A031102: A Randomized Phase III Trial Comparing Conventional-Dose Chemotherapy Using Paclitaxel, Ifosfamide, and Cisplatin (TIP) with High-Dose Chemotherapy Using Mobilizing Paclitaxel Plus Ifosfamide Followed by High-Dose Carboplatin and Etoposide (TI-CE) as First Salvage Treatment in Relapsed or Refractory Germ Cell Tumors

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Alliance Spring Meeting

May 12, 2016

Presentation Objectives

- Attendees will gain a greater understanding of germ cell tumors (GCT)
  - Epidemiology, staging, and risk stratification
  - Standard treatments and response categorization
- Attendees will gain a better understanding of the treatment arms and study procedures on A031102
  - TIP
  - TI-CE including leukapheresis
- Attendees will be able to accurately complete CRFs and Data Submission

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Outline

- Overview of Germ Cell Tumors
  - Epidemiology, Risk Factors, Staging, Treatment
  - IGCCCG Risk Stratification
- First line and Salvage Chemotherapy
- Overview of High-dose chemotherapy (HDCT)
- A031102 Overview
  - Schema
  - Inclusion / Exclusion
- Registration Questions
- Case Report Form Questions / Toxicity
- Violations

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Germ Cell Tumors (GCT)

- Derived from primordial germ cells (precursor to sperm or ova)
- 90% originate in testis in men
  - Make up 95% of testicular cancers
- 10% start outside of testis (extragonadal)
  - Mediastinum (most common)
  - Retroperitoneum
  - Other – pineal gland, thymus, neck, etc.
- Two major subtypes (50% each)
  - Seminoma – late 30s, slower growth, sensitive to XRT
  - Nonseminoma – late 20s, faster growth, less sensitive to XRT

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Epidemiology of GCT

- ≈ 9,000 cases, 500 deaths per year
- 1% cancers in men
- Incidence = 5 in 100,000 per year

SO, IT's RARE BUT…

- Most common tumor in men 15-40
  - Lifetime risk for man = 1 in 265
- Accounts for the largest average number of life years lost per death of any adult tumor

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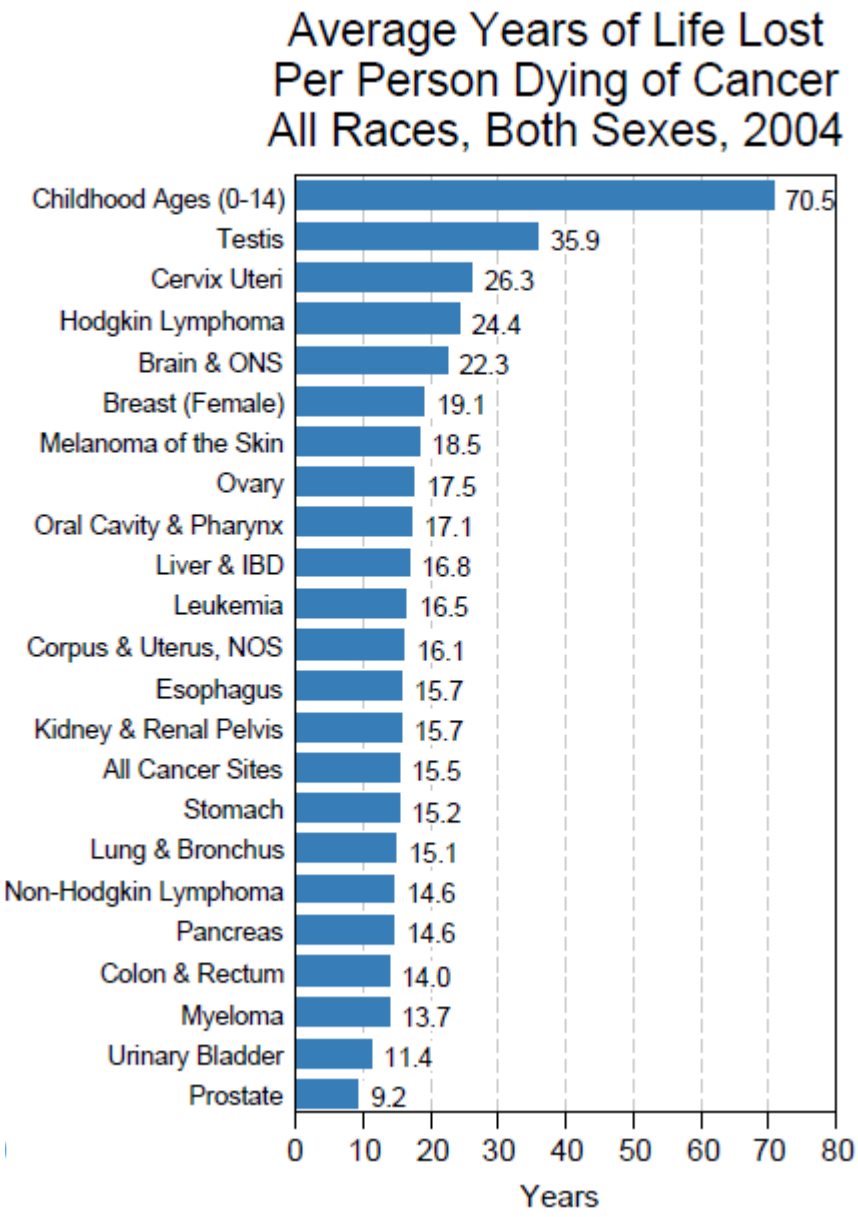
Death from GCT is a Tragedy

- Most cases curable
- But when death occurs, it has an immense impact
- 10 – 26 additional years of life lost vs. other adult malignancies



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Epidemiology of GCT (continued)

- Caucasians >> Hispanics > Asians > African Americans
- Risk Factors
  - Cryptorchidism (undescended testis)
  - Family history
  - Klinefelter's Syndrome (mediastinal NSGCT)
  - Infertility
- Possible Risk Factors
  - Marijuana (nonseminoma)
  - HIV (seminoma)
  - Pesticides (mom while fetus in utero)

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Symptoms/Presentation

- Testicular GCT
  - Pain, swelling, or mass in testis
  - Back pain (from RP lymphadenopathy)
  - Nipple tenderness / breast growth (from elevated HCG)

- Mediastinal GCT
  - Chest pain, SOB, cough
  - Facial or upper extremity swelling (if SVC syndrome)

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Pattern of Spread

- Very predictable
- Retroperitoneal lymph nodes are first
  - Right testicle → interaortocaval nodes
  - Left testicle → left paraaortic nodes
- Other: lung, additional LNs, liver, bone, brain

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Work-up

- CT Chest, Abdomen, and Pelvis
- Tumor markers (AFP, HCG, LDH)
- Discussion of sperm banking
- Bone scan…if symptoms or ↑ Alk Phos
- MRI of brain…if neurologic symptoms, poor-risk disease, high HCG, many lung nodules
- PFTs before bleomycin

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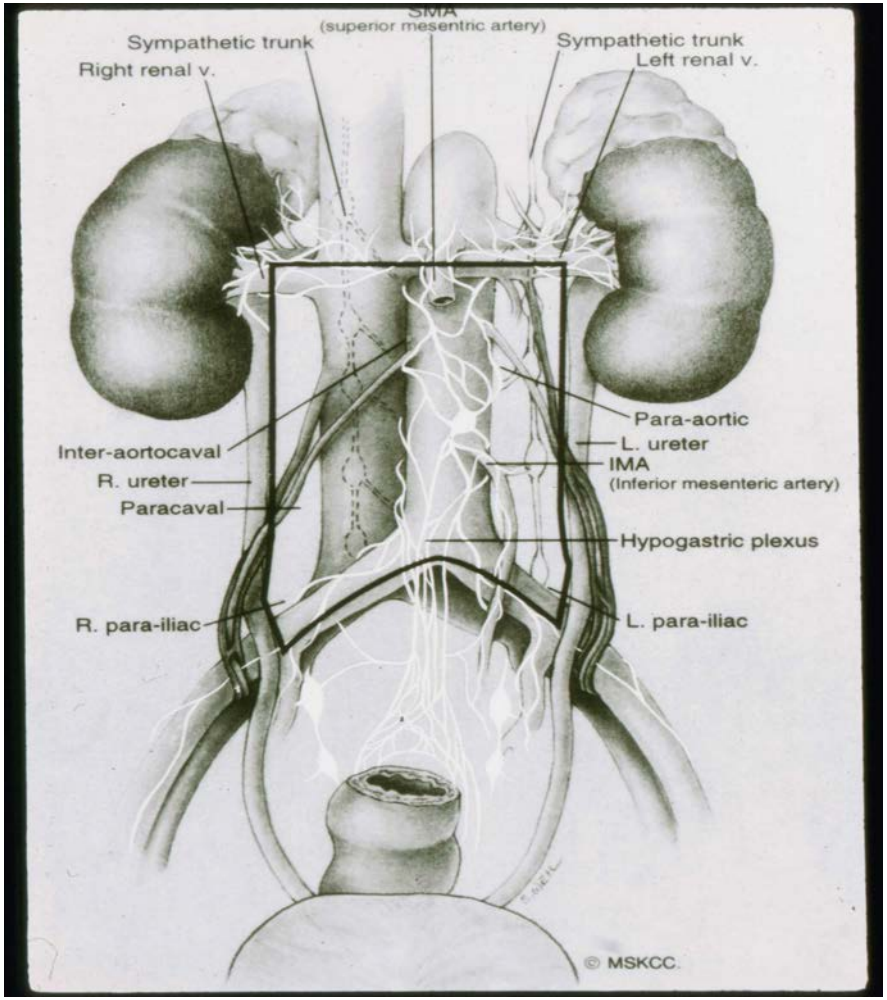
Testicular or RP GCT Staging

- EASY as 1-2-3….
- Stage I – testis only
- Stage II – spread to retroperitoneal nodes
- Stage III – spread outside retroperitoneal nodes



No Stage IV since potentially curable at any stage (Remember Lance Armstrong)

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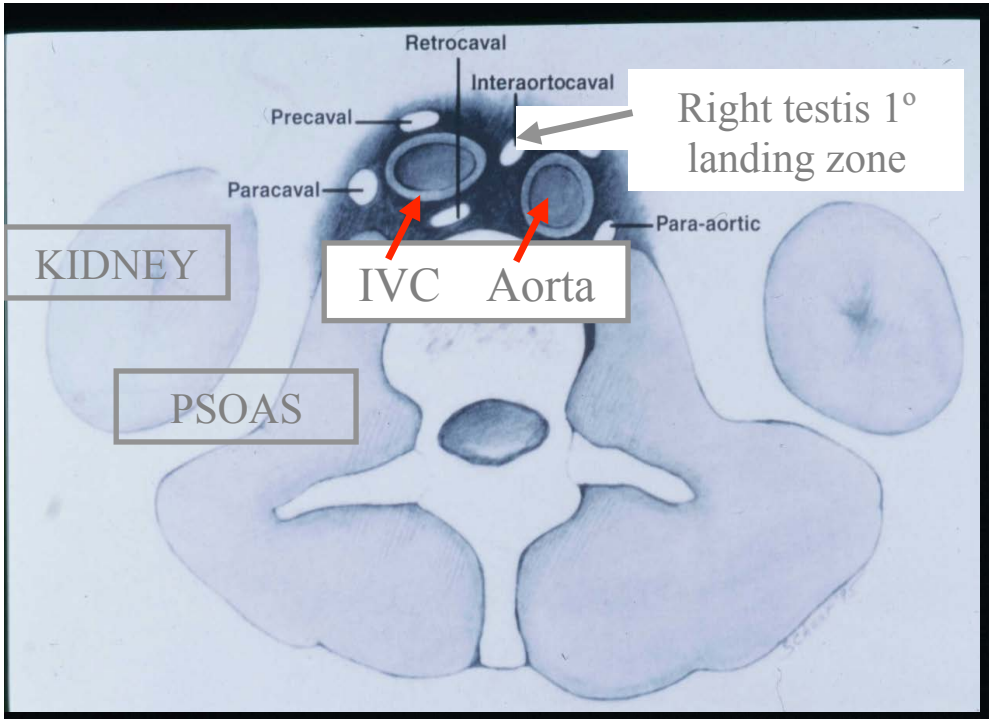
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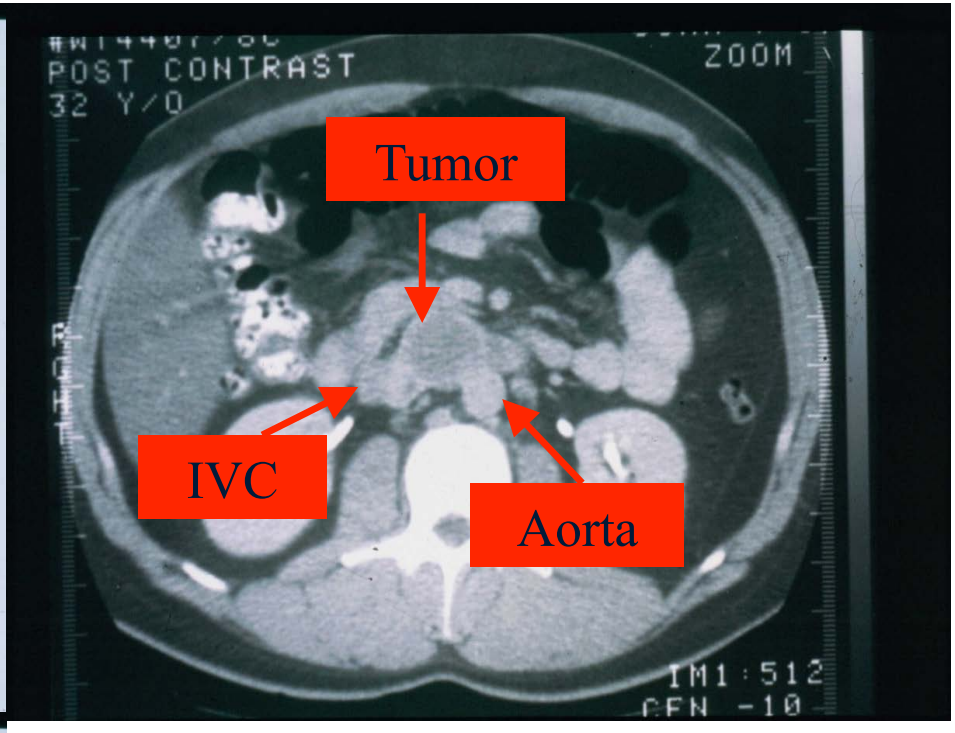
Interaortocaval
Precaval
Paracaval
Para-aortic
Right testis 1° landing zone
KIDNEY
IVC
Aorta
PSOAS


POST CONTRAST
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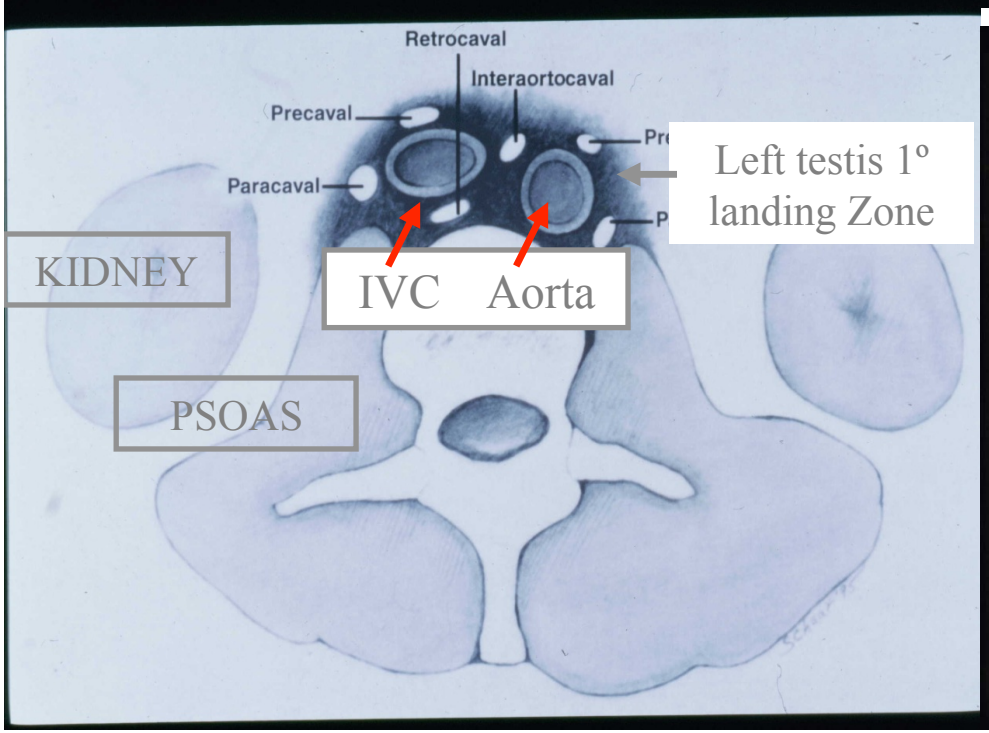
Retrocaval
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Left testis 1° landing Zone
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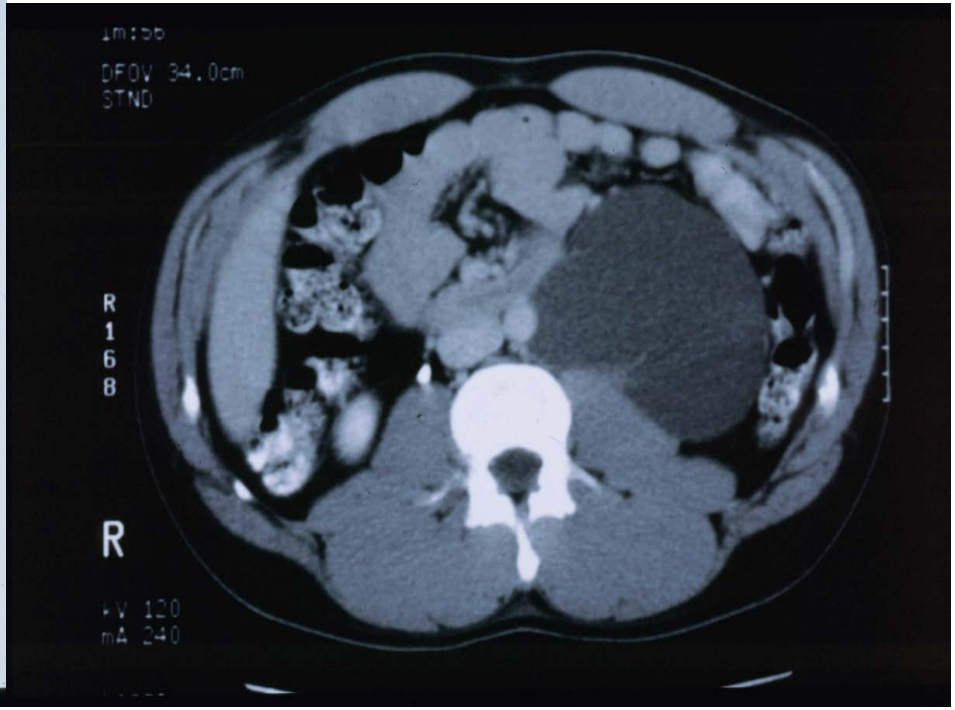
DFOV 34.0cm
STND
R
168
R
kV 120
mA 240

Staging of Mediastinal or Other Primary Site

- Localized – confined to one mass
- Regional – adjacent LN involvement
- Distant – distant LN or organ metastases

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Summary of Management

SEMINOMA

- Stage I: Orchiectomy → **surveillance**
  - Adjuvant options sometimes used: RT or 1-2 cycles of carboplatin
- Stage II (Small; <2cm): RT or full chemo
- Stage II (Larger): Full chemo
- Stage III: Full chemo

NONSEMINOMA

- Stage IA: Orchiectomy → surveillance
- Stage IB: Orchiectomy → surveillance or RPLND or 1-2 cycles BEP
- Stage II (small and normal tumor markers): RPLND or Full Chemo
- Stage II (larger or + tumor markers): Full Chemo
- Stage III: Full Chemo

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Full chemo = 3-4 cycles cisplatin-based treatment (BEP, EP, VIP)

Advanced Disease
(Seminoma and Non-Seminoma)

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Chemotherapy for Advanced Dz

- Based on risk groups (risk = likelihood of cure)
- Good, intermediate, and poor
- Nonseminoma vs. Seminoma (consider separately)
  - Seminomas better outcome than nonseminomas
  - Seminomas NEVER poor-risk
- Organ lesions portend poor prognosis except lung

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International Germ Cell Cancer Collaborative Group (IGCCCG) Risk Classification[1]

Risk Group	Seminoma
Good	NPVM absent
Intermediate	NPVM present
Poor	N/A

RP, retroperitoneal; NPVM, non-pulmonary visceral metastases; ULN, upper limit of normal

[1]IGCCCG, JCO, 1997

Chemotherapy for Good-Risk

- Goal: Minimize toxicity, maintain high cure rate
- Two regimens are accepted as standard of care
    1) 4 cycles of EP
    2) 3 cycles of BEP

EP = Etoposide + cisPlatin

BEP = Bleomycin + Etoposide + cisPlatin

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Intermediate- and Poor-risk GCT

- Seminomas are NEVER poor-risk!
- Standard of Care = BEPx4
  - VIPx4 is an alternative if concern about giving bleomycin
  - VIP = etoposide (**V**P-16), **I**fosfamide, and cis**P**latin
- 40-75% cure rates
  - A significant proportion of these patients will be eligible for A031102

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Response Assignment

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Response Definitions

- Complete Response (CR) – must last 4 weeks
  - **CR to chemo**: marker & radiographic normalization OR marker normalization + full resection c/w necrosis or teratoma
  - **CR to chemo + surgery**: marker normalization + full resection c/w viable GCT and negative margins
- PR neg markers (PR-) – must last 4 weeks: marker normalization + residual mass(es) on imaging but w/o POD
- Incomplete Response (IR): anything other than CR or PR-
- Favorable Response (FR): CR or PR-

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Salvage Treatment of GCT

- 20-30% of patients with advanced GCT require salvage chemotherapy including 40-50% of IGCCCG poor-risk
- Still potentially curable unlike other malignancies

- Salvage chemotherapy options include:

  1) conventional-dose chemotherapy (CDCT) +/- surgery
  2) high-dose chemotherapy (HDCT) with ASCT +/- surgery

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International Prognostic Factors Study Group (IPFSG) Classification at Initial Salvage Therapy

STEP 1	**Calculate Initial Score (sum of points for each variable)**	**Prognostic Factor (Pts)**	**3**	**2**	**1**		**0**	Row Pts
		Primary site	Mediastinum		Retroperitoneum		Testis	_____
		Response to 1st-line CT		POD	PR-pos/SD		PR-neg/CR	_____
		Progression-free interval			≤ 3 months		> 3 months	_____
		HCG at initial salvage			>1000		≤1000	_____
		AFP at initial salvage		> 1,000	>ULN but ≤1000		Normal	_____
		Liver, bone, or brain mets			Present		Absent	_____
		Initial Score	0	1 2	3	4	≥ 5	_____
STEP 2	**Reclassify Initial Score***	**Reclassified Score**	0	1	2		3	_____
STEP 3	**Subtract 1 point for seminoma histology**							_____

STEP 4	**Calculate Final Score**	**Final IPFSG Group (Score)**	**Very low (-1)**	**Low (0)**	**Intermediate (1)**	**High (2)**	**Very High (3)**
STEP 5	**Consolidate for A031102**	**Final IPFSG Risk Group for A031102**	**Low**		**Intermediate**	**High**	

Adapted from Lorch et al., JCO, 2010

IPFSG Classification System for Initial Salvage Therapy in GCT

Final Category	Score	N	2-Yr PFS	3-Yr OS
Very low	-1	76	**75**	**77**
Low	0	132	**51**	**66**
Intermed.	1	219	**40**	**58**
High	2	122	**26**	**27**
Very high	3	36	**5.6**	**6.1**

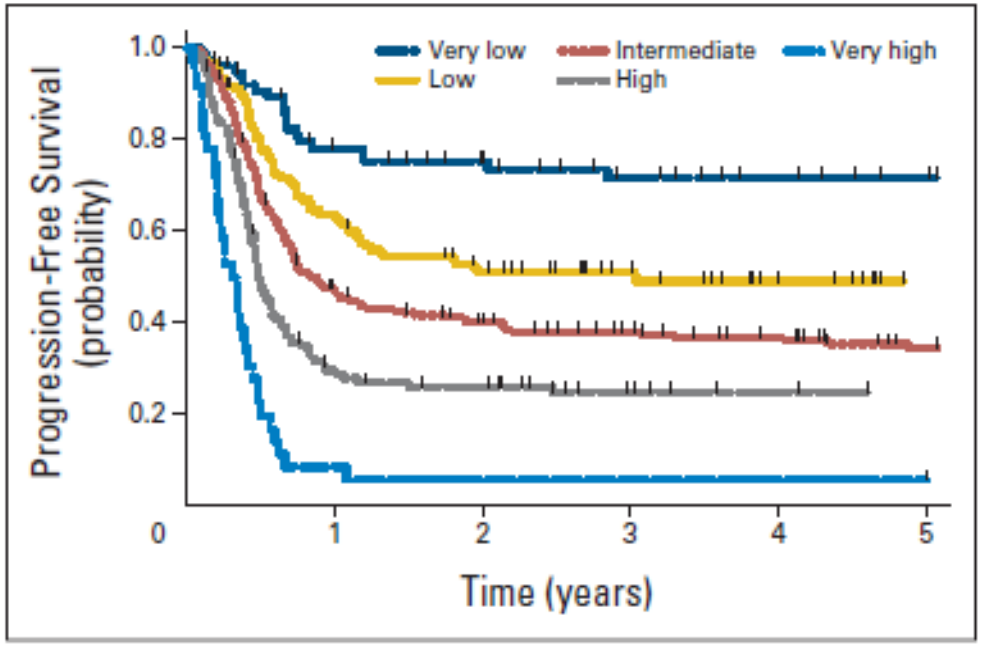

Fig 1. Progression-free survival according to prognostic category (validation set plus patients with seminoma).

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Lorch, *JCO*, 2010

CDCT for Initial Salvage: VIP/VeIP

Author (Year)	Regimen	N	CR	Durable CR
Pizocarro (1992)	VIP or VeIP	36	56%	42%
Farhat (1996)	VIP or VeIP	54	44%	19%
McCaffrey (1997)	VIP or VeIP	56	36%	23%
Loehrer (1998)	VeIP	135	50%	23%
Total	VIP or VeIP	281	47%	25%

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TIP Results at MSKCC

Eligibility: Gonadal primary tumor AND achieved a CR or PR- lasting ≥ 6 months with 1st line regimen

N=46; Median f/u 69 months

Outcome	N	%
CR Chemotherapy Chemotherapy + surgery	32 29 3	70 63 7
IR (PR- marker negative)	14 (2)	30 (4)
Relapse From CR	3	7
Continuously NED	29	63
Two-Year Overall Survival	36	78

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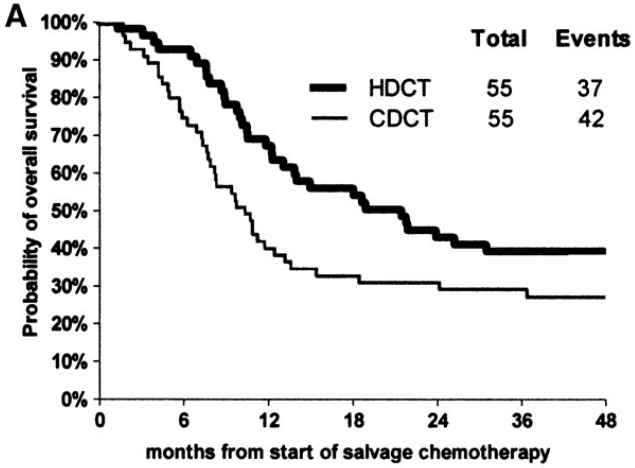
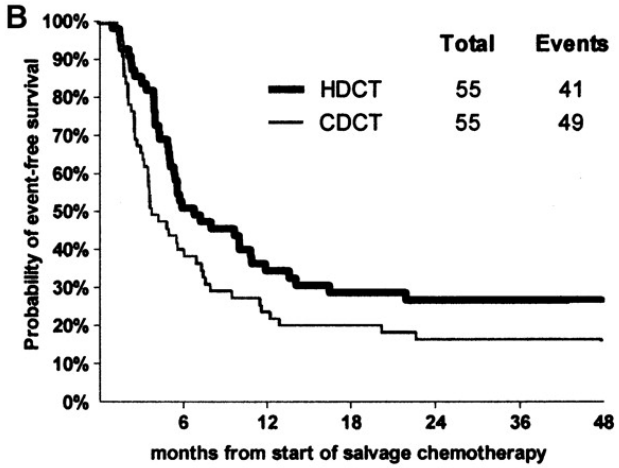
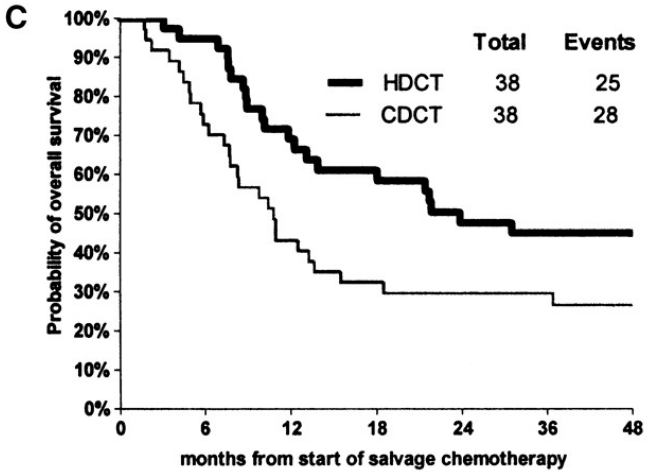
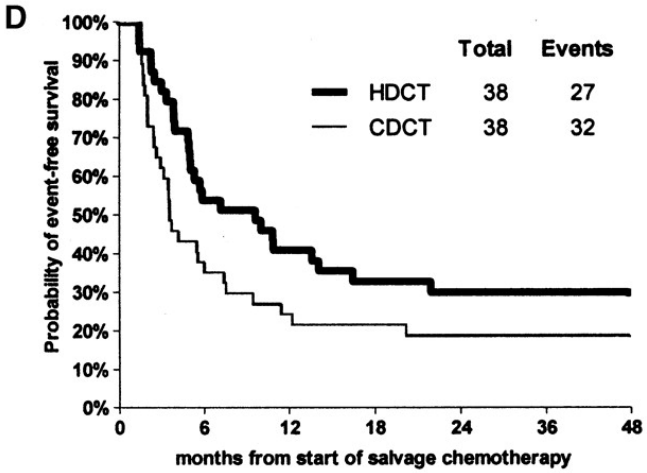
High-dose versus conventional-dose chemotherapy as first-salvage treatment in patients with non-seminomatous germ-cell tumors: a matched-pair analysis

J. Beyer[1+] , S. Stenning[2], A. Gerl[3], S. Fossa[4] and W. Siegert[5]









A. OS for 55 pairs w/ at least 4 matches
B. EFS for 55 pairs w/ at least 4 matches
C. OS for 38 pairs w/ 5 full matches
D. EFS for 38 pairs w/ 5 full matches

Summary

- EFS improved by 6-12% w/ HDCT
- OS improved by 9-11% w/ HDCT

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Beyer, *Ann Oncol*, 2002

Prognostic Factors From HDCT Series

TI-CE (Feldman, JCO, 2010)

Table 4. Multivariate Analysis of Prognostic Factors for DFS and OS

DFS Variable	Hazard Ratio	95% CI	P
Primary site			
Gonadal/retroperitoneal	Reference		.001
Mediastinal	3.2	1.7 to 6.0	
Other/unknown	1.5	0.5 to 4.3	
HCG, U/L			
< 1,000	Reference		.003
≥ 1,000	2.4	1.2 to 4.6	
Prior lines of chemotherapy			
1	Reference		.001
≥ 2	2.7	1.5 to 4.8	
Lung metastases			
Absent	Reference		.02
Present	2.1	1.1 to 3.8	
OS Variable	**Hazard Ratio**	**95% CI**	**P**
Primary site			
Gonadal/retroperitoneal	Reference		.01
Mediastinal	2.8	1.3 to 5.9	
Other/unknown site	2.7	0.7 to 10.0	
No. of metastatic sites			
1-2	Reference		.02
3+	3.2	1.2 to 8.8	
Prior lines of chemotherapy			
1	Reference		.001
≥ 2	3.0	1.6 to 5.6	
IGCCCG risk at initial chemotherapy			
Good	Reference		.006
Intermediate	6.0	2.2 to 16	
Poor	2.8	1.0 to 7.8	
Unknown	3.3	0.80 to 14	

Abbreviations: DFS, disease-free survival; OS, overall survival; HCG, human chorionic gonadotropin; IGCCCG, International Germ Cell Cancer Collaborative Group.

Indiana Regimen (Einhorn, *NEJM*, 2007)

Table 3. Results of Multivariate Cox Proportional-Hazards Analysis and Prognostic Score.*

Prognostic Variable	Hazard Ratio (95% CI)	P Value	β Regression Coefficient	Prognostic Score†
Third-line or subsequent chemotherapy	2.19 (1.35–3.56)	0.002	0.78	3
Platinum-refractory disease	1.74 (1.01–3.00)	0.05	0.55	2
IGCCCG high-risk stage	1.67 (1.00–2.78)	0.05	0.51	2

* The hazard ratio is for disease progression. IGCCCG denotes International Germ Cell Cancer Collaborative Group.
† The score was calculated by dividing the regression coefficient by 0.51, multiplying by 2.0, and rounding to the nearest whole number.

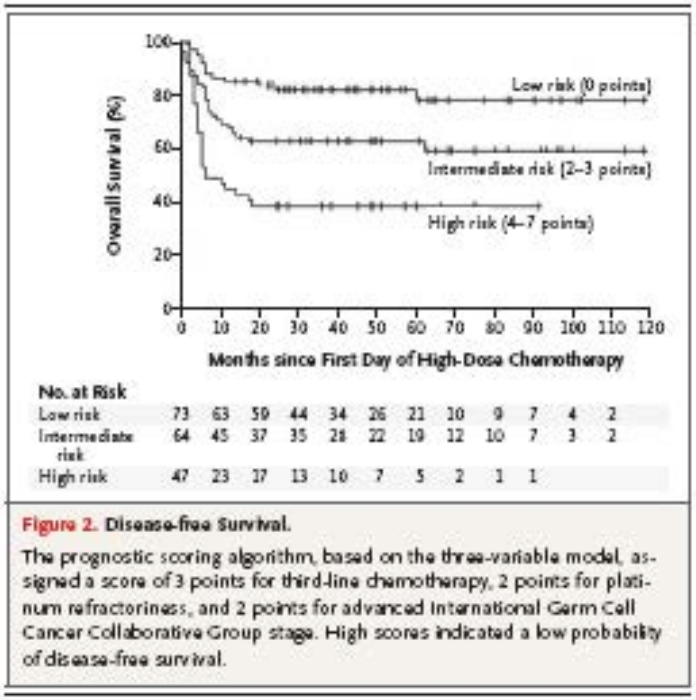

Figure 2. Disease-free Survival.

The prognostic scoring algorithm, based on the three-variable model, assigned a score of 3 points for third-line chemotherapy, 2 points for platinum refractoriness, and 2 points for advanced International Germ Cell Cancer Collaborative Group stage. High scores indicated a low probability of disease-free survival.

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CDCT vs. HDCT as Initial Salvage in the IPFSG Database

PFS

All pts (n=1594)	N	2-yr PFS	P value & HR
HDCT	821	**50%**	p<.001
CDCT	773	**28%**	HR = 0.44

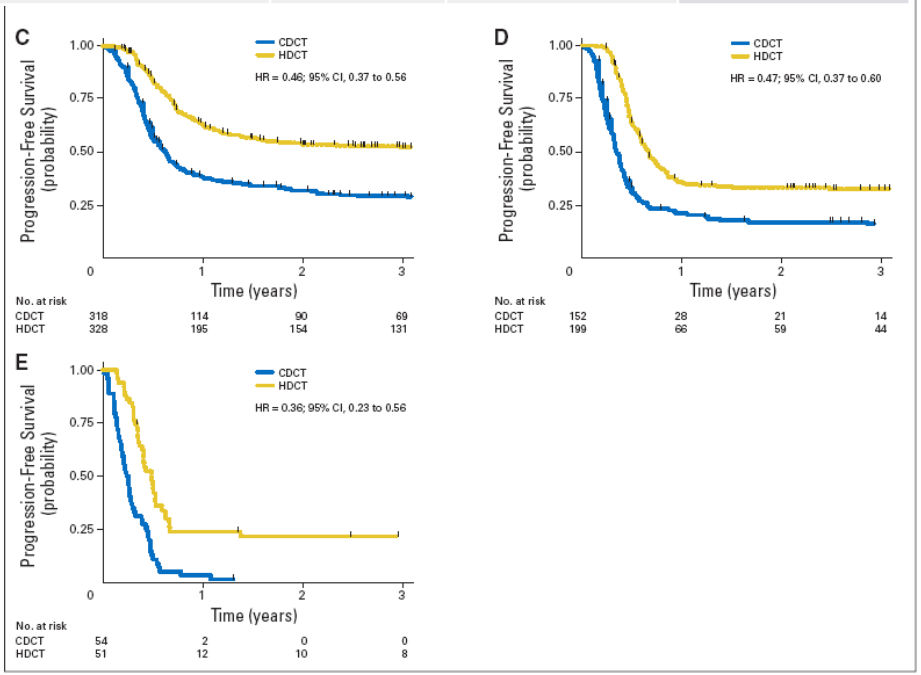

Fig 1. Progression-free survival and corresponding hazard ratios (HR) in each of the five prognostic categories: (A) very low risk; (B) low risk; (C) intermediate risk; (D) high risk; (E) very high risk. CDCT, conventional-dose chemotherapy; HDCT, high-dose chemotherapy.

OS

All pts (n=1594)	N	5-yr OS	P value & HR
HDCT	821	**53%**	p<.001
CDCT	773	**41%**	HR = 0.65

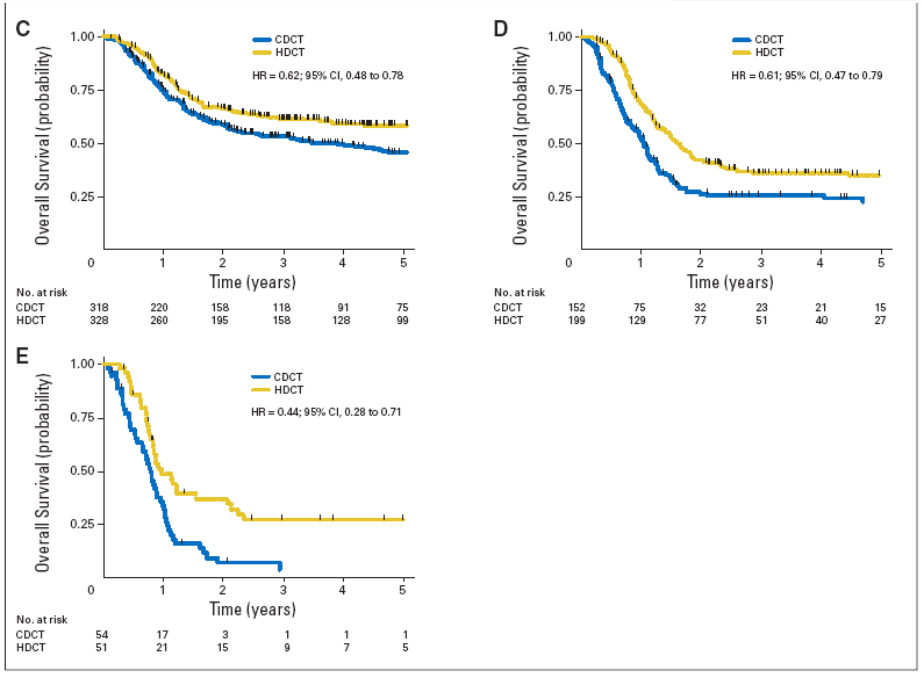

Fig 2. Overall survival and corresponding hazard ratios (HR) in each of the five prognostic categories: (A) very low risk; (B) low risk; (C) intermediate risk; (D) high risk; (E) very high risk. CDCT, conventional-dose chemotherapy; HDCT, high-dose chemotherapy.

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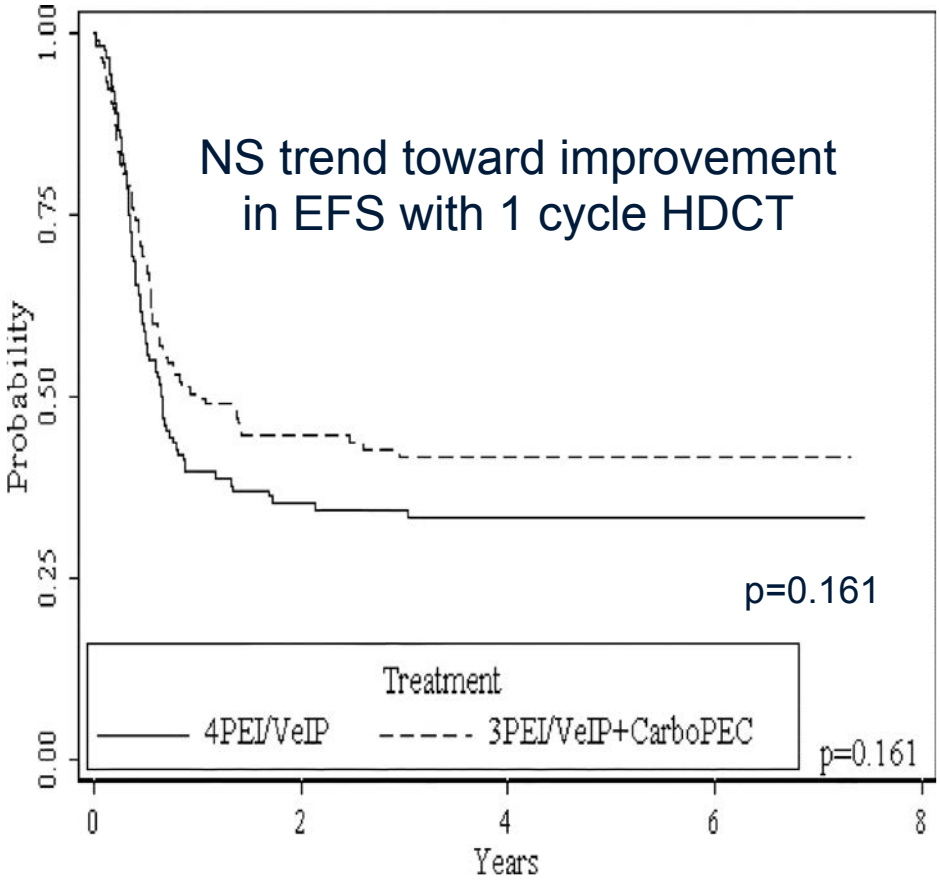
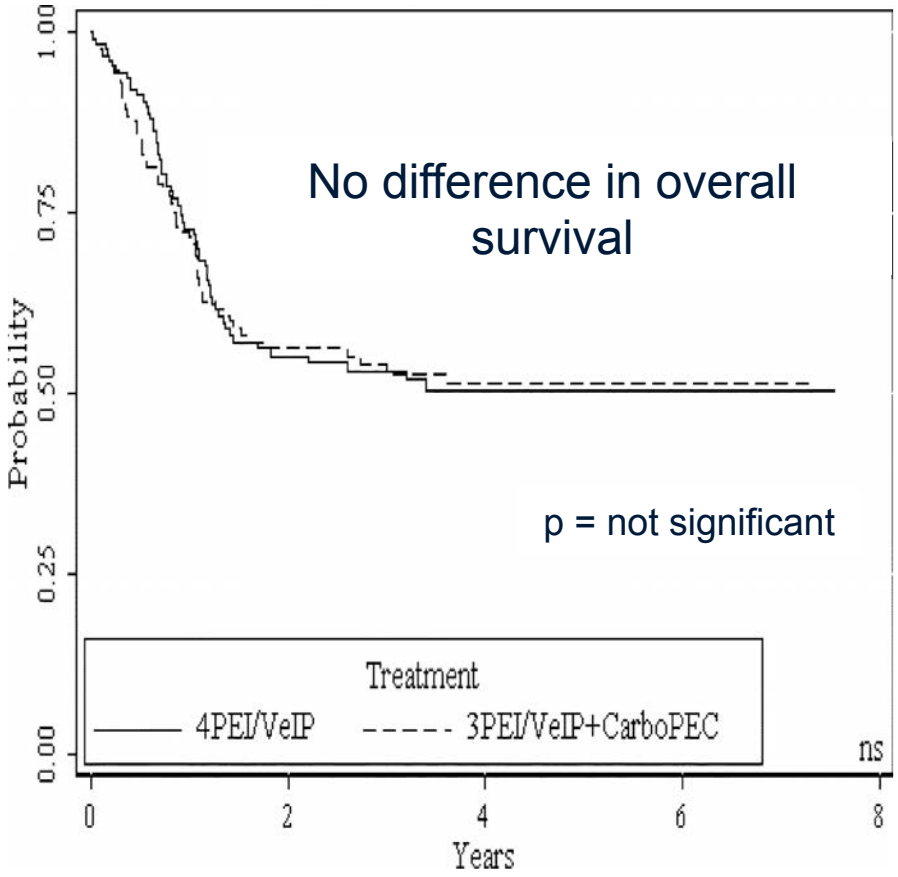
Lorch, *JCO*, 2011

CDCT vs. HDCT as Initial Salvage (IT-94)

Event-free survival



Overall survival



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Pico, Ann Oncol 2005

Difficulties in Interpreting IT-94

- Only one high-dose cycle in HDCT arm
  - Doesn't r/o benefit of sequential HDCT
- Patients with incomplete responses to 1st line chemotherapy were excluded
  - This group might benefit most from HDCT
- High toxic death rate in HDCT arm (7%) vs. CDCT arm (3%)
  - Small numbers of patients enrolled at many centers
- > 25% of pts assigned to HDCT didn't receive it

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Variance in Practices Around the World

Country or Institution	Initial Salvage Approach
United Kingdom	CDCT
Germany	HDCT
MSKCC	Risk-stratified approach Favorable[1] pts → CDCT (TIP) Unfavorable[2] pts → HDCT (TI-CE)
Indiana	HDCT for all patients except those with mediastinal NSGCT and late relapses

[1] Favorable: gonadal or RP primary site + CR (any duration) or PR with negative markers ≥6 months

[2] Unfavorable: does not meet favorable criteria

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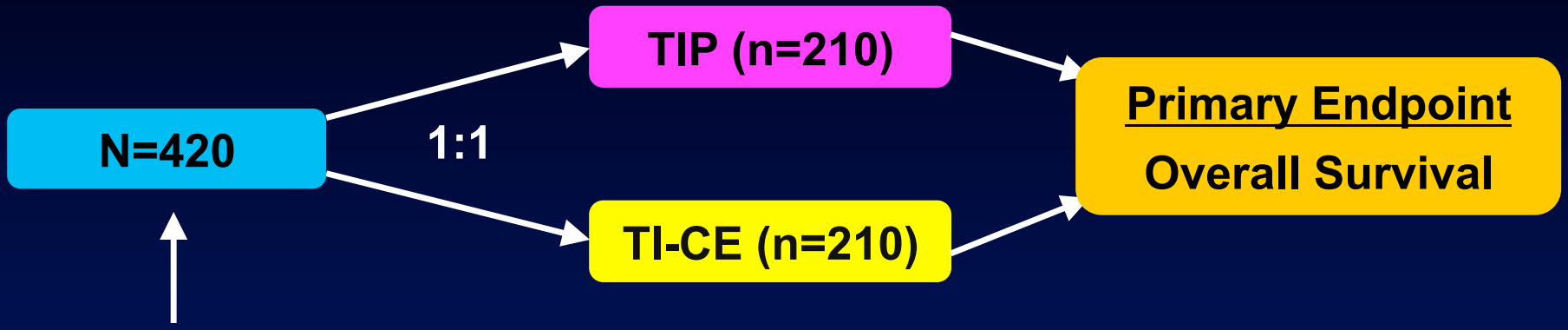
Alliance 031102 Study Design



Stratification:
- IPFSG risk class
- Continent

81% power to distinguish a 29% improvement in OS (HR of 0.71)

Secondary Endpoints
- PFS
- Favorable RR (CR / PR-m)
- Toxicity & treatment-related mortality
- Validation of IPFSG model
- Biological correlates (SNP & whole exome analyses)

PR-m = PR with normal tumor markers

IPFSG = International Prognostic Factors Study Group

Why is this Study Important?

- Most important remaining question in management of pts with advanced GCT
- No clear standard of care
- Young curable population, orphan disease
- Answer will improve outcomes independent of the result
  - HDCT is superior → save lives
  - HDCT is not superior → spare toxicity
  - HDCT superior for some subgroups → more tailored tx

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Eligibility

- Inclusion Criteria
  - Male
  - Age ≥ 14
  - Confirmed GCT histology (any primary site)
    - Exception: No tissue available and patient with clinical situation c/w GCT (testicular, retroperitoneal or mediastinal mass, HCG ≥ 500 or AFP ≥ 500, and typical pattern of metastasis
  - Definite evidence of progression after 1 line of cisplatin-based chemotherapy:
    - Tumor biopsy of new, growing, or unresectable lesion c/w viable non-teratomatous GCT
    - Elevated and consecutively increasing AFP or HCG
    - New or enlarging lesions on imaging in setting of elevated AFP or HCG

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Eligibility

- Inclusion Criteria (continued)
  - 3-6 cycles of prior cisplatin-based chemotherapy
    - BEP, EP, VIP will be most common prior regimens
  - No more than 1 prior line of chemotherapy for GCT
    - EPx4, BEPx3, BEPx4, and VIPx4
    - BEPx3 → EPx1 is allowed
    - BEPx2 → VIPx2 also allowed IF switch d/t pulmonary tox and NOT POD
    - BEPx4 → surgery → adjuvant VIPx2 (or EPx2) is allowed
    - BEPx4 → VeIPx2 with switch due to residual elevated tumor markers is NOT allowed
  - Prior adjuvant carboplatin for stage I seminoma allowed
    - Pt must have also received ≥3 cycles of BEP or EP at relapse
  - Prior adjuvant BEP/EP x 1-2 for early stage NSGCT is allowed
    - Pt must have also received ≥3 cycles of BEP or EP at relapse

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Eligibility

- Inclusion Criteria (continued)
  - LABS
    - ANC ≥ 1500
    - PLT ≥ 100,000
    - Bilirubin ≤ 1.5 x ULN
    - AST/ALT ≤ 2 x ULN
    - Creatinine Clearance ≥ 50 mL/minute
  - Eligible for high-dose per FACT
    - Negative serology for HIV-1/2
    - Negative serology for HTLV-1/2
    - Negative serology for Hepatitis B surface antigen
    - Negative serology for Hepatitis C antibody

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Eligibility

- Inclusion Criteria (continued)

Creatinine Clearance (CrCl)

- Age ≥ 18 y/o
  - Use Jeliffe formula
  - If CrCl >70, patient is eligible
  - If CrCl ≥ 50 but ≤ 70, then 2nd method (12- or 24-hr urine Creatinine clearance (CrCl) or radioisotope method) must be ≥ 50

- Age <18 y/o:
  - Use radioisotope method preferentially
  - If radioisotope not available, can use12- or 24-hr urine CrCl or Schwartz Formula as primary method
  - If primary method CrCl ≥ 50 but ≤ 70, then 2nd method must have CrCl ≥ 50 for patient to be eligible
    - 2nd method can be any of the above not used as the primary method

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Eligibility

- Exclusion Criteria
  - Prior treatment with high-dose chemotherapy
  - Prior treatment with TIP
    - 1 cycle of Prior TIP is allowed as bridge to the protocol
  - Prior radiation within 14 days
  - Prior chemotherapy within 16 days (bleomycin within 5 days)
  - Inadequate recovery from prior surgery
  - Concurrent malignancy
  - Large hemorrhagic or symptomatic brain metastases
    - Become eligible ≥ 7 days after local treatment (surgery or RT)
  - Fully resectable late relapse (≥ 2 years before relapse)
  - Concurrent malignancy

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Arm A: TIP Regimen

TIP Regimen:

- Paclitaxel 250 mg/m^2 over 24 hrs (d 1)
- Ifosfamide 1.5 g/m^2 (d 2-5)
- Mesna support (mixed 1:1 with ifosfamide or 3 doses per day at discretion of treating site)
- Cisplatin 25 mg/m^2 over 30 minutes (d 2-5)
- Peg-filgrastim 6mg SQ on day 6 or 7 (or Filgrastim daily from day 7 to day 18 or ANC recovery)
- Prophylaxis: Levofloxacin 500mg daily (d7 – 13)

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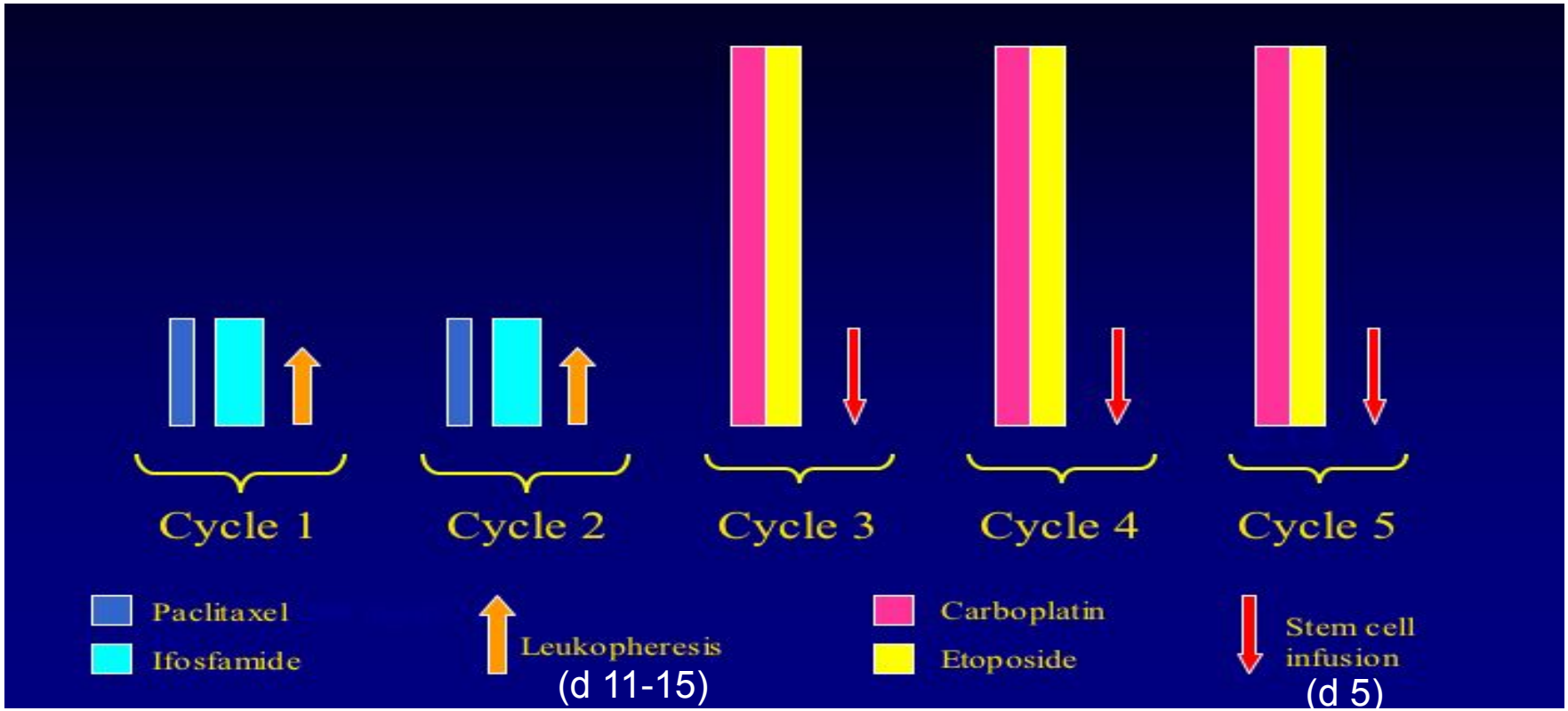
Kondagunta et al., *JCO*, 2005

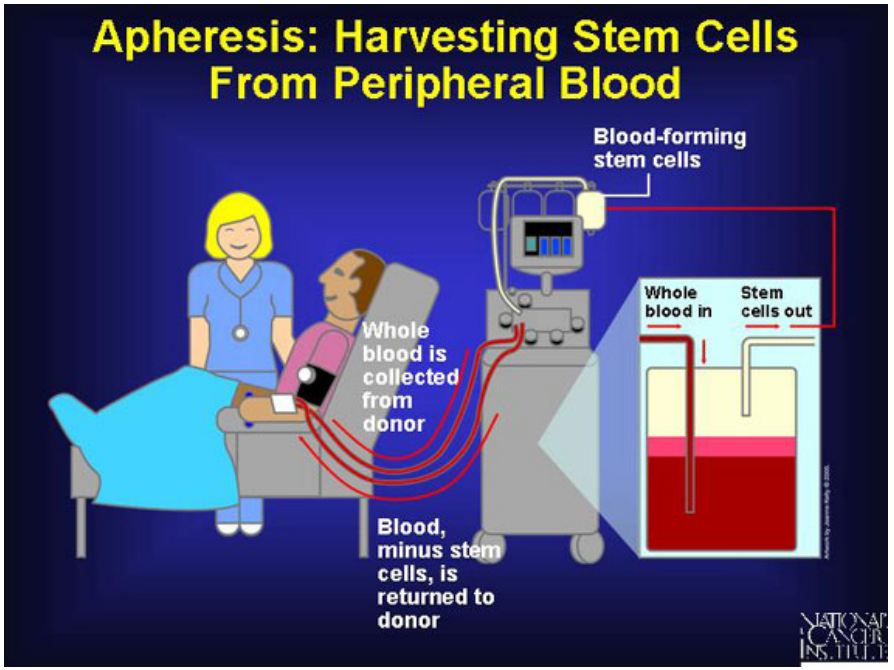
Arm B: TI-CE Regimen

• Cycle #	Cycle Length	
• 1–2	14 days	Paclitaxel 200 mg/m^2 x 3 hrs (d 1) Ifosfamide 2 g/m^2 w/ mesna (d 1-3)
• 3,4,5	21 days	Carboplatin AUC=8/d (d 1-3) Etoposide 400 mg/m^2/d (d 1-3) Peg-filgrastim (d 5)



TI-CE (Arm B)

- G-CSF and Leukapheresis
  - G-CSF 10mcg/Kg daily from d3 to completion of collection
  - Collection starts ≈ D11
    - D1 Friday = D11 Monday
  - Goal ≥ 8 x 10^6 CD34+ cells/Kg
  - If adequate collection with C1, then do not collect with C2
  - Plerixafor allowed for C2 if poor collection with C1



- Patients can start C2 if meet the following criteria:
  - ANC ≥ 1000/mm^3 ; PLT ≥ 50,000/mcL (self-sustaining), adequate GFR
  - Must be off ABX except for C. Difficile and ECOG must be ≤2
  - Non-hematologic toxicities (renal, pulmonary, cardiac, hepatic) related to TIP have returned to ≤ G2 prior to therapy.
  - **Max delay of 3 weeks is allowed.**

TI-CE (Arm B): Appendix IV

Progression status?	Cell Collection?	Criteria met?	Pathway	Next cycle should be:
No Progression	Optimal ($\geq 8x10^6$ cells/ kg)	Yes	1	Cycle 2 with no further Leukapheresis
		No	2	- Delay until criteria met. - If ≥3 week delay, remove from study. - Once criteria met → Cycle 2 w/o leukapheresis.
	Suboptimal ($<8x10^6$ cells/ kg)	Yes	3	Cycle 2 with additional leukapheresis
		No	4	- Delay until criteria met - If ≥3 week delay, remove from study. - Once criteria met → Cycle 2 with leukapheresis
Progression	Adequate ($\geq 6x10^6$ cells/ kg)	Yes	5	Skip Cycle 2 and proceed with Cycle 3
		No	6	- Delay until criteria met - If ≥3 week delay, remove from study. - Once criteria met, proceed to Cycle 3
	Inadequate ($<6x10^6$ cells/ kg)	Yes	7	Cycle 2 with additional leukapheresis
		No	8	- Delay until criteria met or remove from study. - If ≥ 3 week delay, remove from study treatment Once criteria met → Cycle 2 with leukapheresis

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TI-CE (Arm B)

- Cycle length
  - Cycles 1 – 2: 14 – 21 days
  - Cycles 3 – 5: 21 – 28 days

- Prophylaxis:
  - Cycles 1 and 2: Levofloxacin 500mg daily (d 6 -10)
  - Cycles 3 – 5: Levofloxacin 500mg daily (d 7 – 15 or until ANC ≥ 1
    Antifungal and additional (antiviral, PCP, etc.) prophylaxis left to discretion of treating physician

- Neutropenic Fever:
  - Asked to record the IV ABX given for treatment of neutropenic fever

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Statistical Design

- Primary Endpoint: Overall survival
- Sample size = 420 pts (expected # deaths = 232):
  - 168 pts from N. America / 252 pts from Europe
- A cure rate model is used: 35% of patients will be cured and the median survival time with TIP = 1.5 years.
- Power 81%, one sided type I error rate = 0.05 where TI-CE will reduce the hazard by 29% (θ =0.71).
- Enrollment =100 pts/yr x 4.2 yrs with post-accrual period of 4.5 yrs after study closure.
- Efficacy and Futility analysis regularly per Alliance policy
- Formal analysis based on the toxicity endpoint

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Secondary Endpoints

- Progression-free survival
- Validation of the International Prognostic Factor Study Group (IPFSG) prognostic model
- Toxicity including treatment-related mortality (TRM)
- Pharmacogenomics for SNPs associated with platinum response
- Whole Exome Sequencing
- QOL using the EORTC QLQ30 and TC-26

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A Global Collaboration

Participating Countries

- North America
  - USA and Canada (via US cooperative groups)
- Europe via EORTC:
  - United Kingdom, Italy, France, Germany, Belgium, Netherlands
  - Scandinavia: Denmark
  - Possibly Spain and Norway
- Australia, and New Zealand likely to join via ANZUP

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Pre-Treatment Evaluation

- **Within 21 days before registration:**
  - All laboratory studies.
  - History and physical.
  - **Within 21 days before registration**
- **Within 28 days before registration:**
  - **All imaging studies (CT, MRI) used for tumor measurement**
- **Within 42 days before registration:**
  - **All imaging studies not used for tumor measurement (example: MRI brain)**

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Study Calendar

	Prior to Registration*	Arm A	Arm B		Post treatment follow up***
		Cycles 1-4, Day 1*	Cycles 1-2, Day 1*	Cycles 3-5, Day 1*	
Tests & Observations					
History	X				
Height Ω	X	X	X	X	
Physical Exam and Weight **	X	X	X	X(1)	X(2)
Pulse, Blood Pressure, Temp., Respir. Rate	X	X	X	X(1)	X(2)
Adverse Event Assessment	X	X	X	X	X (2)
ECOG Performance Status	X	X	X	X	
Reg. Fatigue/Uniscale Assessment	X(4)				
Laboratory Studies					
Complete Blood Count (incl. PLTs)	X	X(3)	X	X(1)	X(2)
Na, K, Cl, bicarbonate, BUN, creatinine, glucose, calcium	X	X	X	X	X(2)
AST, ALT, Alk. Phos., Bili, total protein, albumin, Mg, Phos	X	X	X	X	X(2)
AFP, HCG, LDH #	D	X(3)	X	X(3)	X(2)
Testosterone, LH, FSH, lipid profile	X(8)				X(8)
FACT blood tests	A				
GFR estimation	B	B	B	B	

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Study Calendar

	Prior to Registration*	Arm A	Arm B		Post treatment follow up***
		Cycles 1-4, Day 1*	Cycles 1-2, Day 1*	Cycles 3-5, Day 1*	
Staging					
Histologic Confirmation of Diagnosis#	X(5)				
CT or MRI brain w/ and w/o contrast#	X				C
CT chest w/ or w/o contrast#	X(6)				X(6)
CT abdomen and pelvis w/contrast#	X(6)				X(6)
Chest X-ray (CXR)#					X(9)
Other tumor imaging#	X(7)				C
Correlative studies: For patients who consent to participate					
EORTC QLQ-C30 and QLQ-TC26 (A031102-HO1)	*≤ 21 days prior to treatment, end of treatment, month 12, and month 24, see Section 6.2*				
Blood specimen samples (A031102-PP1)	*≤ 21 days prior to treatment, see Section 6.3.*				
Tumor tissue (A031102-ST1)	*Prior to treatment or within 30 days of treatment initiation, see Section 6.3*				

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Correlative Studies

- Patients will be asked to consent to participate in the correlative studies at the time of the consent
- If yes, the following will take place:
  - Patients will complete a QOL ≤ 21 days prior to treatment, EOT, and fu months 12 and 24
  - EDTA whole blood to be taken ≤ 21 days prior to treatment
    - *If whole blood is not collected, normal tissue should be collected whenever possible*
  - Tumor tissue prior to treatment or within 30 days of treatment initiation

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Correlative Studies Objectives

- Whole blood (**A031102-PP1**): The primary objective of the pharmacogenetic companion is the investigation of the effect of platinum SNP rs1649942 on PFS in the entire study population.
- Tumor biopsy (**A031102-PP1**): The primary objective is to determine whether genetic alterations in the RAS, PI3K, p53,and DNA repair pathways are prognostic of overall survival.

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Radiology (cont.)

End of protocol treatment

- Arm A: ≤ 28 days from last day of cisplatin
- Arm B: ≤ 28 days from last stem cell reinfusion
- CT CAP
- CT or MRI brain, bone scan, MRI spine, CT neck required only if signs or symptoms suggest metastases develop or if results were abnormal at baseline

Post-Treatment Follow up:

- CT CAP at months 12 and 24
  - Months 12 and 24, CT chest is optional and can be substituted with a CXR
- CXR at months 9, 15, 18, and 36
- Bone scan, MRI spine, CT neck at investigator's discretion

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Dose Modifications and Toxicities

- There will be no dose escalations. There will be no routine dose reductions of chemotherapy
- Treatment can be held for reasons specified in section 8.2 of the protocol
- If treatment is delayed for > 3 weeks, patients should be removed from protocol

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Response & Removal from Protocol Treatment

- Response and progression will be evaluated via clinical, radiographic, and biochemical evidence
- Patients who are in CR, PR or SD will continue therapy until POD.
- POD during therapy will result in discontinuation, except if it occurs during cycles 1 and 2 of Arm B (TI-CE)
- The growing teratoma syndrome is not a criteria for removal from the trial
- Patients who discontinue study drug will be followed for survival per study calendar.
- **Extraordinary Medical Circumstances**: If the constraints of the protocol are detrimental to the patient's health and/ or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued.

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Registration & Randomization

- Patient must meet eligibility criteria
- Try to get insurance coverage for transplant prior to registration
  - For questions or for a sample LOMN, contact me at feldmand@mskcc.org
- Additional information needed (stratification):
  - Continent of enrollment (N. America vs. Europe)
  - IPFSG risk group (High vs. Intermediate vs. Low)

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Toxicity Recording

- All Grades (1-5) toxicity need to be recorded for the following:
  - Ototoxicity (Tinnitus or Hearing impairment
  - Neuropathy (peripheral sensory neuropathy
  - Diarrhea
  - Encephalopathy (typically ifosfamide-related)
  - Cystitis, non-infective (typically hemorrhagic)
- For all other toxicities, only G3 – G5 need to be recorded
- SAE recording is the same as for any other protocol

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Sample Patients / Scenarios

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Case 1

RA is a 30-year-old man with history of IGCCCG poor-risk germ cell tumor. He received 4 cycles of BEP. His HCG was 100,000 at the start and declined to 58 but then rose to 110 and most recently 280. Brain MRI demonstrates no evidence of brain metastasis.

Is RA eligible for A031102 based on prior treatment history and evidence of disease progression?

A. Yes

B. No, he has not received adequate cisplatin-based chemo

C. No, he does not have adequate evidence of POD

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Case 2

JA is a 25-year-old man with history of IGCCCG poor-risk germ cell tumor who was planned to receive 4 cycles of BEP. However, the bleomycin was dropped for cycles 3 and 4 due to lung toxicity. His HCG (50,000 pre-treatment) normalized after chemo but 3 months later, increased, first to 25, and most recently to 90.

Is JA eligible for A031102 based on prior treatment history and evidence of disease progression?

A. Yes

B. No, he has not received adequate cisplatin-based chemo

C. No, he received more than 1 line of prior treatment

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Case 2B

JA is a 25-year-old man with history of IGCCCG poor-risk germ cell tumor who was planned to receive 4 cycles of BEP. However, the bleomycin was switched to ifosfamide for cycles 3 and 4 due to slow marker decline. His HCG (50,000 pre-treatment) normalized after chemo but 3 months later, increased, first to 25, and most recently to 90.

Is JA eligible for A031102 based on prior treatment history and evidence of disease progression?

A. Yes

B. No, he has not received adequate cisplatin-based chemo

C. No, he received more than 1 line of prior treatment

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Eligibility

- Inclusion Criteria (continued)
  - 3-6 cycles of prior cisplatin-based chemotherapy
    - BEP, EP, VIP will be most common prior regimens
  - No more than 1 prior line of chemotherapy for GCT
    - EPx4, BEPx3, BEPx4, and VIPx4
    - BEPx3 → EPx1 is allowed
    - BEPx2 → VIPx2 also allowed IF switch d/t pulmonary tox and NOT POD
    - BEPx4 → surgery → adjuvant VIPx2 (or EPx2) is allowed
    - BEPx4 → VeIPx2 with switch due to residual elevated tumor markers is NOT allowed
  - Prior adjuvant carboplatin for stage I seminoma allowed
    - Pt must have also received ≥3 cycles of BEP or EP at relapse
  - Prior adjuvant BEP/EP x 1-2 for early stage NSGCT is allowed
    - Pt must have also received ≥3 cycles of BEP or EP at relapse

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Case 3

SS is a 42-year-old man with history of IGCCCG good-risk GCT with metastasis to lungs and lymph nodes and normal tumor markers. He received 4 cycles of EP. After completion, he is noted to have an enlarging retroperitoneal lymph node. AFP and HCG remain normal.

Is SS eligible for A031102 based on prior treatment history and evidence of disease progression?

A. Yes

B. No, he has not received adequate cisplatin-based chemo

C. No, he does not have adequate evidence of POD

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Eligibility

- Inclusion Criteria
  - Male
  - Age ≥ 14
  - Confirmed GCT histology (any primary site)
    - Exception: No tissue available and patient with clinical situation c/w GCT (testicular, retroperitoneal or mediastinal mass, HCG ≥ 500 or AFP ≥ 500, and typical pattern of metastasis
  - Definite evidence of progression after 1 line of cisplatin-based chemotherapy:
    - Tumor biopsy of new, growing, or unresectable lesion c/w viable non-teratomatous GCT
    - Elevated and consecutively increasing AFP or HCG
    - New or enlarging lesions on imaging in setting of elevated AFP or HCG

NOTE: Rising LDH is not adequate proof of disease progression

ALLIANCE
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Case 4

DD is a 15-year-old boy is status post left orchiectomy and 4 cycles of BEP for intermediate-risk seminoma with metastasis to lymph nodes and bones. AFP and HCG were normal at diagnosis but LDH was 8 times the upper limit of normal. His LDH initially normalized but now has risen to 5 times the upper limit of normal.

Is DD eligible for A031102 based on prior treatment history and evidence of disease progression?

A. Yes

B. No, he has not received adequate cisplatin-based chemo

C. No, he does not have adequate evidence of POD

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Eligibility

- Inclusion Criteria
  - Male
  - Age ≥ 14
  - Confirmed GCT histology (any primary site)
    - Exception: No tissue available and patient with clinical situation c/w GCT (testicular, retroperitoneal or mediastinal mass, HCG ≥ 500 or AFP ≥ 500, and typical pattern of metastasis
  - Definite evidence of progression after 1 line of cisplatin-based chemotherapy:
    - Tumor biopsy of new, growing, or unresectable lesion c/w viable non-teratomatous GCT
    - Elevated and consecutively increasing AFP or HCG
    - New or enlarging lesions on imaging in setting of elevated AFP or HCG

NOTE: Rising LDH is not adequate proof of disease progression

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Case 4 continued

DD undergoes a biopsy of an enlarging retroperitoneal lymph node that is consistent with seminoma meeting criteria for A031102. A ^{51}Cr-EDTA radioisotope test indicates his creatinine clearance is 68mL/minute.

Is DD eligible for A031102?

A. Yes, no further testing is needed

B. Yes, only if an approved second method of assessing creatinine clearance is ≥ 50ml/min

C. No, his renal function is inadequate for the study

ALLIANCE
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Case 4 continued

DD undergoes a biopsy of an enlarging retroperitoneal lymph node that is consistent with seminoma meeting criteria for A031102. A ^{51}Cr-EDTA radioisotope test indicates his creatinine clearance is 68mL/minute.

Which of the following is an approved second method of assessing creatinine clearance in this case?

A. Schwartz Formula

B. 24-hour urine creatinine clearance

C. Jeliffe formula adjusted for BSA

D. Both A and B

E. Both B and C

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Case 5

JE is a 24-year-old man who recently completed 4 cycles of VIP for poor-risk primary mediastinal nonseminoma. His HCG was 13,000 before treatment, nadired at 54, and is now rising rapidly (79 and then 1,300).

Which of the following should be used as the primary method to estimate his creatinine clearance?

A. Jeliffe formula adjusted for BSA

B. Schwartz formula

C. 12-hour urine creatinine clearance

D. 24-hour urine creatinine clearance

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Case 5 (continued)

JE's creatinine clearance by the Jeliffe formula adjusted for BSA is 105ml/min

Which of the following should be used as the secondary method to estimate his creatinine clearance?

A. Schwartz formula

B. 12-hour urine creatinine clearance

C. 24-hour urine creatinine clearance

D. Radioisotope method

E. No secondary method is necessary in this case.

ALLIANCE
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Case 5 (continued)

JE's creatinine clearance by the Jeliffe formula adjusted for BSA is 55ml/min

Which of the following should be used as the secondary method to estimate his creatinine clearance?

A. Schwartz formula

B. 12-hour urine creatinine clearance

C. 24-hour urine creatinine clearance

D. Radioisotope method

E. B, C, and D

F. B and C but not D

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FOR CLINICAL TRIALS IN ONCOLOGY

Eligibility

- Inclusion Criteria (continued)

Creatinine Clearance (CrCl)

- Age ≥ 18 y/o
  - Use Jeliffe formula
  - If CrCl >70, patient is eligible
  - If CrCl ≥ 50 but ≤ 70, then 2nd method (12- or 24-hr urine Creatinine clearance (CrCl) or radioisotope method) must be ≥ 50

- Age <18 y/o:
  - Use radioisotope method preferentially
  - If radioisotope not available, can use12- or 24-hr urine CrCl or Schwartz Formula as primary method
  - If primary method CrCl ≥ 50 but ≤ 70, then 2nd method must have CrCl ≥ 50 for patient to be eligible
    - 2nd method can be any of the above not used as the primary method

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FOR CLINICAL TRIALS IN ONCOLOGY

Case 6

PT is a 32-year-old man with history of primary mediastinal nonseminoma with metastasis to lungs. He completed BEPx4 with decline in AFP from 1,500 to 35 but it is now rising (55 and then 120). Repeat imaging demonstrates enlarging lung nodules and no new sites of metastasis.

What was the patient's IGCCCG risk group at diagnosis

A. Good-risk

B. Intermediate-risk

C. Poor-risk

D. Inadequate information is available

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International Germ Cell Cancer Collaborative Group (IGCCCG) Risk Classification[1]

Risk Group	Seminoma	Nonseminoma	5-yr PFS Old	5-yr PFS Modern
Good	NPVM absent	Testis/RP primary, absent NPVM, and all marker levels ≤ S1	88%	92%
Intermediate	NPVM present	Testis/RP primary, absent NPVM, and at least one S2 marker	**70%**	**80%**
Poor	N/A	Mediastinal primary site or NPVM present or at least one S3 marker	**41%**	**50 – 55%**
Marker Definitions	S1: HCG<5,000, AFP<1,000, LDH <1.5xULN S2: HCG 5,000–50,000, AFP 1,000–10,000, LDH 1.5–10 x ULN S3: HCG >50,000, AFP>10,000, LDH >10xULN			

RP, retroperitoneal; NPVM, non-pulmonary visceral metastases; ULN, upper limit of normal

[1]IGCCCG, JCO, 1997

Case 6

PT is a 32-year-old man with history of primary mediastinal nonseminoma with metastasis to lungs. He completed BEPx4 with decrease in size of mediastinal mass and decline in AFP from 1,500 to 35. However, 1 month later, his AFP is now rising (55 and then 120). HCG is normal. Repeat imaging demonstrates enlarging lung nodules and no new sites of metastasis.

What is his IPFSG risk group for A031102?

A. Low-risk

B. Intermediate-risk

C. High-risk

D. Inadequate information is available

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

International Prognostic Factors Study Group (IPFSG) Classification at Initial Salvage Therapy

STEP 1	**Calculate Initial Score (sum of points for each variable)**	**Prognostic Factor (Pts)**	**3**	**2**	**1**		**0**	Row Pts
		Primary site	Mediastinum		Retroperitoneum		Testis	_____
		Response to 1st-line CT		POD	PR-pos/SD		PR-neg/CR	_____
		Progression-free interval			≤ 3 months		> 3 months	_____
		HCG at initial salvage			>1000		≤1000	_____
		AFP at initial salvage		> 1,000	>ULN but ≤1000		Normal	_____
		Liver, bone, or brain mets			Present		Absent	_____
		Initial Score	0	1 2	3	4	≥ 5	_____
STEP 2	**Reclassify Initial Score***	**Reclassified Score**	0	1	2		3	_____
STEP 3	**Subtract 1 point for seminoma histology**							_____

STEP 4	**Calculate Final Score**	**Final IPFSG Group (Score)**	**Very low (-1)**	**Low (0)**	**Intermediate (1)**	**High (2)**	**Very High (3)**
STEP 5	**Consolidate for A031102**	**Final IPFSG Risk Group for A031102**	**Low**		**Intermediate**	**High**	

Adapted from Lorch et al., JCO, 2010

International Prognostic Factors Study Group (IPFSG) Classification at Initial Salvage Therapy

STEP 1	**Calculate Initial Score (sum of points for each variable)**	**Prognostic Factor (Pts)**	**3**	**2**	**1**		**0**	Row Pts
		Primary site	~~Mediastinum~~		Retroperitoneum		Testis	3
		Response to 1st-line CT		POD	PR-pos/SD		PR-neg/CR	1
		Progression-free interval			≤ 3 months		> 3 months	1
		HCG at initial salvage			>1000		≤1000	0
		AFP at initial salvage		> 1,000	>ULN but ≤1000		Normal	1
		Liver, bone, or brain mets			Present		Absent	0
		Initial Score	0	1 2	3	4	≥ 5	6
STEP 2	**Reclassify Initial Score***	**Reclassified Score**	0	1	2		3	3
STEP 3	**Subtract 1 point for seminoma histology**							3
STEP 4	**Calculate Final Score**	**Final IPFSG Group (Score)**	**Very low (-1)**	**Low (0)**	**Intermediate (1)**		**High (2)**	**Very High (3)**
STEP 5	**Consolidate for A031102**	**Final IPFSG Risk Group for A031102**	**Low**		**Intermediate**		**High**	

Adapted from Lorch et al., JCO, 2010

Case 7

MB is a 19-year-old man with history of good-risk testicular seminoma with metastasis to retroperitoneal lymph nodes and lungs. Post-orchiectomy HCG was 35, AFP normal, and LDH 1.5xULN. He completed EPx4 with resolution of retroperitoneal lymphadenopathy and lung nodules and normalization of HCG. Six months later, his HCG increased to 25 and new lung nodules appeared. AFP is normal.

What is his IPFSG risk group for A031102?

A. Low-risk

B. Intermediate-risk

C. High-risk

D. Inadequate information is available

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

International Prognostic Factors Study Group (IPFSG) Classification at Initial Salvage Therapy

STEP 1	**Calculate Initial Score (sum of points for each variable)**	**Prognostic Factor (Pts)**	**3**	**2**	**1**		**0**	Row Pts
		Primary site	Mediastinum		Retroperitoneum		Testis	0
		Response to 1st-line CT		POD	PR-pos/SD		PR-neg/CR	0
		Progression-free interval			≤ 3 months		> 3 months	0
		HCG at initial salvage			>1000		≤1000	0
		AFP at initial salvage		> 1,000	>ULN but ≤1000		Normal	1
		Liver, bone, or brain mets			Present		Absent	0
		Initial Score	0	1 2	3	4	≥ 5	1
STEP 2	**Reclassify Initial Score***	**Reclassified Score**	0	1	2		3	1
STEP 3	**Subtract 1 point for seminoma histology**							0

STEP 4	**Calculate Final Score**	**Final IPFSG Group (Score)**	**Very low (-1)**	**Low (0)**	**Intermediate (1)**	**High (2)**	**Very High (3)**
STEP 5	**Consolidate for A031102**	**Final IPFSG Risk Group for A031102**	**Low**		**Intermediate**	**High**	

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Adapted from Lorch et al., JCO, 2010

Case 8

BH is a 37-year-old man with history of poor-risk testicular nonseminoma with metastasis to RP nodes and liver. Post-orchiectomy HCG was 35, AFP 3,000 normal, and LDH 1.5xULN. He completed BEPx4 with marker normalization and then underwent RPLND and liver wedge resection demonstrating viable yolk sac tumor in the liver. He received 2 additional cycles of EP. He remained disease-free until 4 months later when he developed severe R shoulder pain and his AFP rose to 50 and then 1,100 and CT showed new liver lesions and bone lesions. He was given 1 cycle of TIP due to rapid progression. His current AFP is 500 and HCG is normal.

What is his IPFSG risk group for A031102?

A. Low-risk

B. Intermediate-risk

C. High-risk

D. Inadequate information is available

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

ANSWER with the PRE-TIP RESULTS

STEP 1	**Calculate Initial Score (sum of points for each variable)**	Response to 1st-line CT		POD	PR-pos/SD	PR-neg/CR	0
		Progression-free interval			≤ 3 months	> 3 months	0
		HCG at initial salvage			>1000	≤1000	0
		AFP at initial salvage		> 1,000	>ULN but ≤1000	Normal	2
		Liver, bone, or brain mets			Present	Absent	1
		Initial Score	0	1 2	3 4	≥ 5	3
STEP 2	**Reclassify Initial Score***	**Reclassified Score**	0	1	2	3	2
STEP 3	**Subtract 1 point for seminoma histology**						2

STEP 4	**Calculate Final Score**	**Final IPFSG Group (Score)**	**Very low (-1)**	**Low (0)**	**Intermediate (1)**	**High (2)**	**Very High (3)**
STEP 5	**Consolidate for A031102**	**Final IPFSG Risk Group for A031102**	**Low**		**Intermediate**	**High**	

Adapted from Lorch et al., JCO, 2010

Conclusion

- Questions from Audience
- Answers from Presenter

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY