Incontri
di aggiornamento
del Dipartimento
Oncologico

Negrar, 11 ottobre 2016

Criteri di valutazione della risposta in oncologia

Criteri in immuno-oncologia

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Oncologia Medica
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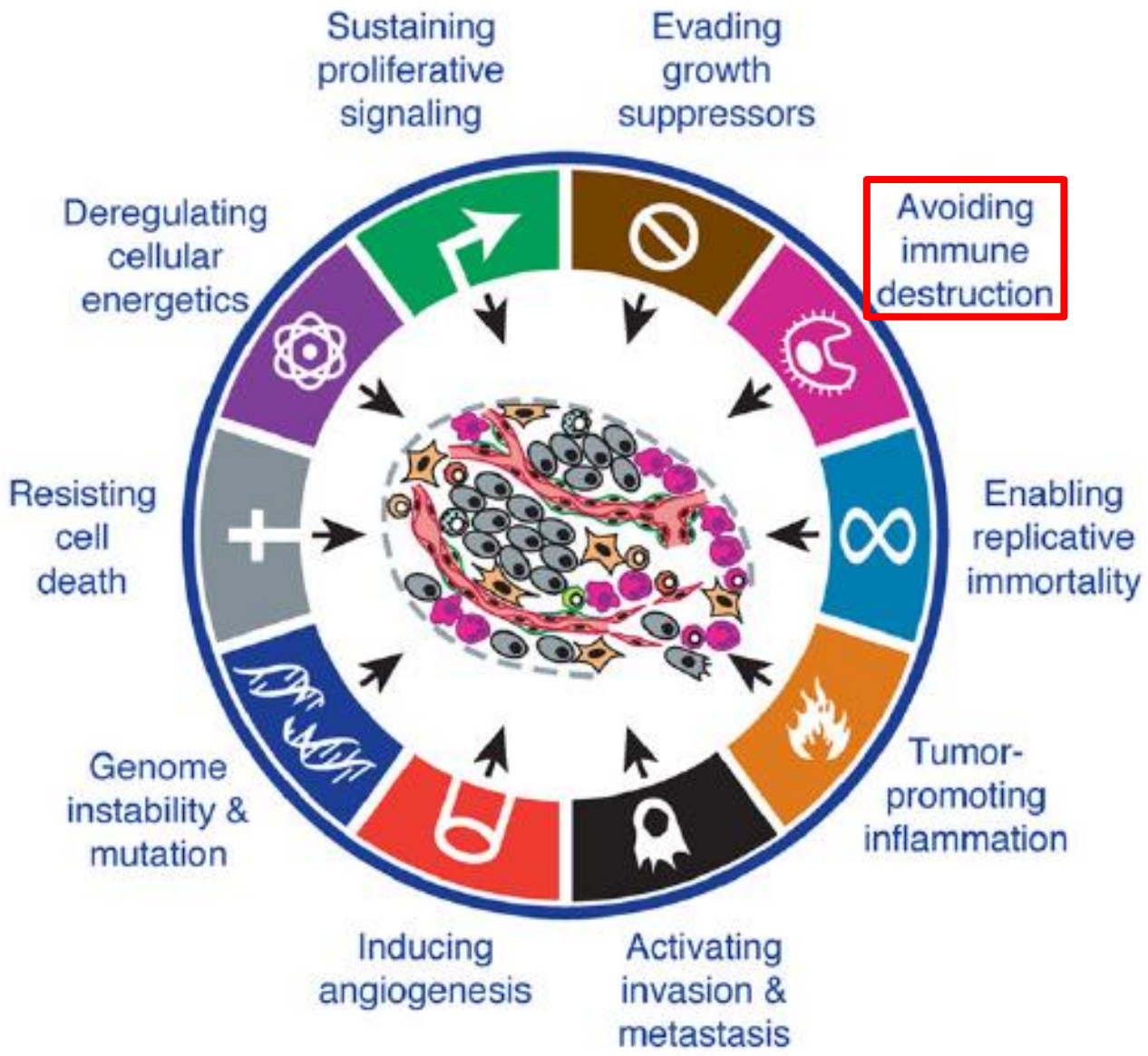
Negrar - Verona

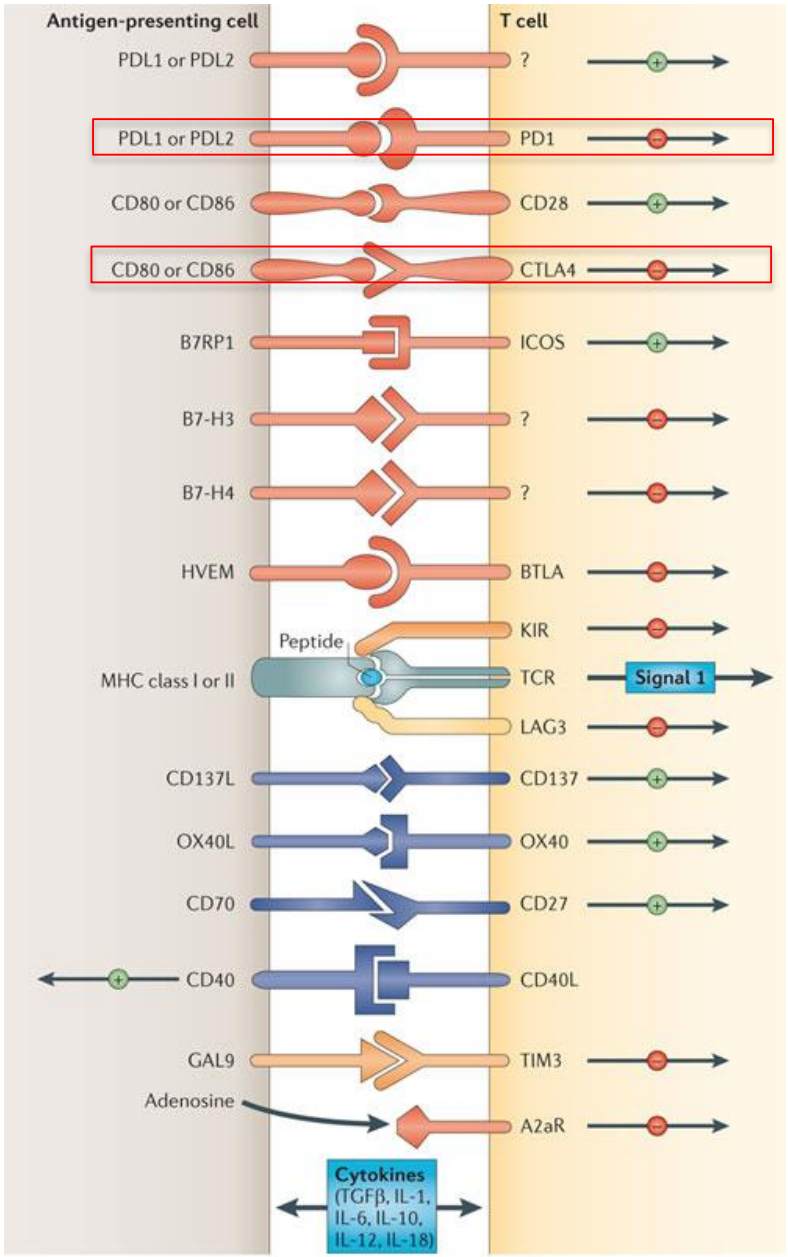

Science
Breakthrough of the Year
Cancer Immunotherapy
T cells on the attack
AAAS

Hallmarks of cancer



Hanahan D et al. Cell 2011; 144:646-74

Immune checkpoints



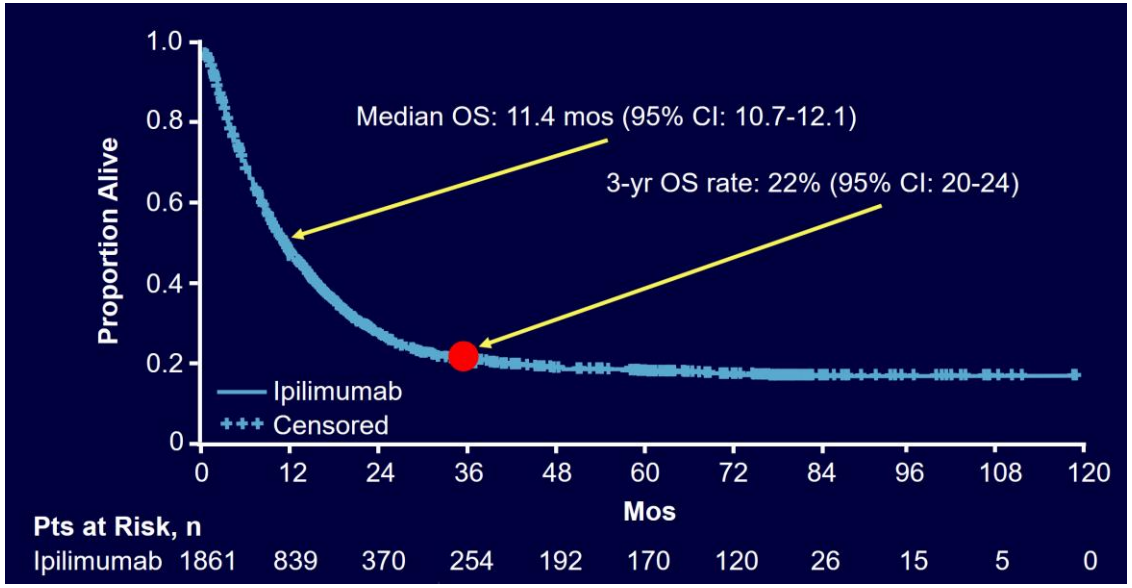
Anti PD1/PDL1

Anti CTLA4

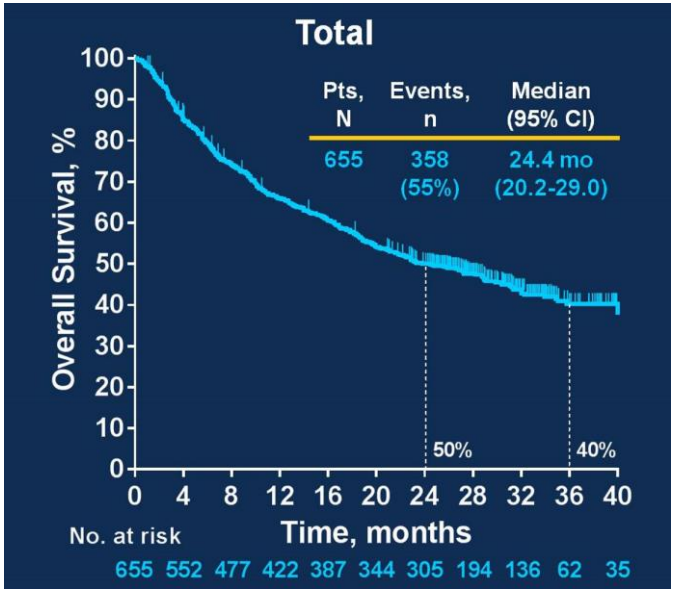
Pardoll DM. Nat Rev Cancer 2012;12:252-64

OS of MM pts treated with anti-CTLA4 and anti-PD1

Ipilimumab



Pembrolizumab



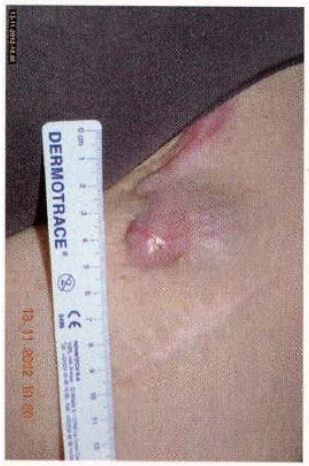
Schadendorf D et al. J Clin Oncol 2015; 33:1889-94.
Robert C et al. ASCO 2016 Annual Meeting

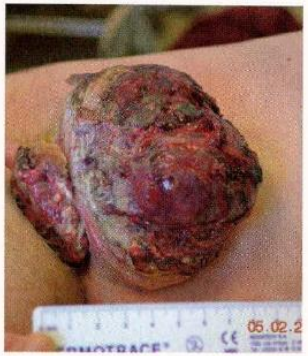
Clinical development of checkpoint inhibitors in solid tumors

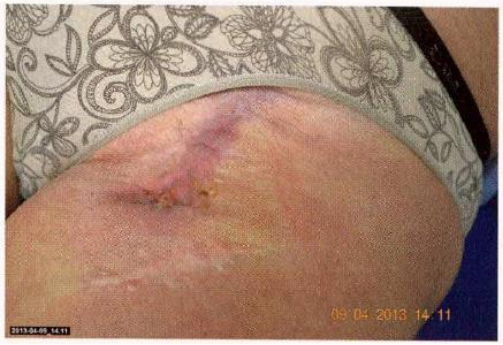
Antibody	Molecule	Development Stage
Nivolumab	Anti-PD-1 Fully human IgG4	Approved (US): advanced melanoma (with or w/o ipilimumab), advanced NSCLC after CT, advanced renal cell carcinoma after anti-angiogenic therapy, Hodgkin Lymphoma after HSCT Phase III in multiple tumors
Pembrolizumab	Anti-PD-1 Humanized IgG4	Approved (US): advanced melanoma, advanced NSCLC with PD-L1 expression after CT Phase III multiple tumors (HNSCC, melanoma, bladder, gastric/GE)
Atezolizumab	Anti-PD-L1 Engineered human IgG1	Approved (US): locally advanced or metastatic urothelial carcinoma after CT Phase III multiple tumors (NSCLC, RCC, TNBC)
Durvalumab	Anti-PD-L1 Engineered human IgG1	Phase III multiple tumors (bladder, NSCLC, HNSCC)
Avelumab	Anti-PD-L1 Fully human IgG1	Phase III (NSCLC, Merkel carcinoma)
Ipilimumab	Anti-CTLA4 Humanized IgG1	Approved (US): advanced melanoma Phase III multiple tumors (melanoma, NSCLC, SCLC, CRPC, GBM, RCC)

Pseudoprogression

56-year-old woman with advanced melanoma

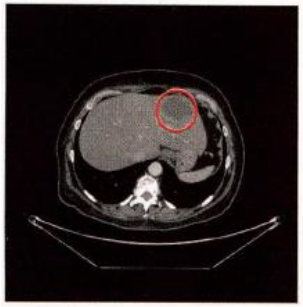


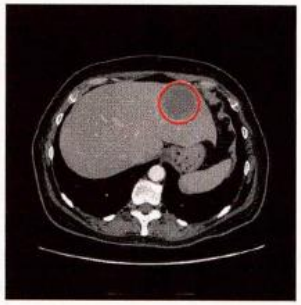


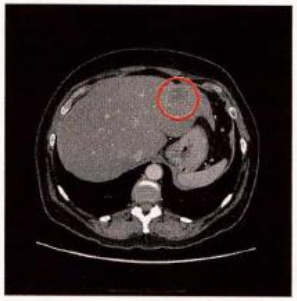


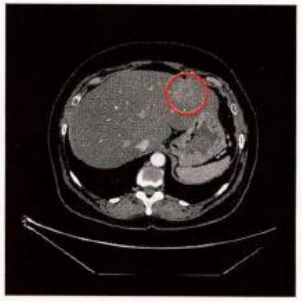
Baseline | Week 12 | Week 24 | Week 52 | Week 96

28 months





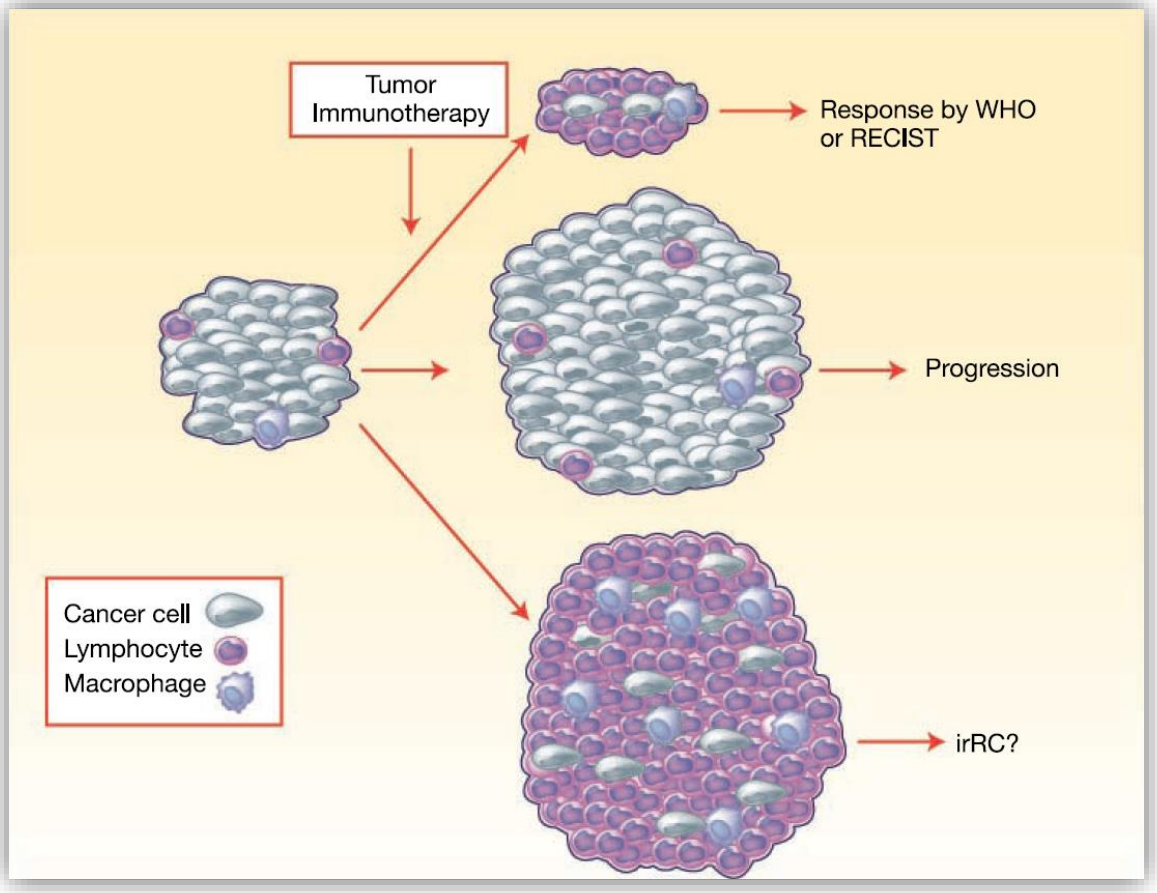




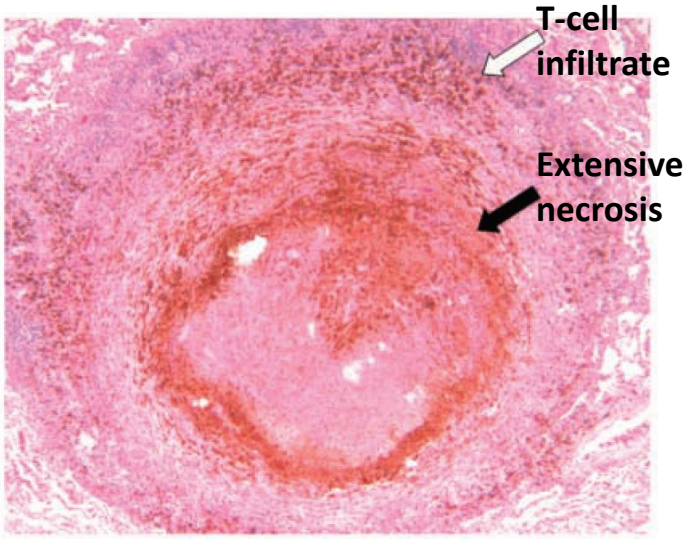
Complete Response

Hodi FS et al. J Clin Oncol 2016; 34:1510-1517

Mechanims underlying pseudoprogression



Resected metastatic melanoma tumor nodule of the lung

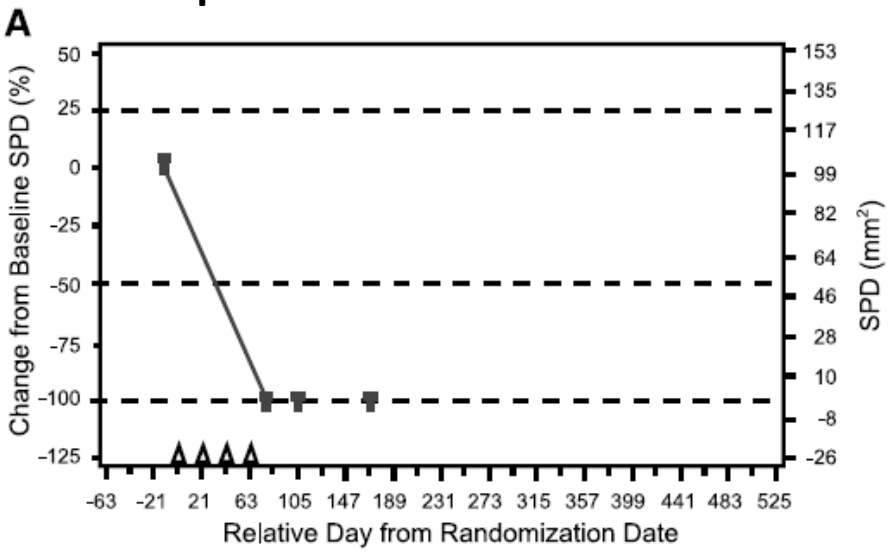


Wolchok JD et al. Clin Cancer Res 2009;15:7412-20

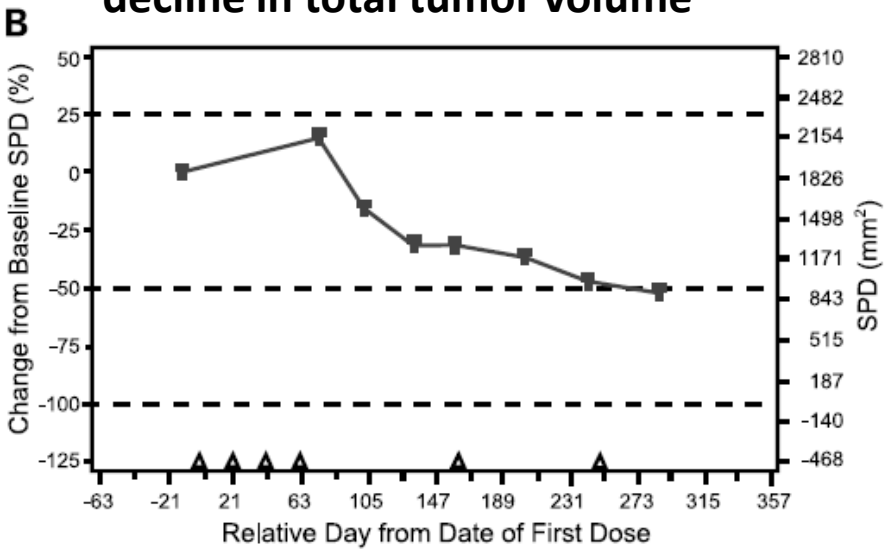
Four patterns of response (1 and 2)

2 meet conventional criteria for response

Response in baseline lesions



"stable disease" with slow, steady decline in total tumor volume

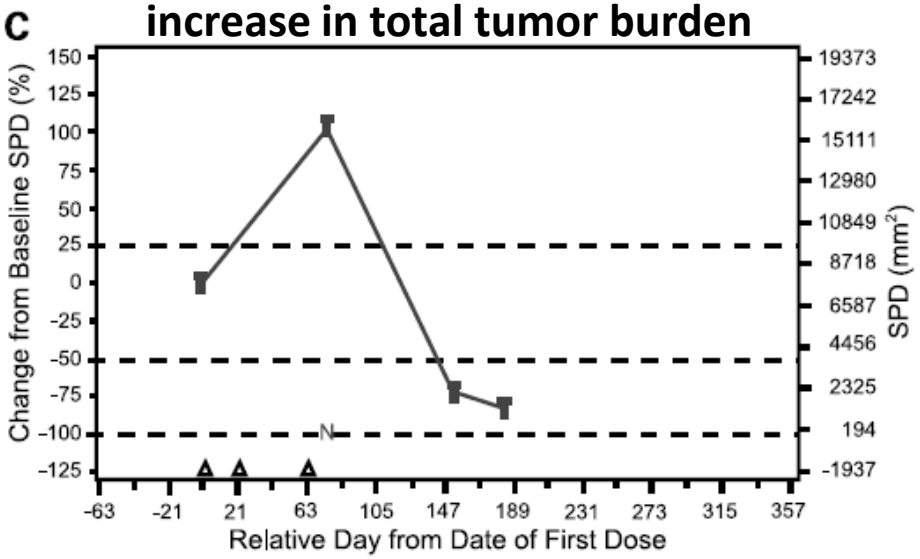


Wolchok JD et al. Clin Cancer Res 2009;15:7412-20

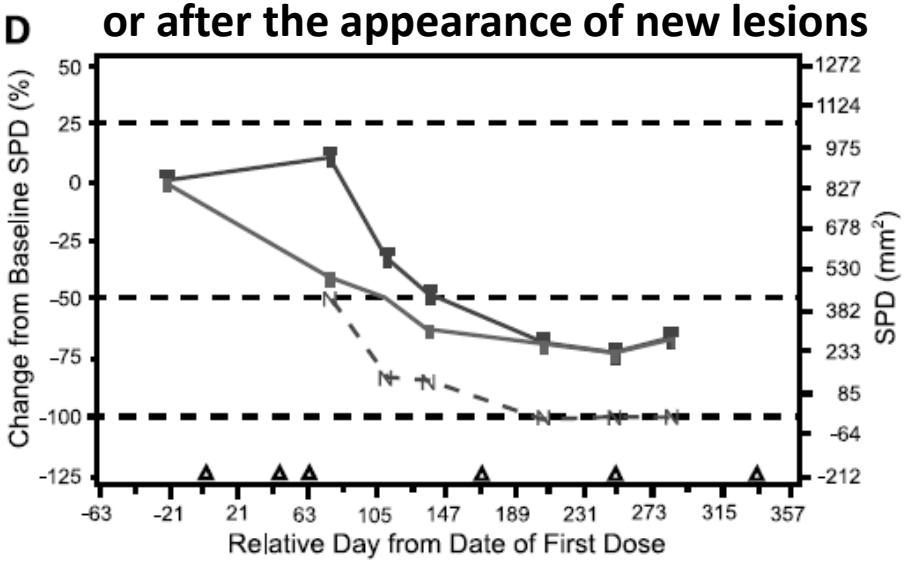
Four patterns of response (3 and 4)

The other 2 patterns go against the standard criteria for response

Responses after an initial increase in total tumor burden



Reduction in total tumor burden during or after the appearance of new lesions



Wolchok JD et al. Clin Cancer Res 2009;15:7412-20

Immune Related Response Criteria (irRC)

Category	RECIST v 1.1	WHO	irRC
Measurement of tumor burden	Unidimensional	Bidimensional	Bidimensional
Target lesions	Maximum, 5	No maximum specified	Maximum, 15 index lesions
New lesion	Always represents PD	Always represents PD	Up to 10 new visceral lesions and 5 cutaneous lesions may be added to the SPD of all index lesions at any time point
Complete response	Disappearance of all target and nontarget lesions Nodes must regress to < 10 mm short axis No new lesions Confirmation required		
Partial response	≥ 30% decrease in LD compared with baseline Confirmation requierd	≥ 50% decrease in SPD compared with baseline Confirmation required	≥ 50% decrease in SPD compared with baseline Confirmation required
Progressive disease	≥ 20% + 5-mm absolute increase in LD compared with nadir Appearance of new lesions or progression of nontarget lesions	≥ 25% increase in SPD compared with nadir Appearance of new lesions or progression of non-index lesions	≥ 25% increase in SPD compared with nadir. New lesions added to tumor burden Confirmation required
Stable disease	Neither partial response nor progressive disease		

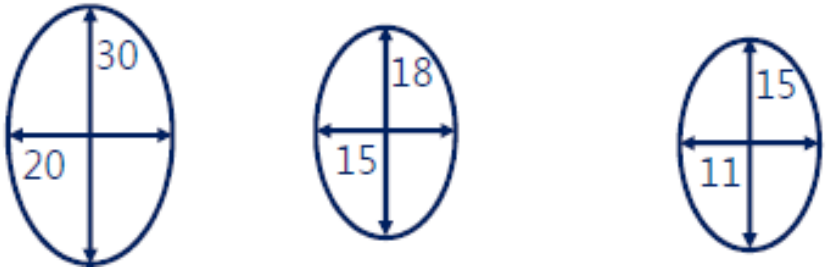
Wolchok JD et al. Clin Cancer Res 2009;15:7412-20
Hodi FS et al. J Clin Oncol 2016; 34:1510-17

Definition of Disease Progression

	RECIST v 1.1	WHO	irRC
Target lesions	≥20% increase in the sum of diameters of target lesions and the sum demonstrates an absolute increase of at least 5mm	≥25% increase in the sum of the products of the two largest perpendicular diameters of all index lesions	**≥25%** increase in the **tumor burden** (index + new measurable)
Non-target lesions	Unequivocal progression of nonindex lesions.	Unequivocal progression of nontarget lesions	Do **not define progression**
New lesion	Appearance of new lesions	Appearance of new lesions	**Measurable**: incorporated in tumor burden **Unmeasurable**: do not define PD
Time point	Any single time point	Any single time point	**Two consecutive observations** at least 4 weeks apart

Wolchok JD et al. Clin Cancer Res 2009;15:7412-20
Hodi FS et al. J Clin Oncol 2016; 34:1510-17

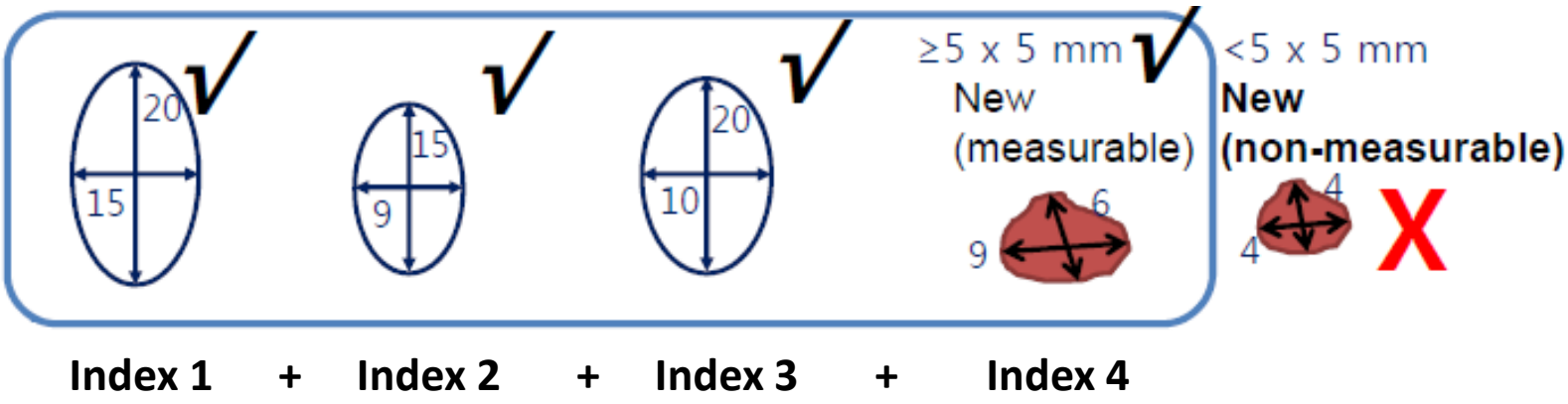
irRC: baseline assessment



Index 1 + **Index 2** + **Index 3**

- **The sum of the products of largest perpendicular diameters (SPD) of all index lesions is documented**
- **All index lesions might include 5 lesions per organ, up to 10 visceral lesions and 5 cutaneous index lesions.**

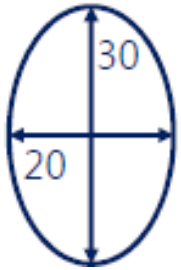
irRC: subsequent assessment



- **<u>Tumor burden:</u>** $SPD_{index\ lesions} + SPD_{new\ lesions}$
- **New non-measurable lesions do not define progression (but preclude irCR)**
- **The SPD of new, measurable lesions: ≥5 x 5 mm, up to 5 new lesions per organ, 5 new cutaneous lesions and 10 new visceral lesions**

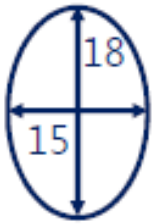
irRC: response evaluation

Baseline Assessment



Index 1
600 mm²

\+



Index 2
270 mm²

\+

Index 3
165 mm²

1035 mm²

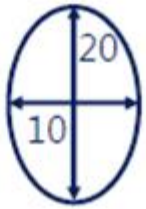
Subsequent Assessment

Index 1
300 mm²

\+

Index 2
135 mm²

\+



Index 3
200 mm²

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Index 4
54 mm²

689 mm²

33% decrease in SPD compared with baseline = STABLE DISEASE

irRC in ipilimumab phase 2 trials

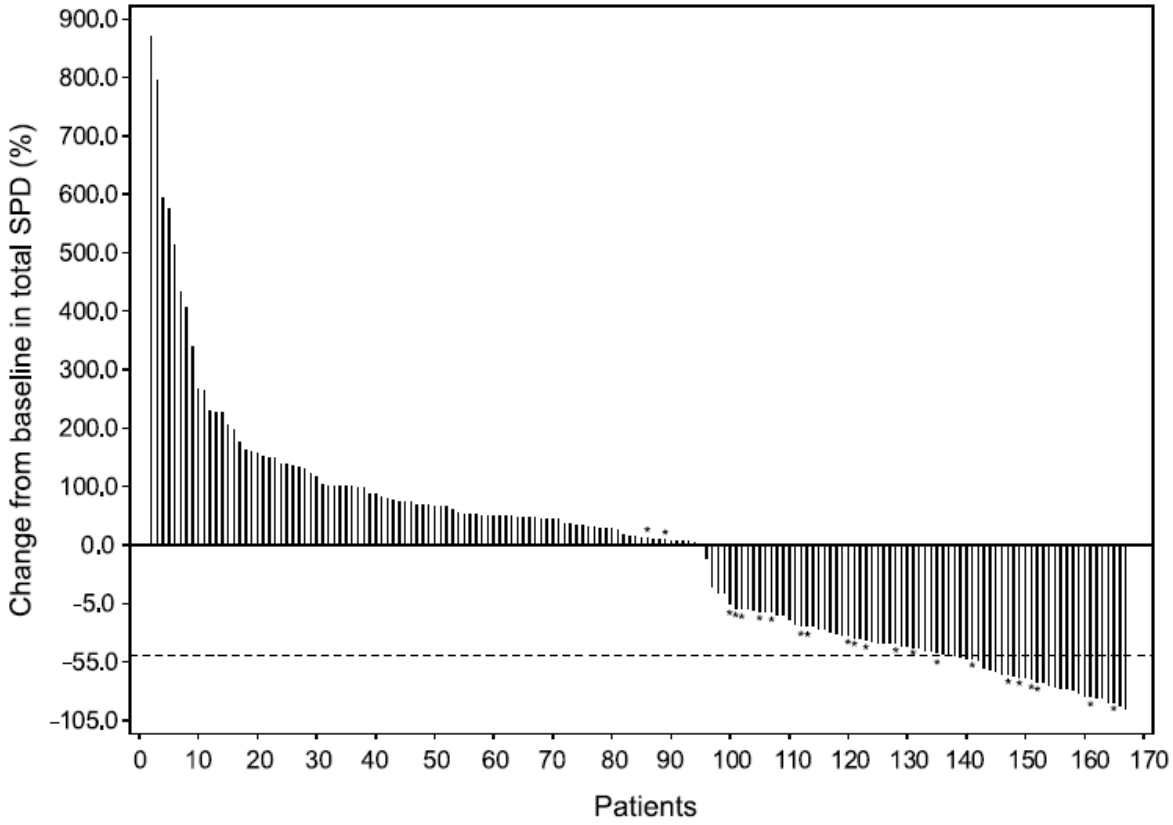
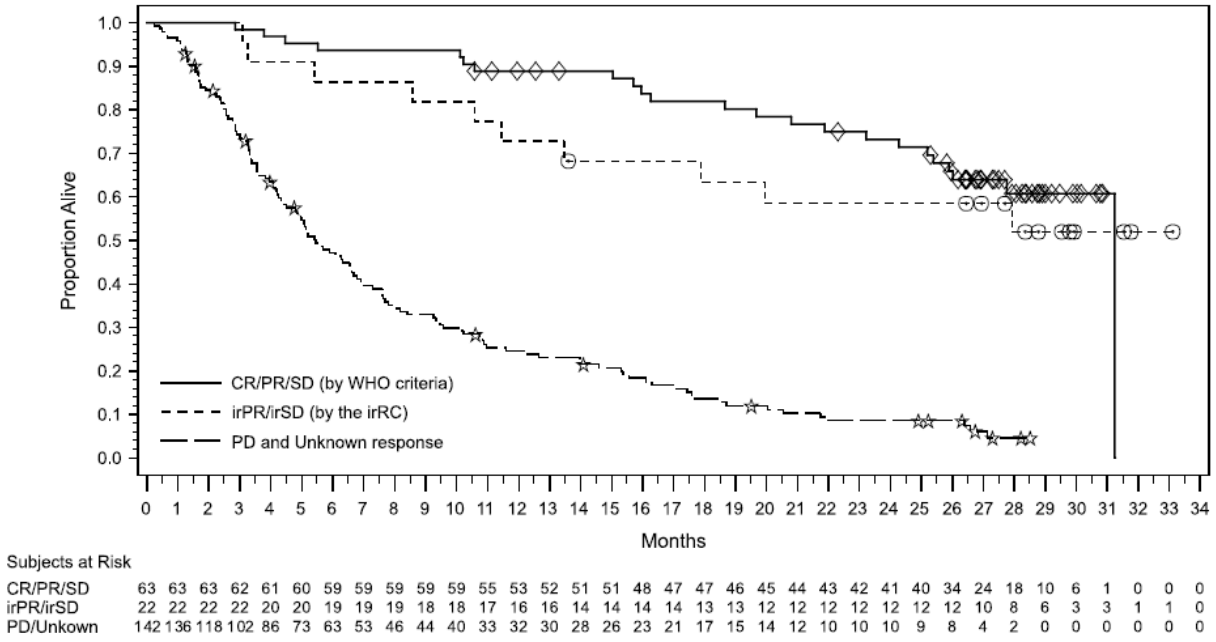


Fig. 2. Waterfall plot of maximum percentage reduction from baseline in total tumor burden. Included are advanced melanoma patients treated with, or randomized to, ipilimumab at 10 mg/kg in the CA184-008 and CA184-022 studies; the tumor responses of 167 evaluable patients were assessed using the irRC. Twenty-two patients were characterized as irPR ($n = 5$) or irSD ($n = 17$), who otherwise would have been labeled "PD" by conventional WHO criteria. These patients are indicated by an asterisk. In addition, one patient characterized as SD by WHO criteria was evaluated as irPR (patient #148).

Wolchok JD et al. Clin Cancer Res 2009;15:7412-20

WHO vs irRC: overall survival



Waterfall plot of maximum percentage reduction from baseline in total tumor burden.

Included are advanced melanoma patients treated with, or randomized to, ipilimumab at 10 mg/kg in the CA184-008 and CA184-022 studies; the tumor responses of 167 evaluable patients were assessed using the irRC. Twenty-two patients were characterized as irPR (n = 5) or irSD (n = 17), who otherwise would haw been labeled "PD" by conventional WHO criteria. These patients are indicated by an asterisk.

In addition, one patient characterized as SD by WHO criteria was evaluated as irPR (patient #148)

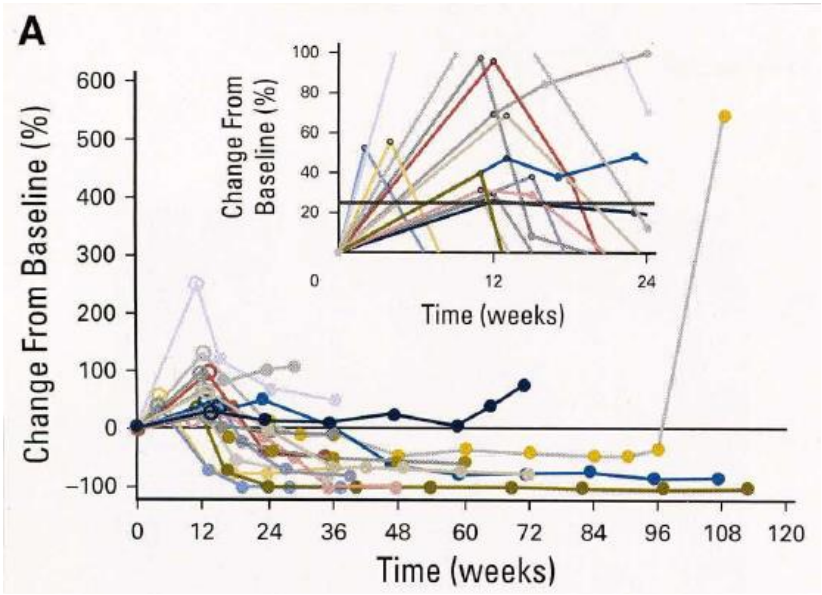
Wolchok JD et al. Clin Cancer Res 2009;15:7412-20

Atypical responses in pembrolizumab trials

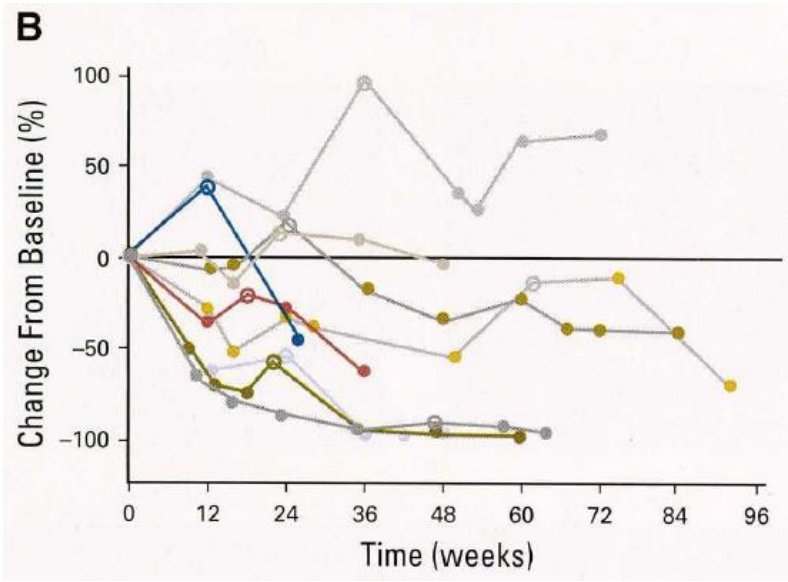
24 (7%) of 327 patients had atypical responses:

- *15 (5%) early pseudoprogression*
- *9 (3%) delayed pseudoprogression*

Early pseudoprogression



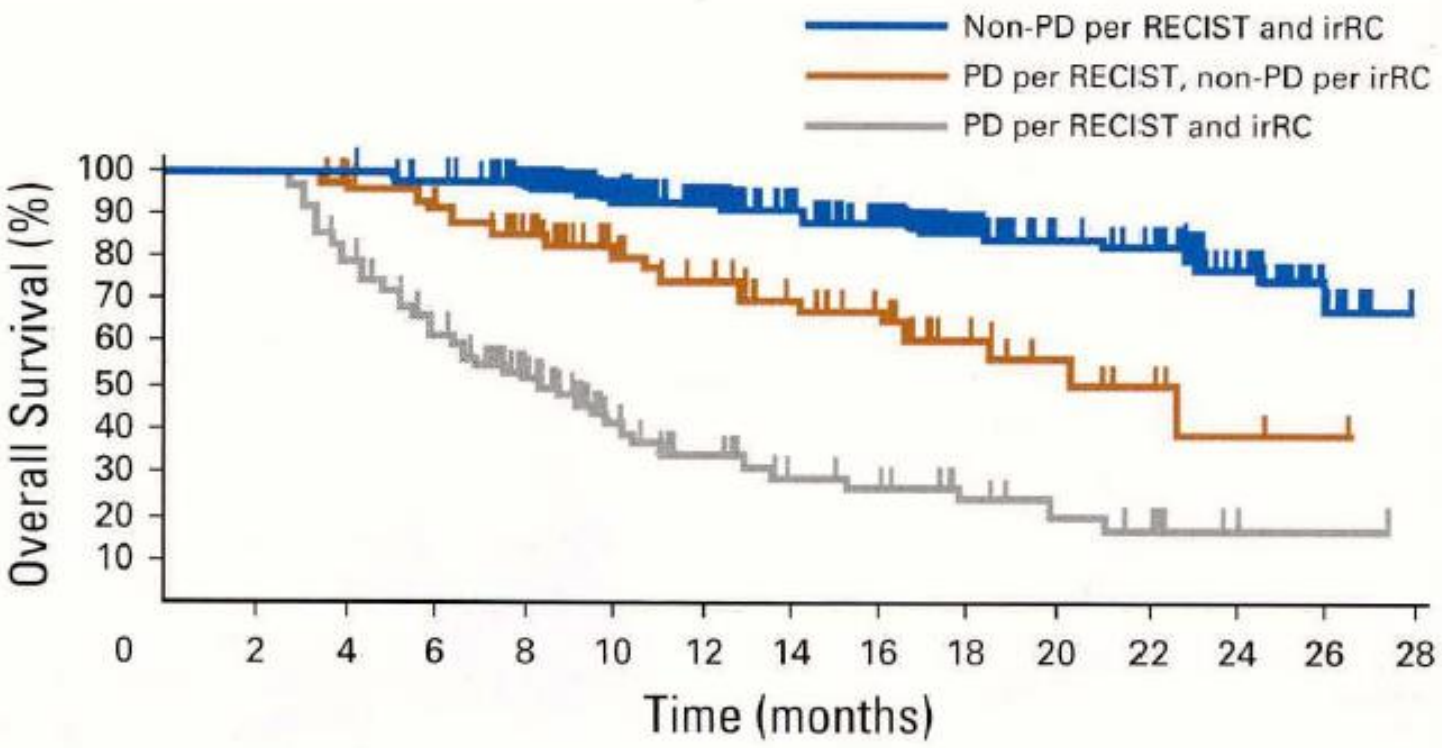
Delayed pseudoprogression



Hodi FS et al. J Clin Oncol 2016; 34:1510-1517

irRC vs RECIST 1.1: overall survival

84 (14%) of 327 patients were PD according to RECIST but not to irRC



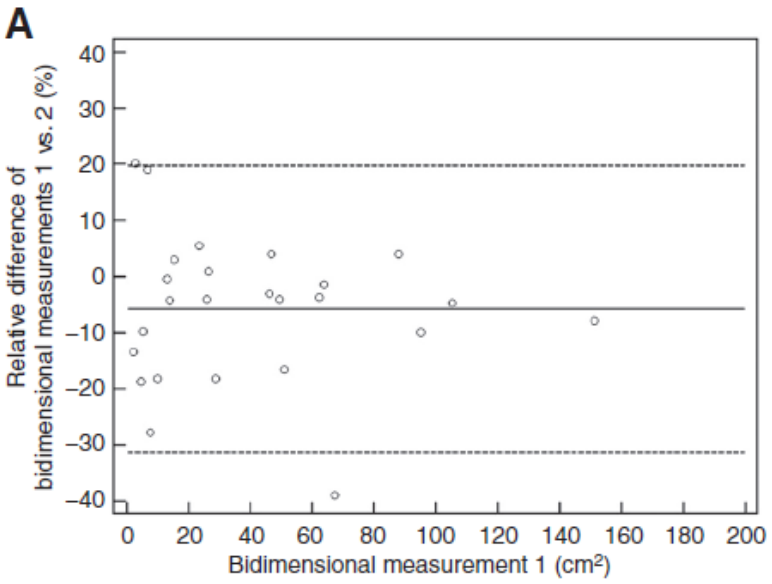
No. at risk

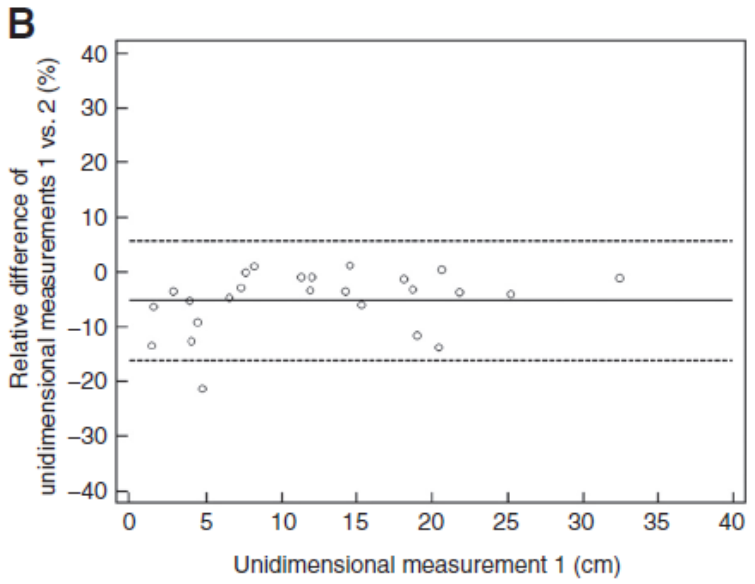
Non-PD per RECIST and irRC	331	331	329	321	301	219	192	159	136	79	60	55	31	8	0
PD per RECIST, non-PD per irRC	84	84	79	71	60	44	37	28	22	13	9	6	3	2	1
PD per RECIST and irRC	177	177	139	109	75	48	33	23	20	15	10	8	1	1	0

Hodi FS et al. J Clin Oncol 2016; 34:1510-1517

Moving from bidimensional to unidimensional

	Bidimensional assessment (the original irRC (7))	Unidimensional assessment
Measurable lesions	≥5 × 5 mm^2 by bidimensional measurements	≥10 mm in the longest diameter
Measurement of each lesion	The longest diameter × the longest perpendicular diameter (cm^2)	The longest diameter (cm)
The sum of the measurements	The sum of the bidimensional measurements of all target lesions and new lesions if any	The sum of the longest diameters of all target lesions and new lesions if any
Response assessment	PD: ≥25% increase from the nadir PR: ≥50% decrease from baseline CR: Disappearance of all lesions	PD: ≥20% increase from the nadir PR: ≥30% decrease from baseline CR: Disappearance of all lesions
New lesions	The presence of new lesion(s) does not define progression. The measurements of the new lesion(s) are included in the sum of the measurements.	
Confirmation	Confirmation by 2 consecutive observations not less than 4 weeks apart was required for CR, PR, and PD	





Nishino M et al. Clin Cancer Res 2013;19:3936-43

Towards irRECIST

ADAPTATION OF THE IMMUNE-RELATED RESPONSE CRITERIA: irRECIST

ESMO 2014, ABSTRACT 4958

Oliver Bohnsack, PAREXEL
Katarina Ludajic, PAREXEL
Axel Hoos, GSK

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AIM

RECIST 1.1 has its shortcomings for targeted immunotherapy in oncology. Using RECIST 1.1 in immunotherapy trials would lead to declaration of progressive disease (PD) too early, when the treatment effect is not yet fully evident. RECIST also neglects the importance of the 'flare effect' - pseudo-progression effect within the so-called flare time window.

Immune related Response Criteria (irRC) based on WHO criteria were published with an aim to provide better assessment of the effect of immunotherapeutic agents. With this poster we introduce irRECIST based on RECIST 1.1, irRC and Nishino et al., 2013 findings. Our aim is to define criteria that better capture antitumor activity and reduce irRC criteria ambiguity.

Consistent implementation of irRECIST by both investigators and blinded independent readers will help reduce site-central discordance.

METHODS

The adaptations from irRC and WHO criteria, as applicable in immunotherapy clinical studies, are documented in the "irRECIST Modifications and Clarifications" column in a comparative table format within our Blinded Independent Central Review (BICR) Charter.

The modifications we introduce represent adaptations of published criteria based on radiology practice and clinical trial experience, and they provide more objective and reproducible response assessments for investigators and for the central independent image review.

RESULTS

irRECIST criteria are based on irRC criteria adapted for unidimensional measurements, as outlined in Nishino et al., 2013. To further align the criteria with RECIST 1.1 we outline the approach for the assessment of baseline-selected non-target lesions and new non-measurable lesions, and discuss the impact of those lesions on the overall tumor response assessment.

Guidelines for the evaluation of patients with non-target disease only and patients in adjuvant setting is provided.

Original irRC, Including WHO Criteria References	irRECIST Modifications and Clarifications	Rationale for Modification
At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated.	**1. 0 Baseline: Measurable Lesion Definitions and Target Lesion Selection** Follow the definitions from RECIST 1.1. Measurable lesions must be accurately measured in at least one dimension with a minimum size of: • 10 mm in the longest diameter by CT or MRI scan (or no less than double the slice thickness) for non-nodal lesions and ≥15 mm in short axis for nodal lesions • 10 mm caliper measurement by clinical exam • 20 mm by chest X-ray	Up to 5 target lesions may be selected at baseline. Lesions will be measured unidimensionally. The minimum target lesion size at baseline in irRECIST is aligned with RECIST 1.1, as outlined in Nishino et al., 2013.
WHO 5.1.2 Unmeasurable Disease There are many forms of unmeasurable disease, and only a few are mentioned as examples: Lymphangitic pulmonary metastases. Skin involvement in breast cancer. Abdominal masses that can be palpated but not measured.	**1.1. Baseline: Non-measurable Lesion Definitions** Follow the definitions from RECIST 1.1 Non-target lesions will include: • Measurable lesions not selected as target lesions • All sites of non-measurable disease, such as neoplastic masses that are too small to measure because their longest uninterrupted diameter is < 10 mm (or < two times the axial slice thickness), ie. the longest perpendicular diameter is ≥ 10 and < 15 mm. • Other types of lesions that are confidently felt to represent neoplastic tissue, but are difficult to measure in a reproducible manner. These include bone metastases, leptomeningeal metastases, malignant ascites, pleural or pericardial effusions, ascites, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, ill-defined abdominal masses, skin lesions, etc.	Although irRC does not specifically define non-target lesions, irRC is derived from WHO criteria and indicates accordance with the same for the purposes of definitions of non-target lesions. Further clarifications in alignment with RECIST 1.1 are provided.
Not specified.	**1.2 Baseline: Target and Non-Target Lymph Node Lesion Definitions** Follow the definitions from RECIST 1.1	No change in definition of target and non-target lymph nodes from RECIST 1.1.
Not specified.	**1.3 Baseline: Non-Target Lesion Selection** All lesions or sites of disease not recorded as target lesions should be recorded as non-target lesions at baseline. There is no limit to the number of non-target lesions that can be recorded at baseline.	In alignment with RECIST 1.1, all malignant lesions have to be selected at baseline. The excess of measurable lesions and all true non-measurable lesions will be selected as non-target lesions at baseline and followed at subsequent timepoints.
Not specified.	**1.4 Baseline: Bone Lesions** Follow the definitions from RECIST 1.1. Regardless of the imaging modality blastic bone lesions will not be selected as target lesions. Lytic or mixed lytic-blastic lesions with a measurable soft tissue component ≥ 10 mm can be selected as target lesions.	Bone lesions are to be handled the same as in RECIST 1.1.
Not specified.	**1.5 Baseline: Brain Lesions** detected on brain scans can be considered as both target or non-target lesions.	Brain lesions can be selected as target or non-target lesions at baseline, depending on the protocol definition, indication, and study design.

Original irRC, Including WHO Criteria References	irRECIST Modifications and Clarifications	Rationale for Modification
Not specified.	**1.6 Baseline: Cystic and Necrotic Lesions as Target Lesions** Lesions that are partially cystic or necrotic can be selected as target lesions. The longest diameter of such a lesion will be added to the Total Measured Tumor Burden (TMTB) of all target lesions at baseline. If other lesions with a non-liquid/non-necrotic component are present, those should be preferred.	RECIST 1.1 does not integrate viability of tumor tissue into the assessment, and that is carried over into irRECIST.
Not specified.	**1.7 Baseline: Lesions With Prior Local Treatment** During target lesion selection the radiologist will consider information on the anatomical sites of previous intervention (e.g. previous irradiation, RF-ablation, TACE, surgery, etc.). Lesions undergoing prior intervention will not be selected as target lesions unless there has been a demonstration of progress in the lesion.	In order to minimize site vs. central discrepancy information about prior intervention needs to be available to both the investigators and independent reviewers.
Not specified.	**1.8 Baseline: No Disease at Baseline** If a patient has no measurable and no non-measurable disease at baseline the radiologist will assign 'No Disease' (irND) as the overall tumor assessment for any available follow-up timepoints unless new measurable lesions are identified and contribute to the TMTB.	irND is a valid assessment in studies with adjuvant setting where the protocol and study design allow to include patients with no visible disease. This had not been addressed at all in any prior immune-response related criteria but needs to be included to also allow for these patients to be assessed accurately.
At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (≥5×5 mm; up to 5 new lesions per organ; 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total tumor burden: SPDindex lesions + SPDnew measured lesion	**2.0 Follow-up: Recording of Target and New Measureable Lesion Measurements** The longest diameters of non-nodal target and new non-nodal measurable lesions, and short axes of nodal target and new nodal measurable lesions will be recorded. Together they determine the Total Measured Tumor Burden (TMTB) at follow-up.	In alignment with Nishino et al., 2013, unidimensional measurements are used. Measurements of all measured lesions (baseline-selected target lesions and new measurble lesions) are combined into TMTB at follow-up.
	2.1 Follow-up: Definition of Measurable New Lesions In order to be selected as new measurable lesions (≠ 2 lesions per organ, ≠ 5 lesions total, per timepoint), new lesions must meet criteria as defined for baseline target lesion selection and meet the same minimum size requirements of 10 mm in long diameter and minimum 15 mm in short axis for new measurable lymph nodes. New measurable lesions shall be prioritized according to size, and the largest lesions shall be selected as new measured lesions.	Proposed selection of up to 5 new measurable lesions of at least 10 mm each versus 10 new measurable lesions as suggested in the irRC criteria is due to the following: 5 new measurable lesions add up at least 50 mm to the TMTB. Since PD is determined by at least a 20% increase in TMTB compared to nadir, this would mean that for irPD assessment the nadir TMTB had to be 25 cm, or 10 cm for 2 lesions in one organ, which is a significant tumor burden already for any cancer patient. That is why measuring up to 5 new lesions in total is sufficient and will not obstruct an irPD assessment. Measuring more than 5 new lesions is not needed. Larger lesions must be preferred as new measurable over smaller lesions, because there will be a greater impact of the TMTB %-increase by these larger lesions for irPD, to support a most conservative approach.

Original irRC, Including WHO Criteria References	irRECIST Modifications and Clarifications	Rationale for Modification
Non-index lesions at follow-up timepoints contribute to defining irCR (complete disappearance required).	**2.2 Follow-up: Non-Target Lesion Assessment** The RECIST 1.1 definitions for the assessment of non-target lesions apply. The response of non-target lesions primarily contributes to the overall response assessments of irCR and irNon-CR/Non-PD (irNN). Non-target lesions do not affect irPR and irSD assessments. Only a massive and unequivocal worsening of non-target lesions alone, even without progress in the TMTB is indicative of irPD.	Non-target lesions have a subordinate function. In the event that non-target lesions massively progress one cannot ignore such worsening and in these rare cases irPD based only on non-target lesions will be a valid assessment option.
New, non-measurable lesions at follow-up timepoints do not define progression, they only preclude irCR.	**2.3 Follow-up: New Non-Measurable Lesions Definition and Assessment** All new lesions not selected as new measurable lesions are considered new non-measurable lesions and are followed qualitatively. Only a massive and unequivocal progression of new non-measurable lesions leads to an overall assessment of irPD for the timepoint. Persisting new non-measurable lesions prevent irCR.	When new non-measurable lesions substantially worsen in these rare cases irPD based only on new non-measurable lesions will be an assessment option.
irRC Overall Tumor Assessments **irCR**, complete disappearance of all lesions (whether measurable or not, and no new lesions) • Confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented **irPR**, decrease in tumor burden ≥50% relative to baseline • Confirmed by a consecutive assessment at least 4 weeks after first documentation **irSD**, not meeting criteria for irCR or irPR, in absence of irPD **irPD**, increase in tumor burden ≥25% relative to nadir (minimum recorded tumor burden) • Confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented	**2.4 irRC Overall Tumor Assessments** **irCR**, complete disappearance of all measurable and non-measurable lesions. Lymph nodes must decrease to < 10 mm in short axis. Confirmation of response is not mandatory. **irPR**, decrease of ≥ 30% in TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions. **irSD**, failure to meet criteria for irCR or irPR in the absence of irPD. **irNN**, no target disease was identified at baseline and at follow-up the patient fails to meet criteria for irCR or irPD. **irPD**, minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions. Confirmation of progression is recommended minimum 4 weeks after the first irPD assessment. **irNE**, used in exceptional cases where insufficient data exists. **irND**, in adjuvant setting when no disease is detected.	The irRECIST overall tumor assessment is based on TMTB of measured target and new lesions, non-target lesion assessment and new non-measurable lesions. The thresholds for irPR and irPD assessment are aligned with RECIST 1.1, and confirmation of response is not required. An irPD confirmation scan may be recommended for patients with a minimal TMTB %-increase over 20% and especially during the flare time-window of the first 12 weeks of treatment, depending on the compound efficacy expectations, to account for expected delayed response.

CONCLUSIONS

irRECIST criteria as outlined here introduce the needed clarifications and adjustments to irRC criteria and Nishino et al., 2013 publication to allow for treatment evaluations that better meet both investigators' and patients' needs and with that better reflect sponsors' demands for more reliable and reproducible study data in targeted immunotherapy in oncology studies. The main adaptation of the existing immune-response criteira lies in the assessment of all detected lesions. Unequivocal and substantial increase of non-target and new non-measurable lesions prevents irCR and may also lead to irPD. Reduction of the tumor burden in patients in an adjuvant setting may lead to irPR and such patients may therefore be enrolled in studies with response endpoints.

Clinical relevance of these adaptations needs to be confirmed.

SUMMARY AND ADDITIONAL GUIDANCE

1. **TMTB:** Baseline-selected target lesions and new measurable lesions should NOT be assessed separately. Measurements of those lesions should be combined into the Total Measured Tumor Burden (TMTB), and one combined assessment provided.
2. **NEW MEASURABLE LESIONS:** According to irRC a measurable new lesion has to be at least 5 mm x 5 mm to be selected as an index lesion. For bidimensional measurements this threshold was acceptable. In irRECIST, criteria for unidimensional lesion measurement apply to both target and new measurable lesions: a minimum 10 mm in the longest diameter for non-nodal lesions, and a minimum 15 mm in short axis for lymph nodes. Smaller lesions contribute to the non-target or new non-measurable tumor burden, but do not get measured.
3. **irPR IF NO TARGET LESIONS:** If new measurable lesions appear in patients with no target lesions at baseline, irPD will be assessed. That irPD timepoint will be considered a new baseline, and all subsequent timepoints will be compared to it for response assessment. irPR is possible if the TMTB of new measurable lesions decreases by ≥ 30% compared to the first irPD documentation.
4. **irPR IN ADJUVANT STUDIES:** irRECIST can be used in the adjuvant setting, in patients with no visible disease on CT/MRI scans. The appearance of new measurable lesion(s) automatically leads to an increase in TMTB by 100% and leads to irPD. These patients can achieve a response if the TMTB decreases at follow-up, as a sign of delayed response.

   Considering 3 and 4, sponsors may consider enrolling patients with no measurable disease and/or patients with no visible disease at all in studies with response related endpoints.
5. **NON-TARGET LESIONS:** In alignment with RECIST 1.1, baseline selected non-target lesions can never convert to measurable lesions, not even if they increase in size at subsequent timepoints and become measurable. Only true new lesions can be measured and contribute to the TMTB.

   Example: A patient has multiple lung metastases, all smaller than 10 mm and selected as non-target lesions at baseline. If, at a subsequent timepoint some of these non-target lesions increase and become > 10 mm, and one new lesion >10 mm appears, only the new measurable lesion will contribute to the TMTB, and not the baseline selected non-target lesion that increased in size. Otherwise such an increase would make persisting non-target lesions switch into the new measurable lesion category which would be inaccurate, as the lesion existed at baseline.
6. **irPD BASED ON NON-TARGET LESIONS:** Unlike irRC that neglect non-target lesions for the assessment of irPD, in irRECIST a substantial and unequivocal increase of non-target lesions is indicative of progression.
7. **irPD BASED ON NEW NON-MEASURABLE LESIONS:** According to irRC, a patient with multiple new lesions of 9 mm would be considered non-PD, whereas a patient with just one new lesion of 10 mm may be assessed as irPD if the TMTB of such a patient increases > 20% compared to nadir. According to irRECIST, the reviewer may assign irPD for the patient with multiple new lesions of 9 mm if they are considered to be a sign of unequivocal, massive worsening (see 2.3)
8. **irPD CONFIRMATION:** Progression confirmation no less than 4 weeks after the initial irPD assessment is recommended especially in case of marginal disease growth and if the first irPD assessment is within the compound-specific tumor flare window.

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Limitations of irRC

- **Risk of high interobserver variability (but unidimensional criteria are under development)**
- **Developed in melanoma patients treated with anti-CTLA4/anti-PD1. Are they valid also for other tumors/immunotherapy agents?**
- **The overall reported incidence of pseudoprogression in solid tumors is low (with an approximate overall incidence of 4%)[1]**
- **Risk of rapid clinical deterioration in true progressing patients**
- **More prospective data needed**

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