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

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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 (e.g., 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
Mixture model of TGD describes qualitatively different patterns of 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

* Modification of TGD model proposed by Wang et al, CPT (2009)
Key Results of CA184169: IPI 3 mg/kg vs 10 mg/kg

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

- **Ascierto PA, Vecchio M Del, Robert C, et al.** Ipilimumab 10 mg/kg versus ipilimumab 3 mg/kg in patients with unresectable or metastatic melanoma: a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol.* 2017;18:611-622
