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Clinical Endpoints

Michael Morse, MD

Duke University Medical Center

Endpoint overview

- Endpoint: In clinical trials, an event or outcome that can be measured objectively to determine whether the intervention being studied is beneficial. (cancer.gov)

- "…several oncology endpoints can serve different purposes (i.e., clinical endpoint that represents clinical benefit for traditional approval, surrogate endpoint to support traditional approval, surrogate endpoint to support accelerated approval) based on the specific context of use.
  - The determination is based on the specific diseases and is highly dependent upon factors such as effect size, effect duration, depth of response (e.g., number of CRs), available therapy, disease setting, location of disease, the clinical consequences of delaying or preventing disease progression or delaying administration of more toxic therapies, and the risk-benefit relationship" (https://www.fda.gov/media/71195/download)

"Direct" Endpoints

- Clinically meaningful endpoints that directly measure how a patient **feels**, **functions**, or **survives**
- Endpoints that in themselves represent or characterize the clinical outcome of interest
  - Objective: survival, disease exacerbation, clinical event (e.g. MI, stroke), etc.
  - Subjective: symptom score, "health related quality of life" (validated instrument), etc.
- Customarily, the basis for approval of new drugs

Note: The term "direct" is used here to distinguish from "surrogate" endpoints, but this term is not uniformly utilized. Others may refer to these as "true" or "clinically meaningful" endpoints

EJ Sullivan, https://www.fda.gov/media/84987/download

Surrogate Endpoints

- A surrogate endpoint is a laboratory measure or a physical sign that is intended to be used as a substitute for a clinically meaningful endpoint.
- Changes induced by a therapy on a surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint.
- This expectation must be supported by strong data ("validation").
  - Examples of failures of apparently reasonable proposed surrogate endpoints have led to significant skepticism.
- Ideally, the surrogate should exist within the therapeutic pathway between the drug and meaningful benefit
  - i.e. the drug results in the therapeutic benefit by virtue of its effect on the surrogate

EJ Sullivan, https://www.fda.gov/media/84987/download

Endpoint	Type of Endpoint			Study Design Recommendations		
	Clinical Endpoint	Surrogate Endpoint for TA*	Surrogate Endpoint for AA**	Randomized	Single-Arm	Independent Blinded Review
Overall Survival	X			X		
Symptom Endpoints (patient-reported outcomes)	X			X		
Disease-Free Survival or Event-Free Survival	X	X	X	X		X***
Objective Response Rate	X	X	X	X	X	X
Complete Response	X	X	X	X	X	X
Progression-Free Survival or Time to Progression	X	X	X	X		X***

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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

https://www.fda.gov/media/71195/download

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

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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

https://www.fda.gov/media/71195/download

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

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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

https://www.fda.gov/media/71195/download

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

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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

https://www.fda.gov/media/71195/download

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

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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		

https://www.fda.gov/media/71195/download

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

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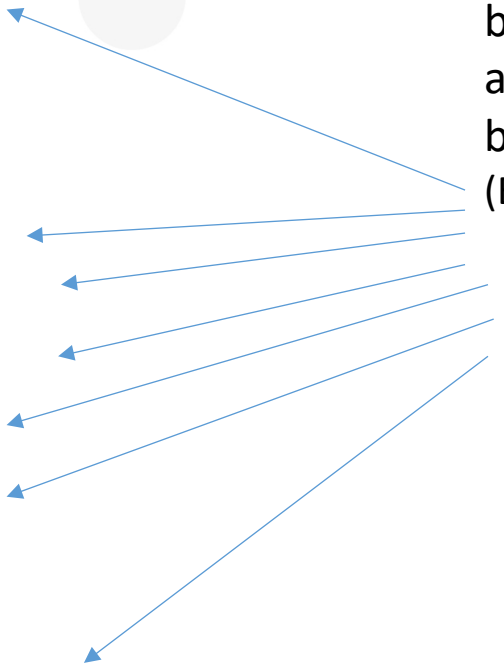
Other Clinical endpoints

- Composite and Co-primary endpoints (OS + PFS)
  - See: “Multiple Endpoints in Clinical Trials: Guidance for Industry” (https://www.fda.gov/media/102657/download)
- Improvement (or lack of decline) in QOL scores
- Improvement (or lack of decline) in performance status
  - E.g., time to deterioration from PS 0,1 to PS 2
- Improvement in composite scores (pain, weight loss,…)

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)

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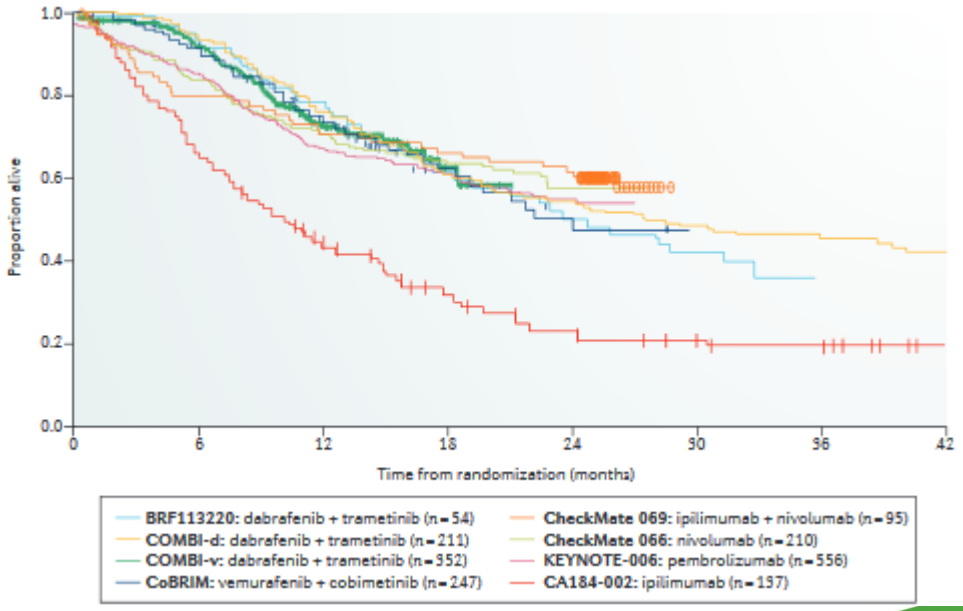
Overall survival

- 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

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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

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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.

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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.

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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.

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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.

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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?

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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 standardiseresponse 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.

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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**.

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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.

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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		

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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.

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

Durable response

- Phase 3 clinical trial of an oncolytic virus for melanoma treatment
  - 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).

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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?

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[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]

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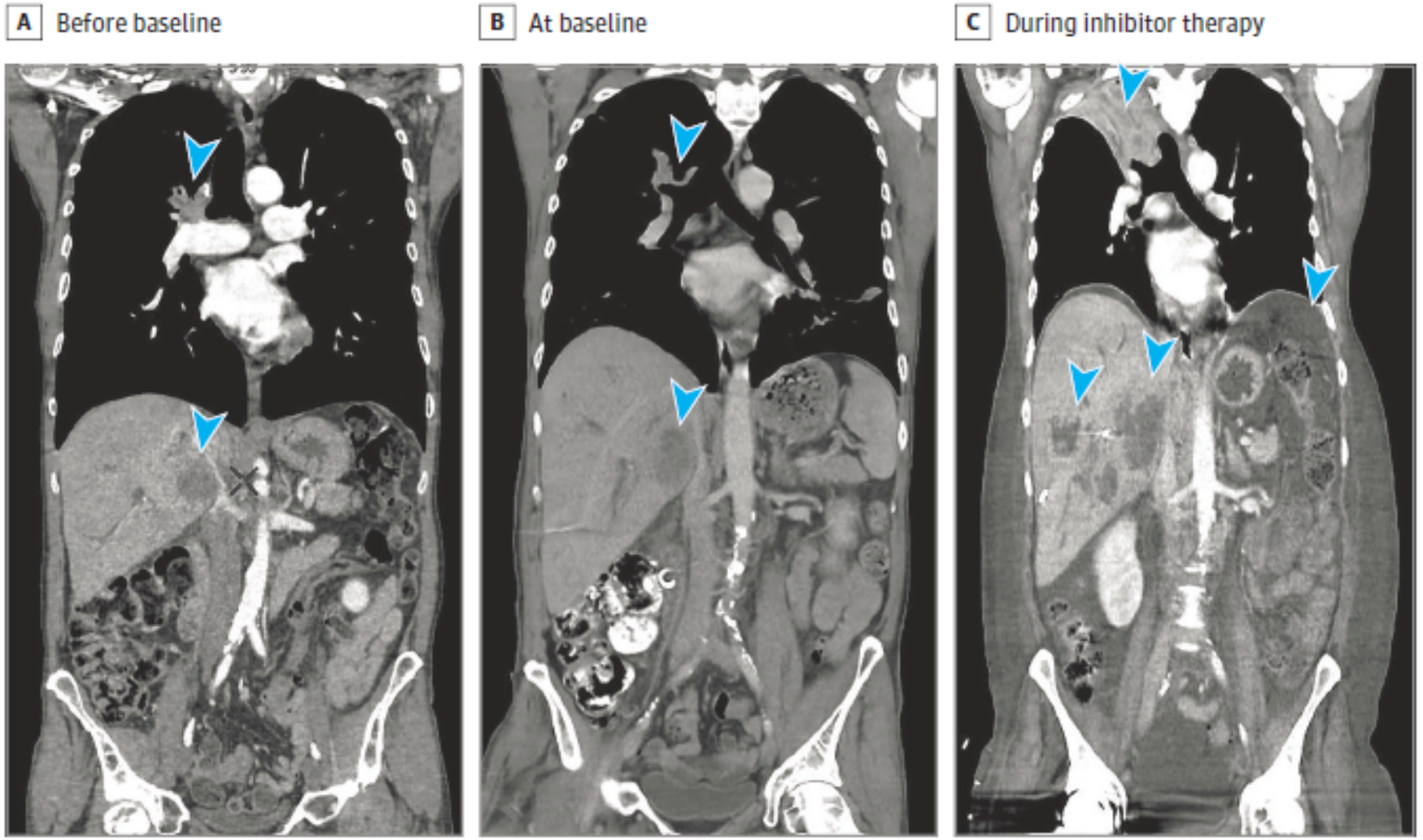
Figure 3. Case Study of a Patient With Non-Small Cell Lung Cancer With Hyperprogressive Disease During Treatment With a PD-1 Inhibitor



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.

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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

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

TABLE 1 | Biomarkers for tumor responses.

Biomarkers	Cancer type	Patient number	Treatment	Key data and clinical significance
Sex	Melanoma, NSCLC	6,096	Ipilimumab, anti-PD-1 antibodies	PFS and OS of male patients were significantly longer than those of female patients.
Age	Melanoma	315	Anti-PD-1 antibodies	Males were significantly associated with better ORR. Ages older than 65 years correlated with better ORR.
	Melanoma, prostate cancer, NSCLC, RCC	5,265	Anti-CTLA-4 antibodies, anti-PD-1 antibodies	Ages younger than 75 years correlated with better ORR.
Tumor size	Melanoma	459	Pembrolizumab	Tumor size was independently associated with OS, suggesting that early detection of metastatic lesions may be important for better response to ICIs.
TILs	Melanoma	46	Pembrolizumab	High density of $CD8^+$ TILs at the invasive margin correlated with better tumor response. An increase in $CD8^+$ TILs from baseline to post-treatment was associated with tumor regression.
PD-L1 expression in tumors	Melanoma	277	Nivolumab after treatment with anti-CTLA-4 antibodies	Better ORR were observed in patients with positive PD-L1 expression in tumors.
	Melanoma	451	Pembrolizumab	Better PFS and OS were observed in patients with positive PD-L1 expression in tumors.
	NSCLC	410	Pembrolizumab + chemotherapy	Higher PD-L1 expression was associated with better PFS and OS.
ICOS	Melanoma	14	Ipilimumab	Increased expression of ICOS on $CD4^+$ T cells that is sustained for more than 12 weeks correlated with improved OS.
TIM-3	Melanoma	67	Ipilimumab	Increased TIM-3 expression on circulating T and NK cells prior to and during treatment was associated with shorter OS.
IDO	Melanoma	82	Ipilimumab	Baseline IDO expression in tumor tissue assessed by IHC correlated with better ORR.
	NSCLC	26	Nivolumab	IDO activity as assessed by serum kynurenine/tryptophan ratio was negatively associated with longer PFS and OS.
Soluble CTLA-4	Melanoma	113	Ipilimumab	Higher serum levels of soluble CTLA-4 at baseline had both better ORR and OS.
Soluble PD-L1	Melanoma	446	Ipilimumab, anti-PD-1 antibodies	Higher levels of baseline soluble PD-L1 were associated with worse response. Increases in soluble PD-1 after treatment was associated with favorable clinical responses.
	NSCLC	39	Nivolumab	Higher levels of baseline soluble PD-L1 were associated with shorter OS.
Soluble CD163	Melanoma	59	Nivolumab	Serum levels of soluble CD163 were increased after 6 weeks in responders compared to non-responders after initial treatment for cutaneous melanoma.
Soluble NKG2D	Melanoma	194	Anti-CTLA-4 antibodies, anti-PD-1	Higher levels of circulating soluble ULBP-1, soluble ULBP-2 and LDH at baseline were independent factors of shorter OS.

Nakamura Y (2019) Biomarkers for Immune Checkpoint Inhibitor-Mediated Tumor Response and Adverse Events. Front. Med. 6:119.

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Biomarkers	Cancer type	Patient number	Treatment	Key data and clinical significance
IFN-γ	Melanoma	45	Ipilimumab	The post-treatment expression levels of IFN-γ responsive genes in tumor tissues were associated with longer OS.
	NSCLC	97	Durvalumab	High levels of pre-treatment IFN-γ expression and its related genes in tumor tissues were associated with longer OS.
	Melanoma	43	Atezolizumab	High expression of IFN-γ and CXCL-9 was associated with better ORR.
TNF-α	Melanoma	15	Nivolumab	Patients who showed complete remission, partial remission or long-term stable disease due to nivolumab response had lower serum levels of TNF-α compared to non-responders.
Lymphocyte counts	Melanoma	209	Ipilimumab	Higher levels of relative lymphocyte counts at baseline were associated with longer OS.
	Melanoma	50	Ipilimumab	Absolute lymphocyte counts after treatment were associated with longer OS.
	Melanoma	98	Nivolumab	Absolute lymphocyte counts after treatment correlated with better OS.
Eosinophil counts	Melanoma	209	Ipilimumab	High absolute and relative eosinophil counts at baseline were associated with a longer OS.
	Melanoma	616	Pembrolizumab	Relative eosinophil counts at baseline were an independent factor for longer OS and better ORR.
	Melanoma	59	Ipilimumab	Early increases in absolute eosinophil counts from baseline during treatment were an independent factor for better responses.
NLR	Melanoma	90	Nivolumab	NLR was associated with poor tumor response.
	NSCLC	175	Nivolumab	NLR was associated with poor tumor response.
	Melanoma	44	Anti-PD-1 antibodies	NLR was the only factor associated with both poor ORR and shorter PFS.
Tregs	Melanoma	209	Ipilimumab	High levels of circulating Tregs at baseline were associated with longer OS.
	Melanoma	95	Ipilimumab	Decreasing levels of circulating Tregs were associated with better responses.
MDSC	Melanoma	92	Ipilimumab	The baseline frequency of MDSCs in blood correlated with shorter OS.
	Melanoma	83	Nivolumab	The baseline frequency of MDSCs in blood correlated with shorter OS.
	Prostate cancer	28	Ipilimumab plus a cancer vaccine	The baseline frequency of circulating MDSCs correlated with shorter OS.
LDH	Melanoma	73	Ipilimumab	High baseline LDH was associated with poor anti-tumor response.
CRP	Melanoma	95	Ipilimumab	A decrease or no change in serum levels of CRP from baseline was associated with longer OS.
Mutation burden	Melanoma	64	Ipilimumab	High mutation burden was associated with a longer OS.
	Melanoma	150	Ipilimumab	High mutation burden was associated with tumor responses.
MSI	Colorectal cancer	74	Nivolumab	A high response to anti-PD-1 antibodies in colorectal cancer with high levels of MSI compared to traditional treatments was observed.
HLA	Melanoma	13	Nivolumab	HLA-A expression in pre-treatment was elevated in responders compared to non-responders.

Biomarkers	Cancer type	Patient number	Treatment	Key data and clinical significance
	Melanoma	69	Nivolumab	HLA-A26 correlated with tumor response to nivolumab in Japanese melanoma patients.
T cell repertoire	Melanoma	12	Ipilimumab	Both higher richness and evenness in pre-treatment peripheral blood were associated with a better response.
	Melanoma	46	Pembrolizumab	TILs with less diversity were associated with clinical response.
Gut microbiome	Melanoma	26	Ipilimumab	Patients whose baseline microbiota was enriched with *Faecalibacterium* genus and other Firmicutes showed a longer PFS and OS than those whose baseline microbiota was enriched with *Bacteroides*.
	Melanoma	43	Anti-PD-1 antibodies	A higher diversity of gut microbiome and relative abundance of *Ruminococcaceae* family bacteria correlated with better ORR and longer PFS.
	NSCLC, RCC	100	Anti-PD-1 antibodies	The relative abundance of *Akkermansia muciniphilia* was associated with better responses.
ctDNA	Melanoma	76	Anti-PD-1 antibodies	Patients with a persistently elevated cDNA during the treatment showed a worse response and shorter PFS and OS. ctDNA may be a useful marker for differentiating pseudoprogression from true progression during immune checkpoint inhibitor treatment.
Exosomal molecules	Melanoma	44	Pembrolizumab	Lower baseline levels and increases during the treatment in exosomal PD-L1 protein correlated with tumor response.
	Melanoma, NSCLC	26	Anti-PD-1 antibodies	Baseline exosomal PD-L1 mRNA expression was higher in responders, and exosomal PD-L1 mRNA expression in responders was decreased after treatment whereas it was stable in stabilized patients and increased in progressive disease cases.
	Melanoma	59	Ipilimumab	Increased exosomal PD-1 and CD28 levels in T cells were associated with longer PFS and OS while increased exosomal CD80 and CD86 in dendritic cells correlated with longer PFS.
irAE development	RCC	40	Ipilimumab	Overall irAEs were associated with tumor responses.
	NSCLC	43	Nivolumab	Early development of all irAEs was associated with better ORR and longer PFS.
	NSCLC, RCC, HNSCC, urothelial carcinoma	142	Anti-PD-1 antibodies	Only low grade irAEs were associated with better responses.
	Melanoma	60	Ipilimumab after nivolumab	Occurrences of endocrine irAEs were associated with longer OS.
	Melanoma	5,737	Anti-CTLA-4 antibodies, anti-PD-1 antibodies	Development of vitiligo correlated with better responses.

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

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