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Presentaciones más destacadas en tumores germinales y otros tumores genitourinarios

Dra. María José Lecumberri

Hospital Universitario de Navarra, Pamplona

- **Germ-cell tumours of the testis**
  - Metastatic pure seminomas with early relapse: Pronostic roles of high dose chemotherapy and surgery of residual disease.
  - Longitudinal evaluation of circulating tumor DNA (ctDNA) as a prognostic biomarker to detect minimal residual disease(MRD) in testicular cancer.
  - Management of relapsed stage I nonseminomatous germ-cell tumor with retroperitoneal only relapse.
  - High dose chemotherapy in male patients with germ cell cancer: A population-based study by the SWENOTECA group.
  - Multicenter analysis og high-dose chemotherapy (HDCT) regimens for the treatment of patients (pts) with recurrent germ cell tumors (GCTs).

- **Penile cancer**
  - A phase II trial of pembrolizumab plus platinum-based chemotherapy as firts-line systemic therapy in advanced penile cancer: HERCULES (LACOG 0218) trial.

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Abstract 5031

Metastatic Pure Seminomas with Early Relapse: Prognostic Roles of High-Dose Chemotherapy and Surgery of Residual Disease.

Lucile Duval; Benoit Allignet; Christine Chevreau; Gwenaelle Gravis; Camille Mazza; Marine Gross-Goupil; Brigitte Laguerre; Patrice Peyrat; Floriane Izarn; Anna Patrikidou; Aude Fléchon.

1 BACKGROUND

Limited evidence for current treatment guidelines of relapsed metastatic seminomas (mSGCT)

No distinction between situations of relapse after 1st-line ChT and progression during 1st-line ChT

mSGCT may be **aggressive** in early relapse (<1y)

Should salvage treatment for early relapse in metastatic seminomas be intensified?

2 METHODS

- Retrospective study (2005-2022)
- 91 patients from 7 French expert centers
- Patients with early recurrence (<1 year) after initial favorable response to cisplatin-based 1st-line ChT

→ *OBJECTIVES :*

Clinical characteristics — **Survival outcomes**

- Prognostic impact of **surgery of residual disease (RPLND)**
- Prognostic impact of **high-dose chemo-therapy (HDCT)**

3 RESULTS

Characteristic	No. (n=91)	%
Age at initial metastatic diagnosis, years		
Median (range)	37 (18-60)	
Primary tumor site		
Testis	84	92
Retroperitoneum	5	6
Missing data	2	2
N		
N0 - N1 - N2	5 - 1 - 22	5.5 - 1 - 24
N3	58	64
Missing data	5	5.5
M		
M0	61	67
M1a	20	22
M1b	10	11
PreChT serum markers		
Normal LDH level	18	20
Elevated LDH level (LDH <2.5UNL - LDH 2.5UNL+)	56 (27 - 29)	61 (30 - 32)
Missing data on LDH	17	19
Normal serum HCG value	27	30
Elevated serum HCG value (HCG <1000 - HCG 1000+)	44 (40 - 4)	48 (44 - 4)
Missing data on HCG	20	22
UICC CS		
II (IIB - IIC)	39 (18 - 21)	43 (20 - 23)
III (IIIA - IIIB - IIIC)	51 (9 - 25 - 17)	56 (10 - 27 - 19)
Missing data	1	1
Prior CS I		
Yes	26	29
No	65	71
IGCCCG prognostic category		
Good	81	89
Intermediate	10	11

Characteristic	No. (n=91)	%
IGCCCG with 2021 update prognostic category		
Good with LDH <2.5N	39	43
Good with LDH ≥2.5N	26	28
Intermediate	10	11
Missing data	16	18
First-line therapy		
3xBEP	52	57
4xEP	19	21
4xBEP	16	18
4xVIP	1	1
Other	3	3
Response to first-line therapy		
CR	16	18
PRm-	64	70
SDm-	2	2
Missing data (PD excluded)	9	10
Time from CR to ER		
≤3 months	24	26
>3 months	67	74
IPFSG seminoma score		
Very low risk	31	34
Low risk	31	34
Intermediate risk	8	9
No unequivocal classification	21	23
Number of relapse sites		
One - including only retroperitoneum	47 - 35	52 - 38
Multiple	44	48
Marker only	0	0
Serum markers at relapse		
Elevated serum HCG value	34	37
Elevated LDH level	48	53

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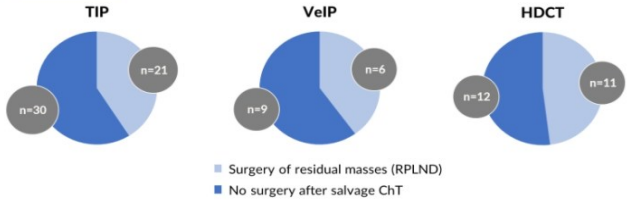
3 RESULTS



Response to salvage therapy	**TIP** *(n=51; 56%)*	**VeIP** *(n=15; 17%)*	**HDCT** *(n=23; 25%)*	**Other ChT** *(n=2; 2%)*
CR	10 (19%)	6 (40%)	4 (17%)	1 (50%)
PRm-	35 (69%)	5 (34%)	13 (57%)	0
PRm+	0	0	0	0
SD	1 (2%)	2 (13%)	2 (9%)	0
PD	1 (2%)	0	0	1 (50%)
Missing data	4 (8%)	2 (13%)	4 (17%)	0

		RPLND	**No RPLND**
Visceral metastases (lung, liver, bone)		19%	**33%**
Relapse ≤3 months after 1st-line		39%	17%
Prognostic score at relapse *(IPFSG)*	*Very low risk*	18%	45%
	Low risk	53%	21%
	Intermediate risk	13%	6%

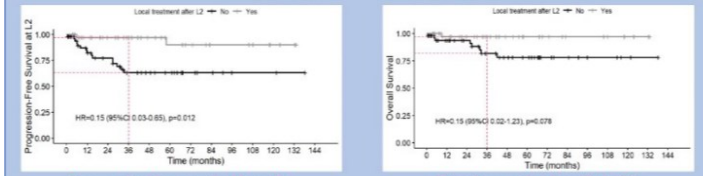
→ **Outcomes in overall population :**

median follow-up of 55.6 months
3-year **PFS** = **77.6%** (95%CI, 68.3-88.1)
3-year **OS** = **88.4%** (95%CI, 81.0-96.4)

Retroperitoneal lymph node dissection after salvage ChT significantly improves PFS in mSGCT patients with 1st-year relapse, and shows a promising trend towards enhancing OS.

RPLND after salvage ChT

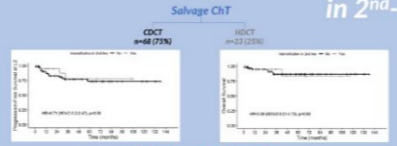
Yes *n=38 (42%)* | ***No*** ***n=53 (58%)***



Progression-free survival benefit
3-year: 97,1% *vs.* **63%**

Trend towards a benefit in OS
3-year: 97% *vs.* **81,8%**

High-dose ChT does not improve survival outcomes *compared to standard-dose ChT in 2nd-line treatment settings.*



No significant difference
in either PFS (77,6% *vs.* 77%) or OS (95,2% *vs.* 86,7%).

4 PERSPECTIVES

- Consider **surgical removal of accessible residual masses** in early relapsed patients, when feasible.
- Conduct a **prospective trial** to validate findings, given the **associated surgical morbidity.**
- Identify **mSGCT subpopulations that may benefit** from HDCT-HSCT.
- **Enhance disease characterization** through advances in **biopathology and molecular biology.**

Longitudinal Evaluation of Circulating Tumor DNA (ctDNA) as a Prognostic Biomarker to Detect Minimal Residual Disease (MRD) in Testicular Cancer

Rebecca Hassoun[1], Reuben Ben-David[2], John P. Sfakianos[2], George Laliotis[3], Clint Cary[1], Timothy A. Masterson[1], Samuel Rivero-Hinojosa[3], Kevin Manage[3], Punashi Dutta[3], Neeraja Tillu[2], Shivaram Cumarasamy[2], Jennifer King[1], Jordan Rich[2], Adam Rock[4], Tanya B. Dorff[4], Adam ElNaggar[3], Minetta C. Liu[3], Lawrence H. Einhorn[1], Alex Chehrazi-Raffle[4], Nabil Adra[1]

[1]Indiana University Simon Comprehensive Cancer Center, Indianapolis, IN; [2]Icahn School of Medicine at Mount Sinai, New York, NY; [3]Natera, Inc., Austin, TX; [4]City of Hope Comprehensive Cancer Center, Duarte, CA

BACKGROUND

- Serum tumor markers (STM) (AFP, hCG) are currently utilized in the management of patients (pts) with testicular cancer[1]
- STM can be normal or falsely elevated in a substantial proportion of pts, hence biomarkers that reliably predict patient outcomes are needed
- We evaluated the clinical utility of longitudinal circulating tumor DNA (ctDNA) monitoring as a prognostic marker in pts with testicular cancer

METHODS

- Longitudinal analysis was performed on a multi-institutional cohort of pts with stage I-III testicular cancer (table 1) using a clinically validated, personalized, tumor-informed 16-plex mPCR-NGS ctDNA assay (Signatera™, Natera Inc.)
- ctDNA testing was performed commercially and prospectively
- ctDNA was evaluated during the pre-orchiectomy, minimal residual disease (MRD), and surveillance windows
  - Pre-orchiectomy window: anytime before radical orchiectomy
  - MRD window: within 1-12 weeks of orchiectomy and prior to any therapy (chemotherapy or RPLND)
  - Surveillance window: 12 weeks post-orchiectomy, after RPLND and/or chemotherapy
- The correlation between ctDNA status and event-free survival (EFS) was assessed
- EFS was defined as interval from orchiectomy to the date of radiological recurrence or any evidence of residual/persistent disease post-completion of chemotherapy or RPLND

Table 1: Patient and Disease Characteristics

Characteristic (N)	N=55 (IQR/%)
Median age (years)	34 (16 - 67)
Stage	
• I	23 (42%)
• II	12 (22%)
• III	20 (36%)
Histology	
• Non-seminoma	38 (69%)
• Seminoma	17 (31%)
Primary treatment	
• Surveillance	15 (27%)
• RPLND	5 (9.1%)
• Chemotherapy	19 (35%)
• Chemotherapy + RPLND	16 (29%)
Pre-orchiectomy serum tumor markers (AFP, hCG)	
• Normal	13 (24%)
• Elevated	35 (64%)
• Unknown	7 (12%)
Serum tumor markers at any point post-orchiectomy	
• Normal	26 (47%)
• Elevated	29 (53%)
Median follow-up (months)	16 (2 - 84)

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Figure 1: Study Population

Patients with at least 1 ctDNA test and annotated clinical data (N=55)†

ctDNA detection rate

Pre-orchiectomy window (N=15)	MRD window (N=29)	Surveillance window (N=36)	Anytime post-orchiectomy positivity (N=53)
Stage I: 91.6% (11/12) Stage II: 100% (1/1) Stage III: 100% (2/2) Overall: 93.3% (14/15)	Stage I: 0% (0/16) Stage II: 60% (3/5) Stage III: 87.5% (7/8) Overall: 34.5% (10/29)	Stage I: 4.8% (1/21) Stage II: 37.5% (3/8) Stage III: 42.9% (3/7) Overall: 19.4% (7/36)	Stage I: 4.6% (1/22) Stage II: 83.3% (10/12) Stage III: 84.2% (16/19) Overall: 50.9% (27/53)

7 pts ctDNA testing pre-RPLND: ctDNA+ in 6 pts.

6 pts ctDNA testing pre and post-QT: ctDNA median reduction of 96% post-tto completion.

17 pts ctDNA testing post RPLND or QT: Relapsed 0/9 ctDNA- Relapsed 4/8 ctDNA+

RESULTS

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

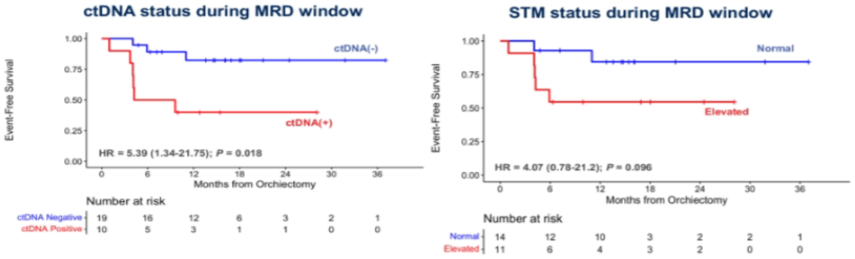
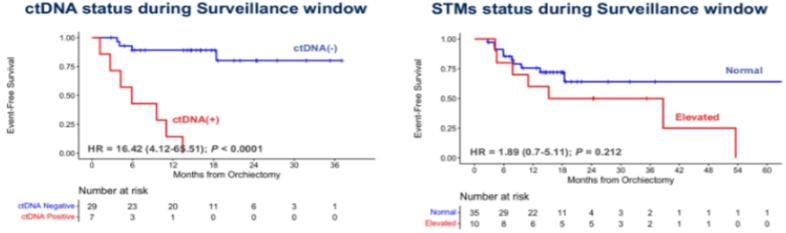


Figure 3: EFS by ctDNA & STM status at the Surveillance Window



All 7 pt with ctDNA+ at the Surveillance Window experienced disease progression at most recent follow-up.

CONCLUSIONS

- Detectable vs. undetectable ctDNA, both during the MRD and surveillance windows was associated with significantly inferior EFS; while elevated vs. normal STMs were not
- Tumor-informed ctDNA analysis shows promise for MRD detection in pts with testicular cancer
- Larger prospective trials are planned for validation of clinical utility of ctDNA in testicular cancer

Management of relapsed stage I nonseminomatous germ-cell tumors with retroperitoneal only relapse

Ahmed Khalid, Rebecca Hassoun, Sandra Althouse, Tareq Salous, Clint Cary, Timothy Masterson, Lawrence Einhorn, Nabil Adra, Jennifer King
Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN

ABSTRACT # 5035

➢ **For correspondence:** Ahmed Khalid, MBBS Email: ahkhalid@iu.edu
➢ **Session Title:** Genitourinary Cancer-Prostate, Testicular and Penile

BACKGROUND

➢ For patients with stage 1 non-seminomatous germ cell tumor (NSGCT) who are on active surveillance (AS), the most common site of relapse is the retroperitoneum (RP). For those with RP only relapse and normal tumor markers, treatment (tx) options include chemotherapy (chemo) or retroperitoneal lymph node dissection (RPLND).
➢ In this study, we describe the characteristics and clinical course/outcomes of patients on AS with stage I NSGCT who relapsed in RP only and were treated w/ either chemo or RPLND.

METHODS

➢ The prospectively maintained Indiana University testicular cancer database was queried for patients with stage 1 NSGCT on AS w/ RP relapse only between 1990-2023.
➢ Patients were categorized into a chemotherapy or surgery group based on tx at relapse. Comparisons between groups were done using Chi-square tests for categorical variables or Wilcoxon test for continuous variables. Kaplan-Meier method was used to analyze progression-free survival (PFS) and overall survival (OS) using the log rank test to compare groups.

RESULTS

➢ 143 patients with stage 1 NSGCT on AS w/ disease relapse in the RP only were identified
➢ At time of RP relapse, 116 patients (81.1%) were treated with chemo and 27 (18.9%) w/ RPLND.
➢ For those treated w/ chemo, the median time to relapse on stage I AS was 5.2 months (0.5-259.2) vs. 9.0 months (1.68-75.24) for those treated w/ RPLND (p=0.01).

Table 1: Patient Characteristics

	N=143
Median Age (range)	**28.8 (15.6-61.5)**
Predominant Histology	
• Embryonal	70 (49.0%)
• Mixed	23 (16.0%)
• Seminoma	22 (15.4%)
• Teratoma	15 (10.5%)
• Yolk sac tumor	11 (7.7%)
• Choriocarcinoma	1 (0.7%)
• Other	1 (0.7%)
IGCCCG Risk	
• Good	140 (98.0%)
• Intermediate	3 (2%)
Chemotherapy Regimen	
• BEPX3	98 (82.5%)
• EPX4	12 (9.8%)
• BEPX3 + EPX1	2 (2.1%)
• Other	7 (5.6%)
Intervention at RP only Relapse	
• Chemotherapy	116 (81.1%)
• RPLND	27 (18.9%)

Table 2: Clinical outcomes

Outcome	Chemotherapy Group (N=116)	Surgery group (N=27)	p-value
Relapse after initial Tx	**17 (14.7%)**	**3 (11.1%)**	**0.7662**
5-year PFS	**81%**	**74%**	**0.7218**
5-year OS	**93%**	**100%**	**0.3713**

RESULTS

➢ **For those treated with chemo:**
  ➢ 55 of the 116 patients (47.4%) treated w/ chemo required a post-chemo RPLND (pcRPLND).

➢ **For those treated with RPLND:**
  ➢ Tumor markers were normal for all 27 patients treated w/ surgery.
  ➢ All but two patients treated w/ surgery had RP lymph nodes <3cm in size.
  ➢ RPLND path was pure GCT in 59%, pure teratoma in 15%, malignant transformation (MT) of teratoma in 11%, both GCT and teratoma in 7%, both teratoma and MT in 4%, and normal lymphatic tissue in 4%.
  ➢ The 3 pts in the surgery group who relapsed were treated w/ chemo at time of relapse; 2 of those patients remain NED. The other patient remains AWD w/ MT of teratoma.

CONCLUSIONS

➢ In patients on AS with stage I NSGCT w/ RP only relapse, there was no difference in 5-yr PFS or OS for those treated w/ RPLND vs. chemotherapy.
➢ Almost half of the patients treated with chemo needed a post-chemo RPLND.
➢ When patients were carefully selected for RPLND at time of relapse(namely normal tumor markers and most with RP lymph nodes <3 cm in size), most were cured with single-modality therapy. In this cohort of patients treated w/ surgery, most had RP lymph nodes <3cm, all had normal tumor markers, and the median time to relapse while on AS for stage I disease was longer.

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#5040: High dose chemotherapy in male germ cell cancer patients – a population-based study by the SWENOTECA group

Authors: Anna K Jansson[1], Gabriella Cohn-Cedermark[2,3], Helene Negaard[4], Torgrim Tandstad[5,6], Olof Ståhl[7], Annika Hedlund[8], Åsa Karlsdottir[9], Martin Hellström[10], Carl Wilhelm Langberg[4], Camilla Sköld[1], Hege S Haugnes[11,12]* and Ingrid Glimelius*[1,] *Contributed equally to last authorship. [1]Department of Immunology, Genetics & Pathology, Uppsala University, Uppsala, Sweden; [2]Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden; [3]Department of Pelvic Cancer, Genitourinary Oncology Unit, Karolinska University Hospital, Stockholm, Sweden; [4]Department of Oncology, Oslo University Hospital, Oslo, Norway; [5]The Cancer Clinic, St. Olavs University Hospital, Trondheim, Norway; [6]Department of Clinical and molecular Medicine, NTNU, Norway; [7]Department of Oncology, Skåne University Hospital, Lund, Sweden. [8]Department of Oncology, Sahlgrenska University Hospital, Gothenburg, Sweden; [9]Department of Oncology, Haukeland University Hospital, Bergen, Norway; [10]Department of Radiation Sciences, Oncology, Umeå University, Umeå, Sweden; [11]Department of Oncology, University Hospital of North Norway, Tromsø, Norway, [12]Institute of Clinical Medicine, University of Tromsø, Norway

Background:

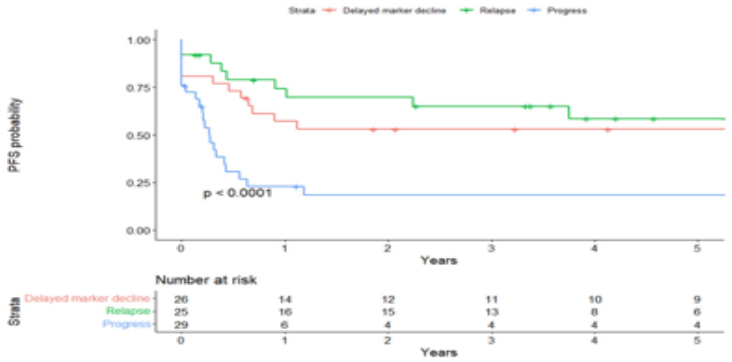
- Selected patients with advanced germ cell tumors have a poor prognosis:
- Patients with brain, bone or liver metastasis, very elevated tumor markers or primary mediastinal tumor.
- High-dose chemotherapy (2 cycles of carboplatin/etoposide) with autologous stem cell support is recommended in SWENOTECA guidelines in selected poor risk patients with poor response to/relapse after intense primary treatment.

Methods:

Population-based study – all patients treated with high-dose chemotherapy (HDCT) according to guidelines in Sweden and Norway between 2011-2021 (n = 80).

Indications:
1) Delayed tumor marker decline during primary/intensified primary treatment (n = 26),
2) Progressive disease during primary treatment (progression <3 months from last cycle of chemotherapy) (n = 29),
3) Relapse with poor prognosis (n = 25)

Failure-free survival:



Indication HDCT	Patients, n	5 Year Failure-free Survival
Overall	**80**	**43%**
Delayed marker decline	26	**53%**
Progression	29	**18%**
Part of relapse treatment	25	**58%**

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Conclusion:

High-dose chemotherapy treatment for patients with advanced germ cell cancer according to the SWENOTECA cancer care program is achievable and leads to favorable overall survival and failure-free survival rates.

Patients who receive high-dose chemotherapy due to progressive disease have a relatively poor outcome, but 20-30% of patients do achieve long-term survival.

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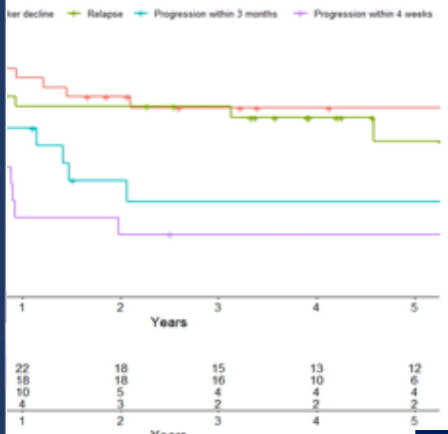

ient	Deaths overall, n	1-year survival probability	2-year survival probability	5-year survival probability
0	36*	70; (60-81)	62; (52-73)	55; (44-68)
6	8	88; (76-100)	80; (66-97)	75; (60-95)
9	20	48; (33-70)	33; (19-56)	29; (16-52)
5	8	76; (61-95)	76; (61-95)	61; (41-91)

Survival probability %; (95% CI). * Mortality due to HDCT-treatment 4/80 (5%)

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City of Hope

Multicenter analysis of high-dose chemotherapy (HDCT) regimens for the treatment of patients with recurrent germ cell tumors (GCTs)

Abstract# 5039

Alex Chehrazi-Raffle[1], Michael Shodiya[2], Edward Maldonado[3], Tamer Othman[4], Hedyeh Ebrahimi[1], Regina Barragan-Carrillo[1], Xiaochen Li[1], Adam Rock[1], Abhishek Tripathi[1], Sumanta K. Pal[1], Tanya B. Dorff[1], Ali Zhumkhawala[1], Rasmus Hoeg[4], Caspian Oliai[2], Rebecca L. Olin[3], Matthew Mei[1]

Background

- HDCT is an established salvage treatment for pts with recurrent GCTs.
- The two most common dosing regimens:
  1. Carboplatin 700 mg/m2 and etoposide 750 mg/m2 (CE) given for two cycles.
  2. Carboplatin AUC 7-8 and etoposide 400 mg/m2 given for three cycles after two cycles of paclitaxel 200 mg/m2 and 2000 mg/m2 (TICE).
- We sought to assess and compare the clinical efficacy of these two HDCT approaches.

Design and Methods

- Adult patients who received HDCT for recurrent GCT from 1/1/2010 to 1/1/2023 and received either CE or TICE in the following four referral centers were included:
  1. City of Hope Comprehensive Cancer Center
  2. University of California Los Angeles
  3. University of California San Francisco
  4. University of California Davis
- Fisher's exact and the Wilcoxon rank-sum tests were used to test differences among qualitative and quantitative variables, respectively.
- Relapse-free survival (RFS) and overall survival (OS) were estimated and compared using the Kaplan-Meier method and log-rank test.

Figure 1. Kaplan–Meier estimates of relapse-free survival (RFS)

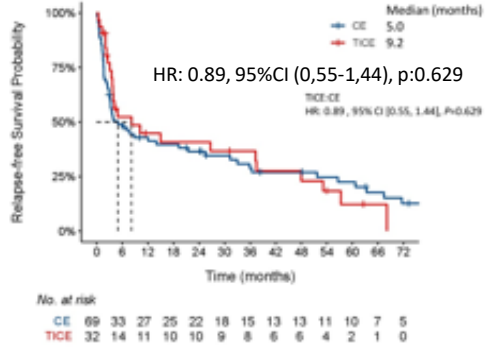
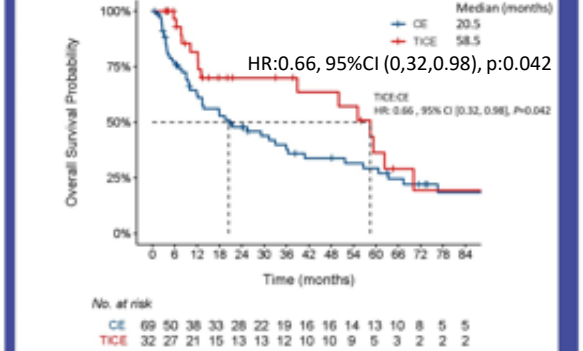


Figure 2. Kaplan–Meier estimates of overall survival (OS)



Post-transplant relapse (%)	Overall (N:101)	CE (N:69)	TICE (N:32)	P-value
No	40 (39,6%)	27 (39,1%)	13 (40,6%)	0,999
Yes	**61 (60,4%)**	**42 (60,9%)**	**19 (59,4%)**	0,999

CONCLUSION & MAIN TAKEAWAY

- While no difference in RFS between CE and TICE was observed, a significant increase in survival among patients who received TICE was noted.

- Elevated pre-transplant tumor markers (particularly serum hCG level) were among the most prognostic factors for both RFS and OS.

- **Germ-cell tumours of the testis**
  - Metastatic pure seminomas with early relapse: Pronostic roles of high dose chemotherapy and surgery of residual disease.
  - Longitudinal evaluation of circulating tumor DNA (ctDNA) as a prognostic biomarker to detect minimal residual disease(MRD) in testicular cancer.
  - Management of relapsed stage I nonseminomatous germ-cell tumor with retroperitoneal only relapse.
  - High dose chemotherapy in male patients with germ cell cancer: A population-based study by the SWENOTECA group.
  - Multicenter analysis og high-dose chemotherapy (HDCT) regimens for the treatment of patients (pts) with recurrent germ cell tumors (GCTs).

- **Penile cancer**
  - A phase II trial of pembrolizumab plus platinum-based chemotherapy as firts-line systemic therapy in advanced penile cancer: HERCULES (LACOG 0218) trial.

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A phase II trial of pembrolizumab plus platinum-based chemotherapy as first-line systemic therapy in advanced penile cancer: HERCULES trial (LACOG 0218)

Fernando C. Maluf[1, 2, 3], Karine Trindade[1,4], Daniel D. Preto[5], Murilo de A. Luz[6], Patrícia M. M. Beato[7], Diogo A. Bastos[1,8], João Paulo H. Soares[9], Victor M. Lopes[10], Luis Eduardo W. de Carvalho[11], David Q. B. Muniz[12], Douglas Racy[2], Rafaela G. de Jesus[1], Taiane F. Rebelatto[1], Susan Halabi[13], Gustavo Werutsky[1], Fernando S. M. Monteiro[1,14, 15], Andre P. Fay[1,16, 17].

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Background

- Penile Squamous Cell Carcinoma (PSCC) is a rare disease with an incidence of 38,000 new cases/year worldwide[1]
  - Up to 10X higher incidence in low-income countries (Africa, Asia and Latin America)[2]
- No improvements have been made over last decades in **advanced Penile Squamous Cell Carcinoma (PSCC)**:
  - advanced PSCC has **poor prognosis (OS ~ 6-7months)**
  - platinum-based chemotherapy has been the standard of care
  - doublet-platinum based regimen - limited efficacy (ORR 20-30%, PFS 3 months)[3]
  - triplet-platinum based regimen - ORR 38%-45%, at cost of higher toxicity (33-46% neutropenia Grade 3-4; 25% sepsis), with high rate of treatment discontinuation[4-7]
- **Immune Checkpoint Inhibitors (ICI)** have been associated with efficacy in different tumor types, including HPV16 positive tumors, such as cervical and head and neck squamous carcinoma[8,9]

STUDY HYPOTHESIS: We hypothesized that adding pembrolizumab to platinum-based chemotherapy in first-line treatment of advanced penile cancer patients will improve efficacy outcomes with manageable safety profile.

1. IARC, Cancer Today. 2023. **2.** Coelho RWP, et al. *BMC Urol*. 2018; 18(1):50. **3.** Di Lorenzo G, et al. *BJU International* 2012;110. **4.** Zhang S, et al. *Oncotarget* 2015; 6: 32212–9 **5.** Pagliaro LC, et al. J Clin Oncol. 2010; 28(24):3851-7. **6.** Azizi M, et al. J Urol. 2020 Jun;203(6):1147-1155 **7.**Nicholson S, et al. *Br J Cancer* 2013; 109:2554-9. **8.**Burtness B, et al. *The Lancet* 2019; 394: 1915–28. **9.** Colombo N, et al. N Engl J Med. 2021;385(20):1856.

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Study Design

- **Phase 2, single-arm study**

ELIGIBILITY CRITERIA (N=33)

- ✓ ECOG PS 0-1
- ✓ Patients with penile squamous cell carcinoma:
  - Metastatic disease (de novo or recurrent),
  - Locally advanced disease (TanyN3M0 or T4NanyM0) not amenable to curative-intent therapy,
  - Loco-regional recurrence not amenable to curative-intent therapy
- ✓ No prior exposure to chemotherapy for advanced disease
- ✓ Prior (neo)adjuvant chemotherapy is allowed if progression after 12 months

INTERVENTION

Cisplatin 70mg/m² or **Carboplatin** AUC 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

Tumor assessment per RECIST v1.1 by investigator every 6 weeks.

PRIMARY ENDPOINT

Confirmed Overall response rate (RECIST 1.1) by investigator assessment

SECONDARY ENDPOINTS

- Confirmed ORR by central review
- Progression-free survival
- Overall survival
- Safety
- Translational research: PD-L1, HPV16, MMR, NGS

Number of research sites:
11 Brazilian sites.

Statistical consideration: 33 pts were needed to reject the null hypothesis that cORR is 20% or less, if the true cORR is 40% (0.1 two-sided alpha level, 78.5% power), considering a drop-out rate of 10%.

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Patient Characteristics

Demographic and disease characteristics	All Patients (N=37)
Age, in years — Median (range)	56 (30 – 76)
ECOG performance status score	
0	10 (27.0%)
1	27 (73.0%)
Race or ethnic group	
White	15 (40.5%)
Black or African American	22 (59.5%)
Disease stage	
Locally advanced disease (TanyN3M0 or T4NanyM0)*	5 (13.5%)
Loco-regional recurrence*	8 (21.6%)
Metastatic disease	**24 (64.9%)**
Non-regional lymph node	12 (50.0%)
Lung	4 (16.7%)
Liver	2 (8.3%)
*Other***	6 (25.0%)

*Patients not amenable to curative-intent therapy. **(Sub)cutaneous, bone, and bladder

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Efficacy Outcomes

Efficacy Outcome	N=33*
Confirmed ORR by investigator	13 (39.4%); (95% CI, 22.9 – 57.9)
Best overall response by investigator	
Complete Response	1 (3.0%)
Partial Response	12 (36.4%)
Stable Disease	7 (21.2%)
Progressive Disease	11 (33.3%)
Unevaluable**	2 (6.1%)
Confirmed ORR by central review	14 (42.4%); (95% CI, 25.5 – 60.8)
Clinical benefit rate by investigator (CR, PR, SD ≥ 24 weeks)	**15 (45.5%); (95% CI, 28.1 – 63.7)**

*Four patients were ineligible for efficacy analysis due to major protocol violation: three patients had active infection at enrollment and one patient had received prior chemotherapy and progressed within four months **Two patients were not evaluable due to study withdrawal (n=1) and sudden death (n=1) prior to the first scheduled assessment
cORR= confirmed overall response rate by RECIST 1.1
Lower boundary of the 95% CI of cORR by investigator and by central review are higher than the null hypothesis of 20% cORR

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Best Change from Baseline

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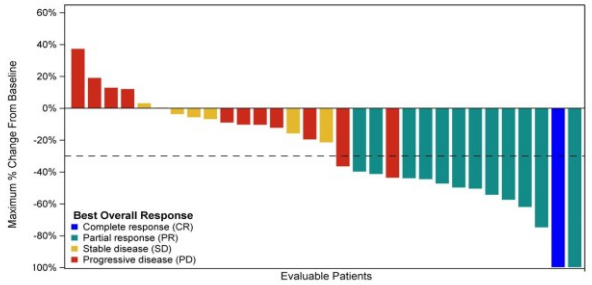
Tumor shrinkage of any magnitude was observed in 75.8% of patients.



Patients with measurable disease at baseline and the at least one post-baseline assessment (N=31)

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Duration of Response

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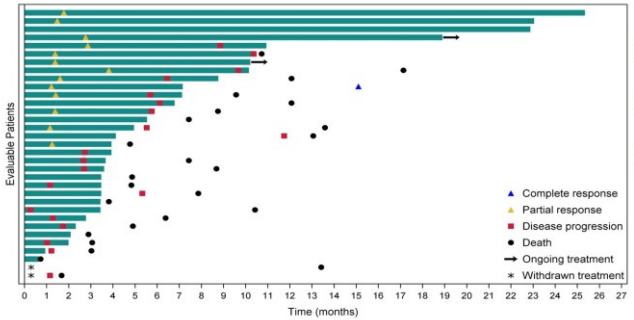

Median duration of response:
5.9 months (95% CI, 4.4 – 9.0).

Median time to response:
1.4 months (95% CI, 1.3 – 1.8).

Median follow-up:
24.0 months (95% CI, 13.5 – 26.4);
Cut-off date 24 Jan 2024.

Treatment is ongoing in 2 patients, 3 completed study treatment.

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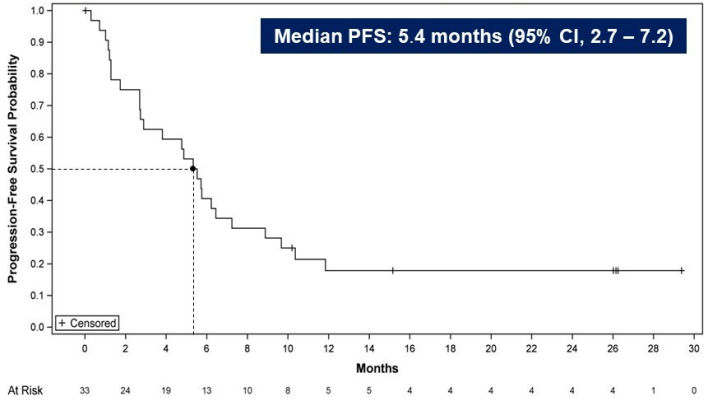
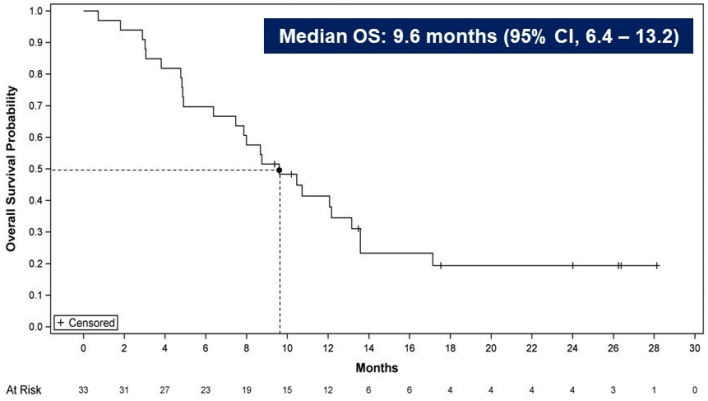
Survival outcomes

Progression-Free Survival (PFS)



Overall Survival (OS)



Median follow-up: 24.0 months (95% CI, 13.5 – 26.4); cut-off date 24 Jan 2024.

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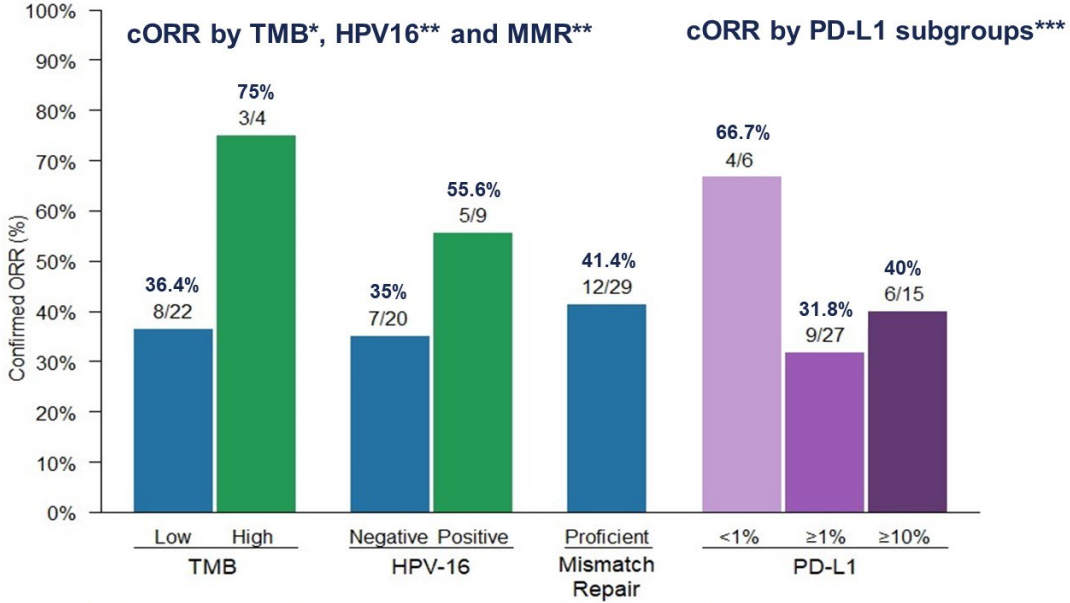
Biomarkers exploratory analysis



*TMB-low (<10 mut megabase); TMB-high (≥10 mut megabase) **HPV16 and MMR assessed centrally by immunohistochemistry
***PD-L1 assessed centrally by immunohistochemistry 22C3 antibody assay

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Treatment-related Adverse Events

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Treatment-Related Adverse Event* (N=37)	Any Grade	Grade ≥3†
Any, n (%)	**34 (91.9%)**	**19 (51.4%)**
Anaemia	16 (43.2%)	4 (10.8%)
Nausea	16 (43.2%)	1 (2.7%)
Decreased appetite	9 (24.3%)	1 (2.7%)
Neutropenia	**8 (21.6%)**	**6 (16.2%)**
Vomiting	7 (18.9%)	1 (2.7%)
Diarrhea	6 (16.2%)	0 (0%)
Mucosal inflammation	6 (16.2%)	0 (0%)
Stomatitis	6 (16.2%)	2 (5.4%)
Thrombocytopenia	5 (13.5%)	1 (2.7%)
Fatigue	4 (10.8%)	0 (0%)

* Occurred in >10% of patients. † No treatment-related adverse event grade 5 were reported. One patient had Febrile Neutropenia grade 3.

Immune-related Adverse Event (N=37)	Any Grade	Grade ≥3†
Any, n (%)	**8 (21.6%)**	**2 (5.4%)**
Hypothyroidism	3 (8.1%)	1 (2.7%)
Adrenal insufficiency	1 (2.7%)	1 (2.7%)
Anaemia	1 (2.7%)	1 (2.7%)
ALT increased	1 (2.7%)	0 (0%)
Alkaline phosphatase increased	1 (2.7%)	0 (0%)
Drug hypersensitivity	1 (2.7%)	0 (0%)
Hyperthyroidism	1 (2.7%)	0 (0%)
Pruritus	1 (2.7%)	0 (0%)
Rash	1 (2.7%)	0 (0%)
Thrombocytopenia	1 (2.7%)	0 (0%)

† No adverse event grade 5 were reported

Two patients discontinued treatment due to TRAE adrenal insufficiency (n=1) and cardiotoxicity (n=1).

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Conclusions

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- **HERCULES trial (LACOG 0218) met its primary endpoint** (cORR of 39.4% by investigator assessment).
- cORR of 42.4% by central review
- HPV16-positive (cORR 55.6%) and TMB-high (cORR 75%) are potential predictive biomarkers for efficacy with chemotherapy + ICI regimen in advanced PSCC.
- First trial to demonstrate **the efficacy of ICI in advanced PSCC** with manageable safety profile.
- **Pembrolizumab plus platinum-based therapy is a new treatment option for advanced PSCC.**

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