Evaluation and Application of a Tumor Growth Dynamic – Overall Survival (TGD-OS) Model for Advanced Melanoma

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FDA-ISoP Workshop on Oncology Drug Development
Silver Spring, MD
1-Feb-2018

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Challenges in Oncology Dose Selection

- **Data on clinical benefit is generally limited prior to Ph3**
  - **Efficacy endpoints in Ph1/2 oncology studies is often different from the efficacy endpoint in Ph3 studies**
    - **Ph1/2 efficacy: typically ORR or PFS based on RECIST**
    - **Ph3 efficacy: typically overall survival (OS)**
  - **Assessment of ORR does not use all available data**
    - **usually requires a minimum duration of follow-up (eg 6 months)**
    - **tumor response data beyond specified follow-up is not utilized**
  - **Limited number of subjects**
- **The dose selection design space increases markedly for drugs being developed as combination therapy**

Need to utilize all available data as a means of reducing uncertainty in extrapolating Ph1/2 data to Ph3 by

ORR: overall response rate of complete or partial response
PFS: progression-free survival

Proposed Approach to Predict OS from Tumor Response Data

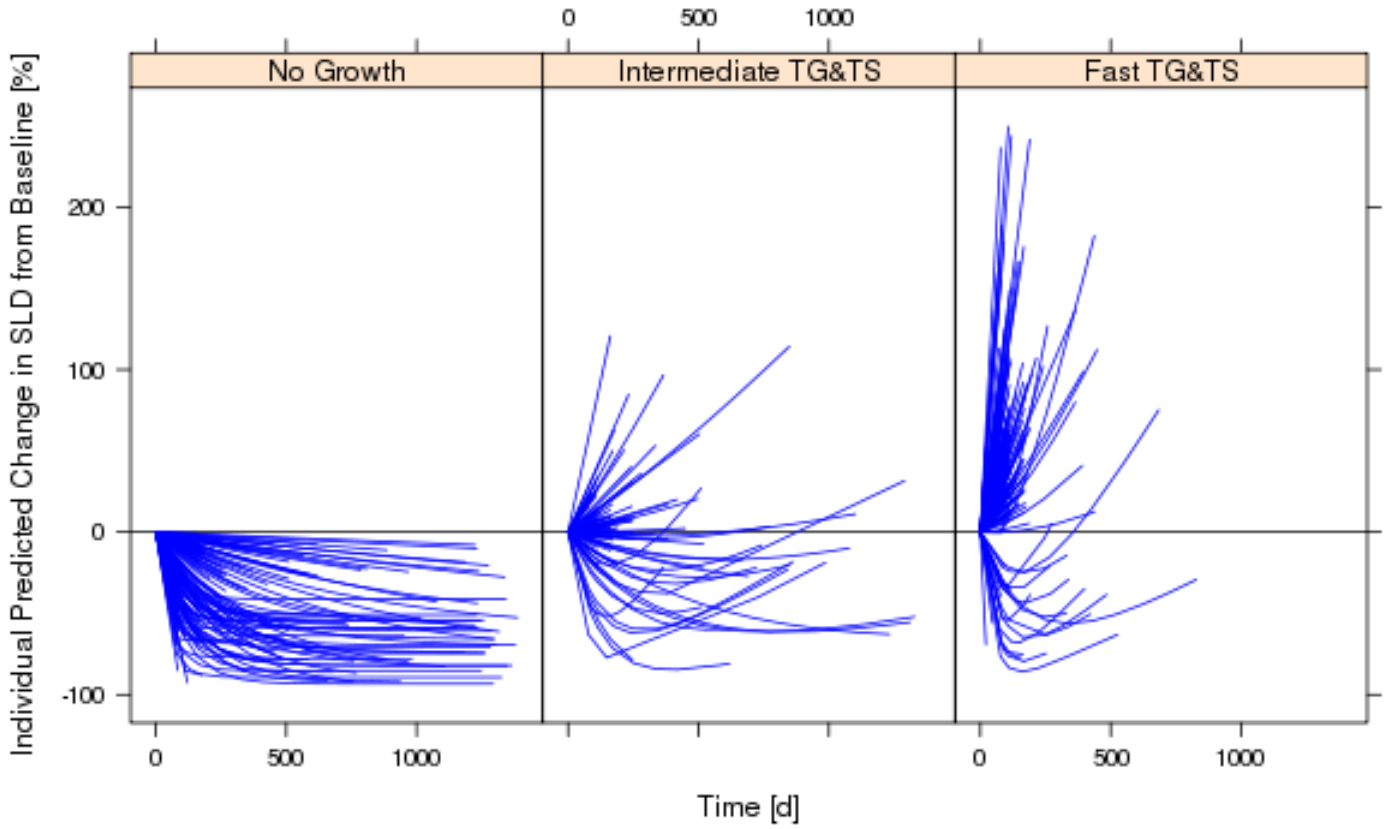
- **Characterize relationship between tumor growth dynamics (TGD) and OS for a given tumor type**
  - **Characterize TGD by an appropriate nonlinear mixed-effects model**
  - **Characterize OS by a time-to-event model incorporating:**
    - **known baseline prognostic factors**
    - **time dependent tumor burden related factors (growth rate and size) determined by the TGD model (including uncertainty)**
    - **Account for non-random drop out (baseline only tumor assessments), and time dependent appearance of new lesions**
- **Assume the TGD-OS model is agnostic to MoA**
- **Apply the TGD-OS model to predict OS for investigational drug, conditional on available Ph1/2 data for that drug**
- **Utilize the predicted OS to inform dose selection and go/no-go decisions**

Case Study: TGD-OS Model Developed with Nivolumab Applied to Predict OS with Ipilimumab

- **Ipilimumab is an anti-CTLA4 mAb, and was the first immune-checkpoint inhibitor (ICI) to demonstrate an improvement in OS**
  - MoA: Stimulates activation and proliferation of T-cells
  - Approved for advanced (stage III/IV unresectable metastatic) melanoma (3 mg/kg Q3W)
  - RECIST tumor response was higher with 10 mg/kg Q3W (Ph2 dose-ranging study)*
  - The benefit-risk of 3 vs 10 mg/kg Q3W (4 doses) was assessed in a Ph3 PMC study
- **Nivolumab is an anti-PD1 mAb ICI, which has shown an improvement in OS in advanced melanoma (as well as several other tumor types)**
  - MoA: Reactivates quiescent T-cells in the tumor microenvironment
  - Initial pivotal clinical studies were performed with 3 mg/kg Q2W
  - Dose was subsequently changed to 240 mg Q2W in several tumor types

* Wolchok et al, Lancet Oncology 2010

TGD Model Describing Tumor Response to I-O Therapy



Tumor Growth Dynamic (TGD) Model*

- Describes longitudinal target tumor burden
  TB (t) = TS (t) + TG (t)
  TS: exponential tumor shrinkage term
  TG: linear tumor growth term
- Mixture model incorporates sub-population with no growth and asymptotic tumor burden

Mixture model of TGD describes qualitatively different patterns of tumor response to I-O therapy

* Modification of TGD model proposed by Wang et al, CPT (2009)

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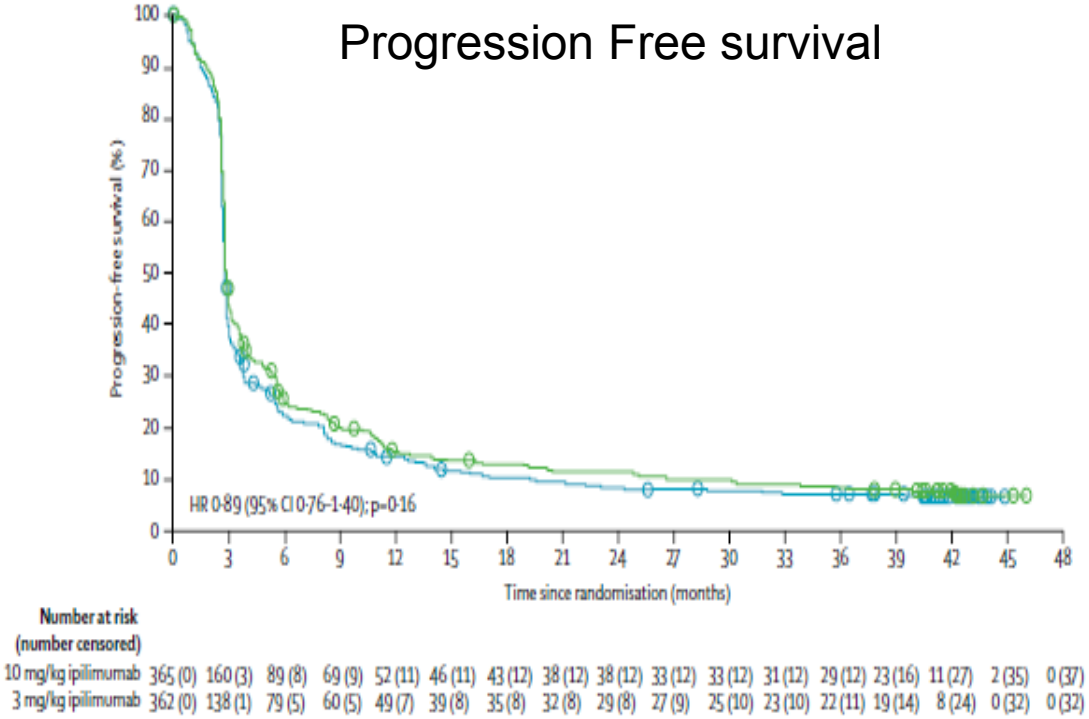
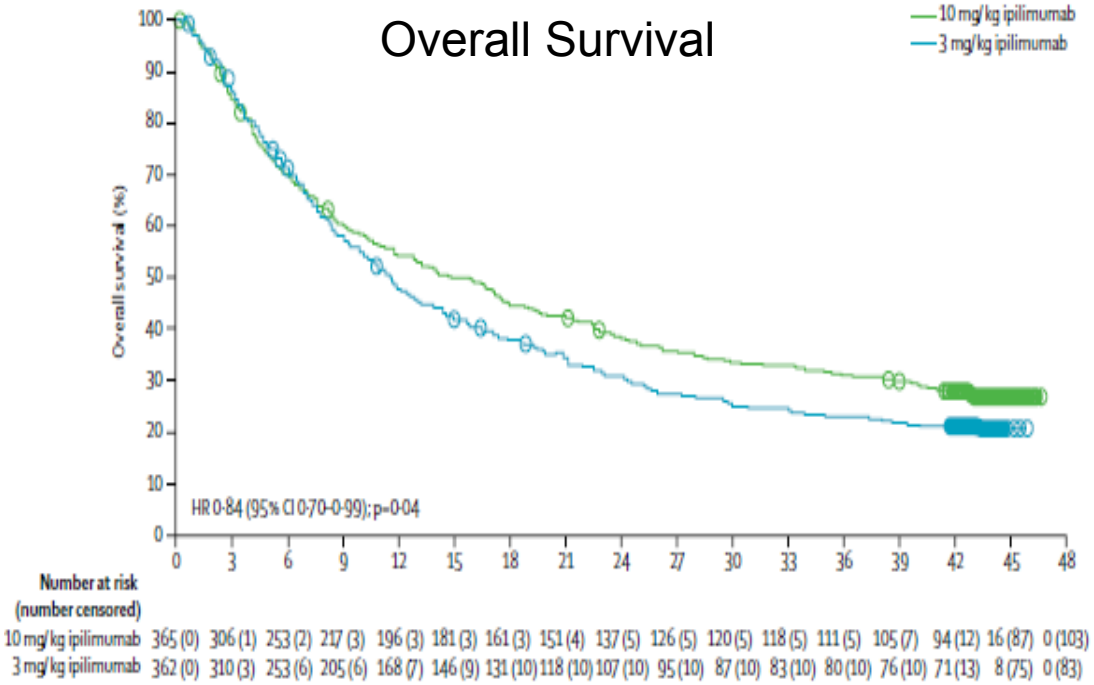
Key Results of CA184169: IPI 3 mg/kg vs 10 mg/kg

Progression Free survival



Overall Survival



- ***PFS was not significantly different, and ORR was similar (12% with 3 mg/kg, and 15% with 10 mg/kg)***
- ***OS was significantly better with 10 mg/kg relative to 3 mg/kg***
- ***Serious adverse events and treatment discontinuation were more frequent with 10 mg/kg***

Ascierto et al, Lancet Oncology (2017)

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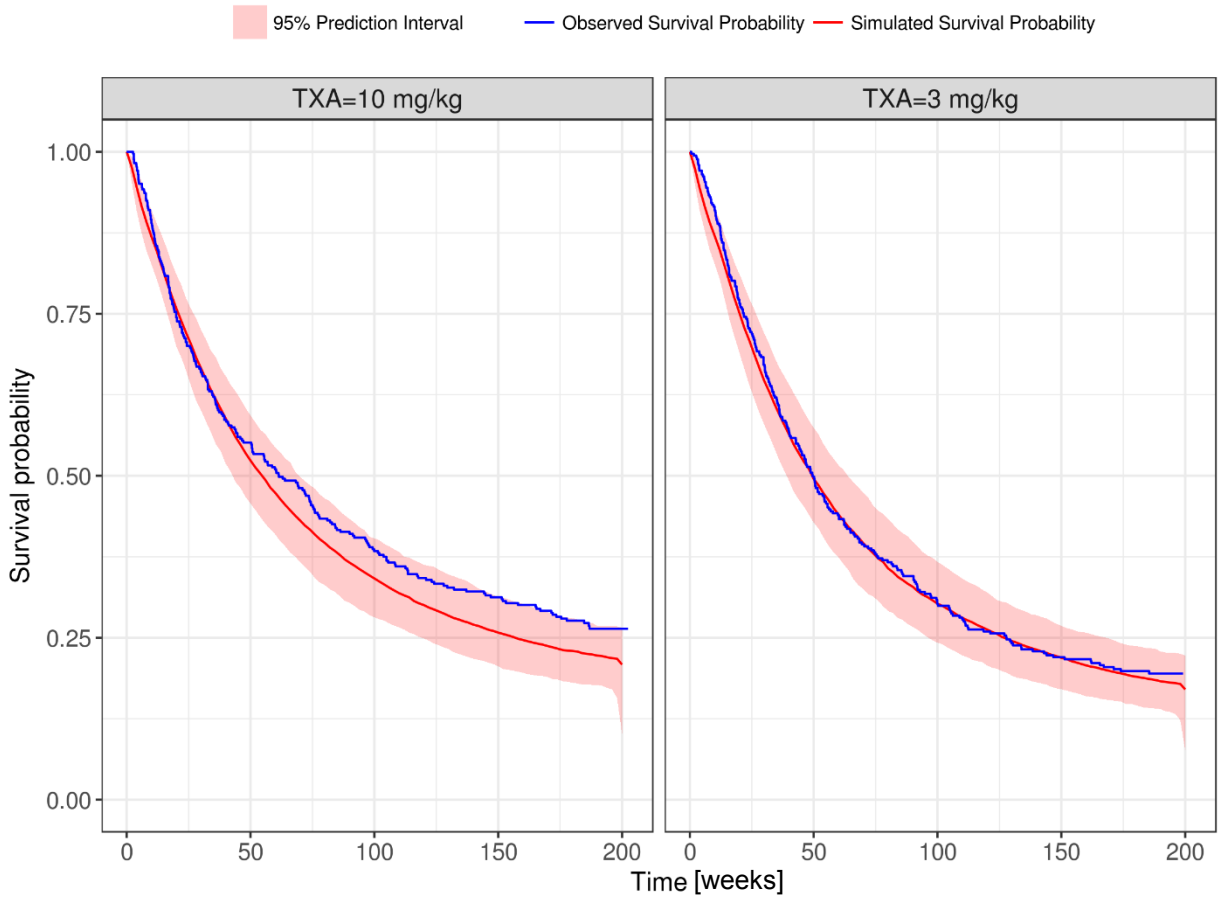
External Evaluation of TGD-OS Model for Advanced Melanoma



TGD-OS model developed with data from subjects treated with nivolumab describes OS of subjects treated with ipilimumab

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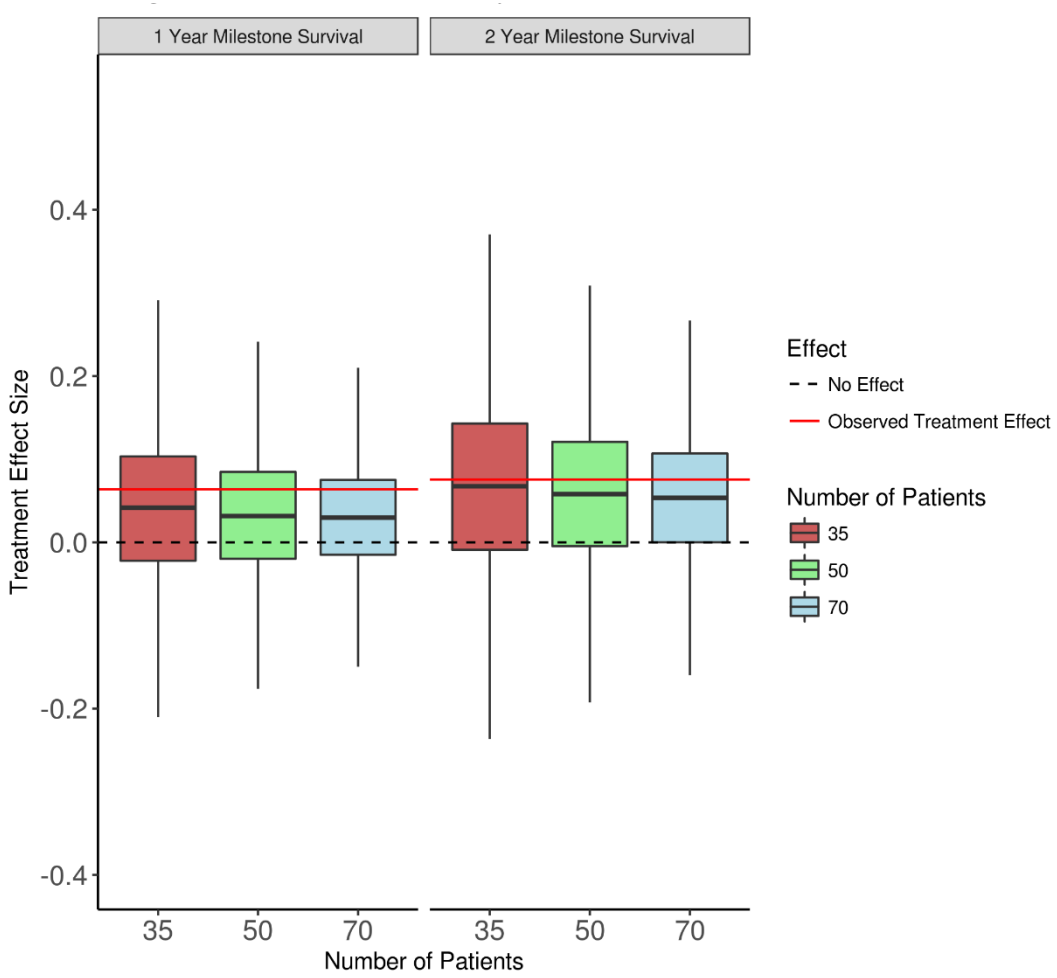
Probability of Predicting Improvement in OS
(with Smaller Sample size and Limited Follow-up)



- ***TGD-OS model predicts improvement in OS with 10 mg/kg relative to 3 mg/kg***
- ***Increasing sample size improves precision, but not power to detect an improvement***
- ***Extent of improvement is under-predicted by the current TGD-OS model***

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Summary

- A TGD-OS model for advanced melanoma developed with data from one drug (nivolumab) successfully predicted the OS with a different drug (ipilimumab)
  - Provides proof-of-principle that the TGD-OS model is agnostic to the drug inducing the tumor shrinkage
  - Longitudinal tumor-response may be sufficient to predict the effect of a drug on OS
- TGD-OS models could be applied to leverage all available Ph1/2 data from subjects with a given tumor type to inform sample size, dose, and go/no-go decisions for investigational agents
- Improvements in the TGD-OS model may further improve accuracy of the predictions of OS

Acknowledgements

- BMS: Dave Clawson, Yan Feng, Manish Gupta, Satyendra Suryawanshi
- Metrum: Jonathon French, Ramon Garcia, CJ Godfrey, and Curtis Johnston
- Patients and their families and caregivers

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