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Pseudoprogression and Current Clinical Challenges in Management of Patients on Immunotherapy

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Society for Immunotherapy of Cancer

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Historical perspective and basic ground rules

- Cytotoxic therapies have limited benefits and substantial toxicities
- FDA approvals require evidence of patient benefit
  - Survival prolongation
  - Relief of malignancy-related morbidities
- Accelerated approval granted for probable surrogates of benefit
  - Requires confirmatory data to achieve full approval
  - Makes little difference in payor approval, practice uptake, trial design
- Bidimensional measurements→RECIST criteria

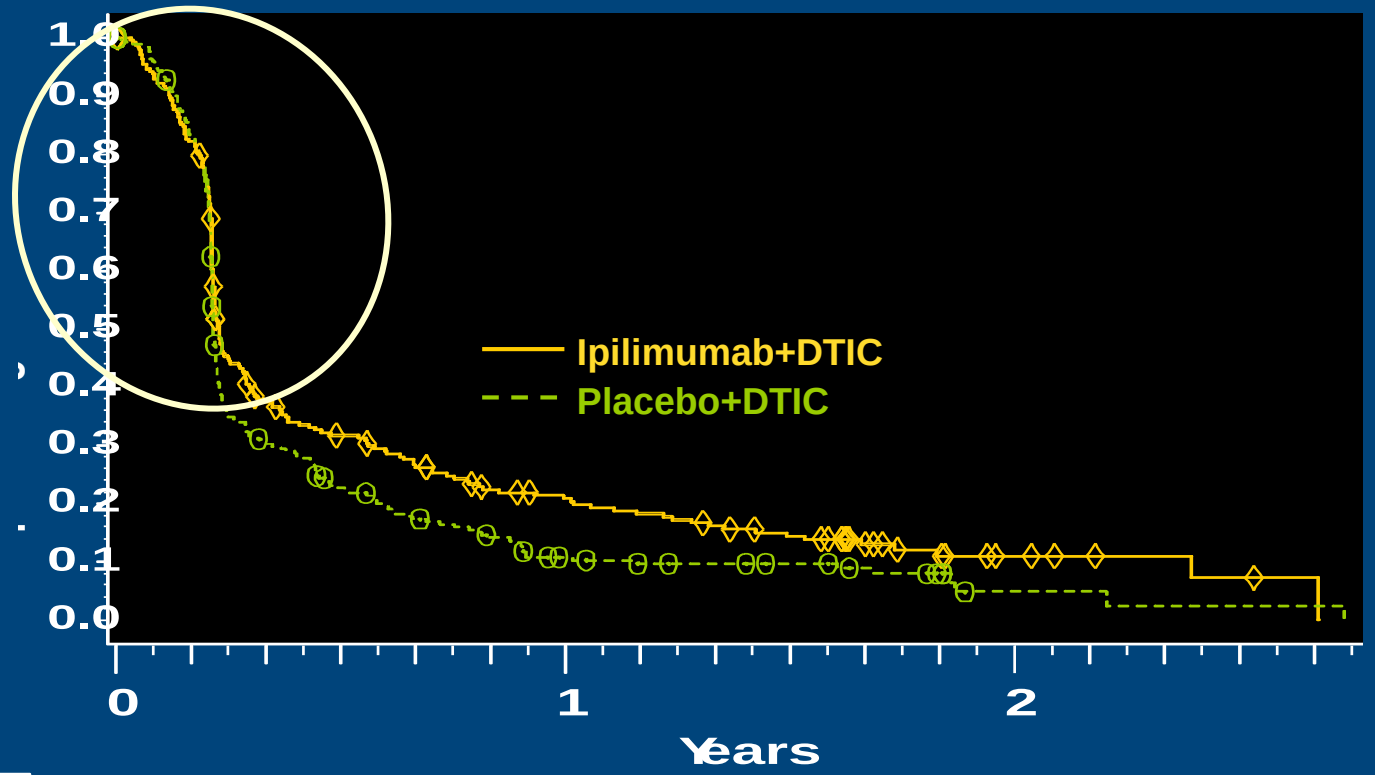
FDA flexibility in assessing benefit

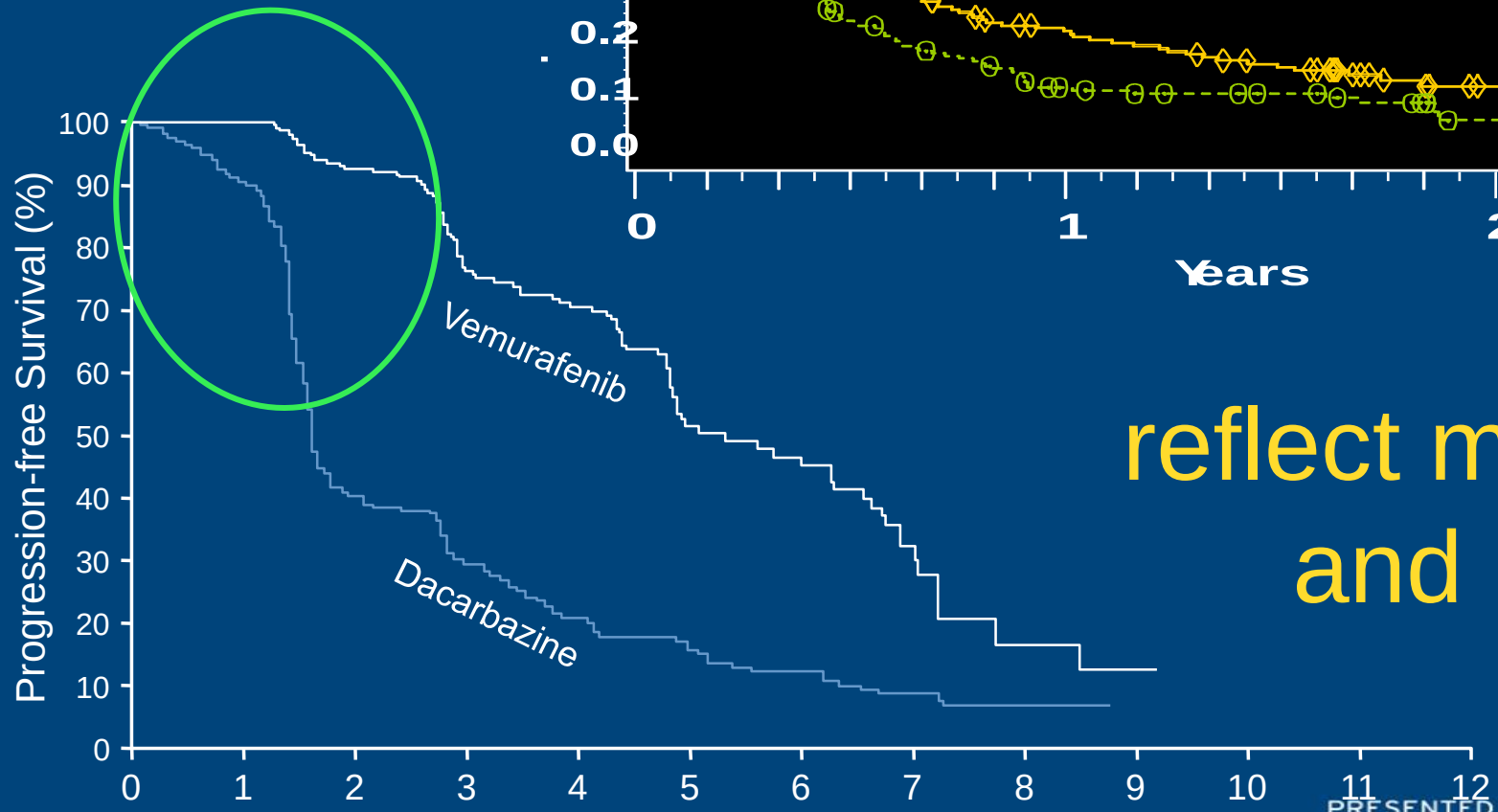
- Increasing numbers of post-treatments available
  - OS not a feasible endpoint
  - PFS may be a good measure of benefit
- Newer drugs have dramatic response rates that may be sufficient to support regulatory approval
- Waterfall plots may over-estimate benefits (do not measure duration or account for QoL)
- Swimmer plots are hard to interpret and are single-patient experience
- Mechanistic insights and targeted Rxs
  - Larger effect size→smaller trials
  - Easier to accept results as meeting benefit endpoints

Endpoints in the era of immune checkpoint block

- Atypical mechanisms raise questions of how to interpret traditional measurement-based assessments
- Alternative methods of assessment remain unvalidated
  - Metabolic/PET
  - Vascular/MRI
- Timing and pattern of regression using standard measures challenge standard principles of tumor assessment
  - Immunotherapy has slow onset of action
  - Appearance on scans may lag behind antitumor effects
  - Size of lesions may not correlate w/ viable tumor—immune effector infiltrate?

PFS curves



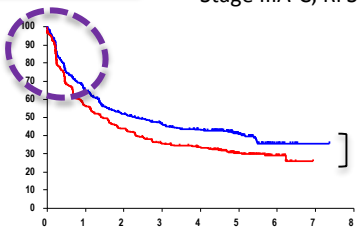


reflect mechanisms and kinetics

Key efficacy landmarks in the adjuvant Rx of melanoma

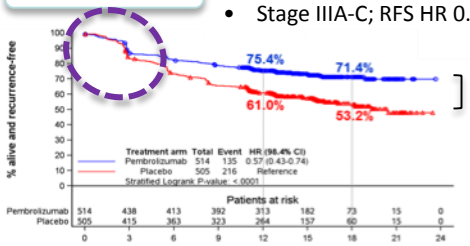
EORTC 18071

- Ipilimumab 10 mg/kg vs placebo,
- Stage IIIA-C; RFS HR 0.76, OS HR 0.72



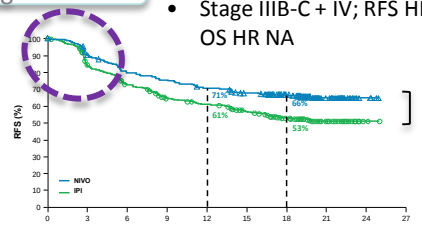
EORTC 1325

- Pembrolizumab vs placebo,
- Stage IIIA-C; RFS HR 0.57, OS HR NA



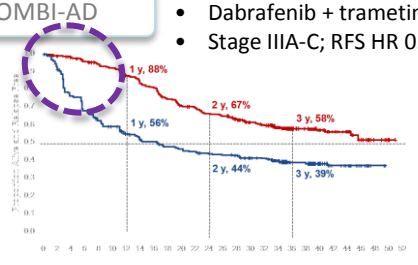
Checkmate 238

- Ipilimumab 10 mg/kg vs nivolumab,
- Stage IIIB-C + IV; RFS HR 0.65, OS HR NA



COMBI-AD

- Dabrafenib + trametinib vs placebo
- Stage IIIA-C; RFS HR 0.47, OS HR 0.57



Current adjuvant options shown in orange

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PRESENTED BY: Olivier Michielin, MD-PhD

(note the initial shape of the curves—we saw this in advanced melanoma starting in 2011)

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Points to consider in today's FDA:SITC dialogue

- Regulatory stance for recent immune checkpoint Ab approval
  - Discussions between FDA and sponsors
  - FDA review of registrational data
- Ongoing trial endpoints and methods
- Lessons learned
  - Change of direction for trial design?
  - Change of criteria for drug approval?

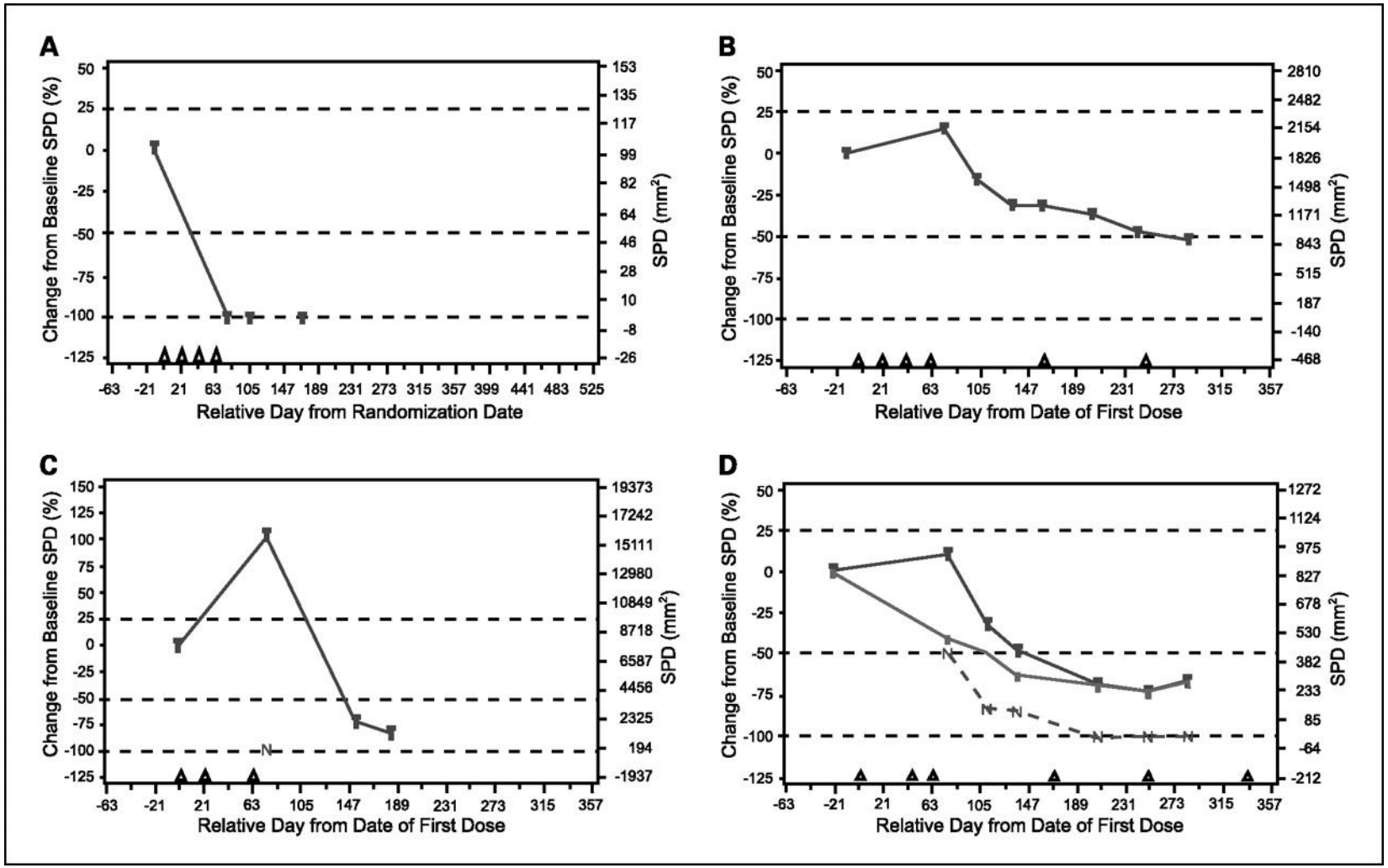
Pseudoprogression (and immune-related RC)

- How is it determined?—can only be a retroactive assessment
- Can it be incorporated reliably into assessments?—consensus methods and approach needed
- What does it mean
  - For regulatory approvals—Keegan
  - For clinical trial design—Goel
  - For patient care—remainder of this overview

First reports of pseudo-progression

- ”liver man” from Jedd Wolchok (ipilimumab/melanoma)
- Ipilimumab series from Hamid
- Hodi, Hoos, others—outcomes vs type of response
- Parallel emergence of RECIST1.1 as the most widely-used system of response assessments
- Development of immune-related response-assessment systems
- Incorporation of concept of pseudo-PD, “treat beyond PD”
  - Not exactly the same as ir criteria
  - May represent a similar phenomenon/challenge to assess atypical Rx mech

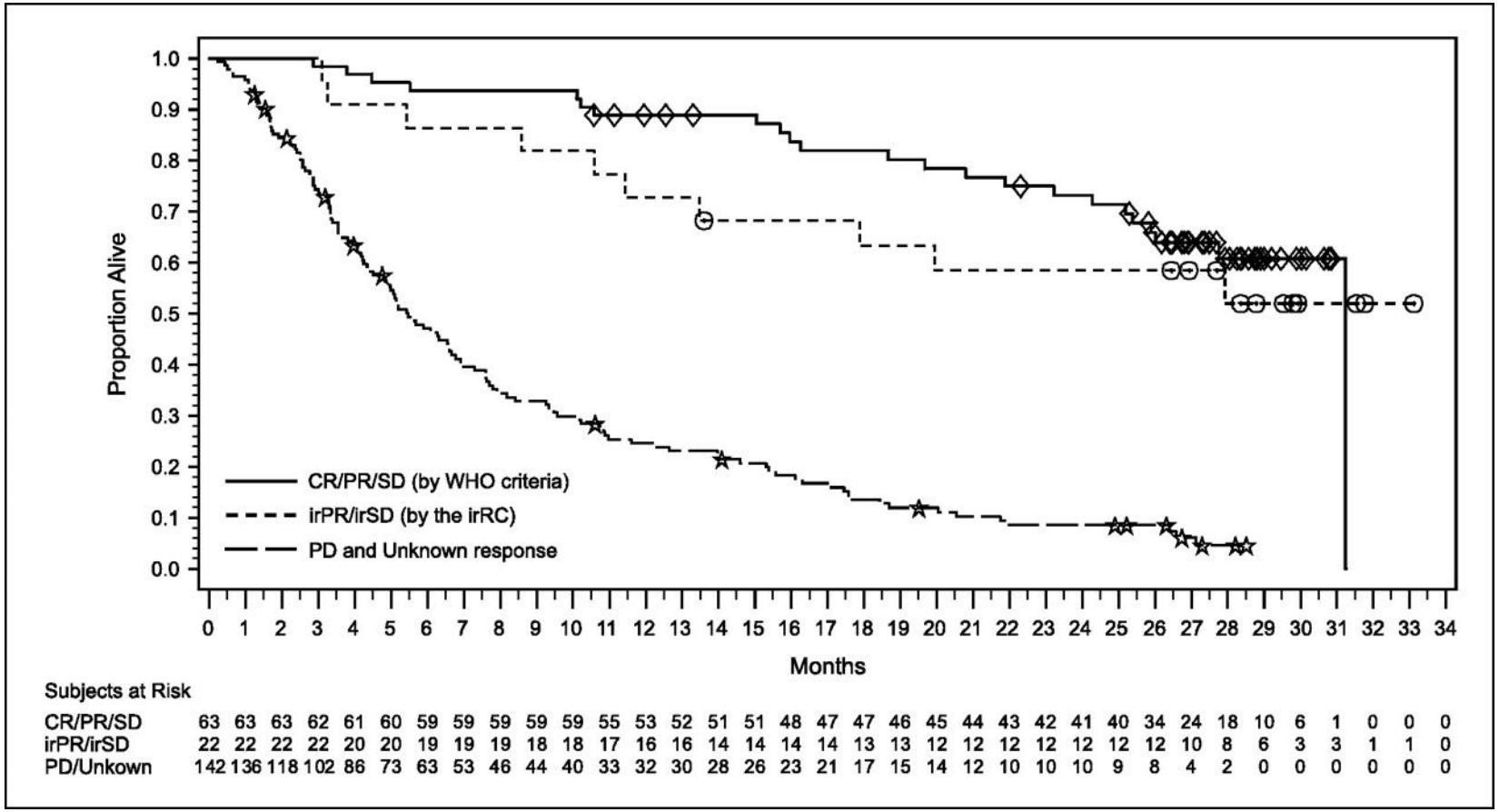
Patterns of response to ipilimumab observed in advanced melanoma.



Jedd D. Wolchok et al. Clin Cancer Res 2009;15:7412-7420

Clinical Cancer Research
AACR American Association for Cancer Research

Association of OS with response using WHO criteria or irRC.



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Conclusions and recommendations

- With ipilimumab or other immune therapies, an increase in tumor burden or the appearance of new lesions before radiographic responses can be partially circumvented by appropriate follow-up at a subsequent time point to confirm PD. Treatment should be continued as tumors may begin to shrink in this interval. Patients treated with immune therapy whose performance status is stable and whose laboratory values have not significantly deteriorated, as well as those with moderate tumor growth on physical exam or radiographic imaging, should be considered for repeat confirmation scans before true PD is defined and the immunotherapeutic agent is withdrawn. This, of course, needs to be balanced against the potential toxicity associated with continued treatment.

Unique dilemma of pseudo-PD in patient care

- Patient perspective
  - If pseudo-PD rate is ~10% (of all comers)/30% (of all initial PDs), the patient with an initial scan PD can hope for a turnaround
  - If pt is asymptomatic or improved, there is no urgency to change Rx
  - Good news or bad news?—initial response is better…
- Physician perspective
  - All of the above
  - Good news or bad news?—delaying the inevitable or staying the course?
  - Change approach to wait longer before assessing [analogous to “milestone” approach]
- Advocate point of view--Silverstein

Attempts to understand and eliminate pseudo-PD

- Circulating tumor DNA (BRAF or NRAS mu ~65-70% of cut. melanoma)
  - MIA group studied 125 pts on PD-1 or CTLA4+PD-1 blockade
  - ctDNA studied by digital droplet pcr methods on plasma
  - 29/125 initial evaluation showed PD
  - 20/29 had true PD—90% with unfavorable ctDNA result
  - 9/29 had pseudo-PD—all with favorable ctDNA result
- Limitations of study
  - Inconsistent use of RECIST vs irRC to describe PD
  - Only applies to BRAF and NRAS mutant tumors
  - Lumped pts on PD-1 and PD-1 plus CTLA4 blockade
- Can we learn more from neo-adjuvant studies, which have enjoyed a re-awakening with improved Rxs for many malignancies?

Figure 2. Overview of Mutation Type, Circulating Tumor DNA (ctDNA), and Immune-Related Response Criteria (irRC) Results in 29 Patients

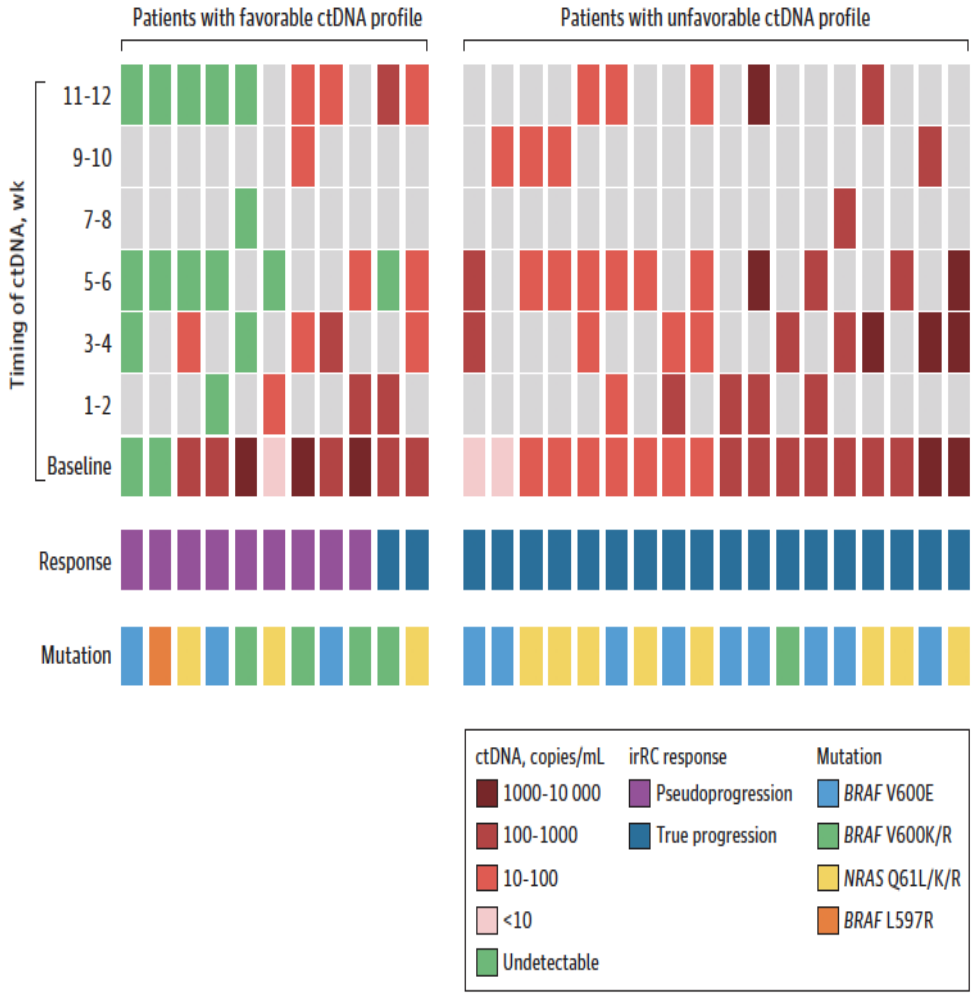
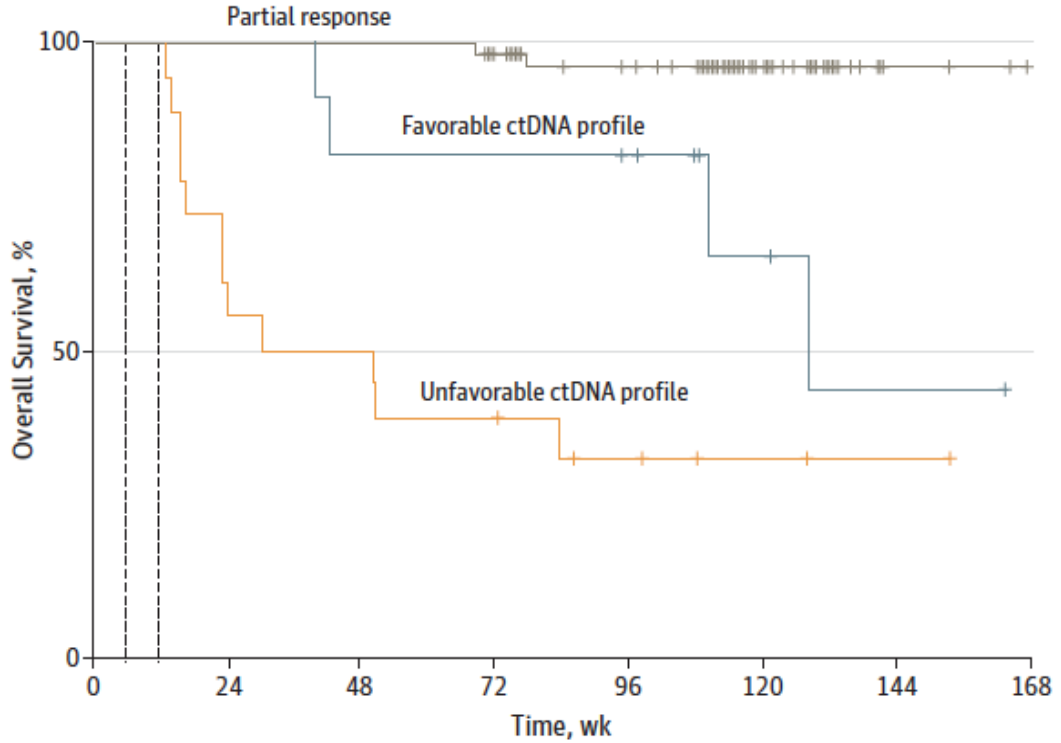


Figure 3. Kaplan-Meier Curves for Overall Survival of Partial Response Patients According to Circulating Tumor DNA (ctDNA) Profile



No. at risk

Partial response	54	54	54	52	44	24	4	1
Unfavorable ctDNA profile	18	11	10	8	5	3	2	1
Favorable ctDNA profile	11	11	10	10	9	5	3	1

Hodi et al…Wolchok: imRECIST (JCO 2018)

- Unidimensional measurements, target lesion number etc per RECIST 1.1
- New lesions do not define PD
  - If measurable, incorporate into total tumor burden
  - If nonmeasurable, cannot count as CR
- PD determined only on the basis of measurable disease
- PD negated by subsequent non-PD assessment ≥ 4 wks from date first documented
  - ≥20% increase in SLD c.f. baseline
  - Best response may occur after any number of PD assessments
- Editorial from Chmielowski raises question of value for imRECIST