Challenges of Modelling Immuno-Oncology

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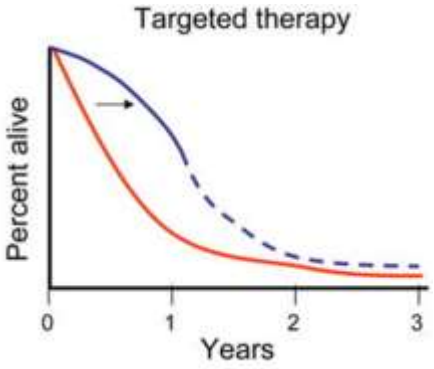
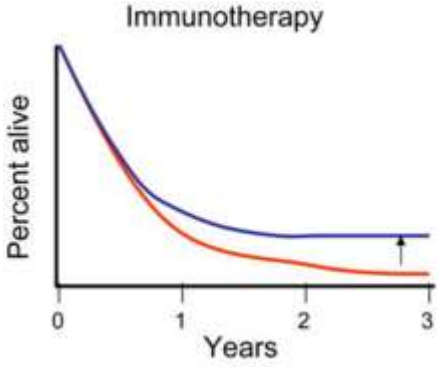
Survival With IOs vs. Targeted Therapies





Source: Ribas et al. 2012

Key Challenges of Modelling IOs

Challenges	Implications
Differences in biomarkers	Increases heterogeneity between trial / label populations
Long-term treatment benefits may be different	Questions around extrapolation of survival curves and long-term QoL
No gold standard for treatment duration	Major driver of cost-effectiveness and can influence model structure
Treatment sequences more complex	Increases heterogeneity between trials questioning feasibility of NMAs, influences model structure
Treatment switching pre and post progression	Increases the uncertainty of long-term extrapolation
Changes in surrogate outcome	**Determines model structure**

Multiple Biomarkers Depending on Tumor Type

- Biomarkers (e.g. EGFR, ALK, HER2, PD-L1) play a pivotal role in treatment selection and vary by tumor type
- Multiple PD-L1 diagnostic assays exist with different attributes
- Rapidly emerging new biomarkers e.g. tumor mutational burden


14 Jun 2018 ANALYSIS

Specialists Rethink Lung Cancer Treatment Plans, With Eye On IO Biomarkers

By Emily Hayes

Plenary speaker at this year's ASCO meeting, Leena Gandhi, envisioned a future where individual patients receive a precisely defined immunotherapy...

ASCO | ImmunoOncology | Research & Development


PINK SHEET

Tumor Mutation Burden Biomarker Inches Closer To Acceptance In Cancer

By Emily Hayes

Data from AACR puts use of tumor mutation burden as biomarker for lung cancer outcomes in spotlight, but some experts...

Clinical Trials | ImmunoOncology | Research & Development

Lack of Data on the Long-Term Benefit of IOs

- Survival
  - Delayed effect
  - Potential for plateau in survival curves
  - Long-term survivors (“cure”)
  - Potential sustained benefit beyond treatment discontinuation
- Quality of life impact
  - Uncertainty due to lack of historical data
  - Trials usually collect data until end of treatment or disease progression

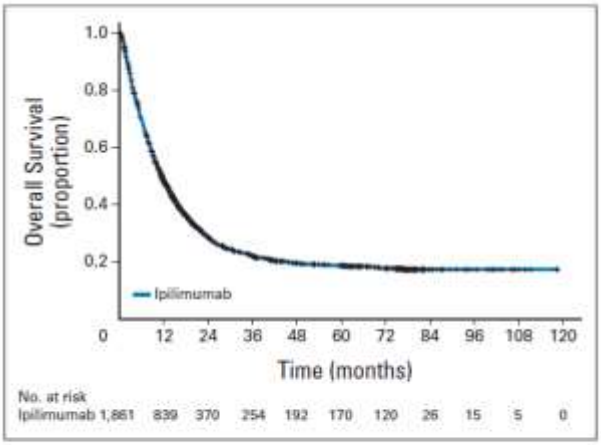


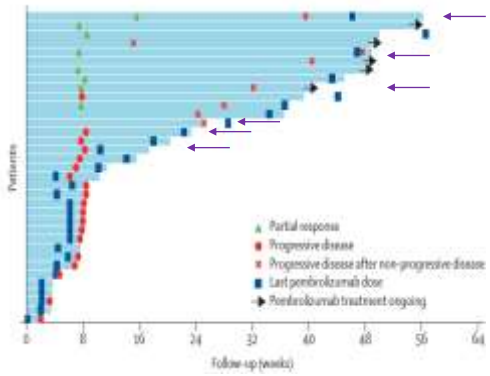
Fig 1. Primary analysis of pooled overall survival (OS) data. Individual patient data were pooled from 10 prospective trials and two retrospective, observational studies of ipilimumab in metastatic melanoma (n = 1,861). Median OS was 11.4 months (95% CI, 10.7 to 12.1 months) with a 3-year survival rate of 22% (95% CI, 20% to 24%). Crosses indicate censored patients.

Source: Schadendorf et al. 2015

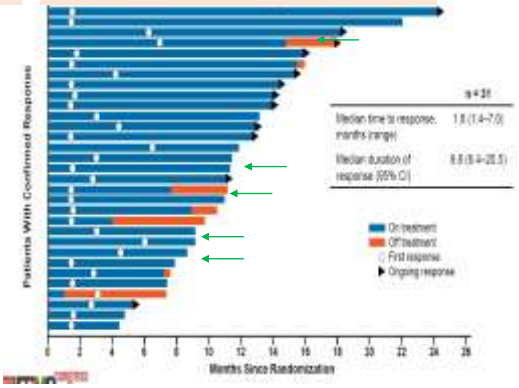
Treatment Duration

- Patients may get treatment beyond progression (purple arrows)
- Patients may experience sustained benefit beyond treatment discontinuation (green arrows)
- Stopping rules may be considered for patients with long-term benefit

Muro 2016 – Pembrolizumab

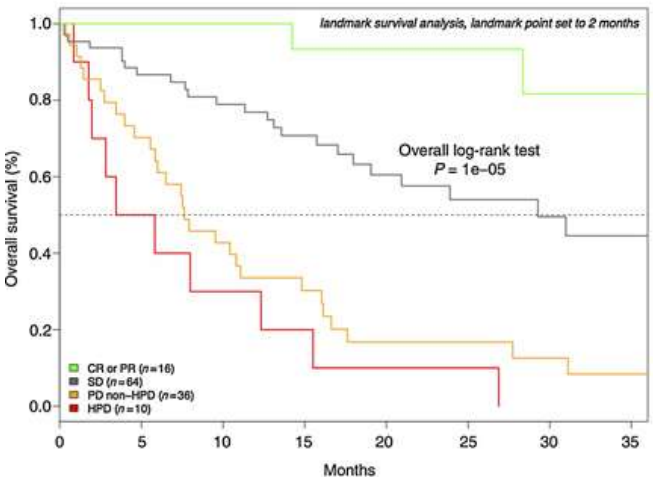


Boku 2017 – Nivolumab



Hyperprogression

- A novel aggressive pattern of hyperprogression in a fraction of patients treated with anti–PD-1/PD-L1[1]
- Incidence varies with age, therapeutic area and biomarker status (e.g. EGFR, MDM2)[2]
- There is no standardized definition available, but usually based on tumor growth rate[1,3]

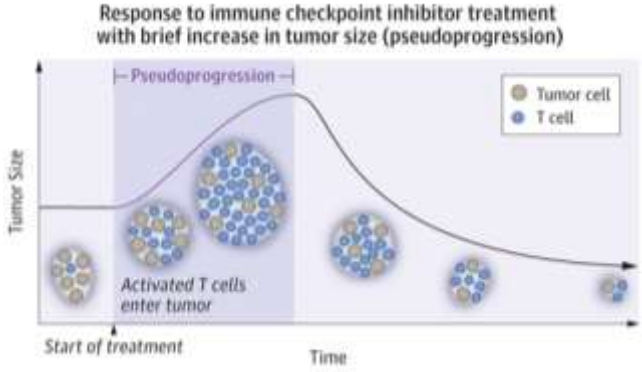


Medical records from all patients (N = 218) prospectively treated in Gustave Roussy by anti–PD-1/PD-L1 within phase I clinical trials
Source: Champiat at. 2017

References: 1 Champiat et al. 2017; 2 Kato et al. 2017; 2 Saada-Bouzid et al. 2017

Pseudoprogression

- Due to the immunotherapy mechanism of action, pseudoprogression can be observed
- Defined as tumor growth when the tumor inflates due to its own necrosis
- RECIST assessment of PFS can confuse pseudoprogression with true tumor progression
- To account for pseudoprogression, treatment beyond disease progression was authorized



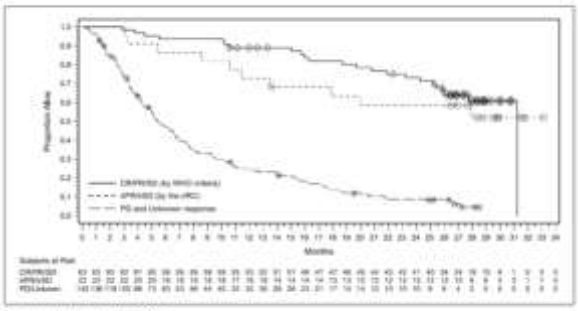
Source: West 2015

Durable Response Prolongs Survival

Example in advanced melanoma

Example in advanced renal cell carcinoma

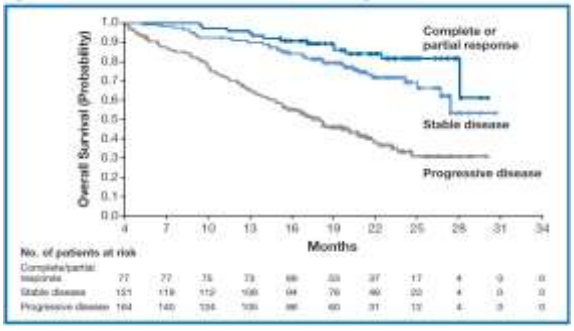
Figure 4. Association between overall survival (OS) and response using WHO criteria or irRC from Ipilimumab in advanced Melanoma



Source: Wolchok et al. 2009

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

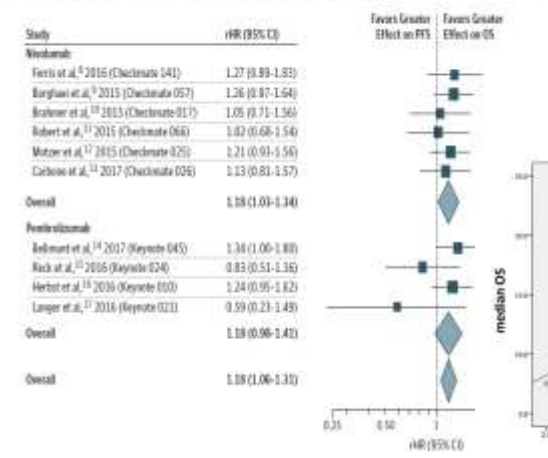
Figure 2. Overall survival with nivolumab based on BOR by month 4



Source: Motzer RJ. et al. 2016

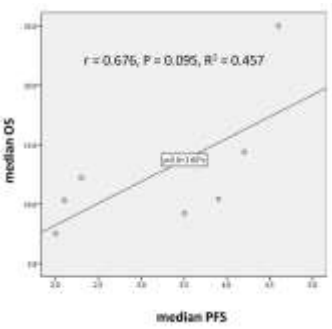
PFS as Surrogate Outcome for OS?

Figure. Pooling of Ratio of Hazard Ratios (HR) of Progression-Free Survival (PFS) and Overall Survival (OS) Among the Randomized Clinical Trials of Programmed Cell Death 1 (PD-1) Inhibitors

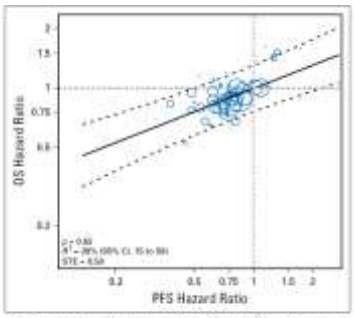


Takeaway:

- No significant correlation between median OS, PFS, and gains in medians
- 10 RCTs showed 18% greater improvement in OS than PFS
- PFS cannot adequately capture the benefit of PD-1 inhibitors in patients with solid tumors



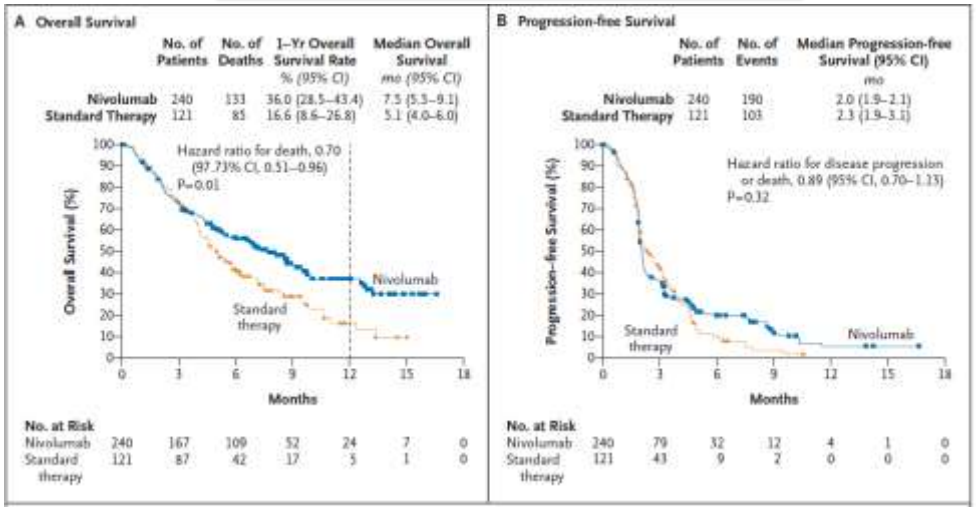
Source: Gyawali et al. 2018



Source: Tan et al. 2017

PFS as Surrogate Outcome for OS?

Example in recurrent squamous-cell carcinoma of the head and neck



Source: Ferris et al. 2016

Early Response to IO Agents May Be Predictive of Improved OS

Figure 1. Kaplan-Meier curve for OS by OR (PR or CR vs no PR/CR) at the Week 7 landmark

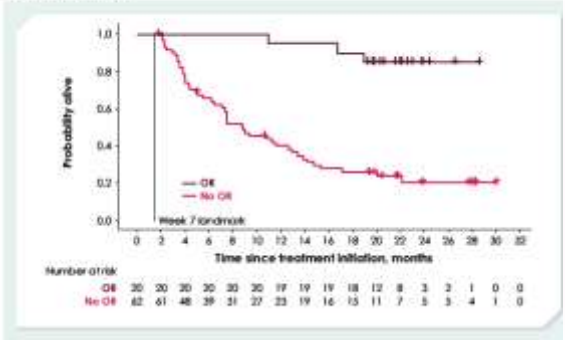
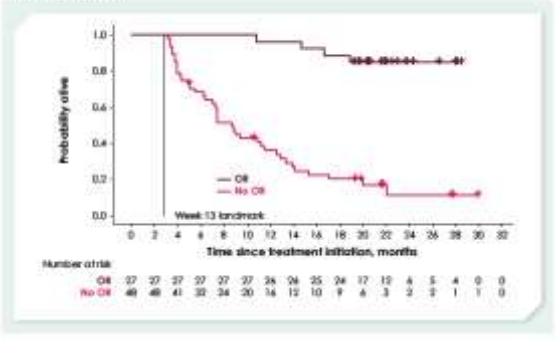


Figure 2. Kaplan-Meier curve for OS by OR (PR or CR vs no PR/CR) at the Week 13 landmark



Responses to immune-targeted agents follow unconventional pattern and appear to be early indications of long-term survival outcomes

Source: D'Angelo et al, 2018; Anagnostous et al, 2017

Increasing Level of Treatment Switch in IO Trials

- Treatment switch pre and post progression increases the uncertainty of extrapolating long-term overall survival
- Implies that sequential modelling by explicitly tracking treatment sequences may be necessary to reconcile treatment pattern in trials and to reflect clinical practice

Percentage of patients who switched treatment in IO trials

Investigational Drug	Clinical Study	Comparator Arm	Investigational Arm
Nivolumab	CheckMate 017	2%	-
Nivolumab	CheckMate 057	2%	-
Pembrolizumab	KEYNOTE-010	13%	1%
Atezolizumab	POPLAR	5%	-
Atezolizumab	OAK	17%	4%
Avelumab	JAVELIN 200	26%	4%