Ovarian Cancer and Modern Immunotherapy: Regulatory Strategies for Drug Development

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Ovarian Cancer Endpoints Workshop

FDA White Oak

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Overview

- Immune agents from a regulatory perspective:
- Efficacy
  - Patterns of response, determining “clinical benefit,” and endpoints
- Regulatory considerations for trial design
- Biomarkers in immunotherapy trials

The Challenge

Challenge assumptions:

The primacy of the drug development paradigm derived from early experience with cytotoxic chemotherapy:

- MTD, PFS, RECIST, toxicity attribution

Preclinical development: direct toxicity and efficacy studies impossible in cells and non-human species

No longer direct molecular action of drug on tumor cell

Interleukin-2

- Described in 1976
- Approved in 1992 (RCC) and 1998 (melanoma)

Disease	Year	ORR	CR	DOR (PR)	DOR (CR)
RCC	1992	15%	7%	20m	NR
Melanoma	1998	16%	6%	6m	NR

  - Melanoma based on 8 trials all analyzed as single-arm
- No mechanism elucidated
- No predictive or prognostic biomarkers
- Toxicities—cytokine-mediated (different from checkpoint inhibitors): Capillary leak. Cardiac conduction. Neurotoxicity. Rash.

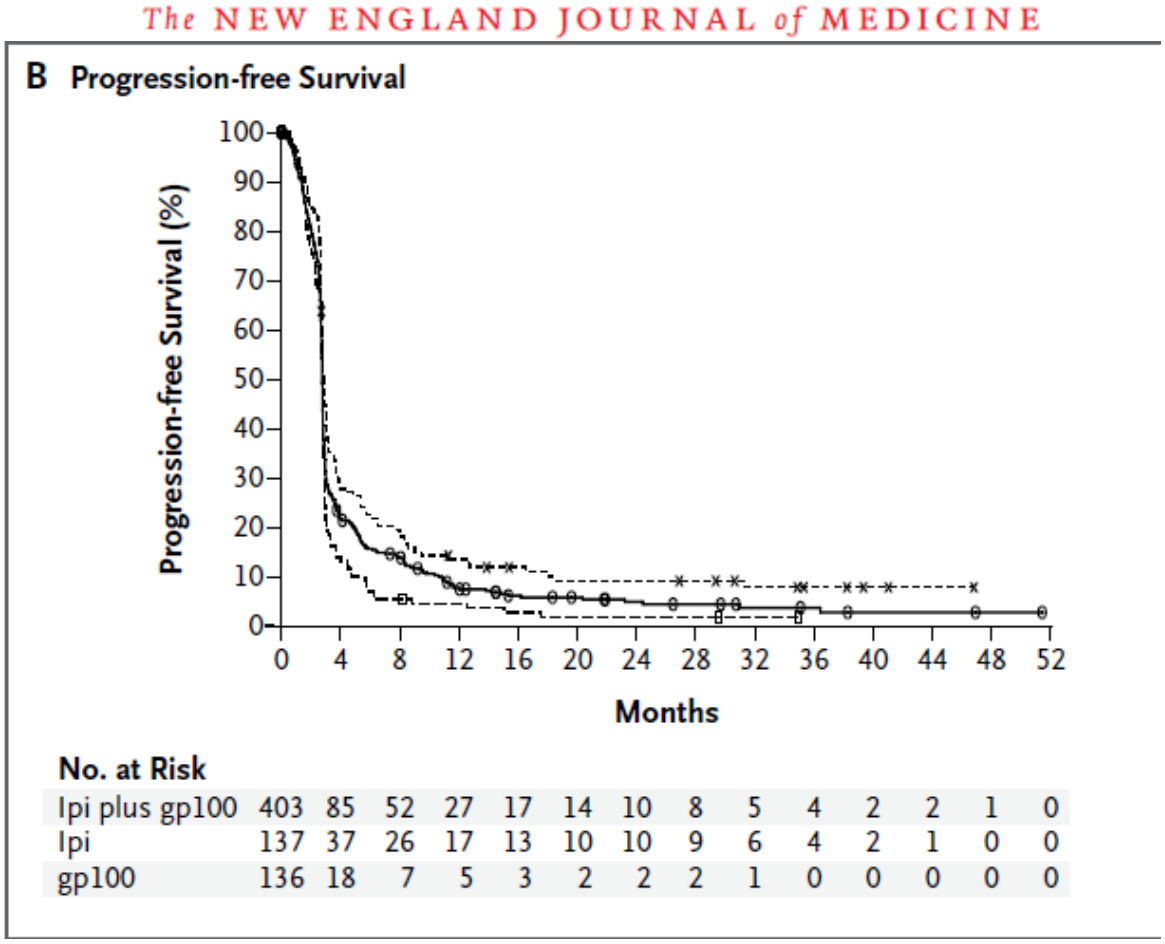
Regulatory Considerations: Efficacy

- Traditional approval relies on overall survival as the gold standard
- Frequently, PFS has been used as a surrogate
- But, in the context of immunotherapy:

  We would not have recognized the benefit of these agents if relying on RR, PFS

Road to Approval: Ipilimumab Limitations of PFS

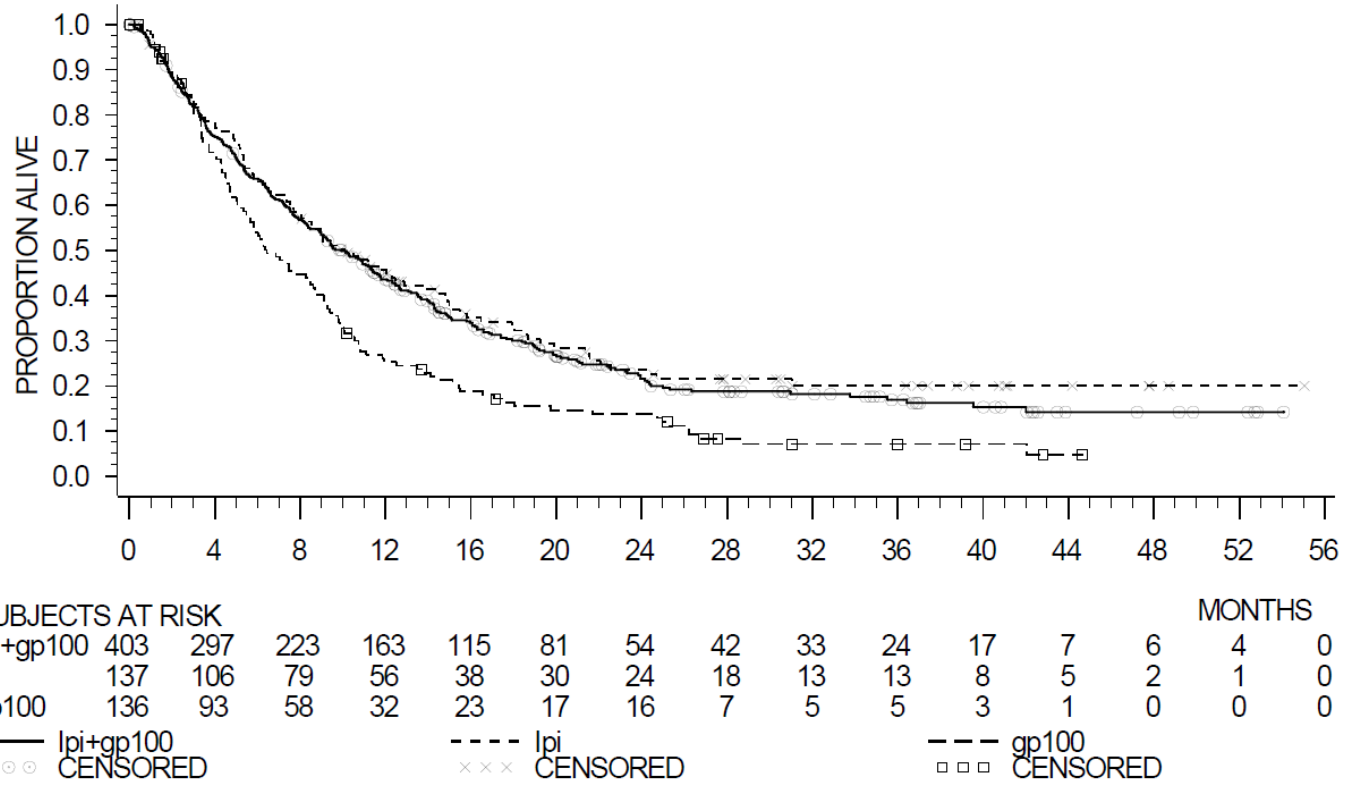
- Approved 2011
- Toxicity spectrum new and challenging
- Toxicity management required new awareness



Hodi, F. S. *et al.* Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. *New England Journal of Medicine* **363,** 711–723 (2010).

Road to Approval: Ipilimumab PFS and ORR Inadequate

Figure 1: Overall Survival

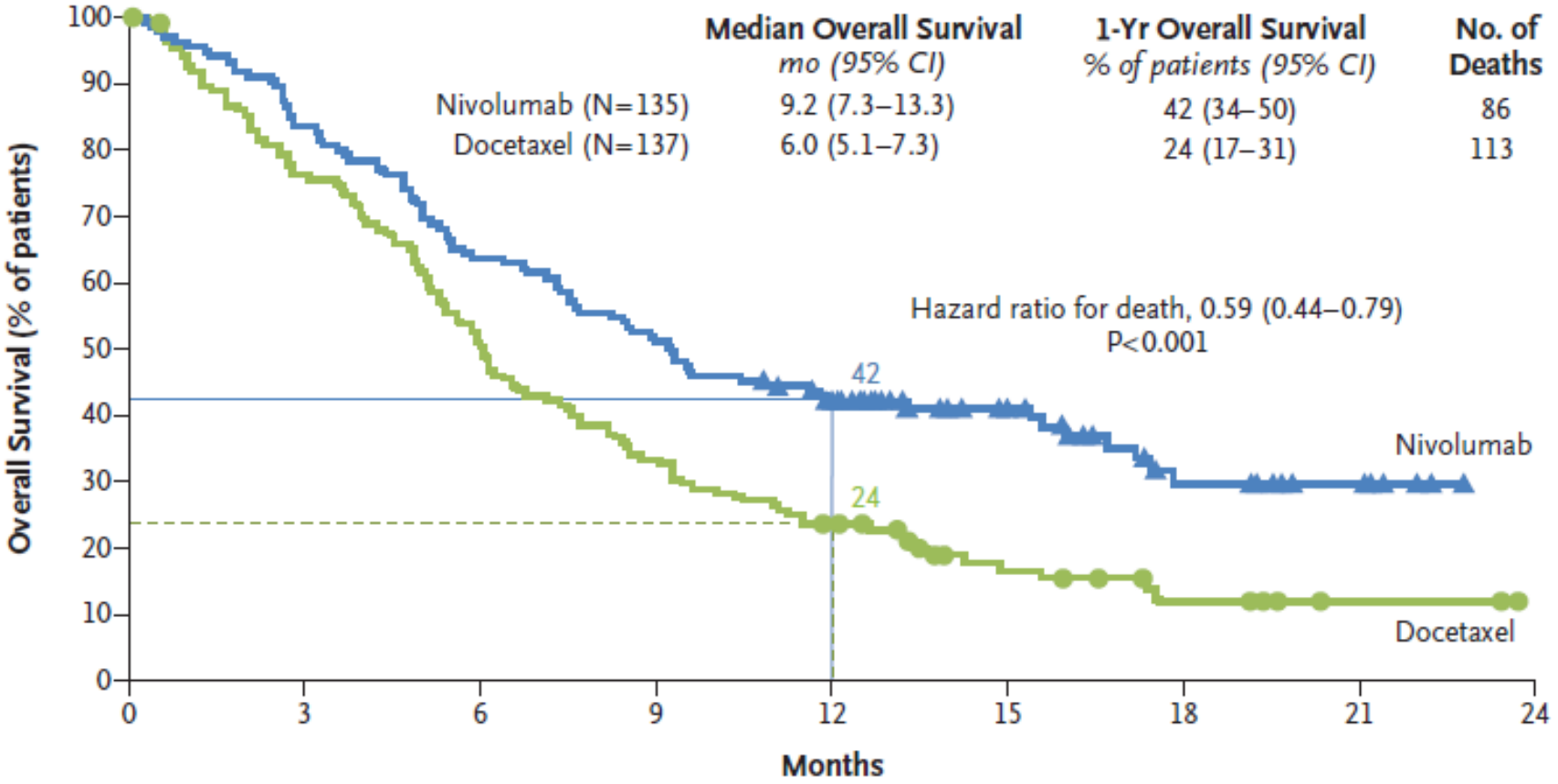


Nivolumab in Squamous NSCLC

- Nivolumab in squamous NSCLC
  - First demonstration of immunotherapy in non-RCC non-melanoma
- 272 patients treated at 3mg/kg q2w vs docetaxel 75mg/m^2 q3w
- PFS: 3.5m v. 2.8m→
- **0.7m** PFS advantage for treatment arm

Nivolumab experience

- OS: 9.2m v. 6.0m
- 1 year survival: 42% v. 24%



Brahmer, J. *et al.* Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer. *NEJM* **373,** 123–135 (2015).

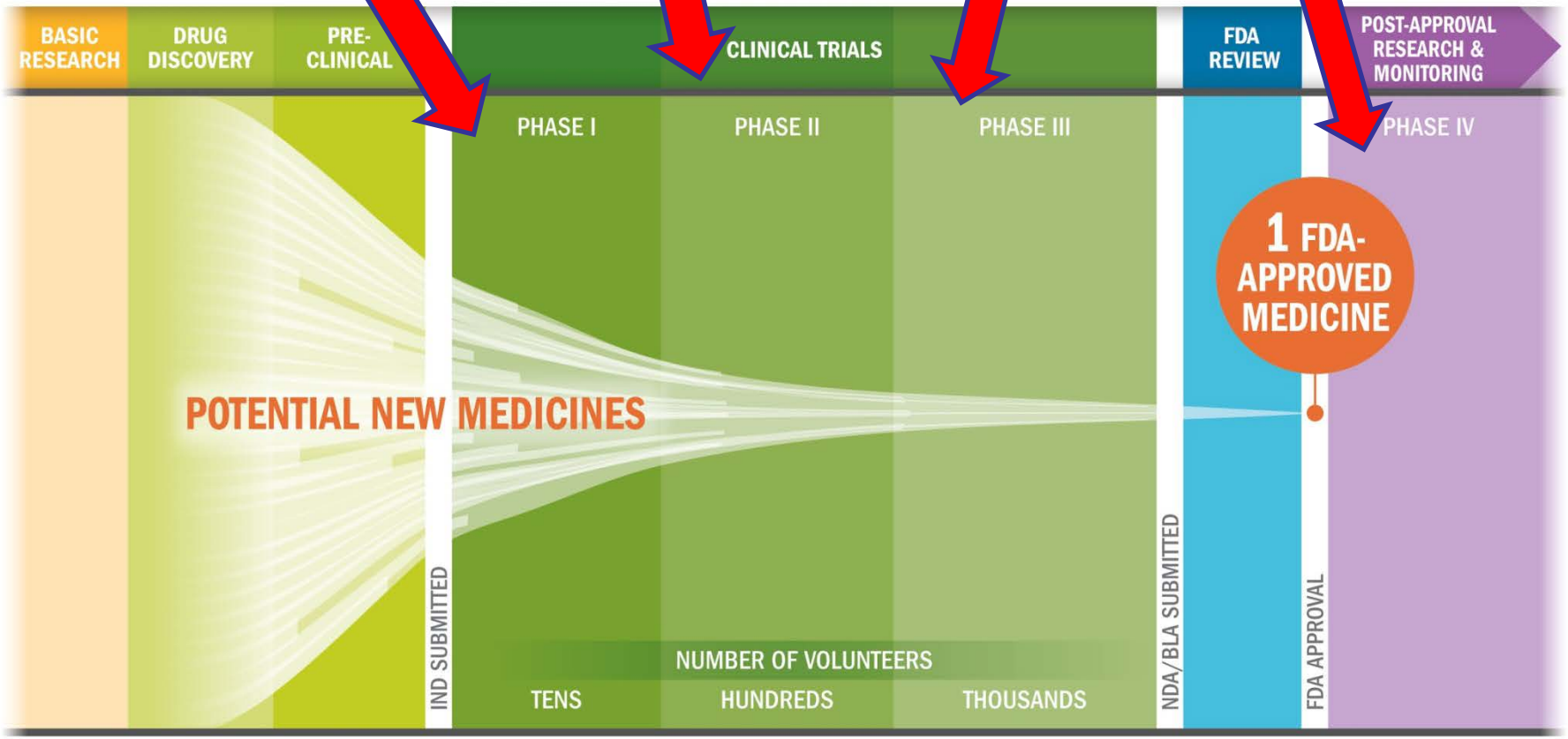
Clinical Regulatory Pathway: Then

Safe dose

Preliminary effectiveness

Pivotal RCT

Post-marketing safety



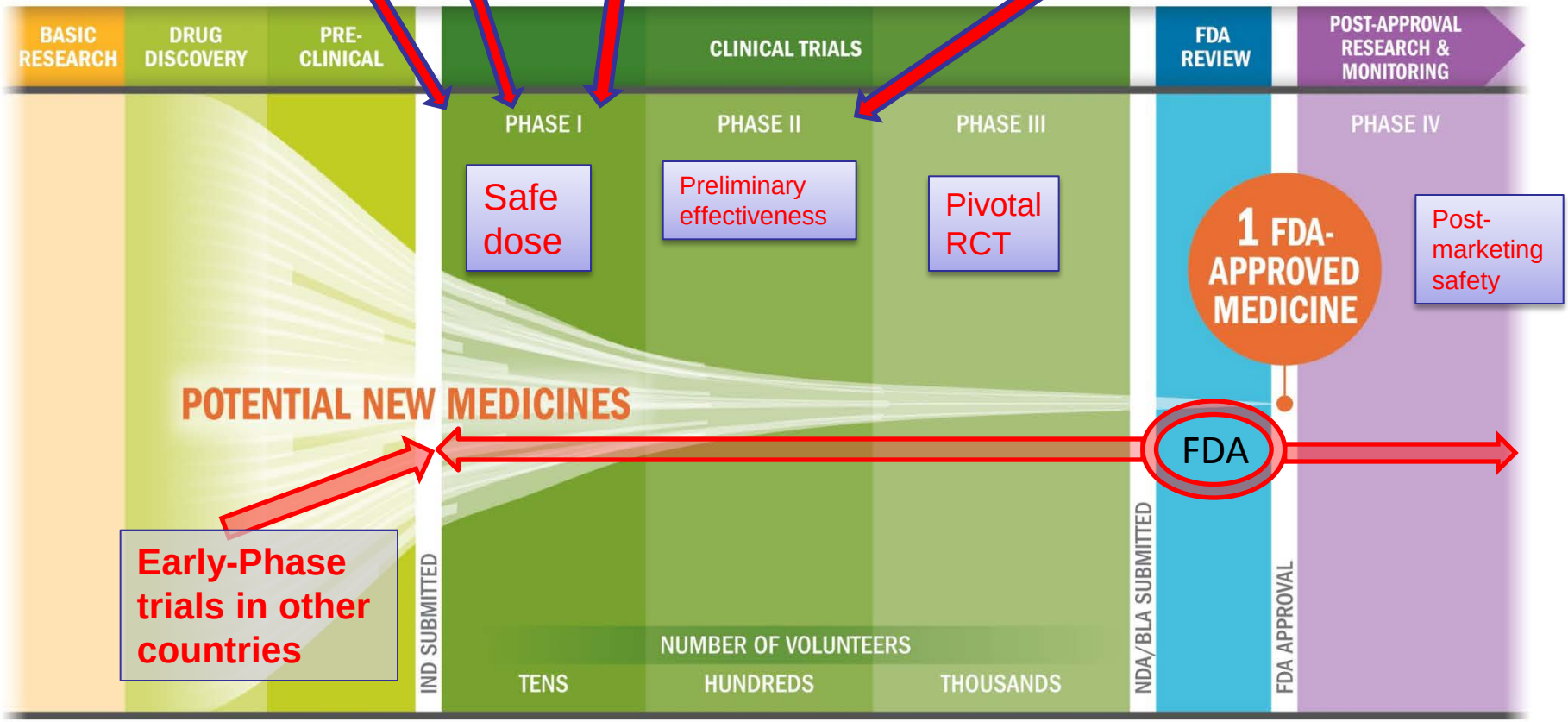
Clinical Regulatory Pathway: Now Options for Rapid Translation

Phase 0: PD evaluation; Biomarkers of target engagement

Phase 1a: Safe dose

Phase 1b: "Dose expansion": Looking for activity in specific population; may be biomarker-selected

Phase 2: Randomized: Accelerated approval

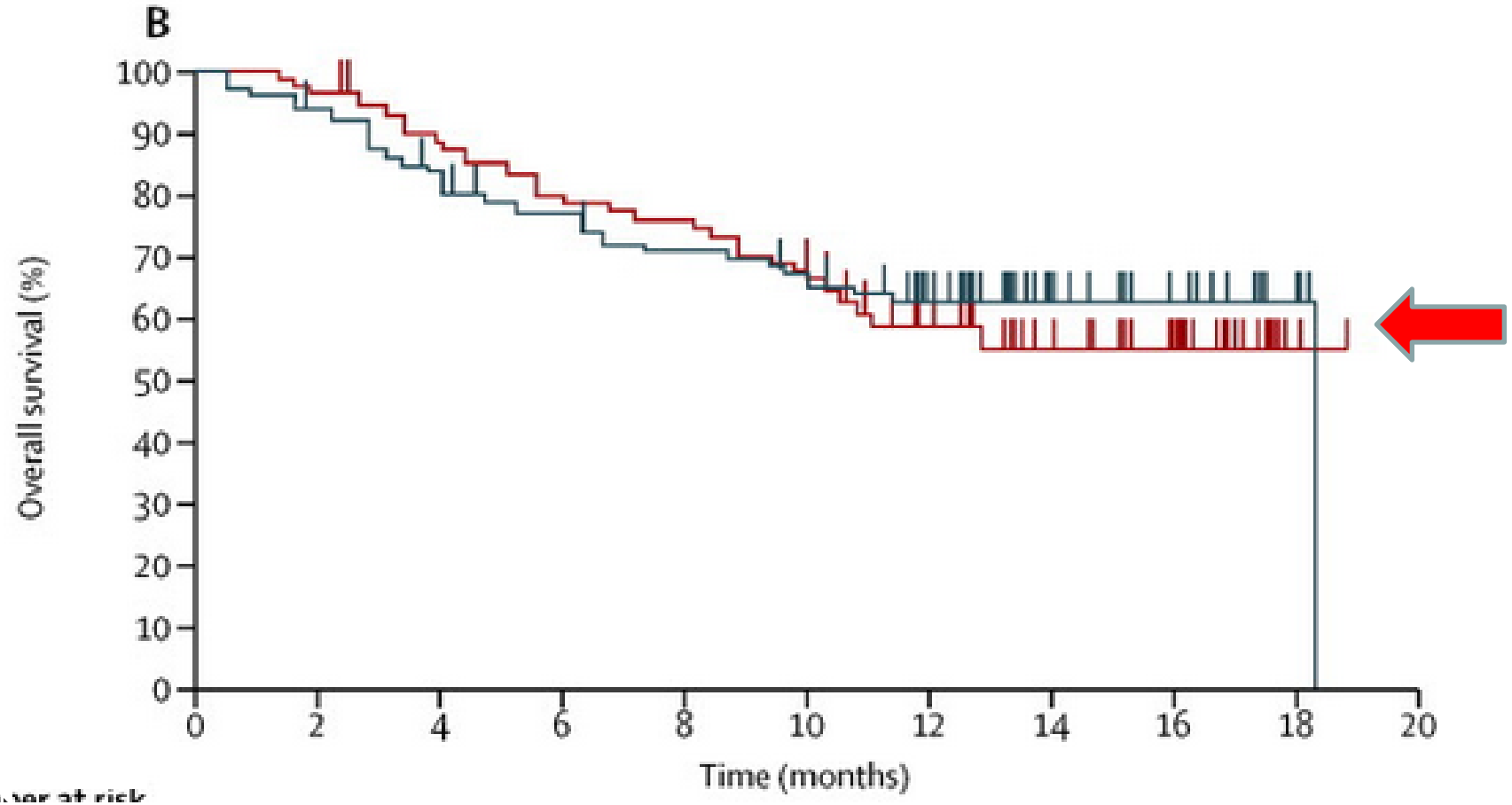


Road to Approval: Pembrolizumab in Melanoma

- Pembrolizumab
  - Accelerated approval: based on a surrogate that requires confirmatory studies
  - **Expansion cohort** within Trial P001
    - 173 patients, post ipilimumab and BRAF inhibitor if V600 mutation, treated with pembro at 2 or 10 mg/kg
    - Several other disease-specific cohorts reported
  - ORR based on RECIST (24% in 2mg arm) with 1 CR and 20 PR, with 18 ongoing responses at data lock

Robert, C. *et al.* Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. *The Lancet* **384,** 1109–1117 (2014).

Road to Approval: Pembrolizumab in Melanoma



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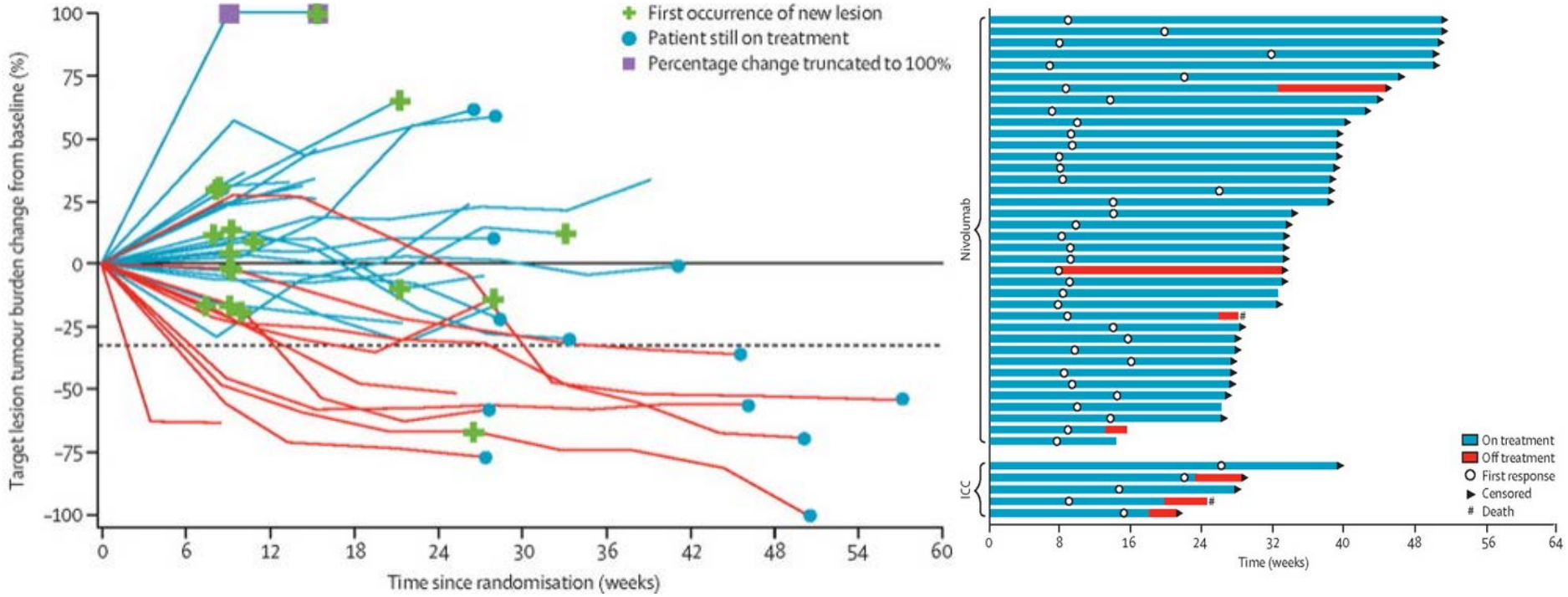
Road to Approval: Nivolumab in Melanoma

- Accelerated approval based on ORR
- Phase 3, ipilimumab-refractory, randomized (2:1), open-label; 631 patients screened
  - Nivolumab
  - Dacarbazine
  - Carboplatin + paclitaxel

- Planned per-protocol **interim analysis as a single arm** after 120 patients were treated with nivolumab for a minimum of 24 weeks.

Weber, J. S. *et al.* Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. *The Lancet Oncology* **16,** 375–384 (2015).

Nivolumab in Melanoma



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Regulatory Considerations: Efficacy

- Regulatory pathways for accelerated approval
- PFS may not be an adequate measure of clinical benefit for these agents
  - irRC changes ORR, but inconsistently (Chiou 2015)
  - irRC is of limited value
- Prolonged DOR has been a hallmark of effective immunotherapy
- Better efficacy endpoints needed:
  - eg, tumor kinetics

Chiou, V. L. & Burotto, M. Pseudoprogression and Immune-Related Response in Solid Tumors. *JCO* JCO.2015.61.6870 (2015). doi:10.1200/JCO.2015.61.6870

Regulatory considerations: AEs

- Standardized approach to tox management
  - Greater community experience→easier trials
  - Early recognition and prompt management
    - Immunosuppression doesn't seem to blunt response
  - Familiarity→**fewer investigations**

- Case definitions for adverse events
  - *Immune-mediated* adverse events vs other
  - Consistency: attribution vs immunosuppression
  - Fewer investigations→greater variability in AE reporting

Biomarkers

- Checkpoint proteins
  - Current IHC strategies are predictive/selective biomarkers in specific diseases, while non-predictive in others

- CDRH rules for companion diagnostics

Anti-PD-L1 in UBC

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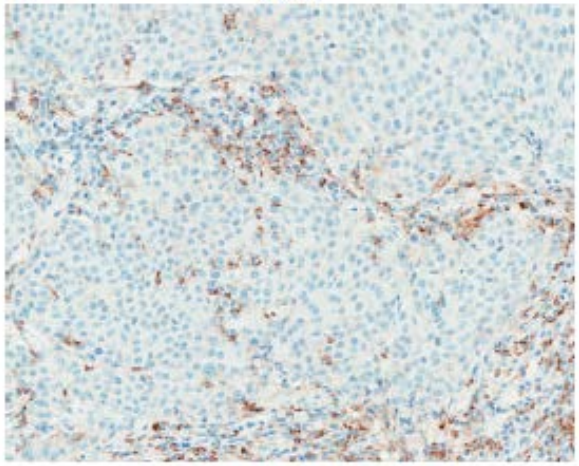
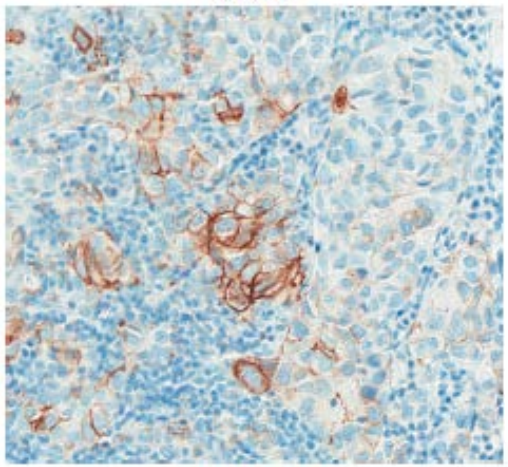
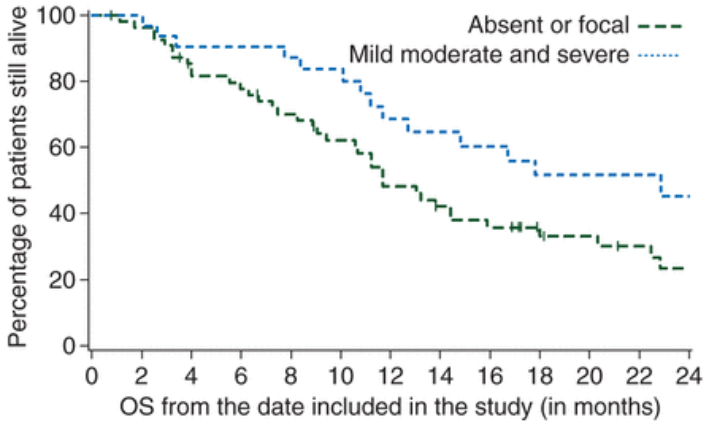


Tumour-infiltrating immune cells



Tumour cells



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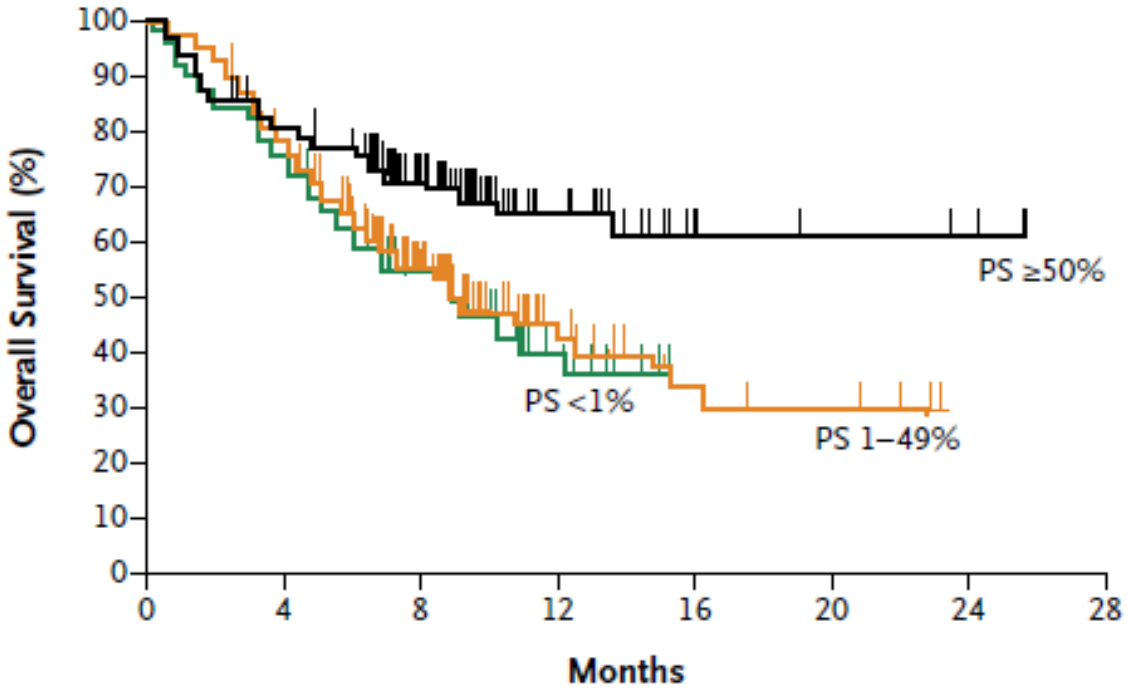
Tumour-infiltrating immune cells and objective response rates

	Objective response rate *n* (%)	Stable disease *n* (%)	Progressive disease *n* (%)
IHC 2/3 (*n* = 30)	13 (43.3) (95% CI: 25.5–62.6)	8 (26.7)	8 (26.7)
IHC 3 (*n* = 10)	5 (50.0) (95% CI: 22.2–77.8)	2 (20.0)	3 (30.0)
IHC 2 (*n* = 20)	8 (40.0) (95% CI: 20.9–63.9)	6 (30.0)	5 (25.0)
IHC 0/1 (*n* = 35)	4 (11.4) (95% CI: 4.0–26.3)	13 (37.1)	13 (37.1)
IHC 1 (*n* = 23)	3 (13.0) (95% CI: 3.7–31.7)	8 (34.8)	8 (34.8)
IHC 0 (*n* = 12)	1 (8.3) (95% CI: 0.4–34.9)	5 (41.7)	5 (41.7)

Bellmunt, J. *et al.* Association of PD-L1 Expression on Tumor Infiltrating Mononuclear Cells and Overall Survival in Patients with Urothelial Carcinoma. *Ann. Oncol.* (2015). doi:10.1093/annonc/mdv009

Powles, T. *et al.* MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. *Nature* **515,** 558–562 (2014).

Anti-PD-L1 in NSCLC



PD-L1 staining in tumor cells of ≥50% correlated with OS with pembrolizumab treatment

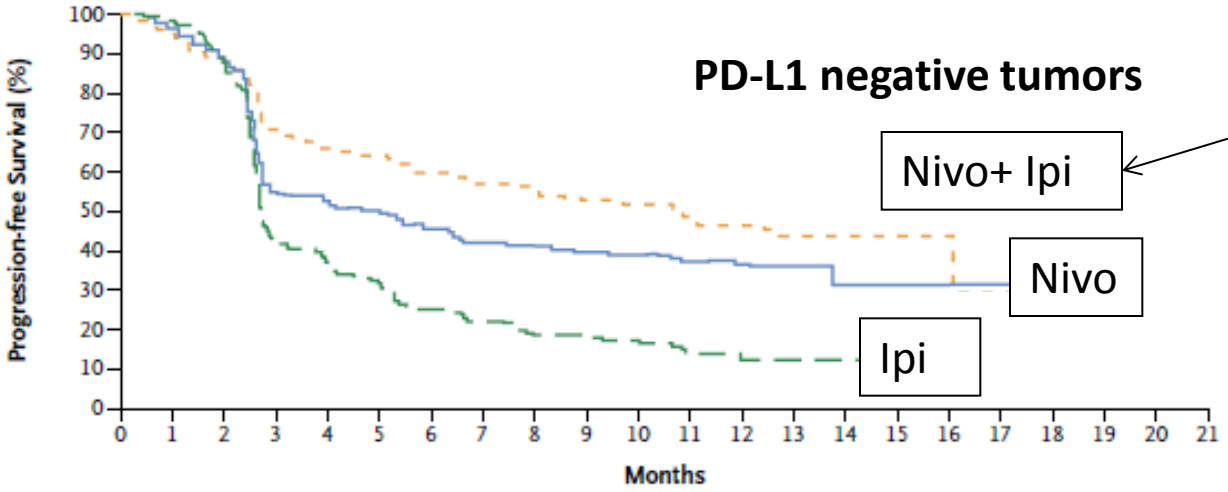
Garon, E. B. *et al.* Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer. *New England Journal of Medicine* **372,** 2018–2028 (2015).

Multiple checkpoint inhibition

- Tune intensity of breaking of self-tolerance to patient and tumor immune characteristics…?

PD-L1 Biomarker Predicts Response

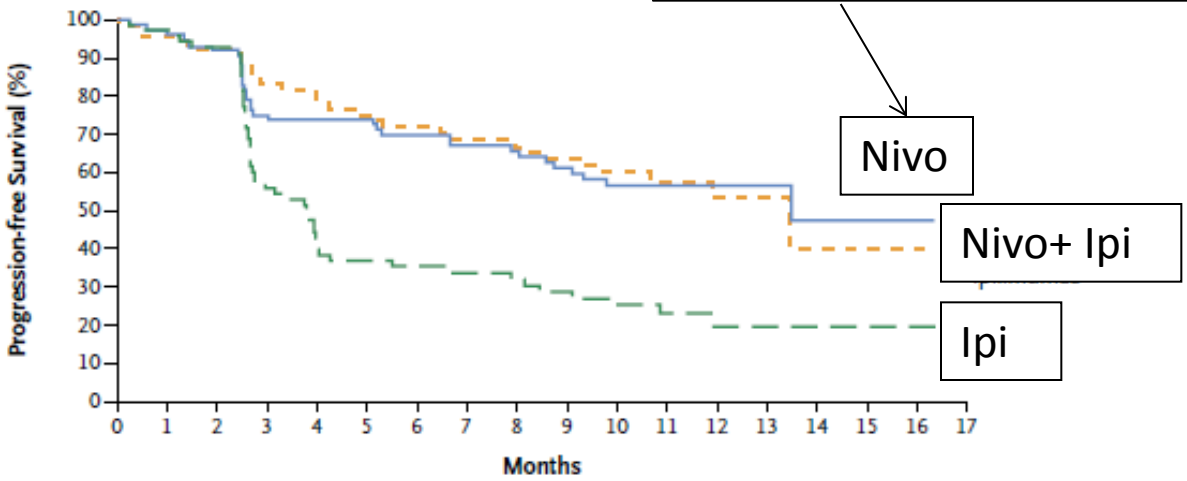
PD-L1 negative tumors



ve:
of nivo + ipi
S over either

e:
pi to nivo
prove PFS

PD-L1 positive tumors

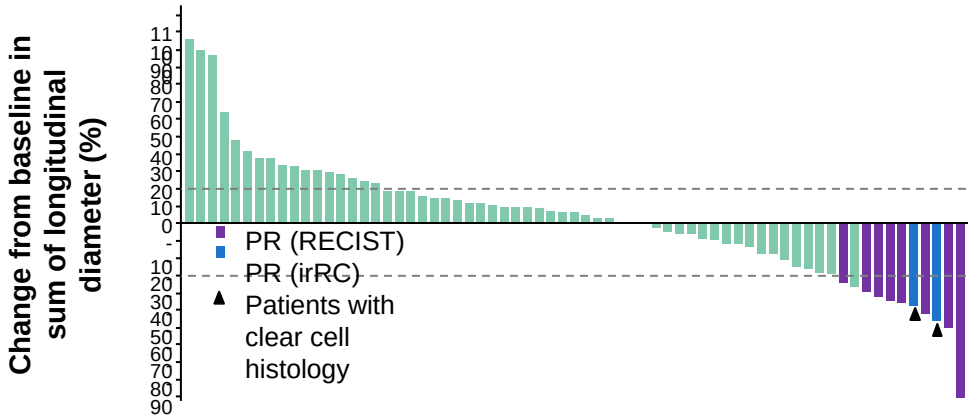


Larkin, J. *et al.* Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *NEJM* **373,** 23–34 (2015).

Avelumab experience in OvCa

- 75 women with refractory/resistant OvCa
  - 51 patients with at least 3 prior regimens
  - 0 CR, 11 PR (15%) by RECIST
  - 2/2 **clear cell** responses

- Breaking the immunoRx barrier?



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Trial Design Considerations

- Does intensity of prior therapy independently impact immune influence?
  - More resistant/more heavily pretreated disease→higher mutational load→more antigen targets

    Vs:
  - More resistance mechanisms; more **senescent** immune system and other **host factors**
- Lines of prior therapy is likely to play a continued role in selecting patients

Trial Design Considerations

- Novel endpoints to consider
  - eg: Tumor kinetics
  - Endpoints for same drug may vary by disease setting
  - Novel analyses of conventional endpoints
    - eg: DOR > ORR
- Prolonged DOR demonstration is key for regulatory evaluation when median PFS benefit may be small

Take-home messages

- Be aware of strategies for accelerated approval
  - eg, planned interim analysis of single arm if adequate follow-up duration
- Consider need for alternative efficacy endpoints
  - DOR vs PFS to support ORR for accelerated approval
  - OS for traditional approval

- Explore single-agent efficacy first

Take-home messages

- Plan for treatment beyond initial RECIST progression
- Early and aggressive toxicity management
- Evaluate checkpoint target expression as predictor of response
  - Correlation with target expression is disease-specific, and perhaps treatment-specific/test-specific
  - Goal: Marker negative population should identify patients who do not respond to treatment