Society for Immunotherapy of Cancer

Clinical Endpoints

Michael Morse, MD

Duke University Medical Center

Endpoints	Definition	Advantages	Limitations
Overall survival (OS)	Time from randomization* until death from any cause	• Universally accepted measure of direct benefit • Easily and precisely measured	• May require a larger trial population and longer follow-up to show statistical difference between groups • May be affected by crossover or subsequent therapies • Includes deaths unrelated to cancer

*In nonrandomized trials, time from study enrollment is commonly used

http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071590.pdf.

https://www.biooncology.com/clinical-trials/efficacy-endpoints.html

sitc
Society for Immunotherapy of Cancer

Endpoints	Definition	Advantages	Limitations
Progression-free survival (PFS)	Time from randomization* until disease progression or death	• Requires small sample size and shorter follow-up time compared with OS • Includes measurement of stable disease (SD) • Not affected by crossover or subsequent therapies • Generally based on objective and quantitative assessment	• Validation as a surrogate for survival can be difficult in some treatment settings • Not precisely measured (ie, measurement may be subject to bias) • Definition may vary among trials • Requires frequent radiologic or other assessments • Requires balanced timing of assessment among treatment arms
Time to progression (TTP)	Time from randomization* until objective tumor progression; does not include deaths		

*In nonrandomized trials, time from study enrollment is commonly used

http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071590.pdf.

https://www.biooncology.com/clinical-trials/efficacy-endpoints.html

Society for Immunotherapy of Cancer

Endpoints	Definition	Advantages	Limitations
Time to treatment failure (TTF)	Time from randomization* to discontinuation of treatment for any reason, including disease progression, treatment toxicity, and death	• Useful in settings in which toxicity is potentially as serious as disease progression (eg, allogeneic stem cell transplant)	• Does not adequately distinguish efficacy from other variables, such as toxicity

*In nonrandomized trials, time from study enrollment is commonly used

http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071590.pdf.

https://www.biooncology.com/clinical-trials/efficacy-endpoints.html

Endpoints	Definition	Advantages	Limitations
Time to next treatment (TTNT)	Time from end of primary treatment to institution of next therapy	• For incurable diseases, may provide an endpoint meaningful to patients	• Not commonly used as a primary endpoint • Subject to variability in practice patterns

http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071590.pdf.

https://www.biooncology.com/clinical-trials/efficacy-endpoints.html

Endpoints	Definition	Advantages	Limitations
Objective response rate (ORR)	Proportion of patients with reduction in tumor burden of a predefined amount	• Can be assessed in single-arm trials • Requires a smaller population and can be assessed earlier, compared with survival trials • Effect is attributable directly to the drug, not the natural history of the disease	• Not a comprehensive measure of drug activity
Duration of response (DoR)	Time from documentation of tumor response to disease progression		

http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071590.pdf.

https://www.biooncology.com/clinical-trials/efficacy-endpoints.html

Society for Immunotherapy of Cancer

Other Clinical endpoints

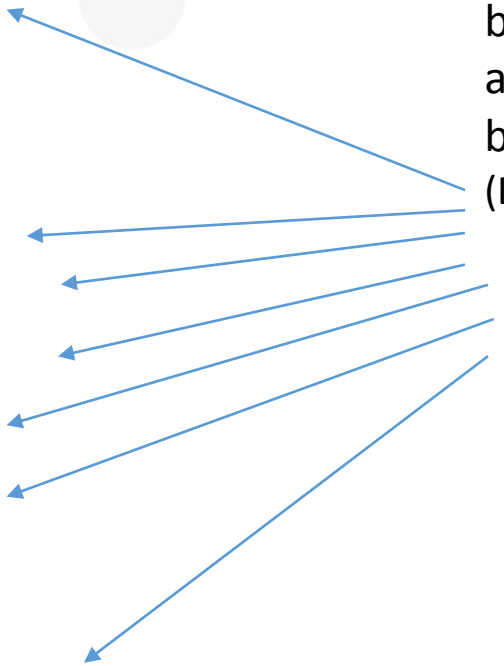
- Composite endpoints (OS + PFS)
- Improvement (or lack of decline) in QOL scores
- Improvement (or lack of decline) in performance status
- Improvement in composite scores (pain, weight loss,…)

sitc
Society for Immunotherapy of Cancer

An example

Combination of Targeted Therapy (Encorafenib and Binimetinib) Followed by Combination of Immunotherapy (Ipilimumab and Nivolumab) vs Immediate Combination of Immunotherapy in Patients With Unresectable or Metastatic Melanoma With BRAF V600 Mutation : an EORTC Randomized Phase II Study (EBIN)

- Primary Outcome Measures :
  - Progression Free Survival (PFS)
- Secondary Outcome Measures:
  - Overall Survival (OS)
  - Complete Response (CR) rate
  - Time to Complete Response
  - Duration of Complete Response
  - Best overall response rate
  - Time to best response
  - Duration of best response
  - Occurrence of adverse events
  - Progression-free survival 2 (PFS2)



These… “are useful only if based on widely accepted and readily applied standard criteria based on anatomical tumour burden.” (Eisenhauer, EUR J CANCER 45 (2009) 228 –247)

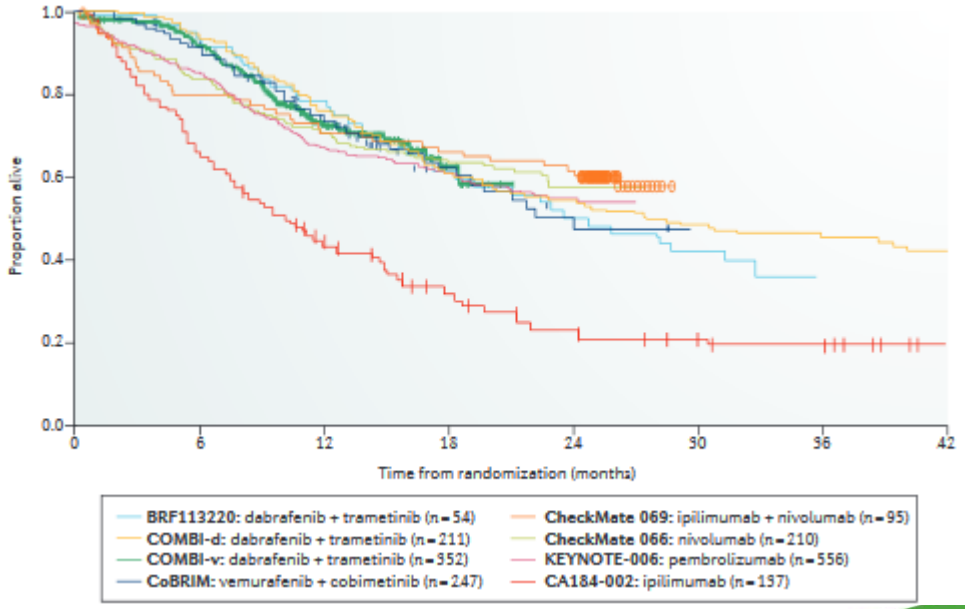
sitc

Society for Immunotherapy of Cancer

Overall survival

- Becoming more difficult to use as an endpoint due to lengthening survival (and impact of subsequent therapies)

Survival in key melanoma studies



Use median or Landmark?

Nat Rev Clin Oncol. 2017 Aug;14(8):463-482

sitc
Society for Immunotherapy of Cancer

Tumor response: History

- 1981: World Health Organization (WHO) first published tumor response criteria
- Overall assessment of tumor burden by summing the products of bidimensional lesion measurements and determined response to therapy by evaluation of change from baseline while on treatment.
- Ad hoc modifications leading to confusion about actual efficacy
- International Working Party formed and new criteria--RECIST (Response Evaluation Criteria in Solid Tumors)---were published in 2000

sitc
Society for Immunotherapy of Cancer

Key advances in RECIST

- **Use of unidimensional, rather than bidimensional, measures for overall evaluation of tumor burden**
  - Works well except in mesothelioma, and except where devascularization occurs (mRECIST)
- Definitions of minimum size of measurable tumors (10mm by CT scan)
- Instructions on how many lesions to follow
  - up to 10; a maximum of five per organ site
- Definitions of PR as “At least a 30% decrease in the sum of diameters of target lesions” compared with baseline.
- Widely adopted by academic institutions, cooperative groups, and industry for trials where the primary endpoints are objective response or progression.
- Regulatory authorities accept RECIST as an appropriate guideline for response/progression assessments.

sitc
Society for Immunotherapy of Cancer

RECISTS1.1

- Questions arose with RECIST
  - Can fewer than 10 lesions can be assessed without affecting the overall assigned response for patients (or the conclusion about activity in trials);
  - how to apply RECIST in randomised phase III trials where progression, not response, is the primary endpoint particularly if not all patients have measurable disease;
  - Whether or how to utilise newer imaging technologies such as FDG-PET and MRI
  - How to handle assessment of lymph nodes;
  - Whether response confirmation is truly needed;
  - The applicability of RECIST in trials of targeted non-cytotoxic drugs.

sitc
Society for Immunotherapy of Cancer

Eisenhauer, EUROPEAN JOURNAL OF CANCER 4 5 (2 0 0 9) 2 2 8 –2 4 7

Highlights of revised RECIST 1.1

- Number of lesions to be assessed: # of lesions required to assess tumor burden for response determination has been reduced from a maximum of 10 to a maximum of five total (and from five to two per organ, maximum).
- Assessment of pathological lymph nodes is now incorporated:
  - Nodes with a short axis of >15 mm are considered measurable and assessable as target lesions.
  - Short axis measurement should be included in the sum of lesions in calculation of tumor response. Nodes that shrink to <10 mm short axis are considered normal.
- Confirmation of response is required for trials with response primary endpoint but is no longer required in randomised studies since the control arm serves as appropriate means of interpretation of data.
- Disease progression is clarified in several aspects:
  - in addition to the previous definition of progression in target disease of 20% increase in sum, a 5 mm absolute increase is now required as well to guard against over calling PD when the total sum is very small.

sitc
Society for Immunotherapy of Cancer

Eisenhauer, EUROPEAN JOURNAL OF CANCER 4 5 (2 0 0 9) 2 2 8 –2 4 7

Highlights of revised RECIST 1.1 (cont'd)

- Guidance offered on what constitutes 'unequivocal progression' of non-measurable/non-target disease
- Section on detection of new lesions, including the interpretation of FDG-PET scan assessment is included.
- Imaging guidance: the revised RECIST includes a new imaging appendix with updated recommendations on the optimal anatomical assessment of lesions.

sitc
Society for Immunotherapy of Cancer

Challenges with RECIST 1.1 in immunotherapy

- Pseudoprogression:
  - Radiologic tumor progression (new lesions, or enlarging lesions) from baseline that is not confirmed as progression on subsequent radiologic assessment.
  - Rate of 7% in melanoma
  - 1.5 – 3.0% (up to 4.7%) In non-small cell lung cancer (NSCLC) and urothelial carcinoma
  - No biomarker to predict pseudoprogression
    - PD-L1 expression level and tumor infiltrating lymphocytes have failed to correlate with the rates of pseudoprogression.
    - Circulating tumor DNA changes?

Society for Immunotherapy of Cancer

Kurra V. *J Clin Oncol* 34, 2016 (suppl; abstr 6580).

More History

- Two-dimensional immune-related response criteria (irRC) were proposed in 2009 (Wolchok, Clin Cancer Res 2009;15:7412e20)
- Simplification of these criteria was proposed in 2013, irRECIST (immune-related) (J Immunother Cancer 2016;4:30).
- RECIST working group published a proposition of new criteria called iRECIST, to standardise response assessment among immunotherapy clinical trials (Lancet Oncol 2017;18: el43ee152.)
  - Responses assigned using iRECIST have a prefix of “i” (ie, immune)—eg, “immune” complete response (iCR) or partial response (iPR), and unconfirmed progressive disease (iUPD) or confirmed progressive disease (iCPD) to differentiate them from responses assigned using RECIST 1.1.

Some details of iRECIST

- “The continued use of RECIST 1.1 is recommended to define whether tumour lesions, including lymph nodes, are measurable or non-measurable, as well as for the management of bone lesions, cystic lesions, and lesions with previous local treatment (eg, radiotherapy; table 1).”
- “No changes have been made to the recommendations regarding the method of measurement, although clinical examination and chest radiograph are rarely used, with the availability of more modern imaging techniques (eg, CT scans and MRI).”
- “The principles used to establish objective tumour response are largely unchanged from RECIST 1.1, but the major change for iRECIST is the **concept of resetting the bar if RECIST 1.1 progression is followed at the next assessment by tumour shrinkage**.

Society for Immunotherapy of Cancer

More details of iRECIST

To allow atypical responses, such as delayed responses that occur after pseudoprogression, to be identified

- iRECIST defines iUPD on the basis of RECIST 1.1 principles;
- iUPD requires confirmation,
  - Observing for further increase in size (or in the number of new lesions) in the lesion category in which progression was first identified in (ie, target or non-target disease), or progression (defined by RECIST 1.1) in lesion categories that had not previously met RECIST 1.1 progression criteria.
- If progression is not confirmed, but instead tumour shrinkage occurs (compared with baseline), which meets the criteria of iCR, iPR, or iSD, then the **bar is reset** so that iUPD needs to occur again (compared with nadir values) and then be confirmed (by further growth) at the next assessment for iCPD to be assigned.
- If no change in tumour size or extent from iUPD occurs, then the timepoint response would again be iUPD.

sitc

Society for Immunotherapy of Cancer

Summary of RECIST, irRECIST and iRECIST Criteria.

	RECIST 1.1	irRECIST	iRECIST
Target and non-target lesions	Sum of the longest diameters of target lesions (uni-dimensional) Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions) Maximum of five lesions (two per organ)		
New lesion	Represents PD	Does not correspond to a formal progression The longest diameter will be added to the total measured tumour burden of all target lesions at baseline.	Does not correspond to a formal progression Is not incorporated in tumour burden
CR	Disappearance of all target and non-target lesions Nodal short axis diameter <10 mm No new lesions		
PR	Decrease of ≥30% in tumour burden relative to baseline Non-unequivocal progression of non-target lesions No new lesions		
SD	Neither PR nor PD		

Society for Immunotherapy of Cancer

Summary of RECIST, irRECIST and iRECIST Criteria.

	RECIST 1.1	irRECIST	iRECIST
PD	Increase ≥20% of the sum of LD compared with nadir (minimum 5 mm) or progression of non-target lesions or new lesion	**irPD** Increase ≥ 20% (minimum 5 mm) in TMTB compared with nadir or progression of non-target lesions or new lesion Confirmation of progression recommended minimum 4 weeks after the first irPD assessment	**iUPD** Increase ≥ 20% of the sum of LD compared with nadir (minimum 5 mm) or progression of non-target lesions or new lesion Confirmation of progression recommended minimum 4 weeks after the first iUPD assessment
Confirmed PD	Not required	New unequivocal progression or worsened progression from initial PD visit Appearance of another new lesion	**iCPD** Increased size of target or non-target lesions Increase in the sum of new target lesions > 5 mm Progression of new non-target lesions Appearance of another new lesion

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease, iUPD, unconfirmed progressive disease; iCPD, confirmed progressive disease; LD, longest diameters; TMTB, total measured tumour burden.

Comparisons of criteria

Table 3
Comparison between irRECIST and iRECIST assessment on progression confirmatory CT.

irRECIST	iRECIST				
	iCPD	iUPD	iSD	iPR	Total
PD	60	3	0	0	63
SD	0	9	4	3	16
PR	0	0	0	1	1
					80

PD, progressive disease; iUPD unconfirmed PD; iCPD confirmed PD; PR, partial response; SD, stable disease.

Atypical responses (PsPD/dissociated response) occurred in 13% of NSCLC patients under immune checkpoint inhibitors

RECIST 1.1 evaluation underestimated the benefit of immune checkpoint inhibitors in 11% of the progressive patients.

Immune-related RECIST and iRECIST identified these unconventional responses, with a 3.8% discrepancy rate.

sitc
Society for Immunotherapy of Cancer

M. Tazdait et al. / European Journal of Cancer 88 (2018) 38e47

Durable response

- Phase 3 clinical trial of an oncolytic virus for melanoma treatmen
- Achieving DR was associated with a statistically significant improvement in OS (at 9, 12, 18 months)

- Achieving a DR was associated with a longer median treatment free interval (HR = 0.33; *P* = 0.0007) and a higher Trial Outcome Index (QOL measure) improvement rate (58.1% versus 30.0%; *P* = 0.025).

Society for Immunotherapy of Cancer

Journal for ImmunoTherapy of Cancer2017;5:72

Hyperprogression: accelerated tumor growth rate (TGR)

- Definitions
  - Progression (RECIST) at the first evaluation and a ≥2-fold increase in TGR during ICI therapy compared with pretreatment kinetics.[1]
  - Time to treatment failure <2 months, >50% increase in tumor burden and >2-fold increase in progression pace.[2]
  - Time to treatment failure <2 months, and an increase of at least 40% in the target tumor burden or at least a 20% increase with the development of new lesions.[3]
  - Disease progression at the first evaluation with ΔTGR exceeding 50%.[4]

- Measurement: change in tumor volume ? Change in the largest diameters of target lesions?

Society for Immunotherapy of Cancer

[1]Champiat, Clin Cancer Res. 2017;23:1920-1928. [2]Kato, Clin Cancer Res. 2017;23:4242-4250.
[3]Matos J Clin Oncol. 2018;36(15 suppl):3032. [4]Ferrara, JAMA Oncol. 2018;4(11):1543-1552

Calculating TGR

Tumor size = sum of the longest diameters of all target lesions (*D*).

Tumor volume = volume of the sphere, for which radius (*R*) = ½ of diameter (*D*).
The tumor volume (*V*) was calculated with the following formula:

$$\text{Tumor volume} = 4\pi R^3/3$$

Tumor growth :

$$V_t = V_0 \exp(\text{Tumor growth} \times t)$$

where V_t is the tumor volume at time *t* in months and V_0 is the volume at the baseline.

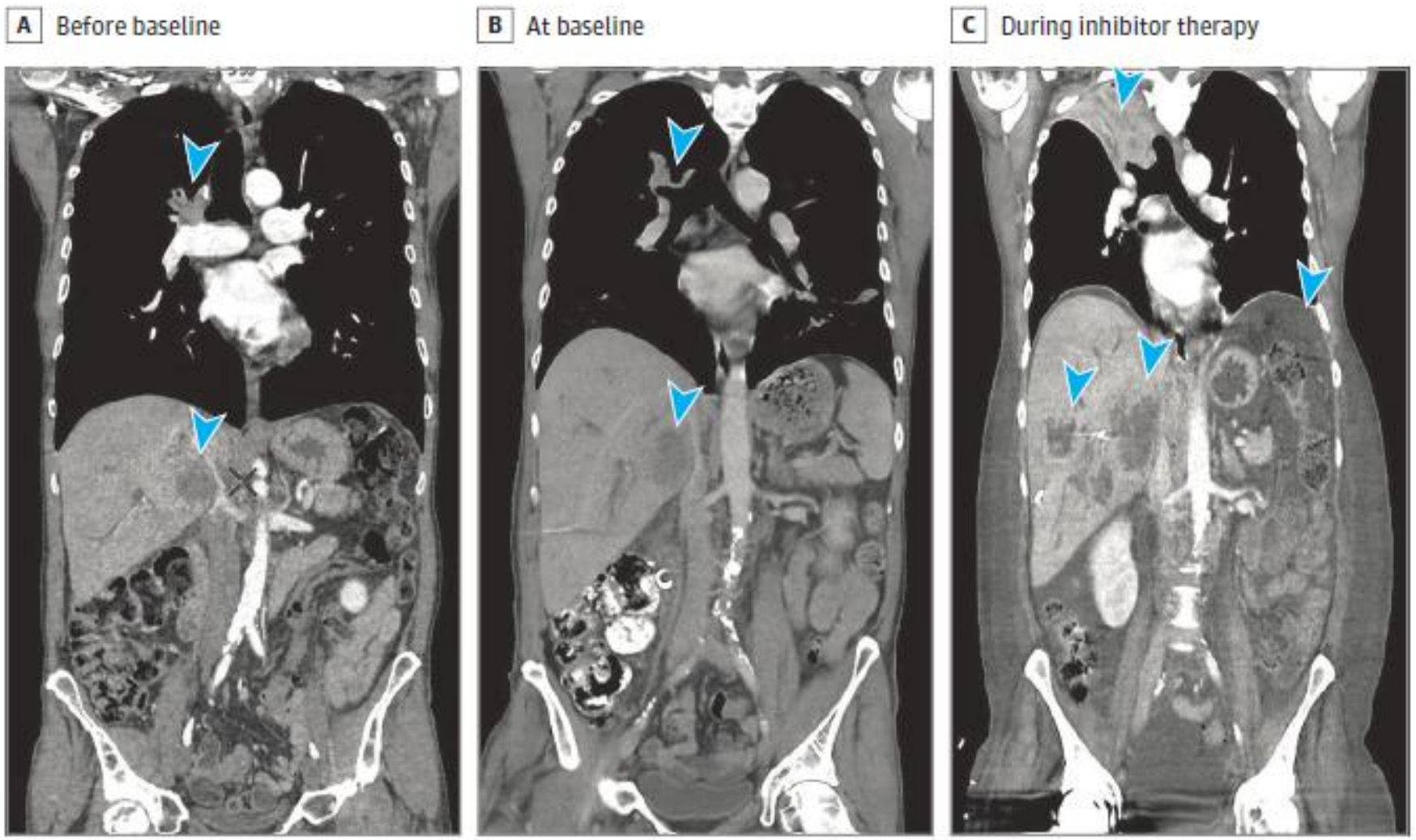
TGR over 1 month : $100\left[\exp(\text{Tumor growth}) - 1\right]$

TGR ratio = TGR in the immunotherapy treatment period (the experimental period)
TGR in the pre-immunotherapy treatment period (the reference period).

Kanjanapan, Cancer. 2019 Feb 15. doi: 10.1002/cncr.31999. [Epub ahead of print]

sitc
Society for Immunotherapy of Cancer

Figure 3. Case Study of a Patient With Non-Small Cell Lung Cancer With Hyperprogressive Disease During Treatment With a PD-1 Inhibitor



Shown are computed tomographic scans before baseline (A), at baseline about 3 weeks later (B), and during programmed cell death (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitor therapy 1 month later (C) in a man in his mid-50s with stage IV (lung, liver, and bone metastases) *HER2*-amplified lung adenocarcinoma treated with anti–PD-1 therapy in the third line. After 2 administrations, there was evidence of extensive lung, liver, and peritoneal progression. Arrowheads show lung and liver metastases before and during anti–PD-1 treatment.

Ferrara, *JAMA Oncol*. 2018;4(11):1543-1552.

Table 1 | Studies using tumour kinetics to identify hyperprogressive disease patterns

Study	Reported frequency for hyperprogressive disease	Tumour types	Factors involved	Criteria used to define hyperprogressive disease[a]	Refs
Champiat et al.	9% (12/131)	• Melanoma (9%; 4/45) • Urothelial carcinoma (25%; 2/8) • Colorectal carcinoma (12%; 1/8) • Lymphoma (14%; 1/7) • Ovarian carcinoma (40%; 2/5) • Cholangiocarcinoma (50%; 1/2) • Uveal melanoma (50%; 1/2)	Older age associated with higher risk of hyperprogressive disease (19% if ≥65 years of age versus 5% if <65 years of age; $P = 0.036$)	• RECIST-defined progressive disease at first evaluation • TGR ratio ≥2 (on-treatment versus before treatment)	13
Kato et al.	6% (6/102)	• NSCLC (8%; 3/38) • Urothelial carcinoma (ND; 1/ND) • Triple negative breast cancer (ND; 1/ND) • Endometrial carcinoma (ND; 1/ND)	Presence of *MDM2* amplifications or *EGFR* alterations associated with median time to treatment failure <2 months ($P = 0.007$ and $P = 0.005$, respectively)	• Time-to-treatment failure <2 months • >50% increase in tumour burden compared with pre-immunotherapy (on imaging) • >2-fold increase in progression pace	14
Saâda-Bouzid et al.	29% (10/34)	HNSCC (all patients)	Regional recurrence associated with higher rate of hyperprogressive disease (90% for TGK ratio ≥2 versus 37% for TGK ratio <2; $P = 0.008$)	• TGK ratio ≥2 (on-treatment versus before treatment)	15
Ferrara et al.	14% (56/406)	NSCLC (all patients)	Number of metastatic sites >2 associated with higher rate of hyperprogressive disease (19% for >2 versus 9% for ≤2; $P = 0.005$)	• RECIST-defined disease progression at first evaluation • ΔTGR increase >1.5 (on-treatment versus before treatment)	16

HNSCC, head and neck squamous cell carcinoma; ND, not defined; NSCLC, non-small-cell lung carcinoma; TGK, tumour growth kinetics; TGR, tumour growth rate.
[a]TGR (assumption of 3D exponential tumour growth) and TGK (assumption of 2D linear tumour growth) are similar concepts but different methods are used to evaluate them according to investigator's preference.

Society fo... Immunotherapy of Cancer

Champiat., Nat Rev Clin Oncol. 2018 Dec;15(12):748-762.

A comment on independent centralized review

- ICR is the process by which all radiologic exams and selected clinical data acquired as part of a clinical protocol are submitted to a central location and reviewed by **independent** physicians who are not involved in the treatment of the patients.
  - blinded to certain components of the data (e.g., treatment arm)
  - Generally 2 radiologist readers and an adjudicator if needed
- Can be used (prospectively or retrospectively) to assess whether patients meet eligibility criteria
- Measurements of tumor size for use in determining response/progression

Causes of site/central discordance

- Workflow differences
- Limited amount of non-radiographic clinical information
- Treatment bias
- Lesion selection for evaluation
- Missing data and conventions for handling missing data
- Inter- reader and intra-reader variability
- Date conventions
- Variability in protocol training
- Understanding of and application of response criteria
- Failure to compare all prior studies
- Perception of new lesions
- Subjective assessment of non-target disease
- Tumor type
- Drug efficacy
- Precision of the response criteria
- Complexity of the response assessment

Society for Immunotherapy of Cancer

Ford, Eur J Cancer. 2009 Jan;45(2):268-74.

Summary

- OS is still the gold standard but harder to prove as more therapies become available
- Will duration of response provide a correlate for overall survival
- RECIST1.1 is still the standard, but iRECIST provides insight on atypical responses
- Is hyperprogression a true phenomenon and will it become an important endpoint

sitc
Society for Immunotherapy of Cancer