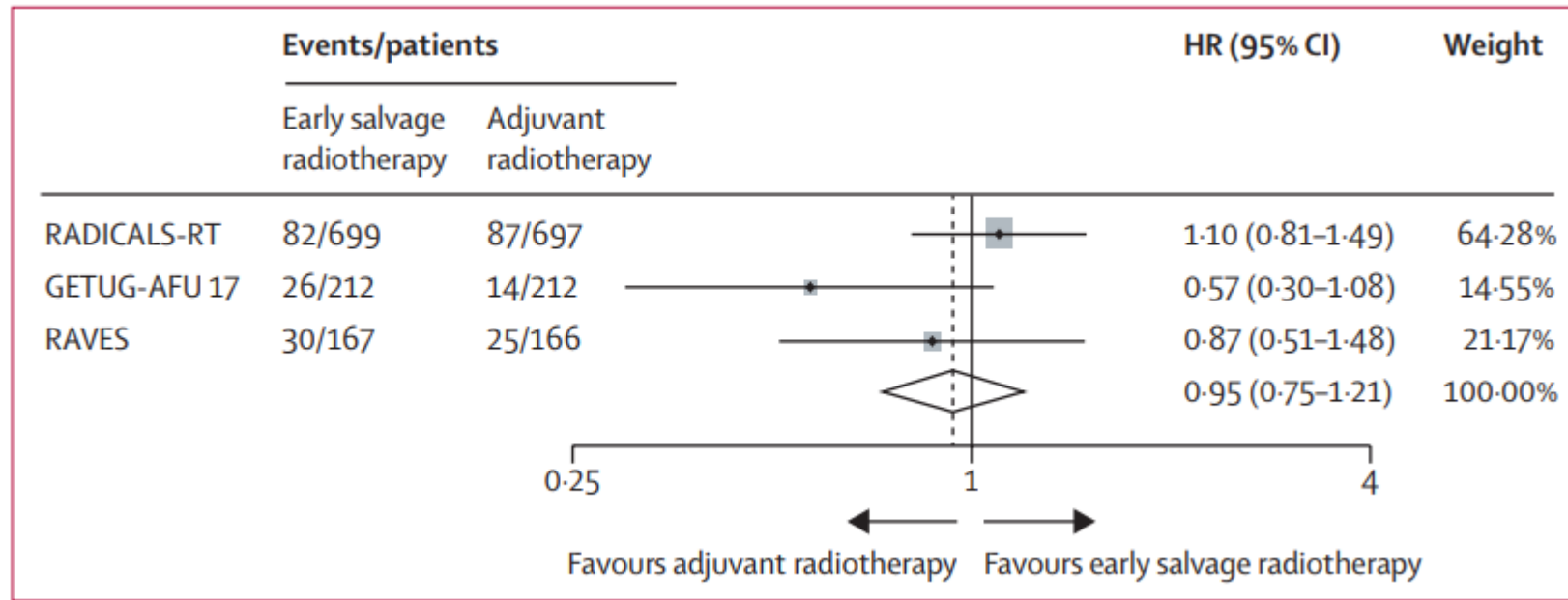
- Primary setting
 - SBRT
 - High-risk N0-1M0
- **Salvage setting**
 - Dose/ADT/pelvic RT
 - **Early salvage vs adjuvant**
- Metastatic setting
 - Local RT

- **Bladder and renal cancer**

- Hypofractionation and bladder preserving treatments
- SBRT + immunotherapy

Adjuvant vs early salvage RT

- No improvement in biochemical event-free survival for adjuvant RT vs early salvage RT
- 37% received salvage RT so far, majority have been spared therapy!
 - More cystitis/hematuria with adjuvant RT



Overview



- **Prostate cancer**

- Primary setting
 - SBRT
 - High-risk N0-1M0
- Salvage setting
 - Dose/ADT/pelvic RT
 - Early salvage vs adjuvant
- **Metastatic setting**
 - **Local RT**

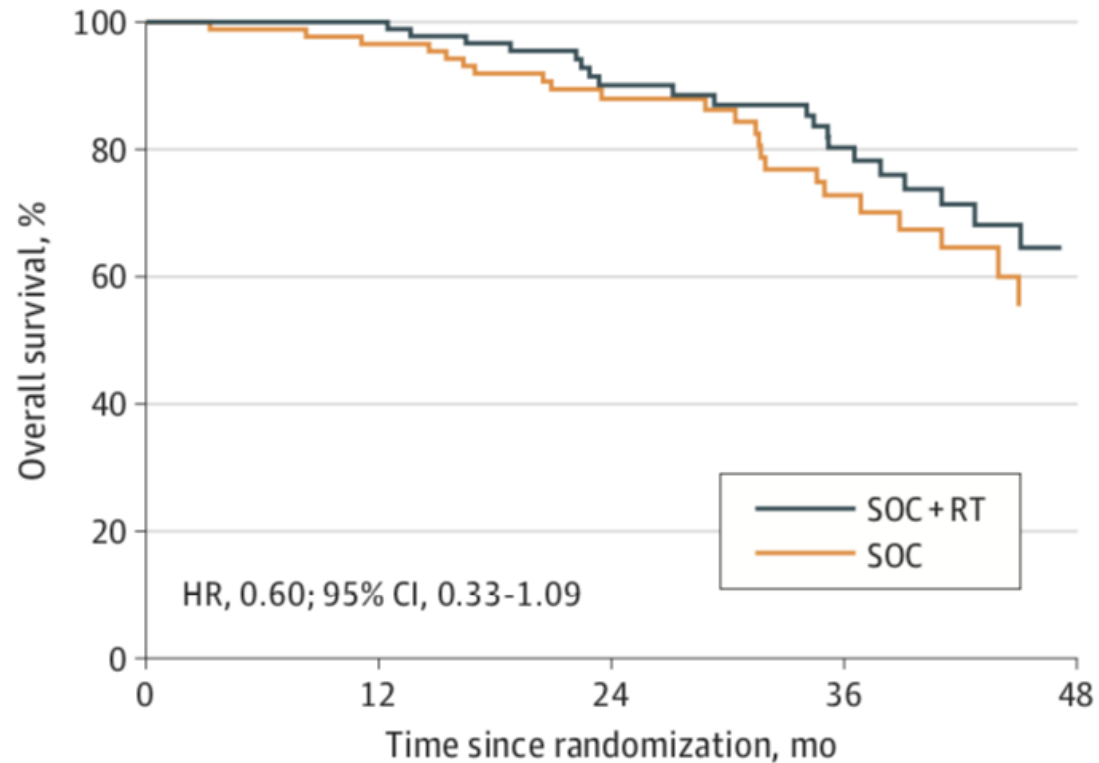
- **Bladder and renal cancer**

- Hypofractionation and bladder preserving treatments
- SBRT + immunotherapy

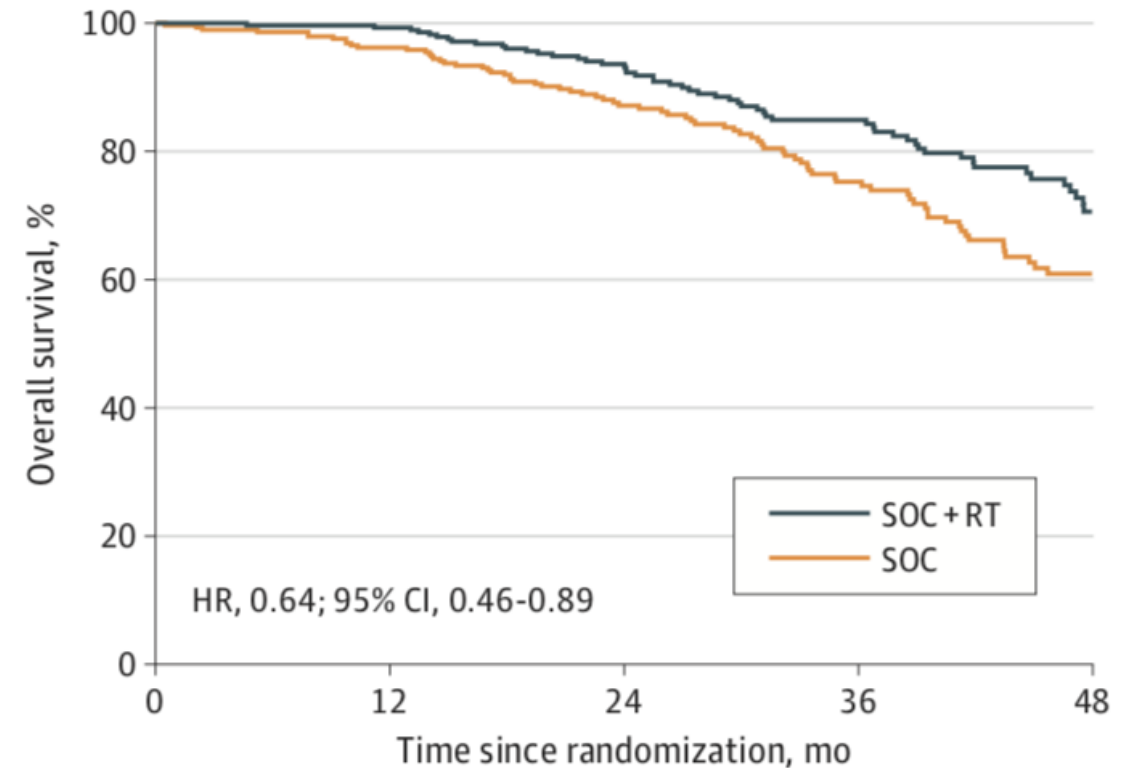
Prostate RT in M1 disease



Overall survival in only NRLN metastasis subcohort



Overall survival in ≤ 3 bone metastases ($\pm$ NRLN) subcohort



Overview

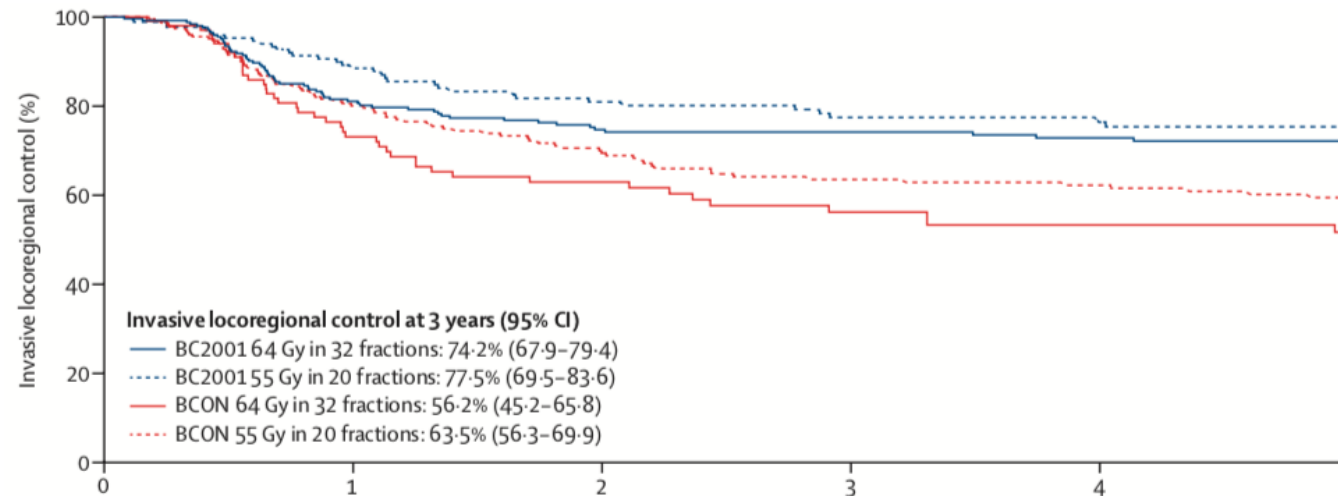


- Prostate cancer
 - Primary setting
 - SBRT
 - High-risk N0-1M0
 - Salvage setting
 - Dose/ADT/pelvic RT
 - Early salvage vs adjuvant
 - Metastatic setting
 - Local RT
- Bladder and renal cancer
 - **Hypofractionation and bladder preserving treatments**
 - SBRT + immunotherapy

Hypofractionated RT: a game changer?



- Individual patient data meta-analysis with data from 2 randomized UK clinical trials (BC2001 and BCON)
- Better locoregional control, not OS, with hypofractionated RT vs conventionally fractionated RT without increase in toxicity
 - Regardless of radiosensitizer
 - Also in RT-alone arm



Hypofractionated RT + chemo, which one?

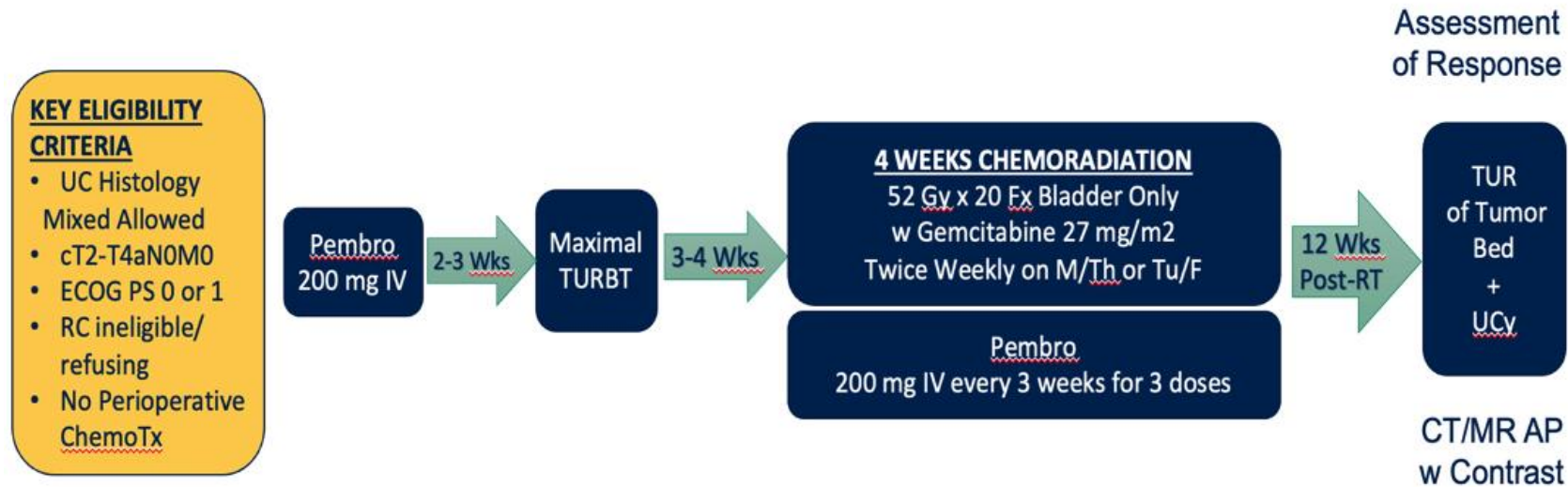


Concomitant therapy received		20f cohort (N=156)		32f cohort (N=176)	
		N	%	N	%
Yes		114	73.1	130	73.9
	MMC/5FU	44	28.2	94	53.6
	Gemcitabine	40	25.6	22	12.5
	Carbogen + nicotinamide	27	17.3	11	6.3
	Cisplatin	3	1.9	3	1.7
No		42	26.9	46	26.1

Surgery sparing approaches

• **Abstract ID 4504:** Pembrolizumab (pembro) in combination with gemcitabine (Gem) and concurrent hypofractionated radiation therapy (RT) as bladder sparing treatment for muscle-invasive urothelial cancer of the bladder (MIBC): A multicenter phase 2 trial.

• *Arjun Vasant Balar*

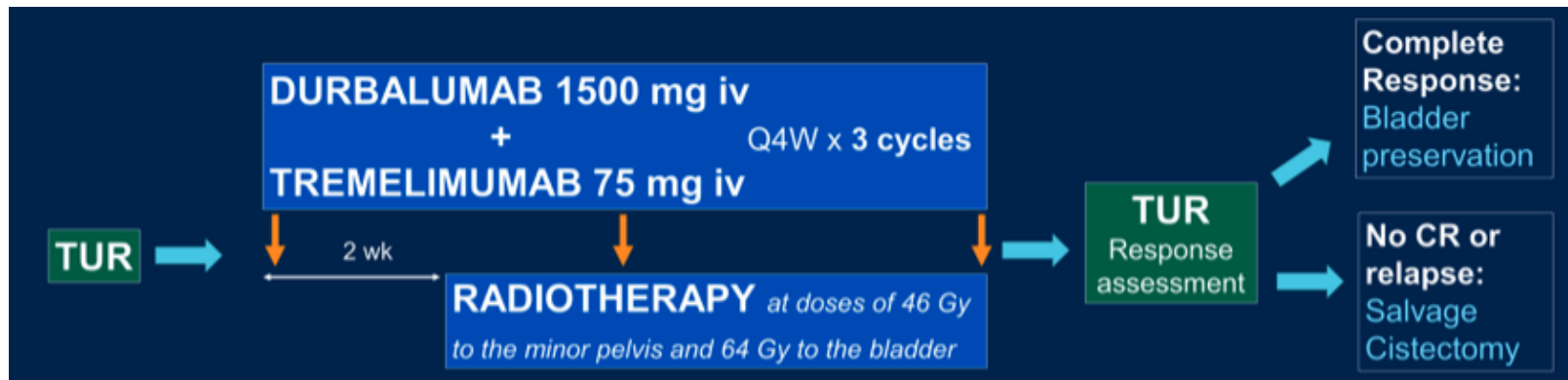


- 1-year bladder-intact DFS: 88%
- 35% grade 3 or more adverse events

Surgery sparing approaches

- **Abstract ID 4505:** Phase II trial of durvalumab plus tremelimumab with concurrent radiotherapy (RT) in patients (pts) with localized muscle invasive bladder cancer (MIBC) treated with a selective bladder preservation approach: IMMUNOPRESERVE-SOGUG trial.

- *Xavier Garcia del Muro*

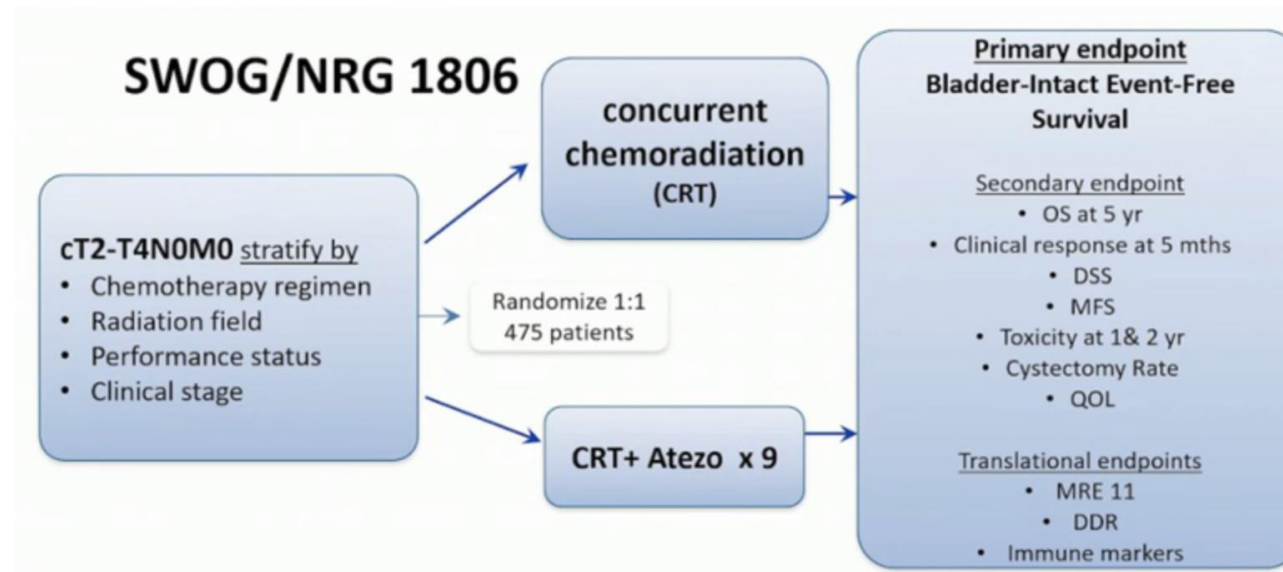


- 1-year bladder-intact DFS: 73%
- 31% grade 3-4 treatment-related adverse events

Ongoing phase III trials: TMT +/- immunotherapy



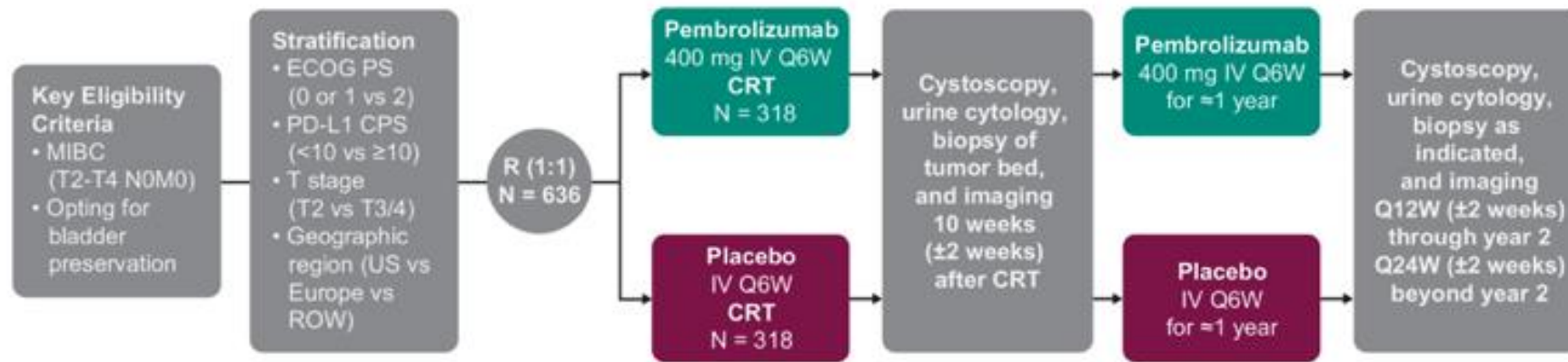
- RT:
 - 64Gy at 2Gy/fraction or 64.8 Gy at 1.8Gy/fraction (bladder +/- pelvic nodes)
- Analysis of first 73 patients: no evidence of increased immune related grade 3 or more AEs:
 - No grade 3 or higher colitis
 - 1 grade 3 radiation cystitis



Ongoing phase III trials: TMT +/- immunotherapy



- RT:
 - 64Gy at 2 Gy/fraction over 6.5 weeks (bladder +/- pelvic nodes)
 - 55Gy at 2.75Gy/fraction over 4 weeks (bladder only)



Keynote-992

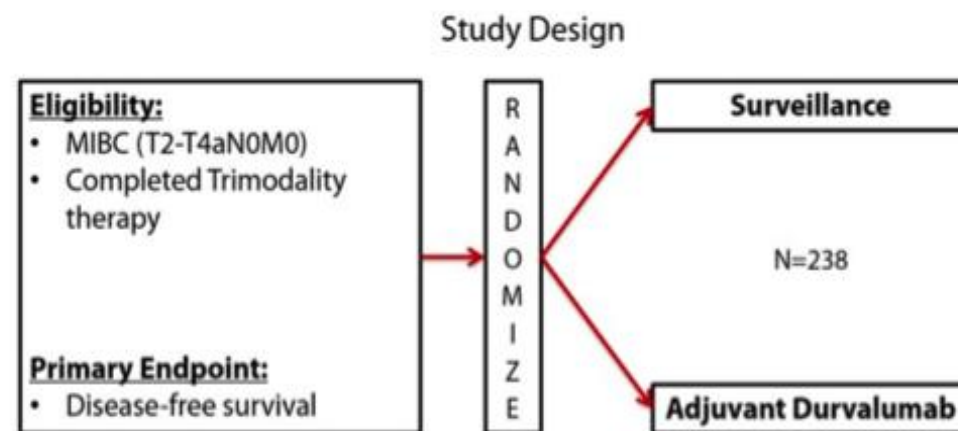
End Points

- **Primary:** bladder-intact EFS
- **Key secondary:** OS
- **Other secondary:** MFS, time to occurrence of NMIBC, time to cystectomy, safety and tolerability

Ongoing randomized phase II trials

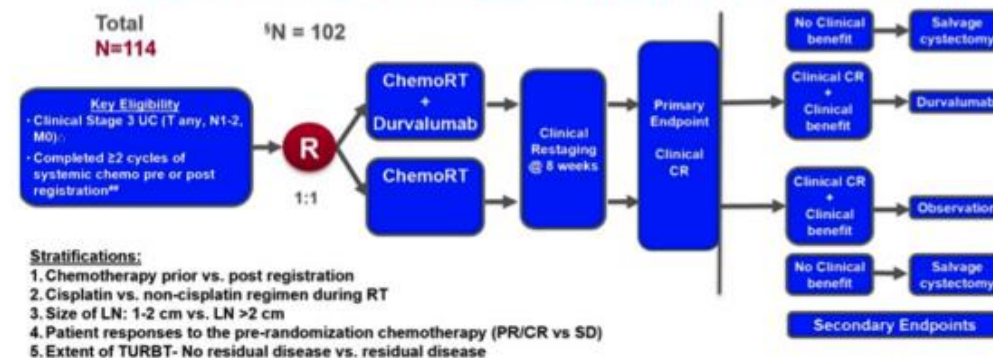
- CCTG BL13:

- Adjuvant durvalumab after TMT



- INSPIRE (ECOG-ACRIN/NRG EA8185)

- Induction chemo followed by TMT + Durvalumab
- N+ disease



Overview



- Prostate cancer
 - Primary setting
 - SBRT
 - High-risk N0-1M0
 - Salvage setting
 - Dose/ADT/pelvic RT
 - Early salvage vs adjuvant
 - Metastatic setting
 - Local RT
- Bladder and renal cancer
 - Hypofractionation and bladder preserving treatments
 - **SBRT + immunotherapy**

Patterns of progression with immunotherapy



- Checkmate 214 (Ipi-Nivo vs Sunitinib)
- In patients who progressed post-response, **51%** in Ipi-Nivo arm progressed in new lesion(s)-only (vs 27% in sunitinib arm)
 - 94% in single organ
 - 32% lymph node
 - 24% brain
 - 15% lung
- Different pattern of disease progression with nivo-ipi => opportunity for focal metastasis-directed therapy?

SBRT + immunotherapy: RAPPORT trial



- Patients with up to 2 lines of prior systemic therapy with 1-5 oligometastases from ccRCC were included
- SBRT 1 x 20Gy (or 10 x 3Gy) to all metastatic sites, followed by pembro 200mg Q3w for 8 cycles was well tolerated with excellent local control
- PFS of 15.6 months and ORR of 63% compared favorably to 1st line KEYNOTE-427 pembro monotherapy outcomes (PFS of 7.1 months and ORR of 34%)
 - Same metastatic load??

Conclusions



- Prostate cancer
 - Primary setting
 - **SBRT for intermediate-risk**
 - **Pelvic RT/ADT + 2 years Abi in high-risk N0-1M0**
 - Salvage setting
 - **Dose**
 - **6 months ADT + pelvic RT**
 - **Early salvage**
 - Metastatic setting
 - **Local RT**
- Bladder and renal cancer
 - **Hypofractionation and bladder preserving treatments**
 - **SBRT + immunotherapy**