WHY LOOK FOR ADDITIONAL DATA TO ENRICH THE KAPLAN-MEIER CURVES?

Immuno-oncology, only an example

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Disclosures

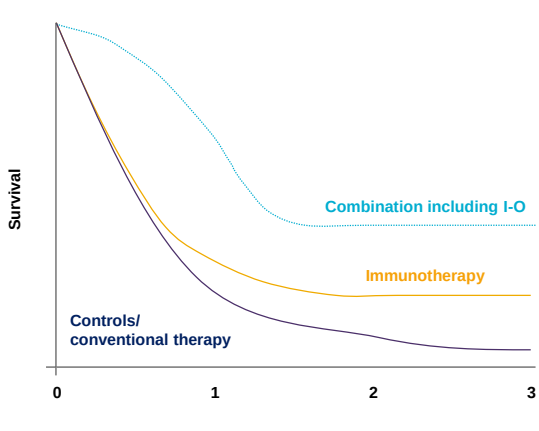
- Yiduo Zhang is an employee of AstraZeneca Pharmaceutical LP.
- The views and opinions expressed herein are his own and cannot and should not necessarily be construed to represent those of AstraZeneca or its affiliates.

Challenges in demonstrating the FULL value of oncology therapies, especially immuno-oncology (I-O)

Immature OS	• Curve flattening for I-O arm • High uncertainty in extrapolation of OS
Heterogeneity in treatment outcome	• OS outcomes differ by response status • OS and response differ by biomarkers (e.g., PD-L1, tumor mutations) • Multiple PD-L1 tests and test cut-offs
Response criteria may no longer fit-for-purpose	• RECIST may not capture main patterns of response • Traditional RECIST-based PFS to OS relationship may be different for I-Os
Subsequent I-O treatment confounds the long term outcomes	• RCTs outcomes, especially OS, might be confounded by subsequent I-Os • First-line studies showed high levels of subsequent use of I-O in control arms (> 50%)

I-O, immuno-oncology; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; QoL, quality of life; RCT, randomized controlled trial; RECIST, Response Evaluation Criteria In Solid Tumors

I-O has the potential to transform cancer treatment

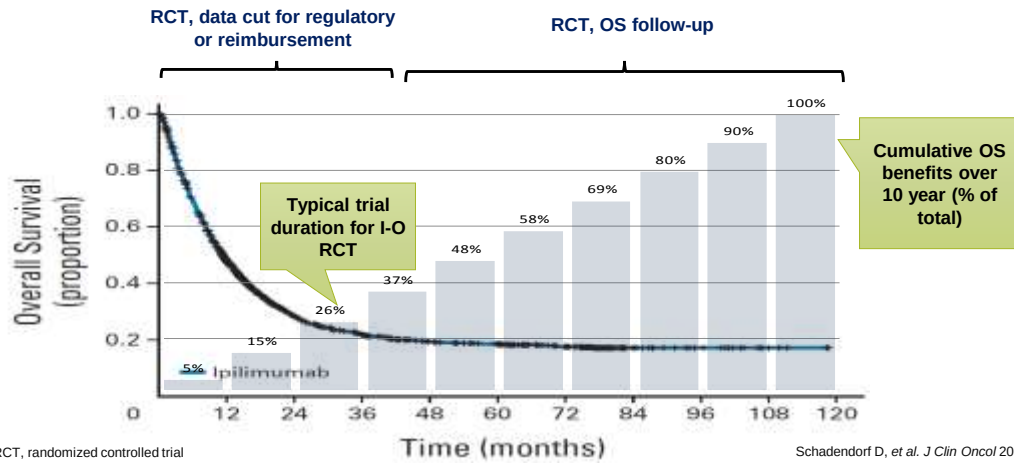


- In a subset of patients, immunotherapy strategies have the ability to induce highly durable tumor responses, resulting in a plateau in the tail of the survival curve
- Combination therapies, among I-O or with targeted therapies may unlock the full potential of immunotherapy, resulting in faster sustained responses and improved survival

Adapted from Ribas A, *et al. Clin Cancer* Res 2012;18:336–41

RCTs may only capture a small fraction of the total OS benefits, highlighting the importance of extrapolation for reimbursement decision-making

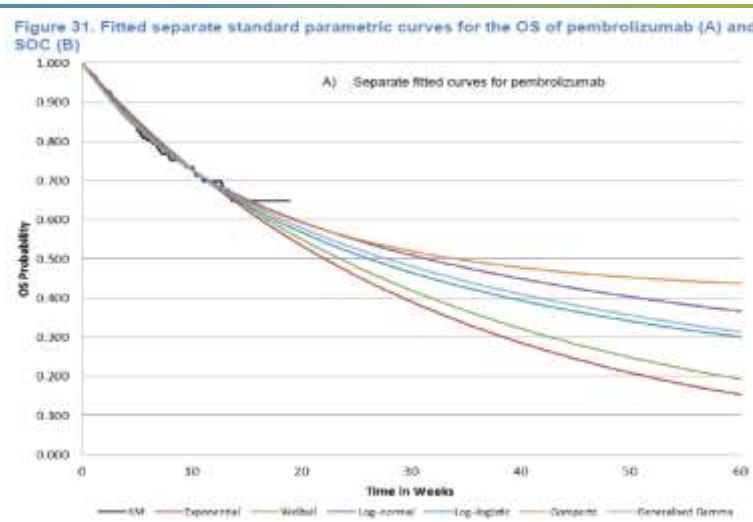
- Simulation based on ipilimumab in second-line metastatic melanoma



OS, overall survival; RCT, randomized controlled trial

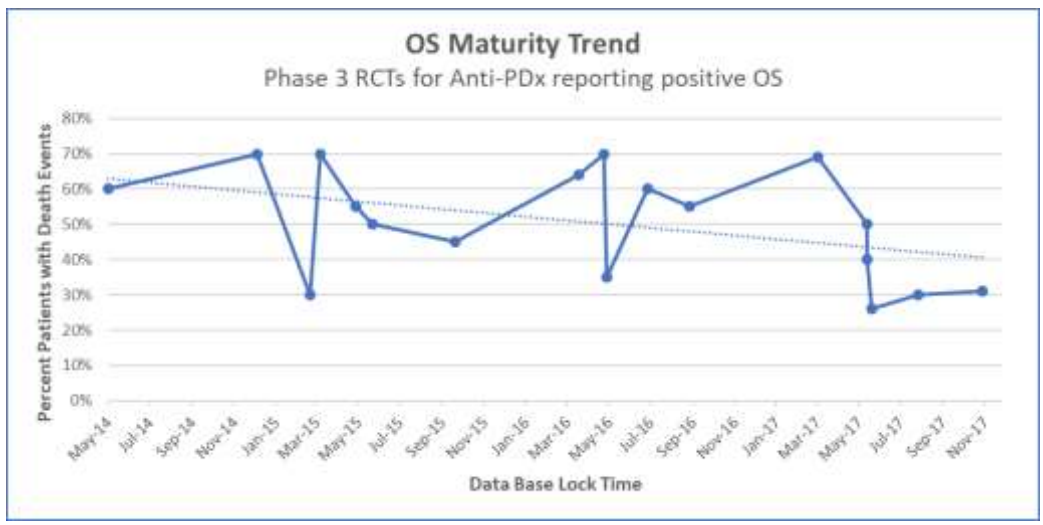
Schadendorf D, *et al. J Clin Oncol* 2015;33:1889–94

High levels of uncertainty arise when extrapolating immature OS data, which demands additional evidence to inform some reimbursement decision-making



Data presented in the Merck, Sharp & Dohme Health Technology Assessment submission for pembrolizumab in untreated PD-L1 positive metastatic non-small-cell lung cancer (ID990)
K-M, Kaplan-Meier; OS, overall survival; PD-L1, programmed death-ligand 1

Improved efficacy from I-O treatments often leads to reduced event rate, resulting in lower OS maturity and certainty for long term outcomes required by reimbursement decision-making

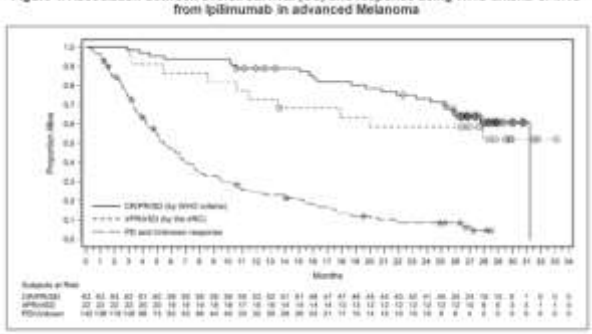


Anti-PDx, anti programmed-death therapy; I-O, immuno-oncology; OS, overall survival; RCT, randomized controlled trial

Why look for additional data to support interpretation to the KM curves?

Pronounced OS difference by response status creates challenge for modeling the patient population as a whole

Figure 4. Association between overall survival (OS) and response using WHO criteria or irRC from Ipilimumab in advanced Melanoma

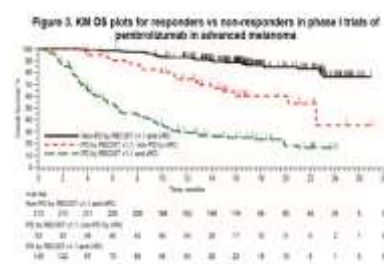


Source: Wolchok et al. 2009

NOTE: Based on phase II. trial of ipilimumab in advanced melanoma

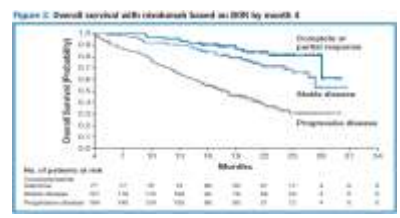
Implication

- Response groups need to be extrapolated individually to reflect potentially different underlying biological process



Source: Hodi et al. 2014

NOTE: Based on phase I trials of pembrolizumab in advanced melanoma



Motzer RJ. 2014

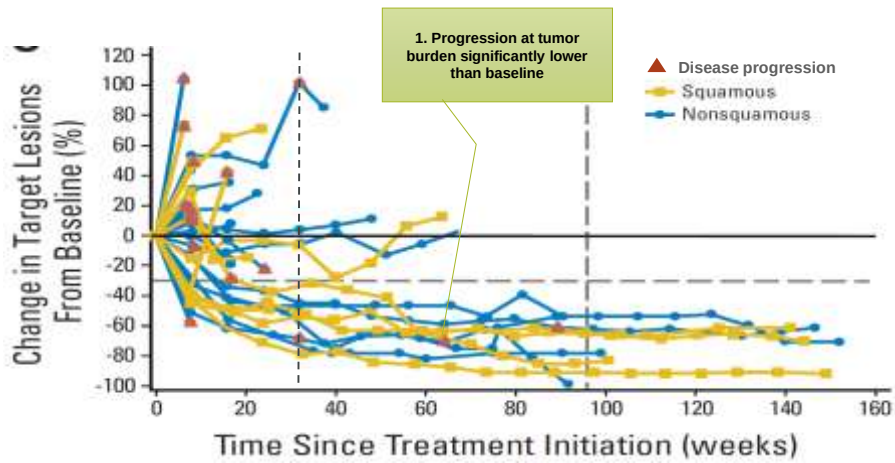
1. Wolchok JD, et al. Clin Cancer Res 2009;15:7412–20;
2. Motzer RJ, et al J Clin Oncol 2016;Abstract 4552;
3. Hodi FS, et al. J Immunother Cancer 2014;2(Suppl 3):P103

BOR, best overall response; CR, complete response; I-O, immuno-oncology; irRC, immune-related response criteria; K-M, Kaplan-Meier; OS, overall survival; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease; WHO, World Health Organization

Why look for additional data to support interpretation to the KM curves?

Patient who progressed, as defined by RECIST 1.1, may have lower tumor burden than baseline, this is commonly observed in I-O

Example: anti-PD1 therapy in previously treated NSCLC patients



Progression criteria according to RECIST 1.1

- Based on CT scan (not symptoms or quality of life)
- Target lesion increase by 20% compared to the lowest point (not the baseline)
- Any new lesions

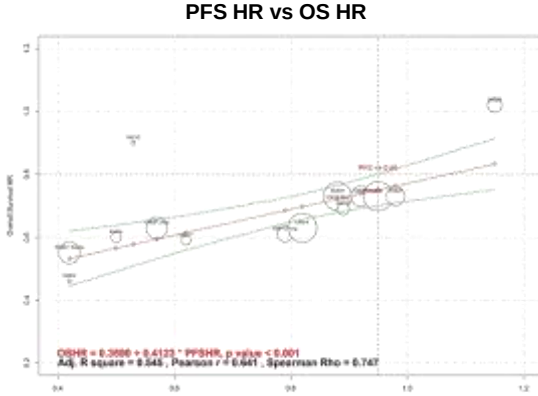
I-O, immuno-oncology; NSCLC, non-small-cell lung cancer; OS, overall survival; PD-1, programmed death-1; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors

Gettinger SN, *et al. J Clin Oncol* 2015;33:2004–12

Why look for additional data to support interpretation to the KM curves?

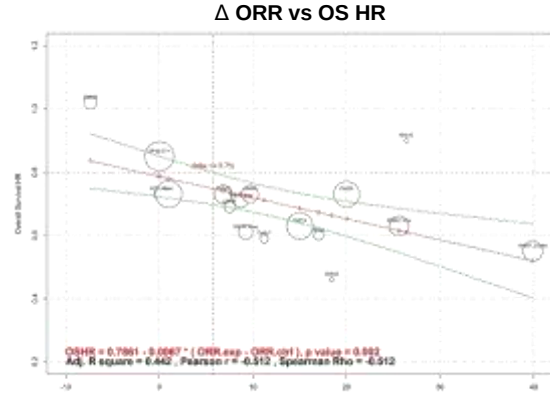
Due to the I-O tumor kinetics, it is possible to observe larger OS gain despite smaller PFS gain or relatively low response rate

PFS HR vs OS HR



Modest improvements in PFS may result in a large improvement in OS

Δ ORR vs OS HR

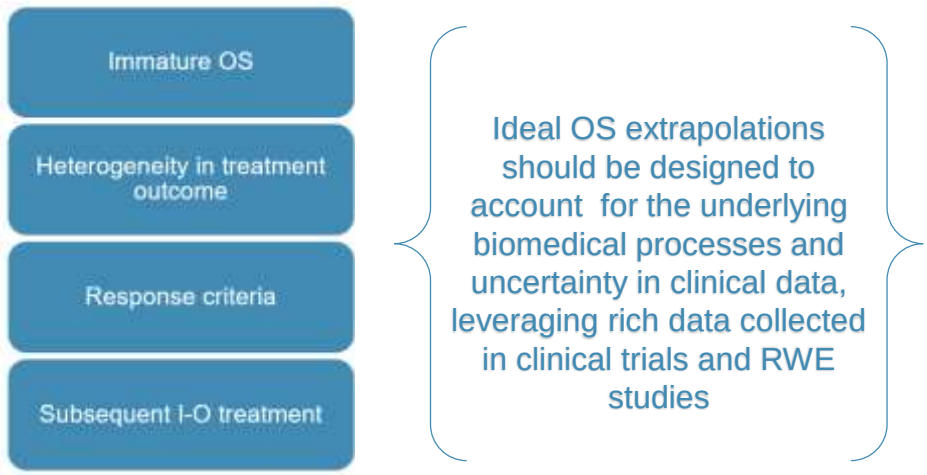


Modest improvements in ORR may result in a large improvement in OS

A PFS HR ≤ 0.9 or Δ ORR > 10% may be associated with an OS HR of ≤ 0.8

HR, hazard ratio; I-O, immuno-oncology; KN, Keynote; ORR, objective response rate; nivo, nivolumab; OS, overall survival; PFS, progression-free survival;

Implications: what good looks like?



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