Patterns of Response and Progression to Immunotherapy

Presented by

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The immune system is able to recognise antigens derived from cancer cells and distinguished cancer cell from normal cell and generate a tumor specific T cell immune response against the tumor.

Immunotherapy

- A type of therapy that uses substances to stimulate or suppress the immune system to help the body fight cancer, infection, and other diseases.
- Few immunotherapy only target certain cells of the immune system. Others affect the immune system in a general way.
- Immunotherapy include cytokines, vaccines, bacillus Calmette-Guerin (BCG), and some monoclonal antibodies.

Types of Immunotherapy

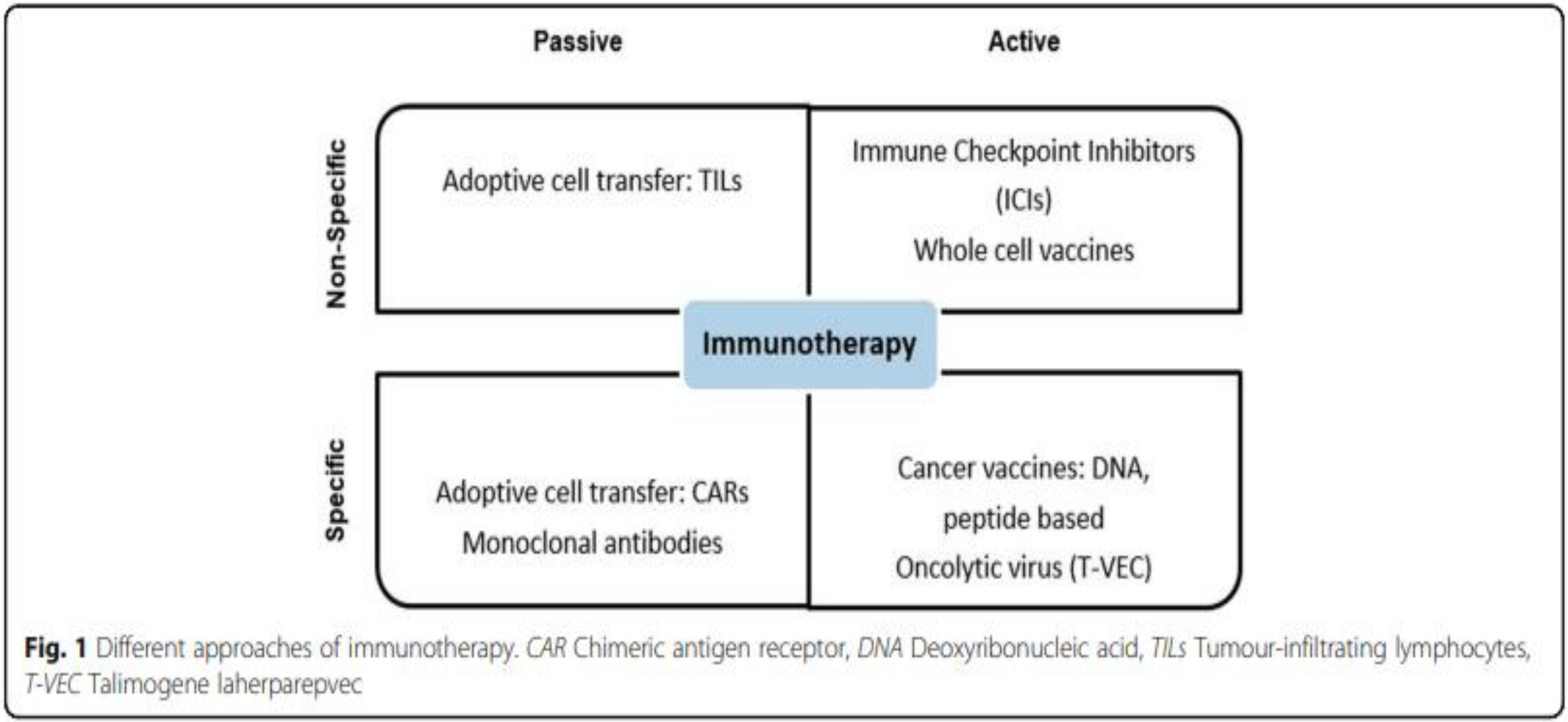

Fig. 1 Different approaches of immunotherapy. *CAR* Chimeric antigen receptor, *DNA* Deoxyribonucleic acid, *TILs* Tumour-infiltrating lymphocytes, *T-VEC* Talimogene laherparepvec

Table 1 Clinical indications of the different immune checkpoint inhibitors

Immune checkpoint inhibitor	Target	Indications
Ipilimumab	CTLA-4	Colorectal cancer, metastatic (microsatellite instability-high or mismatch repair deficient in combination with nivolumab) Melanoma, unresectable, or metastatic in combination with nivolumab Melanoma, adjuvant treatment Advanced renal cell cancer, in combination with nivolumab
Pembrolizumab	PD-1	Recurrent or metastatic cervical cancer Advanced or metastatic gastric cancer Head and neck cancer, squamous cell, unresectable/recurrent or metastatic, alone or in combination with chemotherapy Advanced hepatocellular carcinoma Hodgkin lymphoma, classical, relapsed or refractory Melanoma, adjuvant treatment Melanoma, unresectable or metastatic Merkel cell carcinoma, recurrent or metastatic Microsatellite instability-high cancer, unresectable or metastatic NSCLC, stage III or metastatic, single-agent therapy NSCLC, metastatic, non-squamous, combination therapy with chemotherapy Primary mediastinal large B cell lymphoma, relapsed or refractory Advanced renal cell carcinoma Small cell lung cancer, metastatic Urothelial carcinoma, locally advanced or metastatic
Nivolumab	PD-1	Like pembrolizumab
Cemiplimab	PD-1	Cutaneous squamous cell carcinoma, metastatic or locally advanced
Atezolizumab	PD-L1	Breast cancer (triple-negative), locally advanced or metastatic in combination with nab-paclitaxel NSCLC, metastatic: first line with bevacizumab, paclitaxel, and carboplatin Previously-treated NSCLC: monotherapy Small cell lung cancer, extensive-stage: first-line treatment with carboplatin and etoposide Urothelial carcinoma, locally advanced or metastatic
Durvalumab	PD-L1	NSCLC (stage III), unresectable, initiated within 6 weeks after chemo-radiotherapy Urothelial carcinoma, locally advanced or metastatic
Avelumab	PD-L1	Metastatic Merkel cell carcinoma Advanced renal cell carcinoma, in combination with axitinib Urothelial carcinoma, locally advanced or metastatic

CTLA4 Cytotoxic T-lymphocyte antigen 4, *NSCLC* Non-small cell lung cancer, *PD-1* Programmed cell death protein 1, *PD-L1* Programmed cell death protein ligand 1

Novel patterns of response and progression under immunotherapy

PATTERNS OF RESPONSE

1. Durable responses
2. Pseudoprogression
3. Hyperprogression
4. Dissociated responses

Durable responses

- Immune checkpoint inhibiters restore an active immune infiltrate of T cells and stimulate a cancer-specific immune response, immunotherapy responses should be durable, even after stopping the treatment.
- No standard definition of durable response exists.

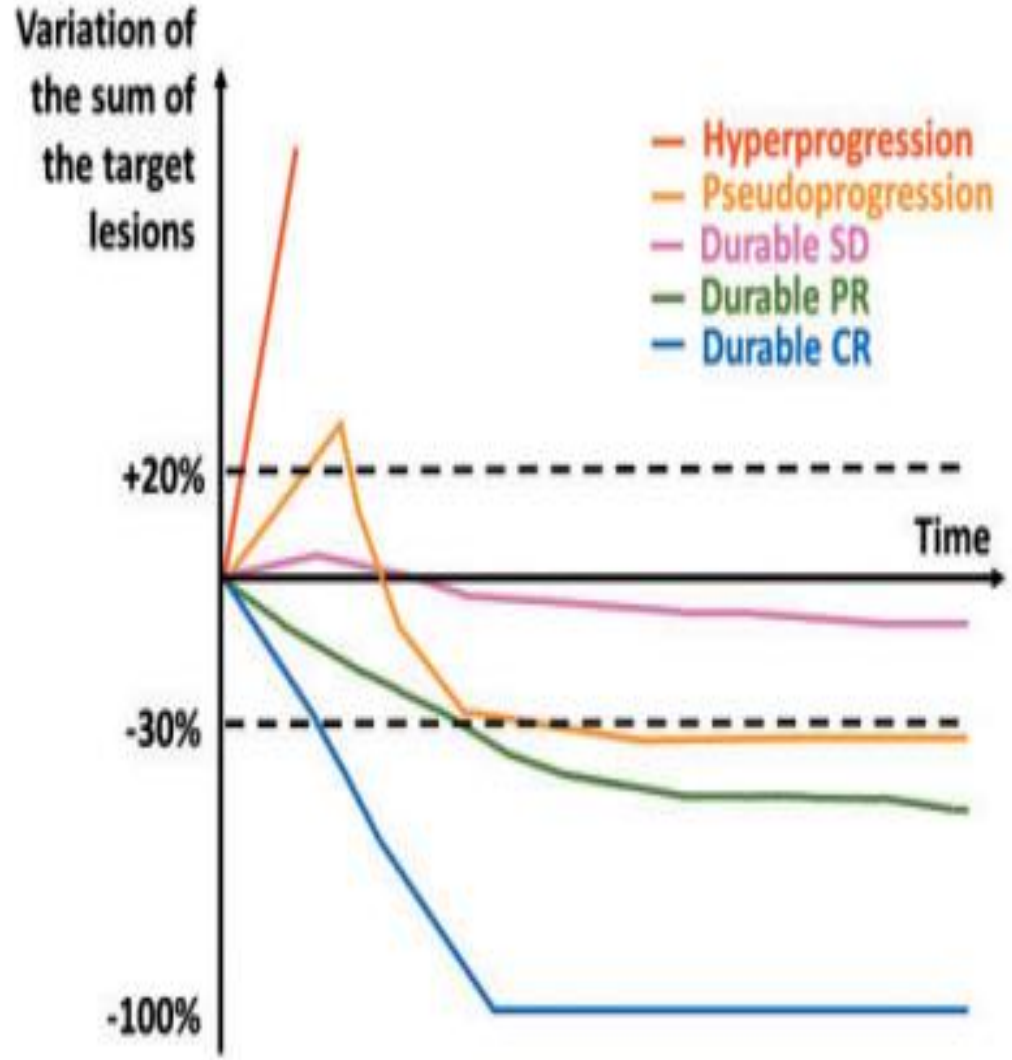

Figure 1. Patterns of response and progression under immunotherapy. SD, stable disease; PR, partial response; CR, complete response.

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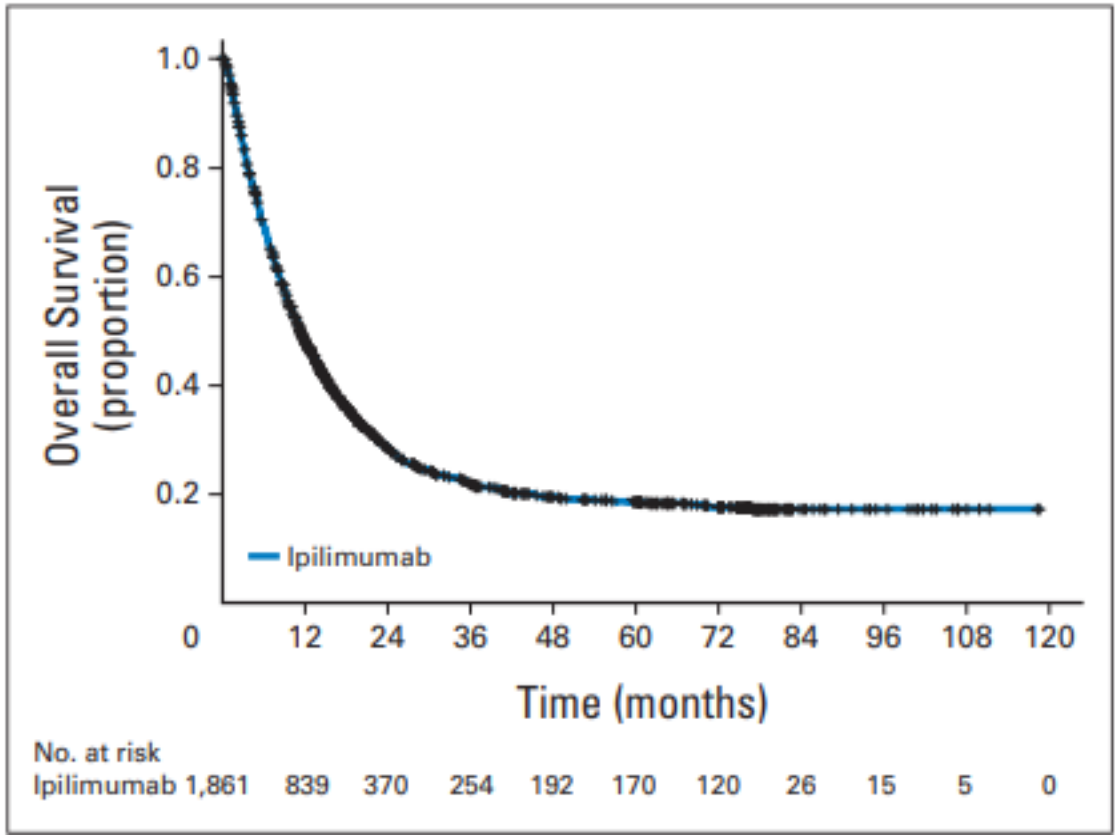
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma

Dirk Schadendorf, F. Stephen Hodi, Caroline Robert, Jeffrey S. Weber, Kim Margolin, Omid Hamid, Debra Patt, Tai-Tsang Chen, David M. Berman, and Jedd D. Wolchok

See accompanying editorial on page 1865 and article on page 1873



Result The primary analysis of 1,861 patients demonstrated a median OS of 11.4 months (95% CI, 10.7 to 12.1 months), with a 3-year survival rate estimated to be 22% (95% CI, 20% to 24%). Median follow-up time was approximately 11 months; 10% of the patients were observed for at least 50 months, with a maximum follow-up time of 119 months.

Conclusion We observed a OS curve plateauing at 21% at 3 years with a follow-up of up to 10 years. These data supporting the durability of long-term survival in ipilimumab-treated patients with advanced melanoma.

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Five-Year Follow-Up of Nivolumab in Previously Treated Advanced Non–Small-Cell Lung Cancer: Results From the CA209-003 Study

Scott Gettinger, Leora Horn, David Jackman, David Spigel, Scott Antonia, Matthew Hellmann, John Powderly, Rebecca Heist, Lecia V. Sequist, David C. Smith, Philip Leming, William J. Geese, Dennis Yoon, Ang Li, and Julie Brahmer

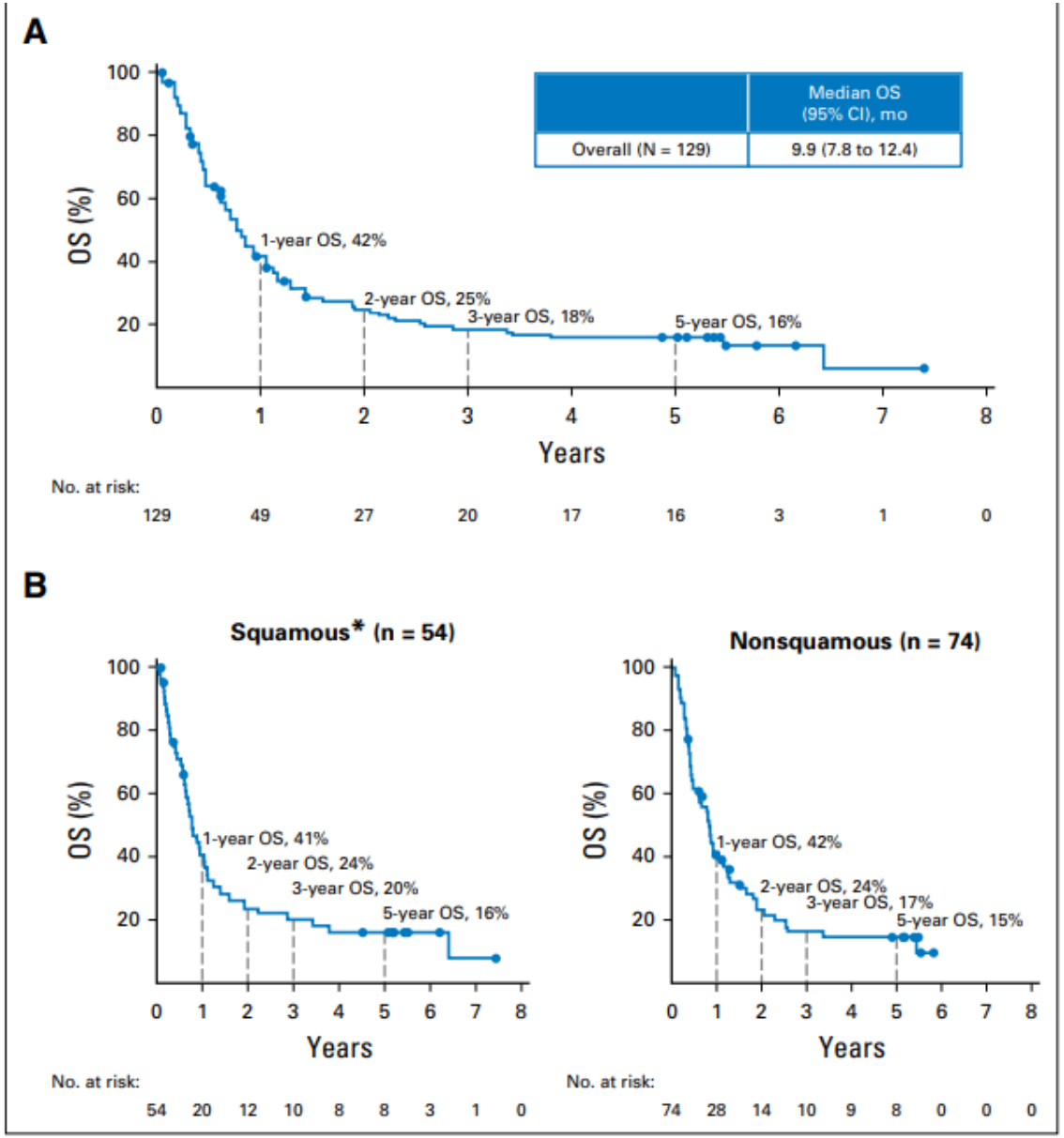
Methods Patients with pretreated, advanced NSCLC received nivolumab 1, 3, or 10 mg/kg every 2 weeks in 8-week, up to 96 weeks.

Results

The estimated 5-year OS rate was 16% for all treated patients (N = 129); 5-year OS rates were similar for squamous (16%) and nonsquamous (15%) NSCLC. Of 16 5-year survivors, most (88%) were

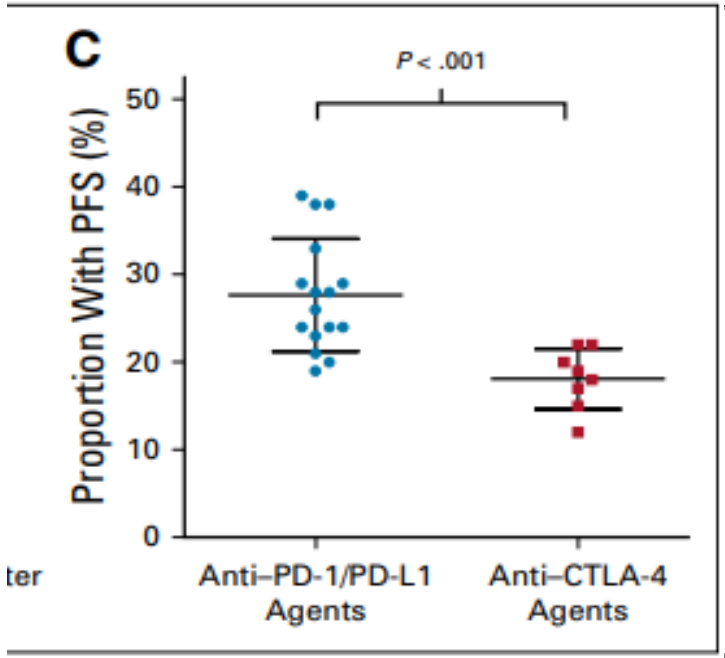
Conclusions

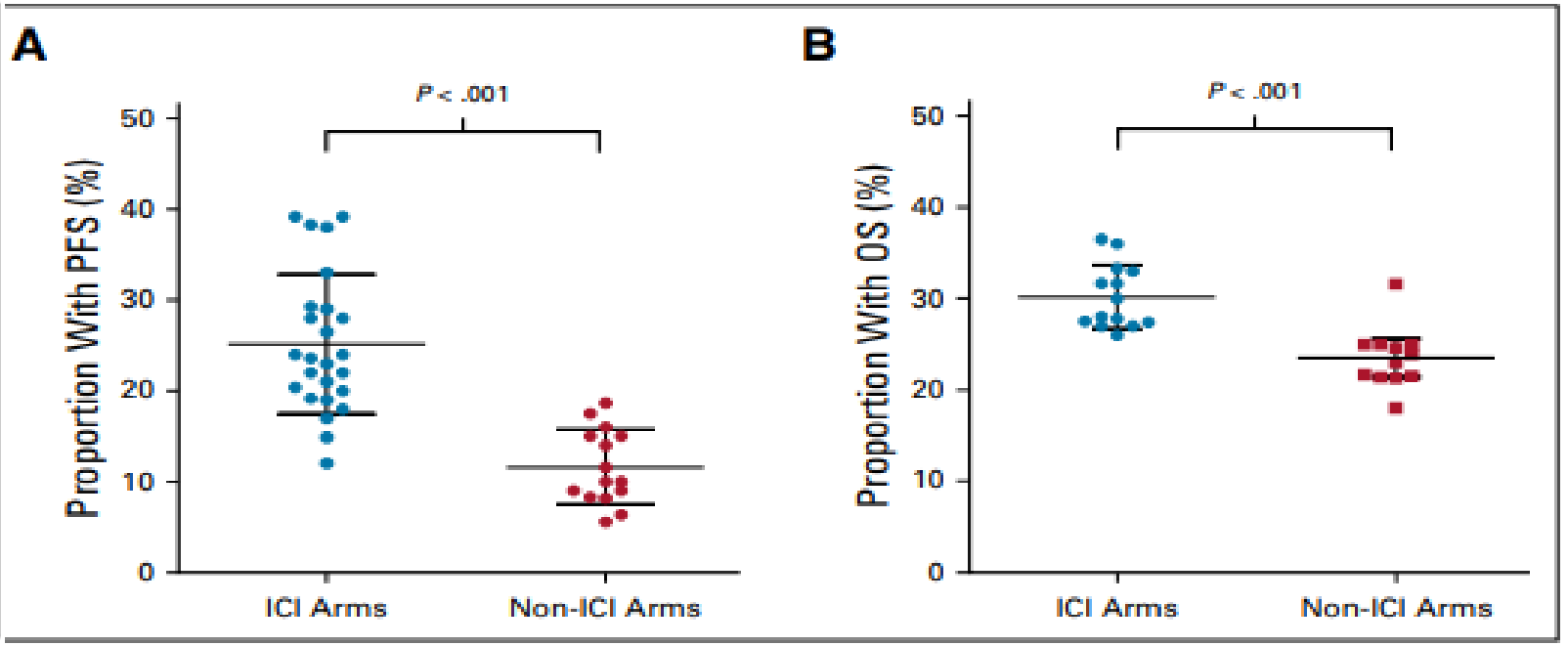
Nivolumab treatment resulted in long-term OS and durable responses in a proportion of patients with pretreated advanced NSCLC. Long-term survivors had diverse baseline and on-treatment characteristics.



Comparative Analysis of Durable Responses on Immune Checkpoint Inhibitors Versus Other Systemic Therapies: A Pooled Analysis of Phase III Trials

Elvire Pons-Tostivint, MD[1,2]; Aurélien Latouche, PhD[3]; Pauline Vaflard, MD[1]; Francesco Ricci, MD, PhD[1]; Delphine Loirat, MD, PhD[1];

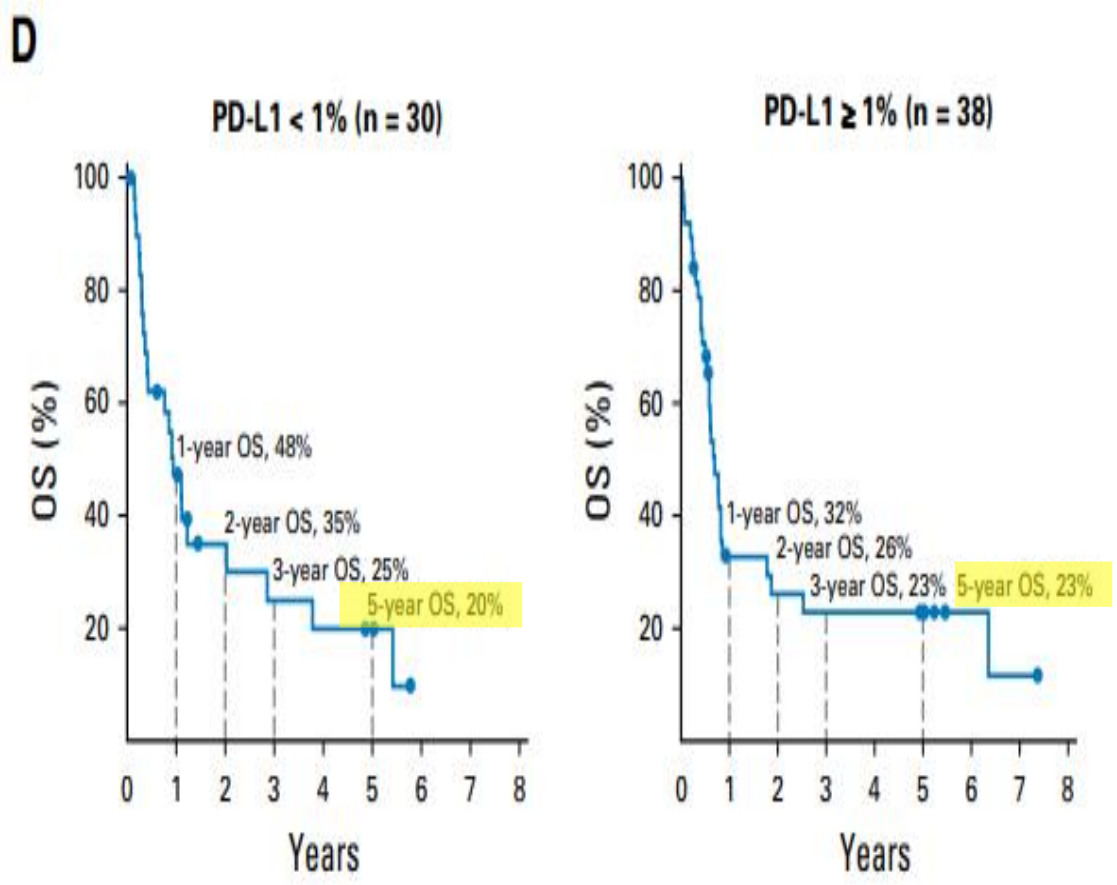




RESULTS Nineteen studies involving 11,640 patients treated in 42 treatment arms (26 ICI and 16 non-ICI arms) were included. The mean proportion of patients who experienced a durable response was 2.3 times higher in those treated with an ICI compared with those treated in the control arms (25% *v* 11%). Durable responses were more frequent in patients treated with anti–PD-1/PD-L1 agents than in patients treated with anti–CTLA-4 agents (28% *v* 18%). The mean proportion of patients who had an OS that exceeded two times the median OS was also higher in those treated with ICIs than in those treated in the control arms (30% *v* 23%). In multivariable analysis, the effects of treatment with anti–PD-1/PD-L1 agents and of first-line treatment were statistically associated with a higher mean proportion of durable responses.

Predictors of durable responses

- Patient tumors expressed PD-L>1% of tumor cells at baseline in comparison to PD-L1 <1%.
- 5 years OS 20% vs 23%.



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JOURNAL OF CLINICAL ONCOLOGY

RAPID COMMUNICATION

Durable Complete Response After Discontinuation of Pembrolizumab in Patients With Metastatic Melanoma

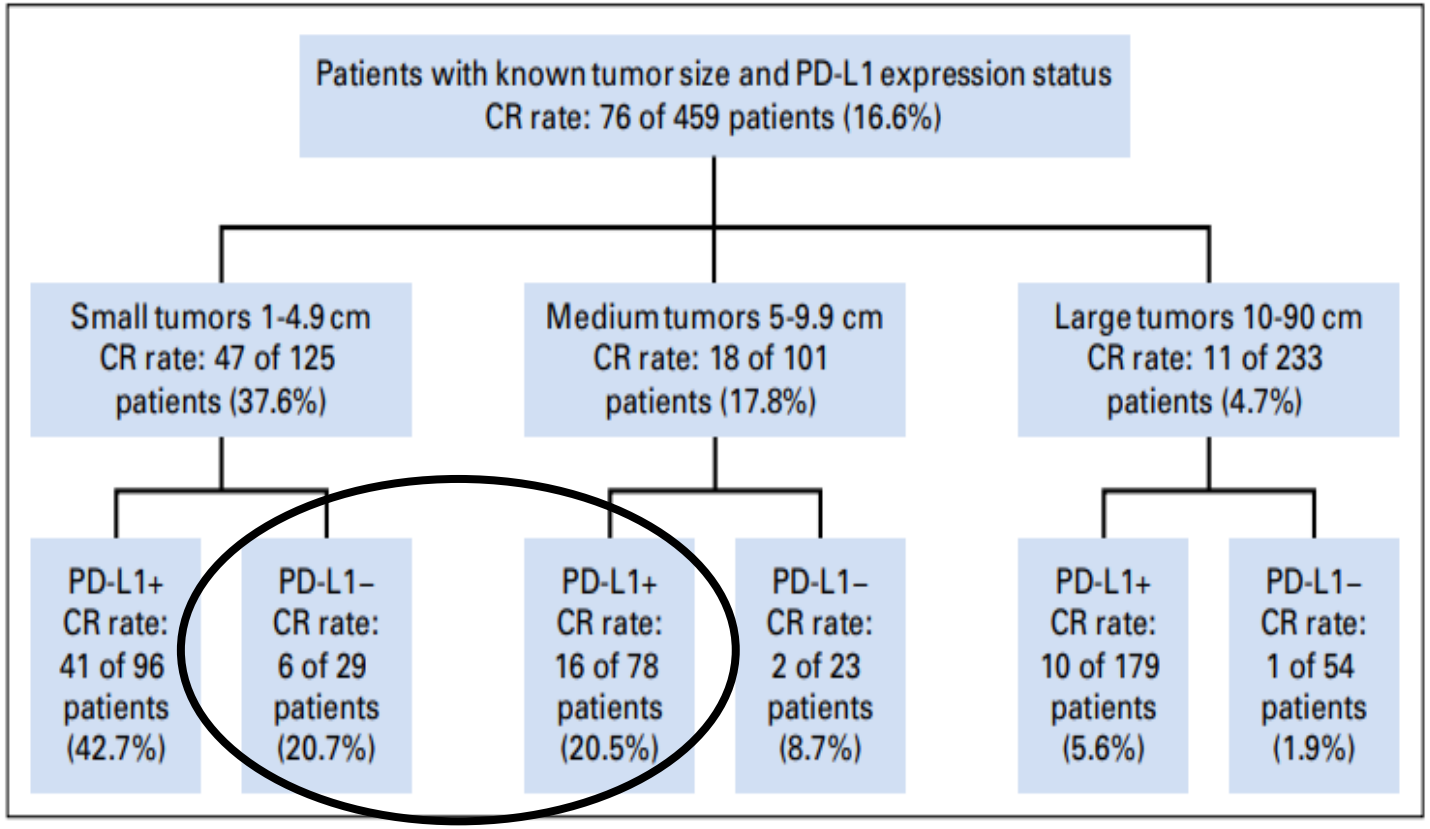
Caroline Robert, Antoni Ribas, Omid Hamid, Adil Daud, Jedd D. Wolchok, Anthony M. Joshua, Wen-Jen Hwu, Jeffrey S. Weber, Tara C. Gangadhar, Richard W. Joseph, Roxana Dronca, Amita Patnaik, Hassane Zarour, Richard Kefford, Peter Hersey, Jin Zhang, James Anderson, Scott J. Diede, Scot Ebbinghaus, and F. Stephen Hodi

Table 2. Response Rates by Baseline Tumor Size and Tumor PD-L1 Status for the Patients With Available Data (n = 459)

Tumor Size, cm	Tumor PD-L1 Status	No.	PR, %	CR, %	ORR, %
≥ 1 to < 5	Positive	96	24.0	42.7	66.7
	Negative	29	6.9	20.7	27.6
≥ 5 to < 10	Positive	78	37.2	20.5	57.7
	Negative	23	8.7	8.7	17.4
≥ 10 to ≤ 90*	Positive	179	24.0	5.6	29.6
	Negative	54	16.7	1.9	18.5

Abbreviations: CR, complete response; ORR, overall response rate; PD-L1, programmed death ligand 1; PR, partial response.

*Patients with tumors measuring 10 to 20 cm or 20 to 90 cm at baseline were pooled because these groups were not statistically different in univariate analysis.



PD-L1 expression does not seem to be a reliable predictor of durable response, since durable responses were also reported in patients with PD-L1 negative tumors.

- The observation of durable responses raises the question of treatment duration.
- The schedule of administration of ipilimumab is four cycles given every 3 weeks.
- ICIs targeting PD1/PD-L1 were evaluated for a longer period of time, ranging from 1 year to until disease progression, depending on the clinical trial designs.
- In some clinical trials, patients were allowed to be *rechallenged with the same ICI* in case patients completed 1 or 2 years of treatment,

1. Without disease progression,
2. At the time of disease progression
3. After serious immune related adverse events (iAEs).

Table 1. Rates and outcomes of patients who stopped immunotherapy after treatment completion or complete response

Study drugs	Rate of patients who stopped immunotherapy agent after treatment completion or CR	Outcomes of patients who stopped immunotherapy agent after treatment completion or CR	Outcomes following drug rechallenge because of disease progression
Melanoma			
Pembrolizumab	19% of patients (103/556) completed 2 years of pembrolizumab	86% of patients (89/103) were progression-free at 20.3 months after pembrolizumab completion	8 patients were rechallenged Median duration of second-course pembrolizumab was 9.7 months with 1 CR, 1 PR, 5 SD, and 1 PD
Pembrolizumab	10% of patients (67/655) among the 105 patients who achieved a CR stopped treatment	90% of patients (60/67) were disease-free at 24 months	–
Ipilimumab[a]	–	34% of patients (13/38) with an objective response maintained an objective response for at least 2 years	31 patients were rechallenged 19% of patients (6/31) had an objective response
Ipilimumab[a]	–	–	51 patients were rechallenged 55% of patients (28/51) had irCR (2), irPR (4), or irSD (22)
Ipilimumab[a]	–	–	122 patients were rechallenged 23% of patients (28/122) had an objective response
NSCLC			
Nivolumab	16% of patients (218/1375) completed 1-year treatment	–	–
Phase I patient population			
Anti-PD1/PD-L1 agents	13 patients discontinued treatment per protocol	Median time free-treatment after discontinuation was 12.6 months	8 patients were rechallenged 25% of patients (2/8) had a PR

[a]Patients received four injections.

CR, complete response; PR, partial response; SD, stable disease; DCR, disease control rate; irSD, immune-related SD; irPR, immune-related PR; irC related CR; irDCR, immune-related DCR; ORR, overall response rate; NSCLC, non-small-cell lung cancer; PFS, progression-free survival; OS, overall

Only one randomized trial NSCLC patients who were not progressing after 1 year of nivolumab between continuing nivolumab until disease progression or to interrupt treatment.

- The rechallenging patients after serious immune related adverse events (iAEs),

1. discontinuation of ICI
2. resolution of the toxicity.

- Prospective data from clinical trials are still limited to clearly answer this question

1. restart ICI after disappearing adverse events
2. performance status
3. alternative treatments after initial life-threatening iAEs.

- In the absence of randomized data, the decision to stop immunotherapy should be carefully discussed between the physician and the patient.
- In case of, disease progression after treatment completion and treatment interruption without disease progression, it remains to be determined whether patients should be rechallenged with the same drug or not . These question should be addressed in clinical trials.

Pseudoprogression

- Pseudoprogression does not reflect tumor cell growth but may be misclassified as progressive disease.
- It could be related to the infiltration of T cells into tumors, resulting initially in an apparent increase in tumor burden rather than true proliferation of tumor cells.
- Associated inflammatory reaction, due to cytokine release, has been also observed in on-treatment biopsy samples performed after radiological progression.
- A pattern of response has been described in this graph experiencing an objective response after having an initial disease progression.

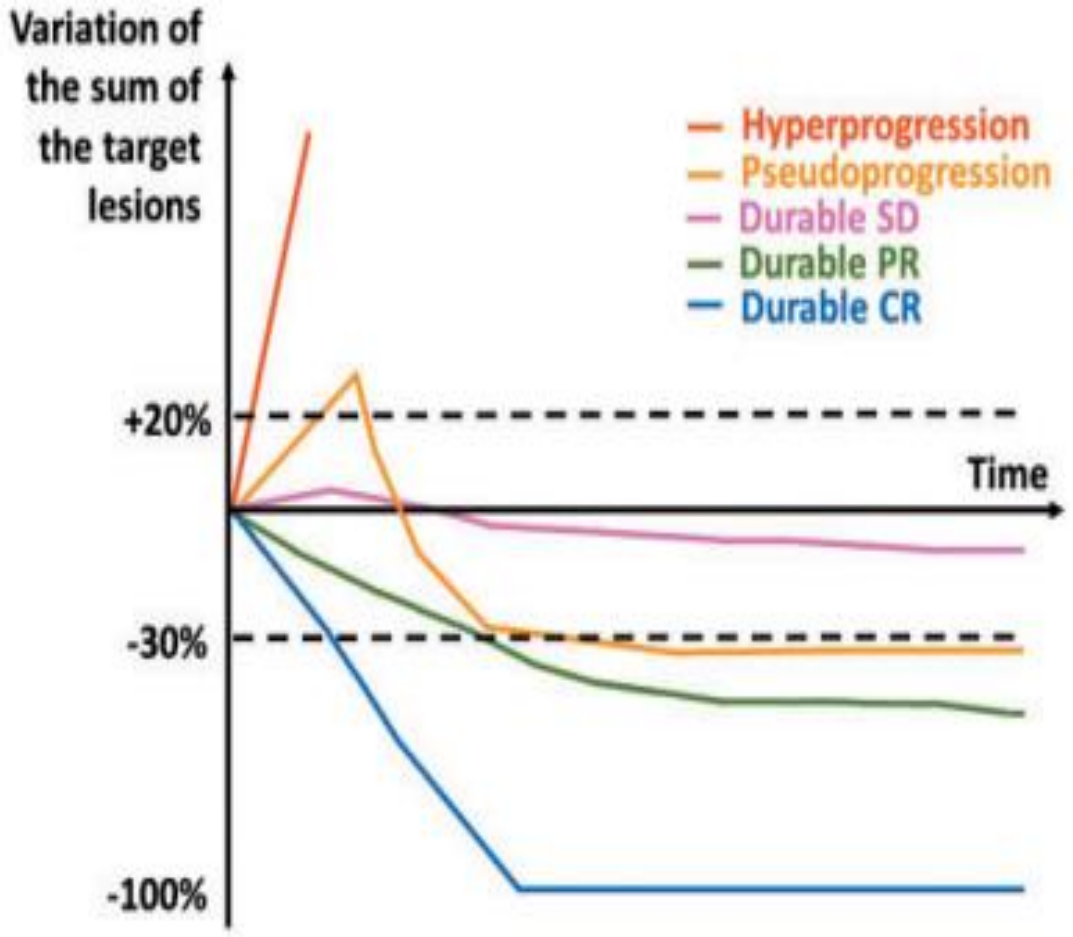


Figure 1. Patterns of response and progression under immunotherapy. SD, stable disease; PR, partial response; CR, complete response.

Table 2 Rate of pseudoprogression in patients with melanoma or NSCLC

First author, year [reference]	Number of patients	Type of cancer	Treatment	Pseudoprogression (%)
Wolchock, 2009 [17]	227	Melanoma	Ipilimumab	9.7
Hodi, 2016 [26]	327	Melanoma	Pembrolizumab	7.0
Nishino, 2017 [24]	107	Melanoma	Pembrolizumab	5.0
Gettinger, 2015 [84]	129	NSCLC	Nivolumab	5.0
Nishino, 2017 [85]	160	NSCLC	Nivolumab or pembrolizumab	0.6
Katz, 2018 [86]	166	NSCLC	Anti-PD1 (nivolumab 80%)	2.0
Fujimoto, 2019 [27]	542	NSCLC	Nivolumab	3.0

PD-1 Programmed cell death protein 1, *NSCLC* Non-small cell lung cancer

Pseudoprogression is rare.

Its more frequent in younger patients, probably because of the better reactivity of the immune system, and may occur at any time after the onset of therapy .

Mostly observed around 12 weeks.

Rate never exceeded >10%, independent of tumor type.

Table 3. Rates of pseudoprogressions in patients receiving PD1/PD-L1 inhibitors in selected phase II/III clinical trials

Study drugs	Assessment of pseudoprogression	Rates of pseudoprogressions
Melanoma		
Nivolumab	PR according to RECIST following a PD	8.1% (17/210)
Nivolumab	PR according to RECIST following a PD	8.3% (10/120)
Pooled retrospective study of two multicenter phase III trials evaluating anti-PD1 antibodies	PR according to RECIST following a PD	4.6% (24/526)
Non-small-cell lung cancer		
Nivolumab	Tumor burden reduction or No further progression for at least two tumor assessments after initial PD according to RECIST	3.4% (4/117)
Nivolumab	Appearance of a new lesion followed by a decrease from baseline of at least 10% in the sum of target lesions or Initial increase from nadir ≥20% in the sum of target lesions followed by a reduction from baseline of at least 30% or Initial increase from nadir ≥20% in the sum of target lesions or Appearance of new lesions followed by at least two tumor assessments showing no further progression defined as >10% additional increase in the sum of target lesions and new lesions	5.5% (16/292)
Nivolumab	Appearance of a new lesion followed by a decrease from baseline of at least 10% in the sum of target lesions or Initial increase from nadir ≥20% in the sum of target lesions followed by a reduction from baseline of at least 30% or Initial increase from nadir ≥20% in the sum of target lesions followed by at least two tumor assessments showing no further progression defined as >10% additional increase in the sum of target lesions and new lesions	6.9% (9/131)
Atezolizumab	PR according to RECIST following a PD	3.6% (12/332)
Pooled retrospective study of three multicenter open-label trials evaluating anti-PD1 antibodies	PR according to RECIST following a PD	1.9% (10/535)
Monocentric retrospective study of consecutive patients treated with anti-PD1 antibodies	PR according to RECIST following a PD	1.8% (3/166)
Monocentric retrospective study of consecutive patients treated with anti-PD1/PD-L1 antibodies	PR according to RECIST following a PD	5% (8/160)
Head and neck squamous cell carcinoma		
Nivolumab	PR according to RECIST following a PD	1.3% (3/240)
Renal cell carcinoma		
Nivolumab	PR according to RECIST following a PD	7.1% (12/168)
Nivolumab	PR according to RECIST following a PD	4.9% (20/406)
Urothelial carcinoma		
Nivolumab	PR according to RECIST following a PD	9.1% (24/265)
Atezolizumab	PR according to RECIST following a PD	1.6% (5/310)

PR, partial response; PD, progressive disease.

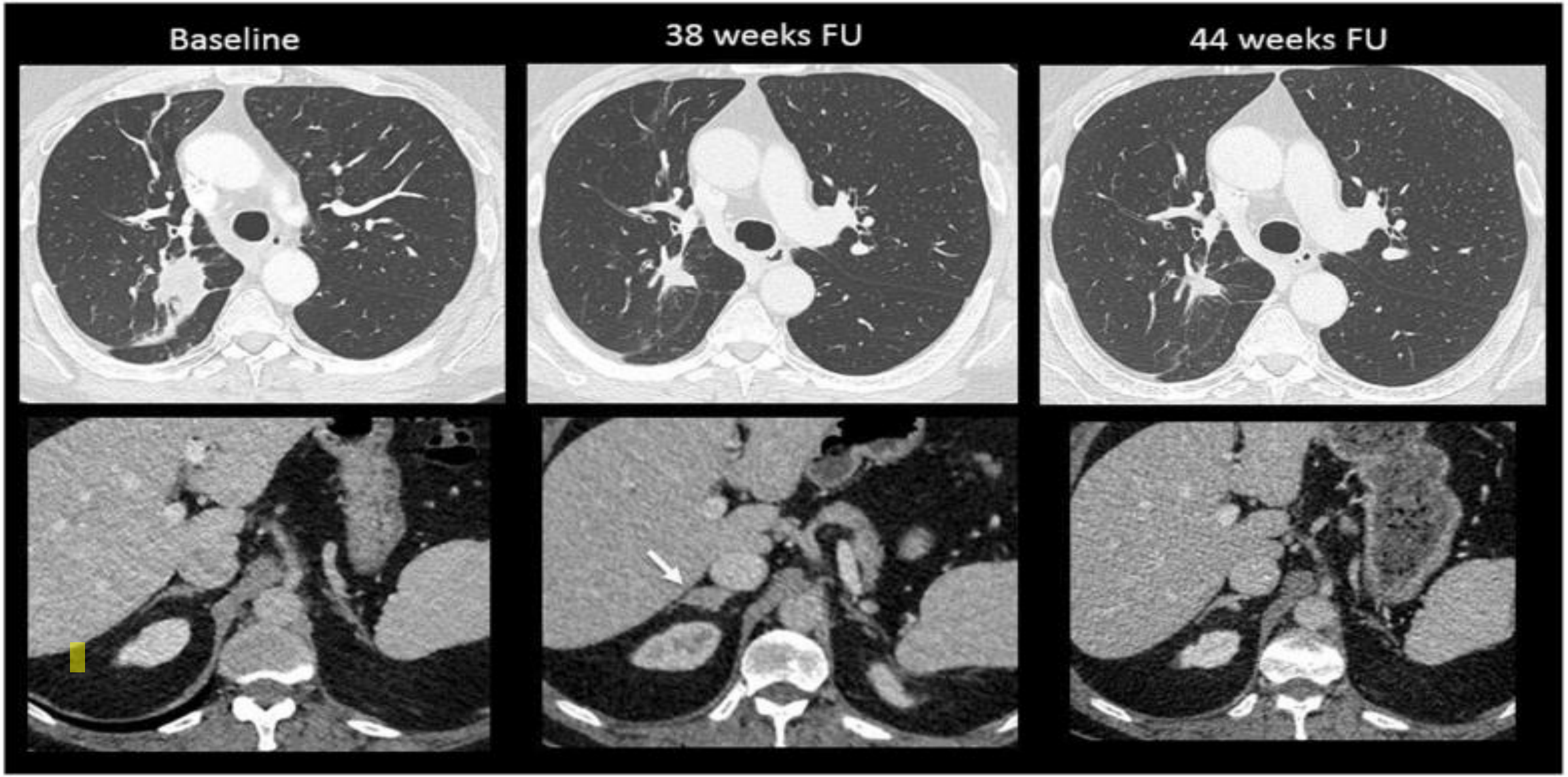


Fig. 3 Pseudoprogression in a 65-year-old patient with lung carcinoma treated with nivolumab (anti-PD-1). Baseline axial CT showed a lung mass in the upper right lobe with normal adrenal glands. At a 38-week follow-up (FU), there was a good reduction in the size of the lung mass, but a new lesion appeared in the right adrenal gland (arrow). The patient was maintained under the same treatment. At 44-week follow-up, the right adrenal mass disappeared, confirming the diagnosis of pseudoprogression

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PMCID: PMC5885201
PMID: 29423503

Association Between Circulating Tumor DNA and Pseudoprogression in Patients With Metastatic Melanoma Treated With Anti–Programmed Cell Death 1 Antibodies

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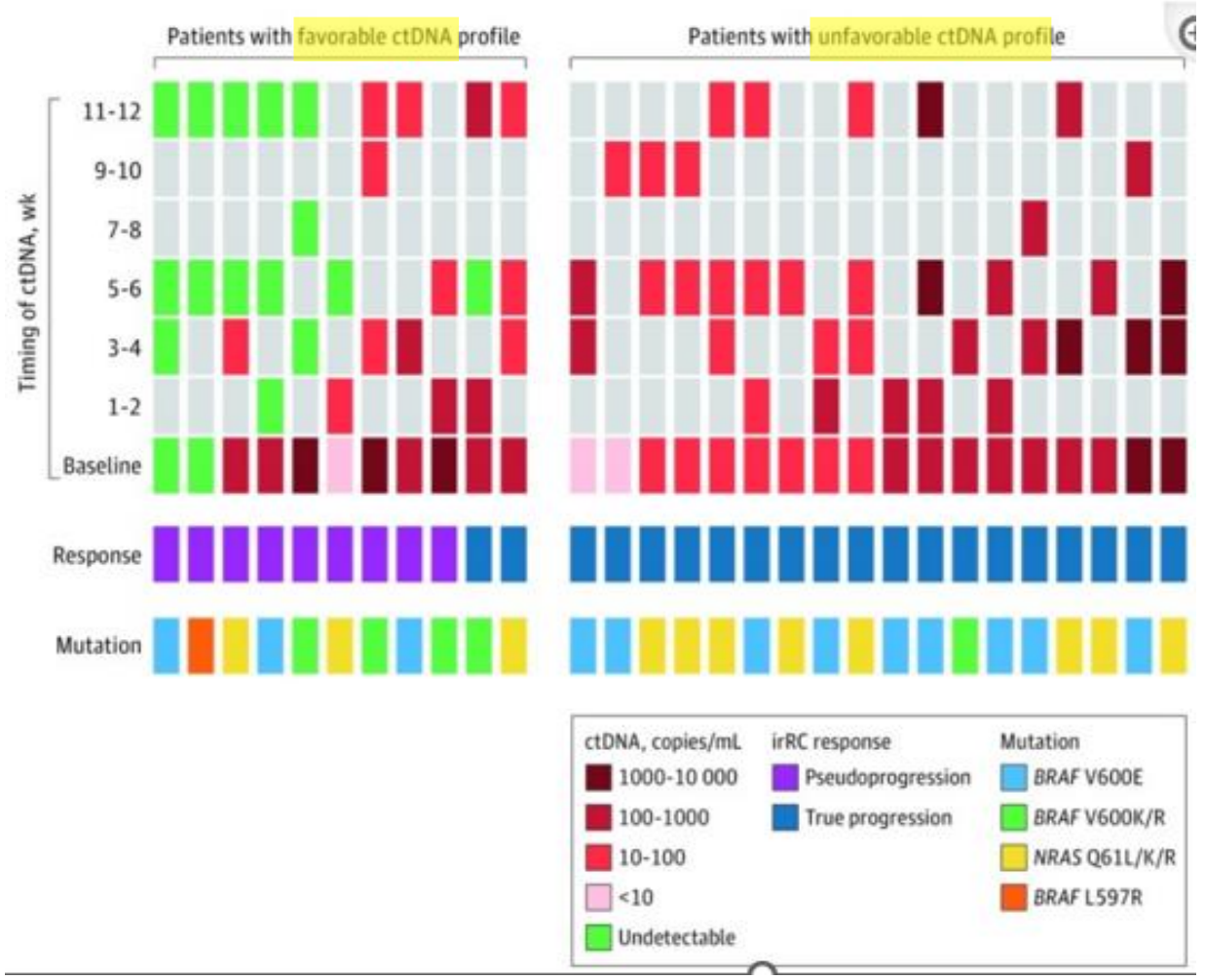
No clear predictors of pseudoprogression exist.

The early assessment of circulating tumor DNA (ctDNA) might help distinguishing pseudoprogression from real progression.

Sensitivity of ctDNA for predicting pseudoprogression was 90% and specificity 100%.

Real-time assessment of ctDNA might help distinguishing pseudoprogression from true progression.

This needs to be validated in larger cohorts of patients.



Hyperprogression

- The concept of hyperprogression was first reported in retrospective studies of patients treated with ICIs based on clinical observations of patients whose disease seemed to grow faster after the initiation of immunotherapy.
- Paradoxical acceleration of tumor growth kinetics.

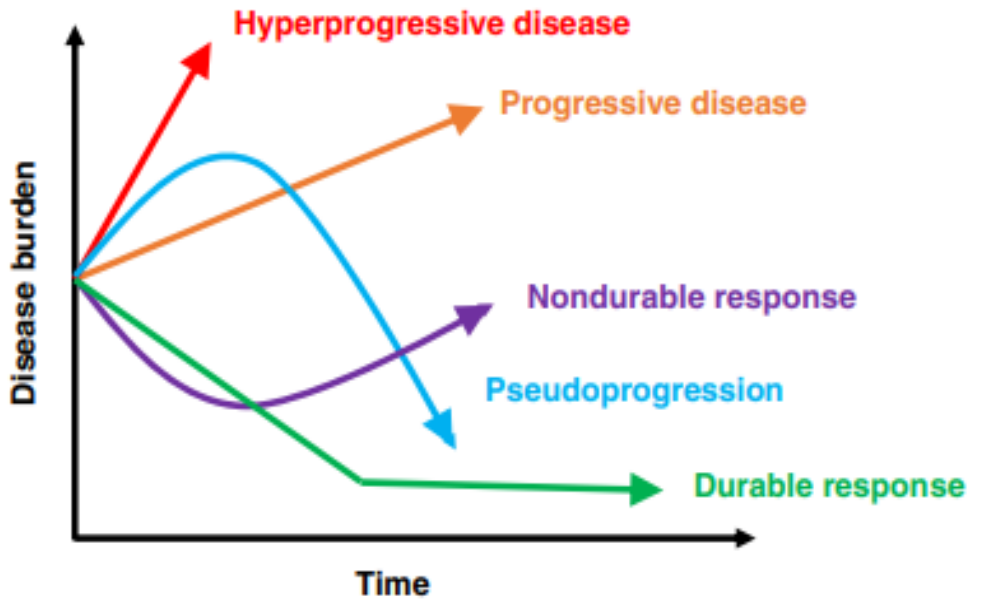


Figure 1. Potential outcomes after initiation of immunotherapy with immune checkpoint inhibitors for the treatment of various cancers over time. **(Green):** Durable response to treatment in which target lesions shrink on imaging and remain attenuated. **(Purple):** Nondurable response in which lesions initially response to therapy, but on subsequent surveillance imaging, lesions become resistant and increase in size. **(Orange):** Disease progression in which target lesions grow >20% from previous imaging. **(Blue):** Pseudoprogression in which tumors enlarge on imaging initially followed by decrease in size seen. **(Red):** Hyperprogressive disease in which rapid growth occurs after initiating immune checkpoint inhibitors.

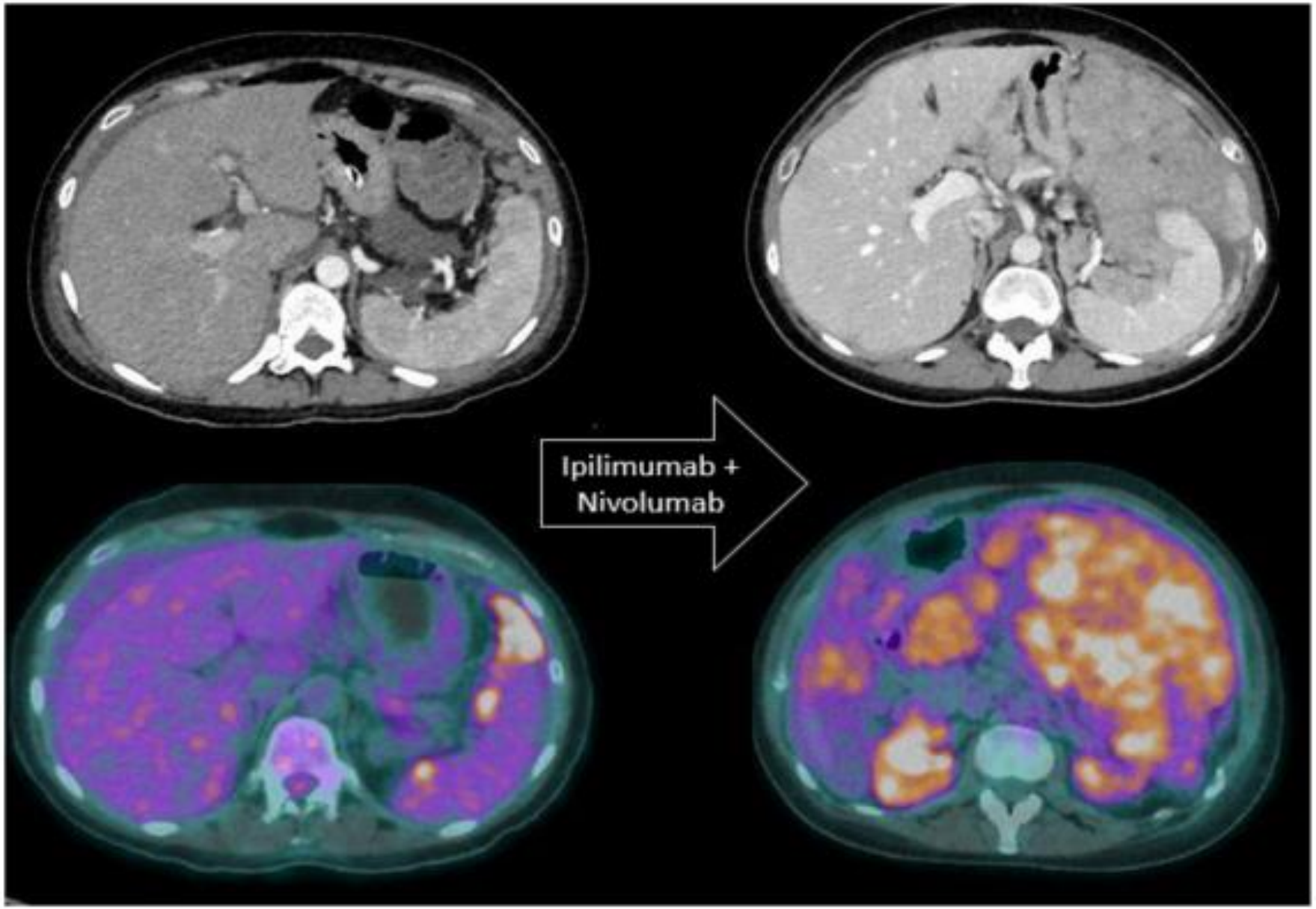
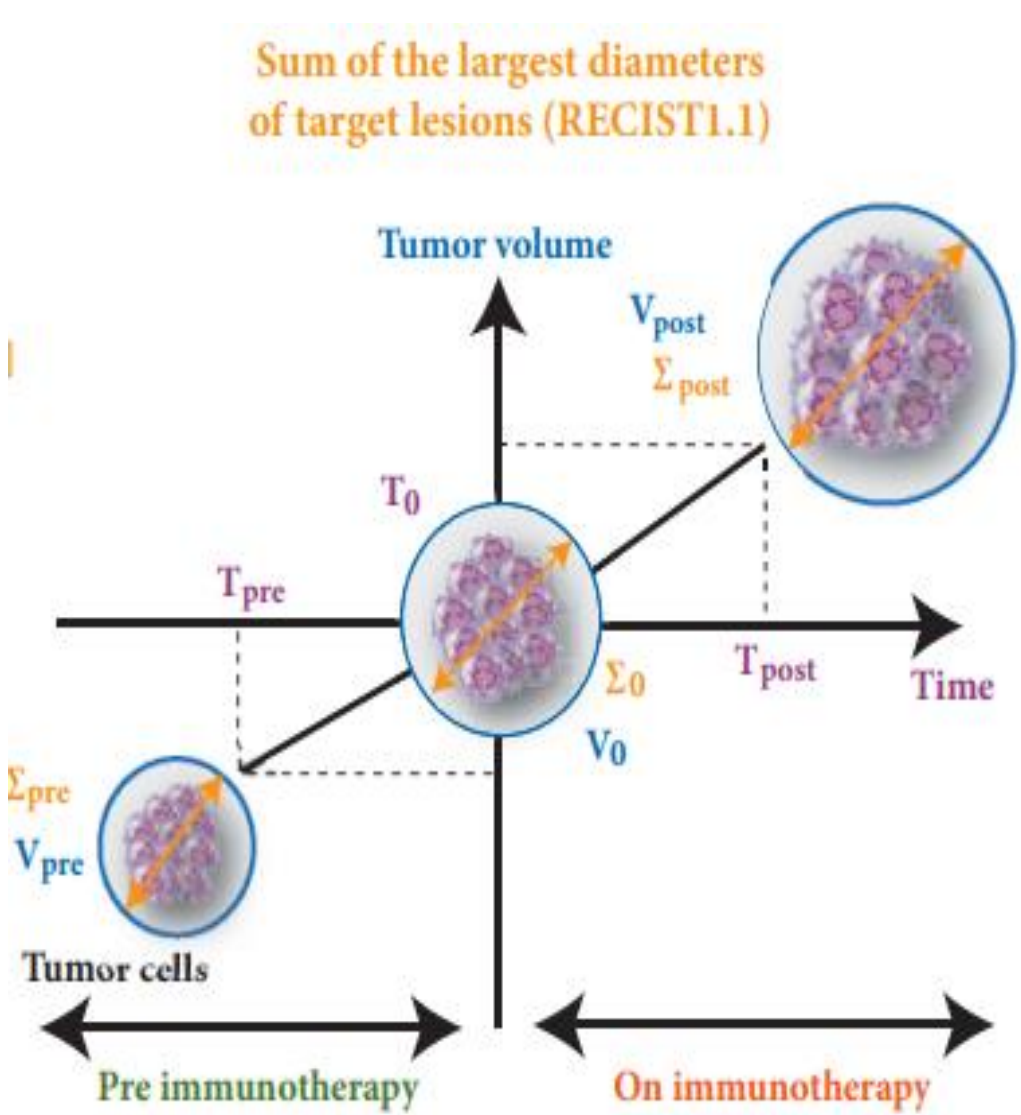


Fig. 4 Paradoxical acceleration of tumour growth kinetics in a patient with metastatic melanoma treated with ipilimumab and nivolumab. Baseline axial CT image and corresponding ^{18}F-FDG PET/CT image show few perisplenic peritoneal metastatic implants. Two months after the initiation of immunotherapy, both imaging modalities show a dramatic increase in peritoneal metastases.



Definitions of Hyperprogression

Institut Curie's study

$$\frac{\Sigma_{POST} - \Sigma_0}{T_{POST} - T_0} \Big/ \frac{\Sigma_0 - \Sigma_{PRE}}{T_0 - T_{PRE}} \geq 2$$

Sum of the largest diameters according to RECIST1.1

Gustave Roussy's study

$$\frac{V_{POST} - V_0}{T_{POST} - T_0} \Big/ \frac{V_0 - V_{PRE}}{T_0 - T_{PRE}} \geq 2$$

Increase in size or volume per unit of time

UC San Diego's study

Time to treatment failure
< 2 months
OR
>50% increase in tumor burden using irRC
OR
>2-fold increase in progression pace

Figure 2. Criteria used in the literature to define hyperprogression. Σ_{pre}, sum of the largest diameters of the target lesions on baseline imaging before starting last prior treatment; Σ_{post}, sum of the largest diameters of the target lesions on imaging postimmunotherapy; V_{pre}, sum of the volumes of the target lesions on baseline imaging before starting last prior treatment; V_{post}, sum of the volumes of the target lesions on imaging postimmunotherapy; T_{pre}, time of baseline imaging before starting last prior treatment; T_{post}, time of imaging postimmunotherapy; TTF, time to treatment failure.

Table 4. Rates of hyperprogressions in patients receiving immune checkpoint inhibitors

Study drugs	Cancer types	Assessment of hyperprogression	Rates of hyperprogression	References
Anti-PD1/PD-L1 antibodies	All	TGR >2 according to tumor volume	9.1% (12/131)	[10]
ICIs and/or costimulatory molecules	All	TGR >2 according to tumor volume	7.1% (13/182)	[60]
Anti-PD1/PD-L1 antibodies	All	TTF <2 months or >50% increase in tumor burden according to irRC or >2-fold increase in progression pace	3.8% (6/155)	[61]
Anti-PD1/PD-L1 antibodies or ICI combinations in phase I trials	All	TTF <2 months and minimum increase in measurable lesions of 10 mm and Increase of ≥40% in target tumor burden compared with baseline or increase of ≥20% plus the appearance of multiple new lesions	15.4% (33/214)	[62]
Anti-PD1/PD-L1 antibodies	HNSCC	TGK > 2 according to RECIST1.1	29.4% (10/34)	[59]
ICIs in phase I/II trials	Gynecological cancers	≥40% tumor burden increase or ≥20% tumor burden increase plus multiple new lesions	23.3% (14/60)	[63]
Anti-PD1/PD-L1 antibodies	NSCLC	Variation of TGR >1.5 according to tumor volume	16.2% (54/333)	[64]

ICI, immune checkpoint inhibitor; TGR, tumor growth rate; TTF, time to treatment failure; TGK, tumor growth kinetics; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small-cell lung cancer.

Rates of hyperprogression ranged from 4% to 29%.

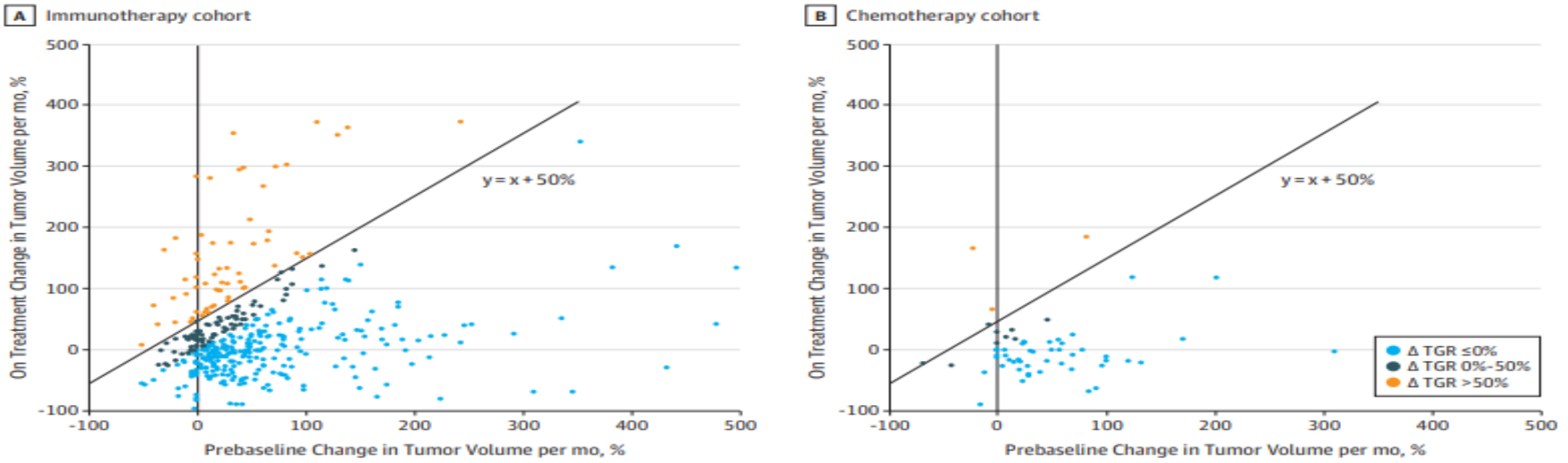
Factor affecting the hyperprogression

- Older age
- Higher number of metastatic sites.
- loco regional recurrence in the radiation field.
- MDM2/MDM4 amplifications and EGFR alterations.
- Innate immunity.
- The concept of hyperprogression is controversial since most of the studies mentioned above did not use a control arm.
- It is not possible to confirm that the acceleration of growth kinetics was induced by immunotherapy, or that similar growth kinetics simply reflects the natural history of the cancer.

JAMA Oncology | Original Investigation

Hyperprogressive Disease in Patients With Advanced Non–Small Cell Lung Cancer Treated With PD-1/PD-L1 Inhibitors or With Single-Agent Chemotherapy

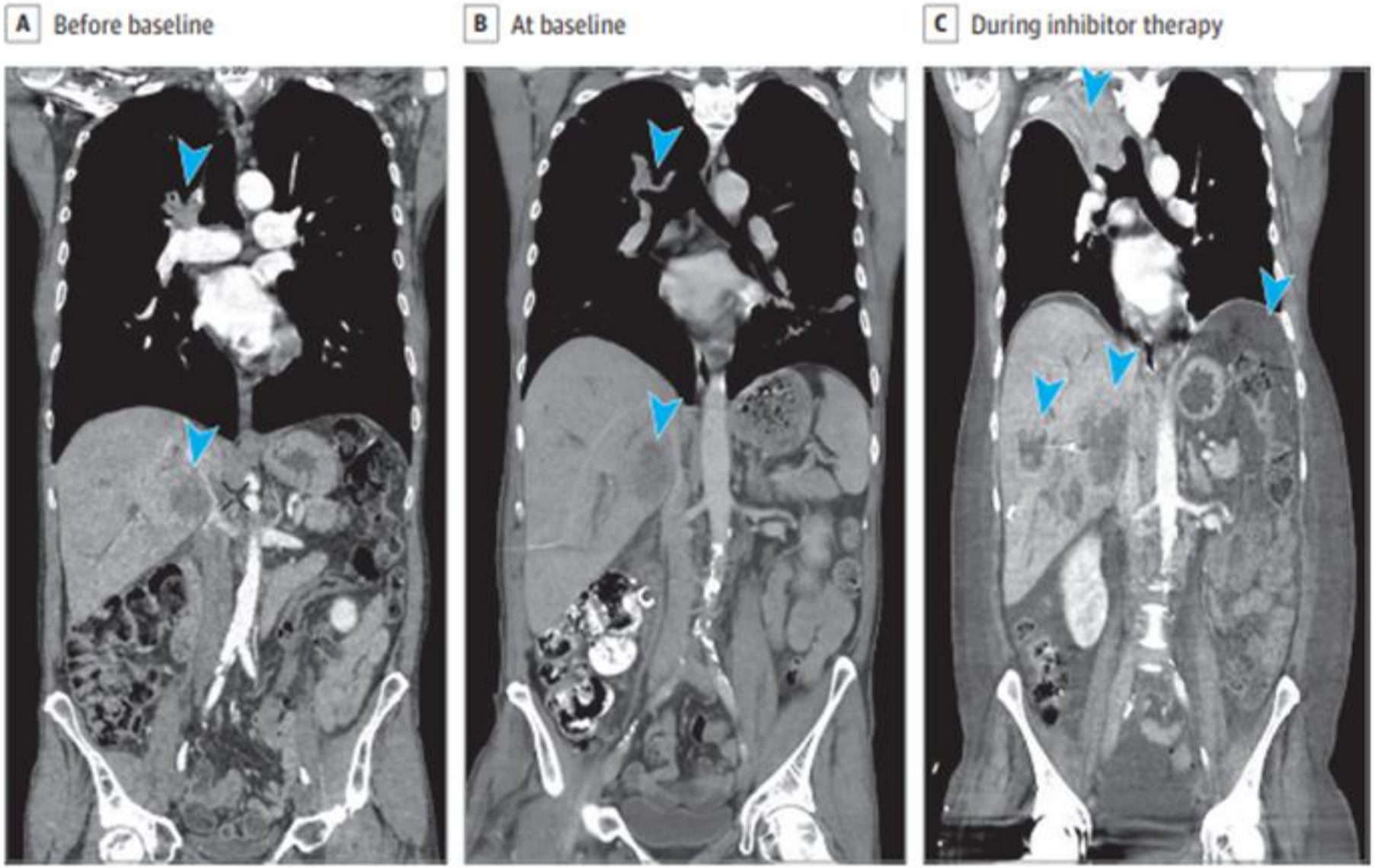
Figure 2. Scatterplots With Response According to Delta Tumor Growth Rate (TGR) in the Immunotherapy and Chemotherapy Cohorts



A, Light blue spots show 266 patients with regressing or stable tumors, dark blue spots show 78 patients with progressing tumors, and orange spots show 62 patients with accelerated tumor growth during programmed cell death (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitor therapy. B, Light blue spots show 47 patients with regressing or stable tumors, dark blue spots show 9 patients with progressing tumors, and orange spots show 3 patients with accelerated tumor growth during chemotherapy. Diagonal lines separate patients with delta TGR exceeding 50% from patients with delta TGR of 50% or less.

CONCLUSIONS The study suggests HPD is more common with PD-1/PD-L1 inhibitors compared with chemotherapy (13.8% vs 5.1%) in pretreated patients with NSCLC and is also associated with high metastatic burden and poor prognosis in patients treated with PD-1/PD-L1 inhibitors.

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.

Summery of Hyperprogression

- Hyperprogression were reported in 4%–29% of patients treated with immunotherapy.
- In clinical point of view, we do not know whether a rapid progression is a hyperprogression or not, inspite of these findings, the attribution of hyperprogression to immunotherapy remains controversial.
- In particular, hyperprogression has been observed in patients having received other therapies, such as surgery, radiotherapy, and/or chemotherapy or even in the absence of treatment.
- The mechanisms underlying hyperprogressive disease have not been clear yet.
- In case of rapid clinical progression, to interrupt immunotherapy.
- An early clinical and imaging assessment should be carried out in order to rapidly switch to another potential effective treatment. When patients have good clinical condition.
- These preliminary data suggest that chemotherapy is a valuable option that should not be underestimated as salvage therapy in case of true progression under immunotherapy.

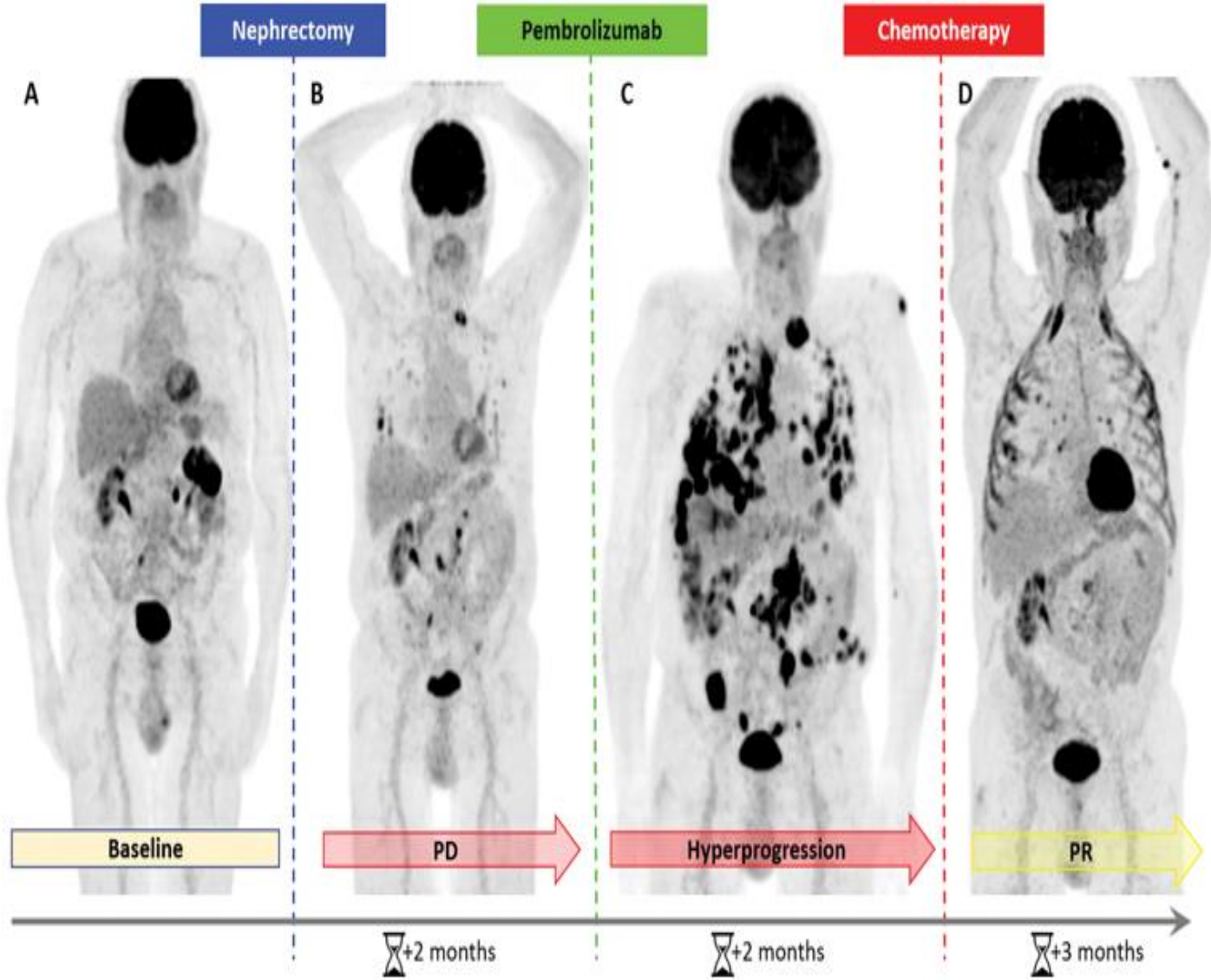


Figure 15. Hyperprogression after immunotherapy in an 89-year-old man with clear cell renal carcinoma. MIP FDG PET images show the baseline appearance at diagnosis *(A)*, progressive disease *(PD)* after nephrectomy *(B)*, and hyperprogression after pembrolizumab therapy *(C)*, with an important partial response *(PR)* after chemotherapy *(D)*.

Dissociated responses

- Dissociated responses are present when some target lesions grow and others regress.
- This response pattern is analogous to mixed responses seen with chemotherapy and targeted therapy .
- This atypical pattern of response was associated with a better survival than true progressions.
- No predictor of dissociated response was identified.
- In case of oligometastatic disease progression, local treatments of the growing lesions might be discussed in tumor boards, while pursing the immunotherapy treatment.

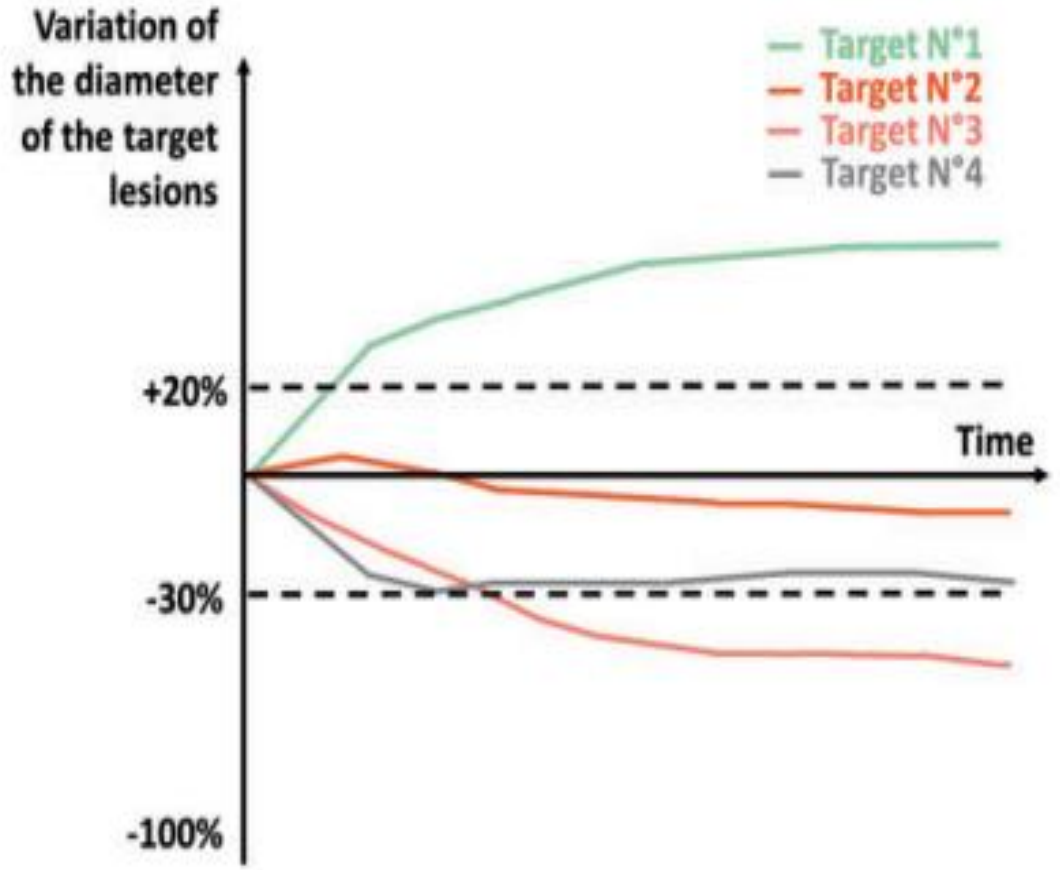


Figure 3. Illustration of a dissociated response to immunotherapy.

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ORIGINAL ARTICLE

Patterns of response in metastatic NSCLC during PD-1 or PD-L1 inhibitor therapy: Comparison of the RECIST 1.1 and iRECIST criteria

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- Only one study was reported Dissociated response in 7.5% of NSCLC patients treated with anti-PD1/PD-L1 agents.

Assessment of response to immunotherapy

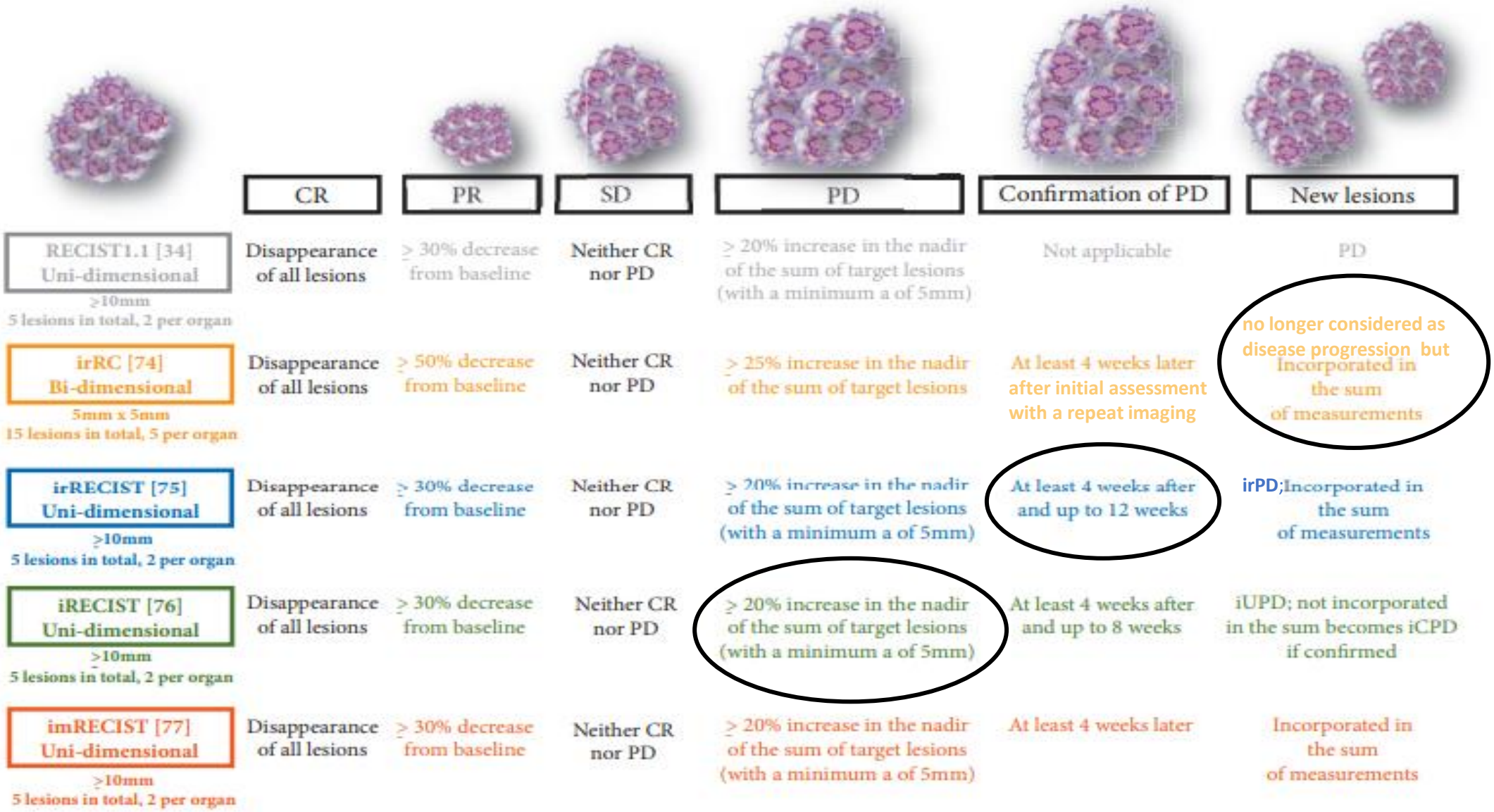
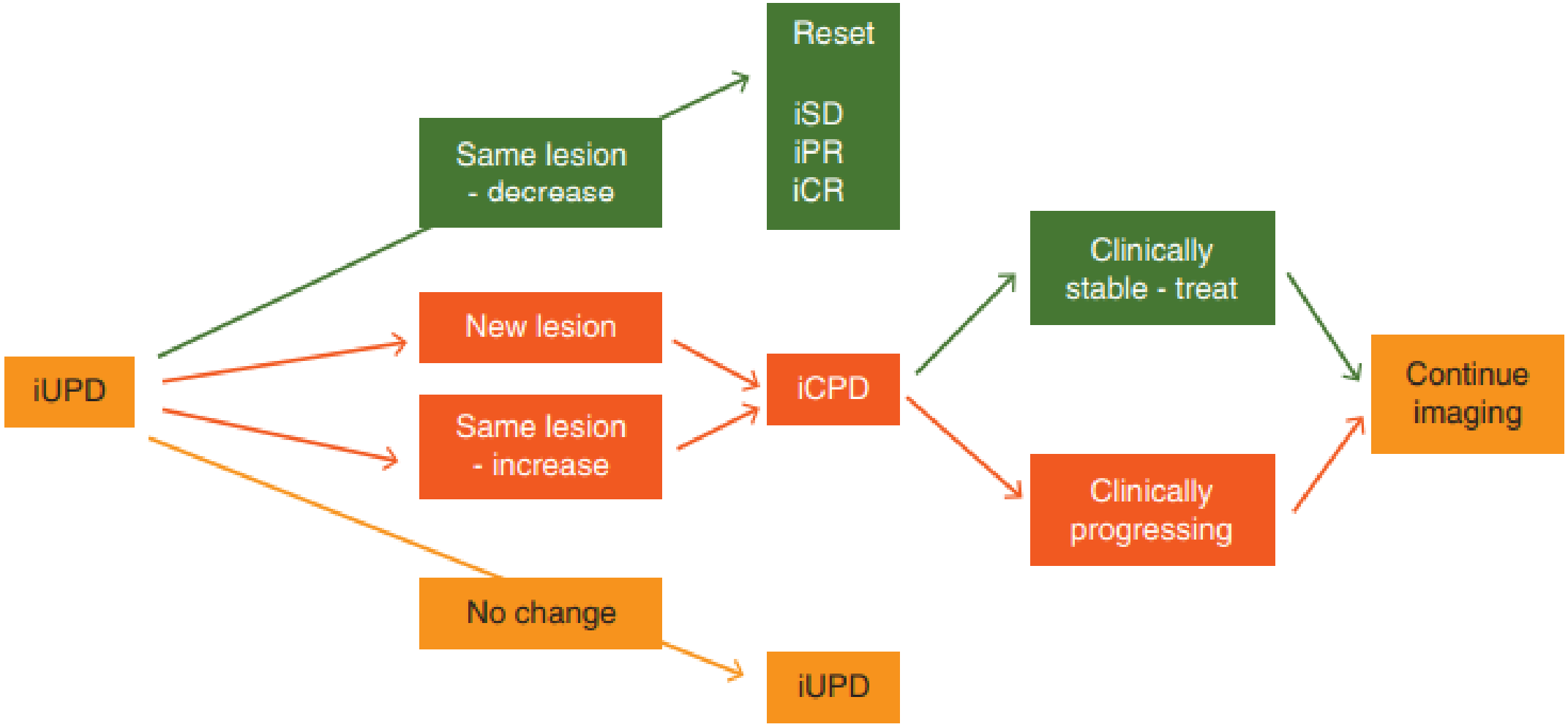


Figure 4. Overview of immune-specific related response criteria reported in the literature. RECIST, response evaluation criteria in solid tumors; irRC, immune-related response criteria; irRECIST, immune-related RECIST; iRECIST, immune RECIST; imRECIST, immune-modified RECIST; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; iUPD, immune unconfirmed progressive disease; iCPD, immune confirmed progressive disease.



iUPD: immune unconfirmed progressive disease (can have multiple iUPD)
iSD: immune stable disease
iPR: immune partial response
iCR: immune complete response
iCPD: immune confirmed progressive disease

Figure 5. Illustration of immune unconfirmed progressive disease (iUPD) in iRECIST.

Conclusion of response criteria

- The main goals of these immune-specific criteria (irRC) with incorporation in clinical trials assessment and analysis between different trials evaluating immunotherapy, and to integrate the atypical patterns of response to immunotherapy.
- However, these many different immune-related criteria can lead to confusion.
- These immune-related criteria do not report such as hyperprogression or dissociated responses.
- None of these criteria have actually been uniformly adopted in routine.
- RECIST1.1 should remain the standard of patient management and decision-making in clinical trials and immune-related criteria (irRC) kept as secondary end points.

Take home message

- Patterns of response and progression have been observed under immunotherapy that differ from conventional therapeutic agents.
- In durable response, the questions of treatment duration and rechallenge patients with the same treatment at disease progression have to be assessed in randomized trials.
- Pseudoprogression is rare and most initial radiographic progressions under immunotherapy reflect true disease progression and assessed by (irRC).
- In case of rapid progression or suspected hyperprogression, treatment should be interrupted, reassess radiologically and switch of the patient to another treatment such as chemotherapy.

Cont.

- Mechanism of pseudoprogression and hyperprogression disease have not been clear yet.
- Dissociated response should be carefully taken, and proposed only in patients with true clinical benefit.
- RECIST1.1 should remain the standard of patient management and decision-making in clinical trial.
- No clear predictors to differentiate from real disease progression during immunotherapy.
- Translational research will help mechanisms of the antitumor immune response, to better understand and predict these resistance mechanisms to immunotherapy.

THANK YOU