Gemcitabine, Oxaliplatin, And Paclitaxel (GOT) on a 2-weekly Schedule In Patients With Refractory Germ Cell Carcinoma:

A phase II study conducted at the University of Southern California

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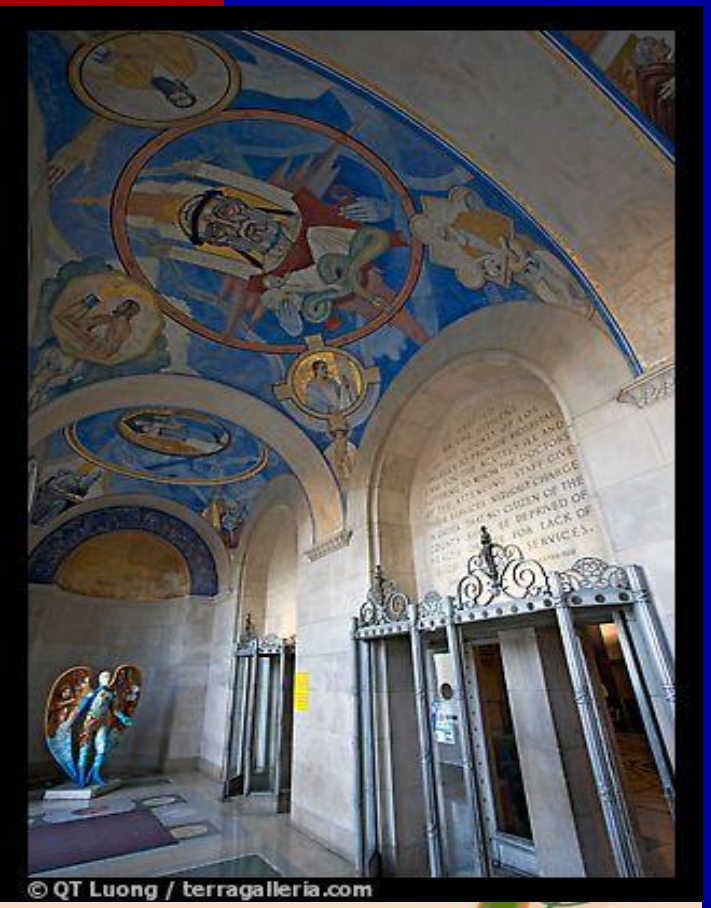

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Introduction and Background

- Germ cell tumor treatment is one of the therapeutic triumphs of the late 20th century
- Despite this, challenges remain:
  - Poor risk GCT at presentation
  - Refractory GCT
  - Late effects from therapy
- In this presentation we will focus on experience with a modified salvage regimen using active agents given in a rapid replicating regimen with a dose escalation option for oxaliplatin in refractory/relapsed GCT

Objectives

- To assess the response rate (confirmed complete and partial responses) in patients with germ cell malignancies who have failed initial cisplatin containing chemotherapy utilizing the combination of oxaliplatin, gemcitabine, and paclitaxel.

- To assess the overall survival and progression free survival in this group of patients.

- To evaluate the qualitative and quantitative toxicities of this GOT regimen

Eligibility

- Male patients, >16 years old, ECOG PS >=2
- Histologically confirmed germ cell tumor
- Progression by marker or RECIST criteria within 4 wks of a standard cisplatin regimen (7) or after salvage (17) or HDC stem cell regimen (6). [note: one patients got HDSCT after this trial protocol]
- Growing teratoma patients (screened, n=5) were excluded by tumor conference consensus.
- 12 patients were considered not to be candidates for HDCSCT because of refractory disease, 11 lacked insurance coverage for HDCSCT, 1 pt declined HDCSCT but received at after PD on this trial

Treatment Regimen 1#

- Chemotherapy day 1 of a 14 day cycle

- Paclitaxel 170mg/m^2 over 3hours
- Gemcitabine 800mg/m^2 over 80mins
- Oxaliplatin 100mg/m^2 over 90min
  - increased to 125mg/m^2 in cycle 2 if no major toxicity.
  - Mg^{2+} & Ca^{2+} infused before oxaliplatin.

Treatment Regimen 2#

- G-CSF was not given prophylactically but allowed after prolonged neutropenia or febrile neutropenia
- The regimen was designed to **maximise oxaliplatin density** with full dosing of pts with recovering marrow & **dose escalation** for pts with limited toxicity in cycle 1.
- Retreatment criteria:
  - **ANC ≥1000 or 700 with monocytosis**
  - **platelets ≥75000**
- Pts with marker normalization had 3 further cycles of therapy.
- CT imaging every 4 cycles on therapy then every 3 months

- Progression was defined by:
  - RECIST criteria 1.0
  - Three successive increases in serum markers at least one week apart

Study conduct

- First patient on study: 4/1/2005
- Last patient on trial: 4/16/2012

Simon two stage design:

- Accrue 10 patients, if more than one responded then accrue an additional 20 patients to completion with a response rate exceeding 20% considered encouraging

30 patients were accrued (29 reported in submitted abstract)

- All 30 patients are reported here, although a further endpoint analysis if planned for 180 days after final patient completed therapy
- 9 patients escalated oxaliplatin dosage after cycle 1
  - 4 of these had dose de-escalation within the next 2 cycles due to haematological toxicity

Table 1. Demographics

	Number Patients	Percent
Age At On Study		
≤ 30	13	43%
> 30	17	57%
Median (Range)	32 (19 - 55)	
Age At Diagnosis		
≤ 25	12	41%
> 25	17	59%
Missing	1	
Median (Range)	26 (18 - 53)	
Ethnicity		
Asian	3	10%
Hispanic	14	47%
Non-Hispanic White	13	43%
Performance Status (ECOG)		
0	20	67%
1	9	30%
2	1	3%
Primary Site		
Left Testis	12	40%
Right Testis	12	40%
Unknown laterality/Bilateral	4	13%
Mediastinum	2	7%

Table 2. Tumor/patient characteristics

	Number Patients	Percent
Risk category at diagnosis		
Good	3	10%
Intermediate	13	43%
Poor	14	47%
Histology		
Pure seminoma	1	3%
Embryonal carcinoma	1	3%
Choriocarcinoma	3	10%
Yolk sac tumor	3	10%
Immature teratoma	5	18%
Mixed NSGCT	16	53%
Other	1	3%
Serum Markers	% elevated	Median (Range)
Alpha Foetal protein	63%	26.7 (2-363002)
B-HCG	77%	2.6 (0.5-247040)
LDH	32%	178 (109-4504)
Prior chemotherapy		
Cisplatin	30	100%
Ifosfamide	20	67%
Taxane	12	40%
Gemcitabine or Oxaliplatin	3	10%
HDSCT	6	20%

Table 3a. Common Toxicities: all grades

Category	Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Allergy/Immunology	Allergic reaction/ hypersensitivity	9	0	1	0
Constitutional Symptoms	Fatigue (asthenia, lethargy, malaise)	10	14	1	2
Skin	Hair loss/alopecia	4	20	0	0
Gastrointestinal	Taste alteration (dysgeusia)	19	4	0	0
	Vomiting	11	4	4	0
Hepatic	ALT, SGPT	15	5	1	0
	AST, SGOT	15	2	1	0
Lymphatics	Edema: limb	6	1	0	0
Neurology	Ataxia/Dizziness	3	1	0	1
	Neuropathy: sensory	14	4	4	0
Pain	Pain (Joint)	5	6	2	0
	Pain (Muscle)	5	4	0	0
Pulmonary	Dyspnea	7	1	1	0
Infection	Pneumonia	0	1	0	1

Table 3b. Toxicities: grade 3 or 4

Grade 5 toxicity: one death due to non-neutropenic pneumonia after cycle 4

Category	Grade 3	Grade 4	%
Blood/Bone Marrow	13	5	60
Neutropenia	8	5	
Thrombocytopenia	5	1	
Constitutional Symptoms	1	2	10
Gastrointestinal	4	0	13
Hepatic	2	0	7
Infection/Febrile Neutropenia	0	1	3
Neurologic	4	1	17
Any Hematologic	13	5	60
Any Non-hematologic	11	3	47

Table 4a. Endpoints summary

	Number Patients	Percent
Total Cycles Of Treatment		
≤ 4 Cycles	9	30%
> 4 Cycles	21	70%
Median (Range)	6 (1 - 14)	
Best Response To Treatment by RECIST criteria		
CR	2	7%
PR	7	23%
uPR	2	7%
SD	13	43%
PD	5	17%
Inevaluable	1	3%
Response Rate For CR/PR (95% CI)	30% (16%, 48%)	
Marker normalisation	7/30 = 23.3%	
Reason Off Treatment		
Treatment Completed Per Protocol	7	23%
Surgical resection	4	13%
Disease Progression (Marker or RECIST)	13	43%
Unacceptable Toxicity/Adverse Event/Death	3	10%
Non-Compliance	2	7%

Table 4b. Endpoints summary

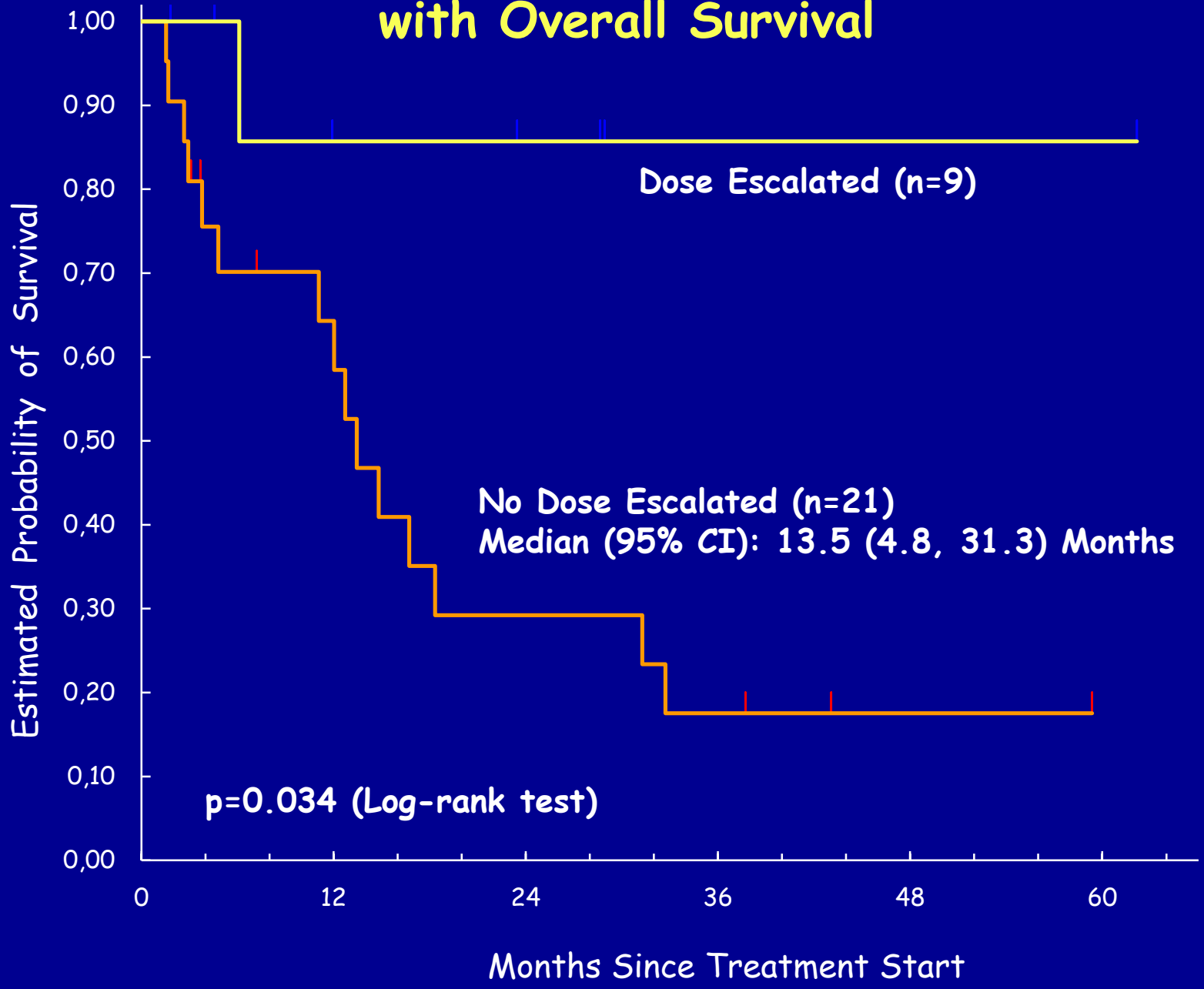
Overall Survival	
Median (95% CI)	16.7 (11.0, 32.7) months
Probability Of Survival At 2 Years ± SE	0.42 ±0.10
Progression Free Survival	
Median (95% CI)	14.8 (4.4, 31.3) months
Probability Of Not Progressing At 1 Year ± SE	0.65 ±0.09
Event Free Survival*	
Median (95% CI)	4.8 (2.9, 14.8) months
Median (Range) Follow Up	
Median (Range)	28 (1.8 - 62) months

*Definition:
Event free survival (time to fail): TTF is calculated from treatment start to any event observed including off treatment due to adverse event or unacceptable toxicity, progression, death due to any reason, patient refused further treatment, new treatment start, or non-compliance.

Association Of Certain Prior Chemotherapies With Overall Survival

	Relative risk (95% CI)	Median (95% CI) Months	p-value
International Risk Group at Diagnosis			0.023
Good (n=3)*		Not Reached	
Intermediate / Poor (n=27)	NA	13.5 (6.1, 31.3)	
Prior High Dose Chemotherapy with Stem Cell Therapy			0.65
No (n=24)	1.00	16.7 (12.4, NA)	
Yes (n=6)	1.29 (0.41, 4.08)	12.0 (2.9, 31.3)	
Prior Ifosfamide Therapy			0.014
No (n=10)	1.00	Not Reached	
Yes (n=20)	3.50 (1.03, (11.9)	12.0 (3.8, 18.3)	
Prior Taxane Therapy			0.011
No (n=18)	1.00	31.3 (12.7, NA)	
Yes (n=12)	3.21 (1.11, 9.32)	11.1 (1.7, 18.4)	
Prior Taxane, Gemcitabine or Oxaliplatin Therapy			0.024
No (n=16)	1.00	32.8 (12.0, NA)	
Yes (n=14)	2.88 (1.02, 8.15)	13.4 (2.7, 31.3)	
Number of Prior Regimens			0.027
1 or 2 (n=22)	1.00	31.3 (12.7, NA)	
3 or More (n=8)	2.87 (1.05, 7.84)	12.0 (2.9, 14.8)	
With Oxaliplatin Dose Escalated			0.034
Yes (n=9)	1.00	Not Reached	
No (n=21)	6.55 (0.87, 49.1)	13.5 (4.8, 31.3)	

Association of Oxaliplatin Dose Escalated with Overall Survival



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What have we learnt?

Phase 2 trials of double- or triple-combination chemotherapy in patients with refractory germ cell tumors

Combination regimen	No. of patients	Previous HD-CTX %	ORR (%)	CR/PR (%)	OS (range)	Long-term survival % of patients (months)	Study
Paclitaxel/gemcitabine	28	36	21	10/NE	8.3 (≥2-25)	7 (≥15-25)	Hinton et al. [17]
Gemcitabine/oxaliplatin	**28**	**14**	**32**	**14/NE**	**8.7 (≥2.5-28)**	**11 (≥14, 19, 28)**	**Pectasides et al. [18]**
Oxaliplatin/irinotecan	18	0	40	22/NE	7.5 (≥1.5-19)	9 (≥11, 14, 19)	Pectasides et al. [19]
Oxaliplatin/gemcitabine	**18**	**22**	**17**	**5/5**	**7 (≥1-44)**	**16 (≥18, 20, 44)**	**De Giorgi et al. [20]**
Gemcitabine/paclitaxel	32	100	31	19/13	8.0 (≥2-63)	13 (≥20, 40, 44, 57)	Einhorn et al. [21]
Paclitaxel/oxaliplatin	26	NE	30	0/4	8.8 (95% CI:5-12)	8 (median: 65)	Theodore et al. [22]
Gemcitabine/oxaliplatin	**35**	**89**	**46**	**9/9**	**6 (1-84)**	**3 (≥59)**	**Kollmannsberger et al. [1]; Oechsle et al**
Gemcitabine/oxaliplatin/paclitaxel	**41**	**78**	**51**	**5/34**	**11 (≥2-48)**	**17 (≥28, 28, 31, 33, 36, 37, 48)**	**Bokemeyer et al. [2]; Oechsle et al**
Cisplatin/paclitaxel/gemcitabine	22	23	36	0/32	13.5 (≥1-99)	18 (≥80, 81, 94, 99)	Nicolai et al. [23]

NE = Not evaluated, Oechsle K et al. Eur Urol 60: 850 – 855, 2011

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Gemcitabine/oxaliplatin/paclitaxel	**30**	**20**	**31**	**7/23**	**16.7 (11.0-32.7)**	**42% at 2 years**	**Dorff et al USC ESMO (2012)**
Cisplatin/paclit							

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Summary

- In the setting a heavily pretreated relapsed and refractory population of germ cell tumor patients, Gemcitabine, oxaliplatin and paclitaxel given every 2 weeks was an active regimen with
  - marker normalization in 23% of patients
  - Complete response in 2 patients and cytoreduction to permit surgical resection to no evaluable disease in a further 4 patients
  - Other patients remain alive with residual disease
  - Seven patients are beyond 1 year without evidence of disease
  - Acceptable toxicity with a single regimen attributed death
- Median overall survival of 16.7 months with 42% alive at 2 years is interesting and requires further follow-up in this and other cohorts.
- Number of prior regimens, prior taxane exposure or prior ifosfamide exposure were associated with poorer overall survival
- Patients who had escalation of oxaliplatin dosage had a better overall survival

Conclusion

- Albeit from a single institution, this is a heterogeneous group of patients where outcomes are hypothesis generating.
- Further evaluation in this trial will focus on predictors of response and outcome including marker kinetics as well as effect of therapy after trial treatment
- The question as to whether schedule and dose density improve outcome in refractory patients should be pursued in larger cohorts in which prognostic characteristics can be balanced
- An extension protocol is planned with G-CSF support to facilitate dose escalation of oxaliplatin.

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