II. Medizinische Klinik, UCCH, Universitätsklinikum Hamburg – Eppendorf

JAHRESTAGUNG 2023 13.–16. Okt. Hamburg

Therapie bei refraktären Patienten

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Chair German Testicular Germ Cell Tumor Working Group

Hubertus Wald Tumorzentrum
Universitäres Cancer Center Hamburg
Ein Kompetenznetzwerk des UKE

Offenlegung potentieller Interessenkonflikte

- **1. Anstellungsverhältnis oder Führungsposition**
  - Universitätsprofessor Universitätsklinikum Hamburg Eppendorf
  - Beirat DGHO, Sprecher CCC Netzwerk, Präsident Hamburger Krebsgesellschaft

- **2. Beratungstätigkeit**
  - Sanofi, Merck Serono, Bayer Heathcare, OncologyDrugConsult, Roche Pharma, Bristol Myers Squibb; Merck Sharp Dohme; Lindis Biontech
  - verschiedene private und öffentliche Stiftungen und Vereine
  - AOK Nordrhein / Hamburg

- **3. Aktienbesitz :** nein

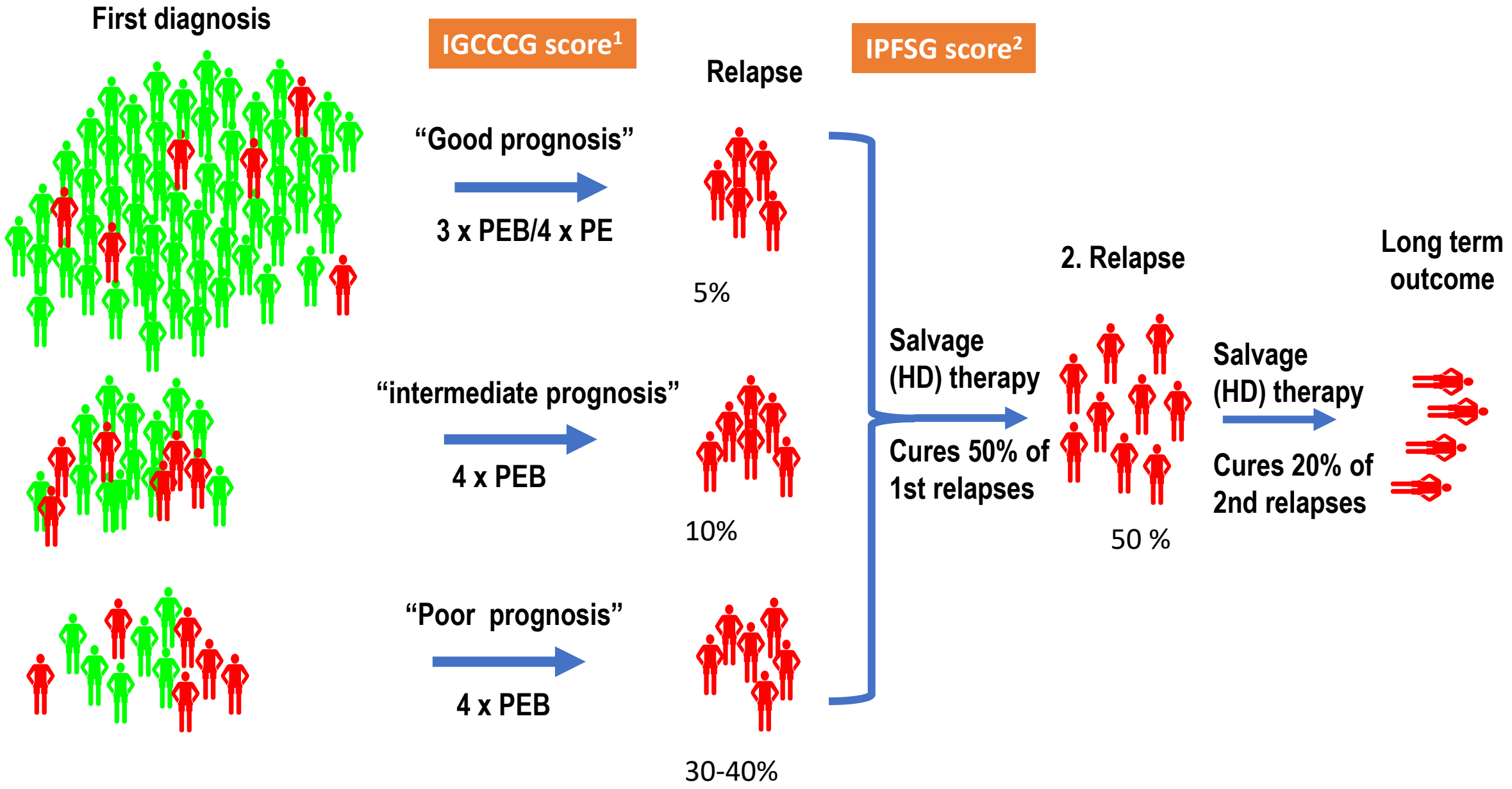
- **4. Honorare**
  - Vortragshonorare bei wiss. Symposien (wechselnde Firmen und Veranstalter, u.a. Onkoupdate, Streamed up und I-med Institut)

- **5. Finanzierung wissenschaftlicher Untersuchungen**
  - Finanzierungen von wissenschaftlichen - klinischen Studien (verschiedene Firmen): Empfänger UKE

- **6. Gutachtertätigkeit**
  - v.a. für Forschungsförderer (DFG; DKH; Wilhelm Sander Stiftung, MRC, SAKK, u.a.)

- **7. Andere finanzielle Beziehungen**
  - Reisefinanzierungen zur Teilnahme an Kongressen (projektbezogen, verschiedene Firmen)

- **8. Immaterielle Interessenkonflikte:** keine



1 IGCCCG 1997 2 IPFSG 2010

Single agent chemotherapy

Drug	Response Rate	% previous HD CTX with ABSCT
Etoposid oral[1]	14%	29%
Paclitaxel[2-6]	11% - 26%	13% - 50%
Gemcitabin[7,8]	15% - 19%	55% - 71%
Oxaliplatin[9,10]	19% - 25%	78% / n.r.
Ifosfamid[11]	23%	23%
Temozolomid[12]	10%	40%

1 Miller & Einhorn 1990
2 Motzer 1994
3 Bokemeyer 1994
4 Nazario 1995
5 Bokemeyer 1996
6 Sandler 1998
7 Bokemeyer 1999
8 Einhorn 1999
9 Kollmannsberger 2002
10 Fizazi 2004
11 Wheeler 1986
12 Maroto 2011

Chemotherapy – Triplet combinations

Drug	Response Rate	% previous HD CTX with ABSCT
Gem / Ox / Pacli[1,2]	31% - 51%	20% - 78%
Gem / Cis / Pacli[3]	67% (DCR)	13%
Ox / Iri / Pacli[4]	49%	0%
EMA / CO[5] (βHCG +ive !)	29%	39%

1 Bokemeyer 2008
2 Sadeghi 2013
3 Necchi 2014
4 Badreldin 2016
5 Raggi 2014

GTCSG-Study GOP

Refractory GCT

- Median 2 previous lines of chemo
- 78% previous HDCT
- Max. 1 of the agents in prior lines

n = 41

Salvage treatment

- Gem 800mg/m² IV d1+8
- Oxaliplatin 130mg/m² IV d1
- Paclitaxel 80mg/m² IV d1+8
- Max. 8 cycles

CR	2 **Pts**	5%
PRm-	14	34%
PRm+	5	12%
SD	8	20%
PD	12	29%
Med. PFS	3 (1-7) Mo.	
Med. OS	6 (1-19) Mo.	

ORR 51%

- Surgical NED 8 Pts (20%)
- Ongoing CR 6 pts (15%)
- Median duration 11 Mo (16-19)

Bokemeyer, Ann Oncol 2008

Importance of residual tumor resection

- Long-term FU of the GO and GOP phase II trials (n = 76pts)[1]

- 8/76 (11%) long-term disease-free: median OS 33 months
- 1/8 pts CR after GOP alone
- 6/8 sCR after complete secondary surgery → 67% with vital GCT

1 Oechsle Eur Urol 2011

Real world Registery study[2]	all patients	patienten with sNED
Medianes PFS (Monate)	**4.0** (3,08-4,94)	**10.2** (4,31-16,01)
Medianes OS (Monate)	**13.3** (9,5-17,06)	**22.6** (0,0 -48,47)

2 Seidel Urol Oncol 2016

Journal of Cancer Research and Clinical Oncology (2020) 146:449–455
https://doi.org/10.1007/s00432-019-03071-2

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Treatment of refractory germ-cell tumours with single-agent cabazitaxel: a German Testicular Cancer Study Group case series

Christoph Oing[1,2,3] · Marcus Hentrich[4] · Anja Lorch[5] · Dietrich Gläser[6] · Holger Rumpold[7] · Sebastian Ochsenreither[8,9] · Stephan Richter[10] · Annette Dieing[11] · Stefanie Zschäbitz[12] · Ronnie Rodrigues Pereira[3] · Carsten Bokemeyer[1] · Christoph Seidel[1]

Received: 21 August 2019 / Accepted: 28 October 2019 / Published online: 14 December 2019

Abstract

Purpose Outcomes of multiply relapsed, refractory germ-cell tumour (GCT) patients remain poor with an overall survival (OS) of a few months only. Thus, new therapeutic advances are urgently needed. Cabazitaxel has shown preclinical activity in platinum-resistant GCT models. Here, we report the first clinical case series of cabazitaxel treatment for platinum-refractory GCT.

Methods Data of multiply relapsed GCT patients receiving single-agent cabazitaxel were retrospectively analysed. Endpoints included 12-week progression-free survival (PFS) rate, disease control rate, tumour marker responses, median PFS and OS, and toxicity.

Results Cabazitaxel showed limited activity in 13 heavily pre-treated GCT patients. After a median follow-up of 23 weeks (IQR 29), 69% of patients were deceased. A median of 2 cycles of cabazitaxel (range 1–7) were applied. The 12-week PFS rate was 31%. Median PFS and OS were 7 and 23 weeks, respectively. Two patients achieved objective responses (15%), three patients (23%) achieved a tumour marker decline ≥ 50%, and the disease control rate was 39%. Cabazitaxel was well tolerated. CTCAE° III–IV haemato-toxicity was most common (54%), and dose reductions were scarce (15%).

Conclusion In this case series, cabazitaxel showed limited activity in heavily pre-treated GCT patients. Two-phase II studies are underway (NCT02115165, NCT02478502) prospectively assessing cabazitaxel in multiply relapsed GCTs.

Keywords Testicular cancer · Germ-cell tumour · Germ-cell cancer · Refractory · Cisplatin resistance · Cabazitaxel · Taxane resistance

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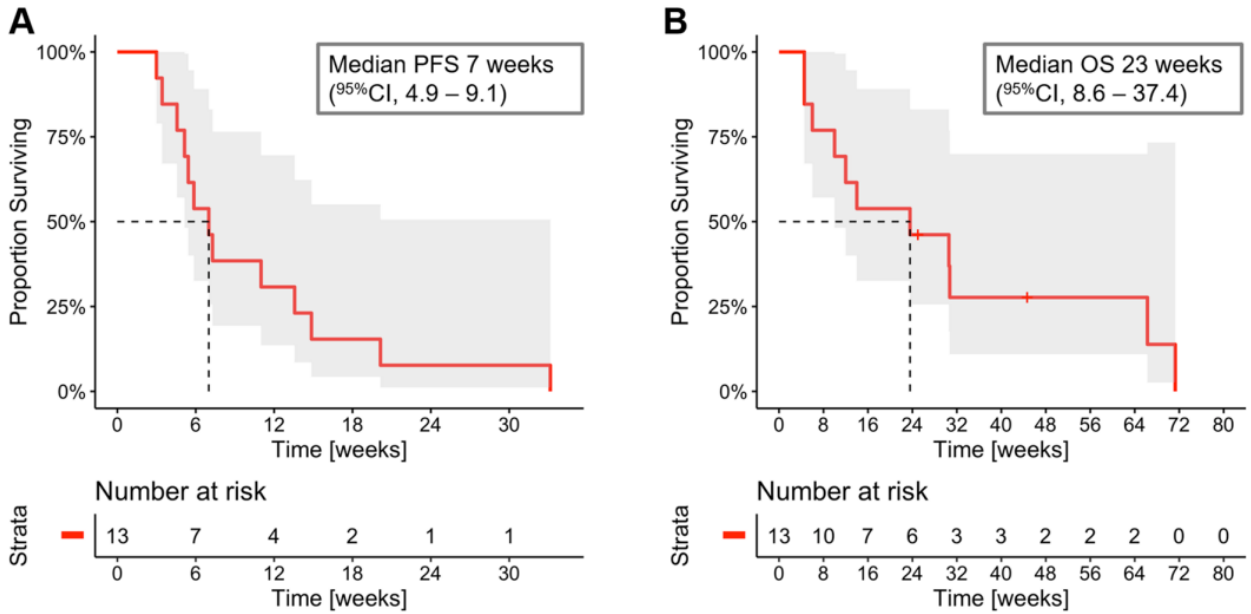
☑ ORR 15% | DCR 39%

☑ 12-week PFS rate 31%



Target Therapies in GCT

- ☑ Rare setting
- ☑ Heterogenous disease
- ☑ Low TMB
- ☑ No typical driver mutations
- ☑ No predictive biomarkers

Anti-angiogenesis trials

- **Thalidomide[1]:**
  - Phase II, N=15; STM decline 5/15, ORR 0%
- **Lenalidomide[2]:**
  - N=4, ORR 0%
- **Bevacizumab (+ Oxaliplatin)[3]:**
  - Phase II, N=24; ORR 29%, med OS 8 mos = Oxaliplatin mono[4]

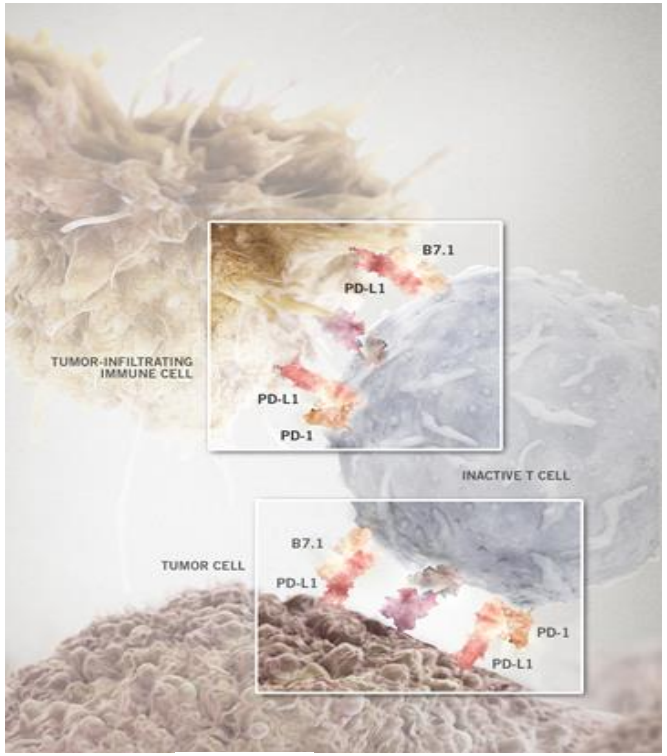
1 Rick et al., Eur J Cancer 2006 2 Oechsle et al., J Cancer Res Clin Oncol 2010 3 Jain et al., JCO 2011 4 Kollmannsberger et al., JCO 2002

RTK-Inhibitors (close to antiangiogensis)

- **Sunitinib[1,2]:**
  - Phase II, N=32; ORR 13%, medPFS 2.0mos, medOS 3.2 mos
  - Phase II, N=10; early termination, ORR 0%
- **Pazopanib[3]:**
  - Phase II, N=43; ORR 0%, STM decline 78%, 2-yr OS rate 24%
- **Sorafenib[4]:**
  - Phase II, N=11, early termination, ORR 0%

1 Oechsle et al., Ann Oncol 2011 2 Feldman et al., Invest New Drugs 2010 3 Necchi et al., Ann Oncol 2017 4 Skoneczna et al., ASCO AM 2014

Immunotherapy



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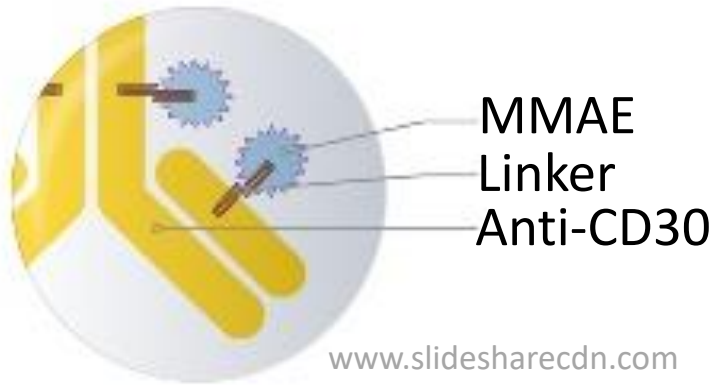
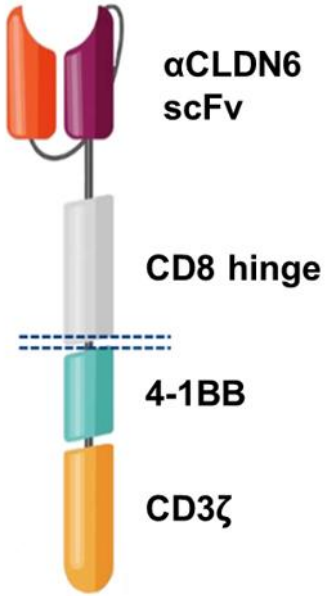


MoAB and ADC



CAR-T

CKI in Germ Cell Tumors

Agent	Author	N pts	ORR	DCR	mPFS [mos]
Pembrolizumab	Adra N[1]	12	0%	17%	n.r.
Pembrolizumab	Tsimberidou A[2]	12	0%	25%	2.4
Avelumab	Mego M[3]	8	0%	0%	0.9
Durvalumab	Necchi A[4]	11	0%	0%	n.r.
Durvalumab + Tremelimumab	Necchi A[4]	11	9%	18%	n.r.

1 Adra et al. Ann Oncol 2018
2 Tsimberidou et al. Oncologist 2021
3 Mego et al. Invest New Drugs 2019
4 Necchi A et al. Eur Urol 2019

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journal homepage: www.europeanurology.com

European Association of Urology

Research Letters

An Open-label Randomized Phase 2 study of Durvalumab Alone or in Combination with Tremelimumab in Patients with Advanced Germ Cell Tumors (APACHE): Results from the First Planned Interim Analysis

Andrea Necchi [a,], Patrizia Giannatempo [a], Daniele Raggi [a], Luigi Mariani [a], Maurizio Colecchia [a], Elena Farè [a], Francesco Monopoli [a], Giuseppina Calareso [a], Siraj M. Ali [b], Jeffrey S. Ross [b,c], Jon H. Chung [b], Roberto Salvioni [a]*

There is growing interest in the potential antitumor effects of immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway. Data from two independent groups have demonstrated that the majority of patients with germ cell tumors (GCTs) express PD-L1 [1,2]. Furthermore, our analysis of the Foundation Medicine database revealed that a small subset of nonseminomatous GCTs featured a high tumor mutation burden (TMB) or microsatellite instability (MSI) that could make these tumors sensitive to immune checkpoint inhibitor therapy [3].

APACHE (NCT03081923) is an open-label randomized phase 2 study. Patients were randomized 1:1 to receive 1500 mg of durvalumab intravenously (arm A) or 1500 mg of durvalumab plus 75 mg of tremelimumab intravenously (arm B) for four cycles followed by durvalumab alone. Treatment was administered every 4 wk in both study arms until disease progression (PD), unacceptable toxicity onset, or a maximum of 12 mo was achieved. The primary endpoint was the objective response rate (according to Response Evaluation Criteria in Solid Tumor [RECIST] version 1.1). The total sample size was divided into a three-stage design. In stage 1, each arm is terminated if no responses are observed in 11 patients (details on the study design are provided in the Supplementary material). Biomarker analyses of the available pretherapy tumor samples included PD-L1 expression (Ventana SP142 assay, details provided in the Supplementary material) and genomic sequencing (FoundationONE assay, Foundation Medicine, Cambridge, MA, USA).

From February 2017 to April 2018, 22 patients were randomized at a single center (11 per arm, Supplementary Table 1). The median follow-up (calculated using the reverse Kaplan-Meier method) was 7.5 mo. No grade 3–4 adverse events occurred in either arm (Supplementary Table 2).

One patient (in arm B, 9.1%) experienced a partial response of multiple lung metastases that was confirmed at the time of data analysis (+8 mo, Supplementary Table 3). The patient was a 43-yr-old male with pure seminomatous testicular GCT who had received two prior lines, including high-dose chemotherapy (Fig. 1A). Another patient in arm B had stable disease (SD) with a decrease in serum tumor markers (STMs) of >10% from baseline and developed PD 3 mo later. All the remaining patients had experienced progression of the primary tumor. Among these patients, hyperprogression features were observed in eight cases in arm A (72.7%) and four cases in arm B (36.4%). These features were reflected in an increase in tumor burden (that we arbitrarily set as an increase of >100% in the sum of the diameters of target lesions, Fig. 1C) or an unequivocal increase in STMs during treatment when compared to two measurements within the 2 mo preceding randomization (Fig. 1D).

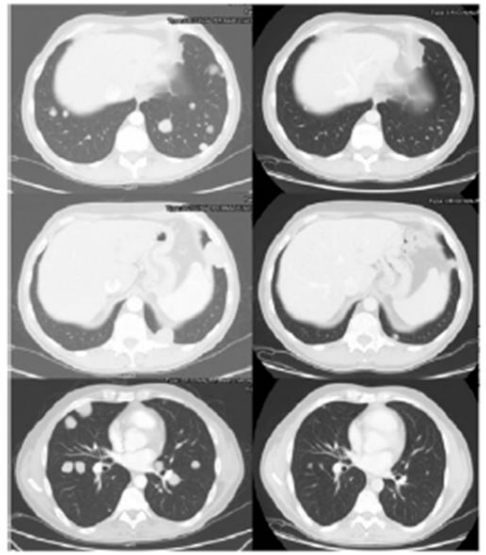
Response and progression occurred regardless of tumor molecular features and PD-L1 expression (Supplementary Table 4). One case in arm B experienced PD even though his tumor exhibited MSI. This case was one of the two GCT patients reported to have MSI in the Foundation Medicine database, and the TMB was elevated in both patients (18 and 23.4 mutations/Mb) [3].

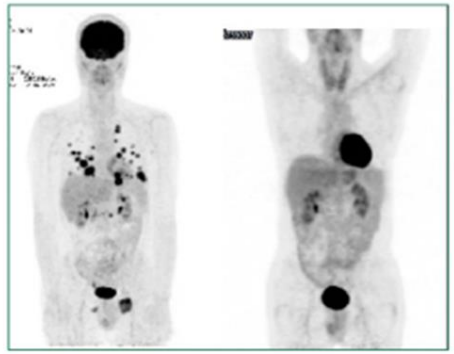
Finally, four patients received further paclitaxel, cisplatin, and gemcitabine chemotherapy after experiencing PD on immunotherapy. One patient experienced a near complete response (in the fifth line; Supplementary Fig. 1), and

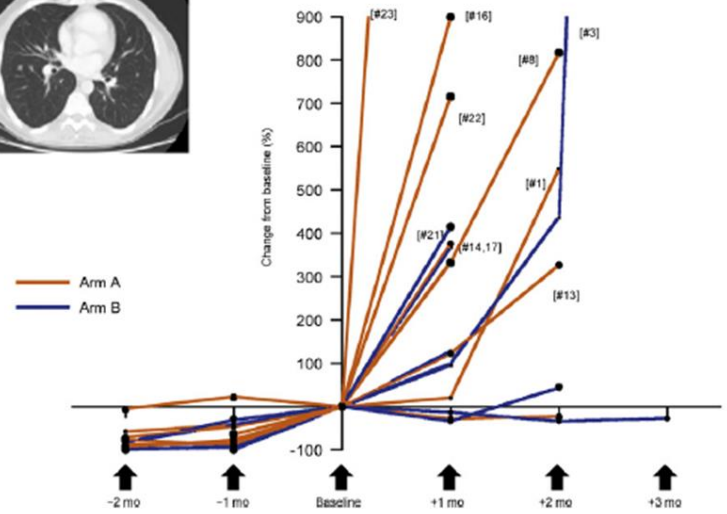
https://doi.org/10.1016/j.eururo.2018.09.010

☑ Combo ORR 9% | DCR 18%

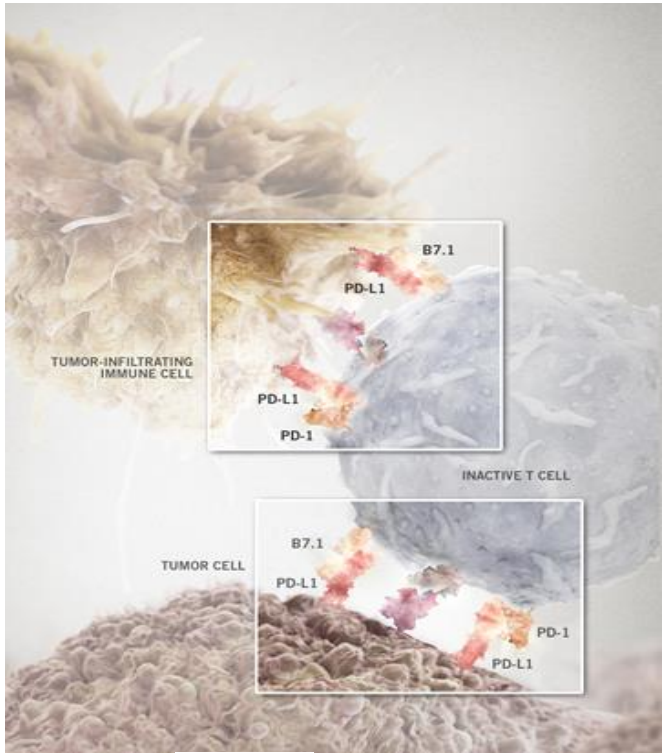
☑ Single agent 73% hyper-PD







Immunotherapy



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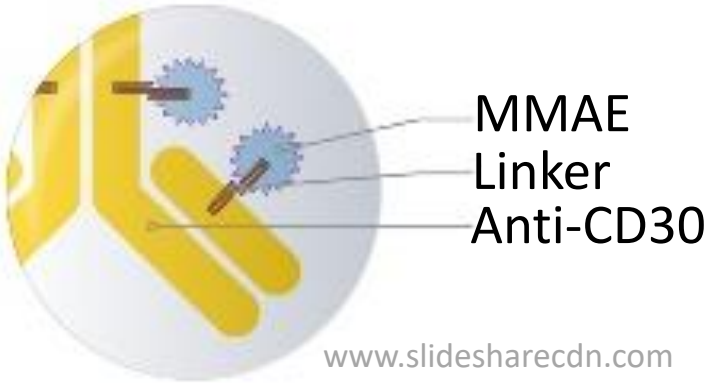
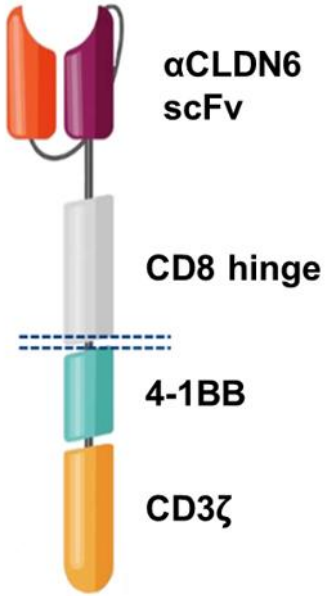


MoAB and ADC



CAR-T

Claudin6-directed antibodies

- ASP1650 (IMAAB027) chimeric mouse/human IGG antibody (ADCC)

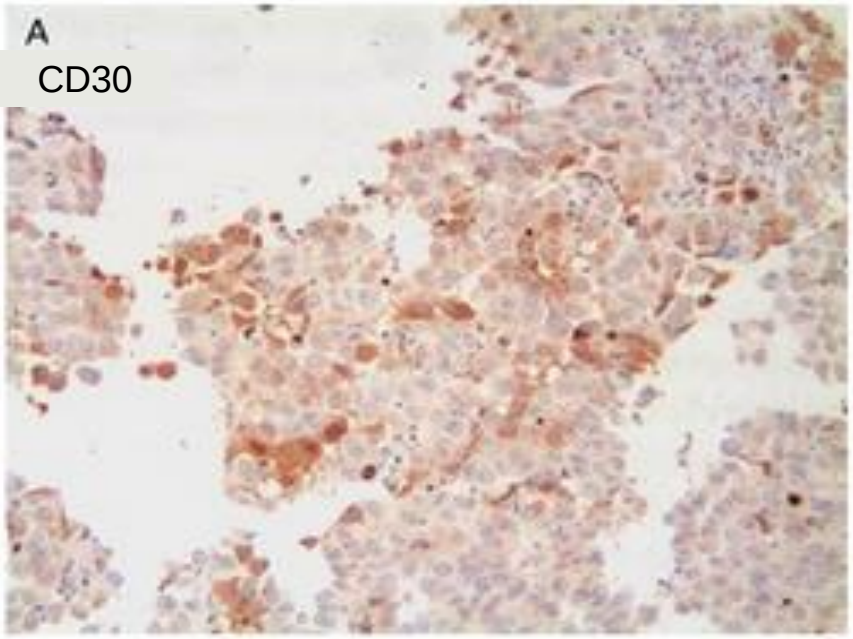
- 19 pts with GCT (17 NS/2 Sem), 13 with previous HD-CTX
- 6 pts 1000mg/m2 q14; 13 pts 1500 mg/m2 q14 days
- 15 had Claudin staining performed
  (med. percentage of positivity 71.6%)

- Side effects: anemia and abdominal pain, no DLT

- Efficacy: CR/PR: 0 / 19 pts

Adra N, et al. Investigat. New Drugs 2022, 40: 1087-1094

ADC Brentuximab targeting CD 30



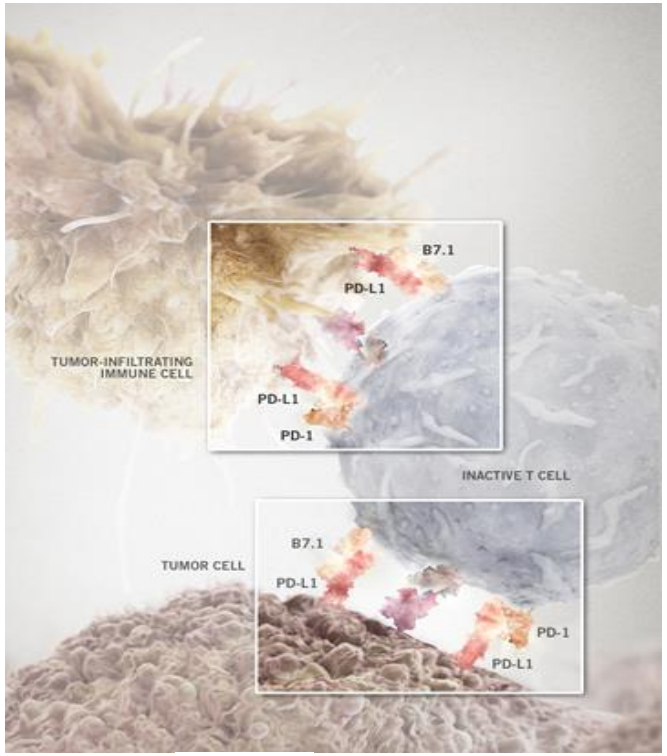
Gallegos et al., AIMM 2010

- ☑ Embryonal Ca, Seminoma (20%)
- ☑ RTR CD30+ → OS/PFS ↓[1]
- ☑ Phase II study discouraging
  - ORR 44% 1st cycle / 22% 2nd cycle (1CR/1PR)
  - Tumor marker responses: 78% / 44%
  - 3-months PFS: 11% (1 pt)!

1 Giannatempo J Urol 2013

2 Necchi ASCO 2016

Immunotherapy



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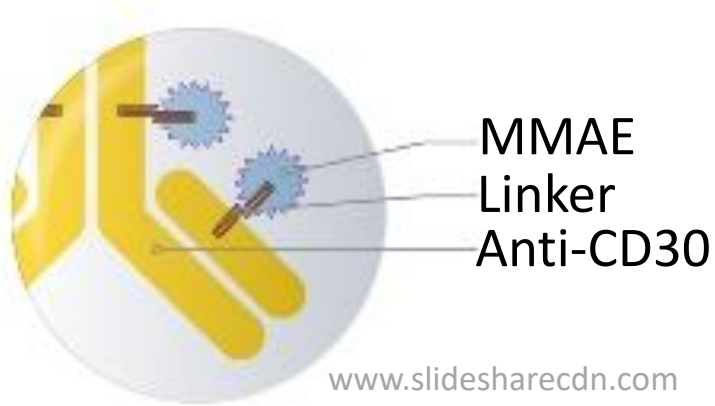
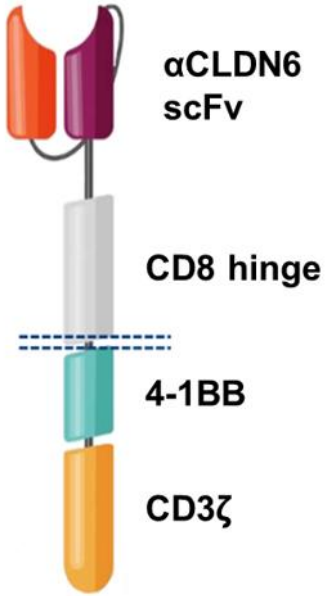


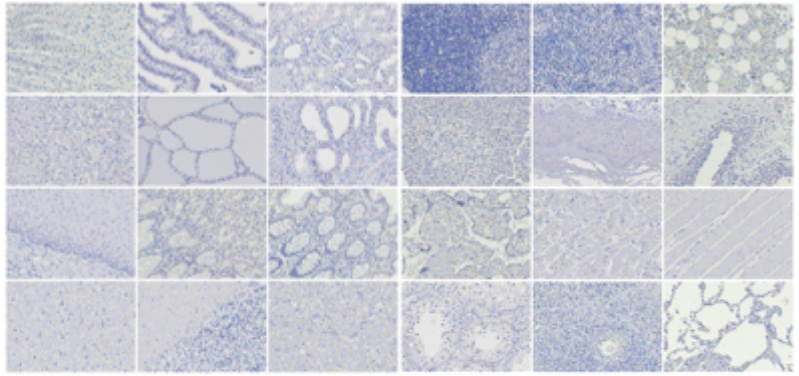
MoAB and ADC



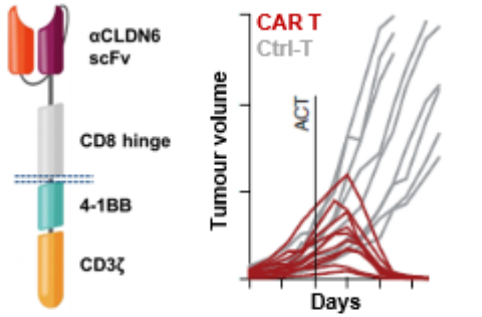
CAR-T

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

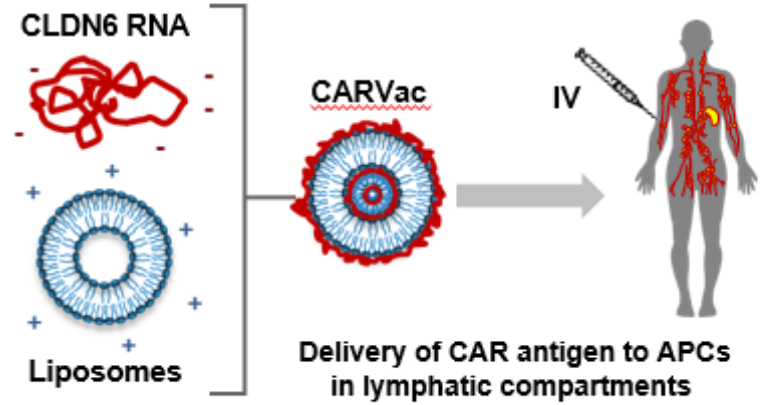
Absent in adult healthy tissue



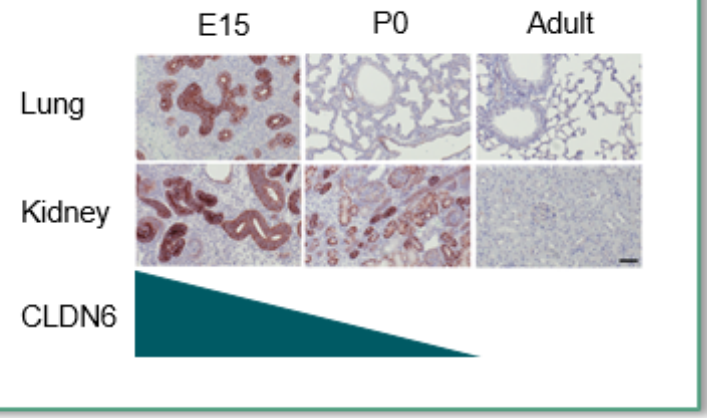
CLDN6 CAR T ± CAR T-cell Amplifying RNA Vaccine (CARVac)



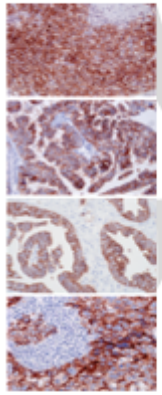
Potent 2nd generation CAR with high sensitivity and specificity



Silenced during organogenesis

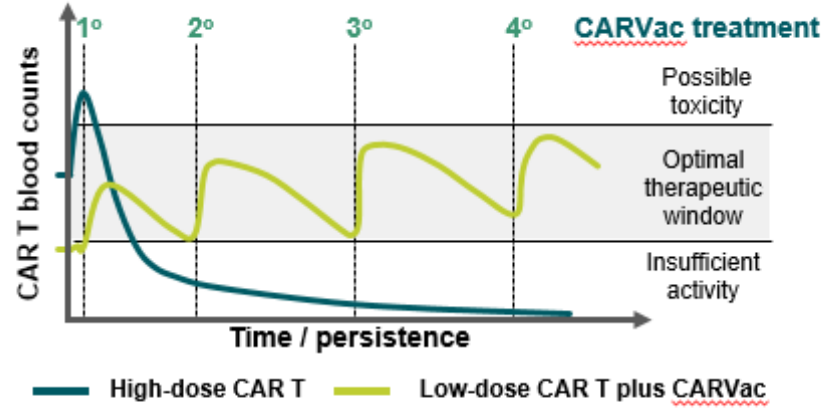


Expressed in various cancers



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

CARVac drives expansion of CAR T cells[1]

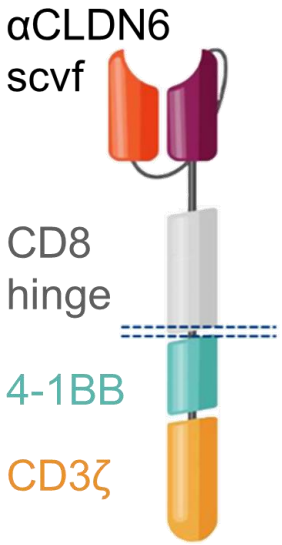


1. Reinhard K, *et al*. *Science* 2020; 367:446–453. ACT = adoptive cell transfer (CAR T-cell infusion); APC = antigen-presenting cell; CARVac = CAR T cell-Amplifying RNA Vaccine; E15 = embryonic Day 15; IV = intravenous; P0 = at birth.

BIONTECH

BNT211: first-in-class approach for CLDN6+ solid tumors

CLDN6 CAR T



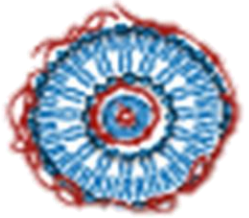
- ✓ Highly sensitive and specific 2nd-generation CAR against CLDN6
- ✓ CLDN6 is absent from healthy adult tissue, but expressed in a variety of cancers[1]

±

CLDN6 CARVac

- ✓ Clinically proven RNA-lipoplex vaccine for body-wide delivery of antigens to dendritic cells[1,2]
- ✓ Amplification and persistence of CAR-T cells by repeat administration[3]

Full-length CLDN6 RNA



Liposomes

BNT211-01: Phase I/IIa, FIH, open-label, multicenter, dose escalation trial

Primary endpoints:

Safety and tolerability, DLTs

Secondary endpoints:

Immunogenicity, ORR, DCR, DoR

Dosing:

- Escalating doses of CLDN6 CAR-T cells ± CLDN6 CARVac (50 µg then 100 µg, if tolerated)
- Lymphodepletion prior to CAR-T cell infusion on Day 1 (DLTs assessed for 28 days)
- CLDN6 CARVac fixed dose (from Day 4) Q3W × 5, then Q6W. CAR-T cell redosing is permitted

Assessments: Efficacy assessments Q6W (RECIST v1.1)

Aim of current analysis

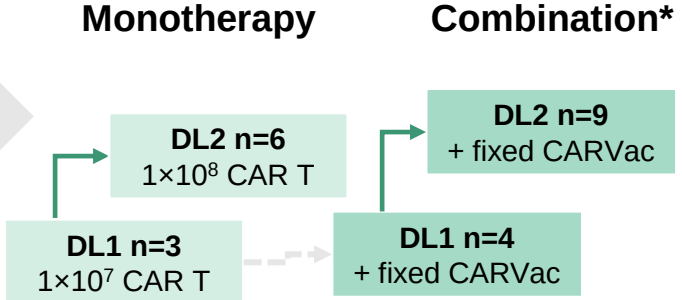
Determine the safety and preliminary efficacy of the automated BNT211 product

R/R advanced CLDN6^{+} solid tumors

Key inclusion criteria

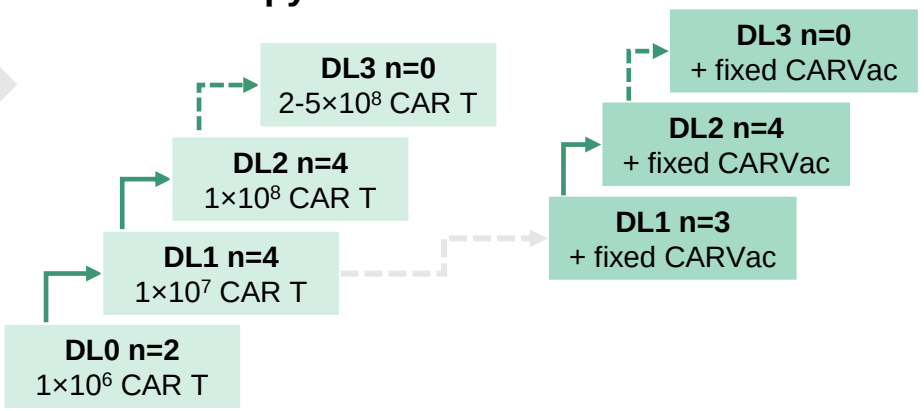
- ≥50% tumor cells with 2+/3+ CLDN6 positivity
- Measurable disease or elevated tumor marker
  ECOG PS 0–1

Phase I dose escalation (manual product): Completed ✓



* Crossover is possible from monotherapy to combination

Phase I dose escalation with an (automated product): Ongoing



Conclusions

- ☑ GO/P established 3rd. line (and byond) salvage therapy
- ☑ Secondary resection of all residual lesions if possible
- ☑ Targeted therapies and ICIs no established role
  (ongoing trials looking at combinations)
- ☑ Phase I CLDN-6 CAR-T study promising
  (other ongoing activity of interest: CLDN6-ADC)
- ☑ Treatment of high-risk / refractory pts in GCT-expert centers strongly recommended

Many thanks
for your attention

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