Immunotherapy for Germ Cell Tumors and Penile Cancer

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Disclosures

- Research support from AstraZeneca (Inst), Genentech/Roche (Inst), Decibel Therapeutics (Inst), Immunai (Inst), and Adaptive (Inst)
- Consultant/advisory board member for Merck and BioNTech
- Stock/equity ownership in Urogen, Allogene Therapeutics, Neogene Therapeutics, Kronos Bio, 76Bio, Vida Ventures, Ginkgo Bioworks, Inconovir, and Doximity.

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A 39 y/o man with poor-risk nonseminomatous germ cell tumor of the left testis has been treated with 4 cycles of bleomycin, etoposide and cisplatin (BEPx4), 4 cycles of paclitaxel, ifosfamide, and cisplatin (TIPx4), and high dose carboplatin and etoposide (TI-CE regimen). He is currently progressing in multiple lung and liver metastases with a rising serum HCG. Which of the following is not an appropriate next step in management?

A. Gemcitabine and oxaliplatin chemotherapy
B. Clinical trial
C. Next generation sequencing
D. Ipilimumab and nivolumab

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Does immunotherapy play a role in the management of patients with germ cell tumors?

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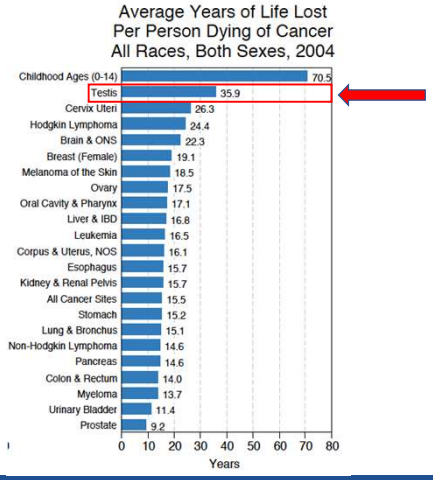
Background – germ cell tumors (GCTs)

- 95% of GCTs are testicular primary tumors, but GCTs may also arise in the retroperitoneum, mediastinum, and pineal gland.
- The incidence is rising steadily and is highest in white and Hispanic men and lowest in Asian and black men.
- Seminoma and nonseminomatous germ cell tumor (NSGCT) each comprise approximately 50% of germ cell tumor cases.
- >80% of patients with metastatic GCTs are cured with cisplatin-based combination chemotherapy and International Germ Cell Cancer Collaborative Group (IGCCCG) risk-adapted treatment, but…

Background – platinum refractory GCT

- There are no curative options for patients with germ cell tumors (GCT) who progress after high-dose chemotherapy
- Outcomes are dismal - median OS < 1 year, PFS 1 mo, 16-week PFS 6%[1]
- Death results in the greatest number of life years lost of any non-childhood malignancy



1. Feldman, et al. *Cancer* 2012

Rationale – immune checkpoint inhibition (ICI) for platinum refractory GCT

- Despite low tumor mutation burden, GCT thought to be immune recognized as evidenced by:
  - Immune cell infiltration[1,2]
  - Anti-tumor humoral responses[3,4]
  - Thymic hyperplasia after chemotherapy[5,6]
  - Spontaneous regression[7,8]
  - Expression of immunogenic cancer testis antigens[8,9]
  - Immune-related genes associated with a favorable outcome[10]
- In the TCGA:
  - A T cell-inflamed tumor microenvironment was present in >50% of GCT specimens including seminoma and non-seminoma[11]
  - Degree of PD-L1 and CD8A RNA expression is similar to melanoma[12]
- Seminoma and NSGCT frequently stain positive for PD-L1 by IHC[13,14]
- Anecdotal reports of response to immune checkpoint blockade[11,15,16]

1. Hvarness T et al. J Reprod Immunol. 2013 **2.** Yakirevich E et al. J Pathol. 2002 **3.** Willis SN et al. J Immunol. 2009 **4.** Dhodapkar KM et al. PNAS. 2010 **5.** Tait DM et al. Eur J Surg Oncol. 1986 **6.** Kissin CM et al . Radiology. 1987 **7.** Qureshi JM et al. J Urol. 2014 **8.** Comiter CV et al. J Urol. 1996 **9.** Yuasa T et al. J Urol. 2001 **10.** Korkola JE et al. J Clin Oncol. 2009 **11.** Shah S et al. Cancer Immunol Res. 2016 **12.** Ock C-Y et al. Clin Cancer Res. 2016 **13.** Fankhauser CD et al. Br J Cancer. 2015 **14.** Cierna Z et al. Ann Oncol. 2016 **15.** van Heijst JW et al. Nat Med. 2013 **15.** Zschabitz et al. Eur J Cancer 2017 **16.** Chi et al. Clin Genitourin Cancer 2017

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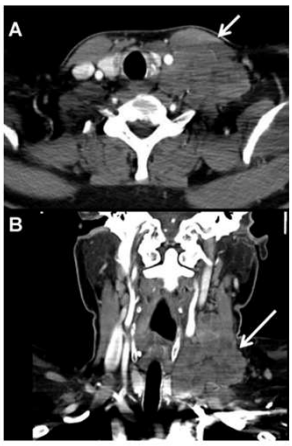
Clinical response of a patient with testicular cancer (embryonal carcinoma) to anti-PD-1 therapy



Shah, et al. *Cancer Immunol Res* 2016

8

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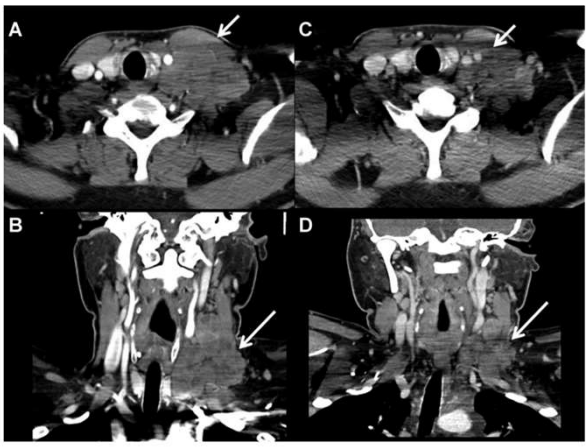
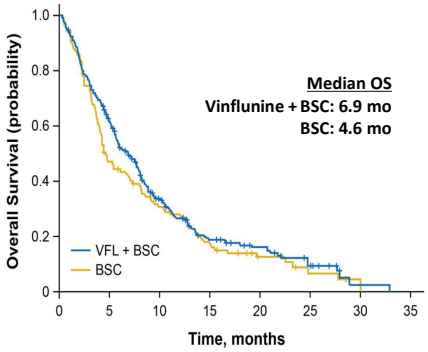


Shah, et al. *Cancer Immunol Res* 2016

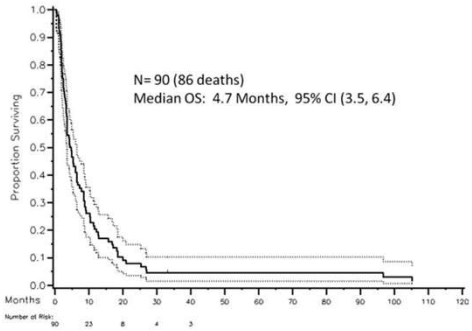
Treatment after platinum resistance - urothelial carcinoma vs germ cell tumors (2013)

Urothelial Carcinoma - Vinflunine



Bellmunt, et al. *JCO* 2009

Germ Cell Tumors – 7 phase II clinical trials

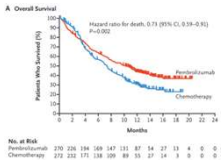


Feldman, et al. *Cancer* 2012

Treatment after platinum resistance - urothelial carcinoma vs germ cell tumors (2023)

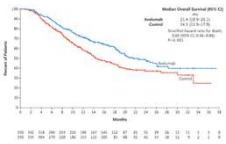
Urothelial Carcinoma – PD-1/PD-L1 Blockade

Pembrolizumab – Platinum refractory



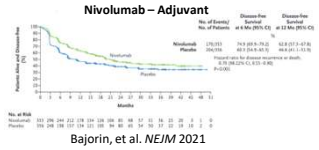
Bellmunt, et al. *NEJM* 2017

Avelumab – Maintenance after platinum



Powles, et al. *NEJM* 2020

Nivolumab – Adjuvant



Bajorin, et al. *NEJM* 2021

Total FDA Approvals Since 2013 – 6 (3 IO)

Germ Cell Tumors – PD-1/PD-L1 Blockade

?

Phase II trials of PD-1/L1 inhibition in patients with platinum refractory GCTs – patient characteristics

	GU14-206[1]	APACHE (A)[2]	Slovakia[3]	Japan[4]	MDACC[5]
Total Patients	**12**	**11**	**8**	**17**	**12 (2 women)**
Drug	Pembrolizumab	Durvalumab	Avelumab	Nivolumab	Pembrolizumab
Location of Primary					
Testis	11 (92%)	8 (73%)	7 (88%)	12 (71%)	7 (58%)
Other	0 (0%)	3 (27%)	1 (12%)	2 (12%)	3 (25%)
Mediastinum	1 (8%)	0 (0%)	0 (0%)	3 (18%)	2 (17%)
Tumor Histology					
Seminoma	0 (0%)	1 (9%)	0 (0%)	3 (18%)	0 (0%)
Nonseminoma	12 (100%)	10 (91%)	0 (0%)	14 (82%)	12 (100%)
Prior High-Dose Chemo	6 (50%)	8 (73%)	2 (25%)	3 (18%)	NR
Non-Pulm Visceral Mets	5 (42%)	9 (82%)	5 (63%)	8 (47%)	6 (50%)

NR, not-reported

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

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Phase II trials of PD-1/L1 inhibition in patients with platinum refractory GCTs – response data

	GU14-206[1]	APACHE-A[2]	Slovakia[3]	Japan[4]	MDACC[5]
Total Evaluable Patients	12	11	8	16	12 (2 women)
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)

NR, not-reported

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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)

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Phase II trials of combination ICI in patients with platinum refractory GCTs – response data

	APACHE-B[1]	Alliance[2]	Alliance[2]	DFCI[3]	MSKCC[4]
Total Evaluable Patients	11	4	2	5	
Treatment	**Durva + Treme**	**Nivo + Cabo**	**Ipi + Nivo + Cabo**	**Ipi + Nivo**	**Durva + Treme**
Best response					To be reported at upcoming meeting
Partial response	1 (9%)	0 (0%)	0 (0%)	0 (0%)	
Stable disease	1 (9%)	1 (17%)	0 (0%)	1 (20%)	
Progressive disease	9 (82%)	3 (83%)	2 (100%)	4 (80%	
Median # doses (range)	NR	NR	NR	NR	
Landmark PFS	9 wk – 18%	NR	NR	NR	
Median PFS, mo (CI)	1.7 (NR)	NR	NR	NR	
Median OS, mo (CI)	3.1 (NR)	NR	NR	NR	

NR, not-reported

1. Necchi, et al. *Eur Urol* 2019; 2. Apolo et al. *JCO* 2020; 3. McGregor et al. *Cancer* 2021; 4. NCT03158064

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Total Evaluable Patients	11	4	2	5	
Treatment	Durva + Treme	Nivo + Cabo	Ipi + Nivo + Cabo	Ipi + Nivo	Durva + Treme
Best response					To be reported at upcoming meeting
Partial response	**1 (9%)**	0 (0%)	0 (0%)	0 (0%)	
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Median OS, mo (CI)	3.1 (NR)	NR	NR	NR	

NR, not-reported

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Phase II trials of immune checkpoint inhibition in patients with platinum refractory GCTs - non-progressor characteristics

Patient	Trial	Therapy	Best OR	Duration	Histology	1º Site	Prior HDCT	PD-L1	TMB
1	GU14-206[1]	Pembro	SD	28 wks	NSGCT	Testis	No (late relapase)	**Neg**	NR
2	GU14-206[1]	Pembro	SD	19 wks	NSGCT	Testis	No	**Neg**	NR
3	JAPAN[2]	Nivo	PR	90.1 wks	NSGCT	Testis	No	**Neg**	High
4	JAPAN[2]	Nivo	SD	68.4 wks	NSGCT	Testis	No	**Neg**	Low
5	JAPAN[2]	Nivo	SD	11.7 wks	Sem	Testis	No	Pos	Low
6	JAPAN[2]	Nivo	SD	5.9 wks	NSGCT	Testis	Yes	**Neg**	Low
7	MDACC[3]	Pembro	SD	10.9 mo	NSGCT	Testis	NR	**Neg**	NR
8	MDACC[3]	Pembro	SD	5.5 mo	NSGCT	Mediastin	NR	**Neg**	NR
9	MDACC[3]	Pembro	SD	4.5 mo	NSGCT	Mediastin	NR	**Neg**	NR
10	APACHE-B[4]	Durva+Treme	PR	6 mo (ongoing)	Sem	Testis	Yes	**Neg**	Low
11	APACHE-B[4]	Durva+Treme	SD	3 mo	NR	NR	NR	**NR**	NR
12	Alliance[5]	Nivo + Cabo	SD	NR	NR	NR	NR	**NR**	NR
13	DFCI[6]	Ipi + Nivo	SD	NR	NR	NR	NR	**NR**	NR

NR, not-reported

1. Adra, et al. *Ann Oncol* 2018; 2. Kawahara et al. *Int J Urol* 2022 3. Tsimberidou, et al. *Oncologist* 2021; 4. Necchi, et al. *Eur Urol* 2019; 5. Apolo et al. *JCO* 2020; 6. McGregor et al. *Cancer* 2021

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Phase II trials of immune checkpoint inhibition in patients with platinum refractory GCTs - non-progressor characteristics

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11	APACHE-B[4]	Durva+Treme	SD	3 mo	NR	NR	NR	NR	NR
12	Alliance[5]	Nivo + Cabo	SD	NR	NR	NR	NR	NR	NR
13	DFCI[6]	Ipi + Nivo	SD	NR	NR	NR	NR	NR	NR

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7	MDACC[3]	Pembro	SD	10.9 mo	NSGCT	Testis	NR	Neg	NR
8	MDACC[3]	Pembro	SD	5.5 mo	NSGCT	Mediastin	NR	Neg	NR
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10	APACHE-B[4]	Durva+Treme	PR	6 mo (ongoing)	Sem	Testis	Yes	Neg	Low
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12	Alliance[5]	Nivo + Cabo	SD	NR	NR	NR	NR	NR	NR
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11	APACHE-B[4]	Durva+Treme	SD	3 mo	NR	NR	NR	NR	NR
12	Alliance[5]	Nivo + Cabo	SD	NR	NR	NR	NR	NR	NR
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Conclusion - Immune checkpoint inhibition has limited activity in patients with platinum refractory GCTs and is not approved for this indication.

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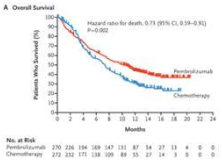
Treatment after platinum resistance - urothelial carcinoma vs germ cell tumors (2023)

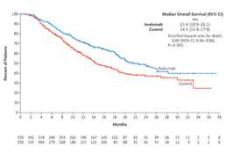
Urothelial Carcinoma – PD-1/PD-L1 Blockade

Pembrolizumab – Platinum refractory



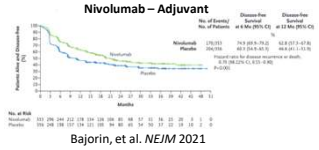
Bellmunt, et al. *NEJM* 2017

Avelumab – Maintenance after platinum



Powles, et al. *NEJM* 2020

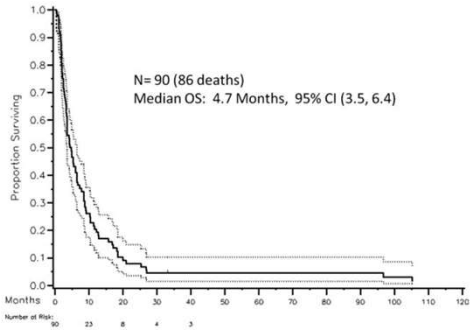
Nivolumab – Adjuvant



Bajorin, et al. *NEJM* 2021

Total FDA Approvals Since 2013 – 6 (3 IO)

Germ Cell Tumors – 7 phase II clinical trials



Feldman, et al. *Cancer* 2012

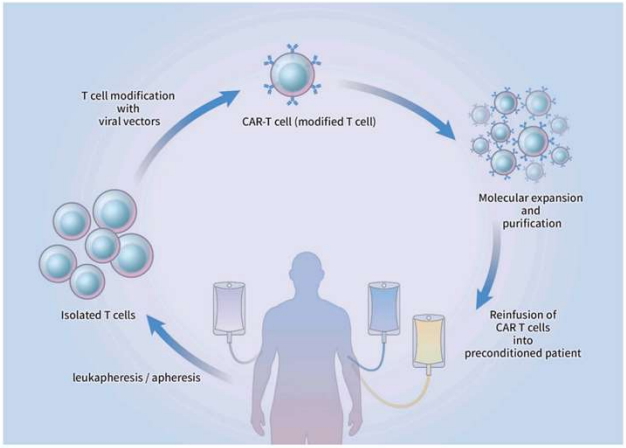
Total FDA Approvals Since 2013 - 0

24

What are other potential immunotherapeutic strategies in patients with GCTs?

25

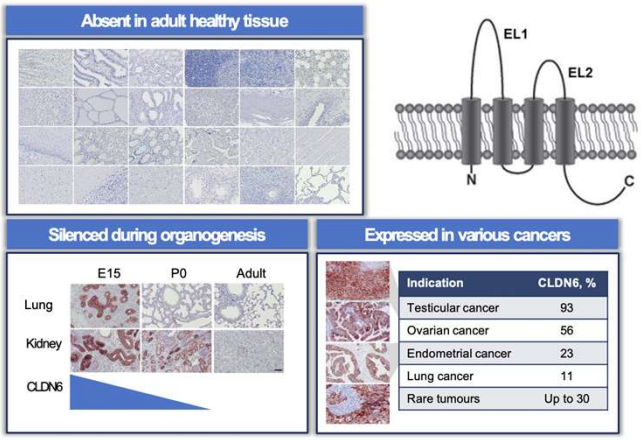
Chimeric Antigen Receptor T Cells (CAR T)



Yu and Kim. *Int. J. Mol. Sci.* 2021

26

The carcinoembryonic antigen **claudin 6** (CLDN6) is a well-suited target for CAR T-cell therapy[1]



Indication	CLDN6, %
Testicular cancer	93
Ovarian cancer	56
Endometrial cancer	23
Lung cancer	11
Rare tumours	Up to 30

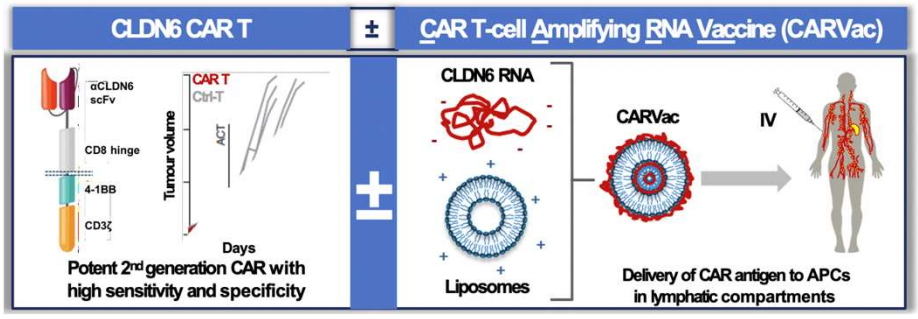
- Primitive tight junction molecule **expressed exquisitely during organogenesis** (embryofetaldevelopment)
- **Expressed in various cancer** types, but **not in healthy** adult tissues

1. Reinhard K, *et al. Science* 2020

SLIDE ADAPTED FROM MAKENSEN ET AL. ESMO 2022

27

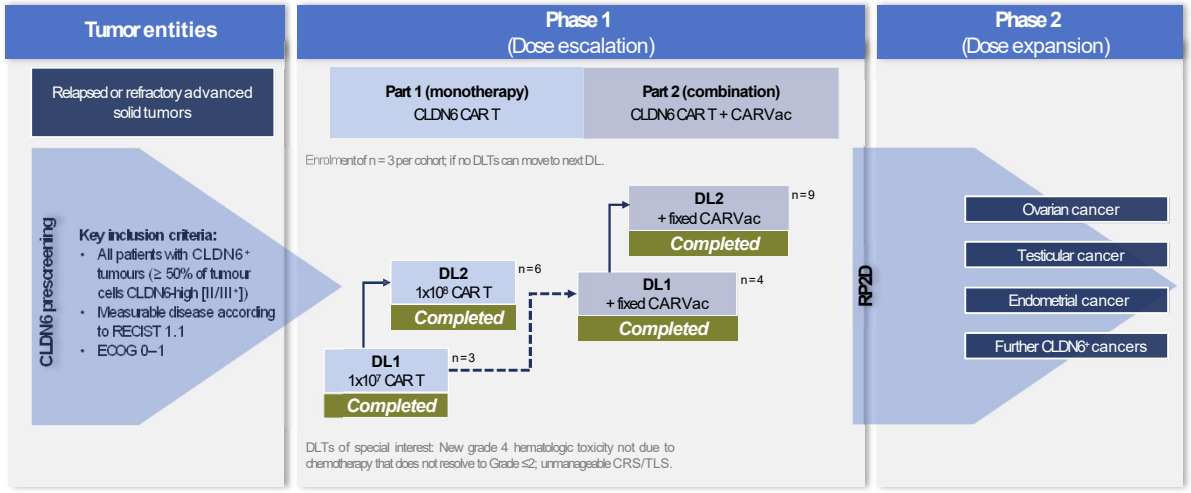
CLDN6 targeting CAR T (BNT 211)



Mackesson et al. ESMO 2022

28

BNT211-01 trial design: 3+3 dose escalation with bifurcation



* Two patients treated in lymphodepletion free cohort and one with 50% reduction

PARIS 2022 ESMO congress

Mackesson et al.

Data cut-off: 15 Jun 2022. ACT = adoptive cell transfer (CAR T-cell infusion); CLDN6 = claudin 6; CRS = cytokine release syndrome; Cy = cyclophosphamide (500 mg/m²/day); DL = dose level; DLT = dose-limiting toxicity; ECOG PS = Eastern Cooperative Oncology Group Performance Status; Flu = fludarabine (30 mg/m²/day); LD = lymphodepletion; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; TLS = tumour lysis syndrome.

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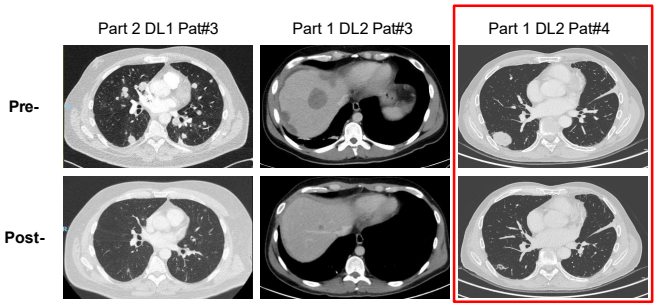
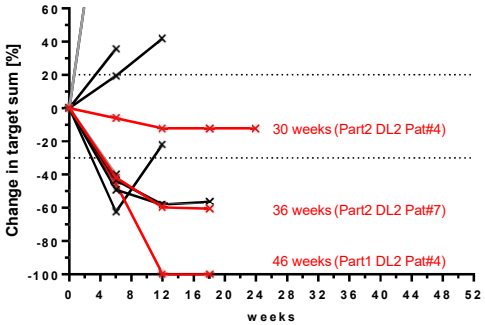
Best response/durability: Testicular cancer patients

Selected scans of testicular cancer patients



One testicular cancer patient was investigator-assessed as CR after 18 weeks (negative PET-CT scan and tumour-marker negative)

Durability of responses (testicular)



	DL1 w/ LD	DL2 w/ LD	Total w/ LD
Testicular, n	4	7	11
ORR, %	25	57	45
DCR, %	25	85	54

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Mackesson et al.

Data cut-off: 16 Aug 2022. CR = complete response; DCR = disease-control rate; DL = dose level; LD = lymphodepletion; ORR = overall response rate. Grey lines indicate patients w/o LD. Red lines indicate ongoing assessments.

30

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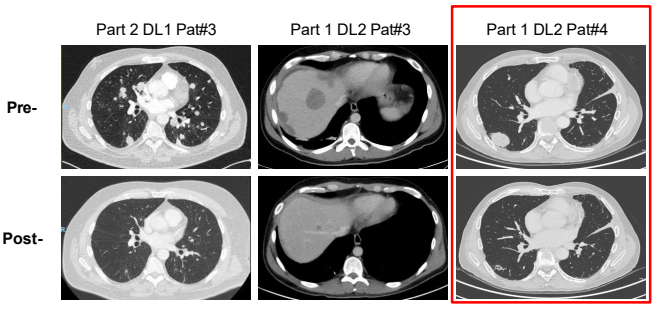

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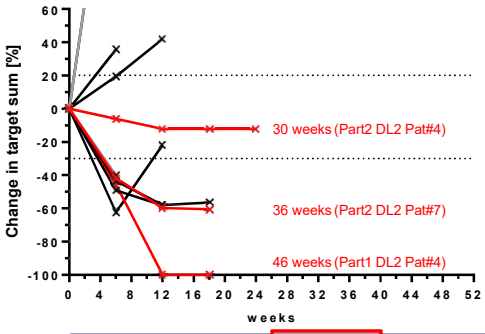

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Mackesson et al.

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BNT211-01 continues to accrue in Europe

ClinicalTrials.gov Identifier: NCT04503278

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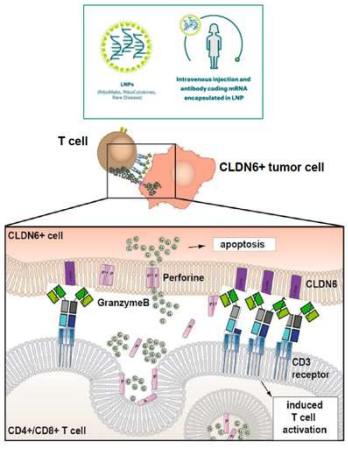
CD30 targeting CAR T (ATLCAR.CD30 cells)

- CD30 is expressed in up to 98% of testicular embryonal carcinoma, with positive staining present in > 50% of tumor cells.[1]
- In one study, CD30 expression was retained in patients with NSGCT after multiple lines of therapy.[2]
- Brentuximab vedotin has been used, but clinical responses were modest with SD in around 10% of patients.[3]
- Prior trials have shown safety & efficacy of autologous CD30.CAR T cells in patients with r/r CD30+ lymphomas.[4]
- **LCCC2048-ATL: CD30 CAR for CD30+ NSGCT (NCT05634785; PI – Matthew Milowsky at UNC)**

1. Goplan et al. Mod Pathol 2009; 2. Silberstein, et al. *J Urol* 2013; 3. Ashkar, et al. *Invest New Drugs* 2021; 4. Ramos et al. *JCO* 2020

CLDN6 targeting lipid nanoparticle (BNT 142)



- The lipid nanoparticle is administered I.V. and the mRNA is translated in the liver to the encoded antibody (BNT 142)
- BNT142 targets CLDN6 on tumor cells and CD3 on T cells
- T cell activation → release of cytolytic molecules and inflammatory cytokines → target cell lysis and clonal T cell expansion
- **BNT142-01 (NCT05262530) is currently accruing patients with platinum refractory GCTs in the United States and Spain**

Slide/information provided by BioNTech

Is immune checkpoint blockage active in penile cancer?

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Background –penile cancer

- Penile cancer is an uncommon malignancy which accounts for 2,300 new cases and 400 deaths annually worldwide.
- In low-income countries from South America, Asia and Africa, incidence corresponds to 10-20% of all malignancies in men.
- HPV is the most important known risk factor.
- Platinum-based chemotherapy has been the standard-of-care for advanced disease for 3 decades with poor outcomes (ORR 20-30%, PFS 3-4 months, OS 7-15 months).

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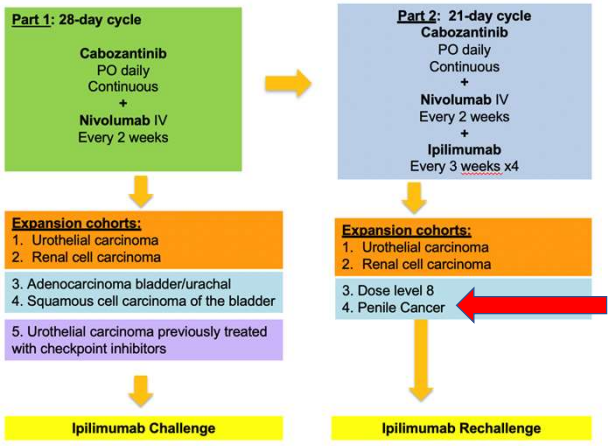
Rationale – ICI for penile cancer

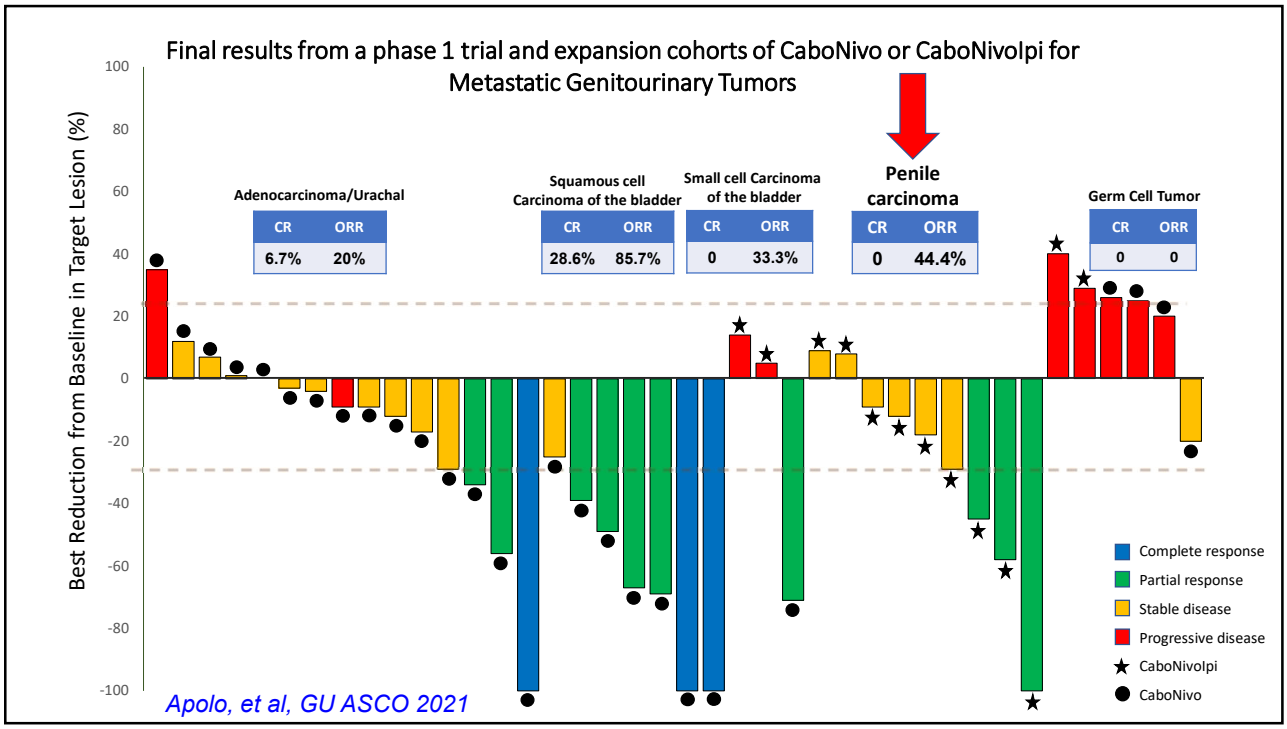
- Immune cell infiltration[1]
- Expression of PD-L1[2]
- ICI is active and approved in another HPV-associated cancers, such as cervical and oropharyngeal cancers.[3,4]
- Anecdotal reports of activity in case reports[5,6] and umbrella trials[7,8]

1. Chu et al. *Cancers* 2020; 2. Udager et al. *Ann Oncol* 2016; 3. Burtness. *Lancet* 2019; 4. Colombo et al. *NEJM* 2021; 5. Chahoud et al. *Front Oncol* 2020; 6. Trafalis et al. *J Immunotherapy* 2018; 7. Apolo et al. *JCO* 2020; 8. Hahn et al. Invest New Drugs 2021

Phase I Study of Cabozantinib and Nivolumab Alone or With Ipilimumab for Advanced or Metastatic Urothelial Carcinoma and Other Genitourinary Tumors



Presented by Andrea Apolo et al. GU ASCO 2021



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Results from a recently reported trial of anti- PD-1/L1 therapy in locally advanced/metastatic penile cancer[1]

- **92 patients treated across North America (68%), Europe and Asia in the Global Society of Rare Genitourinary Tumors (GSRGT) network.**
- **90% of patients had metastatic disease and 80% ≥ prior lines**
- **Treatments were pembrolizumab (28%), nivolumab (17%), cemiplimab (16%), ipi+nivo+cabo (13%), ipi+nivo (12%), other (13%)**
- ORR overall was 13% - CR 2.4%, PR 11%, SD 28%, PD 59%
- ORR with PD-1/L1 monotherapy was 9% - CR 3.4%, PR 5.1%, SD 20%, PD 71%
- mPFS in months in overall cohort (95%CI) – 3.2 (2.4 – 4.2)
- mOS in months in overall cohort (95% CI) – 9.8 (7.7 – 12.8)
- HPV status not a predictor of survival outcomes

1. El Zarif et al on behalf of GSRGT. Presented a GU ASCO 2023

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1. El Zarif et al. Presented a GU ASCO 2023

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How do we overcome the challenges?

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How do we overcome the challenges?

SCIENCE

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How do we overcome the challenges?

SCIENCE

COLLABORATION

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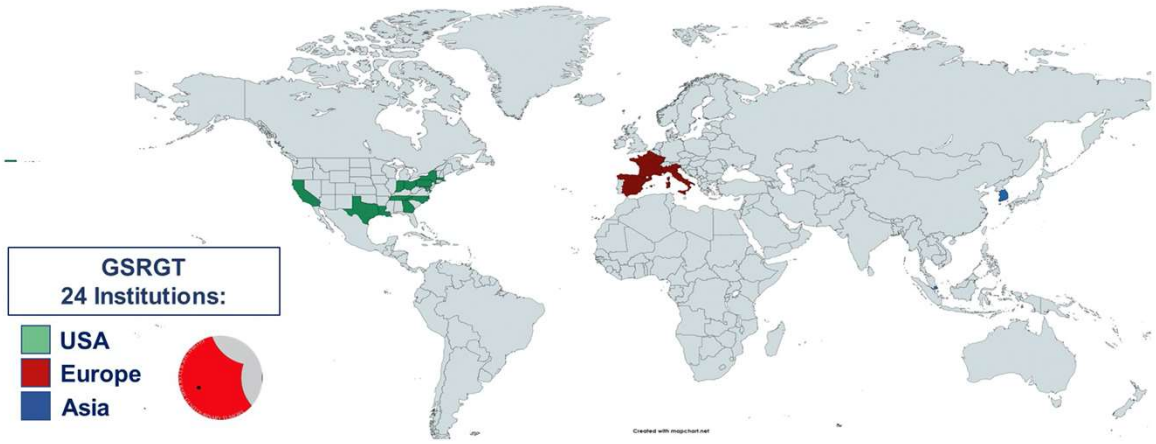
Global Society of Rare Genitourinary Tumors (GSRGT)



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LACOG 0218
HERCULES

PI: Fernando Maluf
Funding: MSD

LACOG GENITOURINARY

- Phase II, single-arm clinical trial

ELIGIBILITY CRITERIA

- Patients with penile squamous cell carcinoma with:
  Metastatic disease (de novo or recurrent),
  Recurrent locally advanced disease not amenable to curative-intent therapy, or
  Tany N3 M0 or T4Nany M0 (clinical stage IV-AJCC 8th) not amenable to curative-intent therapy
- No prior exposure to chemotherapy OR
- Progression after 12 months of (neo)adjuvant chemotherapy

(N = 33)

Intervention

Cisplatin 70mg/m² (or Carboplatin UAC 5) D1 + 5-FU 1000mg/m²/day D1-D4 + pembrolizumab 200mg IV Q3W for 6 cycles

Followed by maintenance with: Pembrolizumab 200mg IV Q3W up to 34 cycles (in total), disease progression or unacceptable toxicity

Tumor assessment per RECIST v1.1 by investigator every 6 weeks for the first 24 weeks

PRIMARY ENDPOINT

Overall response rate by RECIST 1.1 up to week 24

SECONDARY ENDPOINTS

- Progression-free survival
- Overall survival
- Clinical Benefit rate
- Immune related response criteria
- Health related quality of life

EXPLORATORY ENDPOINTS

- Biomarkers predicting response

Number of research sites: 11

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UNIVERSITÉ FRANCHE-COMTÉ | UBFC | CHU BESANÇON | IRFC | GETUG

Maintenance Avelumab Immunotherapy in Patients With Locally Advanced or Metastatic Squamous Cell Penile Carcinoma (PULSE)

- PULSE is a French prospective multicenter open label single arm phase II trial that plans to enroll 32 patients.
- The primary endpoint is the PFS from maintenance avelumab initiation.
- Based on data from the initial 9 patients, the DSMC has recommended continued enrollment **(NCT03774901)**

	IA population n = 9
Survival without progression or death % [95% CI]	
at 3 mo	63.5% [37.7-100]
at 6 mo	63.5% [37.7-100]
at 12 mo	63.5% [37.7-100]
and 15 mo	42.3 % [16.3-100]
Overall survival % [95% CI]	
at 12 mo	88.9% [70.6; 100]
and 15 mo	88.9% [70.6; 100]

Thierry-Vuillemin et al. Presented a GU ASCO 2023

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ALLIANCE: ICONIC study of Ipilimumab, CabOzantinib, and NIvolumab in rare genitourinary Cancers

PI: Andrea B. Apolo

- Squamous cell carcinoma of the bladder
- ^Small Cell Carcinoma of the bladder
- Adenocarcinoma of the bladder
- Plasmocytoid urothelial carcinoma of the bladder
- Sarcomatoid urothelial carcinoma of the bladder
- Urethra (all histologies)
- **Penile Cancer**
- Sarcomatoid Renal Cell Carcinoma
- Collecting Duct Renal Cell Carcinoma
- Medullary Renal Carcinoma
- Miscellaneous GU tract histologic variants
- *Bone-only Rare GU tumor

→ **First-Line or** / **Second-Line and beyond**

N=230

→ Cabozantinib 40 mg + Nivolumab 3 mg/Kg + Ipilimumab 1 mg/Kg Q3 weeks x 4

then..

Cabozantinib 40 mg + Nivolumab 3 mg/Kg + Q2 weeks maintenance

→ OVERALL RESPONSE RATE

Two-stage Simon's design

*Exploratory

^ Only second-line and beyond after platinum-based chemotherapy failure

Presented by Andrea B. Apolo, MD

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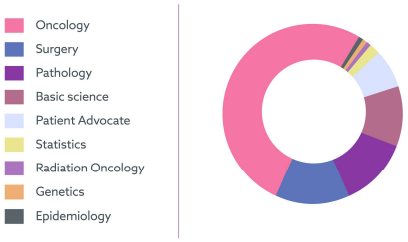
MaGIC (Malignant Germ Cell International Consortium)

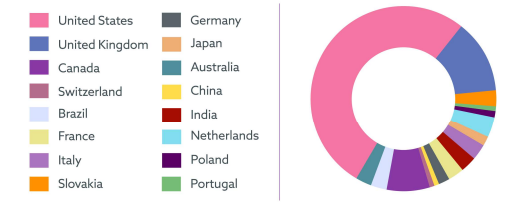
MEMBERS BY SUBSPECIALTY N = 113



MaGIC brings together the world's leading experts in germ cell tumors (GCTs), from across the spectrum of cancer research, with the shared goal of developing more effective treatments for GCTs through scientific inquiry.

MAGIC
Malignant Germ Cell International Consortium

MEMBERS BY COUNTRY N = 16



GIC

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THANK YOU FOR YOUR ATTENTION

QUESTIONS??

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A 39 y/o man with poor-risk nonseminomatous germ cell tumor of the left testis has been treated with 4 cycles of bleomycin, etoposide and cisplatin (BEPx4), 4 cycles of paclitaxel, ifosfamide, and cisplatin (TIPx4), and high dose carboplatin and etoposide (TI-CE regimen). He is currently progressing in multiple lung and liver metastases with a rising serum HCG. Which of the following is not an appropriate next step in management?

A. Gemcitabine and oxaliplatin chemotherapy
B. Clinical trial
C. Next generation sequencing
D. Ipilimumab and nivolumab

53

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