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ORIGINAL ARTICLE

Clinical definition of acquired resistance to immunotherapy in patients with metastatic non-small-cell lung cancer

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Acquired resistance (AR) to programmed cell death protein 1/programmed death-ligand 1 [PD-(L)1] blockade is frequent in non-small-cell lung cancer (NSCLC), occurring in a majority of initial responders. Patients with AR may have unique properties of persistent antitumor immunity that could be re-harnessed by investigational immunotherapies. The absence of a consistent clinical definition of AR to PD-(L)1 blockade and lack of uniform criteria for ensuing enrollment in clinical trials remains a major barrier to progress; such clinical definitions have advanced biologic and therapeutic discovery. We examine the considerations and potential controversies in developing a patient-level definition of AR in NSCLC treated with PD-(L)1 blockade. Taking into account the specifics of NSCLC biology and corresponding treatment strategies, we propose a practical, clinical definition of AR to PD-(L)1 blockade for use in clinical reports and prospective clinical trials. Patients should meet the following criteria: received treatment that includes PD-(L)1 blockade; experienced objective response on PD-(L)1 blockade (inclusion of a subset of stable disease will require future investigation); have progressive disease occurring within 6 months of last anti-PD-(L)1 antibody treatment or rechallenge with anti-PD-(L)1 antibody in patients not exposed to anti-PD-(L)1 in 6 months.

Key words: PD-(L)1 blockade, checkpoint inhibitor, immunotherapy, acquired resistance, lung cancer

BACKGROUND

Programmed cell death protein 1/programmed death-ligand 1 [PD-(L)1] blockade has revolutionized lung cancer treatment with unprecedented durability of responses in patients with advanced disease, but acquired resistance (defined as progression of disease after initial antitumor response) remains a common and insufficiently studied clinical challenge.[1-10] The emergence of acquired resistance (AR) is particularly challenging in patients with lung cancer, where patients develop AR at higher rates than many other tumor types sensitive to PD-(L)1 blockade.[11] The distinct considerations of AR in lung cancer suggest unique underlying determinants of durable clinical benefit and resistance in non-small-cell lung cancer (NSCLC) and warrant disease-specific investigation.

Patterns of primary and AR may be fundamentally distinct[11,12] and could differentially relate to defects in antigen presentation such as alterations in β2-microglobulin, interferon-γ (IFN-γ) signaling, neoantigen loss, tumor-mediated immunosuppression/exclusion, and additional inhibitory checkpoints.[13-19] Relatedly, patients with primary resistance or AR may be sensitive to different types of subsequent therapies. For example, tumors that have AR to PD-(L)1 blockade may have persistent antitumor

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immunity that could be reinvigorated with additional therapies whereas primary resistance may be intrinsically refractory to immunomodulation and could be related to host-specific (not tumor-intrinsic) factors.[20] To date, novel immunotherapies have been investigated in several trials enrolling patients resistant to PD-(L)1, but few of them differentiate primary and AR at study entry and there is lack of uniformity of the definition to standardize enrollment. Perhaps as a result, no clear therapeutic breakthroughs have yet been identified.[20-30] It is possible that activity of specific therapies could be obscured by the undifferentiated inclusion of both patients with primary and AR to PD-(L)1 blockade. For example, the activity of some investigational immunotherapies appears almost exclusive to a patient population with AR to PD-(L)1 blockade.[21,25] Furthermore, the use of radiology criteria to identify true underlying drug resistance has often been questioned and may need to be reconsidered altogether.[31] Future immunotherapy (IO) trials, of which thousands are ongoing,[32] may only be successful in defining new standards of care if designed to differentiate distinct patients groups with primary versus AR, and informed by hypotheses to match molecules to the most biologically-relevant clinical scenario.

To facilitate this goal, a practical, clinical definition of patients with AR to PD-(L)1 blockade in NSCLC is needed for clinical trial eligibility and descriptive clinical reports. In the development and testing of molecularly targeted therapy, such as tyrosine kinase inhibitors (TKIs) for epidermal growth factor receptor *(EGFR)*-mutant lung cancer, establishing such a definition has been critical for clinical and scientific progress.[33] The definition consisted of four primary elements: (i) treatment with a single-agent EGFR-TKI, (ii) objective clinical benefit from the EGFR-TKI documented by complete/partial radiologic response or stable disease (SD) lasting 6 months defined by RECIST or World Health Organization (WHO) criteria, (iii) systemic, radiologic progression of disease within 30 days of last receiving EGFR-TKI treatment, and (iv) no intervening systemic therapy treatment.[33] The criteria have established clear and consistent guidelines for evaluating newer generations of TKIs such as the third generation EGFR-mutant-selective TKI, osimertinib.[34,35]

In this article, adopting a similar approach, we deconstruct the criteria for AR to PD-(L)1 blockade into individual components: type of treatment, depth of response, degree of progression, timing of progression, and continuity of treatment (Figure 1). We also explore the context for applying this definition, and where additional considerations and effort may be needed. We build on recent efforts by the Society for Immunotherapy of Cancer (SITC) Immunotherapy Resistance Taskforce, which have helped highlight specific areas of uncertainty in classification of AR such as the classification of SD and duration of time required for AR classification, which require further data and disease-specific applications.[36] Here, we tackle each of these components, identify sources of controversy, and ultimately propose a synthesized practical definition for AR to PD-(L)1 blockade in patients with NSCLC (Figure 1, Table 1). This initial proposal may be further refined in the future as additional data emerge to clarify the optimal ways to interpret AR.

PROPOSED CRITERIA FOR ACQUIRED RESISTANCE IN IMMUNOTHERAPY IN NSCLC

Type of treatment

- **Prior treatment with PD-(L)1 blockade is required. IO—IO combinations are allowed.**

In order to define who has developed AR to PD-(L)1 blockade, strict and specific documentation of response to PD-(L)1 blockade is required. In the context of PD-(L)1 monotherapy, this determination is straightforward. In the context of combination therapies, however, this becomes more challenging.

Recently, combined checkpoint inhibition with PD-(L)1 and CTLA-4 blockade and combination with chemotherapy have received approval as front-line treatment approaches in metastatic NSCLC.[37,38] Given the related therapeutic mechanisms of action of PD-(L)1 and CTLA-4 checkpoint inhibition, mechanisms of resistance could overlap with PD-(L)1 monotherapy. Unless proven otherwise, we recommend inclusion of those treated with PD-(L)1 and CTLA-4 checkpoint inhibition — as well as other experimental IO combinations with a PD-(L)1 backbone — in this definition of AR.

IO plus chemotherapy presents additional challenges as the combination could induce responses via synergistic immunologic effects and/or independent cumulative drug action of chemotherapy or IO in a heterogeneous patient population.[39,40] In responders to chemotherapy plus IO, it is currently difficult to determine which component (or both) is/are the active agent(s) of response and, by corollary, difficult to ascribe AR to a specific agent (Figure 2). Recent examination of clinical data lends credence to the idea that combination therapy can act additively rather than synergistically,[39] such that not all responders to the combination are alike. The intermediate duration of response among patients treated with chemotherapy plus IO, compared with short duration with chemotherapy alone and longer duration with IO alone, further supports the paradigm of independently acting drugs within some populations characterized by interpatient heterogeneity of sensitivity.[38]

Despite the challenges of determining additive or synergistic activity, the basic tenets of the criteria extend to multiple scenarios involving chemotherapy plus IO and are critical for devising future guidelines. It may be reasonable, for example, to ascribe AR to PD-(L)1 blockade in many cases of progression on maintenance PD-(L)1 blockade in patients who completed initial combined platinum doublet therapy plus PD-(L)1 blockade. Other potential predictors of IO response such as high PD-L1 expression may also enrich for initial responses via synergistic immunologic effects or PD-(L)1 blockade. Further investigations into the relationship of the clinical phenotypes of AR and underlying immune cell dynamics will be critical for adjudicating AR to

combinations with PD-(L)1 blockade. In the interim, guidelines on AR to IO are a necessary step to catalyze the crucial work needed to develop tools and data to examine AR to combination therapy.

Depth of response

- **Patients experience objective response on PD-(L)1 blockade. Stable disease is excluded**.

The definition of AR assumes a prior response to therapy, but the categories that signify clinical responses remain a subject of debate. While the clinical interpretation of partial/complete responses (PR/CR) and progressive disease (PD) as responders and non-responders, respectively, is based on reproducible measurements, antitumor activity is ambiguous in patients with SD. Most likely, 'stable disease' represents a heterogeneous mix of clinically non-responding patients, those with indolent disease, and some patients with true benefit to IO. Prior survival analyses by RECIST response support the notion of a heterogeneous SD population correlating with a modest survival benefit compared with PD, though to a lesser extent than PR/CR.[2,3,6,41] Nevertheless, the tools to distinguish radiologically minor responses from slowly progressing disease (i.e. tumor growth rate) are laborious or frequently inapplicable because they mandate prebaseline imaging.[42]

In the absence of reliable data on the features to better characterize SD, prior reports have variably handled patients with SD in the criteria for AR, sometimes included and other times excluded.[13-16,18,19,43-46] Indeed, the recent report by the SITC Immunotherapy Resistance Taskforce acknowledged challenges in classifying scenarios involving SD. Ultimately, the taskforce proposed including patients with SD if progression-free survival (PFS) is $>$6 months with potential exceptions for tumors that tend to be more indolent.[36] The addition of a PFS threshold (i.e. 6 months) may enrich for a population with minor responses rather than indolent, slow-growing disease, but it remains arbitrarily defined, particularly across various cancer types. Other characteristics such as the best overall response, kinetics and depth of response, imaging techniques, circulating tumor DNA (ctDNA), or immune cell dynamics might also help identify true responses and are worth further investigation.[42,47-49] There are currently insufficient data, however, to show a PFS cut-off alone would isolate the responsive subgroup of patients with SD. In certain tumor types, such as melanoma and head and neck squamous cell carcinoma (HNSCC) where SD rates are generally low (15%-20%), including SD in AR definitions may be reasonable and not have a significant impact on overall analyses. Yet, in NSCLC, SD is a prominent subgroup of PD-(L)1 responses, representing $\sim$30%-40% patients and could confound post-PD-(L)1 blockade trials.[3,50,51] Therefore, for the sake of optimizing success of rationale IO molecules in the AR space in NSCLC, we reached consensus on currently excluding SD until better tools are available to distinguish the 'biological responder' subgroup.

Emerging liquid biopsy techniques appear to be particularly promising for helping to precisely distinguish underlying therapeutic activity and unlock new therapeutic opportunities. For example, recent studies have shown that ultrasensitive ctDNA dynamics could identify patients with locally advanced NSCLC and molecular residual disease that would benefit from consolidation IO.[52] Similarly, in patients with metastatic disease, ctDNA can detect minimal residual disease after long-term response to PD-(L)1 blockade and identify early those patients with disease progression who will need additional therapy.[47-49,53] Moving forward, quantitative ctDNA dynamics could be harnessed as a powerful complement to radiologic criteria in the setting of SD to refine the determination of initial benefit and to more accurately (and/or expeditiously) identify AR.

Timing of progression

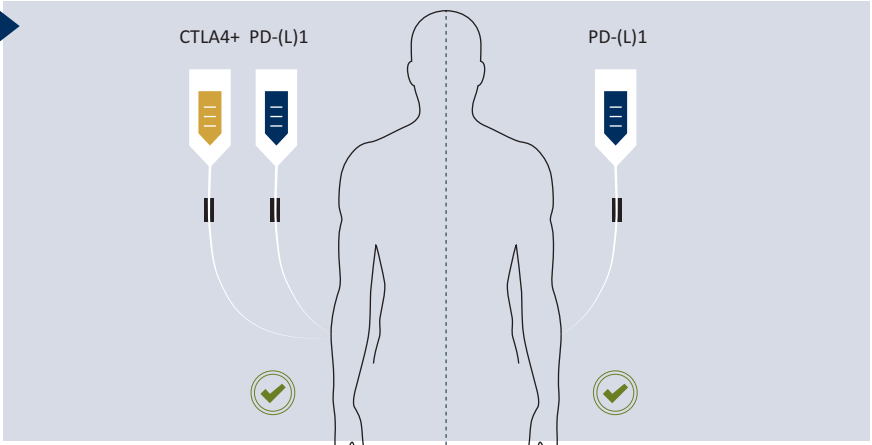
- **No duration of response threshold is required. Confirmatory scans of progression after prior response are not required.**

It is unclear if there are distinct features of 'early' and 'late' AR to PD-(L)1 blockade that warrant classification by timing of progression. In lung cancer, 'early' AR appears common, with $\sim$20% of all cases of AR occurring by 6 months and 35% by 1 year based upon prior clinical trials.[6,11,51] There is no known relationship in patient or molecular characteristics in 'early' AR and primary resistance denoting similar underlying mechanisms. In contrast, patients with short-term responses generally appear to have disease characteristics that are more closely aligned with long-term responses rather than refractory disease.[41,54] The SITC Immunotherapy Resistance Taskforce proposed classification of patients across tumor types with early AR (CR/PR who then develop PD within 6 months of IO initiation) within primary resistance due to lack of clinical data analyses. In NSCLC, however, given the breadth of patients who experience 'early' AR and lack of other identifiable characteristics distinguishing from 'late' AR, we currently propose inclusion of all patients with documented PR/CR response who subsequently develop progression within the AR definition rather than grouping 'early' AR with primary resistance. Nevertheless, duration of response may reflect underlying immune phenotypes and different patterns in T-cell exhaustion and immune editing and thus remains an important factor to consider in future investigations.[55]

In addition, current clinical trials have instituted definitions of progression that include the recommendation for a confirmatory scan demonstrating progression. Although scans to confirm progression are commonly a component of prospective endpoints in clinical trials with IO, they are not routinely carried out in clinical practice. This is especially true in diseases such as NSCLC where pseudo-progression is exceptionally uncommon[56-59] and the intrinsic disease kinetics can be aggressive. Even when pseudo-progression occurs, there is often concurrent clinical improvement, such that a clinician/patient is unlikely to immediately seek

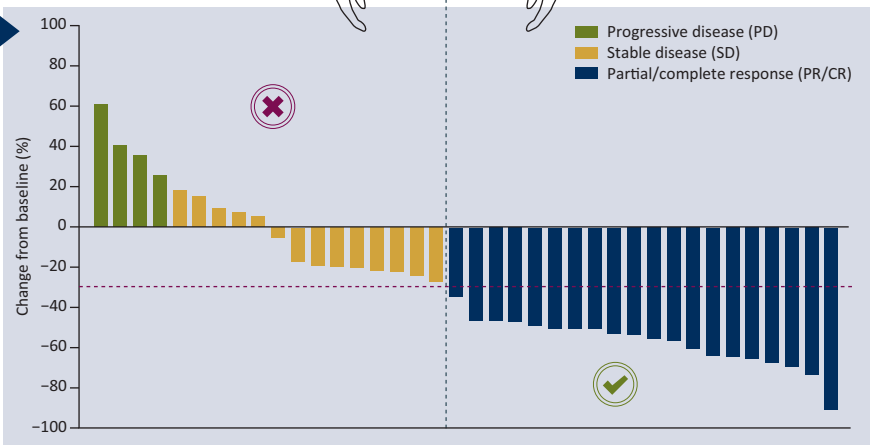
A TYPE OF TREATMENT

- Prior treatment with anti-PD-(L)1 agent is required.
- IO-IO combinations are allowed.



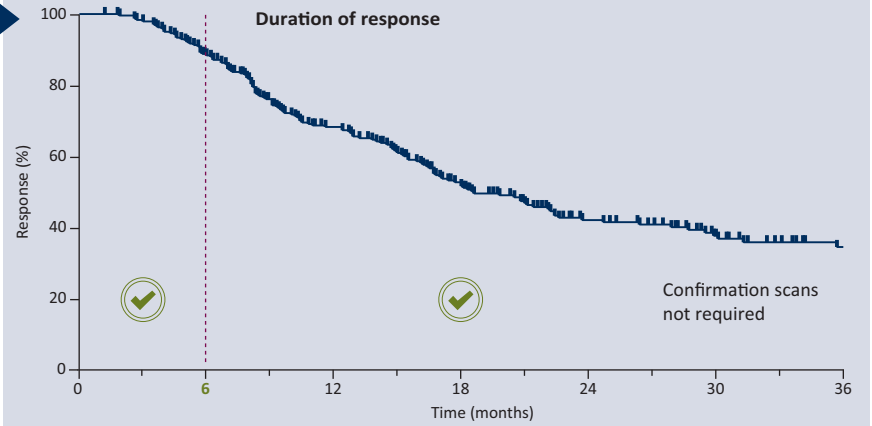
B DEPTH OF RESPONSE

- Patients experience objective response with anti-PD-(L)1 agent.
- Stable disease is excluded.



C TIMING OF PROGRESSION

- No duration of response threshold is required.
- Confirmatory scans of progression after prior response are not required.



D CONTINUITY OF TREATMENT

- Progression within 6 months of last anti-PD(L)1 treatment.
- In patients with progression occuring greater than 6 months since last treatment, anti-PD(L)1 retreatment is required.

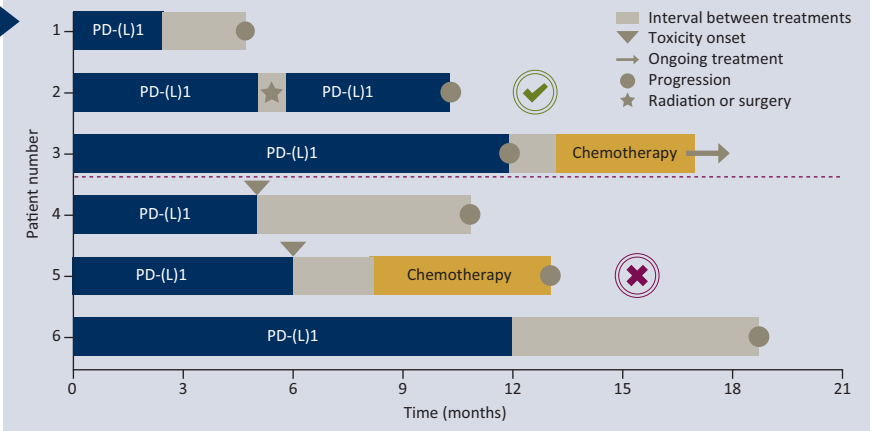


Table 1. Criteria for acquired resistance to PD-(L)1 blockade in patients with NSCLC

1. Type of treatment: • Prior treatment with PD-(L)1 blockade is required. IO—IO combinations are allowed.
2. Depth of response: • Patients experience objective response on PD-(L)1 blockade. Stable disease is excluded.
3. Timing of progression: • No duration of response threshold is required. Confirmatory scans of progression after prior response are not required.
4. Continuity of treatment: • Progression occurs within 6 months of last PD-(L)1 blockade treatment. In patients with progression occurring >6 months since last treatment, PD-(L)1 blockade retreatment is required.

IO, immunotherapy; NSCLC, non-small-cell lung cancer; PD-(L)1, programmed cell death protein 1/programmed death-ligand 1.

an alternative clinical trial. Recommending such confirmation could produce unnecessary and significant delays in initiating subsequent therapy and result in negative, unintended consequences for both patients and clinical trials alike. It would also limit the ability to perform AR-dedicated retrospective exploratory studies/series in a timely fashion. We advocate not requiring a confirmatory scan to determine AR in this definition. Nevertheless, patients with pseudo-progression who develop transient progression followed by objective response may be considered for inclusion in this definition.

Continuity of treatment

- **Progression occurs within 6 months of last PD-(L)1 blockade treatment. In patients with progression occurring >6 months since last treatment, PD-(L)1 blockade retreatment is required.**

Most anti-PD-(L)1 antibodies have a receptor occupancy of many months and could theoretically restore endogenous antitumor immune responses indefinitely after limited exposure to therapy.[60] Indeed, prior clinical reports have shown that some patients may have durable responses to therapy after limited exposure to PD-(L)1 blockade due to immune-related adverse events or completion of 1-2 years of treatment.[1-3,5] Therefore, in patients with progression events after long treatment-free intervals, it could be challenging to determine whether this represents true AR or whether the disease would be sensitive to PD-(L)1 blockade again. This issue may be particularly important given potential routine discontinuation of pembrolizumab after 2 years of treatment even with ongoing benefit and in the absence of toxicity. Prior data on second course PD-(L)1 blockade after progression while off therapy has demonstrated that 'some' patients can respond to re-treatment, although this is hardly guaranteed.[2,8,61-68] When reviewing retreatment data from publicly available prior series including NSCLC,[65,68] the majority of re-treatment responses occurred after a 6 month treatment-free interval (Figure 3, 15/43 response if re-treatment interval >6 months versus 1/18 response if retreated <6 months interval, Fisher's $P = 0.02$,). We, therefore, recommend PD-(L)1 blockade re-treatment of patients who progress after treatment free-interval of 6 months before enrollment in AR clinical trials. This proposal aims to ensure that if activity is seen in next-generation clinical trials focused on patients with AR, it is not simply attributable to redosing/resuming PD-(L)1 blockade.

Patients who develop AR to PD-(L)1 blockade and subsequently receive cytotoxic chemotherapy or local therapies before consideration of clinical trials are included as long as they meet other AR criteria. Patients who discontinued PD-(L)1 blockade for reasons other than progression (e.g. toxicity) who then develop PD during/after treatment on other systemic therapies are excluded since they do not clearly have resistance attributable to PD-(L)1 blockade.

CONTEXT AND APPLICATION

The proposed criteria apply to patient-level analyses including trial eligibility and cohort reports. Separate criteria at the lesion-level may be necessary to interrogate the underlying mechanisms of AR at individual tumor sites. In these cases, documentation of response and progression at individual sites from which tissue is obtained may be necessary for interrogation and further examination of factors such as tumor location and timing of progression.

Moreover, this clinical definition is restricted to advanced NSCLC, unlike the SITC Immunotherapy Resistance Taskforce, to ensure that specific factors unique to this tumor type are addressed. Due to our focus on NSCLC and conservative approach, our recommendations differ from SITC in a number of elements including: (i) current exclusion of SD because of its frequency in lung cancer and possibility that indolent disease may confound clinical trials, (ii) inclusion of patients with partial or complete responses to PD-(L)1 blockade with disease progression <6 months, (iii) no requirement of confirmatory scans after initial disease progression because pseudo-progression is exceptionally uncommon in lung cancer. While we are hopeful the conceptual framework and some components of this definition will be applicable to other tumor types, the criteria here focus on disease-specific qualities and patterns of response and resistance to PD-(L)1 blockade in NSCLC and may need to be adapted to fit other disease types.

Figure 1. Defining acquired resistance to immunotherapy.
(A) Patients who have received treatment with PD-(L)1 blockade as monotherapy or IO—IO combination are included. (B) Objective response on IO. Stable disease is excluded. (C) There is no duration of response time threshold for inclusion in acquired resistance. Confirmatory scans of progression after response or development of resistance are also not required. (D) Progression occurs within 6 months of last anti-PD-(L)1 antibody treatment. Rechallenge with anti-PD-(L)1 antibody is required in patients not exposed to anti-PD-(L)1 in 6 months. Patients who develop acquired resistance to PD-(L)1 blockade and subsequently receive cytotoxic chemotherapy before consideration of clinical trials are included. Patients who discontinued PD-(L)1 blockade for reasons other than progression (i.e. toxicity) who then develop progressive disease during/after treatment on other systemic therapies are excluded.
IO, immunotherapy; PD-(L)1, programmed cell death protein 1/programmed death-ligand 1.

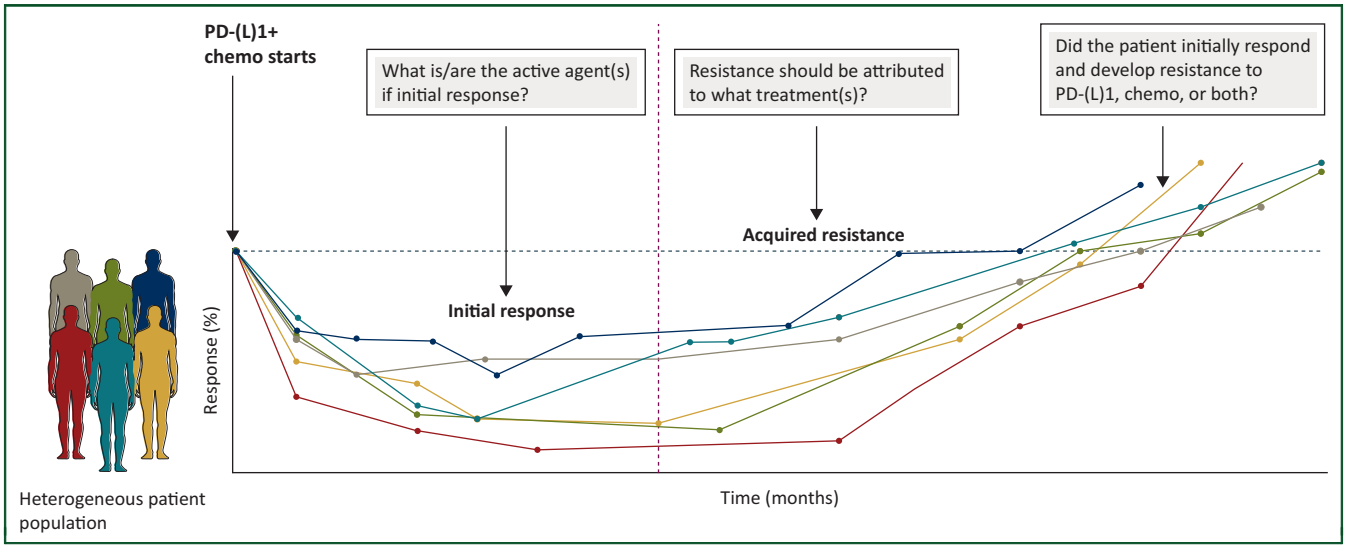


Figure 2. Acquired resistance to chemotherapy and PD-(L)1 blockade.
Heterogeneous patient population receive chemotherapy and PD-(L)1 blockade. Patients could respond to chemotherapy, PD-(L)1 blockade, or the combination, but the active agent(s) are not currently identifiable. Consequently, the treatment associated with acquired resistance is also unknown.
PD-(L)1, programmed cell death protein 1/programmed death-ligand 1.

We have highlighted a number of persistent clinical scenarios that require urgent attention and multi-stakeholder collaboration to clarify the optimal solutions (Table 2). As discussed above, further research is critically required to refine criteria of AR to apply to all treatment scenarios, particularly PD-(L)1 blockade plus chemotherapy combinations. We also currently do not have evidence to suggest distinct patterns or phenotypes of AR among

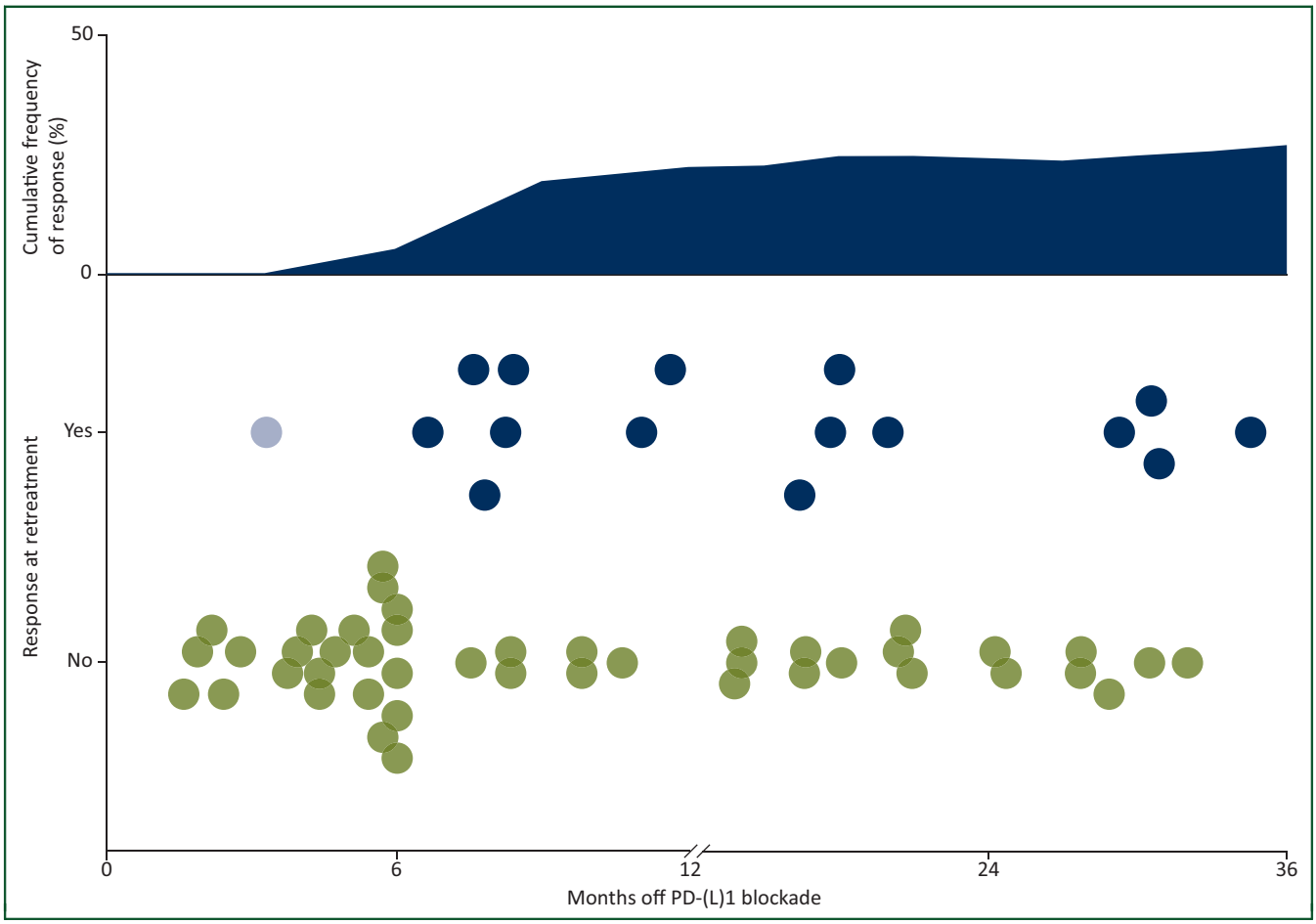


Figure 3. Response to PD-(L)1 retreatment by time since cessation of initial treatment. Blue circles = partial or complete response. Black circles = stable disease or progressive disease. Light blue circle reflects the one patient with a partial response who was off treatment for <6 months. Area under line = cumulative frequency of responses to retreatment over time.
PD-(L)1, programmed cell death protein 1/programmed death-ligand 1.

Table 2. Urgent clinical scenarios for further exploration

Scenario	Current challenge	Potential solutions
Chemotherapy combination therapy (chemo—IO)	The active agent of response/resistance is unclear	• Apply DOR threshold and/or restrict inclusion to patients on maintenance IO-only therapy • On-treatment biomarker signatures (e.g. immunologic, radiomic) to determine active agent
Best response of stable disease	Unknown if this disease state represents naturally indolent disease or minor response	• Use circulating markers and/or ctDNA incorporation as complementary tools • Define a specific subgroup of SD patients benefitting from IO using specific PFS and/or BOR cut-offs and/or incorporating tumor growth rate/change in disease kinetics
IO treatment in adjuvant setting	Initial radiologic response cannot be evaluated since there is no measurable disease to evaluate	• Determining response in early disease may be aided by the emergence of neoadjuvant IO • Circulating markers and/or ctDNA can be used in adjuvant setting to assess response to IO (NCT04385368)

BOR, best overall response; ctDNA, circulating tumor DNA; DOR, duration of response; IO, immunotherapy; PFS, progression-free survival; SD, stable disease.

different histologies within NSCLC (e.g. adenocarcinoma versus squamous cell) and therefore have included all patients with NSCLC within this definition. Additionally, for many reasons that also extend beyond determination of AR, better tools are critically needed to adjudicate responses among patients with best response of SD.

Additionally, a key goal here is to identify a definition of AR to IO that can be used for eligibility in the context of prospective therapeutic studies focused on reversing or circumventing AR. Patients with limited progression that are amenable to locally directed therapies, here termed oligo-acquired resistance (oligoAR), may be prioritized as an initial treatment strategy instead of systemic therapy clinical trials. OligoAR is a relatively common pattern of resistance to PD-(L)1 blockade in NSCLC and does not necessarily lead to subsequent systemic progression.[12,69] Therefore, oligoAR could be successfully and durably treated with local therapies and differentiation of these two scenarios is clinically informative in NSCLC. We propose consideration of locally directed therapies, in addition to systemic therapy clinical trials, for oligoAR. Notably, the strict definition of oligoAR (i.e. number/type of sites of progression) is an ongoing area of active investigation and debate and is a critical subject that requires independent discussion and adjudication in the future as well.

Other scenarios where NSCLC patients treated with PD-(L)1 blockade receive intervening local and/or systemic therapies could also complicate AR evaluation. The criteria here do not apply to earlier stage diseases. The determination of AR in the adjuvant/consolidation setting is challenging due to the involvement of multiple treatments and often the absence of measurable disease, such that it is difficult to differentiate whether a recurrence represents primary or AR.

Finally, although the rationale to define AR based on objective initial response and progression is clear, there are relevant operational challenges and unintended consequences that come with considering retrospective radiology reviews. The application of this approach may require the infrastructure and resources to support such tasks before screening for a clinical trial, which may also contribute to disparities. We hope this proposal will prompt the necessary multi-stakeholder discussion necessary to achieve success in developing the next generation of IOs.

CONCLUSIONS

AR to IO is a common and poorly understood phenomenon in NSCLC that requires urgent attention. A uniform clinical definition is imperative to further characterize patients and develop a personalized approach at overcoming AR. The proposed definition takes a conservative approach to help minimize confounding and unify language for future prospective reports and clinical trials in NSCLC. If successful, this may help define evidence-based subsequent therapies, and will have broader implications for AR in other setting and tumor types.

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DISCLOSURE

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EF reports personal fees from AbbVie, personal fees from Amgen, personal fees from AstraZeneca, personal fees from Bayer, personal fees from Blue Print Medicines, personal fees from Boehringer Ingelheim, personal fees from Bristol-Myers Squibb, personal fees from Eli Lilly, personal fees from GSK, personal fees from Janssen, personal fees from Medscape, personal fees from Merck KGaA, personal fees from Merck Sharp & Dohme, personal fees from Novartis, personal fees from Roche, personal fees from PeerVoice, personal fees from Pfizer, personal fees from prIME Oncology, personal fees from Puma Biotechnology, personal fees from Roche, personal fees from Sanofi Genzyme, personal fees from Springer, personal fees from Takeda, personal fees from TouchIME, grants from Grant for Oncology Innovation (GOI), grants from Fundación Merck Salud, outside the submitted work; and Grífols: Independent Member of the Board. JG reports grants and personal fees from Bristol-Myers Squibb, grants and personal fees from Genentech/Roche, personal fees from Takeda, grants and personal fees from Blueprint, grants and personal fees from Loxo, personal fees from Oncorus, personal fees from Regeneron, personal fees from Pfizer, personal fees from Incyte, grants and personal fees from Novartis, grants and personal fees from Merck, personal fees from Agios, personal fees from Amgen, grants from Array, grants from Tesaro, grants from Moderna, grants from Adaptimmune, grants from Alexo, personal fees from Ironwood Pharmaceuticals, personal fees from Gilead, personal fees from EMD Serono, personal fees from AstraZeneca, personal fees from Mirati. SNG reports personal fees and other from Bristol Myers Squibb, personal fees from Nektar, other from Genentech, other from Ariad/Takeda, other from Iovance Biotherapeutics, during the conduct of the study. FSH reports grants, personal fees and other from Bristol-Myers Squibb, personal fees from Merck, personal fees from EMD Serono, grants, personal fees and other from Novartis, personal fees from Surface, personal fees from Compass Therapeutics, personal fees from Apricity, personal fees from Aduro, personal fees from Sanofi, personal fees from Pionyr, personal fees from 7 Hills Pharma, personal fees from Verastem, personal fees from Torque, personal fees from Rheos, personal fees from Kairos, personal fees from Bicara, from Psioxus Therapeutics, other from Pieris Pharmaceutical, from Zumutor, from Corner Therapeutics, personal fees from Eisai, personal fees from Checkpoint Therapeutics, outside the submitted work; In addition, FSH has a patent Methods for Treating MICA-Related Disorders (#20100111973) with royalties paid, a patent Tumor antigens and uses thereof (#7250291) issued, a patent Angiopoiten-2 Biomarkers Predictive of Anti-immune checkpoint response (#20170248603) pending, a patent Compositions and Methods for Identification, Assessment, Prevention, and Treatment of Melanoma using PD-L1 Isoforms (#20160340407) pending, a patent Therapeutic peptides (#20160046716) pending, a patent Therapeutic Peptides (#20140004112) pending, a patent Therapeutic Peptides (#20170022275) pending, a patent Therapeutic Peptides (#20170008962) pending, a patent Therapeutic Peptides Patent number: 9402905 issued, a patent Methods of using pembrolizumab and trebananib pending, a patent Vaccine compositions and methods for restoring NKG2D pathway function against cancers Patent number: 10279021 issued, a patent Antibodies that bind to MHC class I polypeptide-related sequence A Patent number: 10106611 issued, and a patent Anti- galectin antibody biomarkers predictive of anti-immune checkpoint and anti-angiogenesis responses. Publication number: 20170343552 pending. MLJ reports other from Achilles Therapeutics, grants and other from AstraZeneca, grants and other from Atreca, grants and other from Boehringer Ingelheim, grants and other from Calithera Biosciences, grants and other from EMD Serono, grants and other from Roche/Genentech, grants and other from GlaxoSmithKline, grants and other from Gritstone Oncology, grants and other from Guardant Health, grants and other from Incyte, grants and other from Janssen Research and Development, grants and other from Lilly, grants and other from Merck, grants and other from Mirati Therapeutics, grants and other from Novartis, grants and other from Pfizer, grants and other from Sanofi-Aventis, grants from AbbVie, grants from Acerta Pharma, grants from Adaptimmune, grants and other from Amgen, grants from Apexigen, grants from Array BioPharma, grants from BeiGene, grants from Checkpoint Therapeutics, grants from Corvus Pharmaceuticals, grants from CytomX, grants and other from Daiichi Sankyo, grants from Dynavax Technologies, grants from Genmab, grants from Genocea Biosciences, grants from Hengrui Therapeutics, grants from Immunocore, grants from Jounce Therapeutics, grants from Kadmon Pharmaceuticals, grants from Loxo Oncology, grants from Lycera, grants from Neovia Oncology, grants from OncoMed Pharmaceuticals, grants from Regeneron Pharmaceuticals, grants from Shattuck Labs, grants from Stem CentRx, grants from Syndax Pharmaceuticals, grants from Takeda Pharmaceuticals, grants from Tarveda, grants from University of Michigan, grants and other from WindMIL Therapeutics, grants from TCR2 Therapeutics, grants from Arcus Biosciences, grants and other from Ribon Therapeutics, grants from Seven and Eight Biopharmaceuticals, other from Bristol-Myers Squibb, personal fees from Astellas, personal fees from Otsuka, grants from BerGenBio, grants from Foundation Medicine, other from G1 Therapeutics, grants from Tmunity Therapeutics. 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Permanyer SL, grants, personal fees and other from Pfizer, Inc, personal fees from prIME Oncology, personal fees and other from Puma Technology Inc, personal fees from Research to Practice, grants, personal fees and other from Roche, personal fees and other from Sanofi-Aventis R&D, personal fees and other from Takeda, personal fees from Touch Medical Media, other from Virtus Medical Group, personal fees and other from Yuhan Corporation, other from AstraZeneca PLC, other from Hutchison Chi-Med, other from Sanomics Ltd., grants from Clovis Oncology, grants from SFJ Pharmaceuticals, grants from XCovery, outside the submitted work. 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MR reports personal fees from Amgen, personal fees from AstraZeneca, personal fees from BMS, personal fees from Boehringer-Ingelheim, personal fees from Lilly, personal fees from Merck, personal fees from MSD, personal fees from Mirati, personal fees from Novartis, personal fees from Pfizer, personal fees from Roche, personal fees from Samsung, outside the submitted work. BS reports personal fees from Roche/Genentech, personal fees from Novartis, personal fees from AstraZeneca, personal fees from Amgen, personal fees from Eli Lilly, personal fees from Loxo Oncology, personal fees from Merck, personal fees from Bristol Myers Squibb, personal fees from PharmaMar, personal fees from Pfizer, outside the submitted work. J-CS reports other from AstraZeneca, other from AstraZeneca, during the conduct of the study; other from Gritstone Oncology, other from Daiichi Sankyo, other from Relay Therapeutics, outside the submitted work. DSWT reports grants and personal fees from Novartis, grants and personal fees from Bayer, personal fees from Boehringer Ingelheim, personal fees from Celgene, grants and personal fees from Astra Zeneca, personal fees from Eli Lilly, personal fees from LOXO, personal fees from Merck, grants and personal fees from Pfizer, personal fees from Roche, personal fees from Takeda, grants from GlaxoSmithKline, personal fees from Merrimack, outside the submitted work. SP reports personal fees from AbbVie, personal fees from Amgen, personal fees from AstraZeneca, personal fees from Bayer, personal fees from Biocartis, personal fees from Boehringer-Ingelheim, personal fees from Bistrol-Myers Squibb, personal fees from Clovis, personal fees from Daiichi Sankyo, personal fees from Debiopharm, personal fees from Eli Lilly, personal fees from F. Hoffmann-La Roche, personal fees from Foundation Medicine, personal fees from Illumina, personal fees from Janssen, personal fees from Merck Sharp and Dohme, personal fees from Merck Serono, personal fees from Merrimack, personal fees from Novartis, personal fees from Pharma Mar, personal fees from Pfizer, personal fees from Regeneron, personal fees from Sanofi, personal fees from Seattle Genetics and Takeda, personal fees from AstraZeneca, personal fees from Boehringer-Ingelheim, personal fees from Bristol-Myers Squibb, personal fees from Eli Lilly, personal fees from F. Hoffmann-La Roche, personal fees from Merck Sharp and Dohme, personal fees from Novartis, personal fees from Pfizer, personal fees from Takeda, non-financial support from Sponsored by Amgen, non-financial support from AstraZeneca, non-financial support from Boehringer-Ingelheim, non-financial support from Bristol-Meyers Squibb, non-financial support from Clovis, non-financial support from F. Hoffmann-La Roche, non-financial support from Illumina, non-financial support from Merck Sharp and Dohme, non-financial support from Merck Serono, non-financial support from Novartis, non-financial support from Pfizer, non-financial support from Sanofi, personal fees from Bioinvent, outside the submitted work. All fees to institution. MDH reports personal fees from Merck, personal fees from Genentech/Roche, grants, personal fees and non-financial support from BMS, personal fees and non-financial support from AstraZeneca, personal fees from Mirati, personal fees from Syndax, personal fees and other from Shattuck Labs, personal fees from Nektar, personal fees and other from Immunai, personal fees and other from Arcus, from Eli Lilly, during the conduct of the study; In addition, Dr. Hellmann has a patent A patent filed

by Memorial Sloan Kettering related to the use of tumor mutational burden to predict response to immunotherapy (PCT/US2015/062208) licensed to PGDx.

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