Alliance 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 Of Germ Cell Tumors (TIGER)

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Rationale

- Germ cell tumors (GCT) represent the most common malignancy affecting adolescent and young adult men in both Europe and the United States. [1]
- Up to 30% of pts with advanced GCT are not cured with first-line chemotherapy and require salvage treatment, consisting of either conventional-dose chemotherapy (CDCT) or high-dose chemotherapy (HDCT).
- The optimal initial salvage approach (HDCT vs. CDCT) is not clear; retrospective studies consistently report superior outcomes with HDCT but the one prior RCT (IT-94) found no improvement with HDCT. [2]
- IT-94 had several shortcomings including:
  - Only 1 high-dose cycle in the HCT arm (most effective regimens use 2 or 3)
  - Exclusion of pts with incomplete response to first line chemotherapy (only allowed relapsing pts)
  - >25% of pts assigned to HDCT arm never received the high-dose cycle
- The current TIGER study aims to determine whether HDCT or CDCT is the optimal initial salvage approach.
- Collaboration between Alliance, EORTC, ECOG, SWOG, COG, ANZUP
- Open in 13 countries across 3 continents (North America, Europe and Australia)

References: 1. Feldman *JAMA* 299:672-84, 2008; 2. Pico *Ann Oncol*16:1152–59, 2005

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Endpoints

Primary

Overall Survival (OS)

Sample size = 420 patients (expected deaths = 232)

- 168 patients from US Cooperative Groups; 252 patients from EORTC

- Cure rate model: 35% of patients will be cured with TIP (median OS 1.5yrs)
- Power 81%, 1-sided type I error rate = 0.05 where TI-CE will reduce the hazard by 29% (θ =0.71)
  - Efficacy & futility analyses regularly per Alliance policy
- Formal toxicity analysis for early stopping (90% CI for one-sided difference in treatment-related mortality > 16%)

Secondary

- Progression-free survival (PFS)
- Favorable response rate
  - CR and PR-negative markers
- Treatment-related mortality
- Toxicities by CTCAE v4.0
- Validation of the IPFSG risk model [3]

Correlative Studies

- Quality of life assessment of TIP vs. TI-CE using EORTC QLQ-C30 and the QLQ-TC26
- Pharmacogenomics: correlation of SNP rs1649942 (associated with platinum response) with PFS in the entire study population
- Tumor whole exome analysis assessing for the association of genetic alterations with OS
  - DNA Repair genes (TP53) [6]
  - PI3K/RAS/RAF genes[7]

References: 3. Lorch *J Clin Oncol* 28:4906-11, 2010; 6. Feldman *J Clin Oncol* (Epub 2016); 7. Feldman. *Clin Cancer Res* 20 (14); 3712–20, 2014

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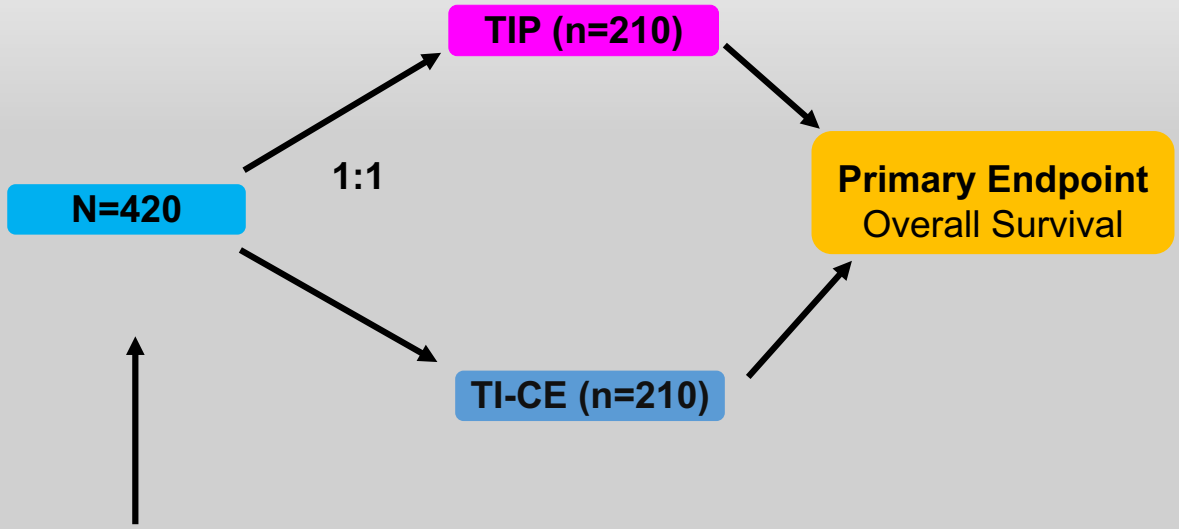
Study Schema



Stratification Factors:

1. International Prognostic Factor Study Group (IPFSG) risk class[3]
2. Continent of enrollment

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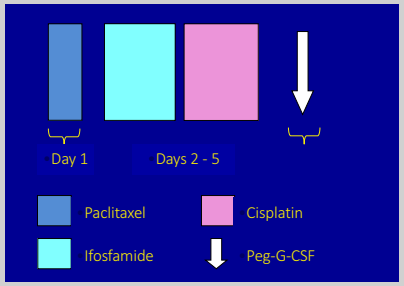
Treatment Plan

ARM A (CDCT): TIP[4]

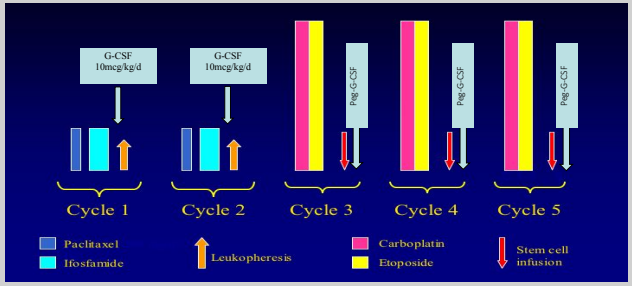
Drugs and Doses	Infusion Time	Days
Paclitaxel 250mg/m^2	24 hours	1
Ifosfamide 1500mg/m^2	1-2 hours	2-5
Mesna	1-2 hours	2-5
Cisplatin 25mg/m2	0.5 – 1 hour	2-5



- 4 cycles given every 21 days
- Exact infusion time at discretion of investigator and institution
- Levofloxacin 500mg daily given as prophylaxis from day 7 to 13 of each cycle

ARM B (HDCT): TI-CE[5]

Cycle #	Cycle Duration	Drugs and Doses	Days
1-2	14 days	Paclitaxel 200mg/m^2	1
		Ifosfamide 2000mg/m^2/d	2-4
3, 4, 5	21 days	Etoposide 400mg/m^2/d	1-3
		Carboplatin AUC 7-8/d	1-3



References: 4. Kondagunta J Clin Oncol 23: 6549–55, 2005; 5. Feldman *J Clin Oncol* 28:1706-13, 2010

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Key Eligibility Criteria

- Male
- Age ≥ 14 years
- ECOG 0 - 2
- Histologic confirmation of GCT diagnosis
- Evidence of progressive disease after one line of cisplatin-based chemotherapy including:
  - Biopsy of new/growing mass consistent with non-teratomatous GCT
  - Rising HCG or AFP
  - New or enlarging lesions in the setting of elevated (even if not rising) HCG or AFP
- Received 1 prior line of cisplatin-based chemo (3 – 6 cycles)
- No prior treatment with TIP or HDCT
- GFR ≥ 50ml/min by 2 methods or ≥ 70ml/min by 1 method
- ANC ≥ 1,500/mm3, PLT ≥ 100,000/mm3
- T bilirubin ≤ 2.5 x ULN and AST/ALT ≤ 2.5 x ULN
- Negative serology for HIV, HTLV, Hep B, and Hep C
- No secondary somatic malignancy arising from teratoma

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Funding Support

Alliance A031102 is funded by the National Institutes of Health through National Cancer Institute grant awards.

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