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Challenges and Opportunities for Clinical Trials in PD-1/L1 Refractory Cancers

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PD-1/L1 resistant cancer is a growing unmet need

- PD-1/PD-L1 blocking antibodies have revolutionized the treatment paradigm of cancer across a wide range of settings and indications
- Despite these advances, most cancer patients do not respond to immune checkpoint therapy, and many initial responders will subsequently progress
- Most efforts into improve upon efficacy of PD-1/L1 mAbs focus on combination approaches in the checkpoint naïve setting. Data to inform best approaches to address PD-1/L1 resistant disease is limited.
- Understanding of the clinical and radiographic behavior and genetic mechanisms underlying resistance to immune checkpoint blockade may inform rational selection of therapies in this setting

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Objective response rate in oncology clinical trials

- To expedite drug development, surrogate endpoints are used to assess efficacy. In oncology, this includes Δ tumor measurement/ time.
- RECIST guidelines, the most commonly used response assessment criteria in oncology clinical research, were initially developed in the era of chemotherapy, which due to its direct cytotoxic effects, has a strong correlation with tumor shrinkage.
- For immune checkpoint therapies, which work indirectly by activating immune cells, objective response rate may underestimate long term survival benefit
- This has led to the development of RECIST- based response criteria that better account for immune therapy behavior, including pseudoprogression.

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Evolution of RECIST for immune therapies

Measurement Modality	irRC: Bidimensional (Longest Diameter × Longest Perpendicular Diameter)	irRECIST: Unidimensional (Longest Diameter)	iRECIST: Unidimensional (Longest Diameter)
Baseline lesion size, mm	5 × 5	≥ 10	≥ 10
Minimum no. of lesions to be measured for assessment	10 lesions in total; 5 per organ	5 lesions in total; 2 per organ	5 lesions in total; 2 per organ
Appearance of new lesions	Incorporated in the sum of the measurements	Incorporated in the sum of the measurements	iUPD; becomes iCPD if PD is eventually confirmed
CR	Disappearance of all lesions	Disappearance of all lesions	Disappearance of all lesions
PR	≥ 50% decrease from baseline	≥ 30% decrease from baseline	≥ 30% decrease from baseline
SD	Neither CR nor PD is met	Neither CR nor PD is met	Neither CR nor PD is met
PD	≥ 25% increase in the nadir of the sum of target lesions	≥ 20% increase in the nadir of the sum of target lesions with a minimum of 5 mm	≥ 20% increase in the nadir of the sum of target lesions with a minimum of 5 mm
Confirmation of PD	Yes	Yes, at least 4 weeks after, and up to 12 weeks	Yes, at least 4 weeks after, and up to 8 weeks

Abbreviations: irRC, immune-related response criteria; irRECIST, immune-related RECIST; iRECIST, immunotherapy RECIST; iUPD, immune unconfirmed progressive disease; iCPD, immune confirmed progressive disease; PD, progressive disease; CR, complete response; PR, partial response; SD, stable disease.

L Seymour et al, Lancet Oncology 2017

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How is PD-1/L1 refractory disease defined in clinical trials?

No clear consensus

Definition for a particular study must take into acct:

- Indication/setting of study
- Response criteria used to define progression (e.g. mRECIST1.1 or iRECIST, ORR +/- SD 6 months or greater)
- Minimum exposure to PD-1/PD-L1 therapy to achieve therapeutic effect (e.g. 2 doses or 2 months) and Maximum time after last dose of PD-1/L1 prior to progression (e.g. 3 months)
  - $T^{1/2}$ Mabs ~days to weeks, meaning drug will remain circulation for months after discontinuation
  - Minimize chance that progression due to inadequate exposure to PD1/L1
  - Minimize chance late response to PD1 erroneously attributed to effect of new therapy since late responses are possible
- Confirmation of progression on a followup scan (e.g. 4-12 weeks after initial)
  - Confirmation on a second scan to minimize chance of pseudoprogression which may be observed in ~1-10% malignancies treated with checkpoint blocking Mab[1]

1. Park et al, Radiology Oct 2020

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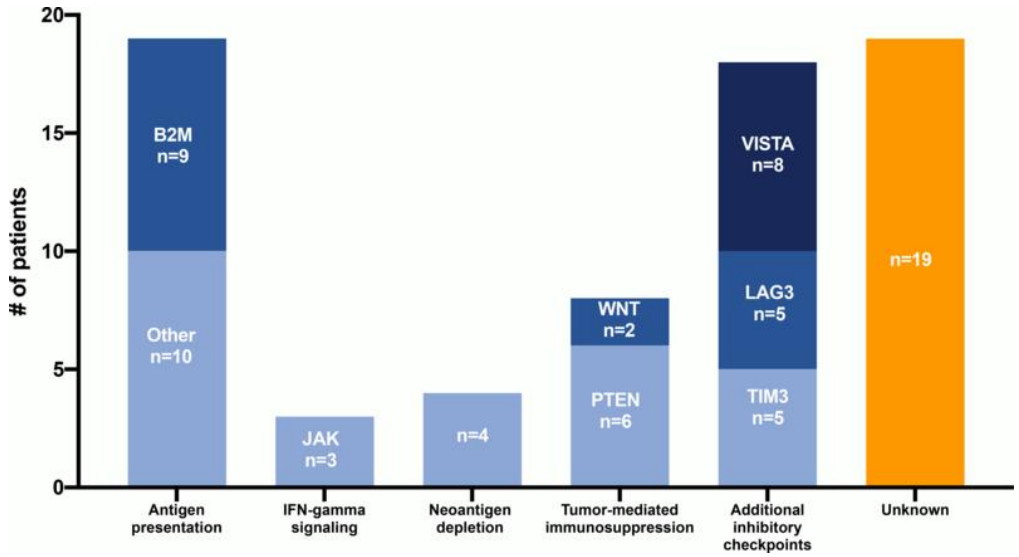
Efforts to define subtypes of PD-1/L1 resistance

Similar to other oncologic therapies, the scientific community[1] has hypothesized there may be differences between patients who never response to a PD-1/L1 (primary resistance) versus those that have initial response or long term stable disease, followed by progression (acquired resistance)

- Studies of acquired resistance have proved useful in isolating mutational changes that may drive progression, but it is not yet clear if there are mutations or selection markers unique to acquired vs primary setting
  - E.g. mutations in JAK1/2 that alter gamma interferon responsiveness, B2M LOF mutations[2,3] identified in subjects with melanoma with acquired resistance are found in skin cutaneous melanoma dataset in TCGA (17% for JAK1/2)

"Of 78 patients with metastatic melanoma who were treated with the anti–PD-1 antibody pembrolizumab at the University of California, Los Angeles (UCLA), 42 had an objective response, of whom 15 went on to have disease progression. Four of these 15 patients met all three selection criteria for this analysis."

58 patients from 13 clinical reports with Acquired ICI resistance across indications



Schoenfeld et al, Cancer Cell April 13, 2021

1.Kluger HM, JITC 2020 2. Nowicki TS , et al. Cancer J 2018; 3 Lavretsky JM, et al . N Engl J Med 2016

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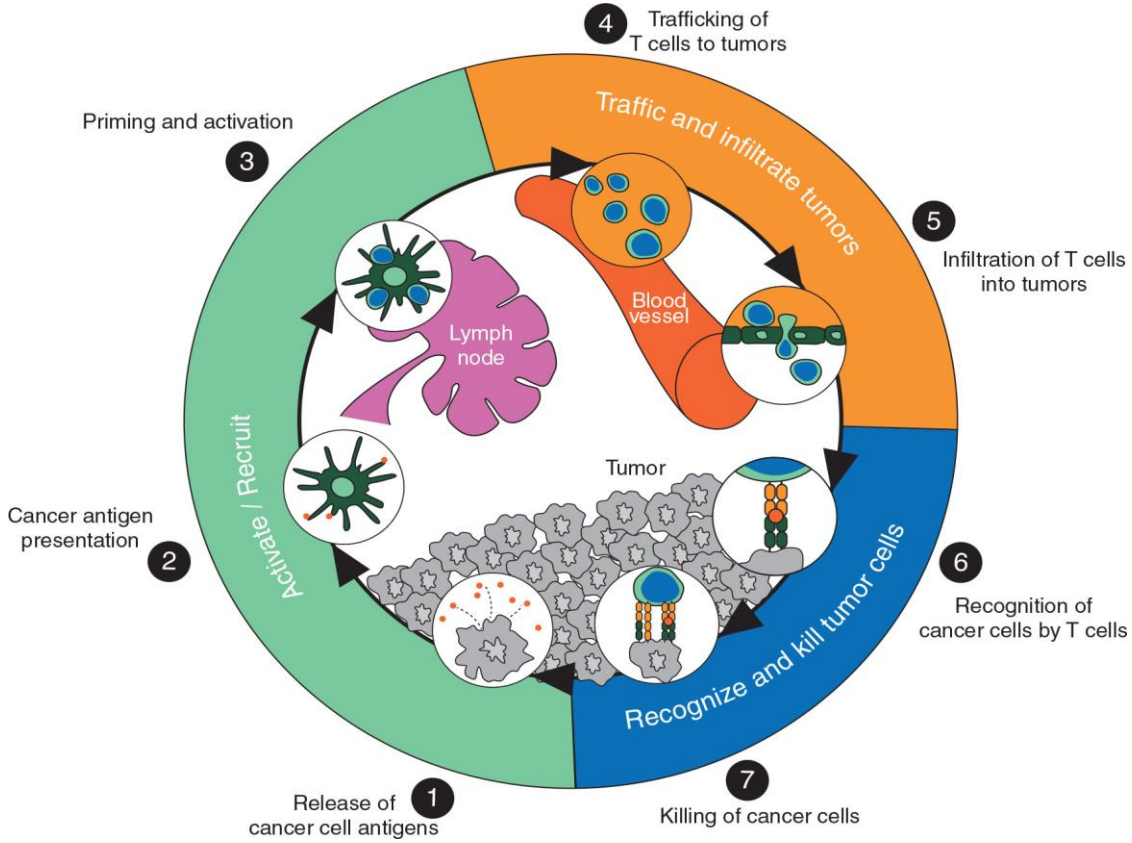
Mechanisms leading to PD-1/L1 resistance

Immune Related

- Impaired T cell trafficking/tumor penetration
- Lack of effective T cell priming
- Impaired T cell activation (e.g. coexpression of alternate immune checkpoints, immune suppression by tumor cells or other cells in TME)

Tumor Related

- Lack of cancer cell sensitivity to or recognition by effector T cell (IFN, PDL1 expression)
- Impaired apoptosis
- Impaired antigen presentation (eg loss of tumor Ag, loss of B2M)
- Immune exclusion of T cells due to immunosuppressive microenvironment.



Chen and Mellman Immunity 2013.

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Combination strategies in PD-1/L1 refractory cancer address multiple mechanisms of IO resistance (NSCLC as an example)

Treatments in randomized controlled trials that address alternate mechanisms either with or without PD-1/L1

Cytotoxics (increased antigen pool/presentation)

- Chemotherapy (e.g. docetaxel)
- ADCs (e.g. Trop2, cMET, Her3)

Multikinase inhibitors (alter TME)

- VEGF/FGF/PDGFR/RET/cKIT

Targeted mutations (enhance proinflammatory TME)

- KRAS G12C

Alternate immune checkpoints (restore T cell activation)

- LAG3, TIGIT, TIM3

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Key areas of improvement for clinical study of PD-1/L1 resistance

- Consensus on assessment criteria and definition of PD-1/L1 refractory disease
- Need for translational work to define mechanisms/patterns of resistance to PD-1/L1 monotherapy or in combination with other SOC
  - Increased routine use/availability of WES and oncogene panels may aid in this
  - Identification of genetic markers/biomarkers that will select for response to particular agents or combinations
- Use of randomized trials to inform activity of various drug classes after PD-1/L1 progression

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