# Regulatory Considerations for Immuno-Oncology Endpoints, Response Criteria, and Patient Selection

SITC Annual Meeting
November 9, 2019

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# Disclosure information

- I have no financial relationships to disclose.

- I will not discuss off label use and/or investigational use in my presentation

# Outline

- Efficacy endpoints in oncology clinical trials
- Immune checkpoint inhibitors and response criteria/endpoint considerations
- Treatment beyond progression
- Patient-oriented programs at OCE

# Efficacy endpoints in clinical trials

- FD&C Act: “Safe and effective”
- PHS Act: “Safe, Pure, and Potent”
- Similar evidentiary framework for drugs and biologics
  - Approval of new drugs/indications requires demonstration of effectiveness in adequate and well-controlled trials
  - Regular vs. accelerated approval

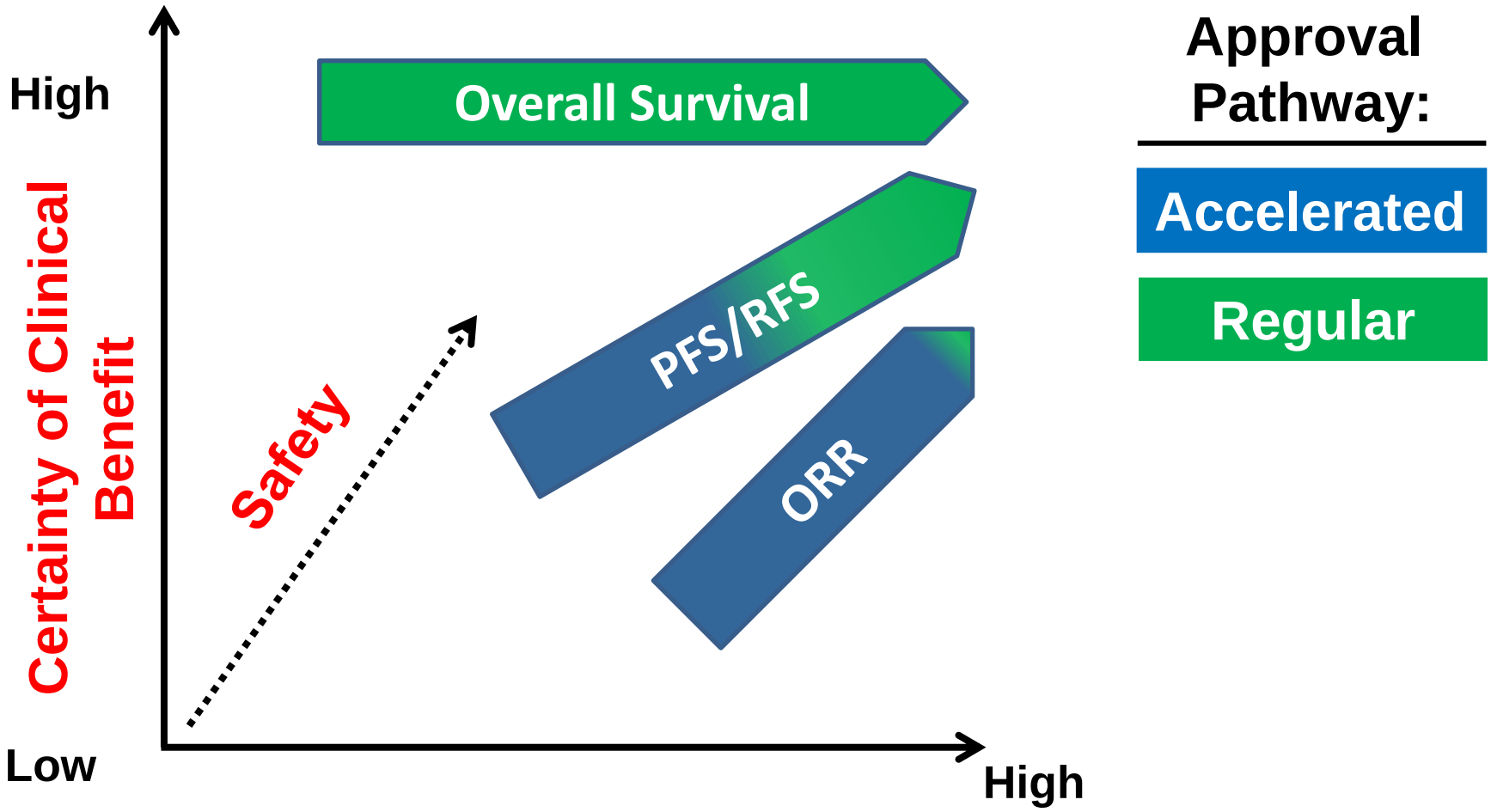
# Efficacy endpoints in clinical trials: FDA approval pathways

- Regular approval
  - Requires substantial evidence of effect on clinical benefit
  - Improvement in how a patient “feels, functions, or survives”
  - Established surrogate for clinical benefit
- Accelerated approval
  - Requires substantial evidence that drug provides meaningful advantage over available therapies based on a surrogate or intermediate endpoint that is reasonably likely to predict clinical benefit

# Efficacy endpoints in clinical trials

- Direct Measures of Clinical Benefit
  - Overall survival
  - Disease-free or event-free survival (adjuvant therapy)
  - Improvement in PROs
  - Decreased serious morbidity
- Surrogate/Intermediate Measures of Clinical Benefit
  - Progression-free survival
  - Overall response rate/duration of response
  - Complete pathologic response (resectable breast cancer)
  - Generally tumor-based endpoints

# Efficacy endpoints in clinical trials: Magnitude of treatment effect






Slide credit: Marc Theoret, MD

# iRECIST Guidelines

- Based on RECIST v1.1
- Progression of Disease (PD) by RECIST v1.1 = iUPD in iRECIST
- PD (iCPD) Requires Confirmation 4 to 8 weeks after iUPD
  - Target Lesions - Further Increase in Tumor Burden (>= 5 mm)
  - New Lesions - Further Increase in Size or Additional New Lesions
  - Nontarget lesions – Further increase from iUPD
- If PD Not Confirmed, an iCR, iPR, or iSD Resets the Bar
  - iUPD must occur again followed by further growth for iCPD

Slide credit: Marc Theoret, MD; Seymour et al., 2017, Lancet Oncol

# Efficacy endpoints in clinical trials

- CDER Oncology had recommended conventional response criteria rather than new immuno-oncology response criteria as primary measures of efficacy use tumor-based endpoints – given lack of information on possible sources of bias & correlation with survival.
- May consider iRECIST as supportive information if:
  - Response criteria are applied in all arms & control
  - Data necessary to derive outcomes is accurate with minimal missing data
- FDA encourages further exploration and validation of tumor-based endpoints per new criteria

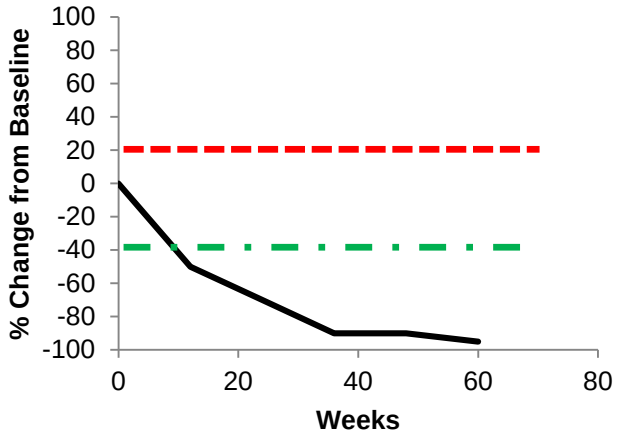


Slide credit: Patricia Keegan, MD

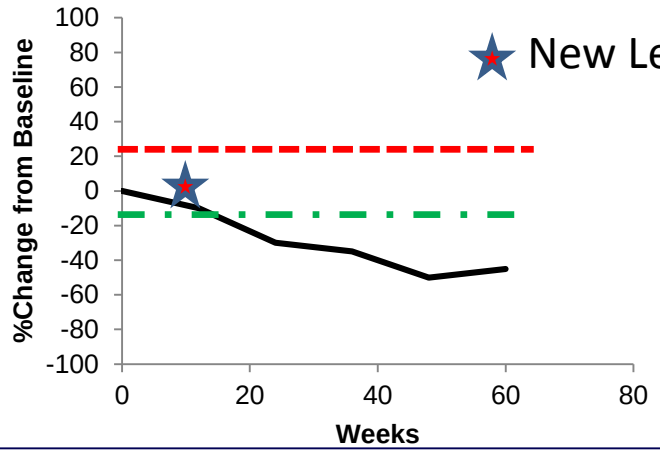
# Immuno-oncology response endpoints: Patterns of tumor growth with immunotherapy

FDA

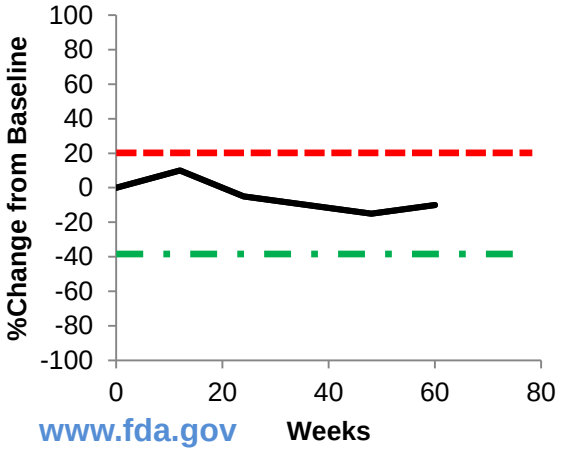
## Continued Reduction in Lesions




## Reduction in Lesions with New Lesions

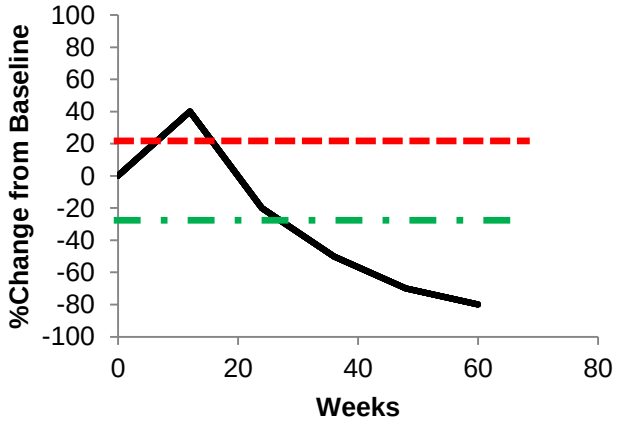



## Stable Lesions



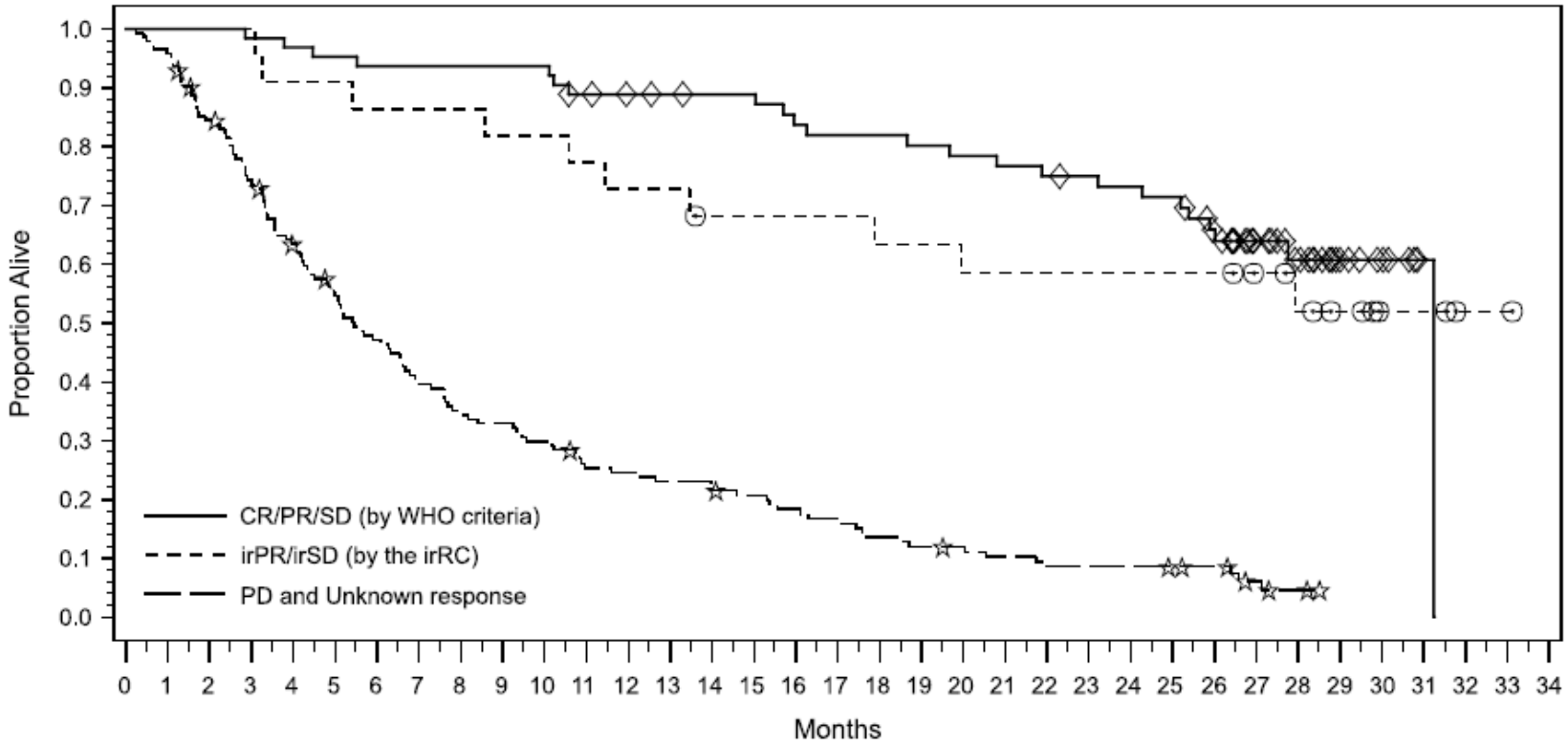

www.fda.gov

## Initial Increase then Decrease in Lesions




Adapted from Wolchok, 2009, Clin Cancer Res

# Ipilimumab – immune-related response criteria (irRC) and OS




Subjects at Risk

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CR/PR/SD | 63 | 63 | 63 | 62 | 61 | 60 | 59 | 59 | 59 | 59 | 59 | 55 | 53 | 52 | 51 | 51 | 48 | 47 | 47 | 46 | 45 | 44 | 43 | 42 | 41 | 40 | 34 | 24 | 18 | 10 | 6 | 1 | 0 | 0 | 0 |
| irPR/irSD | 22 | 22 | 22 | 22 | 20 | 20 | 19 | 19 | 19 | 18 | 18 | 17 | 16 | 16 | 14 | 14 | 14 | 14 | 13 | 13 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 10 | 8 | 6 | 3 | 3 | 1 | 1 | 0 |
| PD/Unkown | 142 | 136 | 118 | 102 | 86 | 73 | 63 | 53 | 46 | 44 | 40 | 33 | 32 | 30 | 28 | 26 | 23 | 21 | 17 | 15 | 14 | 12 | 10 | 10 | 10 | 9 | 8 | 4 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |

Wolchok, 2009, Clin Cancer Res

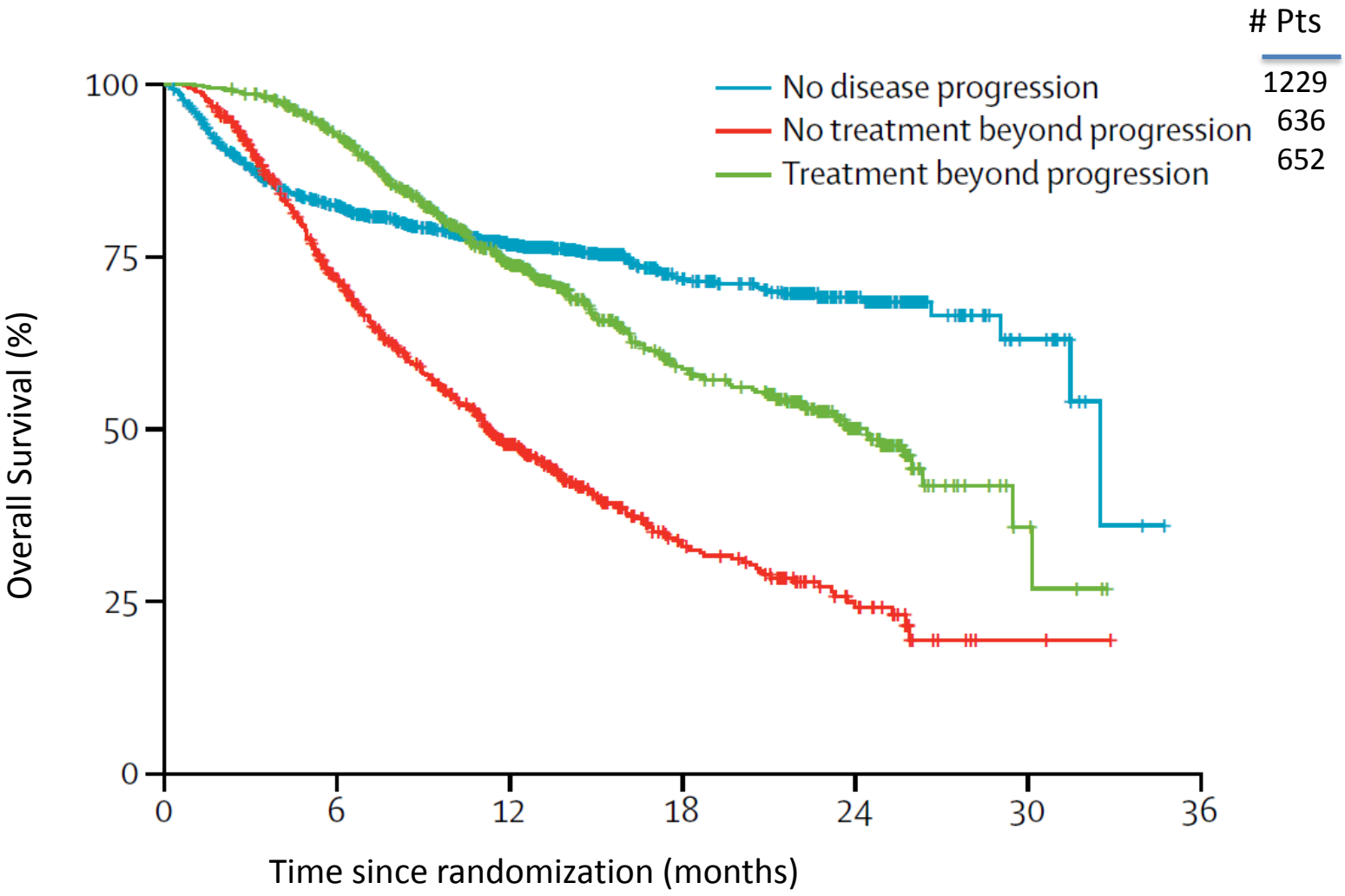
# Treatment beyond progression: Patient management in clinical trials

- FDA has supported the inclusion of provisions in the protocol to allow treatment beyond RECIST v1.1 progression (TBP) based on irRC with provisions to mitigate risks for patients:
  - Absence of signs & symptoms indicating disease progression
  - No decline in performance status
  - Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention
  - Separate informed consent may need to be considered [in patient situations where effective alternative therapies are available to continuing a potentially inefficacious therapy].



Slide adapted from Patricia Keegan and Marc Theoret

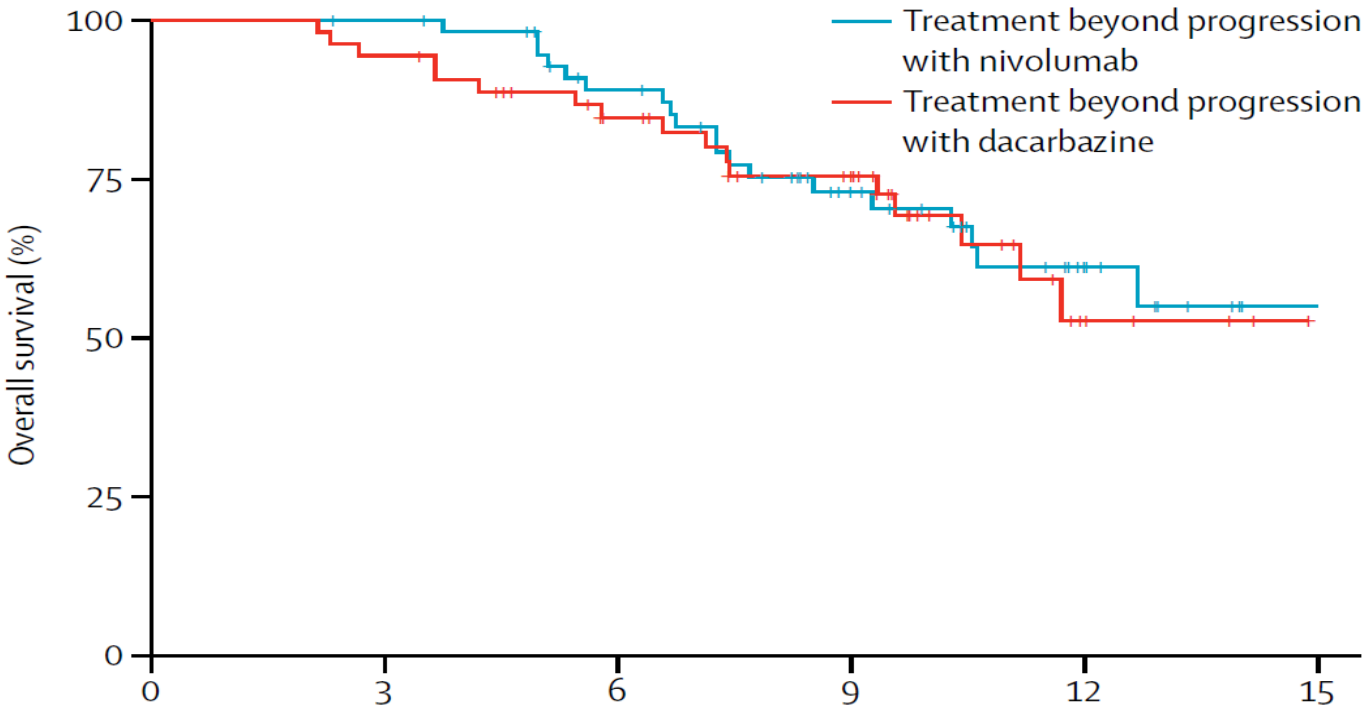
# Treatment beyond progression: Melanoma trials






Beaver, Hazarika, Mulkey, et. al., 2018, Lancet Oncol

# TBP subgroup by treatment arm




| Number at risk (number censored) | | | | | | |
|---|---|---|---|---|---|---|
| Treatment beyond progression with nivolumab | 59 (0) | 58 (1) | 47 (6) | 30 (15) | 12 (29) | 1 (39) |
| Treatment beyond progression with dacarbazine | 54 (0) | 51 (0) | 39 (7) | 30 (12) | 6 (31) | 0 (37) |



Beaver, Hazarika, Mulkey et al., 2018, Lancet Oncol

# Analyses of response to anti-PD-1 mAbs administered beyond progression

| | Disease | N | PD, n | TBP, n (%) | Reference Tumor Burden | TBP Responders[d] | |
|---|---|---|---|---|---|---|---|
| | | | | | | % of All Pts | % of TBP Pts |
| George 2016 | RCC | 168 | 154 | 62 (37%)[a] | Baseline | 7 | 33 |
| Escudier 2017 | RCC | 406 | 316 | 153 (42%)[b] | PD | 5 | 13 |
| Kazandijan 2017 | NSCLC | 535 | 420 | 121 (23%)[c] | Baseline | 2 | 20 |
| Long 2017 | Mel | 526 | 306 | 85 (16%)[b] | Baseline | 5 | 28 |
| Beaver 2018 | Mel | 2624 | 1361 | 692 (26%)[c] | PD | 4 | 14 |

[a] TBP at least 4 weeks
[b] TBP at least 6 weeks
[c] Any TBP
[d] ≥30% Decrease in Target Lesion Tumor Burden

Modified from Blumenthal et al., 2017, JAMA Oncol

# Post-hoc analyses of TBP in clinical trials

- Across tumor types, a minority of patients may derive some benefit from TBP
- More systematic and uniform data collection would better characterize which patients may benefit; iRECIST
- Those who continue TBP may be a select population with a better prognosis/more indolent disease

# Acknowledgments


- Marc Theoret, MD (slides and advice)
- Patricia Keegan, MD (slides)
- Gideon Blumenthal, MD (slides)


# OCE Programs


FDA
U.S. FOOD & DRUG
ADMINISTRATION

# OCE Project Facilitate

- Pilot call center to assist oncology healthcare providers in requesting access to investigational therapies for patients with cancer
- Single point of contact to help process and submit an Expanded Access request
- **Healthcare providers** or regulatory professionals may call Project Facilitate at (240) 402-0004 from 8 a.m. to 4:30 p.m. Eastern time, Monday through Friday. Email: OncProjectFacilitate@fda.hhs.gov.

# Patient eligibility criteria

- Draft guidance published June 2019 to discuss:
  - Broadening eligibility criteria and avoid unnecessary exclusions for clinical trials
  - Developing eligibility criteria and improving trial recruitment so that patients enrolled in trials will better reflect the population to use the drug
  - Applying the recommendations for broadening eligibility criteria to clinical trials for drugs intended to treat rare diseases or conditions

https://www.fda.gov/media/127712/download

# Broadening eligibility criteria

- Narrow exclusion criteria to avoid unnecessary limits
- Consider whether phase 2 criteria can be eliminated in phase 3 protocols
- Consider including children and adolescents when appropriate & pediatric development programs
- Consider adaptive trial designs which allow for changes during the trial, including altering the trial population
- Consider including a broader patient group as part of the secondary analyses

# Other study conduct considerations

- Make trial participation less burdensome when possible
- Adopt enrollment and retention practices that enhance inclusiveness
- Expanded access: use of an investigational drug when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition rather than to obtain information that is generally derived from clinical trials

# Other FDA programs: Master Protocols

- Draft guidance published October 2018 to describe efficient clinical trial design strategies to expedite development of oncologic drugs and biologics
- Facilitating trial designs that test multiple drugs and/or patient subpopulations in parallel under a single protocol
- May be used to conduct exploratory trials or those intended to support a marketing application

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/master-protocols-efficient-clinical-trial-design-strategies-expedite-development-oncology-drugs-and