JADPRO CE Regional Lectures

Clinical Advances and Case Studies in Immune Checkpoint Inhibitors in Oncology

Treatment-Related Issues

Program Chairs

Brianna Hoffner
MSN, ANP-BC, AOCNP®
University of Colorado
Cancer Center

Laura J. Zitella
MS, RN, ACNP-BC, AOCN®
Stanford Health Care

Faculty

Whitney Lewis
PharmD, BCOP
The University of Texas MD
Anderson Cancer Center

Faculty Financial Disclosures

- Ms. Hoffner has received consulting fees/honoraria from Abbott, Array BioPharma, and Merck.
- Ms. Zitella has served on the advisory board for Array Biopharma and has equity interests/stock options in Kite Pharma.
- Dr. Lewis has nothing to disclose.

Planning Committee Financial Disclosures

- Moshe C. Ornstein, MD, MA, Cleveland Clinic Taussig Cancer Institute (Reviewer) has served as a consultant for Pfizer and Eisai.
- Dorothy Caputo, MA, BSN, RN (Lead Nurse Planner) has nothing to disclose.
- Annenberg Center for Health Sciences at Eisenhower
  - John Bayliss, VP, Business Development, spouse is an employee of Amgen, Inc.; Charles Willis, Director, Continuing Education, consults for Pfizer Inc.; all other staff at the Annenberg Center for Health Sciences at Eisenhower have no relevant commercial relationships to disclose.
- Alana Brody, Lynn Rubin, and Patti McLafferty (Harborside Medical Education) have nothing to disclose.
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Learning Objectives

- Summarize data on currently available immunotherapeutic agents as they relate to durable treatment responses.
- Explain the utility of biomarker testing in selecting patients for immunotherapy and in predicting clinical outcomes.

Audience Response Question

PD-L1 protein expression:

A. Upregulates T-cell activation
B. Increases from IDO enzyme
C. May be predictive of response to immunotherapy
D. Indicates a poor response to immunotherapy
E. Unsure

Audience Response Question

Oncogenic alterations found in mismatch repair deficient tumors:

A. Are often somatic mutation events that occur as a result of microsatellite instability
B. Increase the expression of PD-L1 protein
C. Are characterized by instability in a single microsatellite DNA sequence
D. Decrease the likelihood that a patient will respond to immunotherapy
E. Unsure

Audience Response Question

Factors predictive of response to immunotherapy may include all of the following EXCEPT:

A) Mutations of MHC molecules

B) PD-L1 (*CD274*) gene amplification status

C) PD-L1 protein expression

D) Tumor mutation burden and amount of neoantigen

E) Unsure

Audience Response Question

Chemotherapy combined with immunotherapy can lead to improved response rates. One of the ways in which adding chemotherapy augments responses is:

A) By suppressing the immune system to decrease immune-related adverse events
B) By increasing antigen presentation to increase immune recognition
C) By changing the expression of PD-L1 protein to increase immune recognition
D) By inducing nonimmunogenic cell death to decrease immune tolerance
E) Unsure

Audience Response Question

Your patient on immunotherapy presents for a scan review at their first evaluation time point. Per RECIST, the patient has a > 2-fold increase of the tumor growth rate between the time prior to initiating immunotherapy and the time on treatment. You recognize that this response pattern is consistent with:

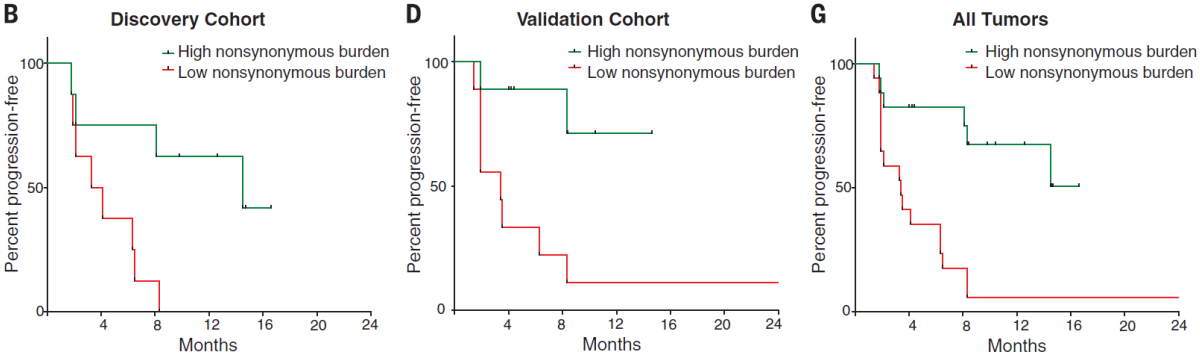
A) Pseudoprogression. You will continue immunotherapy and re-evaluate with imaging in 4–6 weeks.
B) Pseudoprogression. You will discontinue immunotherapy because it is not working.
C) Hyperprogression. You will continue immunotherapy and re-evaluate with imaging in 4–6 weeks.
D) Hyperprogression. You will discontinue immunotherapy because it is not working.
E) Unsure

Factors Predictive of Response

Tumor Mutation Burden, Circulating Tumor DNA, Next-Generation Sequencing, MSI/MMR, and Other

Tumor Mutation Burden

- Higher nonsynonymous mutation burden in tumors has been associated with improved objective response, durable clinical benefit, and progression-free survival
  - Some of the best responses to IO have been in melanoma and lung cancer: cancers largely caused by chronic exposure to mutagens (UV light and carcinogens in cigarette smoke)



Mutation burden associated with clinical benefit of PD-1 in NSCLC

IO = immuno-oncology

Rizvi, N.A., et al. (2015). Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Cancer Immunology, 348(6230).

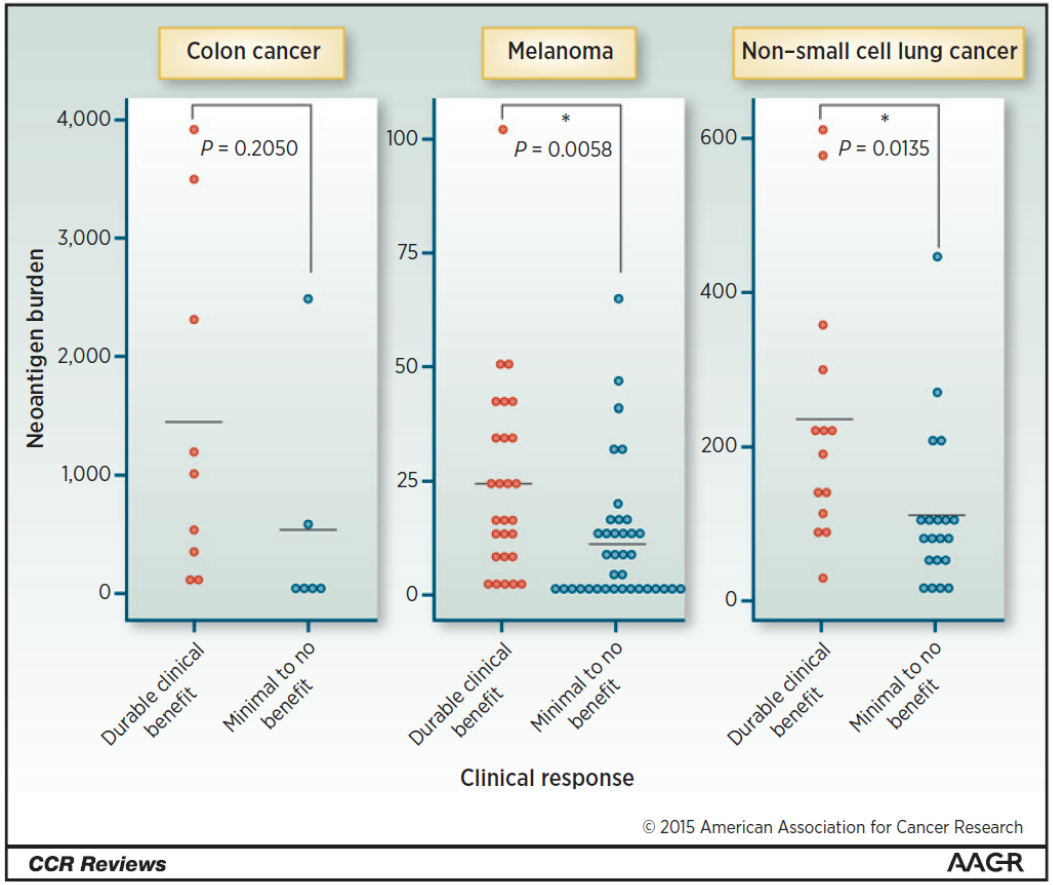
Neoantigens

- Tumor-specific antigens that are generated by somatic mutations[1]
- Can influence patient's response to immunotherapy and contribute to tumor shrinkage[1]
- May be predictors of immune checkpoint blockade response[1]
- Cancer-specific mutated antigens are present in every tumor type regardless of the mutation frequency of the tumor, some of which can be identified as neoantigens recognized by the patient's own T cells[2]

1. Desrichard, A., et al. (2016). Cancer neoantigens and applications for immunotherapy. Clin Cancer Res, 22(4).
2. Wang, R. & Wang, H.Y. (2017) Immune targets and neoantigens for cancer immunotherapy and precision medicine. Cell Research, 27, 11-37.

Neoantigens (cont.)

- Neoantigen load according to clinical benefit to checkpoint blockage immunotherapy



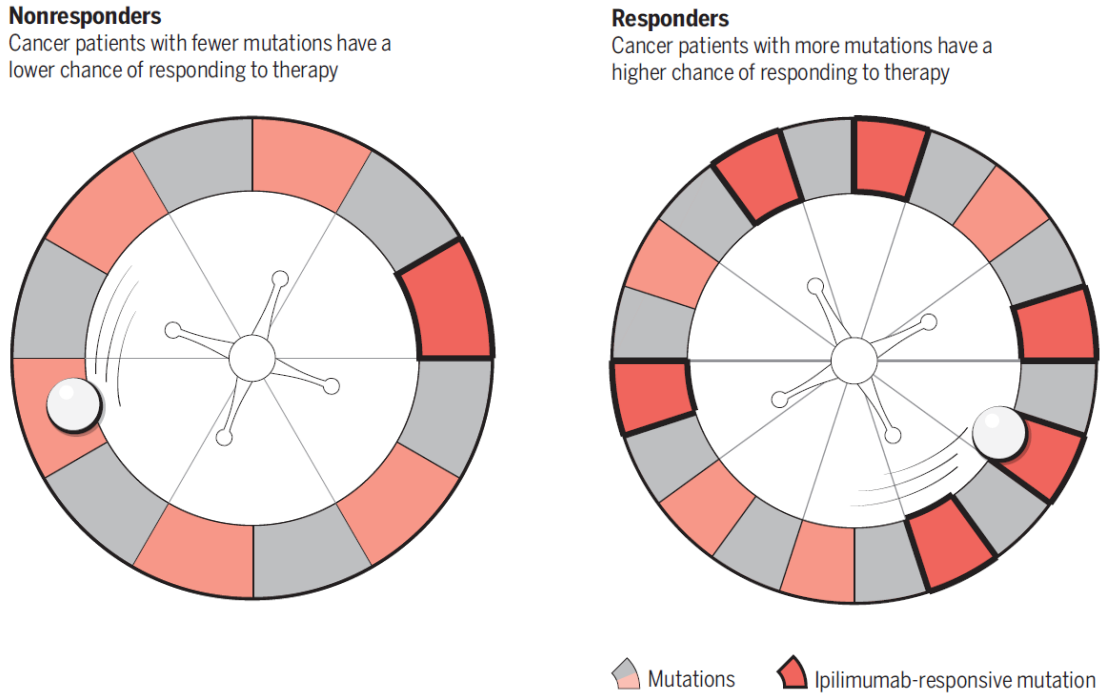
Desrichard, A., et al. (2016). Cancer neoantigens and applications for immunotherapy. Clin Cancer Res, 22(4).

CANCER

The odds of immunotherapy success

Mutation load correlates with the response of melanomas to immunotherapy

- **Neoantigen Roulette:** Melanomas with fewer mutations are less likely to contain "winning" neoantigens and are thus more likely to be unresponsive to immunotherapy



Gubin, M.M., & Schreiber, R.D. (2015) The odds of immunotherapy success. Science, 350(6257).

Next-Generation Sequencing

- Most cancers are genetically complex and are better defined by the activation of signaling pathways rather than a defined set of mutations.
- Next-generation sequencing (NGS) represents an effective way to capture a large amount of genomic information about a cancer.
- NGS has become more affordable and is therefore more widely used.
- NGS helps clinicians
  - Accurately diagnose cancer
  - Identify appropriate “targeted therapy”
  - Identify resistance mutations when a patient stops responding to a targeted therapy.

Gagan, J. & Van Allen, E.M. (2015). Next-generation sequencing to guide cancer therapy. Genome Medicine, 7:80.

NGS Influences Clinical Trial Design

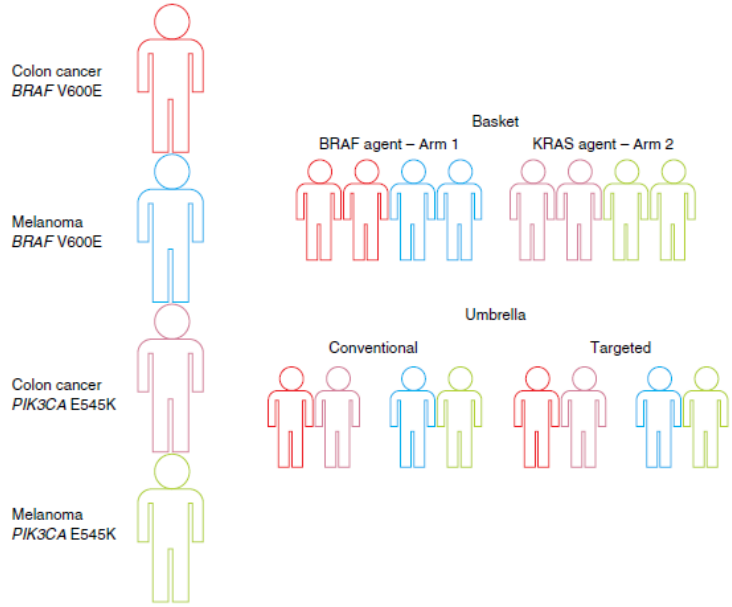


Fig. 4 An illustration of new clinical trial designs. Basket and umbrella trials both incorporate genomic data into the basic construction of the trial. Basket trials are designed around specific mutations, regardless of the primary tumor site. Umbrella trials are first separated by primary tumor site and then split into conventional therapy and precision medicine arms

Gagan, J. & Van Allen, E.M. (2015). Next-generation sequencing to guide cancer therapy. Genome Medicine, 7:80.

Microsatellite Instability

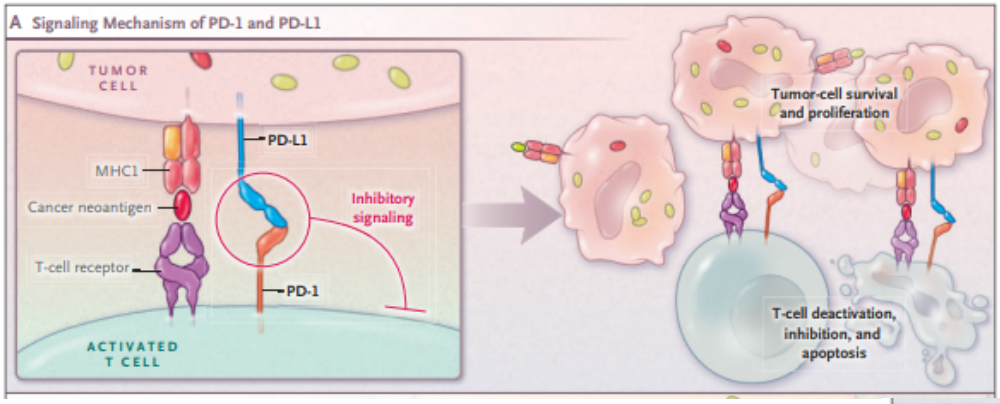
- Microsatellite instability (MSI) is associated with inactivating alterations in mismatch repair (MMR) genes
  - First observed in tumors associated with Lynch syndrome
  - Now noted in some colorectal, gastric, endometrial, ovarian, and others
  - Often designated as MSI-high (MSI-H) or mismatch repair deficient (dMMR)
- MSI tumors develop through a distinctive molecular pathway characterized by genetic instability in numerous microsatellite DNA repeat sequences throughout the genome
- Most oncogenic alterations found in dMMR tumors are somatic mutation events that occur as a result of MSI

Colle, R., et al. (2016). Immunotherapy and patients treated for cancer with microsatellite instability. Bulletin du Cancer, http://dx.doi.org/10.1016/j.bulcan.2016.11.006

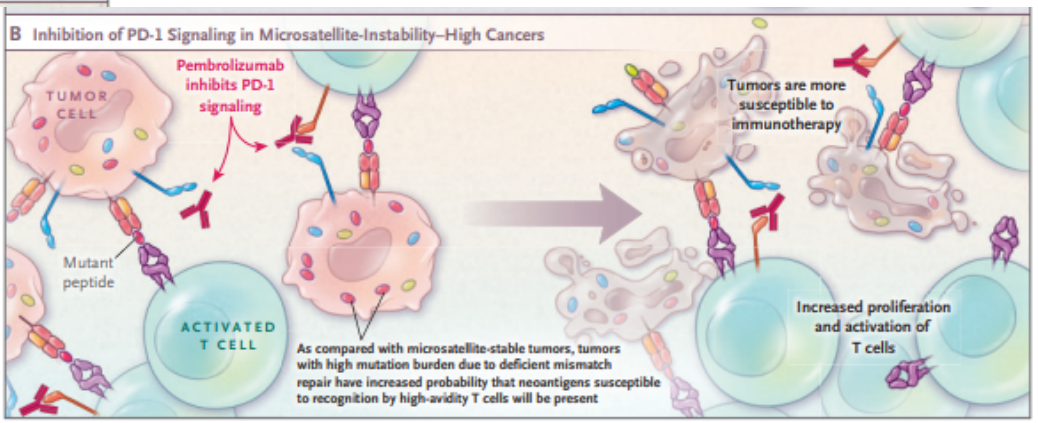
MSI-H/dMMR and IO

- 5/23/2017: FDA approved pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic MSI-H or dMMR tumors
  - First-ever site-agnostic approval
  - MSI-H tumors share common histopathologic characteristics
    - Lymphocytic infiltration
    - Somatic hypermutation
    - Increased neoantigen formation
  - Incidence of MSI-H/dMMR approximately:
    - 30% in endometrial
    - 20% in colon or gastric cancer
    - Less than 5% in most other tumor types

MSI-H/dMMR and IO (cont.)



Signaling mechanism of PD-1 and PD-L1 and inhibition of PD-1 signaling in MSI-H cancers



Lemery, S., Keegan, P., & Pazdur, R. (2017) First FDA approval agnostic of cancer site- when a biomarker defines the indication. *NEJM*, 377;15.

Testing for PD-L1 Amplification May Help Predict Response to Immune Checkpoint Blockade in Solid Tumors

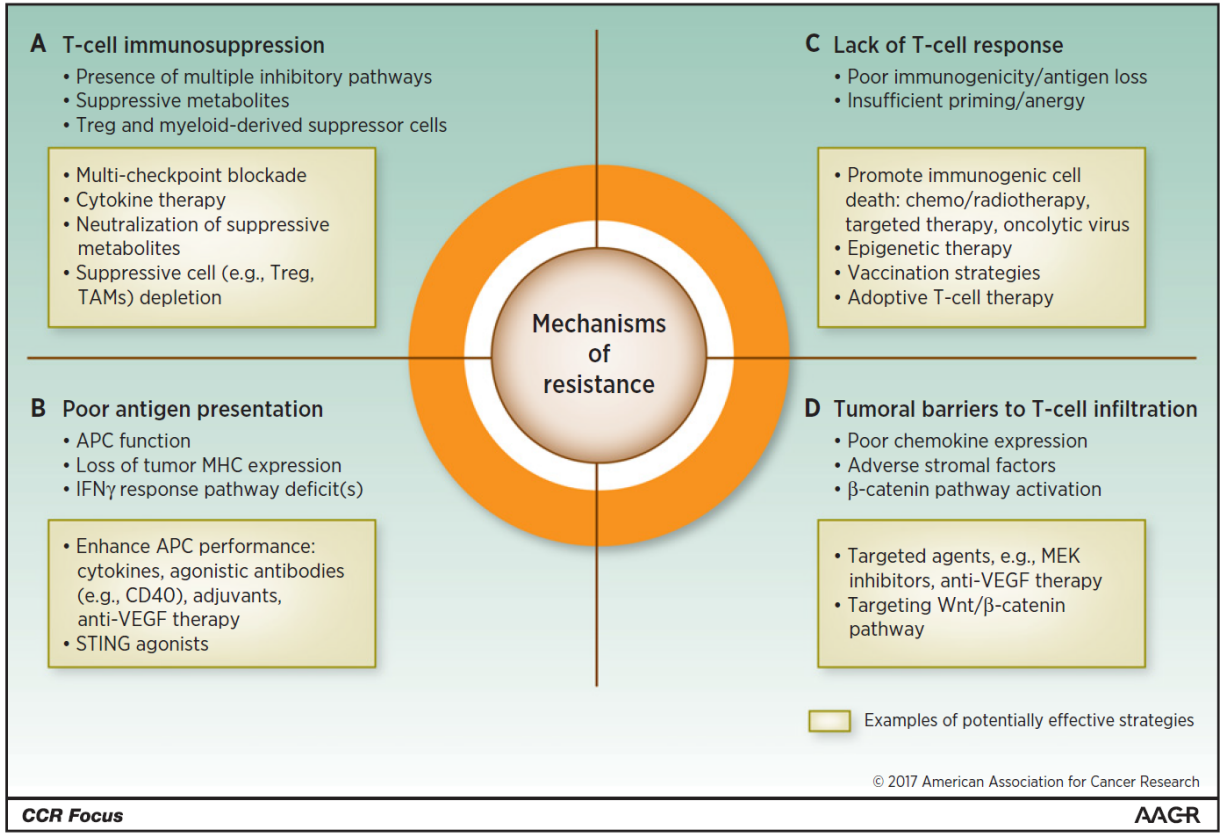
- Study of 118,187 tumor samples from the Foundation Medicine database and a subset of 2,039 clinically annotated patients from UCSD
  - Comprehensive genomic profiling on all samples
  - PD-L1 amplification (gene CD274) called for copy number alterations ≥ 6
- PD-L1 amplification in 0.7% of samples, across 121 unique solid tumor histologies
  - Increased prevalence in breast, HNSCC, squamous lung, undifferentiated soft-tissue sarcoma
- 67% of patients with solid tumors with PD-L1 amplification responded to PD-1/PD-L1 blockade
  - Median PFS of 15.2 months
  - Responses independent of tumor mutational burden

UCSD = University of California San Diego.

Combination Therapies

Immunotherapy/Immunotherapy
Immunotherapy/Chemotherapy
Immunotherapy/Targeted Therapy
Immunotherapy/Radiation Therapy

Combination Therapies: Overcoming Resistance



Day, D. et al. (2017). From famine to feast: Developing early-phase combination immunotherapy trials wisely. Clin Cancer Res, 23(17).

IO + IO

- Combining checkpoint inhibitor-based therapies can
  - Have concomitant effects on reactivation of T cells
  - Increase trafficking of tumor reactive lymphocytes into the tumor tissue
  - Enhance killing of cancer cells
- In metastatic melanoma, ipilimumab + nivolumab demonstrated increased response rates, tumor shrinkage, and median progression-free survival as compared to single agent
- Fundamental challenge for IO field is the rational selection of agents from a vast number of possible combinations while contending with escalating financial costs

Atkins, M. (2015). Immunotherapy combinations with checkpoint inhibitors in metastatic melanoma: Current approaches and future directions. Seminars in Oncology, 42(3), S12-S19.
Day, D. et al. (2017). From famine to feast: Developing early-phase combination immunotherapy trials wisely. Clin Cancer Res, 23(17).

IO + IO (cont.)

- Multitude of IO agents available or in development

Table 1. Immunotherapeutic agents in current development

Coinhibitory molecules (targets of immune checkpoint inhibitors)	Costimulatory molecules (targets of immune-stimulatory agonists)
– CTLA-4	– OX40 (CD134)
– PD-1	– GITR
– PD-L1	– CD137
– LAG3	– CD40
– TIM3	– ICOS
– BTLA	– 4-1BB
– TIGIT	
– VISTA	
– KIR	
Vaccines	Adoptive T-cell therapy
– Tumor antigen-based vaccines	– Tumor-infiltrating lymphocytes (TIL)
– Dendritic cell-based vaccines	– Chimeric antigen receptors (CAR)
	– T-cell receptor (TCR) transduction
	– Natural killer (NK) cells
Immunosuppressive soluble factors	Cytokines
– IDO-1	– IL1
– Adenosine	– IL5
	– IL7
	– IL15
	– IL21
Oncolytic virus	Treg cell depletion therapy
– T-VEC	– Cytotoxic chemotherapy
	– Anti-CD25
Bispecific T-cell–engaging antibody-based technologies	Endogenous adjuvants
– Blinatumomab (CD19/anti-CD3 T cell redirector)	– Stimulator of interferon genes (STING) agonists
– IMCgp100 (TCR/anti-CD3 T cell redirector)	– Toll like receptor (TLR) agonists

Day, D. et al. (2017). From famine to feast: Developing early-phase combination immunotherapy trials wisely. Clin Cancer Res, 23(17).

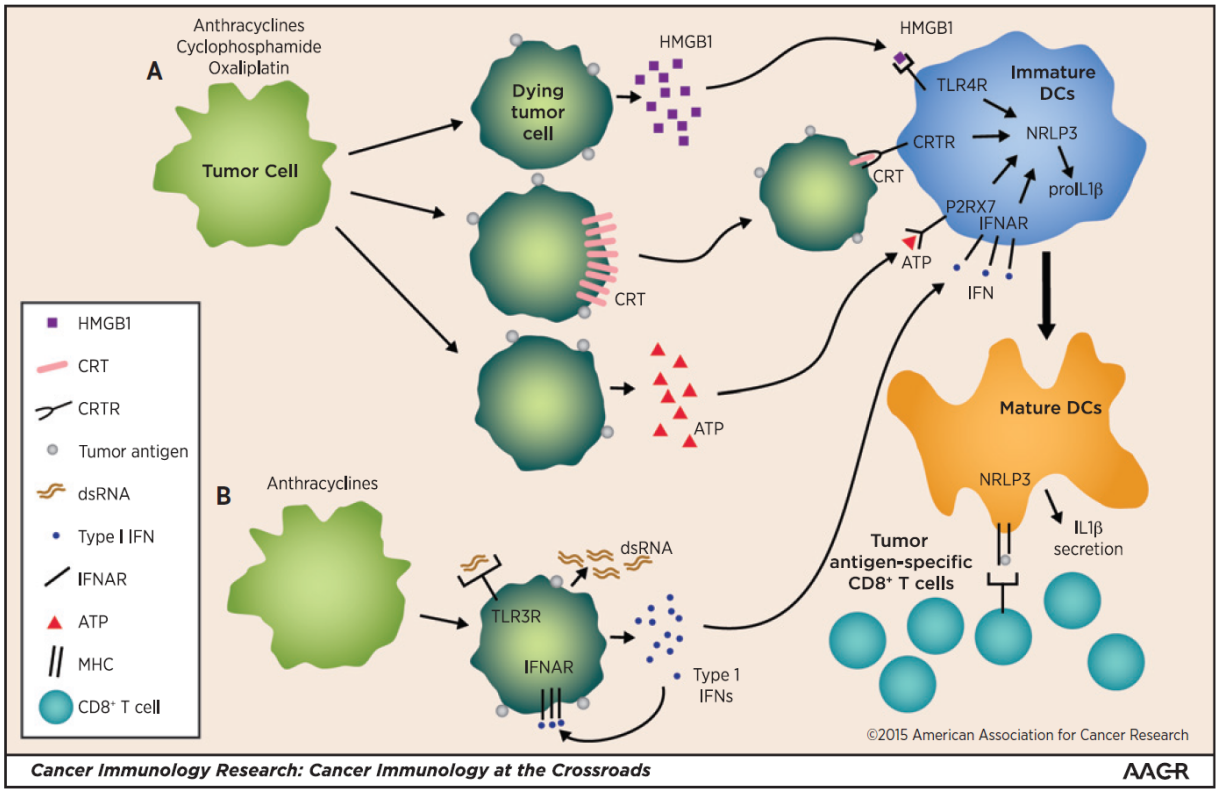
Chemotherapy + IO

- Chemotherapy historically considered immune suppressive; now understood that it can augment tumor immunity
- Chemotherapy can induce immunogenic cell death, increase antigen-presentation, improve tumor cell targeting, and deplete immunosuppressive cells
- Combination of pembrolizumab/pemetrexed/carboplatin FDA approved in metastatic NSCLC based on improved objective response rate and progression-free survival compared to chemotherapy alone.

Cook, A.M., et al. (2016). Chemotherapy and immunotherapy: mapping the road ahead. Current Opinion in Immunology, 36, 23-29.

Chemotherapy + IO (cont.)

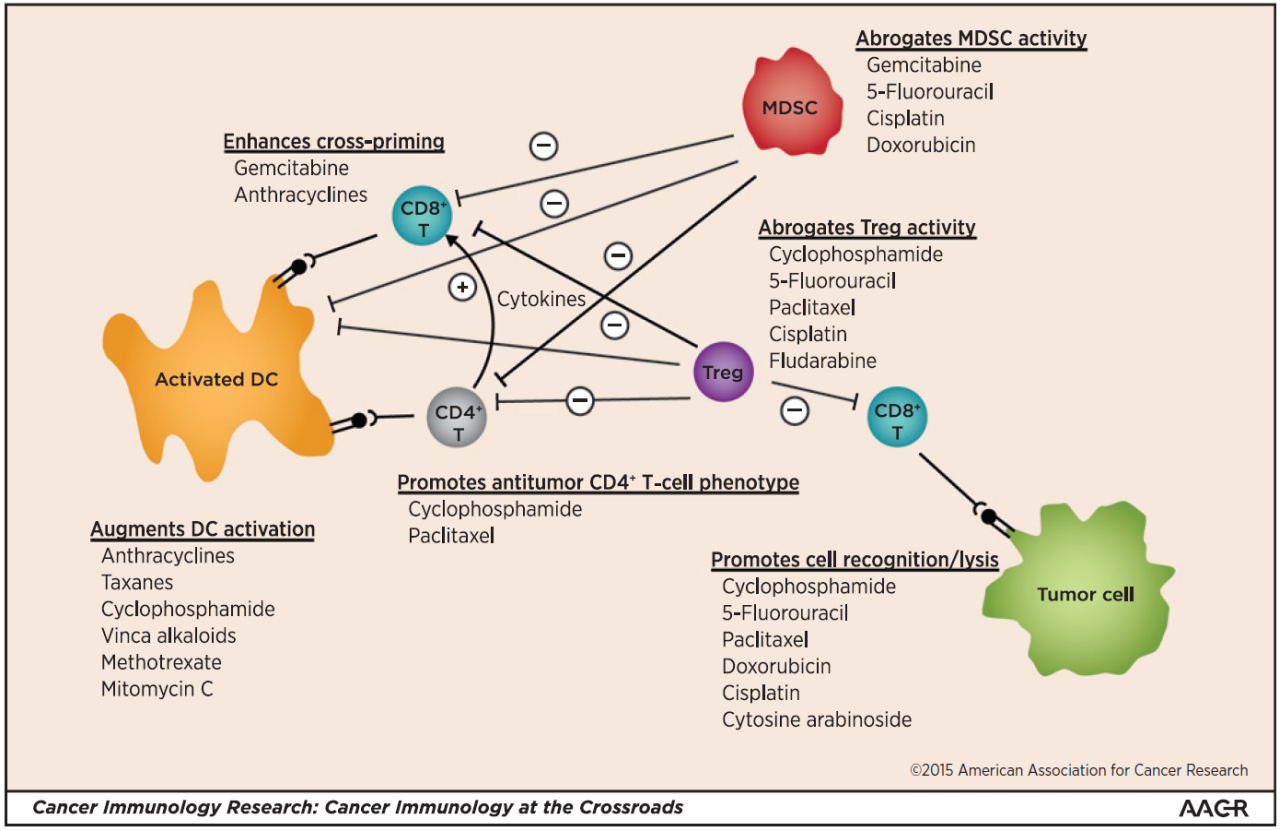
- Mechanisms of immunogenic tumor cell death induced by chemotherapy



Emens, L.A., & Middleton, G. (2015). The interplay of immunotherapy and chemotherapy: harnessing potential synergies. Cancer Immunol Res, 3(5).

Chemotherapy + IO (cont.)

- Chemotherapy modulates tumor immunity by mechanisms distinct from immunogenic cell death.



Emens, L.A., & Middleton, G. (2015). The interplay of immunotherapy and chemotherapy: harnessing potential synergies. Cancer Immunol Res, 3(5).

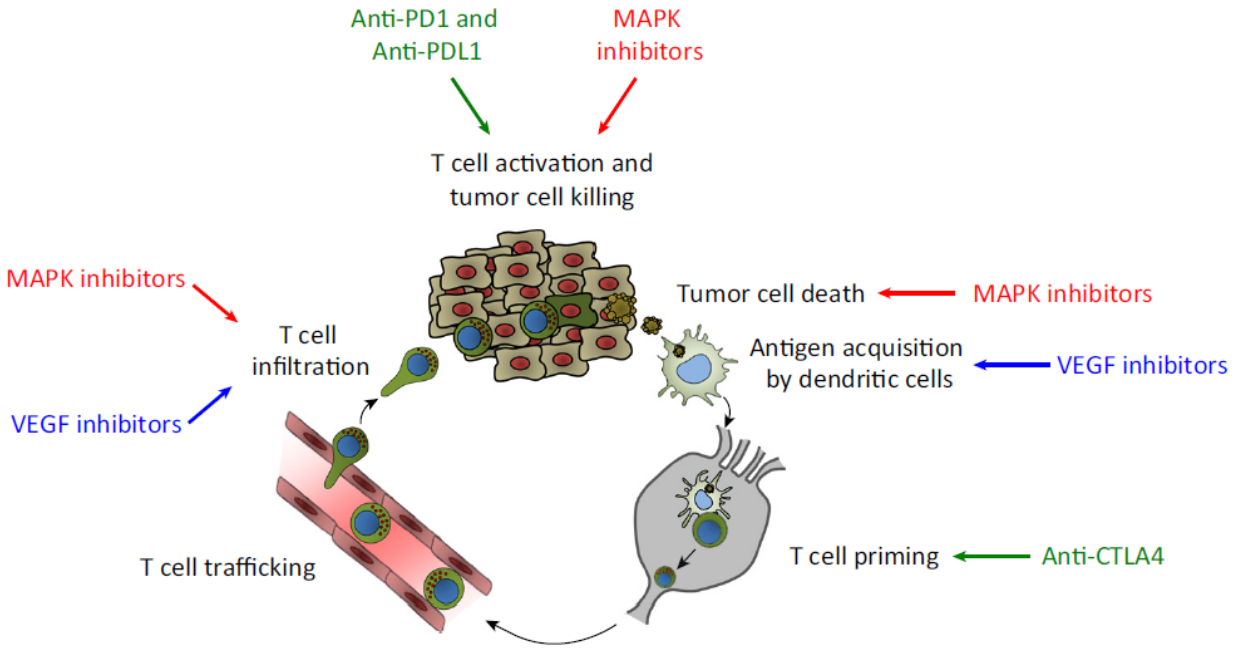
Targeted Therapy + IO

- Targeted therapies inhibit tumor-intrinsic drivers of growth and can elicit significant but transient clinical responses
- Targeted therapies can enhance aspects of cancer immunity including tumor antigenicity, T-cell trafficking and T-cell infiltration into tumors
  - Provides a rationale for combining with checkpoint inhibitors or other cancer immunotherapies
- Considerations with these combinations include optimizing dosing regimens, minimizing treatment-related toxicities, and selecting appropriate biomarkers/endpoints to assess efficacy.

Hughes, P.E., et al. (2016). Targeted therapy and checkpoint immunotherapy combinations for the treatment of cancer. Trends in Immunology, 37(7), 462-476.

Targeted Therapy + IO (cont.)

- MAPK and VEGF inhibitors can compliment T cell checkpoint therapies by enhancing tumor antigen expression, immunogenic tumor cell death, and T cell infiltration into tumors



The Cancer Immunity Cycle

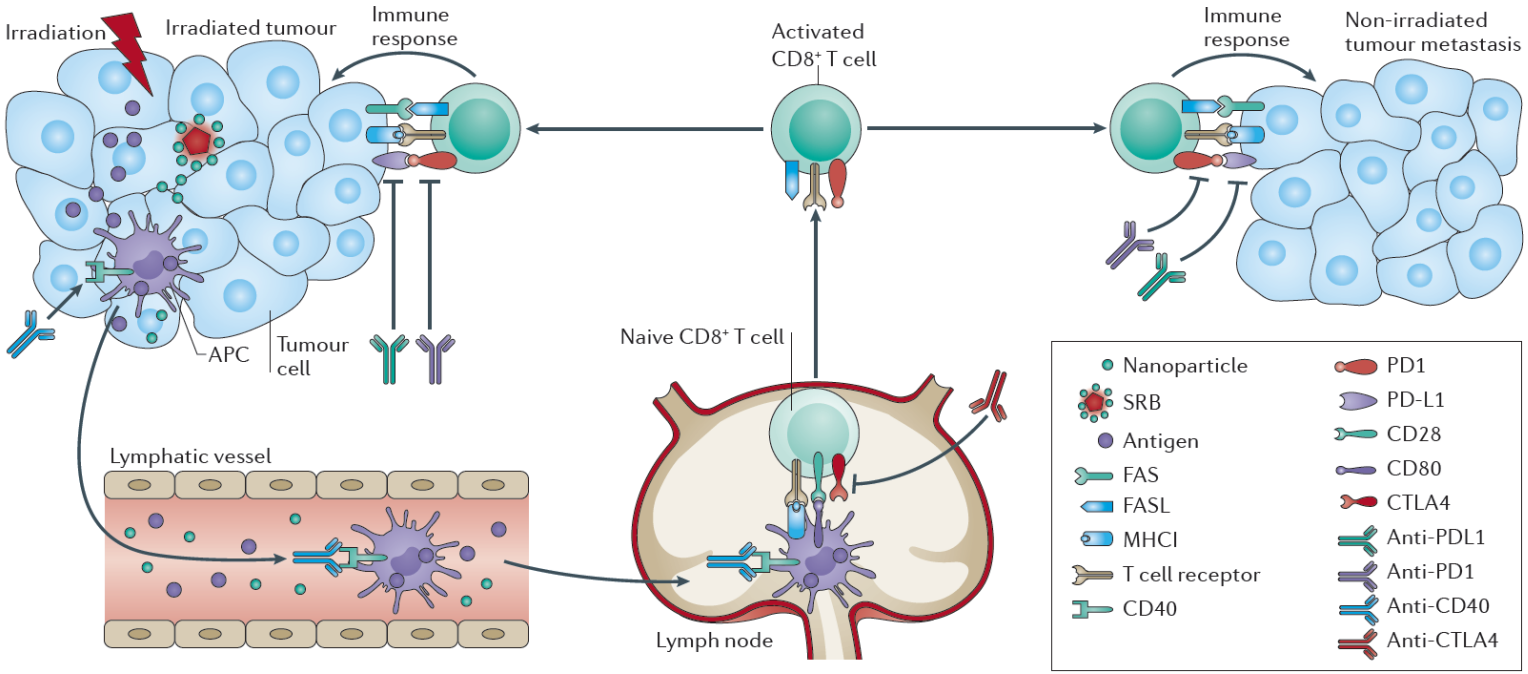
Hughes, P.E., et al. (2016). Targeted therapy and checkpoint immunotherapy combinations for the treatment of cancer. Trends in Immunology, 37(7), 462-476.

Radiation + IO: Abscopal Effect

- The effect whereby radiotherapy at one site may lead to regression of metastatic cancer at distant sites that are not irradiated
  - When a tumor is irradiated, the cellular stress or injury in the tumors may lead to the liberation of neoantigens
  - Increase in number/diversity of neoantigens can stimulate a tumor-specific immune response
  - Antigen-presenting cells engulf neoantigens and present to CD8+ T cells, which then recognize and attack both primary and metastatic disease
  - Rarity of abscopal effect suggests that even primed antitumor CD8+ T cells are unable to overcome the suppressive effect of the tumor microenvironment

Ngwa, W., et al. (2018). Using immunotherapy to boost the abscopal effect. Nature Reviews Cancer, advance online publication.

Radiation + IO: Abscopal Effect (cont.)



Ngwa, W., et al. (2018). Using immunotherapy to boost the abscopal effect. Nature Reviews Cancer, advance online publication.

Radiation + IO: Abscopal Effect (cont.)

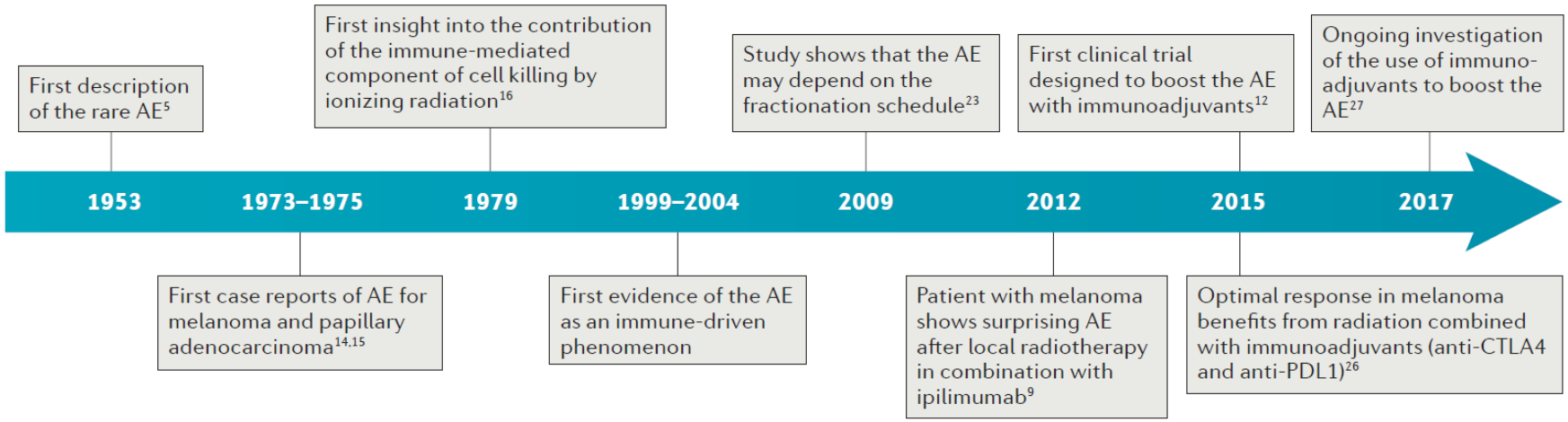


Figure 1 | **Historical timeline of some important developments regarding the abscopal effect.** AE, abscopal effect; CTLA4, cytotoxic T lymphocyte-associated antigen; PDL1, programmed cell death 1 ligand 1.

Ngwa, W., et al. (2018). Using immunotherapy to boost the abscopal effect. Nature Reviews Cancer, advance online publication.

Immunotherapy Response Patterns

Pseudoprogression, Hyperprogression, Treatment Beyond Progression, Abscopal Effect

JADPRO Regional Lectures

RECIST

- Up to 5 measurable target lesions (2 per organ)
  - Selection criteria
    - Measurable
    - Largest: with longest diameter
    - Reproducible repeated measurements (may not be the largest lesion)
    - Be representative of all involved organs
- Nontarget lesions
  - Too small to be considered measurable
    - < 10 mm lesions
    - ≥ 10 mm and < 15 mm lymph nodes
    - Clinical lesions unable to be accurately measured by caliper

RECIST = Response Evaluation Criteria in Solid Tumors

RECIST Response

- CR
  - Disappearance of all target lesions, all nodal lesions have short axis < 10 mm
- PR
  - At least 30% decrease in sum of diameters from baseline sum diameters
- PD
  - 20% increase and ≥ 5 mm absolute increase in sum of diameters from nadir
- SD
  - Neither CR, PR, nor PD

CR = complete response; PR = partial response; PD = progressive disease; SD = stable disease.

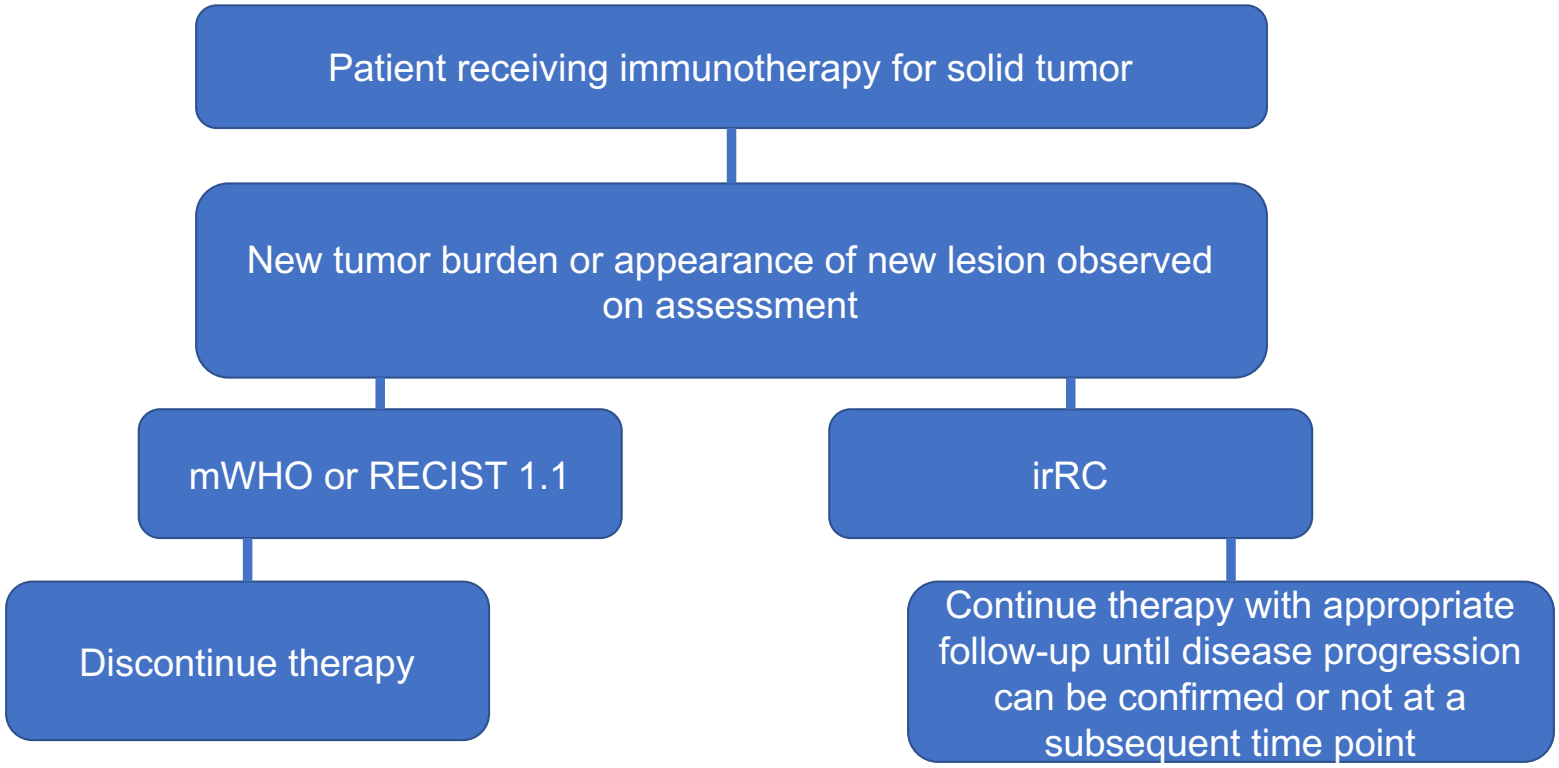
Immune-Related Response Criteria: Key Differences

- Up to 10 target lesions, 5 per organ
- May include an additional five subcutaneous target lesions
- Bi-dimensional measurements

Immune-Related Response Criteria (irRC)

Complete Response (CR)	Complete disappearance of all lesions; confirmed in a repeat, consecutive assessment ≥ 4 weeks from baseline assessment
Partial Response (PR)	≥ 50% reduction in tumor burden from baseline; confirmed in a repeat, consecutive assessment ≥ 4 weeks from baseline assessment
Stable Disease (SD)	Changes in tumor burden do not meet the criteria for CR, PR, or PD
Progressive Disease (PD)	≥ 25% increase in tumor burden relative to nadir (minimum tumor burden) at any time point; confirmed in a repeat, consecutive assessment ≥ 4 weeks from prior assessment

Clinical Implications of irRC



Comparison of Response Criteria

Table 1. Comparison between the RECIST 1.1, the WHO and the irRC criteria (adapted from Wolchok 2009).

Comparison between RECIST, WHO, and irRC criteria			
	RECIST	**WHO**	**irRC**
New, measurable lesions (i.e. ≥5 × 5 mm)	Always represent PD	Always represent PD	Incorporated into tumour burden
New, non-measurable lesions (i.e. <5 × 5 mm)	Always represent PD	Always represent PD	Do not define progression (but preclude irRC)
Non-index lesions	Changes contribute to defining BOR of CR, PR, SD, and PD	Changes contribute to defining BOR of CR, PR, SD, and PD	Contribute to defining irRC (complete disappearance required)
Complete response (CR)	Disappearance of all lesions in one observation in randomised studies. Confirmation is needed for non-randomised studies, according to study protocol	Disappearance of all lesions in two consecutive observations not less than four weeks apart	Disappearance of all lesions in two consecutive observations not less than four weeks apart
Partial response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters, in the absence of new lesions or unequivocal progression of non-index lesions	A ≥50% decrease in SPD of all index lesions compared with baseline in two observations at least four weeks apart, in the absence of new lesions or unequivocal progression of non-index lesions	A ≥50% decrease in tumour burden compared with baseline in two observations at least four weeks apart
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters, in absence of new lesions or unequivocal progression of non-index lesions	A 50% decrease in SPD compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions	A 50% decrease in tumour burden compared with baseline cannot be established nor 25% increase compared with nadir
Progressive disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. The sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression	At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)	At least 25% increase in tumour burden compared with nadir (at any single time point) in two consecutive observations at least four weeks apart

Pseudoprogression

- A response that occurs after the initial development of new lesions or an increase in the size of target lesions
  - Initial report of immune-related response criteria in patients who received ipilimumab for treatment of melanoma found that 9.7% of patients had clinical responses (partial response and stable disease) that would have been misclassified as disease progression by WHO criteria[1]
  - Occurs in up to 10% of patients treated with PD-1 antibodies[2]

1. Wolchok JD, Hoos A, O'Day S, et al: Guidelines for the evaluation of immune therapy activity in solid tumors: Immune-related response criteria. Clin Cancer Res 15:7412-7420, 2009
2. HodiFS,SznolM,KlugerHM,etal.Long-term survival of ipilimumab-naive patients (pts) with advanced melanoma (MEL) treated with nivolumab (anti-PD-1, BMS-936558, ONO-4538) in a phase I trial. *J Clin Oncol*. 2014;32(15)(suppl):9002.

Pseudoprogression and ctDNA

- Circulating tumor DNA (ctDNA) has been shown to predict response and survival in patients with metastatic melanoma treated with anti–programmed cell death protein 1 (PD-1) antibodies
- Explorative biomarker study examined circulating *BRAF* and *NRAS* mutations in a cohort of 125 patients with melanoma receiving PD-1 antibodies alone or in combination with ipilimumab
  - Plasma samples of ctDNA at baseline and while receiving treatment were taken for analysis prospectively over the first 12 weeks of treatment.
  - Favorable ctDNA profile (undetectable ctDNA at baseline or detectable ctDNA at baseline followed by > 10-fold decrease) and unfavorable ctDNA profile (detectable ctDNA at baseline that remained stable or increased) were correlated with response and prognosis.

Lee, JH et al. (2018). Association Between Circulating Tumor DNA and Pseudoprogression in Patients With Metastatic Melanoma Treated With Anti–Programmed Cell Death 1 Antibodies. *JAMA Oncology*, doi:10.1001/jamaoncol.2017.5332

Pseudoprogression and ctDNA (cont.)

- Study results
  - Findings
    - In this cohort study of 125 patients with metastatic melanoma who were treated with anti–PD-1, the number of circulating tumor DNA copies was reduced by greater than 10-fold within 12 weeks of treatment and accurately identified patients with pseudoprogression
    - These profile patterns of ctDNA were significantly associated with overall survival
  - Meaning
    - Reduction in the number of ctDNA copies within 12 weeks of anti–PD-1 inhibitor treatment represents a liquid molecular biomarker profile for prognosis

Lee, JH et al. (2018). Association Between Circulating Tumor DNA and Pseudoprogression in Patients With Metastatic Melanoma Treated With Anti–Programmed Cell Death 1 Antibodies. *JAMA Oncology*, doi:10.1001/jamaoncol.2017.5332

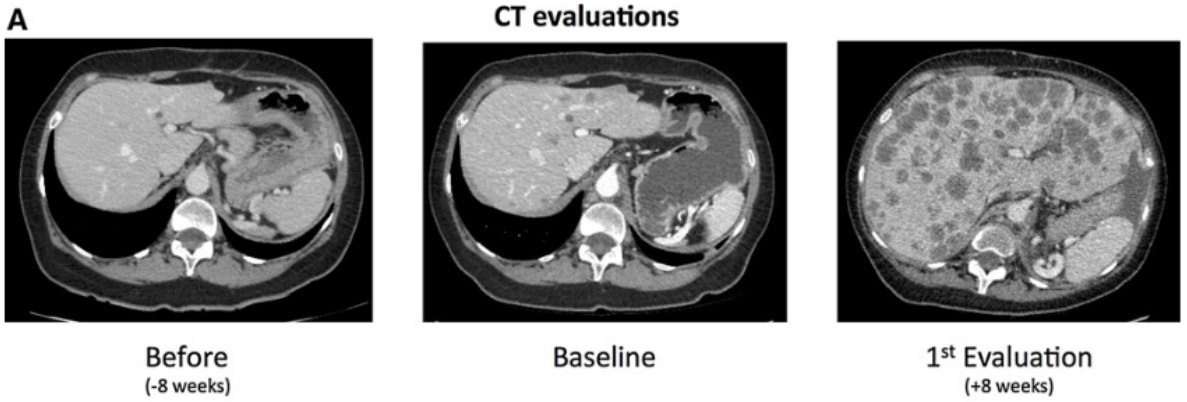
Figure 2. Overview of Mutation Type, Circulating Tumor DNA (ctDNA), and Immune-Related Response Criteria (irRC) Results in 29 Patients

Hyperprogressive Disease (HPD)

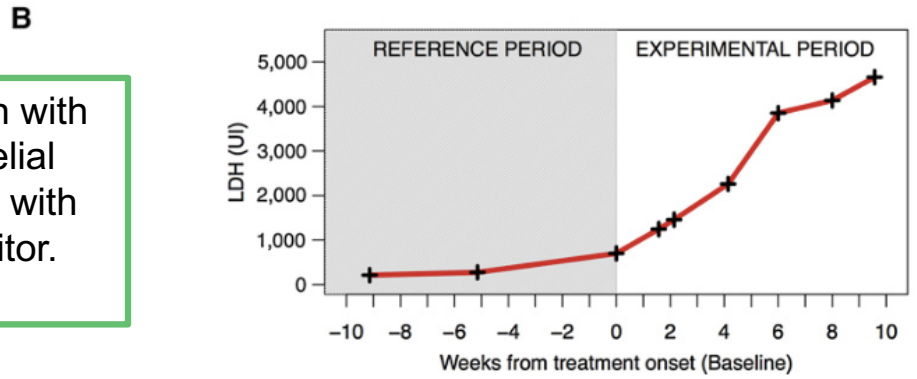
- Defined as RECIST progression at the first evaluation and as a > 2-fold increase of the tumor growth rate (TGR) between the reference (time prior to initiating therapy) and the experimental (treatment with IO) periods.
- In one study, 9% of patients treated with anti–PD-1/PD-L1 had HPD
  - HPD was not associated with higher tumor burden at baseline, nor with any specific tumor type
  - HPD is associated with a higher age ($p < 0.05$) and a worse outcome (overall survival)

Champiat, S., et al. (2017). Hyperprogressive Disease Is a New Pattern of Progression in Cancer Patients Treated by Anti-PD-1/PD-L1. *Clin Cancer Res*, 23(8).

Hyperprogressive Disease (cont.)



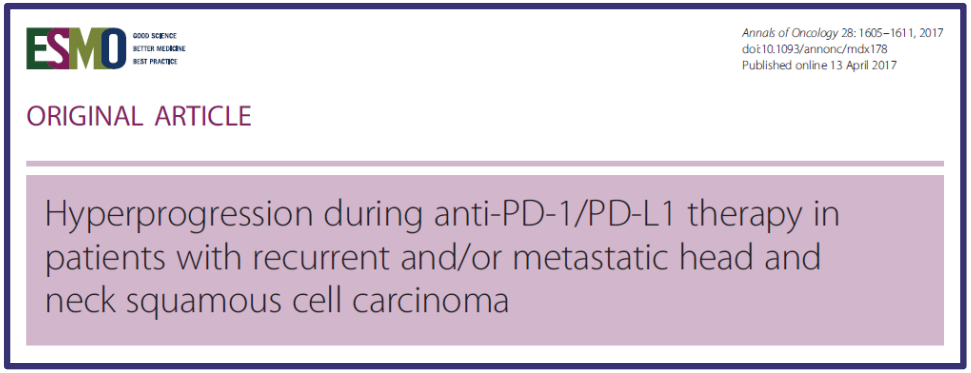
58-year-old woman with metastatic urothelial carcinoma treated with anti–PD-L1 inhibitor.



Champiat, S., et al. (2017). Hyperprogressive Disease Is a New Pattern of Progression in Cancer Patients Treated by Anti-PD-1/PD-L1. *Clin Cancer Res*, 23(8).

Hyperprogressive Disease (cont.)

- Genomic profiling may help to identify patients at risk of HPD
  - Study of 155 patients treated with immunotherapy demonstrated HPD in 6/6 patients with MDM2/MDM4 amplification
  - 2 of 10 patients with EGFR alterations were also hyperprogressors
  - In multivariate analysis, MDM2/MDM4 and EGFR alterations correlated with time to treatment failure < 2 months



- Retrospective evaluation of tumor growth kinetics (TGK) of 34 HNSCC patients treated with PD-1/PD-L1 inhibitors
  - 29% of patients experienced hyperprogression with associated shorter PFS
  - Hyperprogression significantly correlated with presence of regional recurrence but not presence of local recurrence
  - No pseudoprogression reported

HNSCC = head and neck squamous cell carcinoma

Saada-Bouzid, E., et al. (2017) Hyperprogression during anti-PD-1/PD-L1 therapy in patients with recurrent and/or metastatic head and neck squamous cell carcinoma. Annals of Oncology, 28, 1605-1611.

Hyperprogressive Disease (cont.)

- Mechanism of action is not currently understood
- Further investigations are ongoing

> *"In terms of the sheer number of histologies, the breadth of activity seen with inhibitors of programmed death 1 (PD-1) and programmed death ligand 1 (PDL-1) is beyond that of nearly any other class of targeted anticancer therapy available thus far. If there is a potential harm of accelerated progression induced by the therapies, this must be assessed and characterized, and potentially mitigated, as quickly as possible."*

Sharon, Elad. (2017). Can an immune checkpoint inhibitor (sometimes) make things worse? Clin Cancer Res, 23(8).

Treatment Beyond Progression

- Previously established that patients with a wide range of cancers may benefit from treatment with targeted therapy after initial RECIST progression
- Emerging data to suggest that some patients may also benefit from treatment after progression on immunotherapy
- Investigations are ongoing to determine which patients may benefit from treatment beyond progression to avoid excessive duration of therapy

Escudier, B., et al. (2017). Treatment beyond progression in patients with advanced renal cell carcinoma treated with nivolumab in CheckMate 025. *European Urology*, 72, 368-376.

RCC Treatment Beyond Progression

- Subgroup analysis of RCC patients treated with nivolumab in the phase III CheckMate 025 study
  - Patients continuing to tolerate therapy and exhibit investigator-assessed clinical benefit eligible to be treated beyond progression (TBP)
- Of 406 nivolumab-treated patients, 316 (78%) progressed by RECIST
- Of those who progressed, 48% received TBP
- Before TBP, response rate in this group was 20%
- Postprogression, 13% of all patients receiving TBP had ≥ 30% tumor burden reduction
- Incidence of treatment-related adverse events in TBP group was lower after (59%) vs. before (71%) progression

RCC = renal cell carcinoma

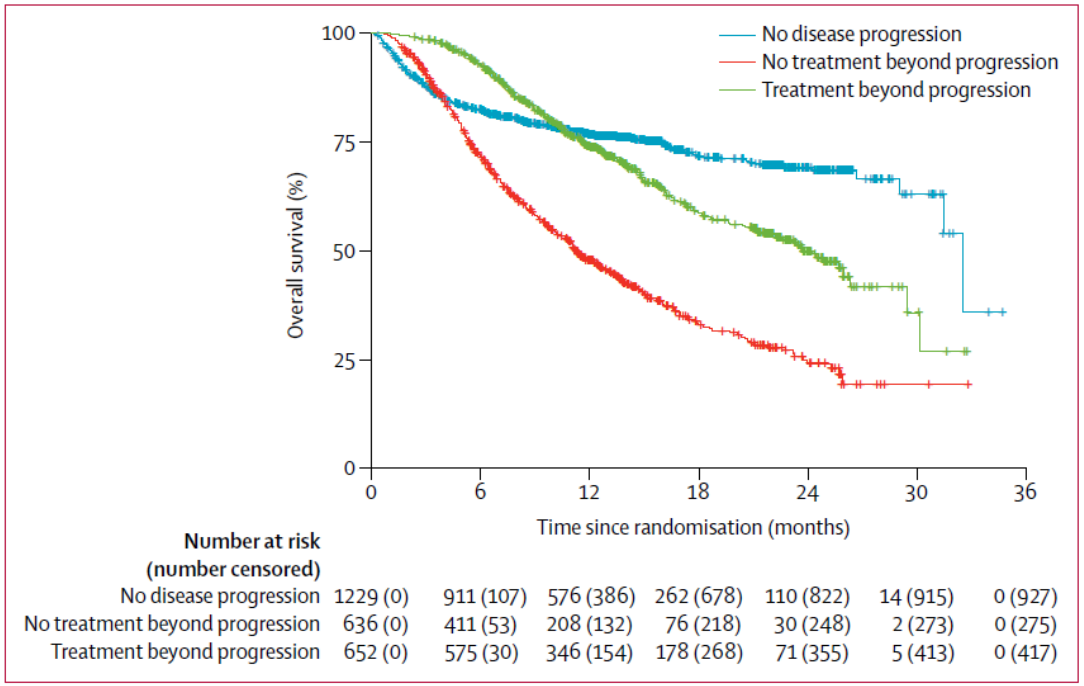
Escudier, B., et al. (2017). Treatment beyond progression in patients with advanced renal cell carcinoma treated with nivolumab in CheckMate 025. *European Urology*, 72, 368-376.

Melanoma Treatment Beyond Progression

- Pooled analysis of 8 multicenter trials investigating anti–PD-1 antibodies in metastatic melanoma patients allowing for treatment beyond progression.
- 2,624 patients evaluated in pooled data set
  - 1,361 (52%) had progressive disease, of whom 692 (51%) received TBP
  - 95 (19%) of 500 patients TBP had ≥ 30% decrease in tumor burden
    - This represents 4% of the total 2,624 patient panel
  - Median overall survival was longer in TBP group vs. non-TBP group

Beaver, J.A., et al. (2018). Patients with melanoma treated with an anti-PD-1 antibody beyond RECIST progression: a US Food and Drug Administration pooled analysis. Lancet Oncology, 19, 229-39

Melanoma Treatment Beyond Progression (cont.)

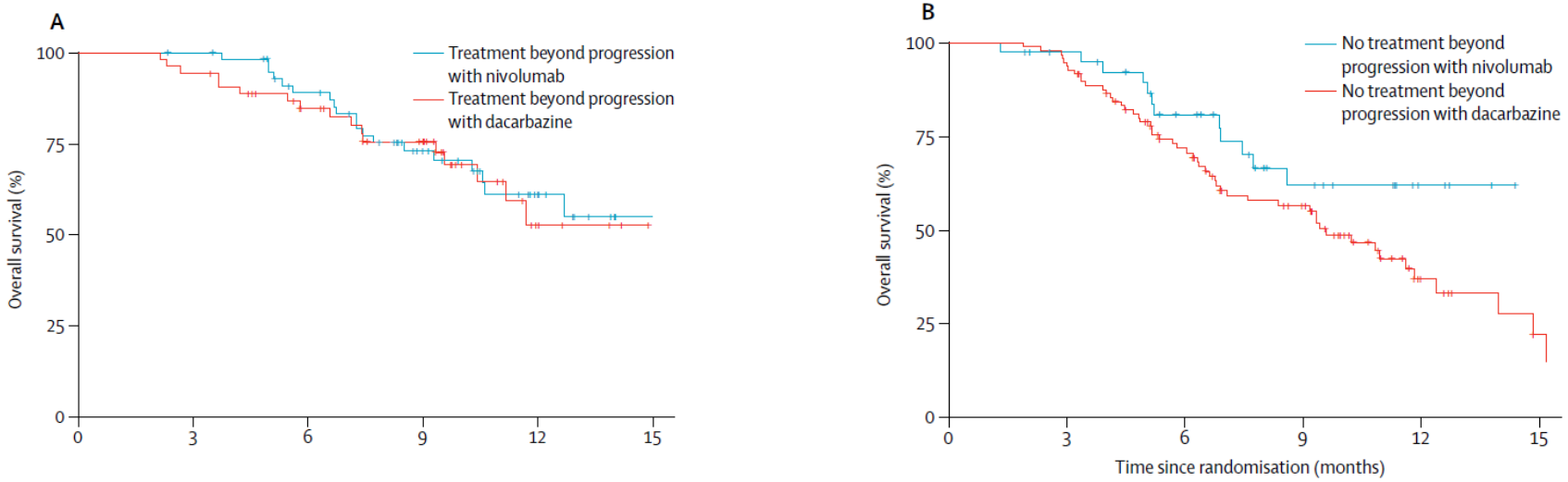


Number at risk (number censored)							
No disease progression	1229 (0)	911 (107)	576 (386)	262 (678)	110 (822)	14 (915)	0 (927)
No treatment beyond progression	636 (0)	411 (53)	208 (132)	76 (218)	30 (248)	2 (273)	0 (275)
Treatment beyond progression	652 (0)	575 (30)	346 (154)	178 (268)	71 (355)	5 (413)	0 (417)

Figure 2: Pooled overall survival analysis

Beaver, J.A., et al. (2018). Patients with melanoma treated with an anti-PD-1 antibody beyond RECIST progression: a US Food and Drug Administration pooled analysis. Lancet Oncology, 19, 229-39

Melanoma Treatment Beyond Progression (cont.)



- CheckMate 066 allowed for treatment beyond progression in both nivolumab and dacarbazine arms
- Patients receiving TBP in the nivolumab and dacarbazine groups had similar outcomes despite a clear improvement in efficacy with nivolumab vs. dacarbazine in overall trial population

Beaver, J.A., et al. (2018). Patients with melanoma treated with an anti-PD-1 antibody beyond RECIST progression: a US Food and Drug Administration pooled analysis. Lancet Oncology, 19, 229-39

Audience Response Question

PD-L1 protein expression:

A. Upregulates T-cell activation
B. Increases from IDO enzyme
C. May be predictive of response to immunotherapy
D. Indicates a poor response to immunotherapy
E. Unsure

Audience Response Question

Oncogenic alterations found in mismatch repair deficient tumors:

A. Are often somatic mutation events that occur as a result of microsatellite instability
B. Increase the expression of PD-L1 protein
C. Are characterized by instability in a single microsatellite DNA sequence
D. Decrease the likelihood that a patient will respond to immunotherapy
E. Unsure

Audience Response Question

Factors predictive of response to immunotherapy may include all of the following EXCEPT:

A) Mutations of MHC molecules

B) PD-L1 (*CD274*) gene amplification status

C) PD-L1 protein expression

D) Tumor mutation burden and amount of neoantigen

E) Unsure

Audience Response Question

Chemotherapy combined with immunotherapy can lead to improved response rates. One of the ways in which adding chemotherapy augments responses is:

A) By suppressing the immune system to decrease immune-related adverse events
B) By increasing antigen presentation to increase immune recognition
C) By changing the expression of PD-L1 protein to increase immune recognition
D) By inducing nonimmunogenic cell death to decrease immune tolerance
E) Unsure

Audience Response Question

Your patient on immunotherapy presents for a scan review at their first evaluation time point. Per RECIST, the patient has a > 2-fold increase of the tumor growth rate between the time prior to initiating immunotherapy and the time on treatment. You recognize that this response pattern is consistent with:

A) Pseudoprogression. You will continue immunotherapy and re-evaluate with imaging in 4–6 weeks.
B) Pseudoprogression. You will discontinue immunotherapy because it is not working.
C) Hyperprogression. You will continue immunotherapy and re-evaluate with imaging in 4–6 weeks.
D) Hyperprogression. You will discontinue immunotherapy because it is not working.
E) Unsure