

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



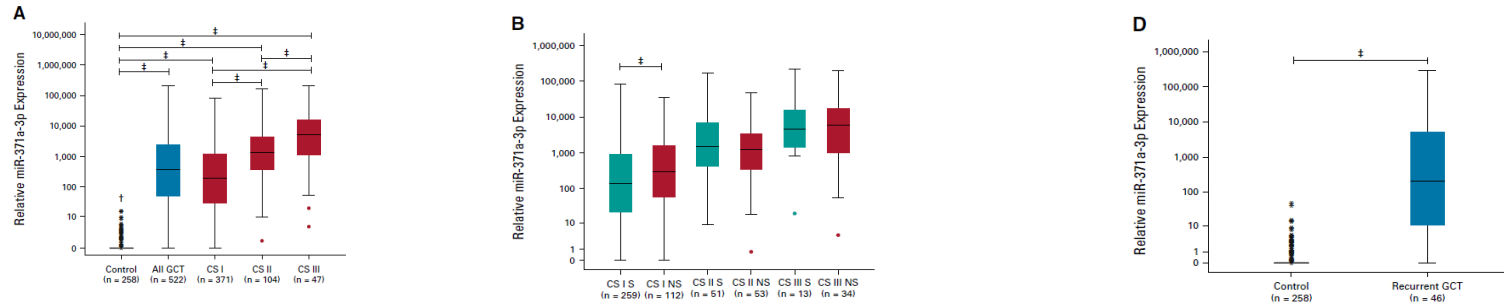
miR-371a-3p vs. Conventional Tumor Markers

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%
Extragenital	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	+	+	+

¹Dieckmann et al. J Clin Oncol 2019



miR-371a-3p Expression

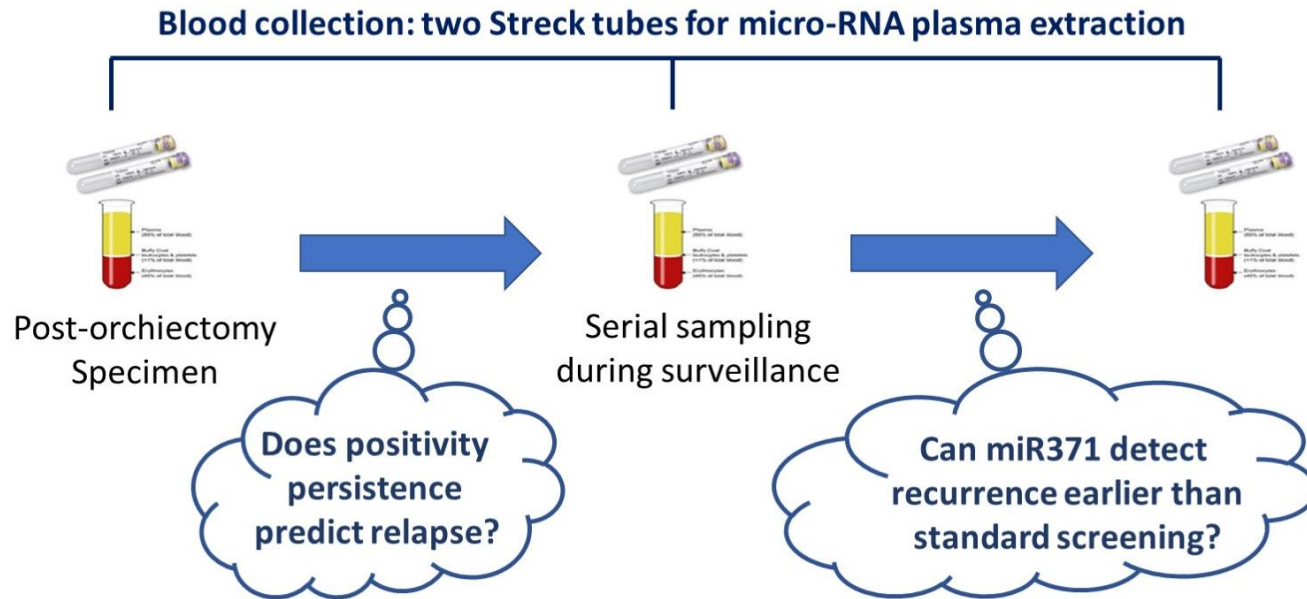


miR371 Expression	GCT History With Clinically Confirmed aGCM (No. of cases)	GCT History With No Clinically Confirmed GCM (to March 2019; No. of controls)	Total No.
Plasma miR371 expression on prospectively obtained sample	44 TP _s	0 FP _s	44 positive tests
No plasma miR371 expression on prospectively obtained sample	2 FN _s	86 TN _s	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



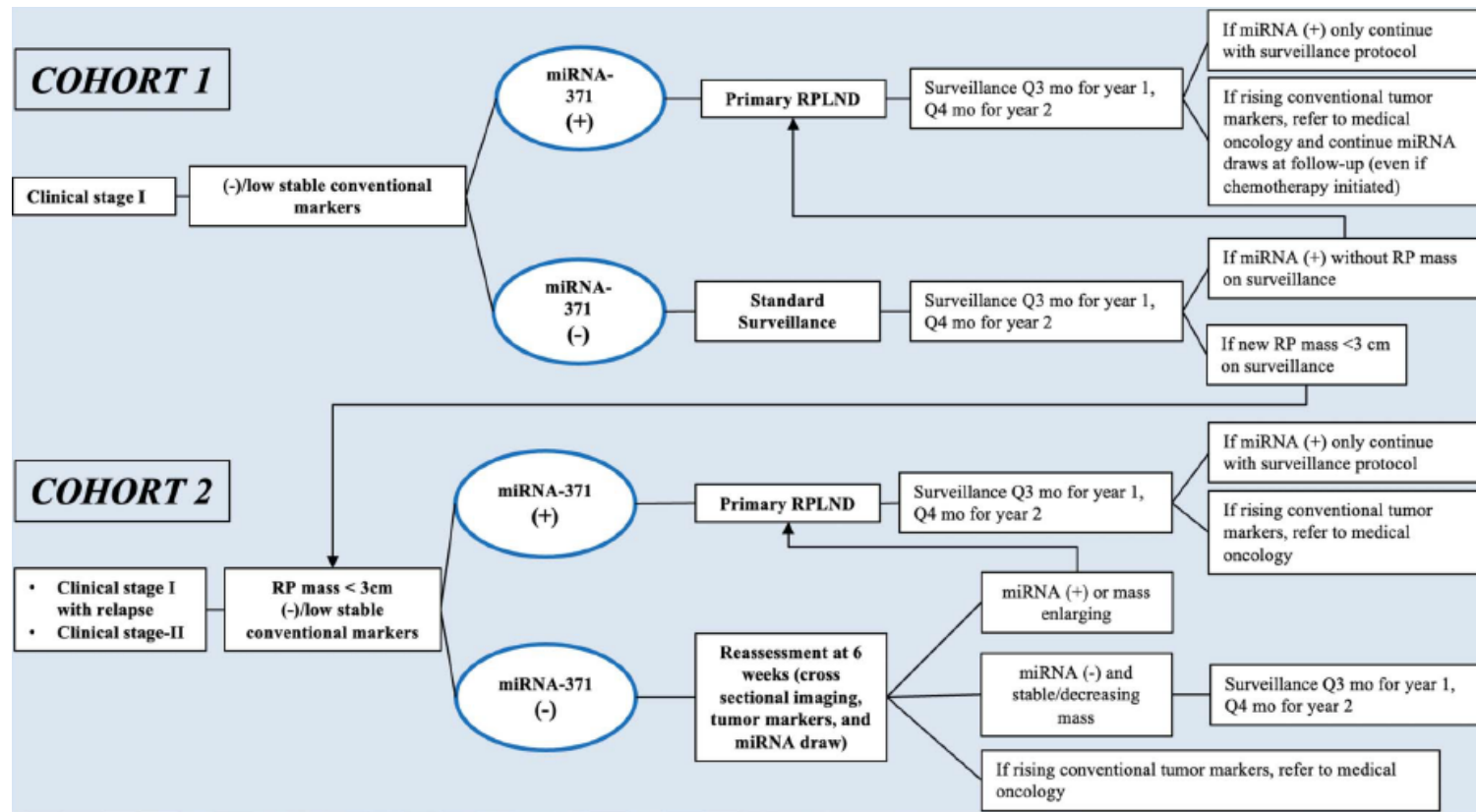
SWOG 1823: Liquid Biomarker microRNA 371a-3p in Newly Diagnosed Germ Cell Tumors



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



MAGESTIC



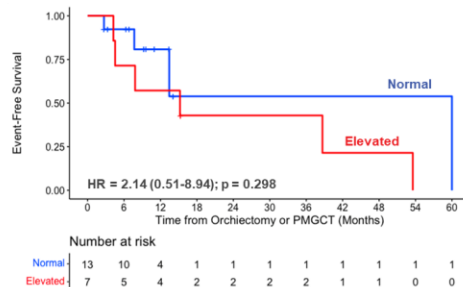
PI: Sia Daneshmad, MD
NCT06060873



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

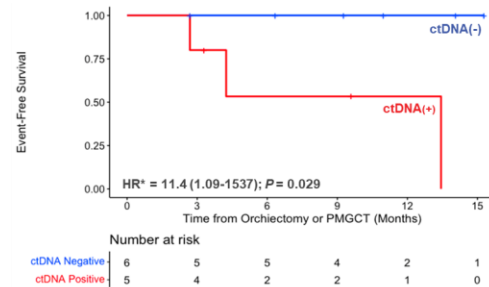
Characteristic	N=25 (IQR/%)
Median age (years)	29 (26.8-38.8)
Stage	
• II	7 (28%)
• III	18 (72%)
Primary treatment	
• RPLND	3 (12%)
• Chemotherapy	17 (68%)
• Chemotherapy + RPLND	5 (20%)
Pre-orchietomy serum tumor markers (AFP, hCG)	
• Normal	6 (24%)
• Elevated	14 (56%)
• Unknown	5 (20%)
Serum tumor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



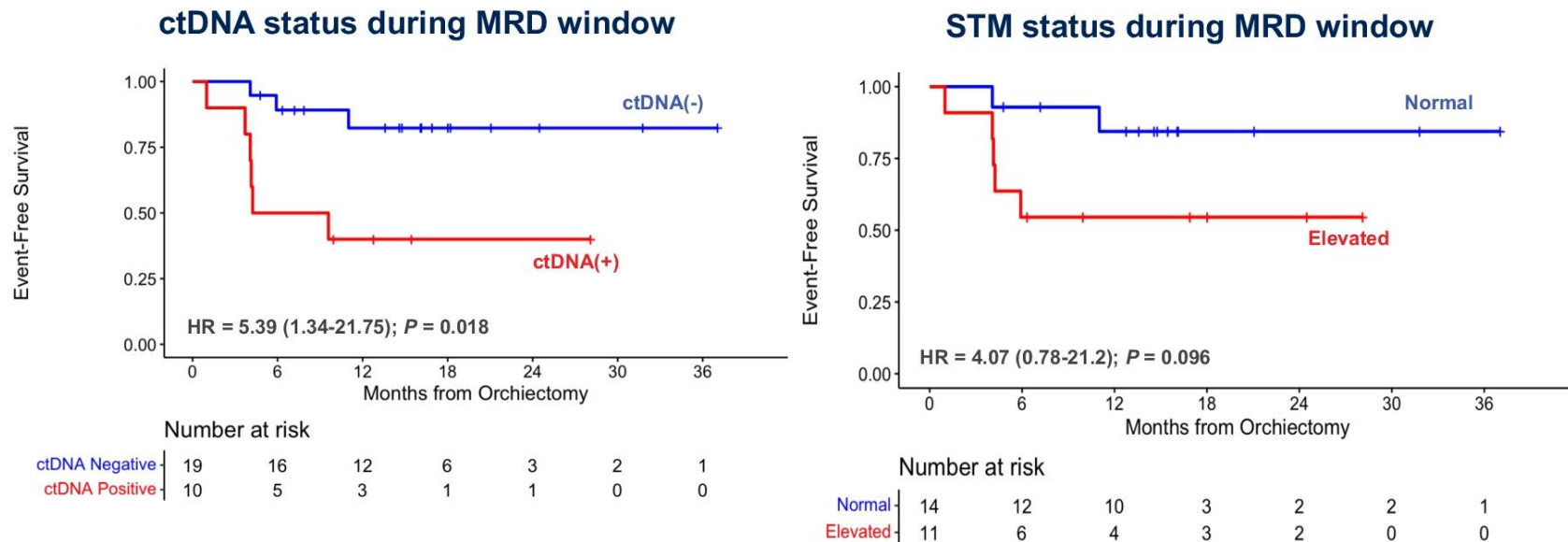
Dynamics	ctDNA Negative	ctDNA Positive
Events %	0 (0/6)	60 (3/5)



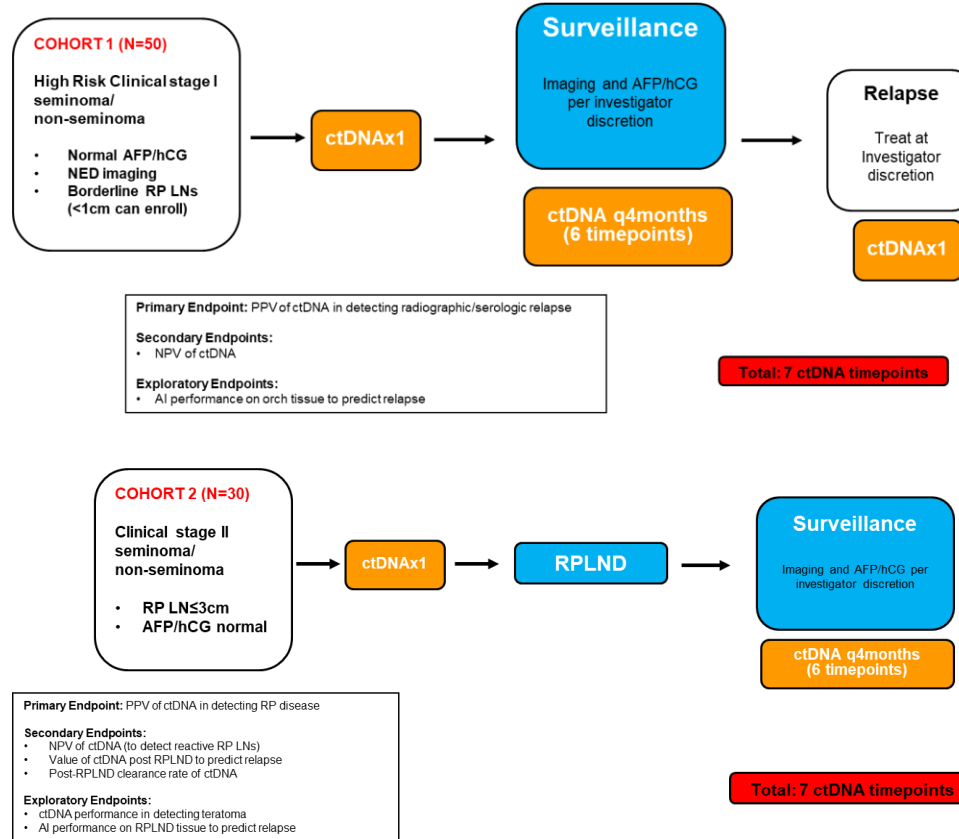
Hassoun et al. GU ASCO 2024

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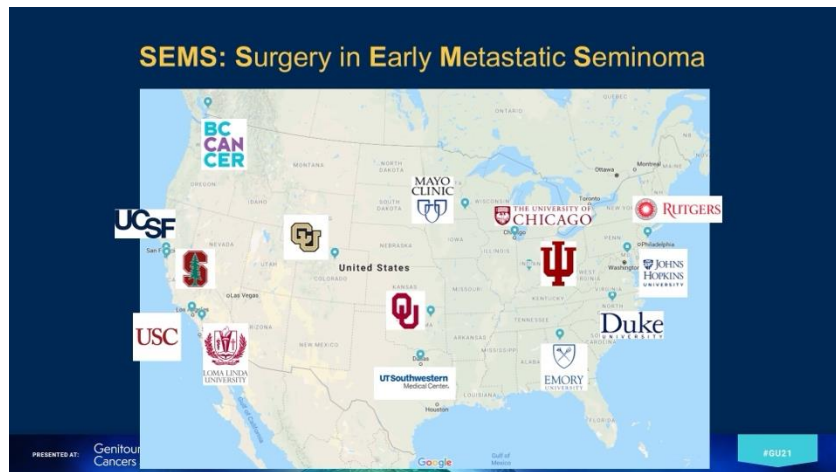
Figure 2: EFS by ctDNA & STM status at the MRD Window



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

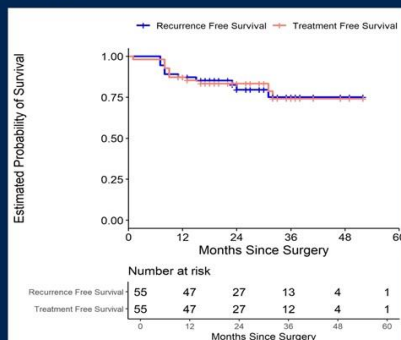


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SEMS Trial: Prospective Phase II Trial of Surgery in Early Metastatic Seminoma

Recurrence Free Survival

- The overall recurrence rate was 18% (10/55) with a median time to recurrence of 8 months.
- The two-year recurrence free survival was 84% (46/55).



- 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%



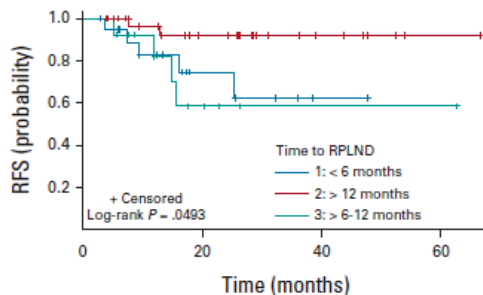
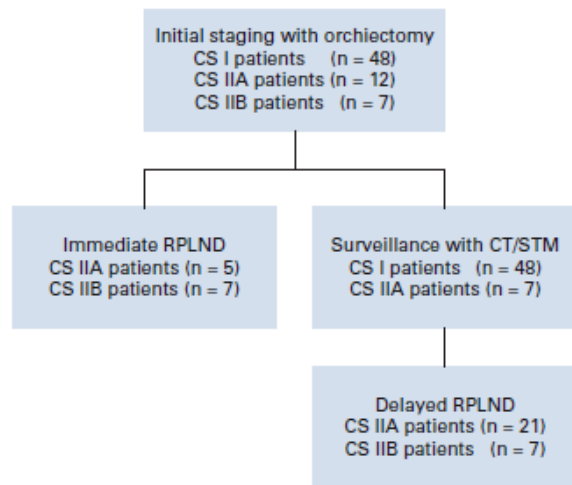
Daneshmand et al. GU ASCO 2021

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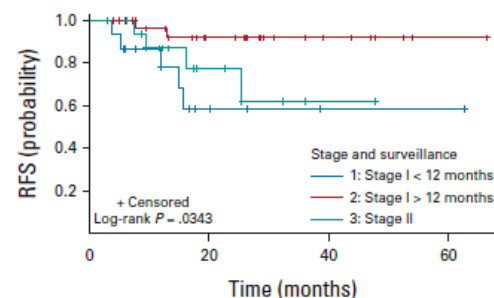
Primary Retroperitoneal Lymph Node Dissection for Stage II Seminoma: Is Surgery the New Path Forward?

Isamu Tachibana, MD¹ ; Andre Alabd, MD¹; Yan Tong, PhD, MS² ; Alex Pirooz, BS¹; Mohammad Mahmoud, MD¹; Sean Q. Kem, MD¹ ; Timothy A. Masterson, MD¹; Nabil Adra, MD³ ; Richard S. Foster, MD¹; Nasser H. Hanna, MD²; Lawrence H. Einhorn, MD³; and Clint Cary, MD, MPH¹ 

- 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)



No. at risk:				
1	20	6	1	0
2	32	17	7	1
3	13	4	1	1



No. at risk:				
1	15	4	1	1
2	32	17	7	1
3	18	6	1	0

Tachibana et al. J Clin Oncol 2023





NCCN Guidelines Version 1.2025

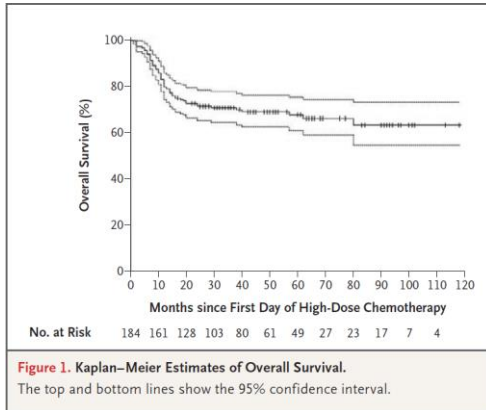
Testicular Cancer - Pure Seminoma

CLINICAL STAGE	PRIMARY TREATMENT ⁱ	FOLLOW-UP	RECURRENCE
Stage IIA/IIB ^{h,q}	RT ^l to include para-aortic and ipsilateral iliac lymph nodes to a dose of 30 Gy (1–2 cm) or 36 Gy (2–3 cm)	See Follow-up for Seminoma, Table 3 (TEST-A 2 of 3)	For recurrence, treat according to extent of disease at relapse ^o
	or		
	<3 cm ^r → First-line chemotherapy ^s : BEP ^u for 3 cycles or EP for 4 cycles	See Follow-up for Seminoma, Table 3 (TEST-A 2 of 3)	
	or	See Follow-up for Seminoma, Table 4 (TEST-A 2 of 3) or 5 (TEST-A 3 of 3)	
	Nerve-sparing RPLND ^{t,v,w} (category 2B for 2–3 cm)		
	or		
	Carboplatin + RT ^{x,y} (category 2B)	See Follow-up for Seminoma, Table 3 (TEST-A 2 of 2)	
3–5 cm →	First-line chemotherapy ^s : BEP ^u for 3 cycles or EP for 4 cycles	See Follow-up for Seminoma, Table 6 (TEST-A 3 of 3)	

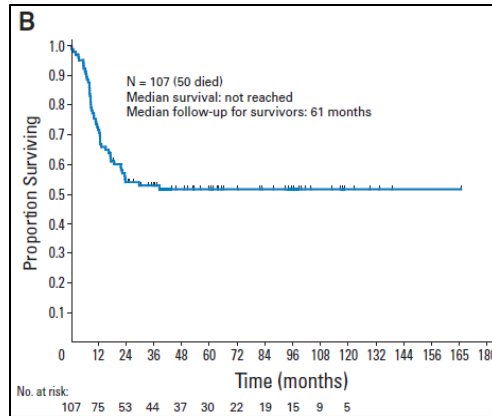
NCCN guidelines 2025



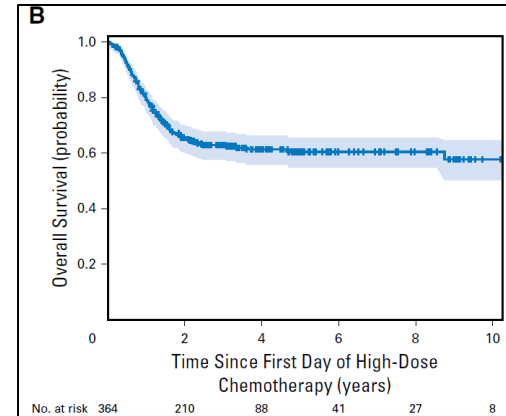
Relapsed Refractory GCT - HDCT



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

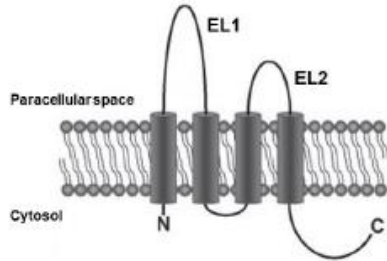
	GU14-206 ¹	APACHE-A ²	Slovakia ³	Japan ⁴	MDACC ⁵
Total Evaluable Patients	12	11	8	16	12 (2 women)
Treatment	Pembrolizumab	Durvalumab	Avelumab	Nivolumab	Pembrolizumab
Best response					
Partial response	0 (0%)	0 (0%)	0 (0%)	1 (6%)	0 (0%)
Stable disease	2 (17%)	0 (0%)	0 (0%)	3 (19%)	3 (25%)
Progressive 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



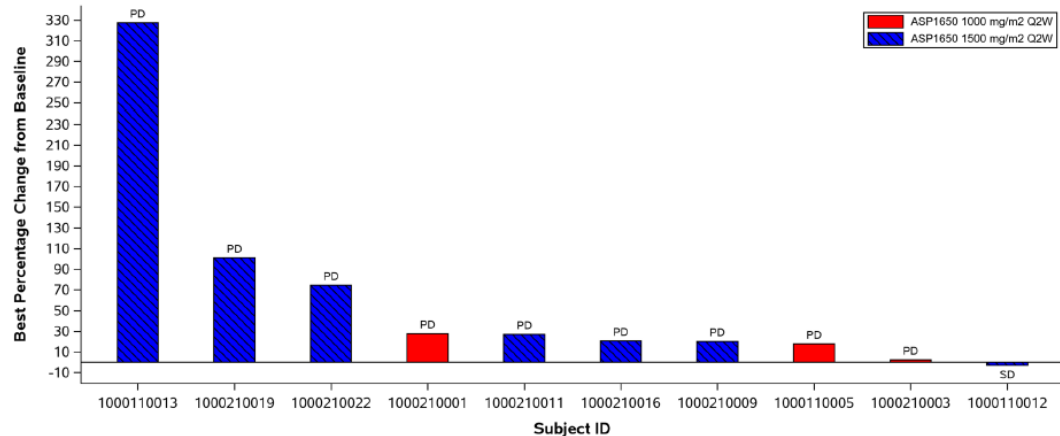
Claudin 6

- 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

BNT142 RNA-LNP

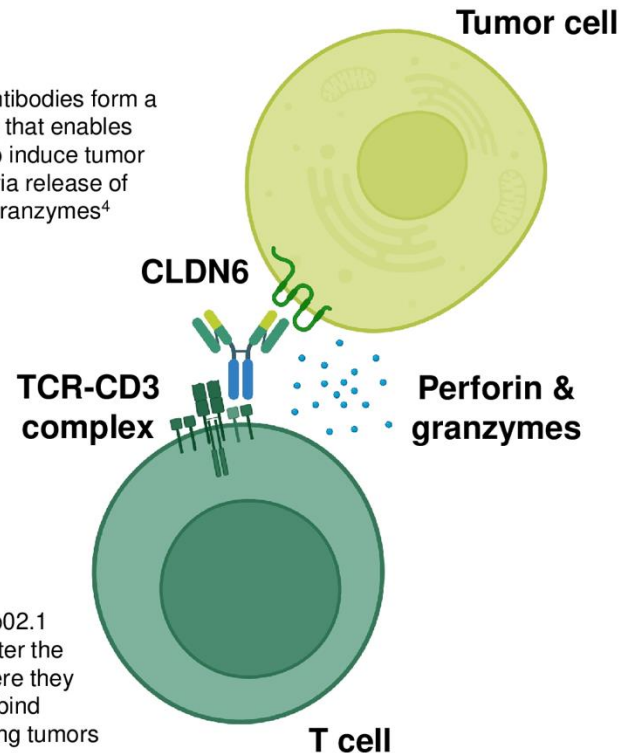
(1) Following IV administration, BNT142 RNA-LNPs localize to the liver where they are translated into RiboMab02.1 antibodies

(2) The resulting antibody comprises two CLDN6-recognizing single-chain variable fragments (**green**) connected by a CD3-binding fragment antigen-binding region (**blue**)

RiboMab02.1

(4) RiboMab02.1 antibodies form a cytolytic synapse that enables activated T cells to induce tumor cell destruction via release of perforins and granzymes⁴

(3) RiboMab02.1 antibodies enter the circulation where they selectively bind CLDN6-expressing tumors



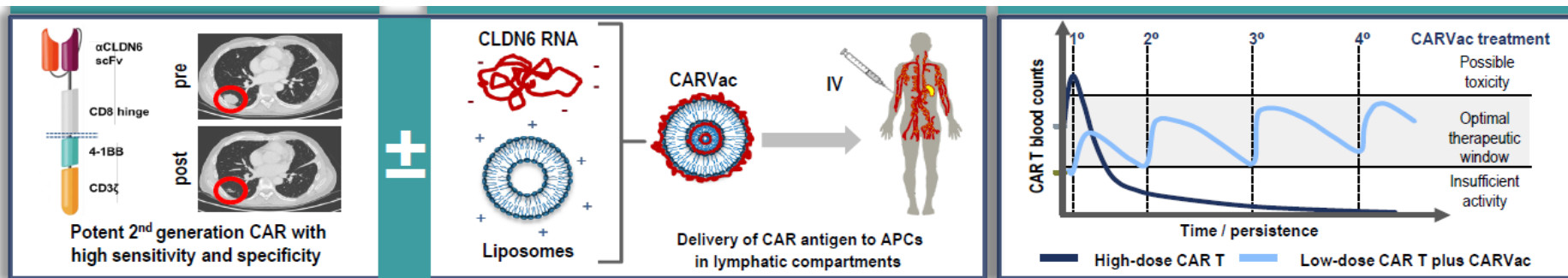
CD3: Cluster of differentiation 3; CLDN6: Claudin 6; IV: Intravenous; RNA-LNPs: Lipid nanoparticle-encapsulated mRNAs; TCR, T cell receptor. Created with BioRender

Yap et al. ASCO 2023
NCT05262530



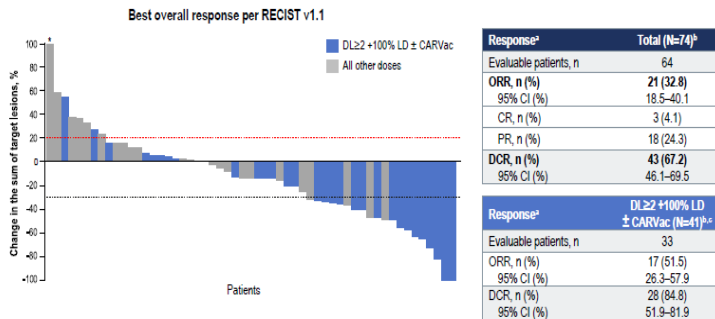
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CLDN6-specific CAR-T cells + amplifying RNA vaccine in relapsed or refractory solid tumors: the phase 1 BNT211-01 trial



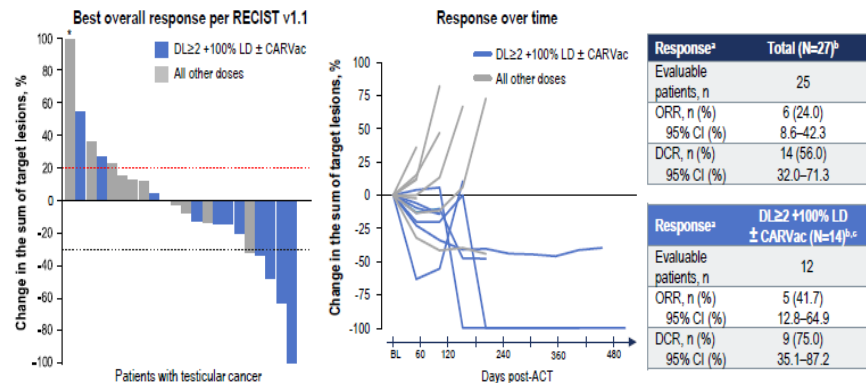
Response – All Patients

BNT211-01: Best overall response



Data cut off: 15 May 2024. Presented are data from patients who received autologous process CAR T and had a tumor assessment at baseline and at least 7 weeks post-ACT (N=77).
^aIncludes tumor marker response. ^bExcludes patients who received an out-of-specification product. ^cDL ≥ 2 +100% LD ≥ 2 +100% LD CAR T cells. ^dSee footnote at 100% (total value was 96%).
 ACT, adoptive cell transfer; CAR, chimeric antigen receptor; CARVax, 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



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)

Patients with **metastatic germ cell tumor** who have relapsed after initial cisplatin-based therapy and ≥ 1 salvage regimen



Cabozantinib 60mg daily continuously until progression or toxicity



-Physical Exam and tumor markers (AFP and hCG) every 3 weeks
-Imaging every 6 weeks for initial 18 weeks and every 12 weeks thereafter



Response $\geq 8.5\%$ per RECIST 1.1
(modified to include tumor markers)

MET overexpression by IHC

MET amplification by NGS

Continue enrollment to the trial (**N=25**)

Yes

No

Discontinue trial

PI: Jennifer King
NCT04876456



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

Relapsed/refractory GCT (up to 9 patients)

- Relapsed after 1st line cisplatin combo and at least 1 salvage regimen

Zanzalintinib +
PO etoposide 50mg
(28 day cycles)

Relapsed GCT (N=29)

- Relapsed after 1st line cisplatin combo
- Initial salvage: HDCT+PBSCT (Carboplatin + Etoposide) x2
- Normal or declining AFP + hCG
- No radiographic progression post HDCT
- Adequate hematologic recovery after HDCT
- Correlative biomarker:
 - Tissue NGS

Zanzalintinib +
PO Etoposide 50mg at
RP2D x3 cycles

Phase I

Phase II

PI: Jennifer King

Primary endpoint: 12-month PFS



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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

