TRC 105 +/- Bevacizumab for Patients with Metastatic Refractory Gestational Trophoblastic Neoplasia

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- I have no conflicts of interest to disclose
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Gestational Trophoblastic Neoplasia

- Invasive mole
- Choriocarcinoma
- Placental site trophoblastic tumor
- Epithelioid trophoblastic tumor

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Gestational Trophoblastic Neoplasia

- Overall cure rate >90%
- Thorough evaluation and staging allow selection of appropriate therapy that maximizes chances for cure while minimizing toxicity.
- Low-Risk GTN (stage I-III, score <7) can be treated with single-agent chemotherapy resulting in a survival rate approaching 100%
- High-Risk GTN (stage II-IV, score ≥ 7) requires initial multiagent chemotherapy with or without adjuvant radiation and surgery to achieve a survival rate of 80-90%

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Salvage Therapy for High-Risk GTN

- Approximately 30% of patients with FIGO-defined metastatic high-risk GTN will have an incomplete response to first-line therapy or will relapse from remission and require salvage therapy.

- Most high-risk GTN patients who fail initial therapy will have:
  - Multiple metastases to sites other than the lung and vagina
  - High FIGO scores
  - Inadequate initial therapy

- The ultimate cure of these high-risk patients who fail inital therapy depends, therefore, on the success of salvage chemotherapy often combined with adjuvant surgical procedures and radiotherapy.

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Primary Treatment of High-Risk Metastatic Gestational Trophoblastic Neoplasia with EMA-CO

Authors	No. of Patients	Complete Response %	Survival %
Bower, et al 1997	151	78	85
Kim, et al 1998	96		91
Soto-Wright, et al 1997*	7	71	100
Matsui, et al 2000*	27	78	89
Lurain, et al 2006	30	67	93
Turan, et al 2006	23	82	91
Lu, et al 2008	45	78	93

*EMA only

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Salvage Chemotherapy for High-Risk GTN

- EMA-EP (etoposide, methotrexate, actinomycin D, etoposide, cisplatin)
- BEP (bleomycin, etoposide, cisplatin)
- VIP (etoposide, ifosfamide, cisplatin)
- ICE (ifosfamide, carboplatin, etoposide)
- TP/TE (paclitaxel & cisplatin/paclitaxel & etoposide)

Filgrastim or Pegfilgrastim used to prevent neutropenia and avoid treatment delays

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Salvage Therapy for High-Risk GTN

- Salvage therapy with etoposide/platinum-based chemotherapy regimens, often in conjunction with surgery to resect resistant foci of disease and/or irradiation to treat newly developed brain metastases will result in cure of approximately 80% of high-risk patients who fail initial multiagent chemotherapy.

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Trial Background

- Endoglin (CD105), a 633 amino acid, 180 kDa membrane receptor is highly expressed by proliferating endothelial cells in solid tumors as well as syncytiotrophoblasts and is required for angiogenesis.
- Endoglin expression is increased in choriocarcinoma compared to normal placenta, it induces trophoblastic outgrowth and migration, and its production is stimulated by methotrexate.
- In observational studies, high levels of endoglin are associated with increased resistance to methotrexate.
- Therefore, endoglin is a potential target for the treatment of GTN.

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Trial Background

- TRC105 is a chimeric IgG1 anti-endoglin monoclonal antibody with high avidity (Kd=5 pM)
- Phase I/II trials of TRC05 have shown activity in a variety of cancers (prostate, renal, breast, liver, GBM) as both single agent and in combination (bevacizumab, sorafenib, and axitinib)
- Mechanisms of action include direct growth suppression of endothelial cells, induction of apoptosis, and antibody-dependent cell-mediated cytotoxicity, competes with BMP9
- Common toxicites include: infusion reaction (rigors, bronchospasm, itch, BP and HR changes) anemia, fatigue, epistaxis, gingival bleeding, headache.

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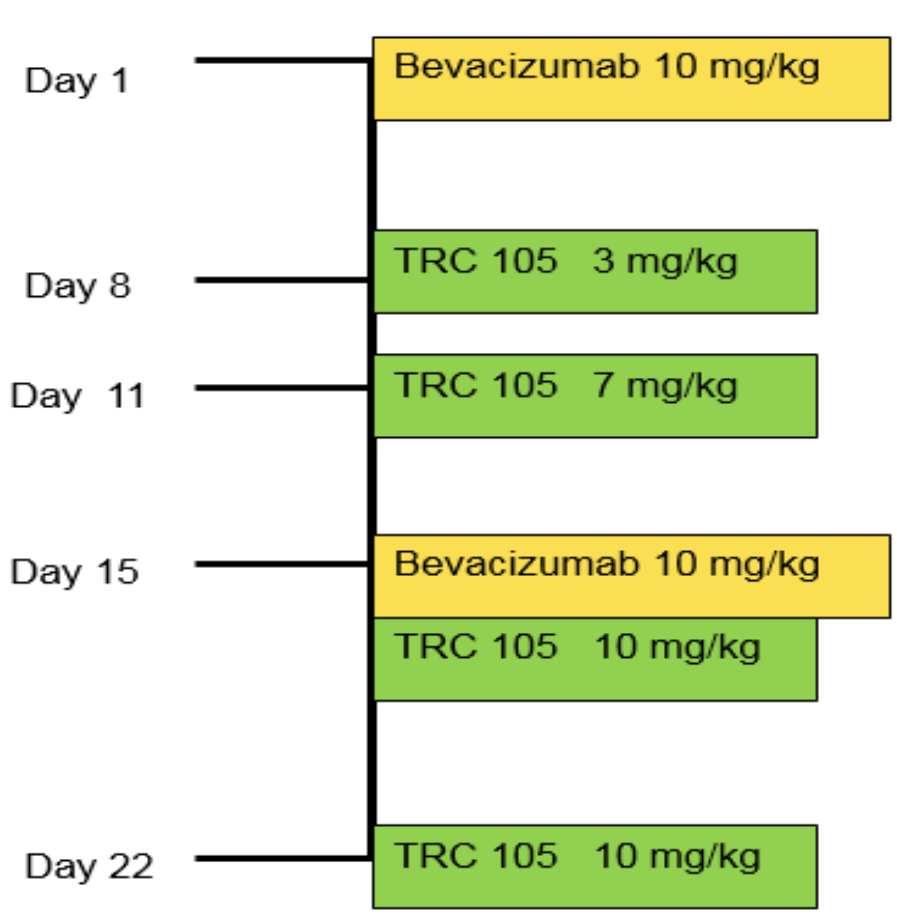
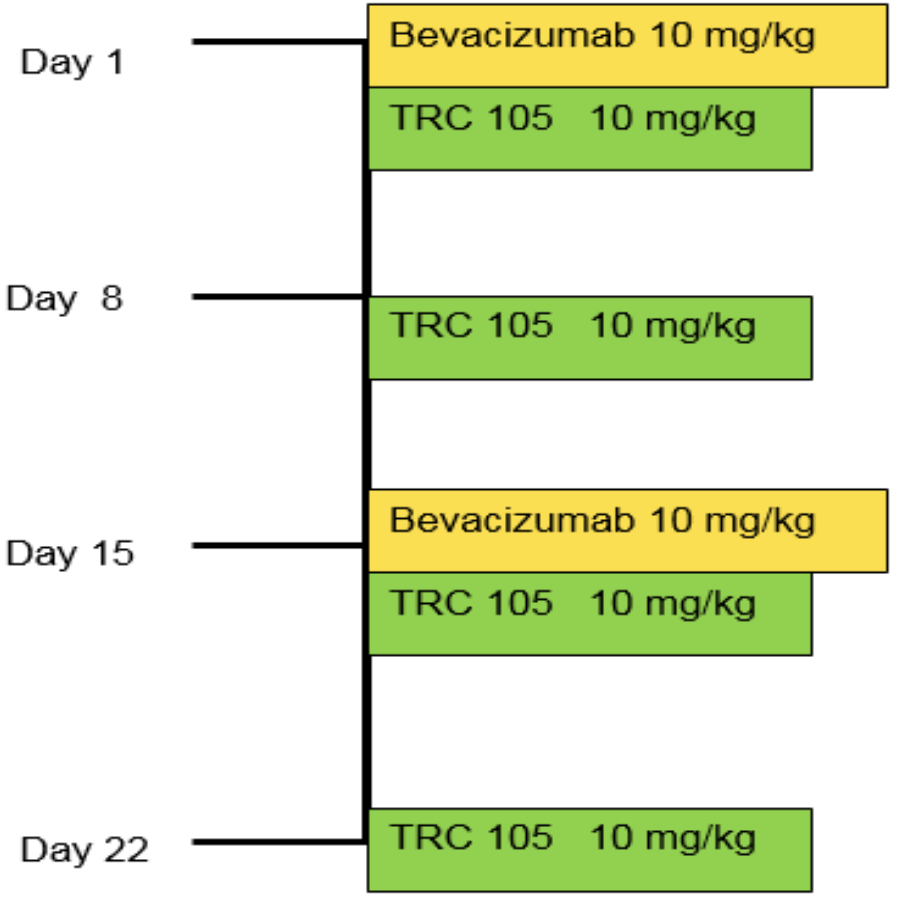
Trial Schema



Cycle 1



Cycle 2 +

* Pre-meds – acetominophen, methyprednisolone, famotidine, cetirizine

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Patient KA History

- 38-year-old with a history of post-molar GTN treated with single-agent weekly MTX in 2007.
- March 2013 miscarriage followed by the development of a uterine mass and persistently elevated ß-hCG suspicious for GTN.
- Treated with single-agent weekly MTX (x2) and then pulsed ACT-D (x2).
- Underwent hysterectomy-pathology c/w choriocarcinoma.
- Initiated EMA-CO with no response; switched to EMA-EP and went into remission in October 2013 after 7 cycles + 3 consolidation cycles.
- December 2013 recurred with multiple pulmonary metastases. Received TP/TE (x3) but progressed, then received ICE (x2).
- May 2014 underwent high-dose chemotherapy with stem cell rescue, resulting in a brief normalization of her ß-hCG
- June/July 2014 multiple pulmonary nodules. Thoracoscopic resection of 10 pulmonary nodules, but continued to have a rising ß-hCG.
- Treated with capecitabine (x3)

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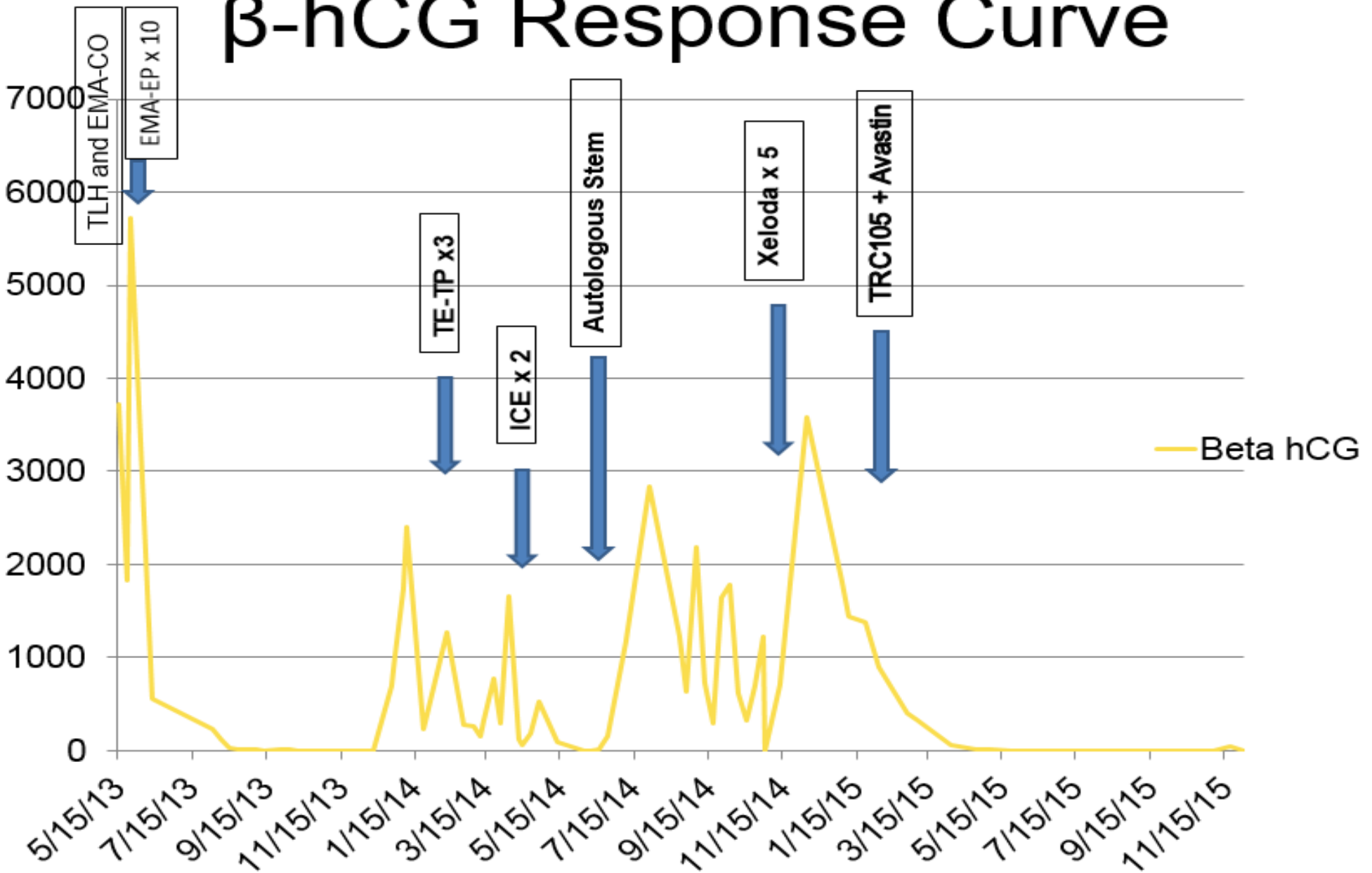
β-hCG Response Curve



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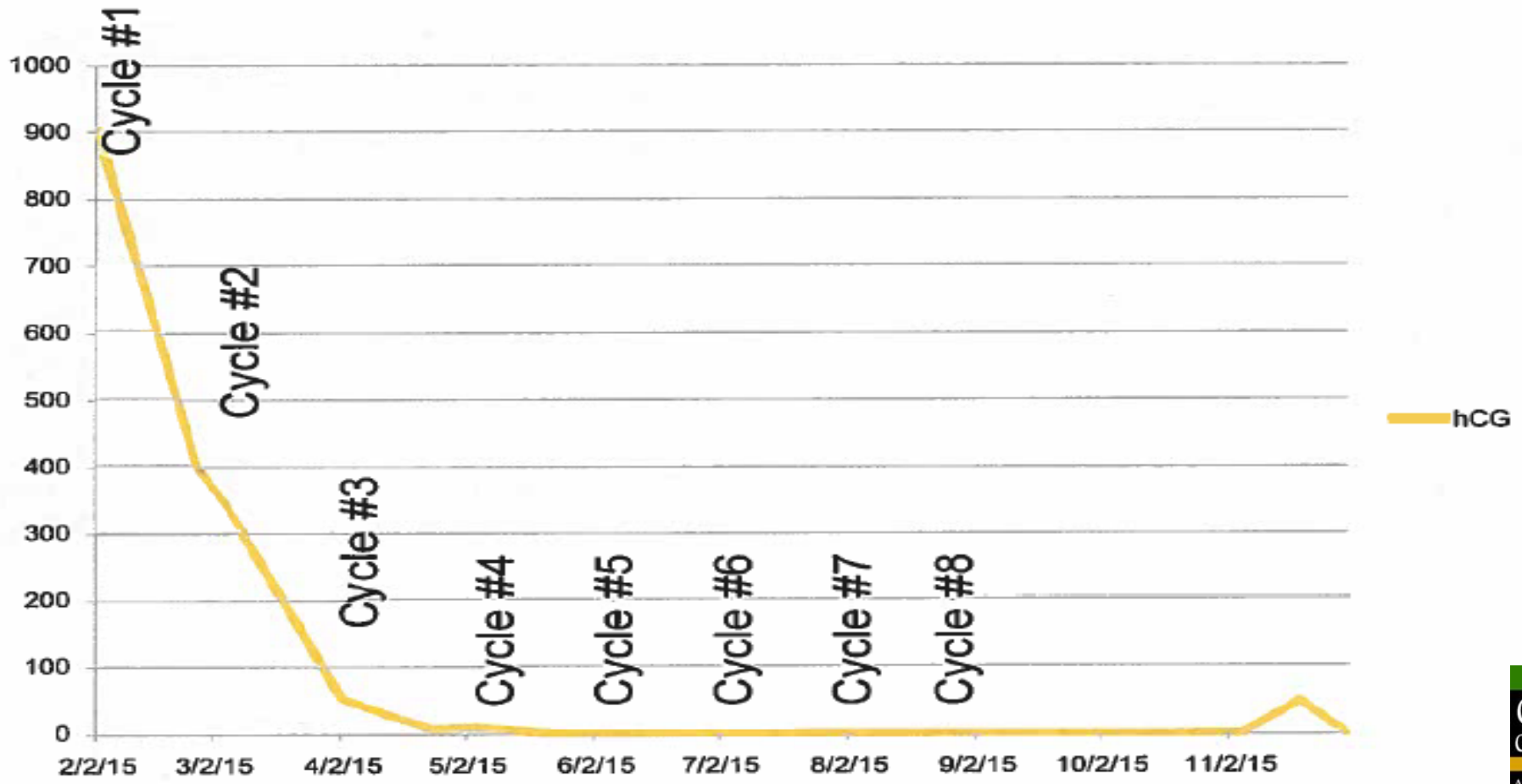
Beta hCG Response Curve while on Trial



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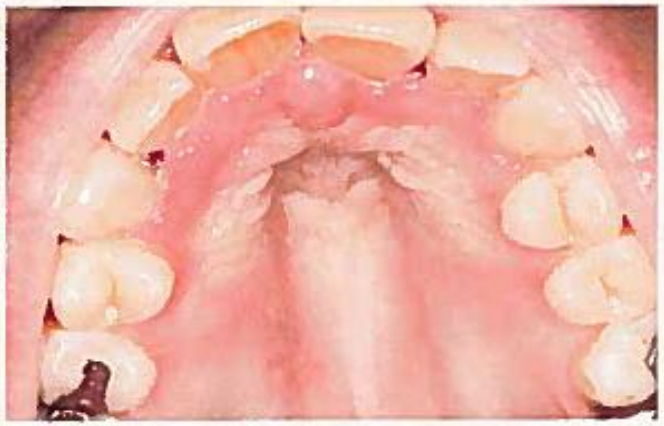
Patient KA -Toxicities

Toxicity	NCI CTCAE (version 4) Grade
Epistaxis	1
Insomnia	1
Skin Rash	1
Thrombocytopnia	1
Anemia	1
Chest heaviness	1
Hoarseness /Sore throat	1
Elevated Alk Phosphotase	1
Gum infection /pain	2
Hypertension	3
Intermittent Migraine	3
Fatigue	3



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Patient AD History

- 33-year-old G2 P1011. 2/2013 diagnosed with post-abortal choriocarcinoma with vascular mass in uterus and > 20 lung metastases, ß-hCG=667
- Received MAC x 4 with partial response- persistent mass in uterus
- TLH 7/2013
- EMA-CO x 4 postop. ß-hCG NL after 1 cycle. Last dose 8/2013
- 1/2014 rise in ß-hCG. CT chest showed LUL lesion- VATS. hCG postop 38. EMA-EP x 6 cycles with normalization of ß-hCG. Last dose 3/2014
- 6/2014 ß-hCG rise to 90. PET/CT negative. TE/TP with ß-hCG nadir =7. Imaging negative.
- October 2014 ß-hCG rise to 57. Carboplatin/Gemcitabine x4 with nadir ß-hCG to 9 then increase to 106.
- 1/2015 ICE x 3 with nadir ß-hCG to 55, then rise to 197
- 4/2015 capecitabine x2 cycles. No response. ß- hCG increase to 351.
- Imaging showed right adrenal mass. Adrenalectomy (+) choriocarcinoma.
- Postop ß-hCG rise with new multiple lung metastases. Olaparib x2 cycles and carboplatin x1 cycle with no response

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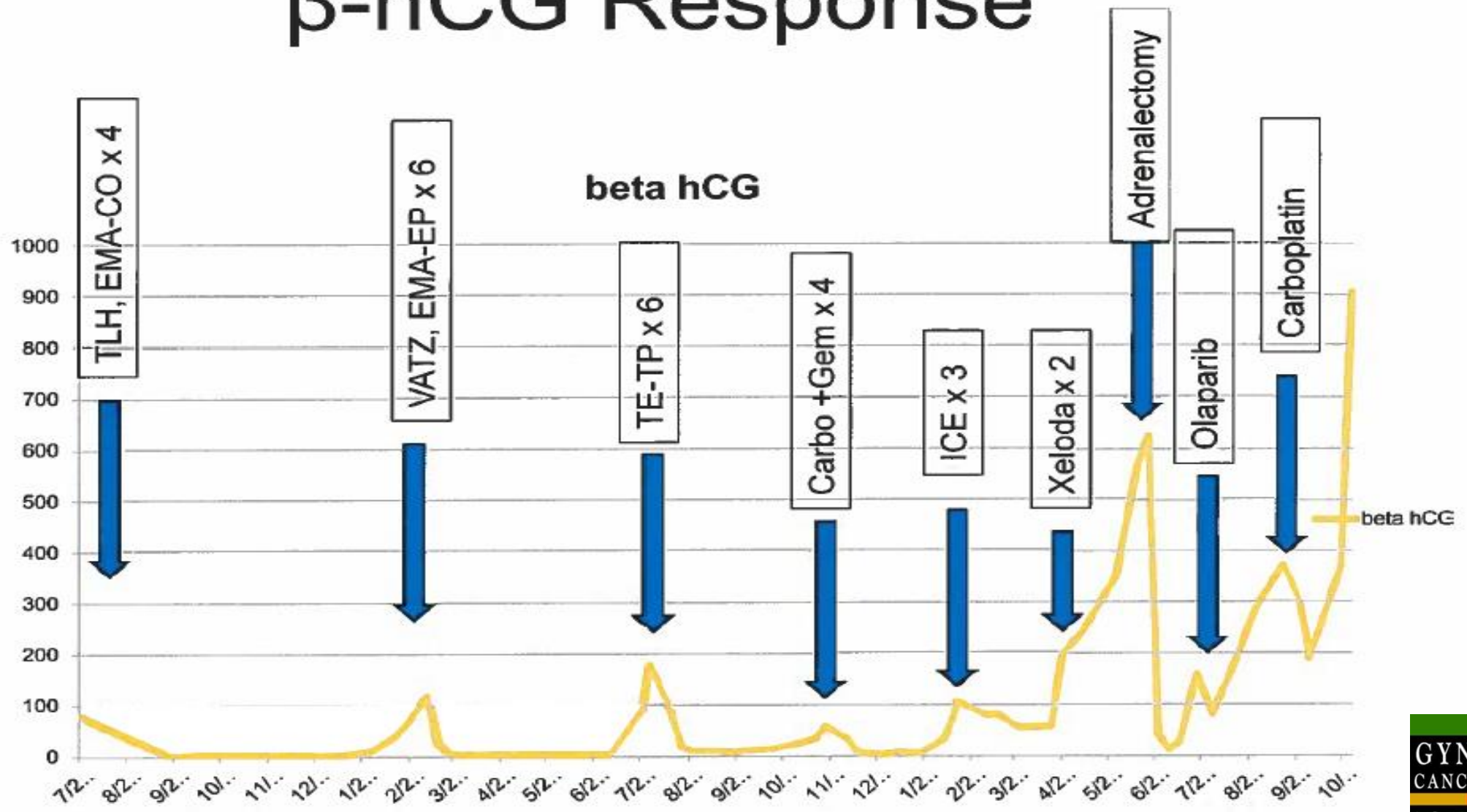
β-hCG Response



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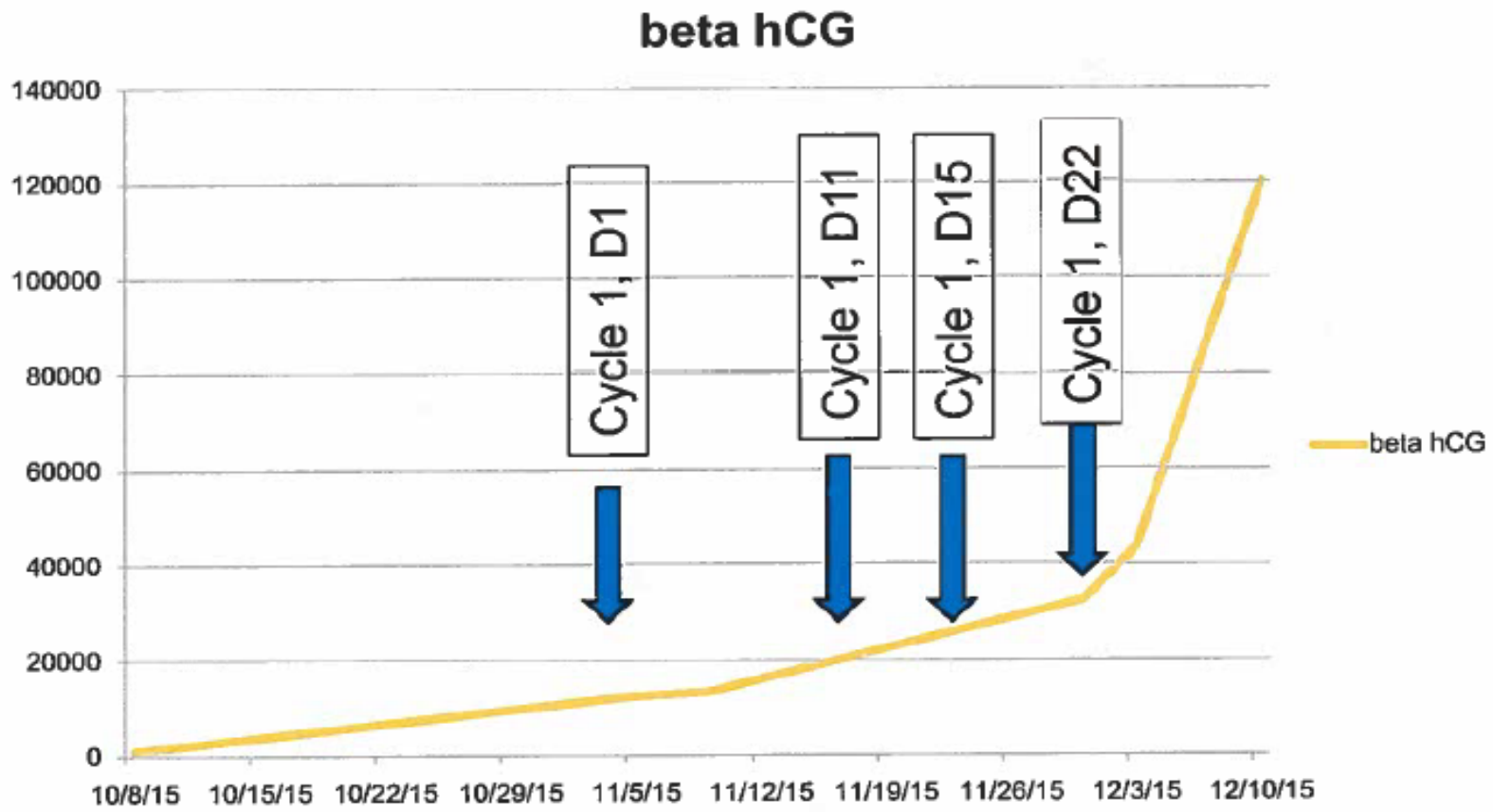
β- hCG Response Curve while on Trial



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Patient AD -Toxicities

Toxicity	NCI CTCAE (version 4) Grade
Fatigue	1
RUQ pain	1
Cough	1
Headache	3
Vomiting	2
Fever	1

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Conclusions

- TRC105+bevacizumab may be an active and well tolerated regimen in patients with multi-drug resistant GTN.
- Given the observed complete response in one patient, a phase II trial of the combination is planned.

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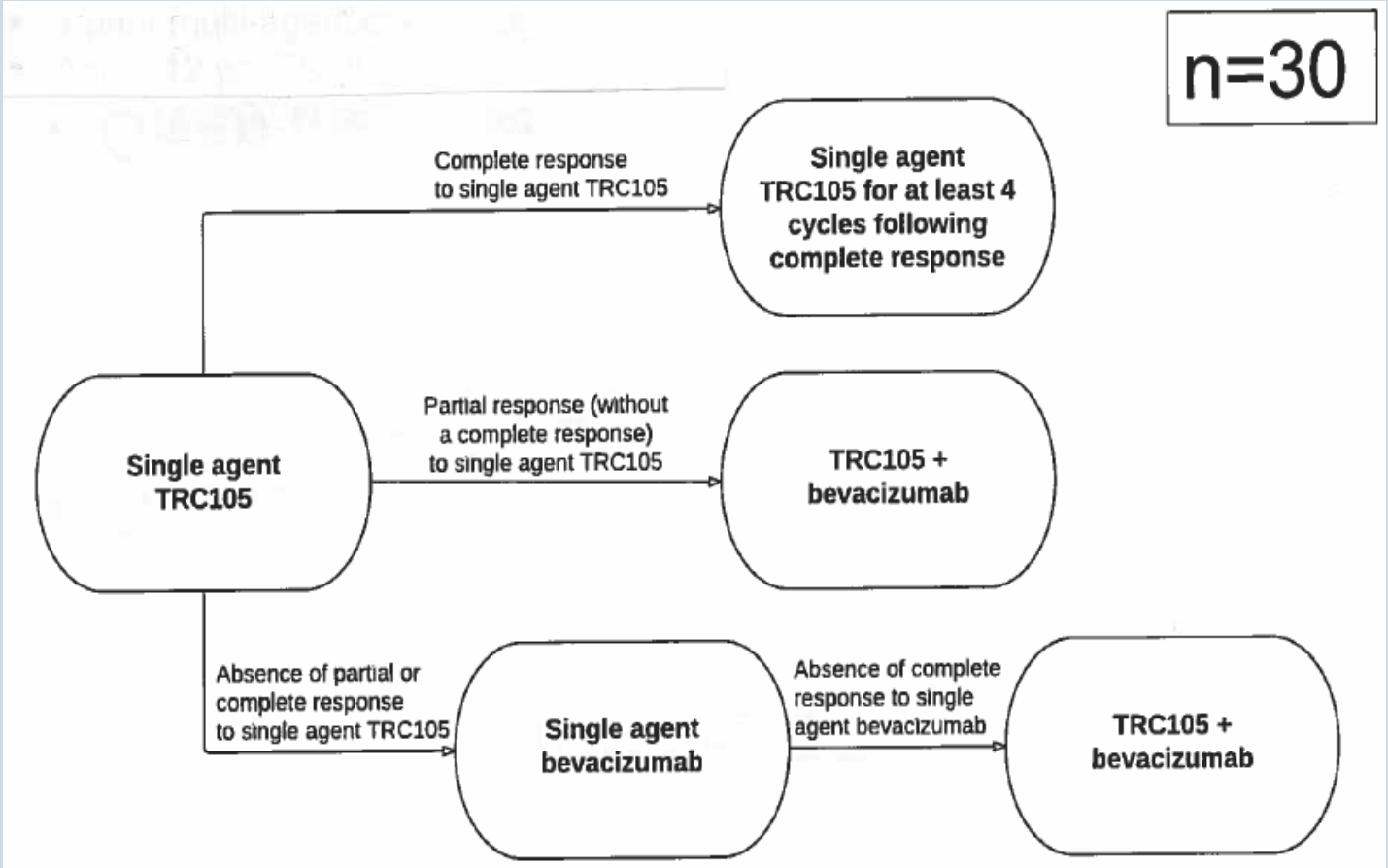
Proposed Phase II Trial

- Post-molar GTN, Choriocarcinoma, PSTT/ETT
- Elevated hCG or measurable disease for PSTT/ETT
- 1 prior multi-agent chemo therapy regimen
- Age > 12 yo, ECOG PS ≤ 1



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Proposed Phase II Trial

- Primary Endpoint:
  - To determine ORR of single-agent TRC105 and the combination of TRC105 and bevacizumab in patients with refractory GTN (choriocarcinoma, PSTT, ETT).
- Secondary Endpoints:
  - To determine PFS
  - To determine ORR of single-agent bevacizumab in patients with TRC105 refractory GTN
  - To evaluate the formation of TRC105 anti-product antibodies
  - To evaluate PK of TRC105 and bevacizumab
  - To determine the frequency and severity of adverse events as assessed by NCI CTCAE (Version 4.03)
  - To explore the effects of TRC105 and bevacizumab on circulating angiogenic protein biomarkers (Day 1, CR or change Rx, EOS)

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Participating ISSTD Member Institutions

- Brigham & Women's Hospital, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA
- Charing Cross Hospital, Imperial College, London, UK
- Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

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