Pasquale Benedetto, MD
Leonard M Miller Professor of Medicine
Robert J and Marion G Fewell Endowed Chair
University of Miami Sylvester Cancer Center

Testicular Cancer: The Old, The New, The Future

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The Medical Educator Consortium

19h Annual New Orleans Summer Cancer Meeting

Outline

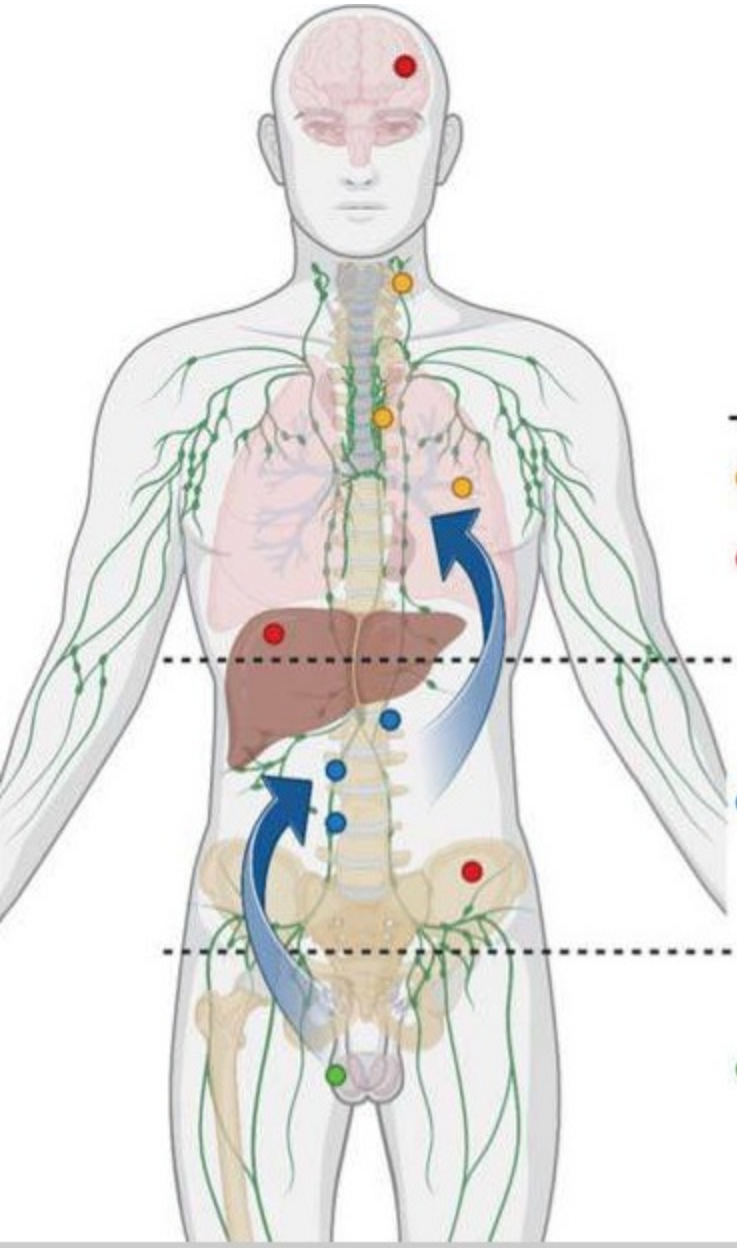
- IGCCCG risk stratification for metastatic disease
- 1L therapy for testis cancer
- Salvage chemotherapy for relapsed disease
- Favorable factors for 2L Rx
- Results of HDCT
- Prognostic factors for relapsed disease
- Comparison of CDCT v HDCT
- New therapies

Testis Cancer/Germ Cell Tumor

- Most common malignancy in men between 15-35y
- Incidence 5.7/100,000; 9760 cases (2024)
- Gonadal (95%)
- Extragonadal (5%)
  - Mediastinum, Retroperitoneum, CNS
- Overall Survival 95%
  - ~ 500 deaths/year

Testicular cancer stage (simplified)

Stage 1	259 (53.40%)
Stage 2	113 (23.30%)
Stage 3	113 (23.30%)



TNM		UICC
M1a	Mediastinal/cervical lymph nodes/ pulmonary metastases	III
M1b	Extrapulmonary visceral metastases (liver, brain, bones, etc.)	
N1	Retroperitoneal lymph nodes < 2 cm	II
N2	Retroperitoneal lymph nodes 2–5 cm	
N3	Retroperitoneal lymph nodes > 5 cm	
T1–4	Tumor confined to testicle	I

IGCCCG vs AJCC Classification

Risk status	Nonseminoma	Stage	Seminoma	Stage
Good	+/- Mets in lung AFP < 1,000 HCG < 5,000 LDH < 1.5 x ULN	I-II S1 IIIA	+/- lung mets	I-II IIIC with lung mets
Intermediate	+/- Mets in lung AFP 1000 -10,000 HCG 5000 - 50,000 LDH 1.5 –10 x ULN	II S2 IIIB	Non-lung mets	IIIC with non-lung mets
Poor	PMGCT or Non-lung visceral mets AFP >10,000 HCG > 50,000 LDH > 10 x ULN	II S3 IIIC		

Testis Cancer Chemotherapy – First Line BEP

Days:	1	2	3	4	5	8	15
Cisplatin 20 mg/m^2	X	X	X	X	X		
Etoposide 100 mg/m^2	X	X	X	X	X		
Bleomycin 30 U	X					X	X

Each cycle repeated every 3 weeks x 3-4 cycles

Good Risk Testis Cancer
BEP 3 v 4

	BEP X 3	BEP X 4
No patients	88	96
CR	86 (98%)	93 (97%)
Minimal Disease	106/107 (99%)	
Moderate Disease	73/77 (95%)	

Einhorn et al, J Clin Onc 7:387-391, 1989

Good Risk Metastatic NSGCT
EP v BEP

	BEP X 3	EP x 4	
No pts	132	130	
IGCCCG good risk	128	128	
Favorable response +/- surgery	124	122	p = 0.34
DFS 4 y	91%	86%	p = 0.135
OS 4y	96%	92%	
Relapse	6	14	

Culine S, Kerbrat P, Kramar A, et al; Ann Oncol. 2007;18(5):917-924.

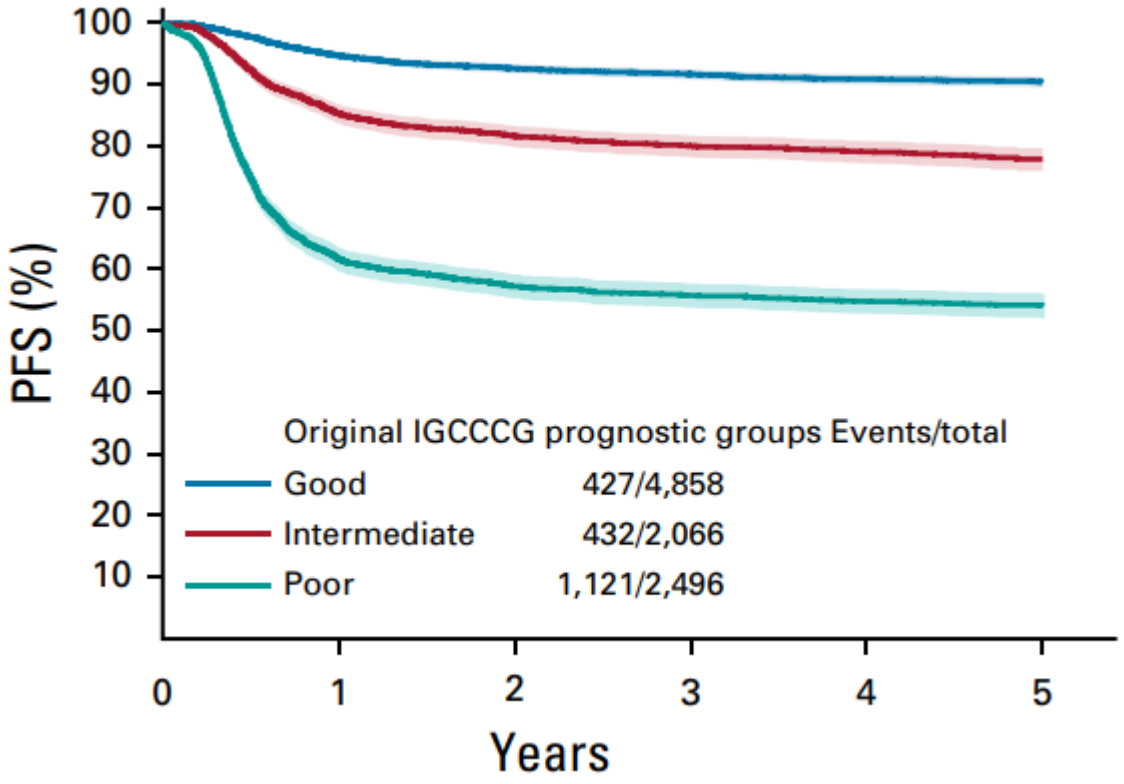
BEP Practical Tips

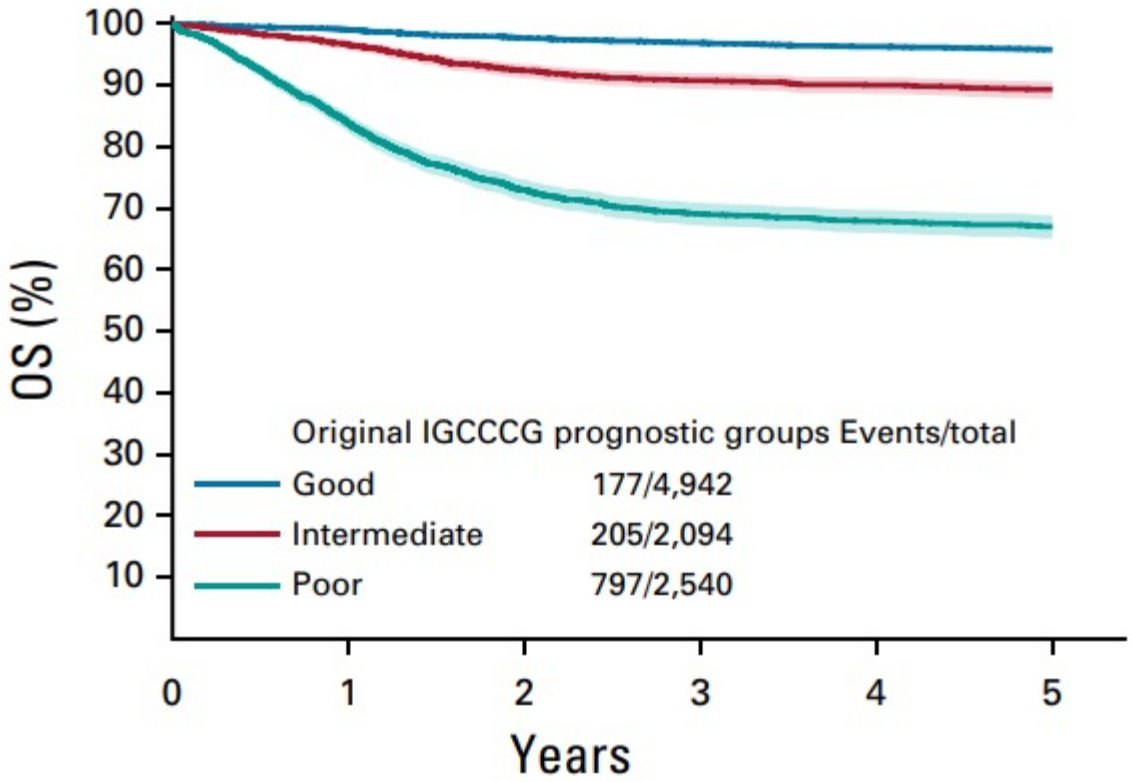
- Maintain treatment intensity; cycles are 21 days
- Do NOT hold any dose of chemotherapy for ANC
- Do NOT modify or skip doses
- Do not need growth factors for the average patient with GCT
- Do not need to repeat CT imaging during the course of chemotherapy; following markers is sufficient and should be repeated at the beginning of each cycle of therapy; if markers are decreasing predictably no change in treatment is necessary

IGCCCG Update 1990-2013

N = 9450

Original IGCCCG Prognostic Groups	5-Year PFS (95% CI)	5-Year OS (95% CI)	Incidence
Good	90 (89 to 91)	96 (95 to 96)	60
Intermediate	78 (76 to 80)	89 (88 to 91)	26
Poor	54 (52 to 56)	67 (65 to 69)	14





- 20-30% relapse after primary therapy
  - Dependent on IGCCCG classification status

- What is the best strategy/regimen for salvage chemotherapy?
  - Conventional dose chemotherapy (CDCT) or
  - High dose chemotherapy with ASCR (HDCT)

Salvage Therapy for Relapsed Testis Cancer Conventional Dose Chemotherapy (CDCT)

Cisplatin + ifosfamide
+ etoposide (VIP)
+ vinblastine (VeIP)
+ paclitaxel (TIP)

Salvage Chemotherapy for Testis Cancer

Table 1: Prospective studies examining the use of initial salvage conventional-dose chemotherapy.

Author (year)	N	CDCT Regimen(s)	Notable inclusion or exclusion criteria	EP/BEP as first-line therapy	CR/PR to first-line therapy	IR to first-line therapy	CR	Median f/u (months)	Durable remission
McCaffrey et al. [4]	56	VeIP or VIP	None	53%	36%	64%	36%	52	23%
Loehrerr et al. [5]	135	VeIP	Cisplatin-refractory patients excluded[a]	100%	100%	0%	50%	72[b]	24%
Kondagunta et al. [14]	46	TIP	Included only patients with CR- or PR-negative marker to first line, gonadal primary, and <6 cycles of cisplatin in first line	74%	100%	0%	70%	69	63%
Fizazi et al. [17]	37	GIP	Included only patients with CR or PR-negative marker to first line, gonadal primary, and <6 cycles of cisplatin in first line	86%	100%	0%	54%	53	51%

CDCT, conventional-dose chemotherapy; EP, etoposide plus cisplatin; BEP; bleomycin, etoposide, and cisplatin; IR; incomplete response; CR, complete response; f/u, follow-up; VIP, etoposide, ifosfamide, and cisplatin; VeIP, vinblastine, ifosfamide, and cisplatin; GIP, gemcitabine, ifosfamide, and cisplatin; [a]progression at <3 weeks after completion of first-line chemotherapy; [b]minimal (not median) follow-up.

McHugh DJ, Feldman, DR Advances in Urology, 2018, doi.org/10.1155/2018/7272541 4 1997

	VIP/VeIP[1]	VeIP[2]	TIP[3]
	Retrospective	Prospective	Prospective
# Pts	56	135	46
CR (%)	36	50	70/50* (Late relapse)
DFS 5 y	23	23.7	63
Inclusion/Exclusion	Extragonadal 18%	Extragonadal 27%	No EGCT Late relapse (30%) Gonadal primary, CR/PRm- > 6 m
Prognostic factors for response		Prior CR, Good risk Testis primary	
	Various 1L Rx NED (testis) 41% EGCT or IR 15%	EGCT 0 disease free	* Late relapse: CR to chemo 29% CR + surgery 21%

[1]McCaffrey, J Clin Oncol 15, 1997: [2]Loehrer, J Clin Oncol 16: 2500. 1998 ; [3]Kondagunta, J Clin Oncol 23:6549, 2005

Factors for response to salvage CDCT 2L

- Favorable
  - Gonadal primary
  - Complete response to 1L treatment
  - Interval between 1L and 2L therapy ≥ 6 m
- Unfavorable
  - Extragonadal primary
  - IR/platinum refractory
- Tumor burden, elevation of markers not prognostic in all reports
- Unresectable late relapse achieved acceptable response to TIP
- Adherence to 1L protocol
  - Intervals, dose modifications, etc.
- ? rate of marker decline[1]
  - Time to normalization (TTN) markers in **first line** poor risk NSGCT
    4-year PFS: favorable decline 64% v unfavorable 38%

[1]Fizazi, et al., Lancet Oncol 2014; 15: 1442–50

Salvage Therapy for Relapsed Testis Cancer

- High dose chemotherapy (HDCT) with autologous stem cell rescue
  - Carboplatin/etoposide

HDCT with ASCR

- First report of Indiana tandem HDCT
- Phase I/II
- 33 pts
  - 20 tandem
  - 13 single
- Heavily pretreated
  - 55% ≥ 3 regimens
- Platinum refractory 67%
- 1/3 “advanced” Einhorn stage
- No cytoreductive chemotherapy prior to HDCT

- ORR 44%
  - CR 8
    4 continuous NED , 11%,
    3 > 1 year
  - PR 6
- Mortality 21%

Nichols et al, J Clin Oncol. 1989;7(7):932–9.

HDCT

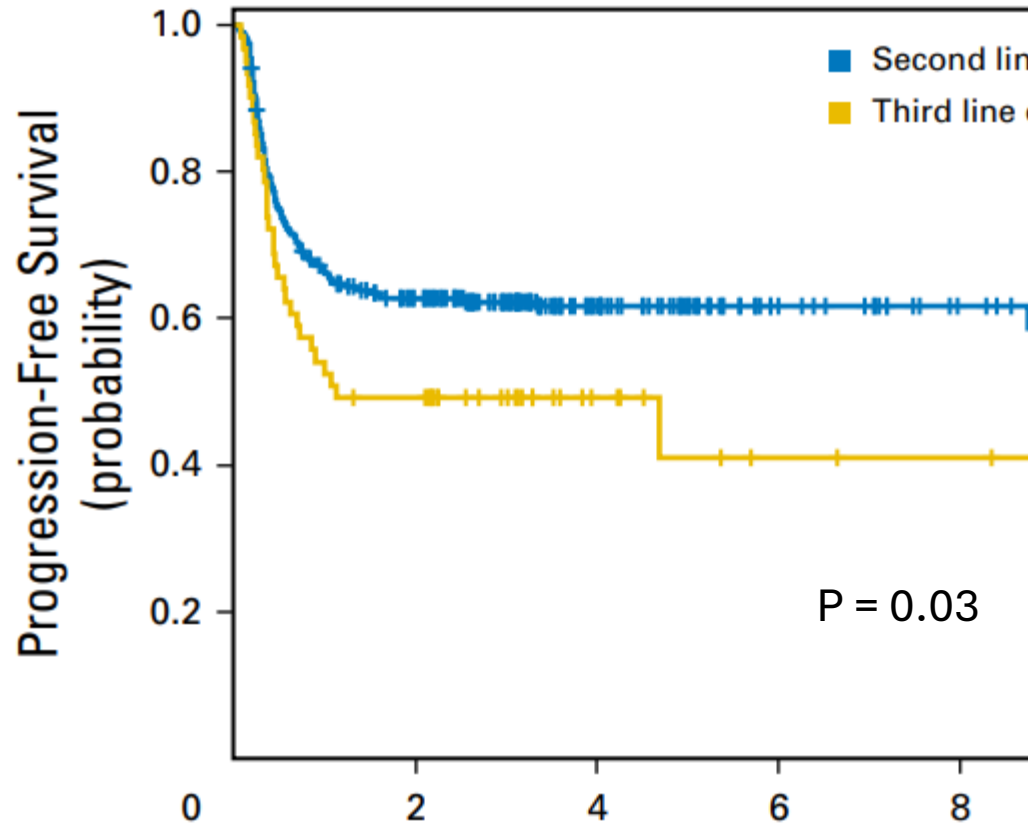
- Indiana University
  - 2004-2014
- 364 pts
  - 122 (33%) platinum refractory
  - 79 seminoma
  - 20 MNSGCT included
  - Late relapse excluded
  - Cytoreductive chemo (VeIP) given to platinum sensitive pts
- PFS 2y 60%
- OS 2y 66%

PFS 2y (%)

- Line of therapy
  - 63% 2L
  - 49 % >2L
- Platinum
  - sensitive 75
  - refractory 33
- Location of primary
  - Testis /RP 63
  - Mediastinum 23
- Seminoma 90

Adra, N. J Clin Oncol 35:2016

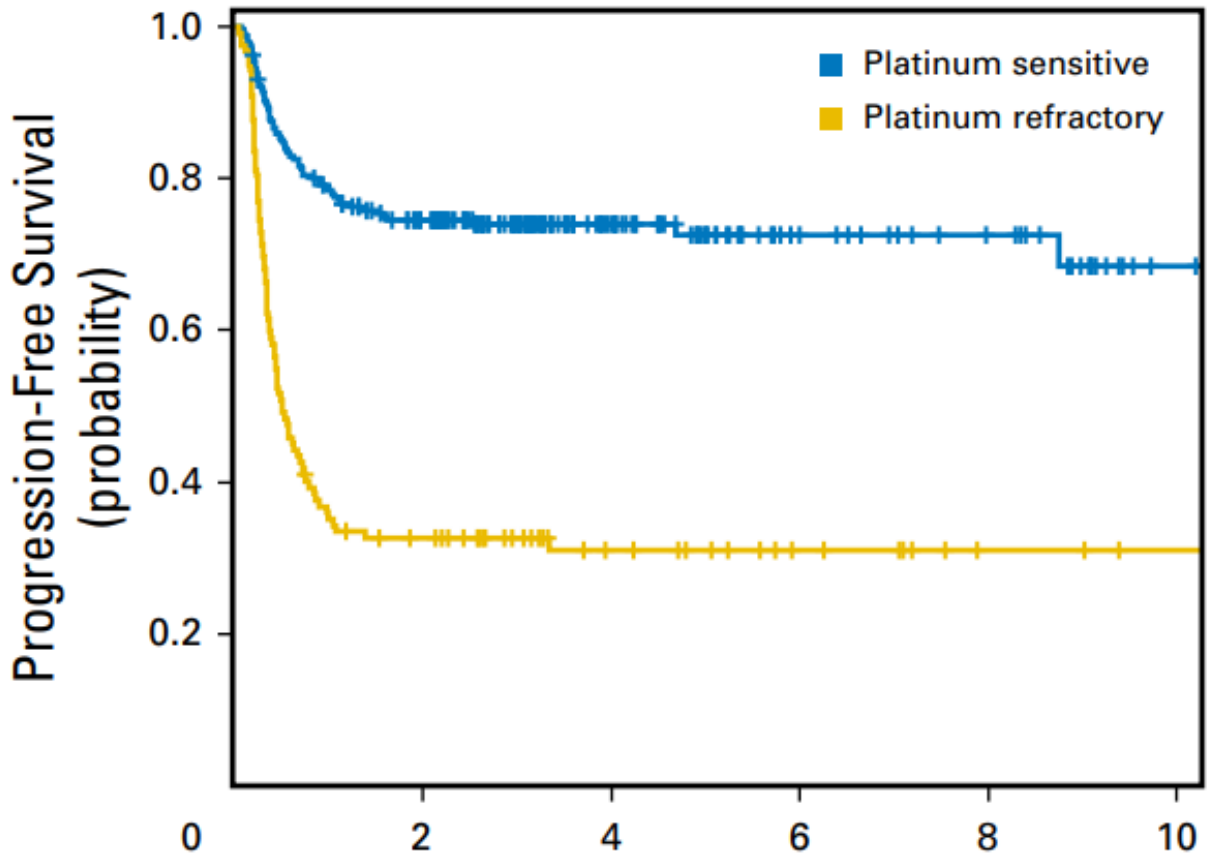
A



No. at risk

Second line	303	168	77	37	24
Third line or later	61	29	9	3	2

B



No. at risk

Platinum sensitive	242	161	68	30	22	5
Platinum refractory	122	36	18	10	4	2

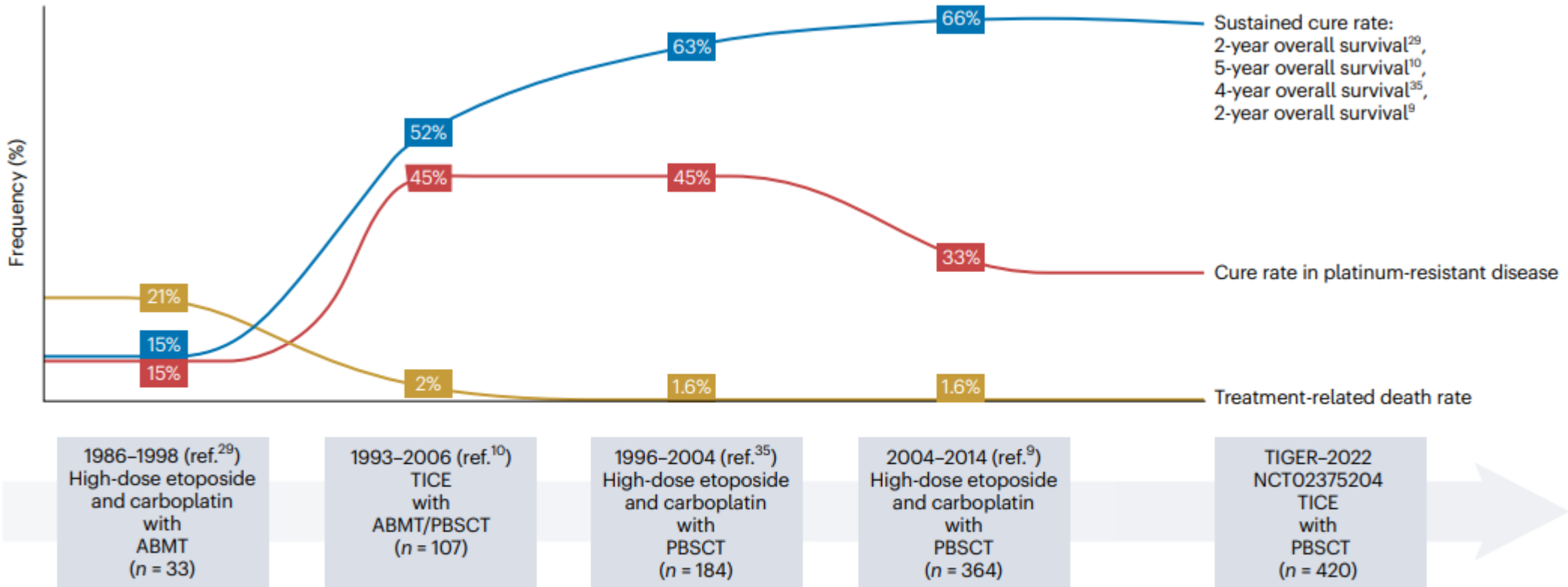


Fig. 1 | Milestones in HDCT for relapsed GCTs. The most reproducible results have been achieved with high-dose chemotherapy (HDCT) with two cycles of etoposide and carboplatin or three cycles of the paclitaxel, ifosfamide, carboplatin and etoposide (TICE) regimen. Using these two regimens, sustained cure rates of 50–66% have been reported in phase I, phase II and retrospective studies published in the past two decades. ABMT, autologous bone marrow transplant; GCT, germ cell tumour; PBSCT, peripheral blood stem cell transplant.

Int'l Prognostic Factors Study Group (IPFSG), Retrospective review

- 1594 pts, 38 centers worldwide
- At least 3 cycles of cisplatin + etoposide based first line chemo
- No progression within 4 weeks of chemotherapy
  - (no platinum refractory disease)
- No HDCT as first line therapy
- No prior salvage therapy
- More advanced disease and older age in HDCT group; primary site and better 1L response in CDCT group

Lorch et al J Clin Oncol 29:2178-2184. 2011

Prognostic Factors in Relapsed Testis Cancer

- Histology
- Primary site: gonadal v extragonadal
- Response to first line Rx
  - Refractory disease
  - Absolute refractory disease
- Progression free interval
- AFP level
- hCG >1000
- Liver, bone, brain involvement (IGCCCG poor risk)

Table 4. Prognostic Score for Patients With Nonseminoma and Seminoma

	Score Points				
Parameter	0	1	2	3	Score
Primary site	Gonadal	Extragonadal	—	Mediastinal nonseminoma	
Prior response	CR/PRm−	PRm+/SD	PD	—	
PFI, months	> 3	≤ 3	—	—	
AFP salvage	Normal	≤ 1,000	> 1,000	—	
HCG salvage	≤ 1,000	> 1,000	—	—	
LBB	No	Yes	—	—	
Score sum (values from 0 to 10)					
Regroup score sum into categories: (0) = 0; (1 or 2) = 1; (3 or 4) = 2; (5 or more) = 3					
Add histology score points: pure seminoma = −1; nonseminoma or mixed tumors = 0					
Final prognostic score (−1 = very low risk; 0 = low risk; 1 = intermediate risk; 2 = high risk; 3 = very high risk)					

Abbreviations: CR, complete remission; PRm−, partial remission, negative markers; PRm+, partial remission, positive markers; SD, stable disease; PD, progressive disease; PFI, progression-free interval; AFP, alpha fetoprotein; HCG, human chorionic gonadotrophin; LBB, liver, bone, brain metastases.

Int'l Prognostic Factors Study Group, J Clin Oncol 28:4906-4911. 2010

Table 5. Survival Rates According to Prognostic Categories (validation set plus patients with seminoma)

Prognostic Category (n = 654)	Score	No. of Patients	%	HR	95% CI	2-Year PFS	3-Year OS
Very low	−1	76	13.0	1		75.1	77.0
Low	0	132	22.6	2.17	1.32 to 3.58	51.0	65.6
Intermediate	1	219	37.4	3.20	2.00 to 5.11	40.1	58.3
High	2	122	20.9	4.85	2.98 to 7.89	25.9	27.1
Very high	3	36	6.1	11.70	6.70 to 20.45	5.6	6.1
No unequivocal classification		69					

Abbreviations: HR, hazard ratio; PFS, progression-free survival; OS, overall survival.

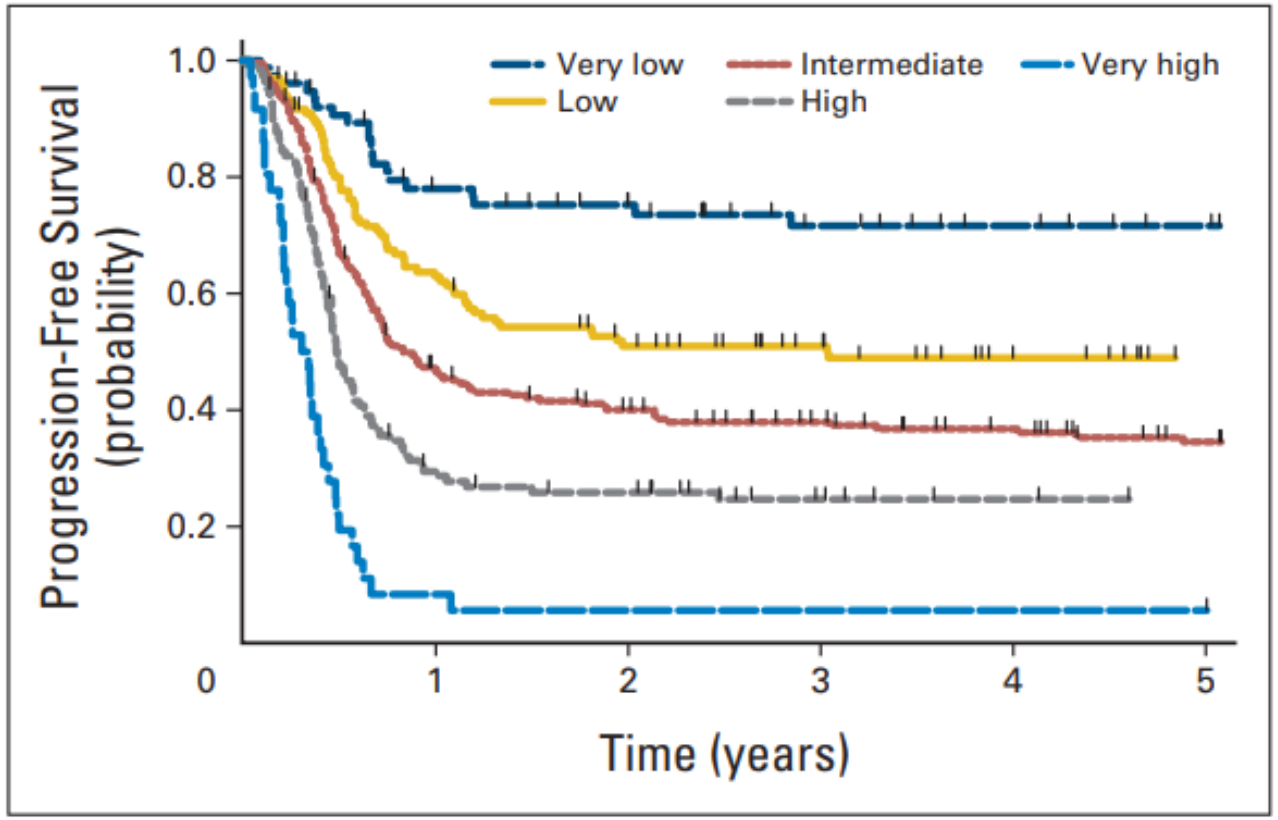


Fig 1. Progression-free survival according to prognostic category (validation set plus patients with seminoma).

Int'l Prognostic Factors Study Group,
J Clin Oncol 28:4906-4911. 2010

CDCT v HDCT

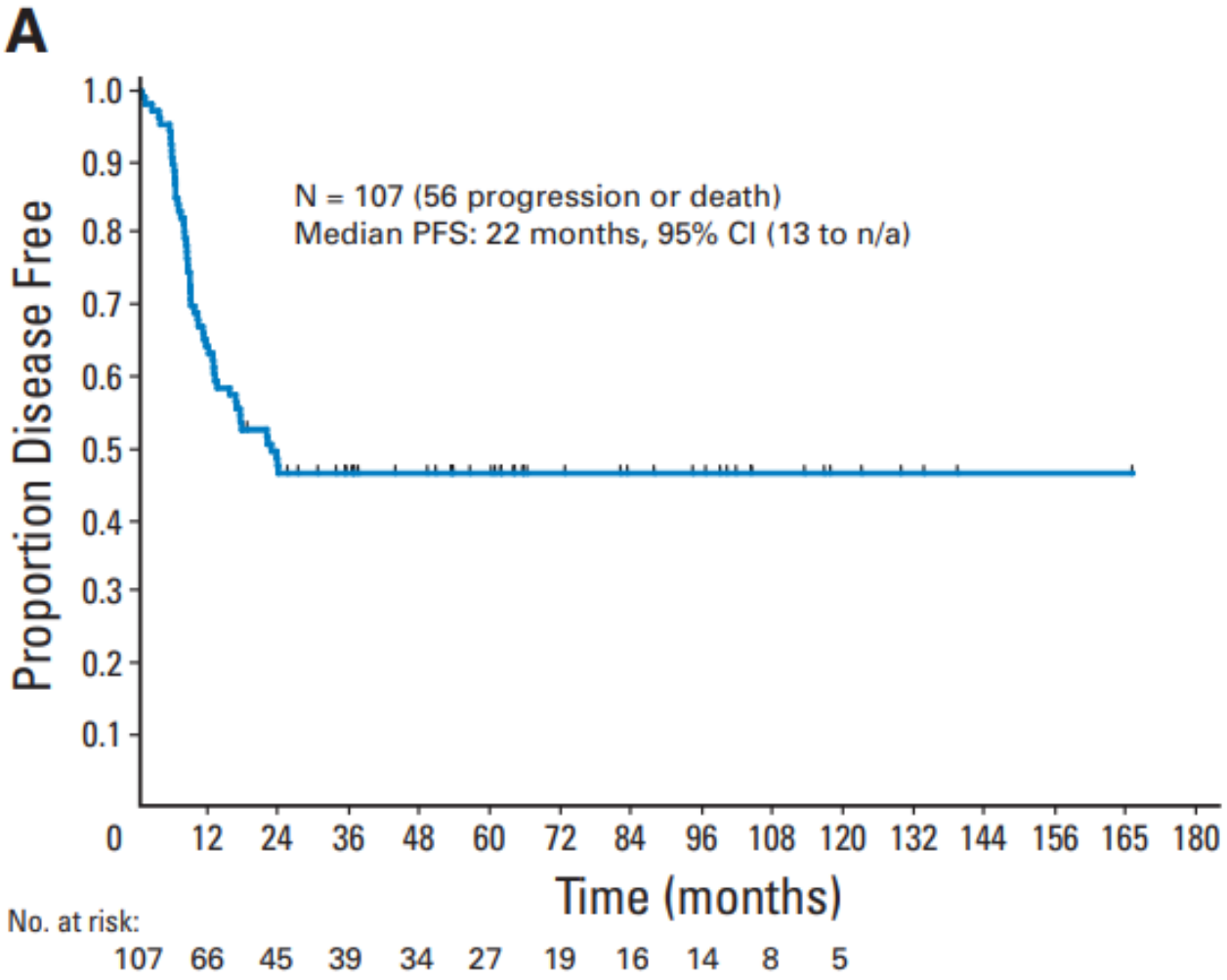
Retrospective Analysis

	CDCT	HDCT	
No Pts	773	821	
TIP	90 (12%)	-	
PFS 2 yr (%)	27.8	49.6	p < 0.001
TIP	35.6		
Other	26.8		
Single 50%		44.1	
Sequential 50%		55	p < 0.001
Liver, brain, bone (LBB) (%)	27.6	35.3	
OS 5 yr (%)	40.8	53.2	p < 0.001

Lorch et al J Clin Oncol 29:2178-2184. 2011

Ti-CE

- Paclitaxel + ifosfamide (TI) q14 days x 2 → Carbo/etoposide (CE) x 3
- 107 pts (2L 76%) with ≥1 unfavorable prognostic factors:
  - Extragonadal GCT
  - IR to 1L
  - PD after salvage CDCT
- 5 yr PFS 47%, OS 52%
- Prognostic factors:
  - Primary site
  - hCG
  - Prior lines therapy
  - Lung metastases



	TIP	TI-CE	HDCT (Indiana)
# Pts	46	107	364
DFS 5 y	63	47	60 (est)
OS 5 y	74	52	64 (est)

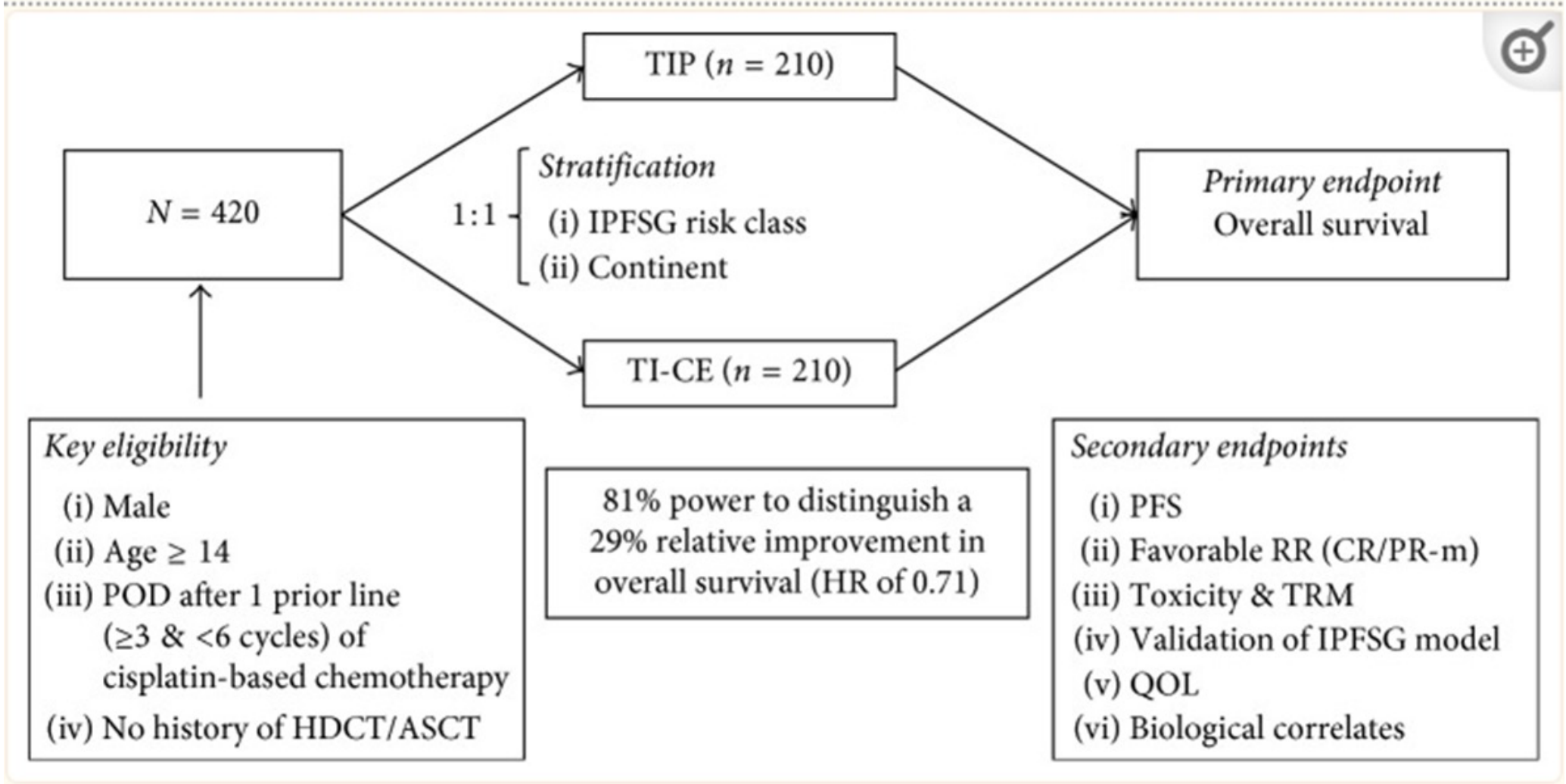
Adverse effects of HDCT

- Mucositis
- Neuropathy
- Hepatotoxicity
- Ototoxicity
- **Secondary leukemia**
- **Death**

Table 4. Grade 3 or Higher Nonhematologic Toxicity of High-Dose Chemotherapy in 364 Patients

Toxicity	No. of Patients	%
GI	50	13.8
Hepatic	12	3.3
Pulmonary	12	3.3
Renal	11	3
Neurologic	9	2.5
Secondary leukemia	5	1.4

TIGER Trial (Alliance A031102)



Other Novel Therapies

- Checkpoint inhibitors exhibit minimal activity in clinical trials
  - Low TMB ~ 0.5 mut/MB
  - Expression of PDL1 in GCT not associated with response
  - Negative studies with Pembrolizumab (0/12), Durvalumab + Tremelimumab, Avelumab, Nivolumab +/- ipilimumab
- Antibody drug conjugates (ADC)
  - Brentuximab
    - CD30-MMAE
    - 2/7 responses, 1 CR
    - Phase II trial NO responses in 18 pts (7 CD30+)
  - CLDN6+MMAE
    - activity against seminoma, embryonal carcinoma, choriocarcinoma, limited against yolk sac tumor in preclinical systems

Novel Therapies
Chimeric antigen receptor T-cells (CAR-T)

- BNT-211
  - directed against the surface antigen **Claudin-6** , a tetraspanin membrane protein that is involved in the formation of primitive tight junctions.
  - only expressed during fetal development and is silenced in adult healthy tissues
  - immunohistochemistry study of 104 testicular cancer samples, CLDN6 protein expression was detected in 97 (93%)
  - preliminary results of a phase I/II study showed a high response rate: 4/7 germ cell tumor patients, ORR 57% (1 CR, 3 PR)
  - Phase II trial pending
- ATLCAR.CD30
  - Phase II trial of CD30CAR-CD28-CD3zeta expressing T lymphocytes in **CD30+** relapsed/refractory NSGCT (ongoing trial UNC-Chapel Hill)

Thank you !