

Stage II A – II B seminoma: How to integrate biology and nuclear medicine in the future decision making

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Disclosures (Past three years)

- Clinical investigator of trials sponsored by : Amgen, Astellas, Astra Zeneca, Boehringer, Bayer, Bicycle Therapeutics, BMS, Dayichii Sanchio, Exelixis, Gilead, Incyte, Janssen, Lilly, Merck KGaA, MSD, Orion, Pfizer, Roche, Seagen, Tahio, TYRA
- Research grants: Amgen, Astellas, Celsius, MSD, One biosciences, Roche, Veracyte
- Lectures: Astellas, Astra Zeneca, BMS, Janssen, Merck KGaA, MSD, Pfizer, Roche

Outline

- Role of PET-scan
- Role of miRNA

Key questions and challenges in germ-cell tumor

- How to ensure delivery of best practice for all patients ?
- How to cure more patients with poor prognosis metastatic GCT ?
- How to envision a reduction in treatment burden for reducing significant long-term side-effects of therapies ?

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Classification of Metastatic seminoma

Stage grouping	T	N	M	S
Stage 0	pTis	N0	M0	S0
Stage I	pT1-T4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2 - pT4	N0	M0	S0
Stage IS	Any pT/TX	N0	M0	S1-3
Stage II	Any pT/TX	N1-N3	M0	SX
Stage IIA	Any pT/TX	N1	M0	S0
	Any pT/TX	N1	M0	S1
Stage IIB	Any pT/TX	N2	M0	S0
	Any pT/TX	N2	M0	S1
Stage IIC	Any pT/TX	N3	M0	S0
	Any pT/TX	N3	M0	S1
Stage III	Any pT/TX	Any N	M1a	SX
Stage IIIA	Any pT/TX	Any N	M1a	S0
	Any pT/TX	Any N	M1a	S1
Stage IIIB	Any pT/TX	N1-N3	M0	S2
	Any pT/TX	Any N	M1a	S2
Stage IIIC	Any pT/TX	N1-N3	M0	S3
	Any pT/TX	Any N	M1a	S3
	Any pT/TX	Any N	M1b	Any S

- Clinical stage IIA/B:
10-10% of seminomas
- Rare scenario from a rare tumor

N - Regional Lymph Nodes – Clinical	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension or multiple lymph nodes, none more than 2 cm in greatest dimension
N2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumour
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension

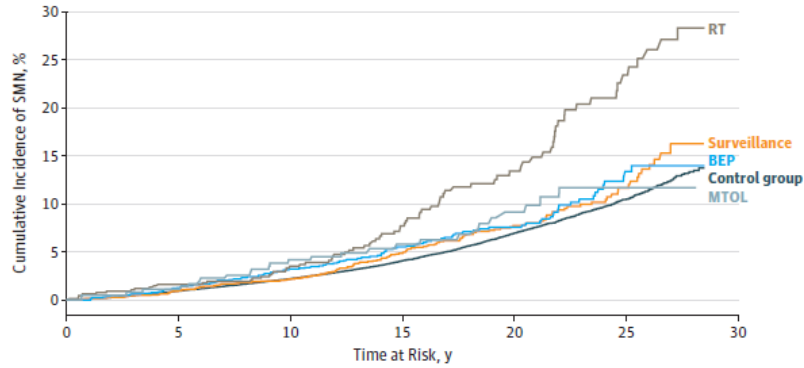
Why reducing treatment burden in metastatic seminoma ?

Compared to the 1997 IGCCCG figures, 5-year OS was substantially better for all risk groups (n=2,451):

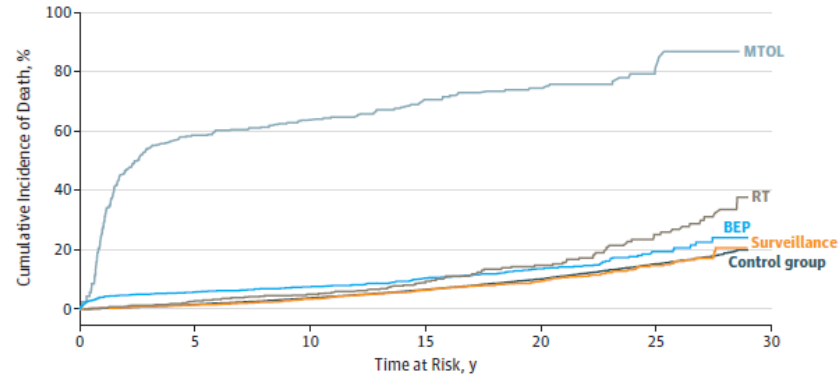
Risk status	Seminoma	5-y OS
Good risk	Any primary site and normal AFP, any hCG, any LDH and NO Non-pulmonary visceral metastases	≈ 95 % (86% in 1997)
Intermediate risk	Any primary site and normal AFP, any hCG, any LDH and Non-pulmonary visceral metastases	≈ 88 % (72% in 1997)
Poor risk	Does not exist	

Limiting the risk of second cancers/ deaths

Danish cohort: 5190 men from 1984 to 2007



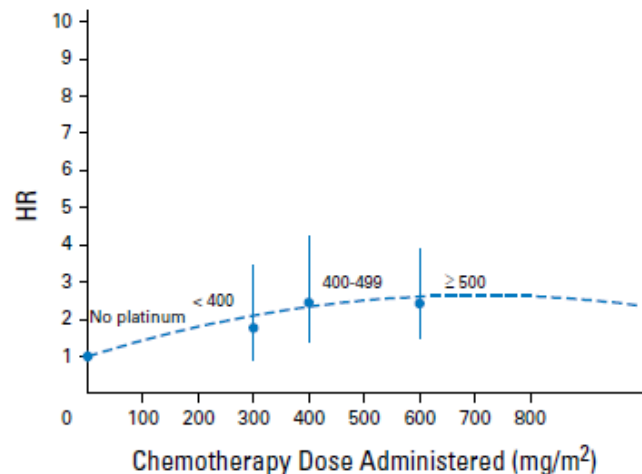
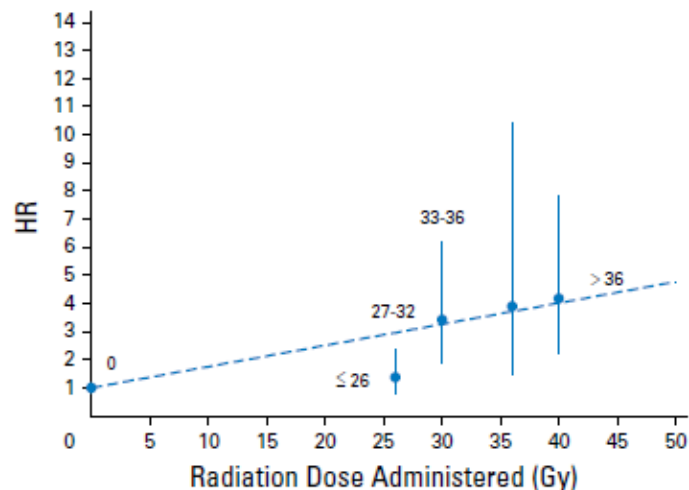
No. at risk						
Control group	51 592	48 335	36 910	25 591	14 623	5 435
Surveillance	2 985	2 345	1 738	1 196	647	231
BEP	1 432	1 452	1 114	769	440	147
RT	588	657	506	315	172	79
MTOL	86	152	105	65	37	7



No. at risk						
Control group	51 929	49 818	38 095	26 898	15 800	6 102
Surveillance	3 333	2 439	1 795	1 257	713	261
BEP	1 296	1 504	1 148	806	477	168
RT	544	673	524	340	182	93
MTOL	17	150	112	67	42	10

Limiting the risk of second cancers/ deaths

Dutch cohort: 5848 men **from 1976 to 2007**



How to proceed ?

1. Modifying the chemotherapy or radiotherapy in seminoma
 - Use of carboplatin instead of cisplatin
 - Reduction of dose and shrinkage of fields of radiation
 - Reintroduction of retroperitoneal lymph node dissection
 - Combination of two treatment approaches at reduced intensity.

#1 :Reintroduction of retroperitoneal lymph node dissection

PRIMETEST trial



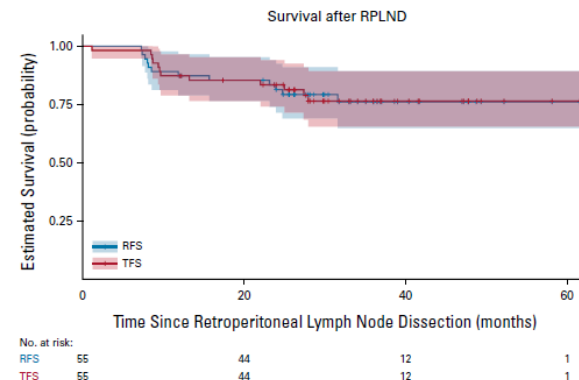
Seminoma stage IIA/IIB
< 5 cm lymph node
Unilateral template
Recurrence after carbo allowed

Follow-up (mo)	
Median (IQR)	32 (23–46)
Patients lost to follow-up (n)	0/33
Recurrences	10/33
Probability of PFS	
12 mo	0.75 (95% CI 0.56–0.87)
24 mo	0.72 (95% CI 0.52–0.84)
36 mo	0.64 (95% CI 0.42–0.80)

SEMS trial



Seminoma stage IIA/IIB
< 3 cm lymph node
Unilateral template
Recurrence after carbo allowed



#2 :combination of 2 therapies at reduced intensity

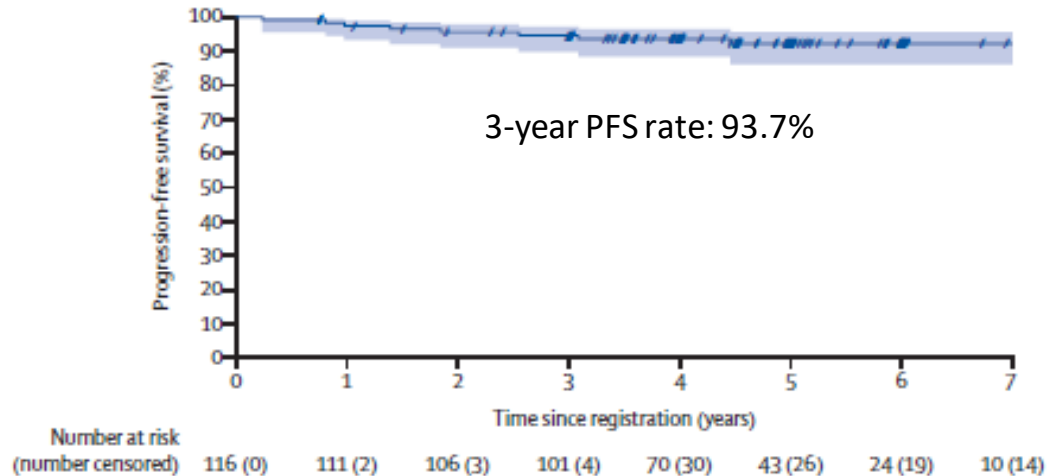
Phase II Trial SAKK 01/10



Objective: target 3-year PFS of 95%

N=120

Median F/U: 4.5 years

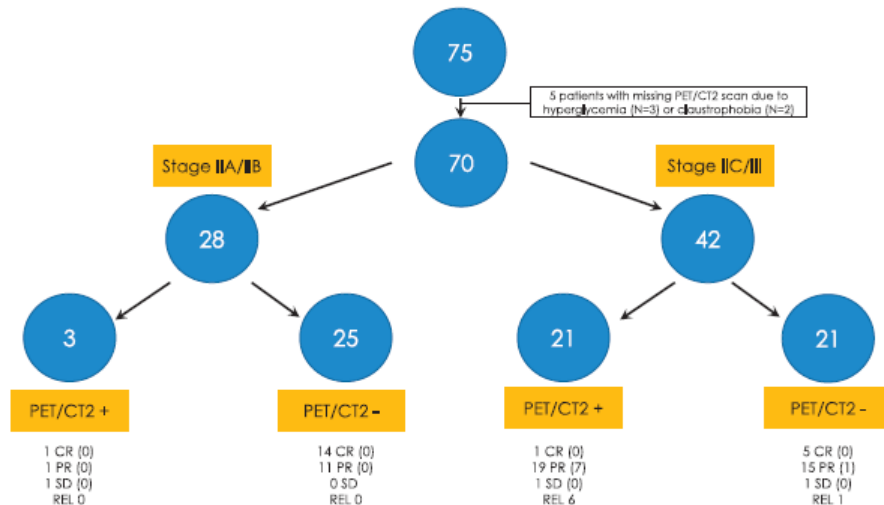


How to proceed ?

2. Use imaging to select patients

The use of Interim PET/CT ?

Observational study from Milan

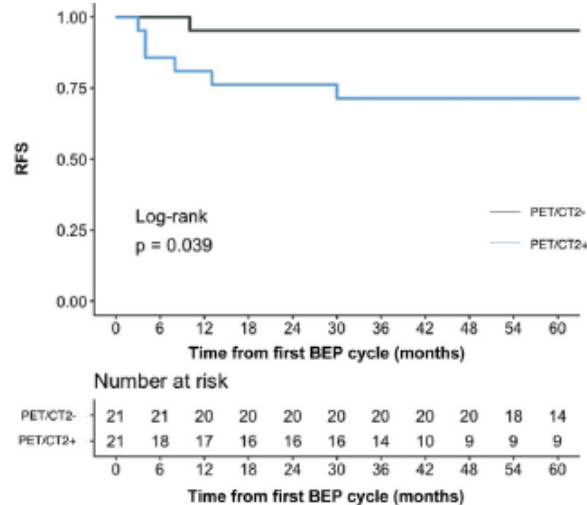
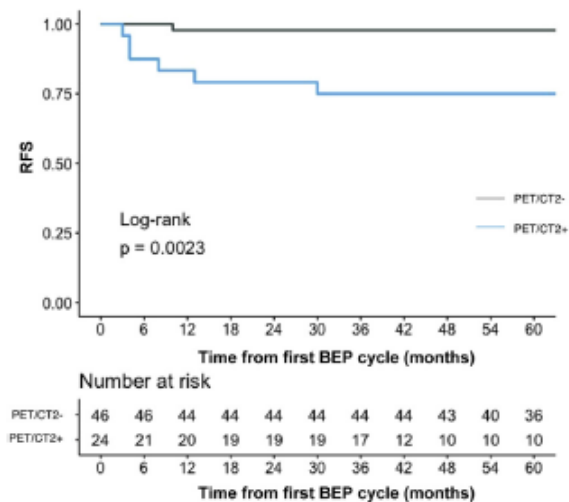


Negative PET/CT in 60%

Negative PET/CT in 46%

- Advanced seminoma, n=70
- BEP X 2
- Interim PET/CT
- BEPx3-4 in 68 pts
- EPx4 in 2 pts

The use of Interim PET/CT ?



PET/CT2 was significantly associated with relapse-free survival

The use of Interim PET/CT ?

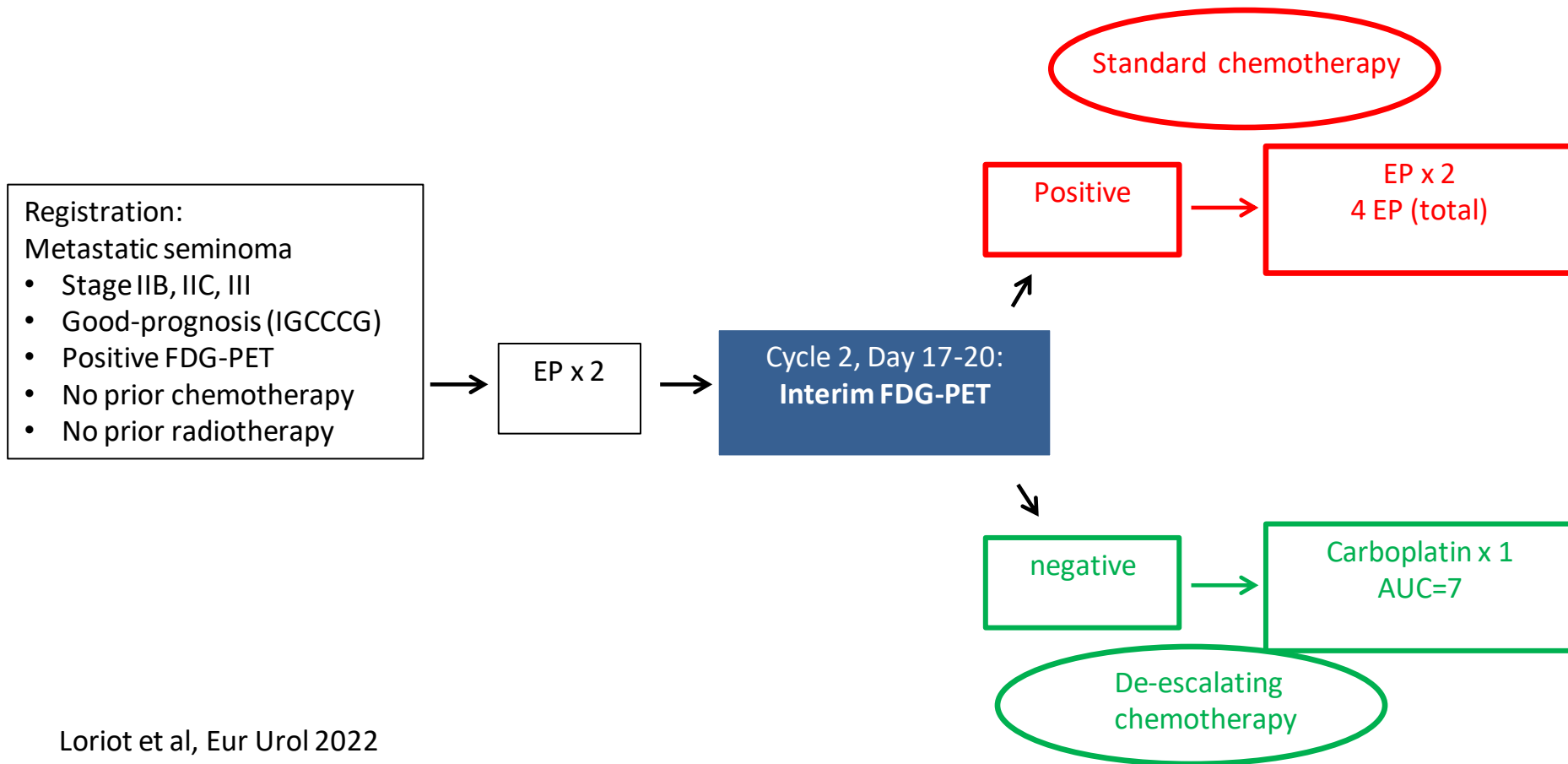
A phase II study of carboplatin AUC-10 guided by positron emission tomography—defined metabolic response in metastatic seminoma

Jonathan Shamash ^{a,c,*}, Rizwan Syed ^b, Shah-Jalal Sarker ^c,
Naveed Sarwar ^d, Anand Sharma ^e, Katherine Mutsvangwa ^a,
Carike Coetzee ^c, Peter Wilson ^a, Gordon J. Rustin ^e

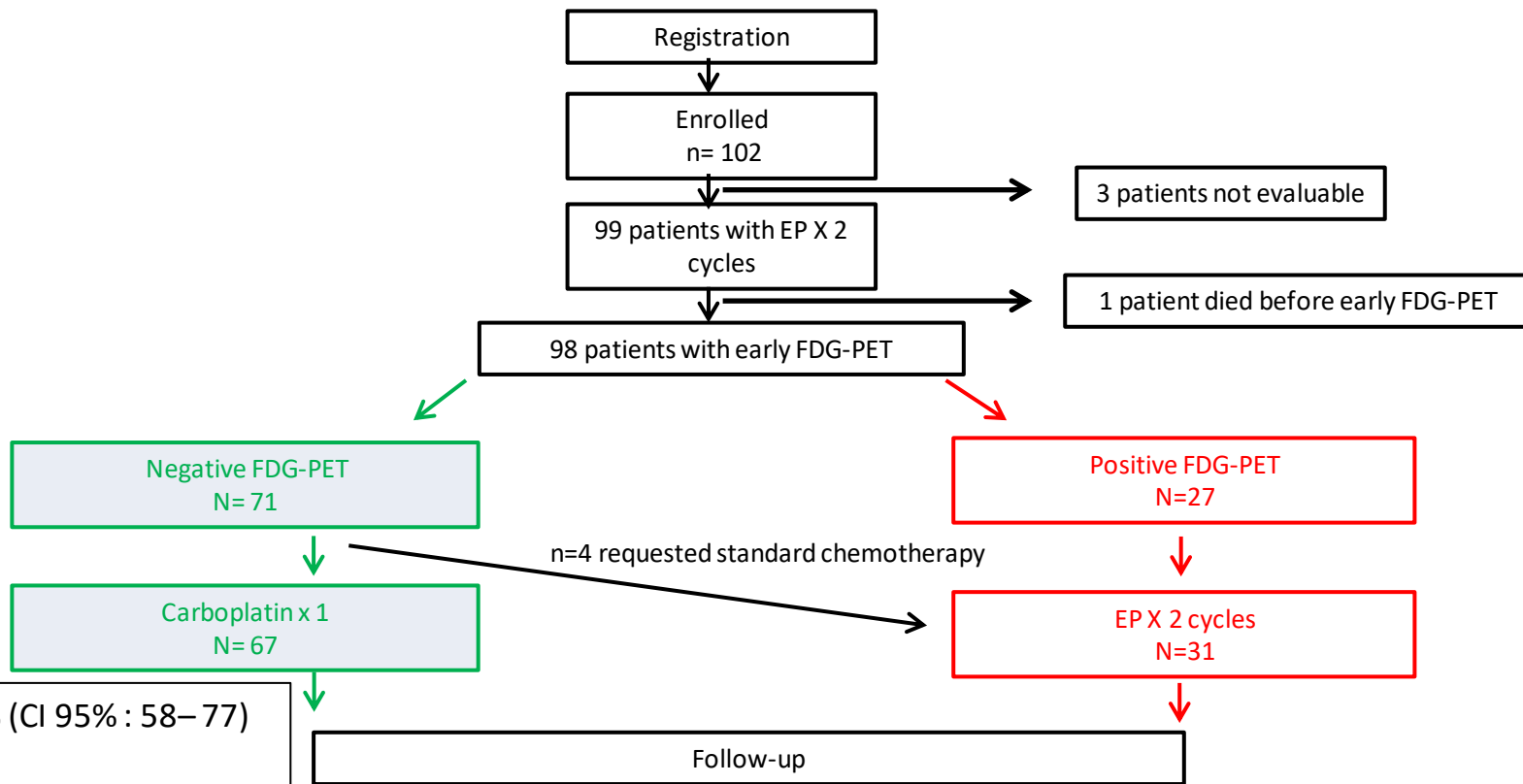
Metabolic response assesment after cycle 1 and overall radiological response at end of treatment		Disease stage			
		2A	2B	2C	Total
Metabolic response at cycle 1	CR	9	12	0	21
	PR	4	11	11	26
	Total	13	23	11	47
Overall response	CR	11	18	3	32
	PR-ve	2	3	7	11
	SD-ve	0	1	1	2
	Total	13	22	11	46

- Metastatic seminoma, n=48
- Carbo AUC=10
- Interim PET/CT
- 2 or 3 addiotinal cycles following interim PET/CT
- 95.6%were progression-free at 2 years

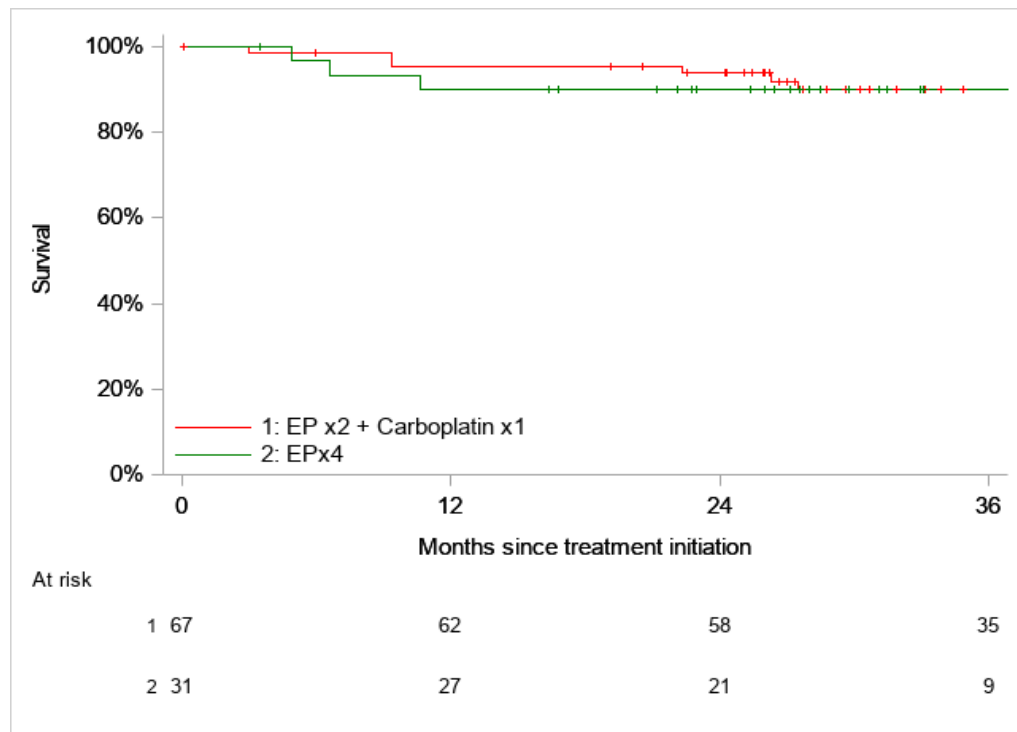
SEMITEP phase II design



Study flowchart



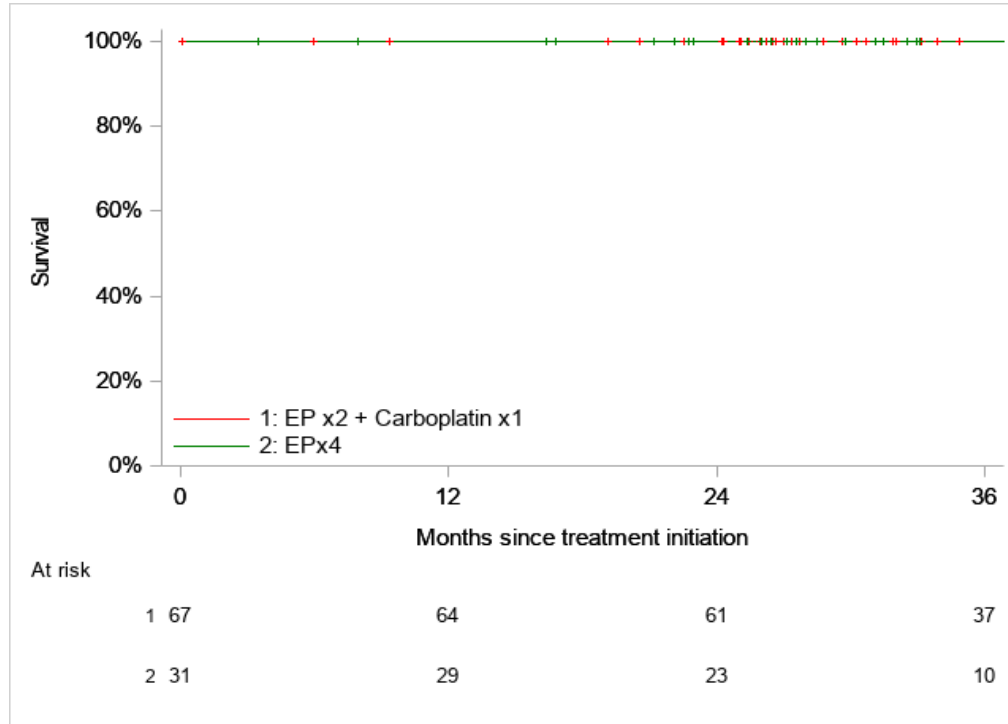
Progression-free survival



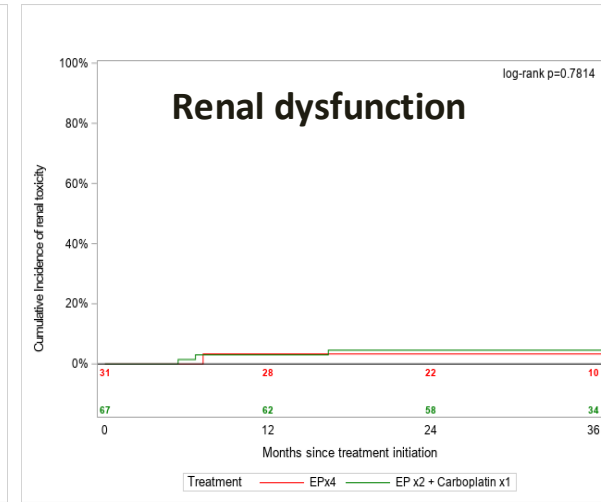
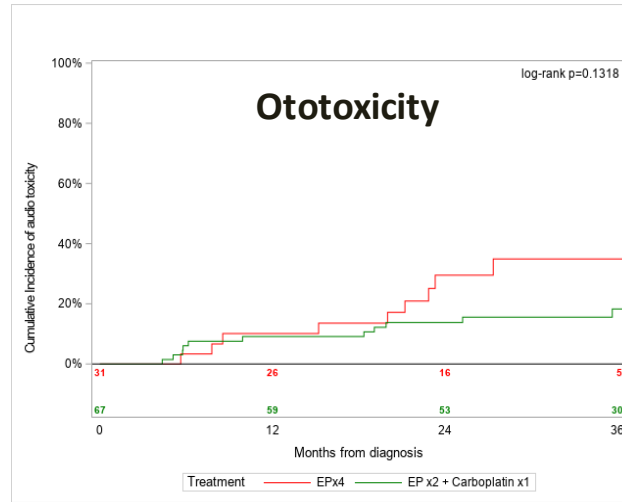
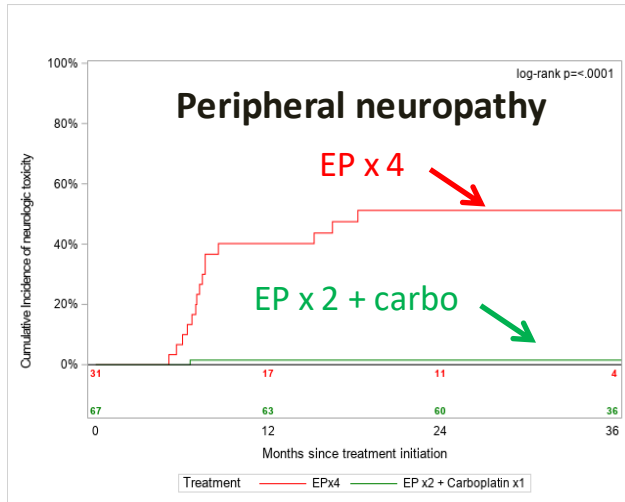
**Median follow-up :
33.9 mo (95% CI: 30.2 –
39.3)**

Time (months)	EP x 4 PFS rate (CI 95%)	EP x 2 + carboplatin x 1 PFS rate (CI 95%)
12	90% (74.4 – 96.5)	95.4% (87.3-98.4)
24	90% (74.4 – 96.5)	93.8% (85.1- 97.6)
36	90% (74.4 – 96.5)	89.9% (79.6- 95.3)

Overall survival of evaluable patients

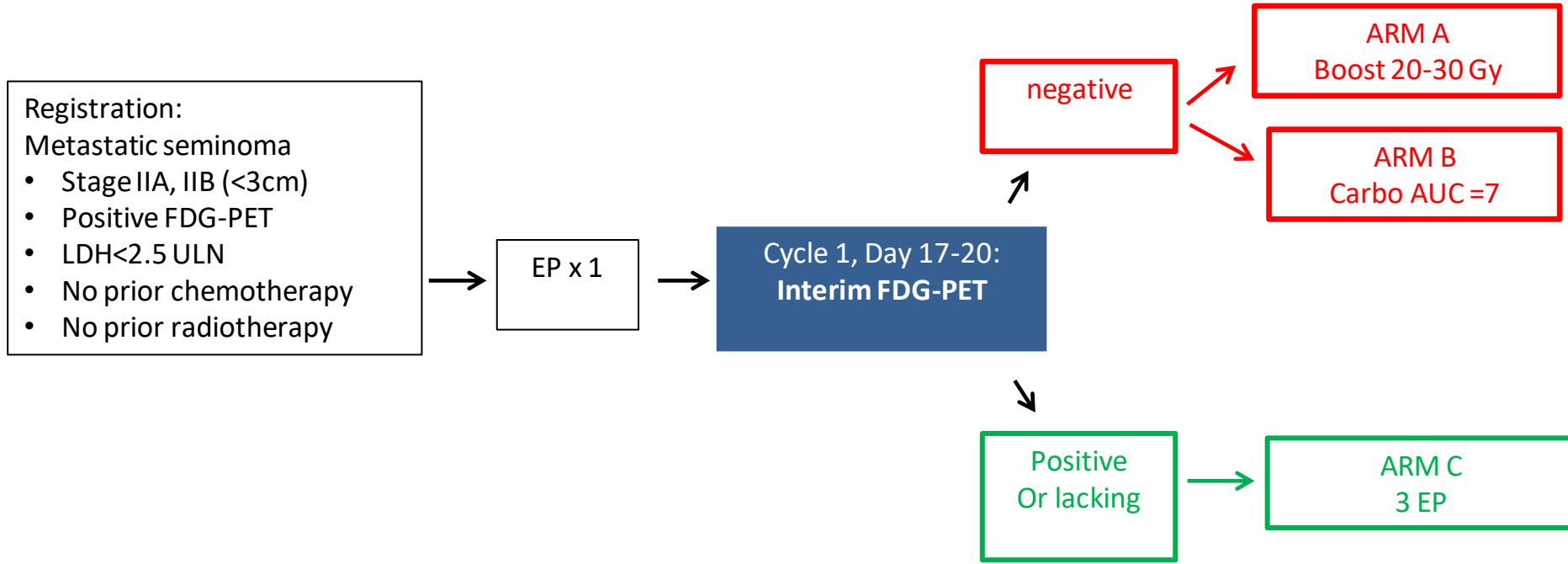


Toxicity : cumulative incidence (Time to toxicity) of all grades



No patient developed cardiac toxicity

Next step : EDEN TRIAL

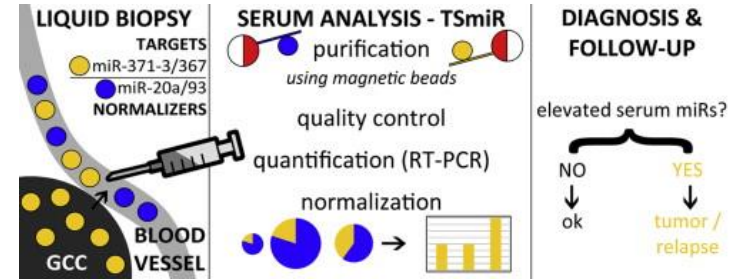
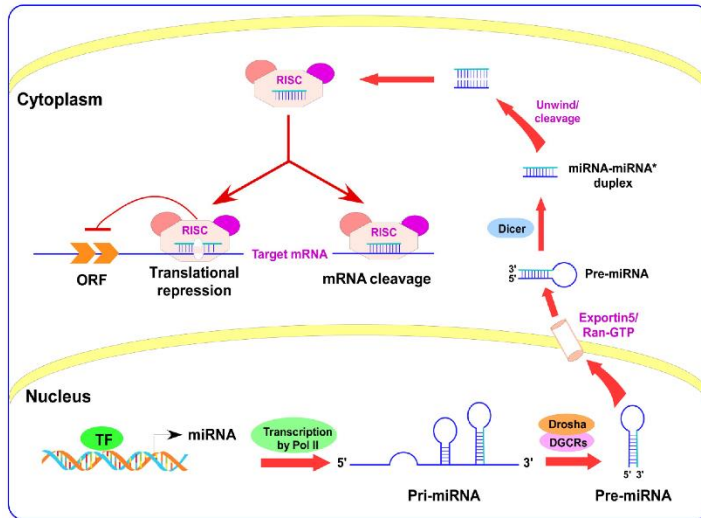


How to proceed ?

3. Use biology to select patients

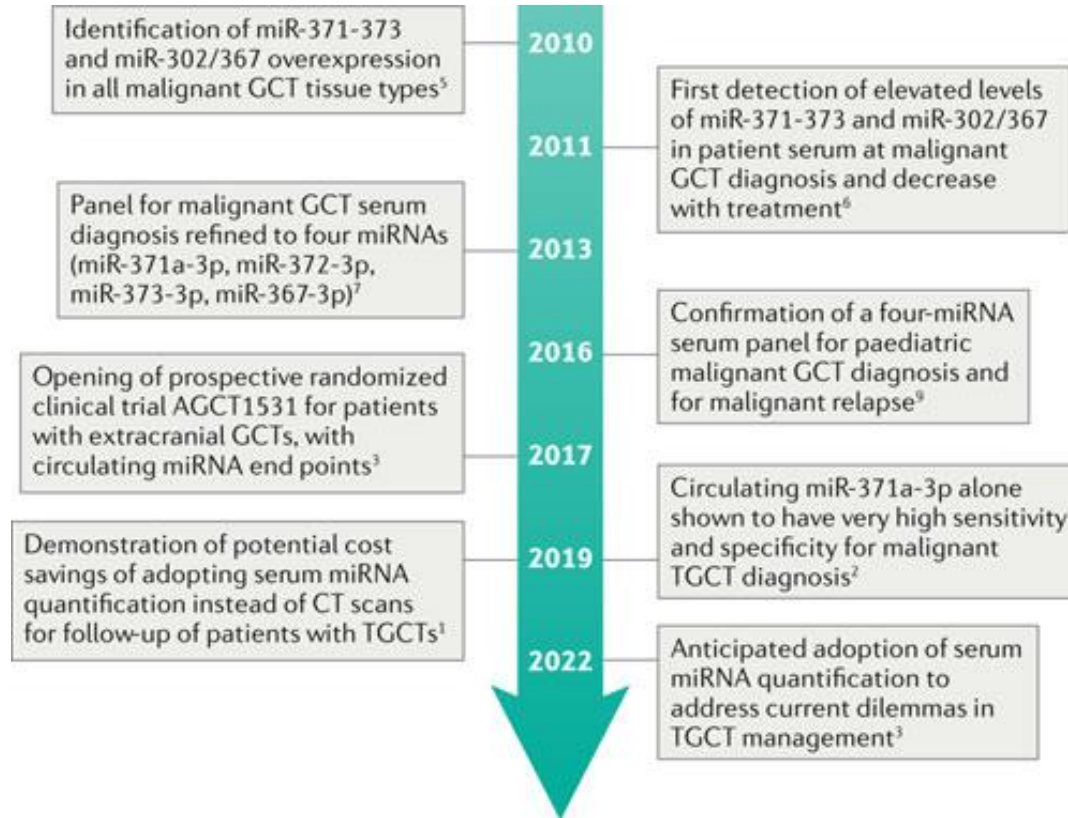
microRNA-371a-3p

MicroRNAs are small, noncoding RNAs that post-transcriptionally regulate gene expression by binding to the 3'-untranslated region of target mRNAs, resulting in mRNA degradation or translation repression

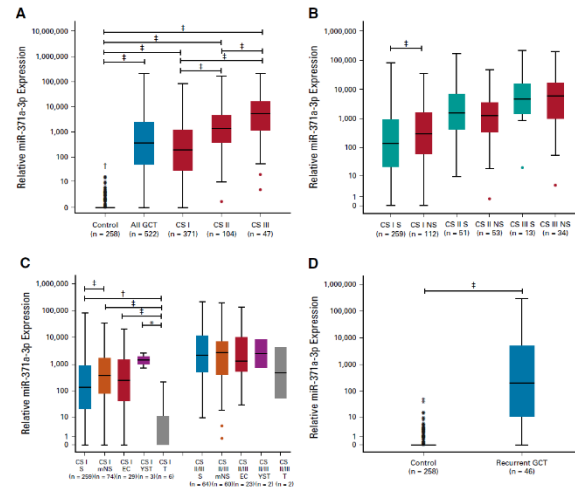


Non consensus about how to interpret positive and negative miR371a results (PCR assay)

A brief history of microRNA-371a-3p in GCT



microRNA-371a-3p



Performance metrics for the miR371 a assay (to predict the presence of LN metastases in patients with IIA/B stage) (n=26)

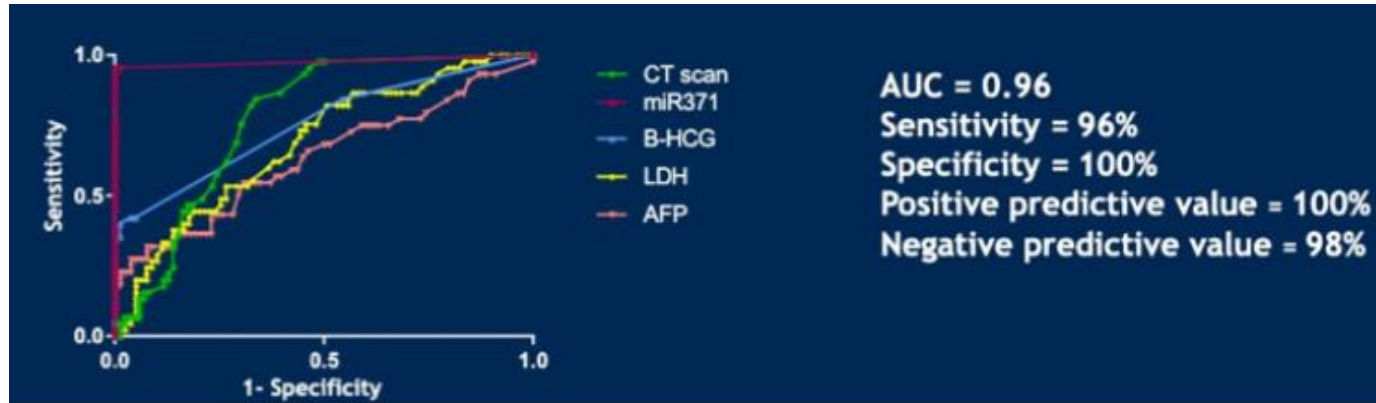
	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Overall	95.7	100	100	75
Clinical stage IIA	91.7	100	100	67
Clinical stage IIB	100	100	100	100

PPV = positive predictive value; NPV = negative predictive value.

- Expressed in >90% of GCT, correlate with the clinical stage and disappear with successful treatment
- Several studies found that miR371a is upregulated in germ cell neoplasia in situ, seminoma, and nonseminoma **apart from teratoma**
- miR371a also correlates with clinical stage and response to treatment

- > Patients with negative miR371a might be managed safely with close monitoring using abdominal CT/MRI scans

microRNA-371a-3p



- miRNA outperforms CT scans and traditional biomarkers in the detection of viable GCT
- S1823 trial to be launched to validate the clinical utility of miR371
- May be helpful to guide adjuvant treatment for high risk clinical stage I patients and **to select patients for RPLND in the post chemotherapy setting.**

Key trials in low volume seminoma

SWOG S1823 (n=956) NCT04435756

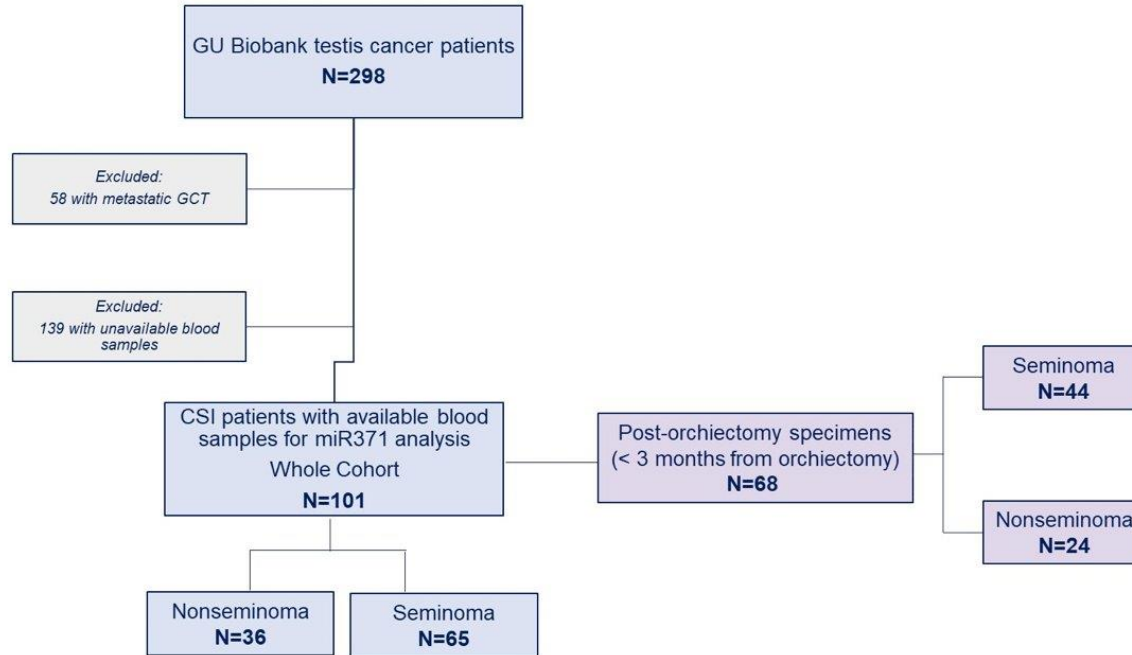
Prospective observational cohort study designed to establish the accuracy of miR371 in detecting active germ cell malignancy in early stage germ cell tumor, primarily focusing on CSI disease.

AGCT 1531(n=2059) NCT03067181

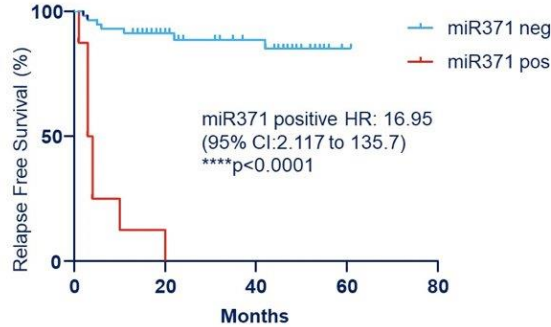
multi-arm phase III interventional study comparing active surveillance, carboplatin-based chemotherapy, and cisplatin-based chemotherapy in low and standard risk pediatric, adolescent, and young adult GCT patients.

Secondary outcome: to assess the utility of miRNA-371-373 and miRNA-302

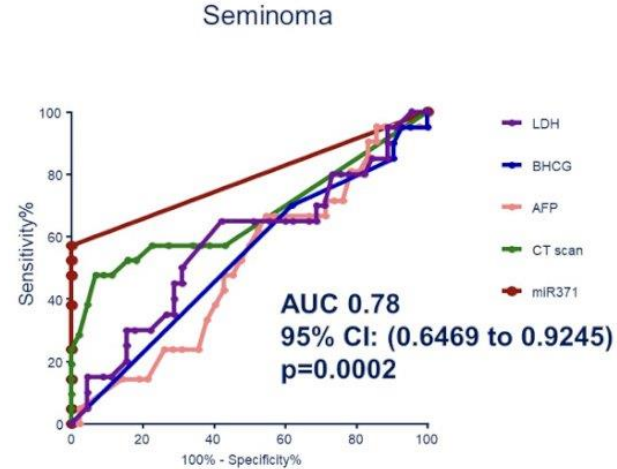
miRNA371 : S1823 trial



miRNA371 : S1823 trial



miR371 negative	60	38	25	1	0
miR371 positive	8	1	0	0	0



Median Follow-up: 46 months

Se = 96% (95% CI 85-99%)

Sp = 100% (95% CI 96-100%)

PPV = 100% (95% CI 92-100%)

NPV = 98% (95% CI 92-100%)

NCT03067181

MIRAGE study: first interventional study based on miRNA (in CS1 non seminoma)

Screening

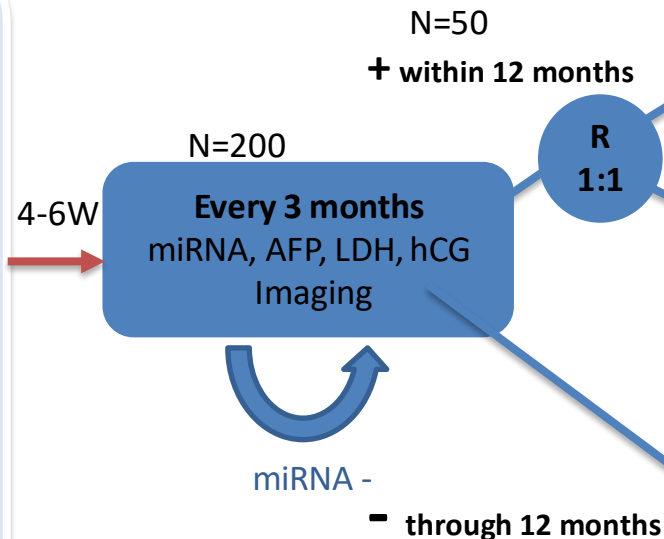
Key eligibility

- ≥11 yo (puberty acquired)
- Stage I NSGCT confirmed
 - NED on CT scan
 - S0
- Available tissue from orchiectomy for LVI status (stratification factor)

Outcomes

Primary outcome : DFS
Secondary outcomes : QoL,
Cumulative chemo dose

Surveillance



Treatment

BEP x1

Bleomycin 30 D1, D8, D15
Cisplatin 20mg/m² D1-D5
Etoposide 100mg/m² D1-D5

Surveillance

(With iterative miRNA dosages)

Surveillance

(With iterative miRNA dosages)

Considerations and future directions for miRNA

Standardizing methodology

- Serum separator tubes used in old studies vs Streck tubes in most recent studies
- Serum vs plasma extraction
- No consensus for a single reference miRNA and use of a combination of reference miRNA would be better for normalization

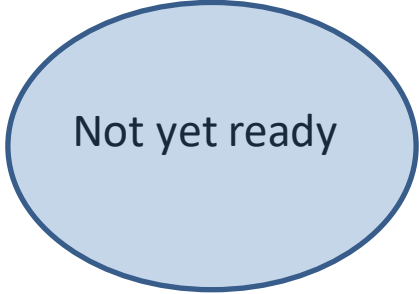
Prognostic marker

High performance for detecting the presence of viable GCT but limited data about its prognostic value

Clinical applications

Potential for

- Detecting low volume metastatic seminoma
- Monitoring response to chemotherapy
- Managing post chemotherapy residual mass



Not yet ready

Conclusion

- There is no question of whether or not we should reduce treatment burden in GCT
- PET/CT is a good candidate to proceed in advanced seminoma
- The better understanding of seminoma biology may be helpful in the coming years

Thank you

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Gustave Roussy, Cancer Campus, Grand Paris

