Immunotherapy for Lung Cancer

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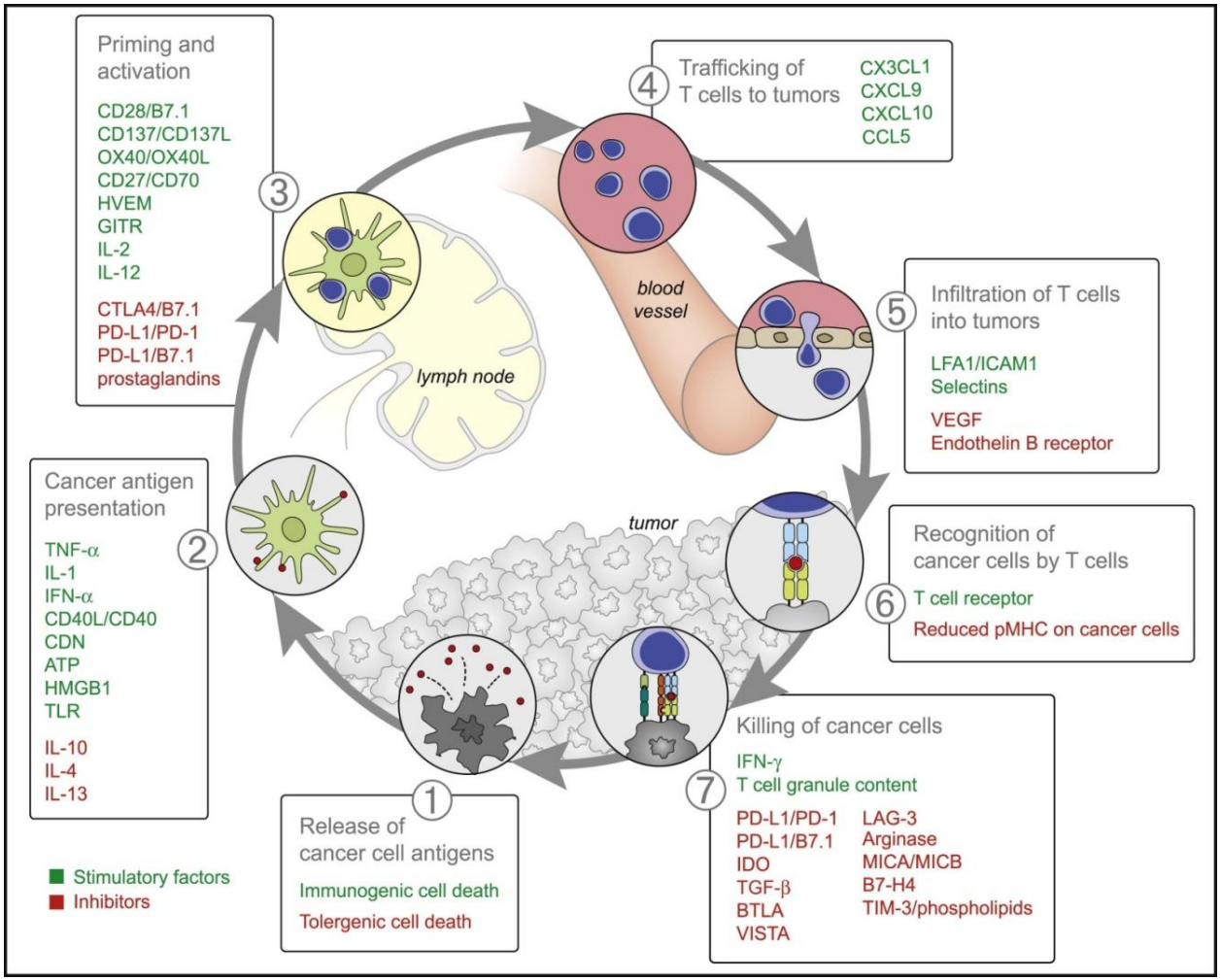
Anti-Tumor Immune Response



Chen DS, et al. Immunity. 2013;39:1-10.

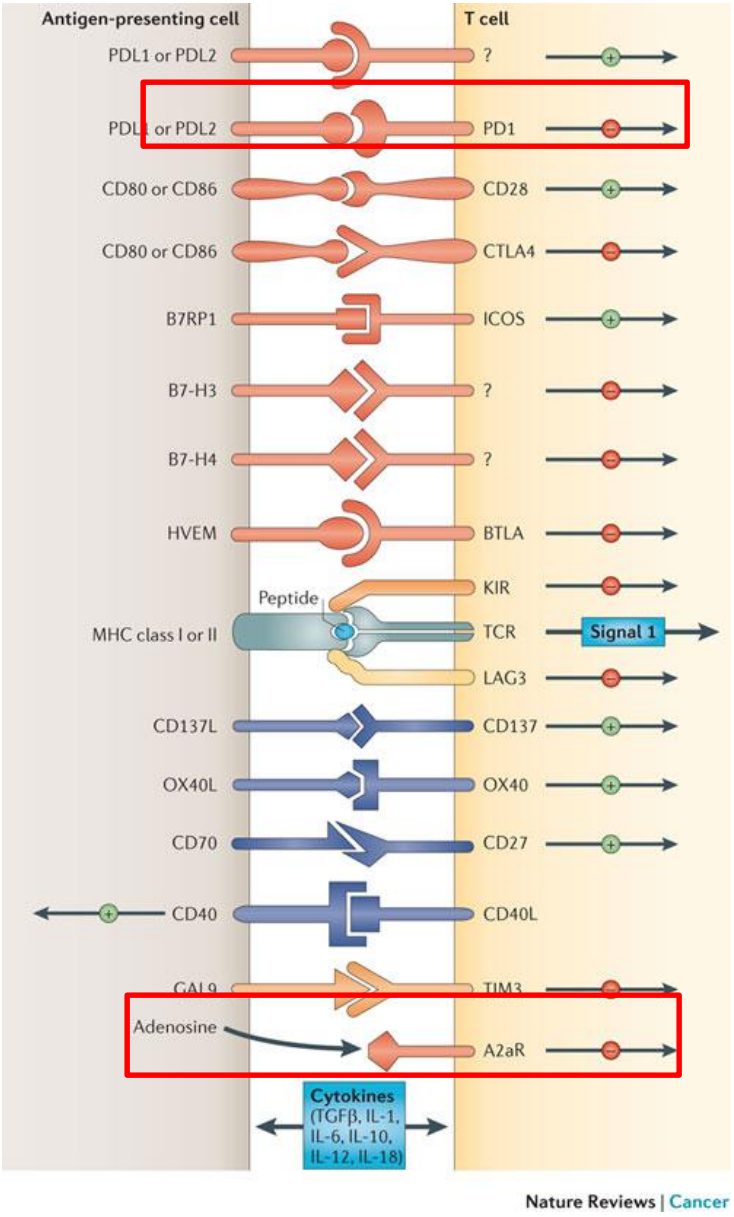
Possible Reasons for Failure of Immune Mediated Rejection of Tumors

1. T cells are inhibited in the tumor microenvironment.
2. Insufficient number of T cells extravasate into the tumor.
3. Insufficient number of T cells are generated within the lymphoid compartment.

1. T cells are inhibited in the tumor microenvironment

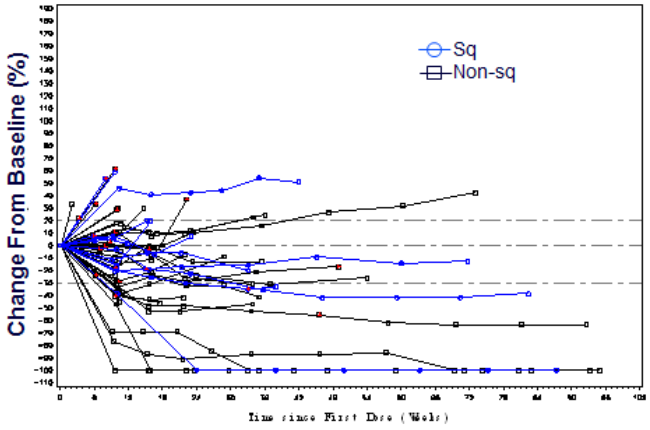
- **Surface membrane proteins- checkpoints**
  - PD1, CTLA4, LAG3, TIM3, BTLA, Adenosine A2AR
- **Soluble factors and metabolic alterations**
  - IL10, TGFβ, Adenosine, IDO, Arginase
- **Inhibitory cells**
  - Cancer Associated Fibroblasts, Regulatory T cells, Myeloid Derived Suppressor Cells, Tumor Associated Macrophages

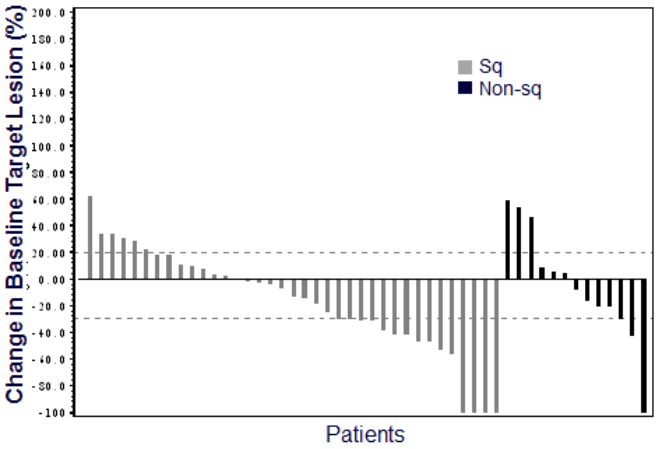
Immune Checkpoints

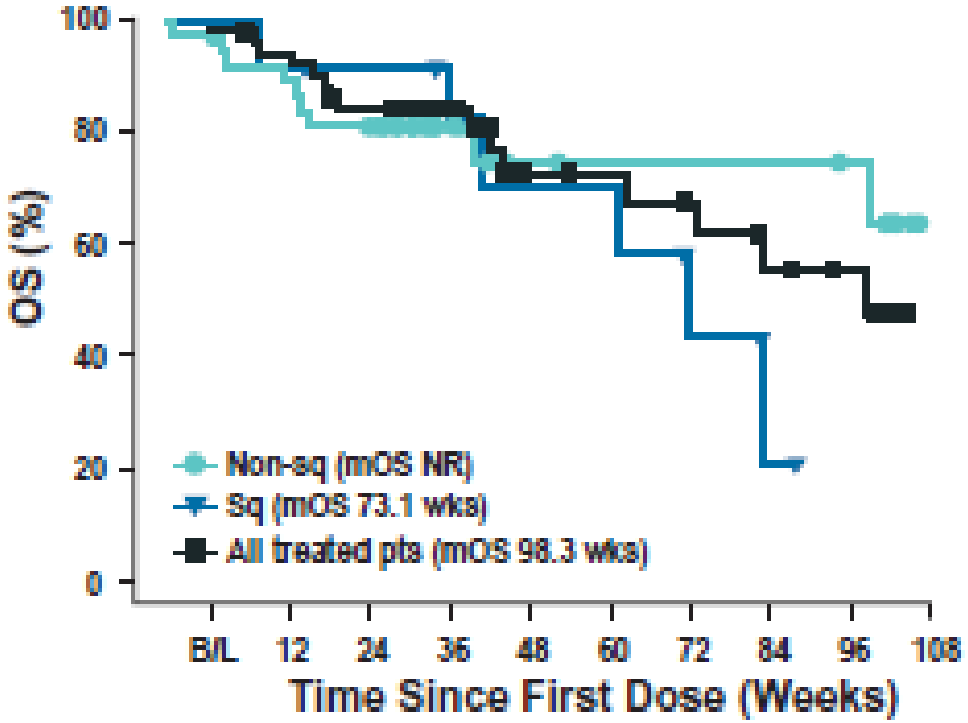


Pardoll, D. Nat Rev Cancer 2012;12:252-64

First Line Therapy with Nivolumab for NSCLC

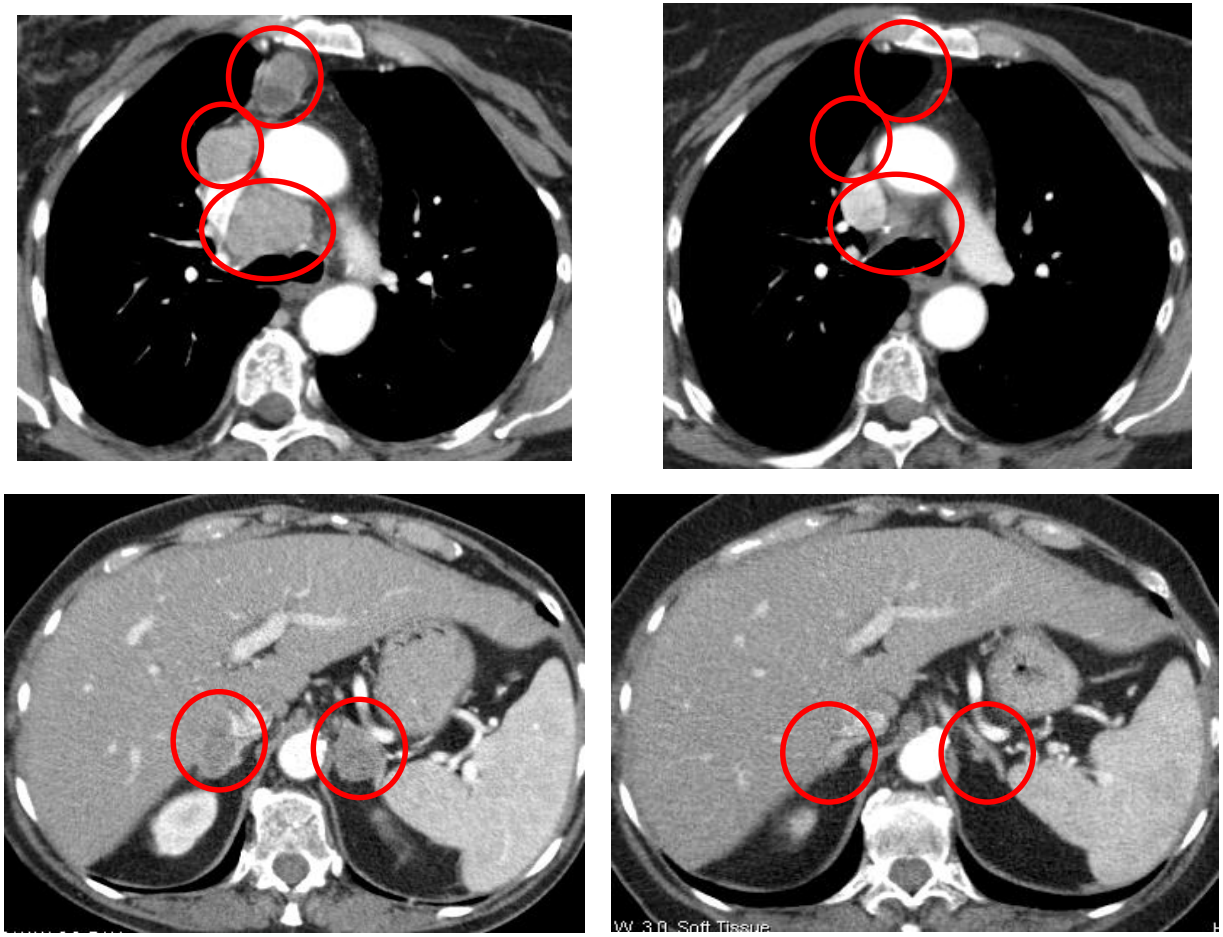






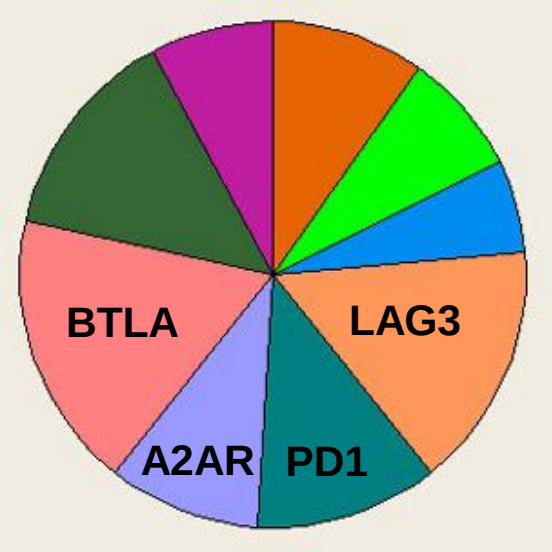
PDL1 Can be a Driver Immunosuppressor

Single Agent Anti-PD1/PDL1 can Produce Durable Responses

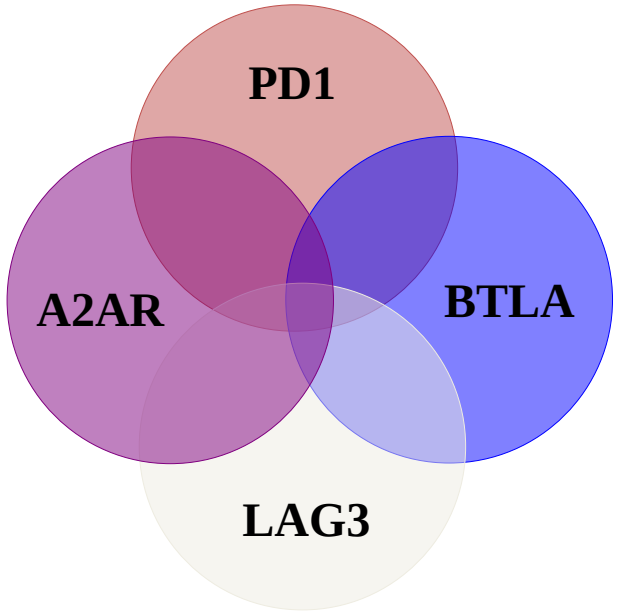


Possibilities for the Non-Responders
(80% "Primary Resistant")

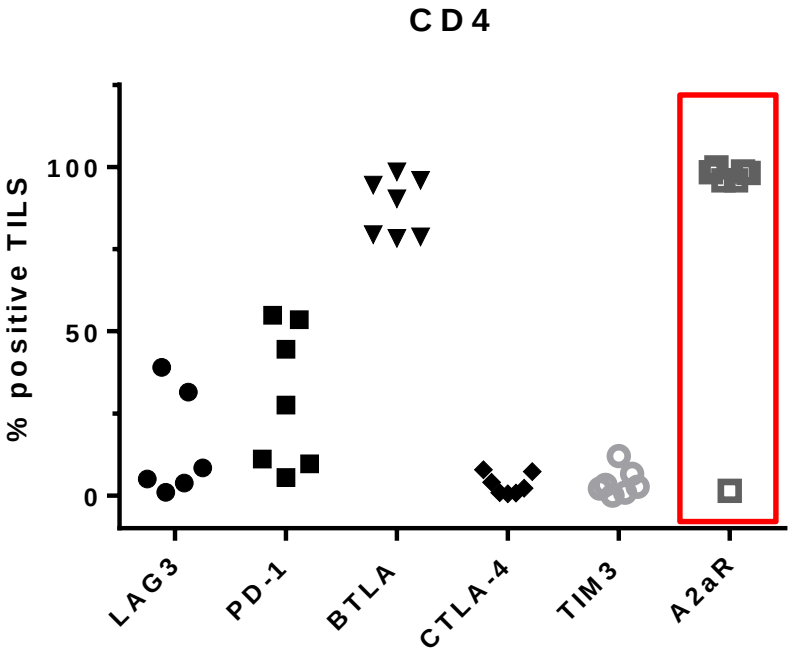
1. Multiple Drivers

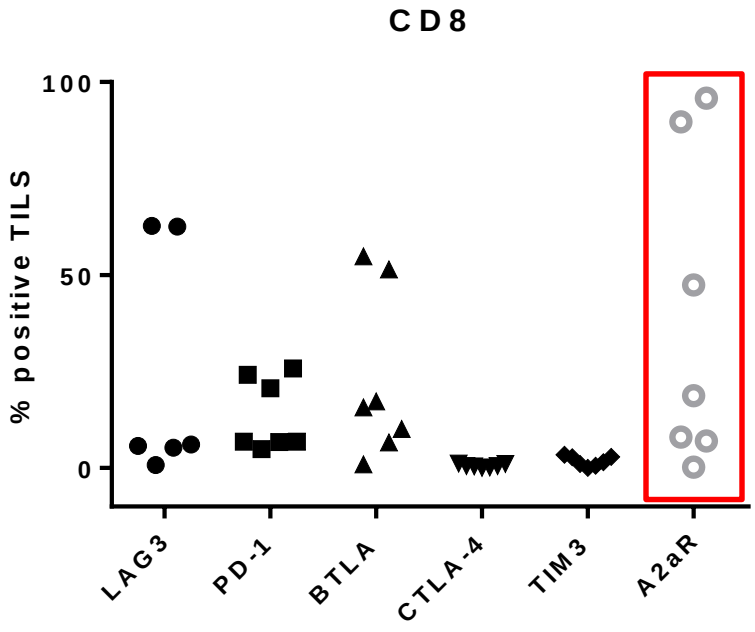


2. Overlapping



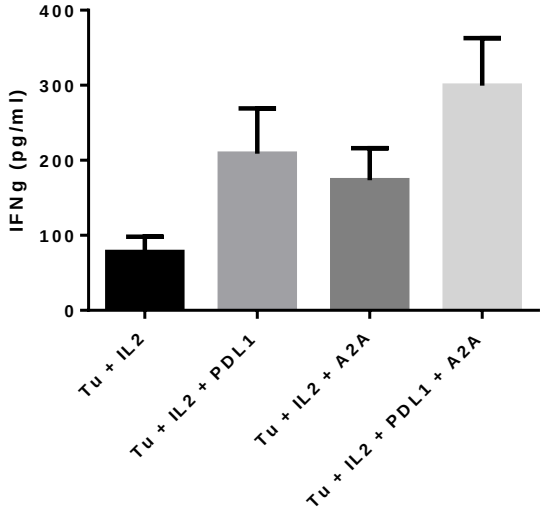
Checkpoint Protein Expression on TILs in NSCLC Tumors

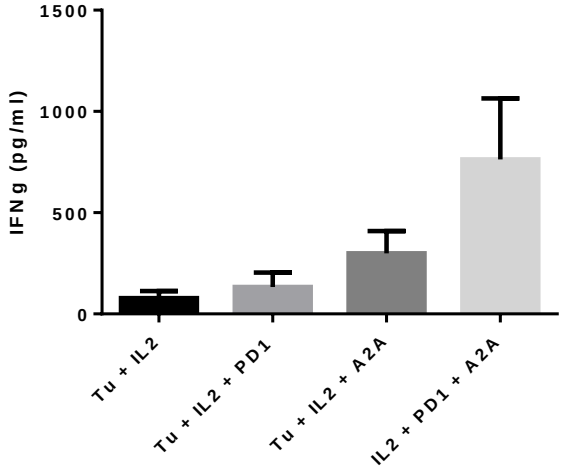


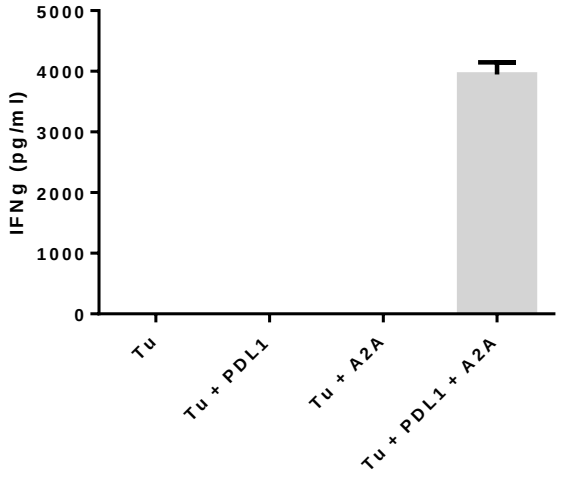


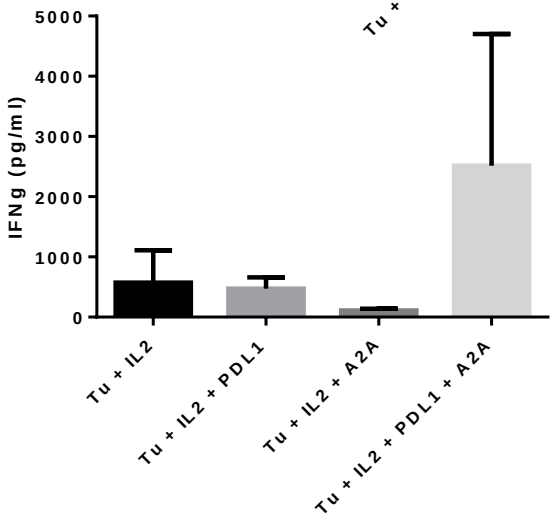
TIL Responses Enhanced with an A2AR Antagonist

NSCLC tumors disaggregated and cultured for 3 days





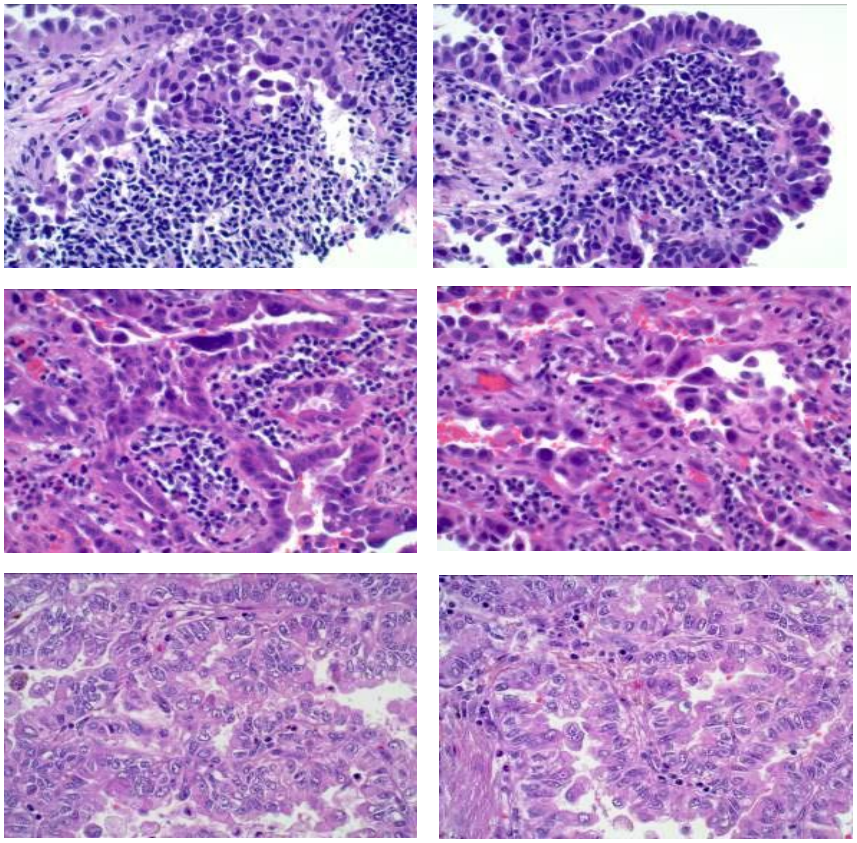




Adenosine A2AR Antagonist Clinical Trial

- Anti-PDL1 + A2AR antagonist phase 1.
- Anti-PDL1 vs Anti-PDL1 + A2AR antagonist randomized phase 2.

2. Insufficient number of T cells extravasate into the tumor.

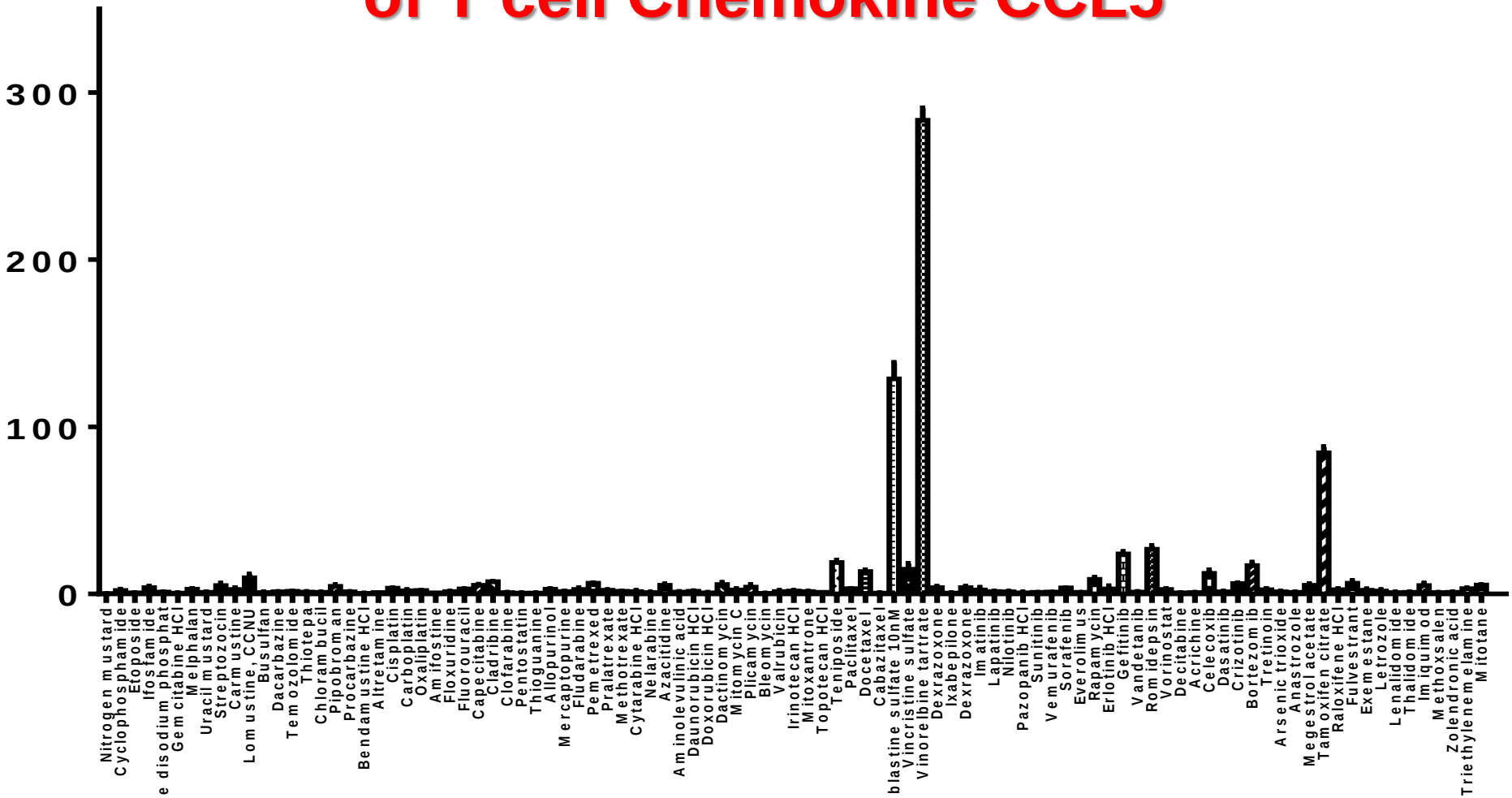


High TIL

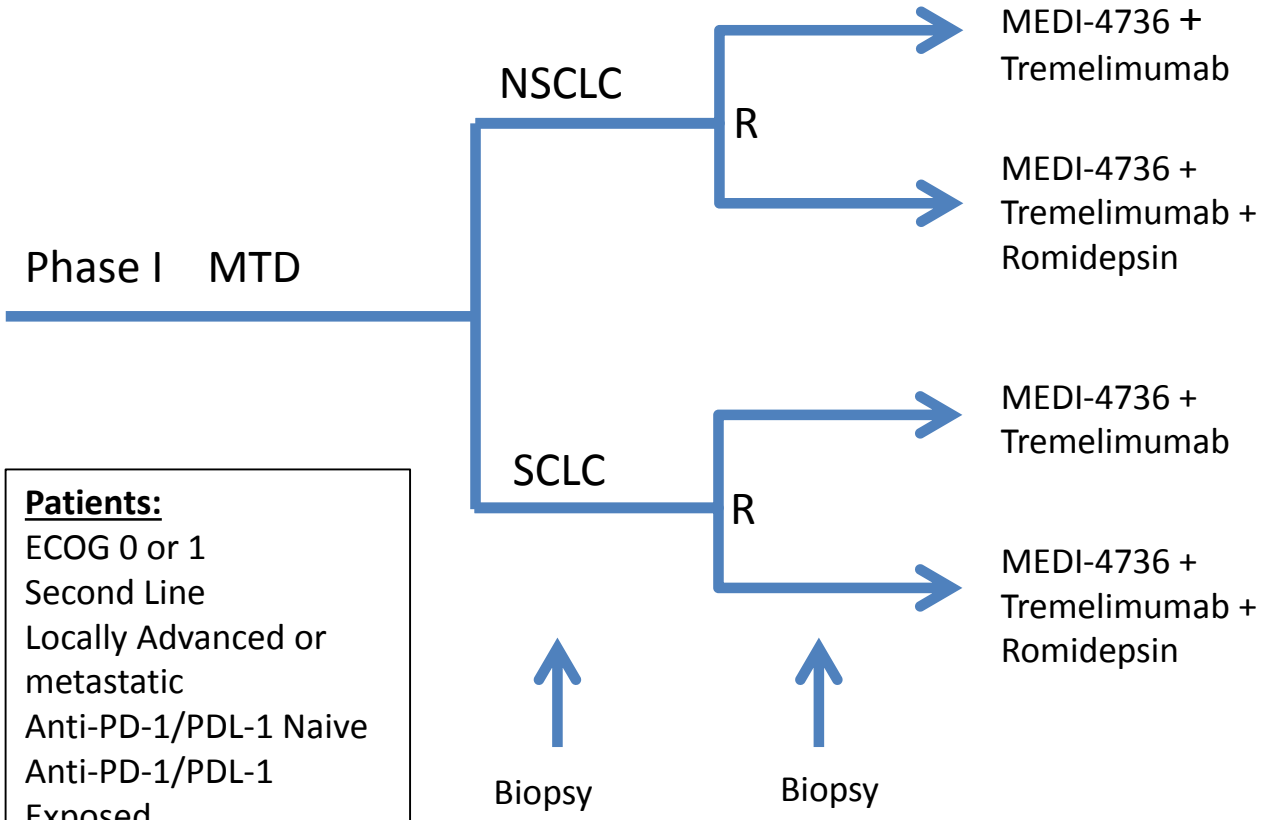
Moderate TIL

Low TIL

Several Oncology Drugs Induce Expression of T cell Chemokine CCL5



HDACi Clinical Trial



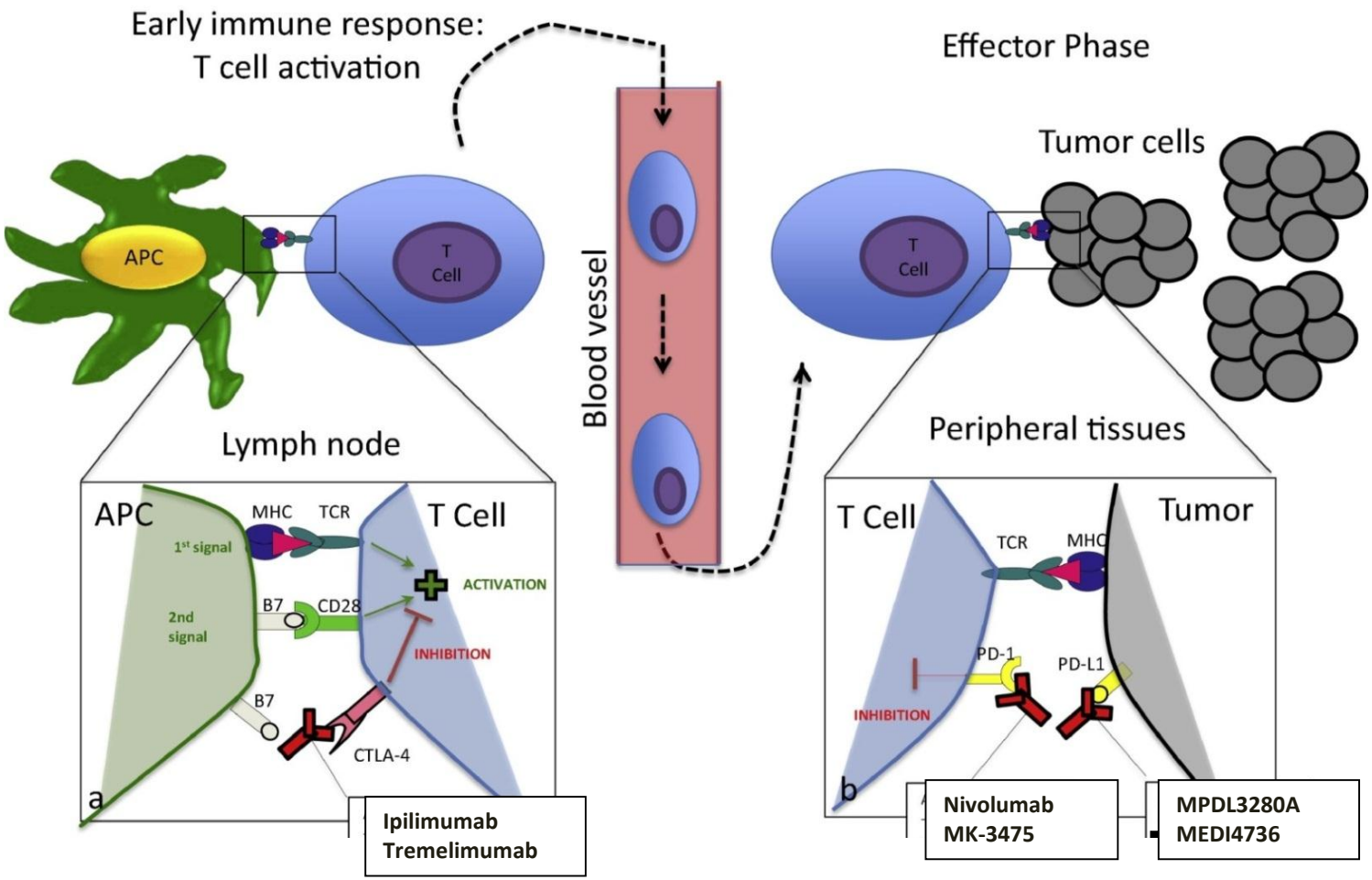
Patients:
ECOG 0 or 1
Second Line
Locally Advanced or metastatic
Anti-PD-1/PDL-1 Naive
Anti-PD-1/PDL-1 Exposed

Dosing:
Fixed MEDI/TREME with escalating Romidepsin

3. Insufficient number of T cells generated within the lymphoid compartment.

1. Anti-CTLA.4.
2. Vaccines.
3. ACT with TILs.

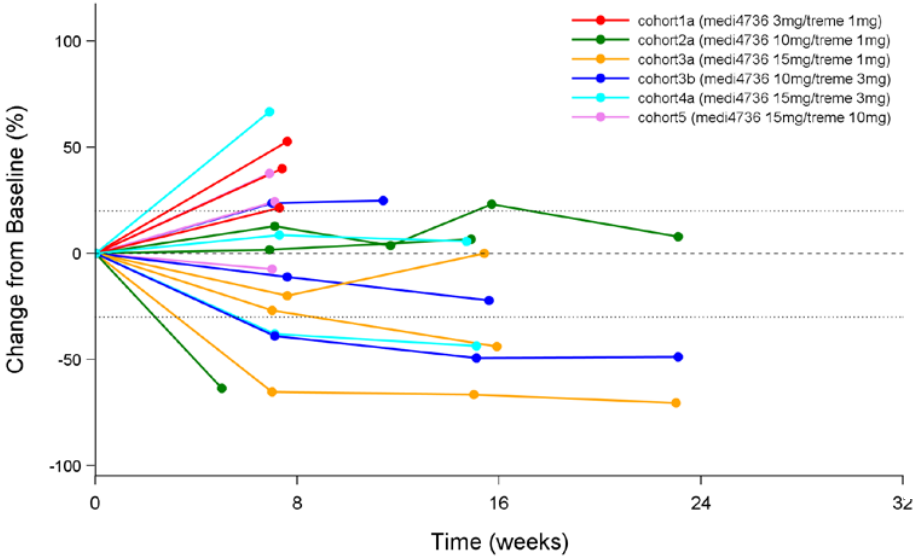
Anti-PD1/PDL1 plus Anti-CTLA.4 to Influence the Lymphoid Compartment

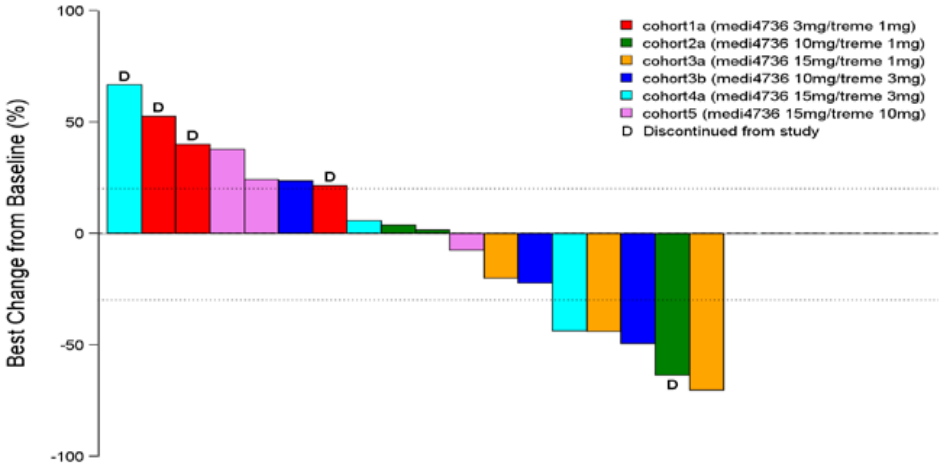


Kyi C, et al. FEBS Lett. 2014;588:368-376

Anti-CTLA.4 Plus Anti-PDL1

MEDI4736 plus Tremelimumab

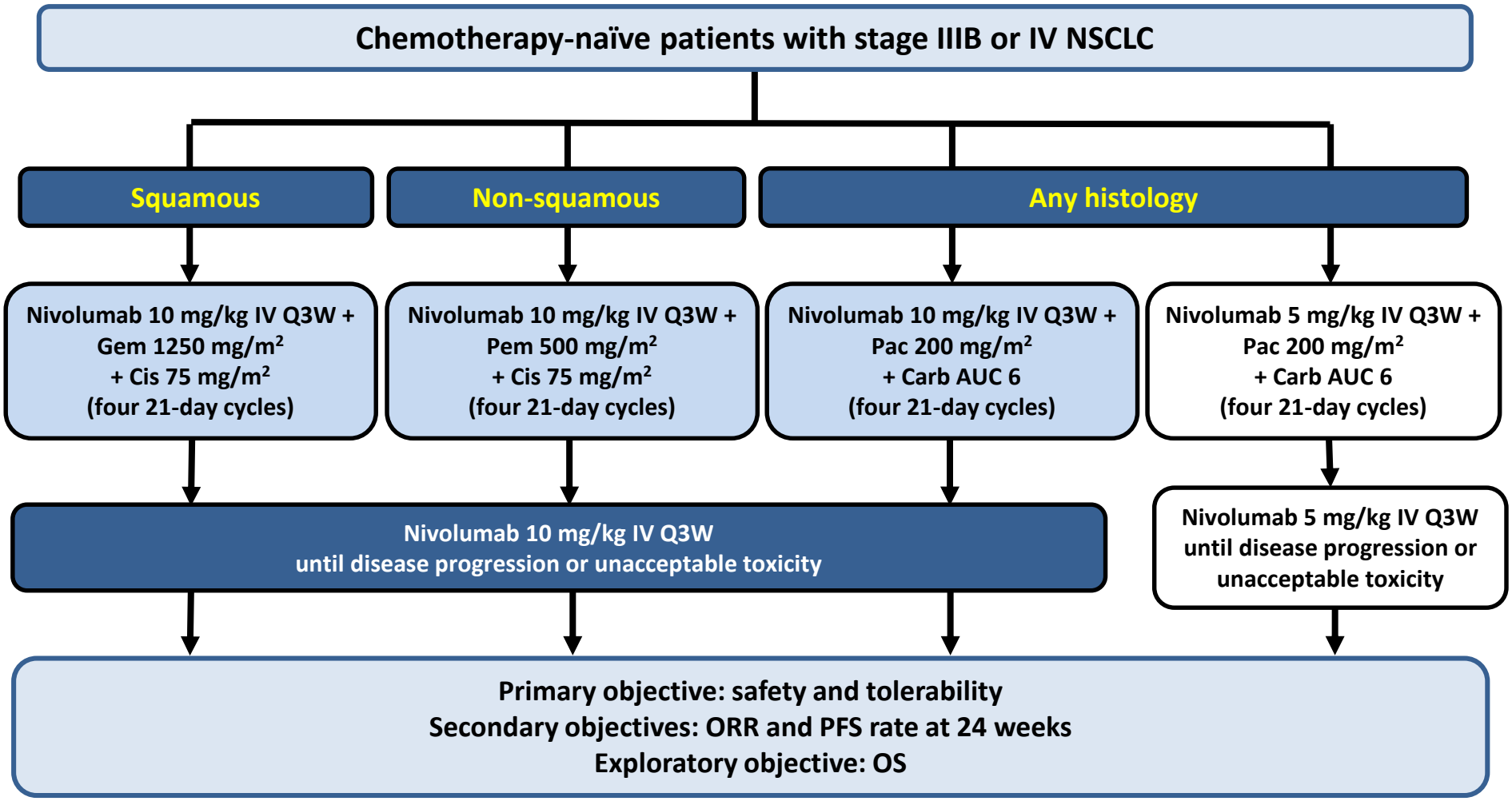




Other Combinations and Clinical Settings

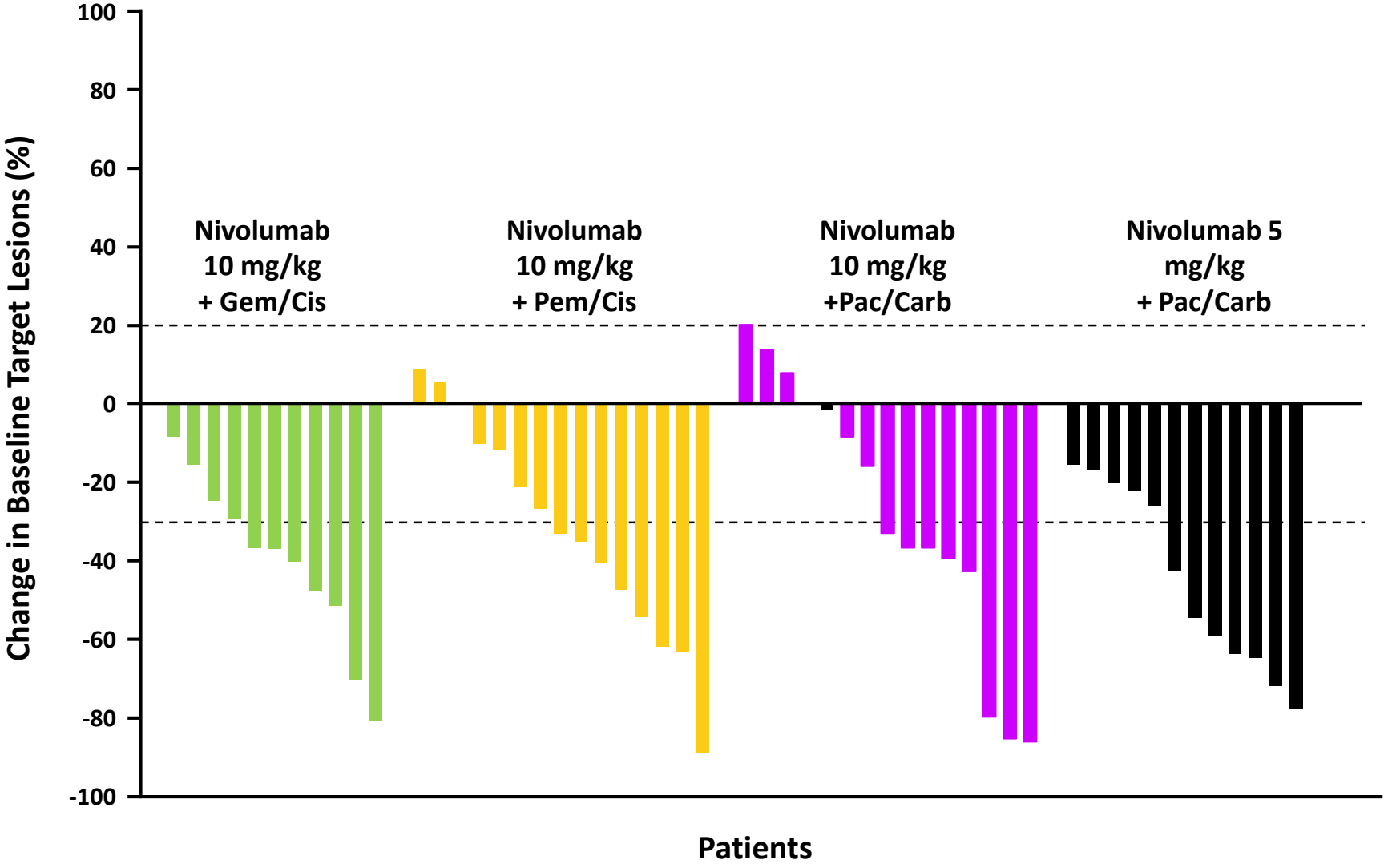
- Chemotherapy.
- TKIs.
- Bevacizumab.
- Other immunotherapeutics.
- First, second, third line.
- Adjuvant for resected.
- Consolidation after chemo/XRT for locally advanced.

CA209-012 Study Design: Nivolumab in Combination With Chemotherapy



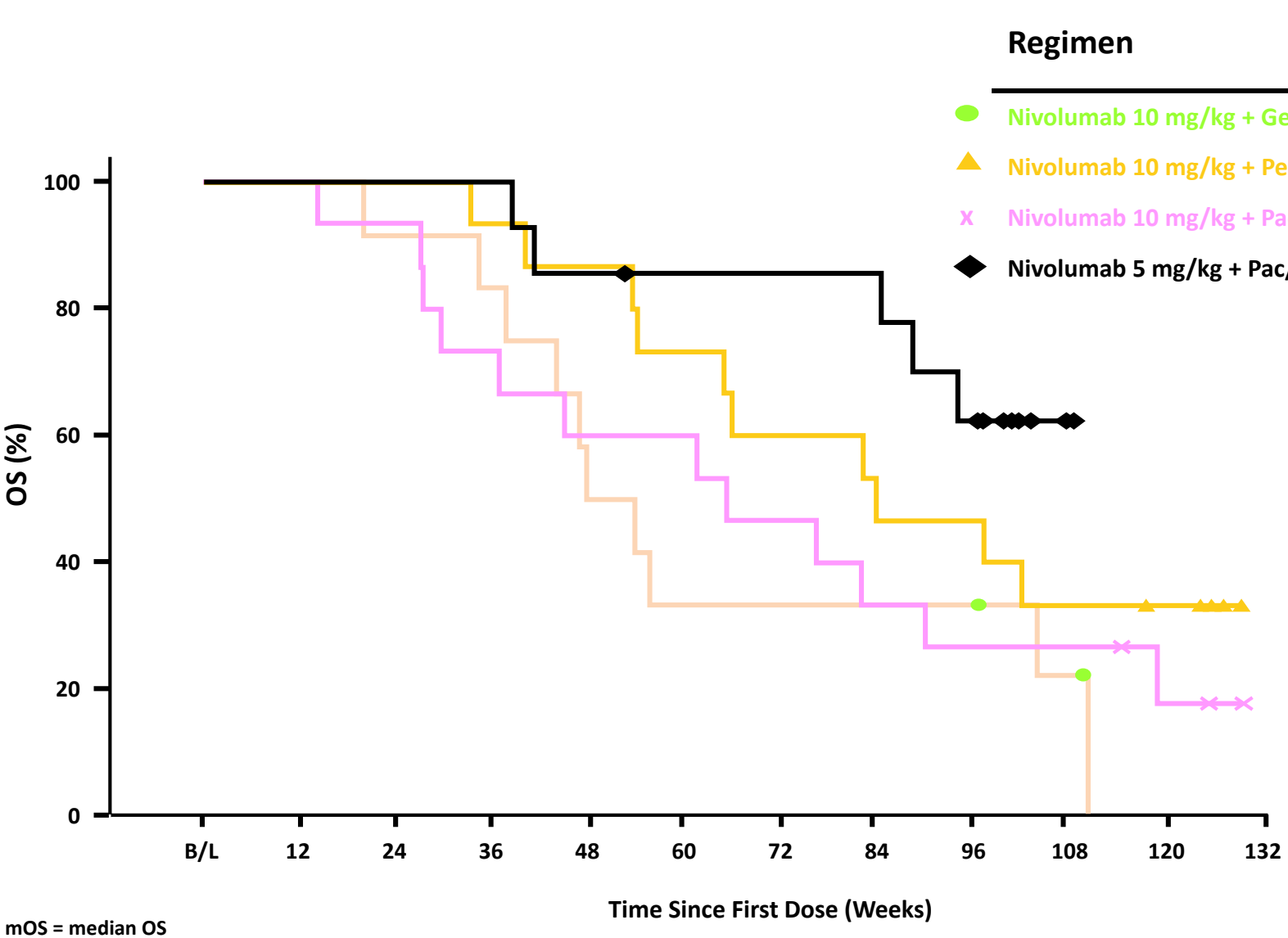
Carb = carboplatin; Cis = cisplatin; Gem = gemcitabine; ORR = objective response rate; OS = overall survival; Pac = paclitaxel; Pem = pemetrexed; PFS = progression-free survival; Q3W = every three weeks

Percent Change in Target Lesions



Only includes patients with baseline target lesions and at least one post-baseline target lesion assessment with non-missing value

Overall Survival by Treatment Arm



mOS = median OS

Optimizing Immunotherapy

- Tumors develop multiple potential mechanisms whereby they evade rejection by the immune system.
  - Strategies need to be developed to thwart these evasive mechanisms.
- “Driver” versus multiple mechanisms.
- Biomarker driven selection of appropriate therapeutic strategy for individual patients.

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Nivolumab Trial

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- Hossein Borghaei
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