Updates in Testicular Cancer

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Remaining Challenges

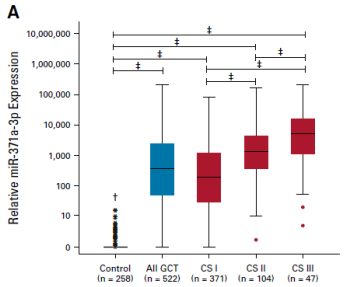
- Biomarkers
- Surgery in early metastatic disease
- Intermediate/Poor Risk GCT
- Brain Metastasis
- Late Relapse
- Mediastinal Non-seminoma
- Relapsed/Refractory GCT
- Survivorship

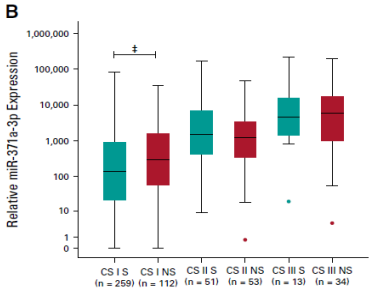
miR-371a-3p vs. Conventional Tumor Markers

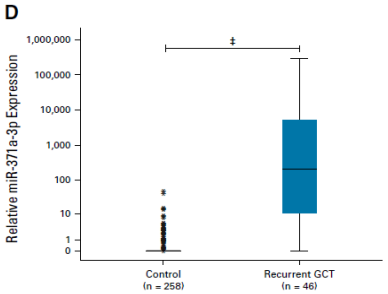
Parameter Studied	AFP	hCG	miR-371a-3p
Seminoma	<3%	18-31%	87%
Non-seminoma	60-70%	53%	94%
Embryonal carcinoma	40%	25%	>90%
Yolk sac tumor	>95%	<5%	>90%
Choriocarcinoma	<5%	>95%	>90%
Teratoma	-	-	<5%
Mixed GCT	Variable	Variable	~90%
Extragonadal	Variable	Variable	>90%
Non-GCT	12%	14%	6%
Half-life after orchiectomy	5-7 days	1.5-3 days	<12 hours
Decrease during/after chemotherapy	+	+	+

[1]Dieckmann et al. J Clin Oncol 2019

miR-371a-3p Expression



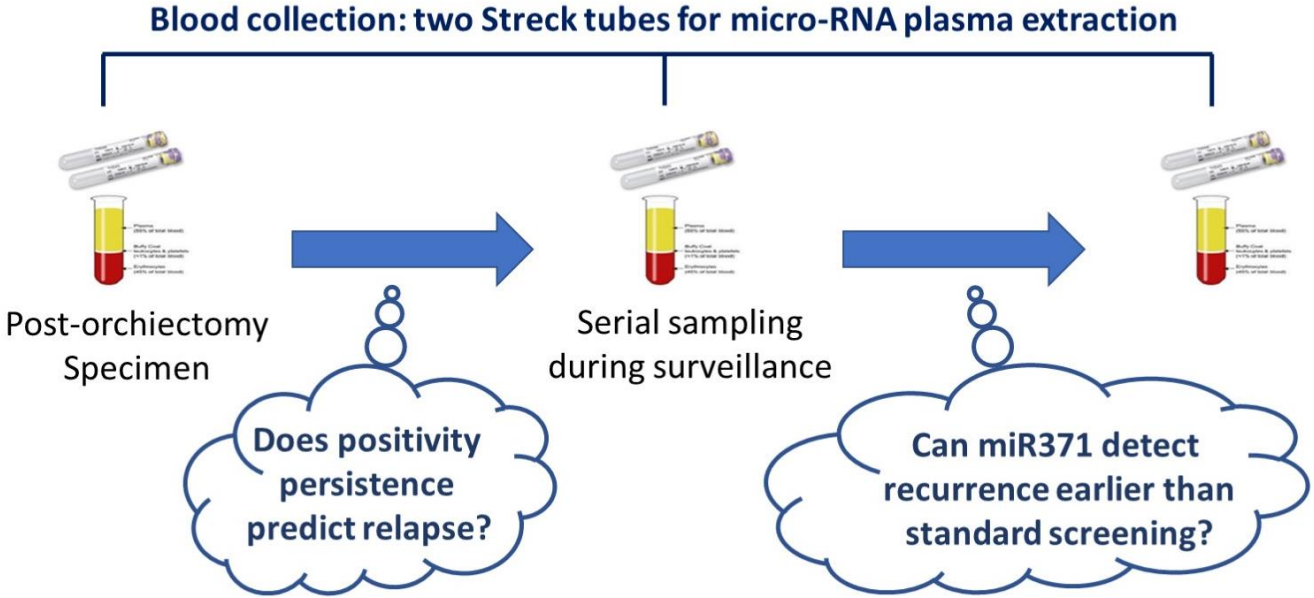




miR371 Expression	GCT History With Clinically Confirmed aGCM (No. of cases)	GCT History With No Clinically Confirmed GCM (to March 2019; No. of controls)	Total No.
Plasma miR371 expression on prospectively obtained sample	44 TPs	0 FPs	44 positive tests
No plasma miR371 expression on prospectively obtained sample	2 FNs	86 TNs	88 negative tests
Total samples	46 with confirmed aGCM	86 with no confirmed aGCM	132

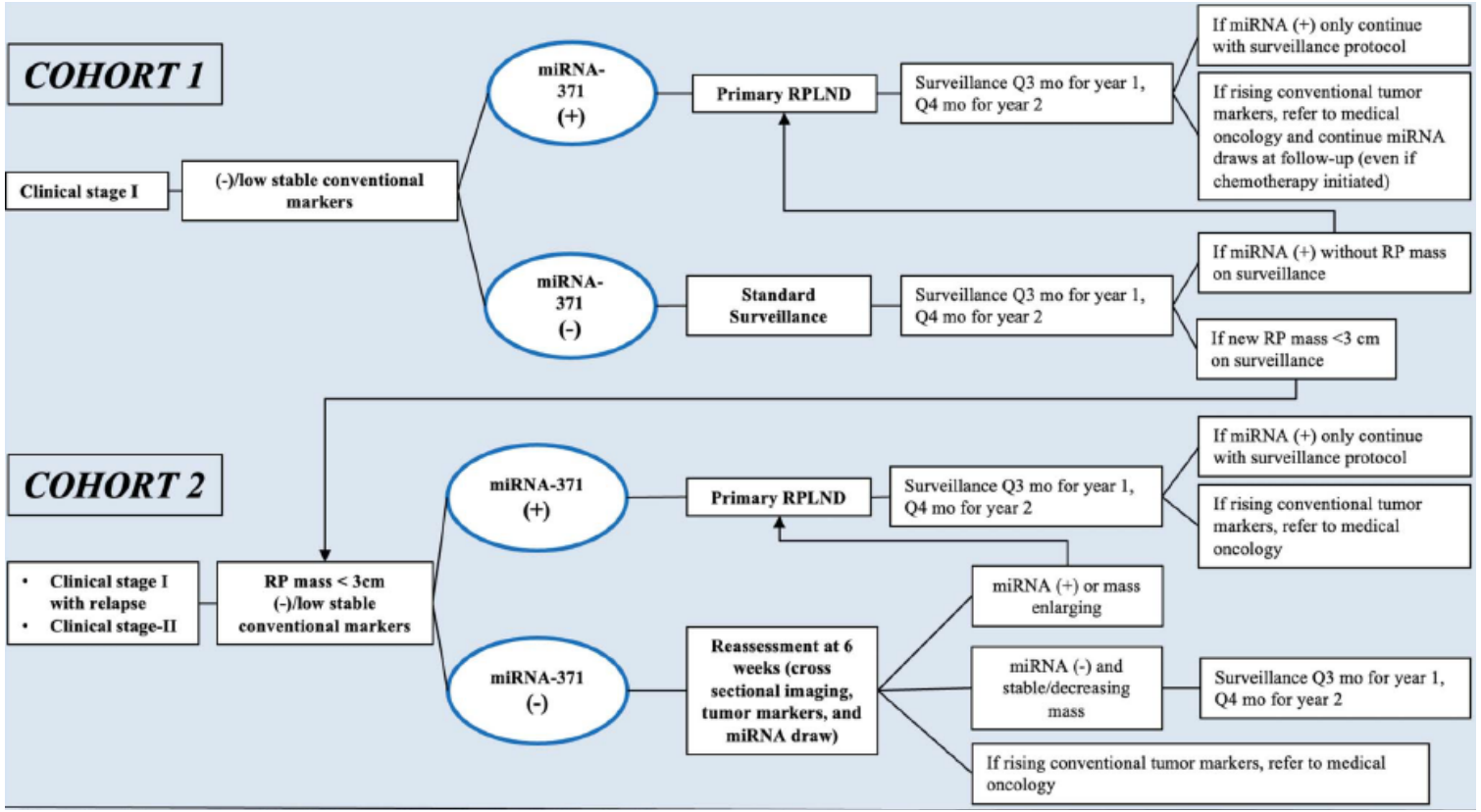
1. Dieckmann et al. J Clin Oncol 2019
2. Nappi et al. J Clin Oncol 2019

SWOG 1823: Liquid Biomarker microRNA 371a-3p in Newly Diagnosed Germ Cell Tumors



PI: Lucia Nappi, MD, PhD; Craig Nichols, MD

MAGESTIC

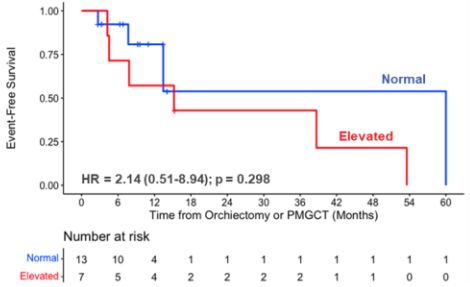


PI: Sia Daneshmad, MD
NCT06060873

Utility of circulating tumor DNA as a predictive biomarker for disease monitoring in patients with non-seminomatous germ-cell tumor

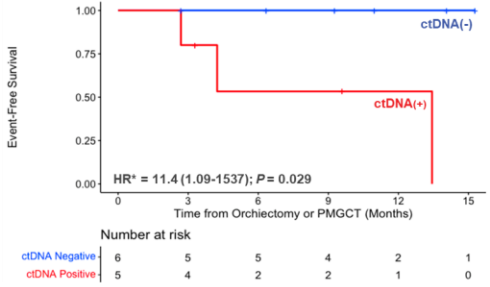
Characteristic	N=25 (IQR/%)
Median age (years)	29 (26.8-38.8)
Stage • II • III	 7 (28%) 18 (72%)
Primary treatment • RPLND • Chemotherapy • Chemotherapy + RPLND	 3 (12%) 17 (68%) 5 (20%)
Pre-orchiectomy serum tumor markers (AFP, hCG) • Normal • Elevated • Unknown	 6 (24%) 14 (56%) 5 (20%)
Serum tumor markers elevated at any point during disease course • Elevated • Normal	 16 (64%) 9 (36%)
Median follow-up (months)	10 (7.2-17.5)

STM status during surveillance post primary RPLND and/or chemotherapy (N=20)



Dynamics	Normal STMs	Elevated STMs
Events %	30.8 (4/13)	85.7 (6/7)

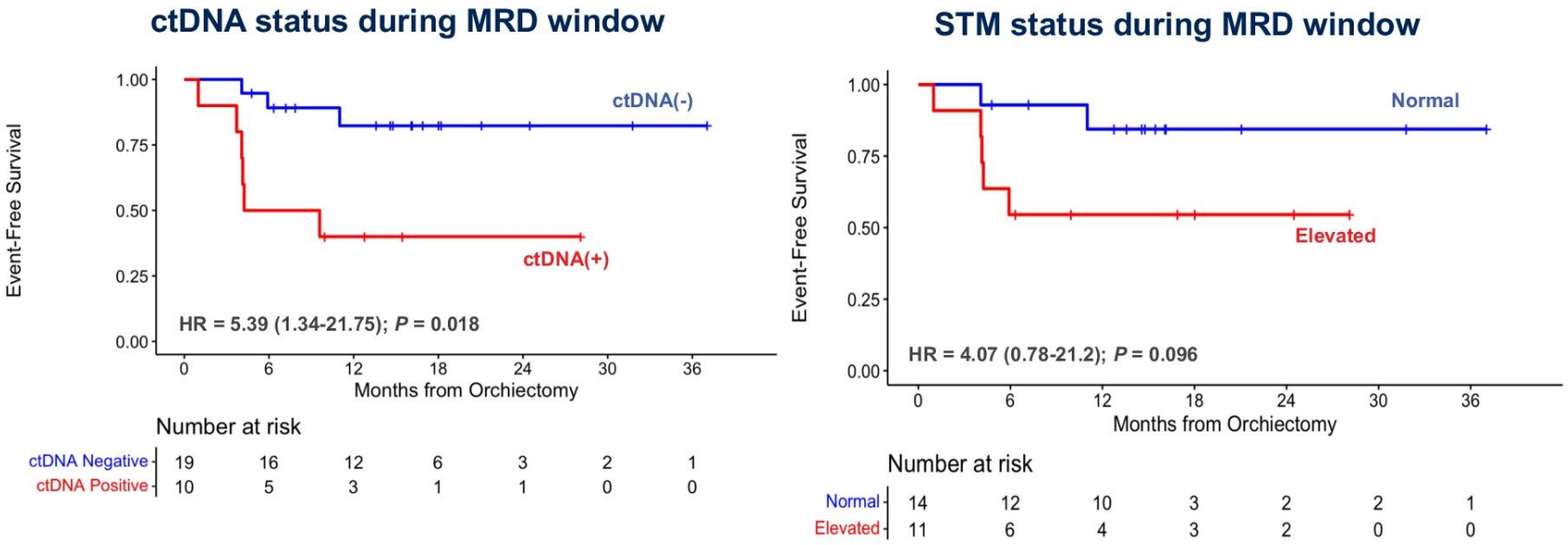
ctDNA status during surveillance post primary RPLND and/or chemotherapy (N=11)



Dynamics	ctDNA Negative	ctDNA Positive
Events %	0 (0/6)	60 (3/5)

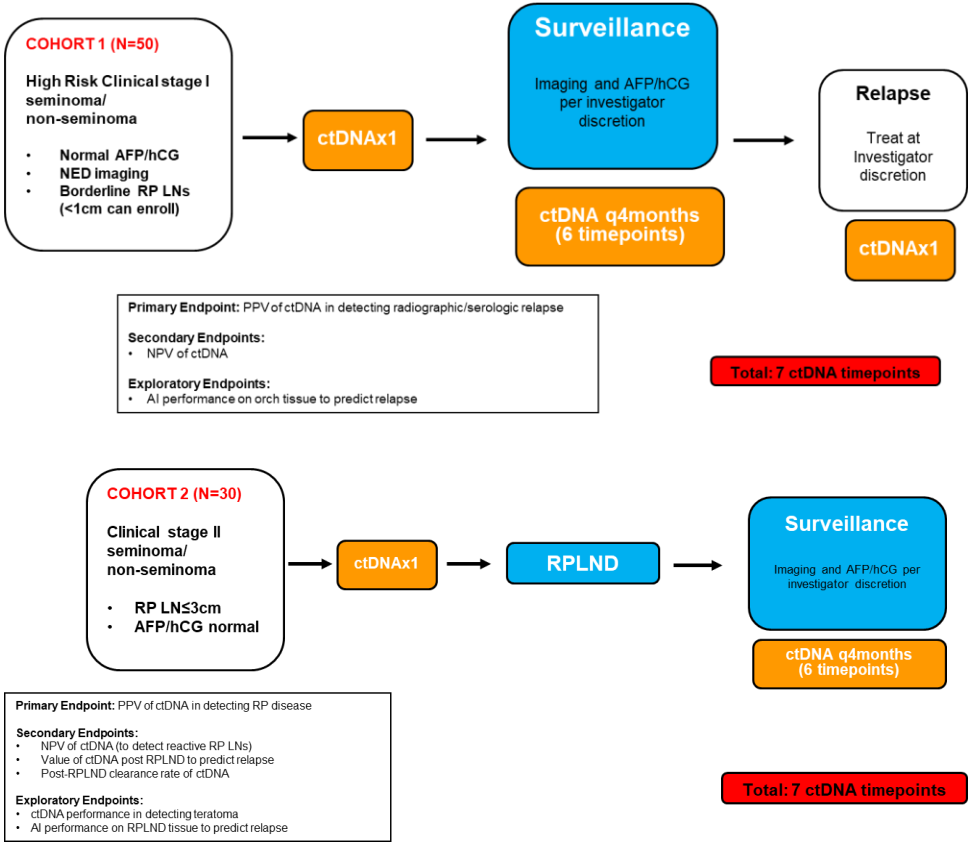
Hassoun et al. GU ASCO 2024

Figure 2: EFS by ctDNA & STM status at the MRD Window

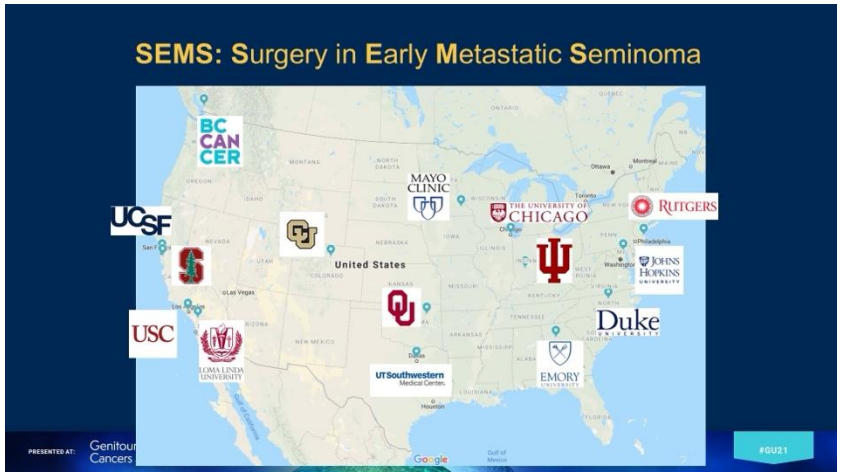


Hassoun et al. ASCO 2024

ctDNA in Early Stage Testicular Cancer



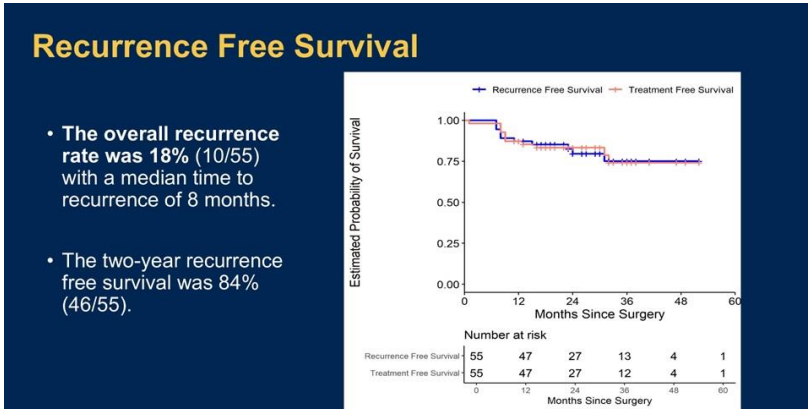
SEMS Trial: Prospective Phase II Trial of Surgery in Early Metastatic Seminoma



- Inclusion
  - Pure seminoma
  - Stage II A/B (no more than 2 LN [1-3cm] in any dimension)
  - Normal tumor markers (1.5 x ULN)
  - Imaging within 6 weeks of surgery
- Treatment: Modified template RPLND (open) – stringent surgeon requirements

Daneshmand et al. JCO 2023

SEMS Trial: Prospective Phase II Trial of Surgery in Early Metastatic Seminoma



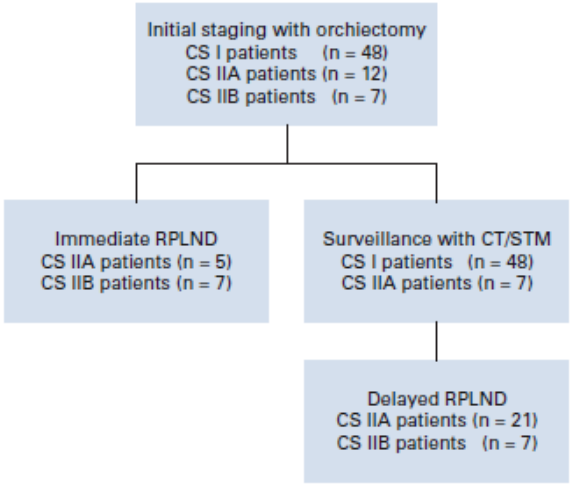
- 10/55 recurrences
- 8 treated with chemotherapy
- 2 treated with further surgery
- Short term complications consistent with known RPLND toxicity
- Median f/u 2 years:
  - Systemic treatment-free survival 85%
  - OS 100%

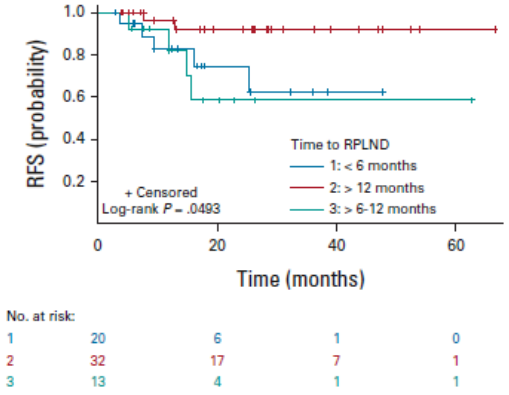
Daneshmand et al. GU ASCO 2021

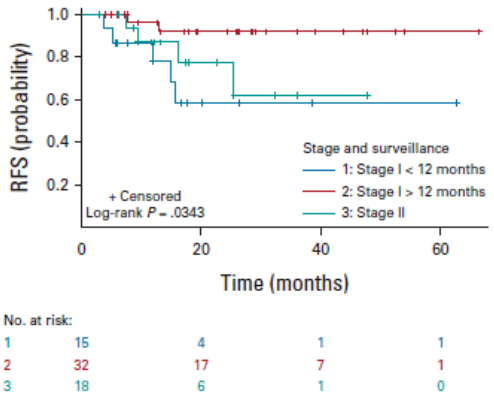
Primary Retroperitoneal Lymph Node Dissection for Stage II Seminoma: Is Surgery the New Path Forward?

Isamu Tachibana, MD[1]; Andre Alabd, MD[1]; Yan Tong, PhD, MS[2]; Alex Piroozi, BS[1]; Mohammad Mahmoud, MD[1]; Sean Q. Kem, MD[1]; Timothy A. Masterson, MD[1]; Nabil Adra, MD[3]; Richard S. Foster, MD[1]; Nasser H. Hanna, MD[3]; Lawrence H. Einhorn, MD[3]; and Clint Cary, MD, MPH[1]

- 67 pts had primary RPLND for RP-only seminoma (2014-2021)
- 1 pt had pN0
- Median f/u 22.4 months
- 2-yr RFS 80.2% (RPLND only pts, no adjuvant chemo)







Tachibana et al. J Clin Oncol 2023

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2025
Testicular Cancer - Pure Seminoma

NCCN Guidelines Index
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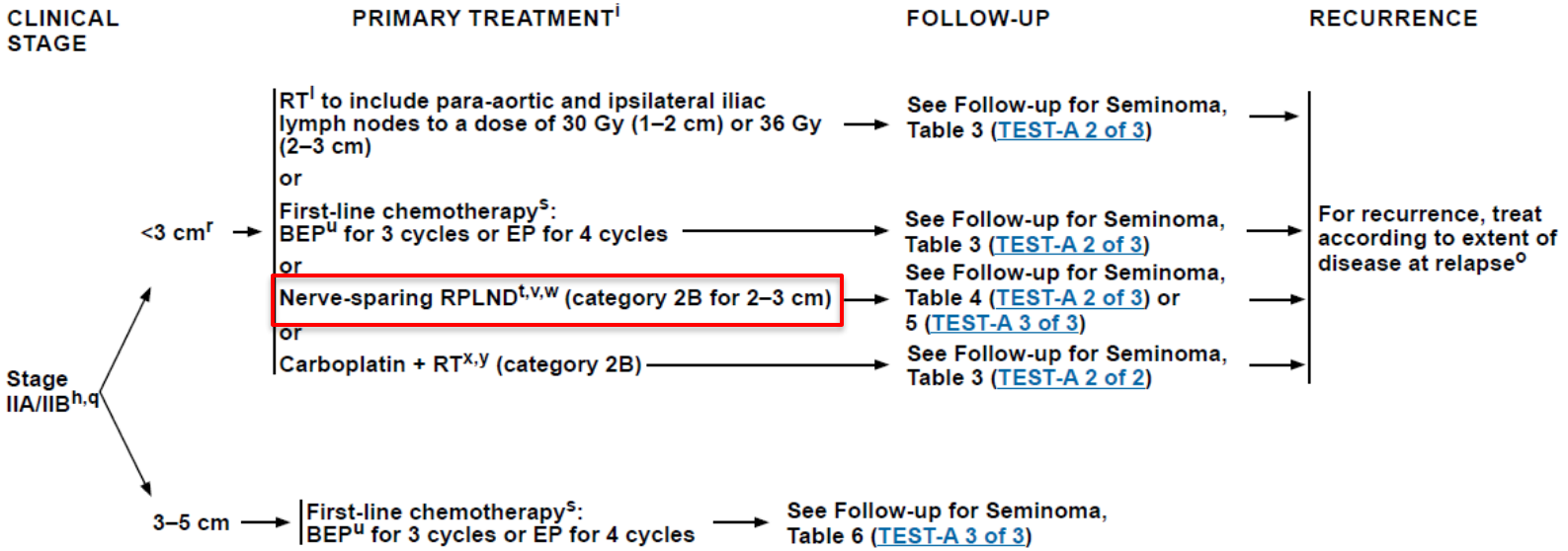


NCCN guidelines 2025

Relapsed Refractory GCT - HDCT

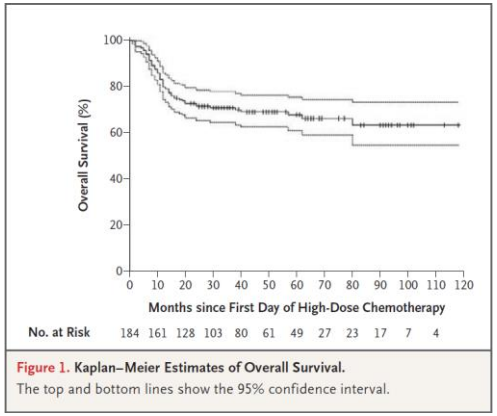
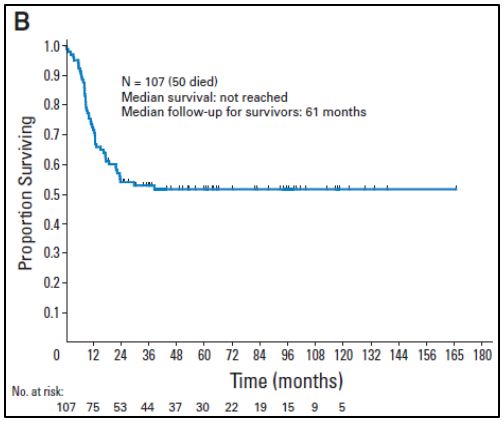
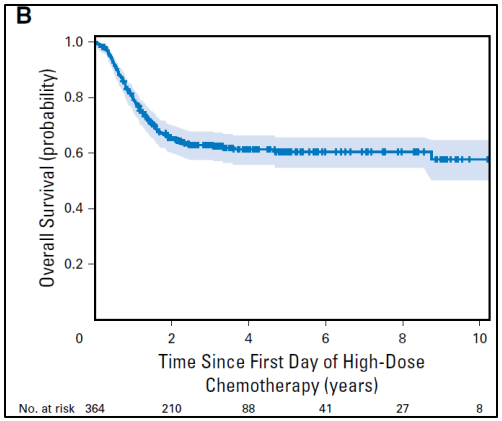


Figure 1. Kaplan–Meier Estimates of Overall Survival.
The top and bottom lines show the 95% confidence interval.

Einhorn et al. NEJM 2007
High dose carbo/etop x2



Feldman et al. JCO 2010
TI-CE



Adra et al. JCO 2017
High dose carbo/etop x2

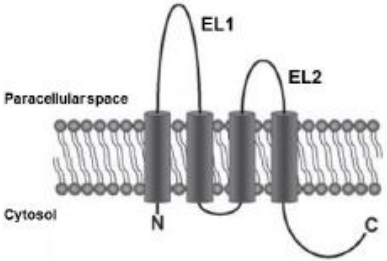
Phase II Trials of PD-1/L1 inhibition in GCT

	GU14-206[1]	APACHE-A[2]	Slovakia[3]	Japan[4]	MDACC[5]
Total Evaluable Patients	12	11	8	16	12 (2 women)
Treatment	Pembrolizumab	Durvalumab	Avelumab	Nivolumab	Pembrolizumab
Best response					
Partial response	0 (0%)	0 (0%)	0 (0%)	1 (6)%	0 (0%)
Stable disease	2 (17%)	0 (0%)	0 (0%)	3 (19%)	3 (25%)
Progressive disease	10 (83%)	11 (100%)	8 (100%)	12 (75%)	0 (0%)
Median # doses (range)	2 (1-8)	NR	NR	3 (2-46)	3 (1-14)
Landmark PFS	12 wk – 17%	9 wk – 0%	12 wk - 0%	NR	3 mo – 33%
Median PFS, mo (CI)	NR	1.5 (NR)	0.9 (0.5-1.9)	1.5 (0-23.6)	2.4 (1.5-4.5)
Median OS, mo (CI)	NR	3.1 (NR)	2.7 (1.0-3.3)	4.1 (1.6-29.8)	10.6 (4.6-27.1)

1. Adra Ann Oncol 2018 2. Necchi Eur Urol 2019 3. Mego Invest New Drugs 2019 4. Kawahara Int J Urol 2022 5. Tsimberidou Oncologist 2021

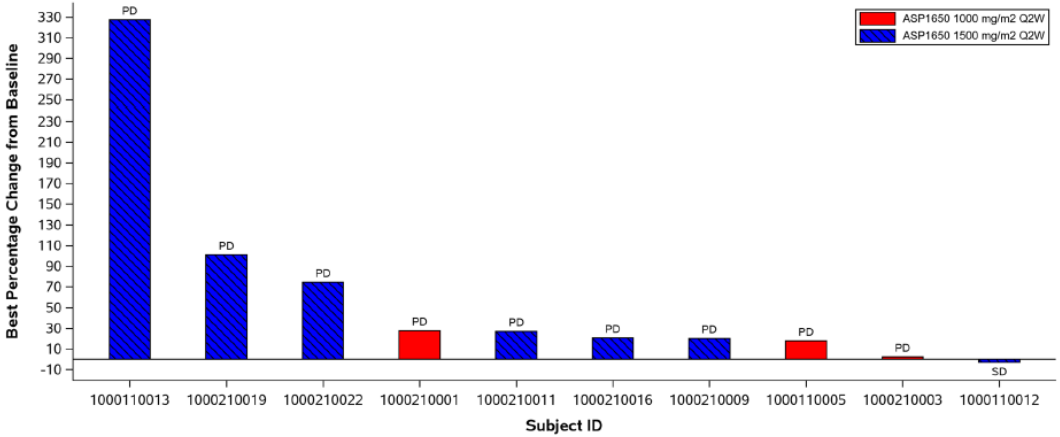
Claudin 6

- Claudin 6 (CLDN6) is a tight junction protein of the claudin tetraspanin family and is one of the earliest molecules expressed in embryonic epithelium
- Preclinical studies have indicated that, in normal tissue, CLDN6 expression is largely confined to embryonic and fetal cells
- CLDN6 is not expressed in normal adult tissues
- CLDN6 is ectopically expressed in several human malignancies including ovarian, testicular, uterine, and lung cancer



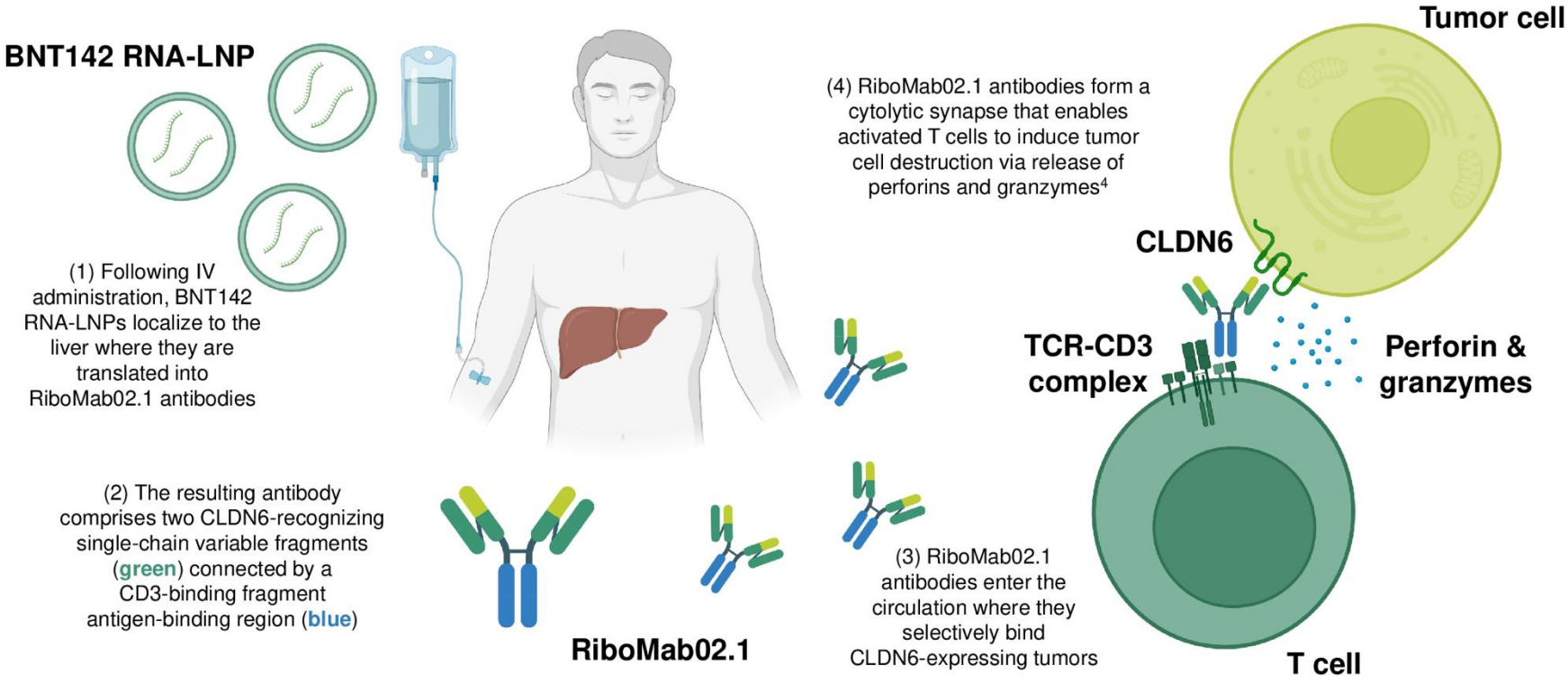
Gunzel et al. Comprehensive Physiology 2012
Hewitt et al. BMC Cancer 2006
Colegio et al. Am J Physiol Cell Physiol 2002

ASP1650 in Refractory GCT – Phase II



Adra et al. Investigational New Drugs 2022

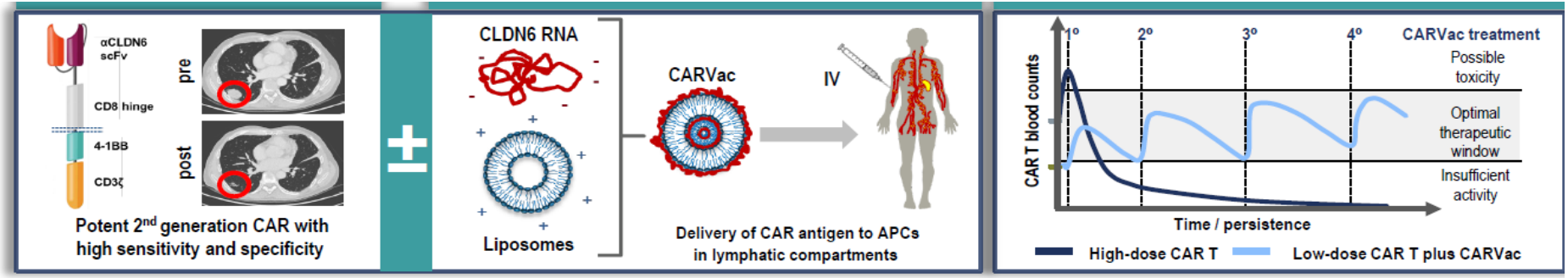
Phase I/II dose escalation trial of BNT142 in claudin-6 positive tumors



CD3: Cluster of differentiation 3; CLDN6: Claudin 6; IV: Intravenous; RNA-LNPs: Lipid nanoparticle-encapsulated mRNAs; TCR, T cell receptor. Created with BioRender

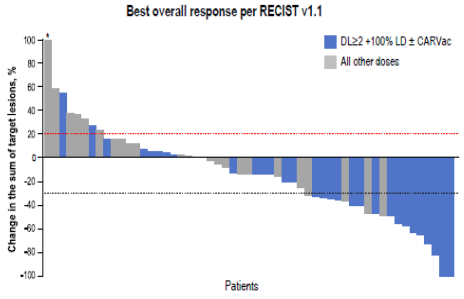
Yap et al. ASCO 2023
NCT05262530

CLDN6-specific CAR-T cells + amplifying RNA vaccine in relapsed or refractory solid tumors: the phase 1 BNT211-01 trial



Response – All Patients

BNT211-01: Best overall response

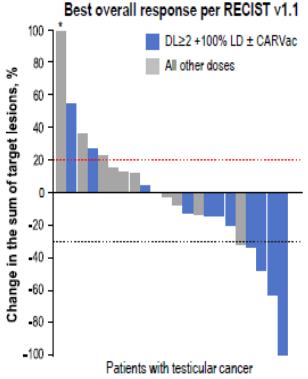


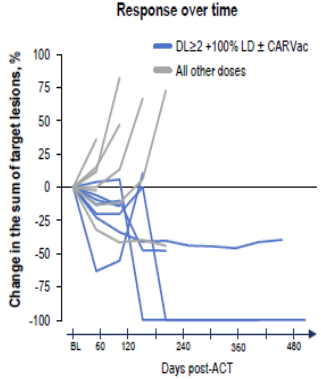
Response[a]	Total (N=74)[b]
Evaluable patients, n	64
ORR, n (%)	**21 (32.8)**
95% CI (%)	18.5–40.1
CR, n (%)	3 (4.1)
PR, n (%)	18 (24.3)
DCR, n (%)	**43 (67.2)**
95% CI (%)	46.1–69.5

Response[a]	DL≥2 +100% LD ± CARVac (N=41)[b,c]
Evaluable patients, n	33
ORR, n (%)	17 (51.5)
95% CI (%)	26.3–57.9
DCR, n (%)	28 (84.8)
95% CI (%)	51.9–81.9

Data cut off: 16 May 2024. Presented are data from patients who received automated process CAR T and had a tumor assessment at baseline and at least 7 weeks post-ACT (N=77).
[b]Includes tumor marker responses. [c]Excludes patients who received an out-of-specification product. [d]DL2=1×10⁸; DL3=3-5×10⁸ CAR T cells. [e]Bar truncated at 100% (actual value was 196%).
ACT, adoptive cell transfer; CAR, chimeric antigen receptor; CARVac, CAR T-cell amplifying RNA vaccine; CI, confidence interval; CR, complete response; DCR, disease control rate; DL, dose level; LD, lymphodepletion; ORR, objective response rate; PR, partial response.

Response – GCT Patients





Response[a]	Total (N=27)[b]
Evaluable patients, n	25
ORR, n (%)	6 (24.0)
95% CI (%)	8.6–42.3
DCR, n (%)	14 (56.0)
95% CI (%)	32.0–71.3

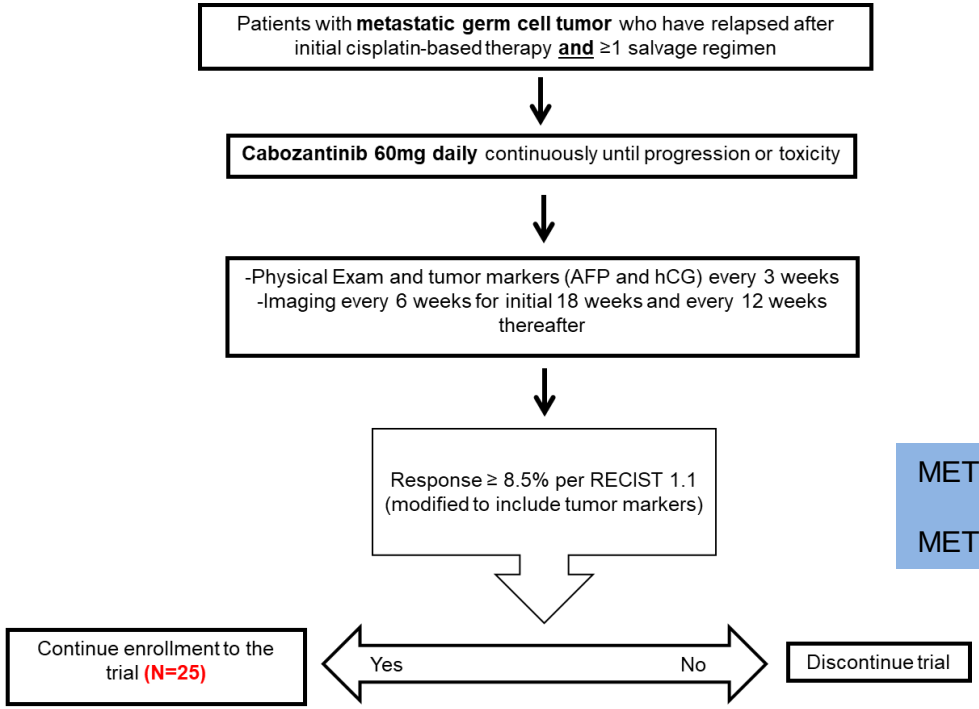
Response[a]	DL≥2 +100% LD ± CARVac (N=14)[b,c]
Evaluable patients, n	12
ORR, n (%)	5 (41.7)
95% CI (%)	12.8–64.9
DCR, n (%)	9 (75.0)
95% CI (%)	35.1–87.2

Haanen et al. ESMO 2024

Phase II Trial Cabozantinib in Relapsed/Refractory GCT

Simon's Stage I:
N=18

Simon's Stage II:
N=43 (total)

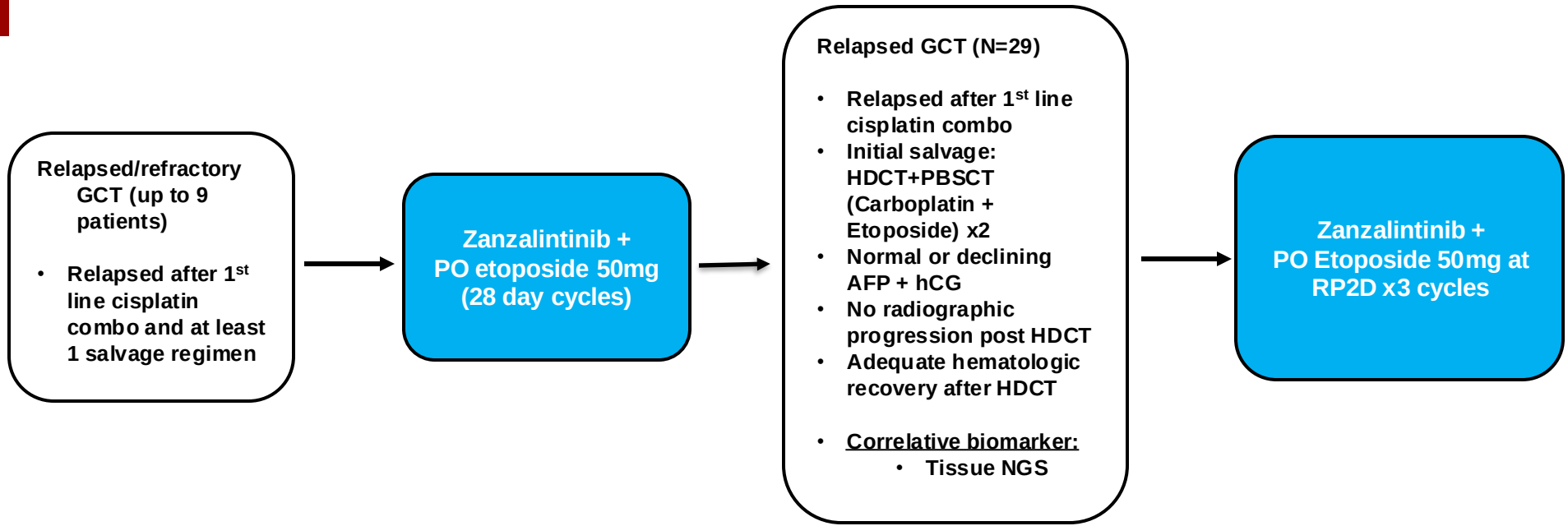


MET overexpression by IHC

MET amplification by NGS

PI: Jennifer King
NCT04876456

Maintenance XL092 with oral etoposide following high-dose chemotherapy in patients with relapsed metastatic GCT



Primary endpoint: 12-month PFS

PI: Jennifer King

Remaining Challenges

- Biomarkers miR371, ctDNA
- Surgery in early metastatic disease SOC non-bulky stage IIA/B
- Intermediate/Poor Risk GCT
- Brain Metastasis
- Late Relapse
- Mediastinal Non-seminoma
- Relapsed/Refractory GCT CLDN6, VEGF/c-MET, hypomethylating agents, GPC3
- Survivorship