

Inmunoterapia

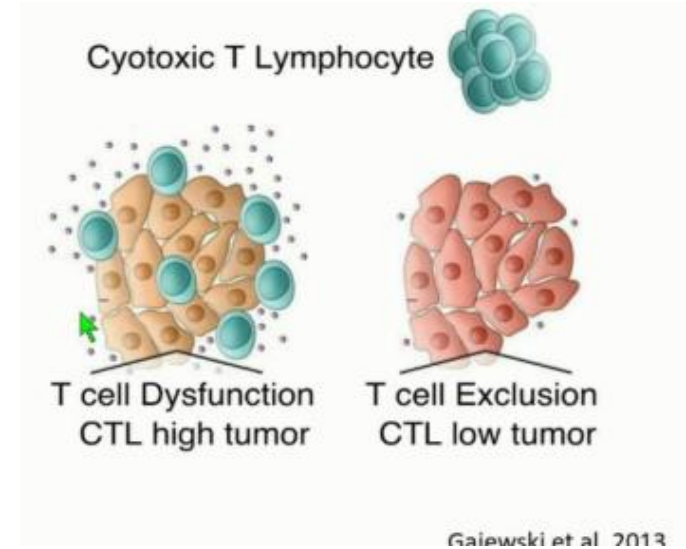
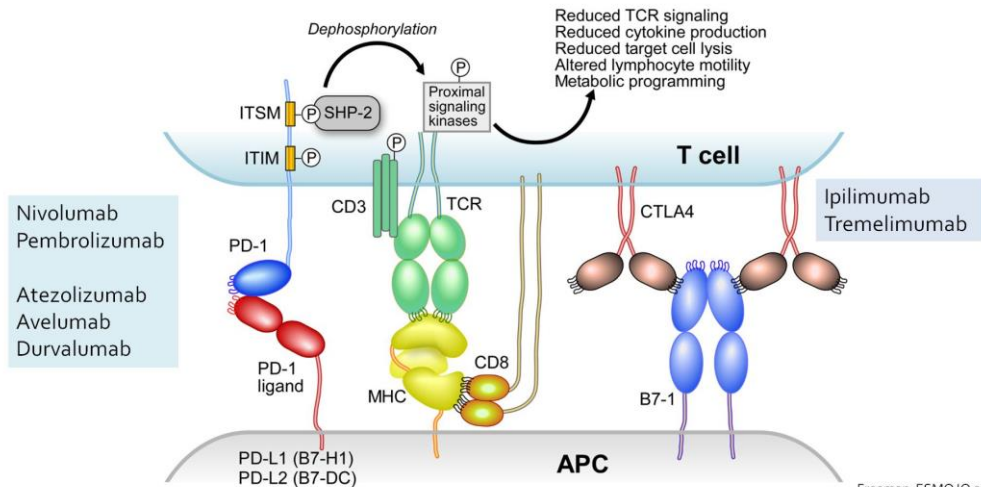
Dr. Bartomeu Massutí

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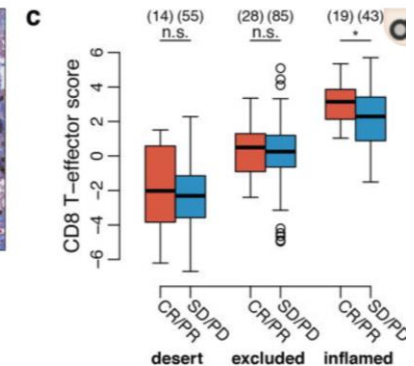
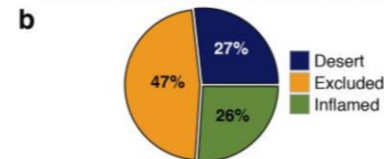
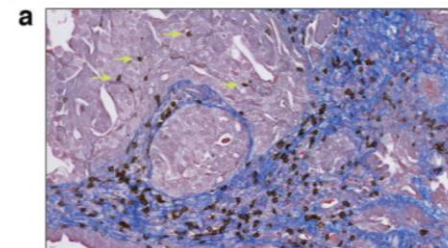


Grupo Español de Cáncer de Pulmón
Spanish Lung Cancer Group

The PD-1 pathway inhibits T cell activation



Freeman, FMO 10 2012



Loss of HLA or B2M highly immunogenic cancers

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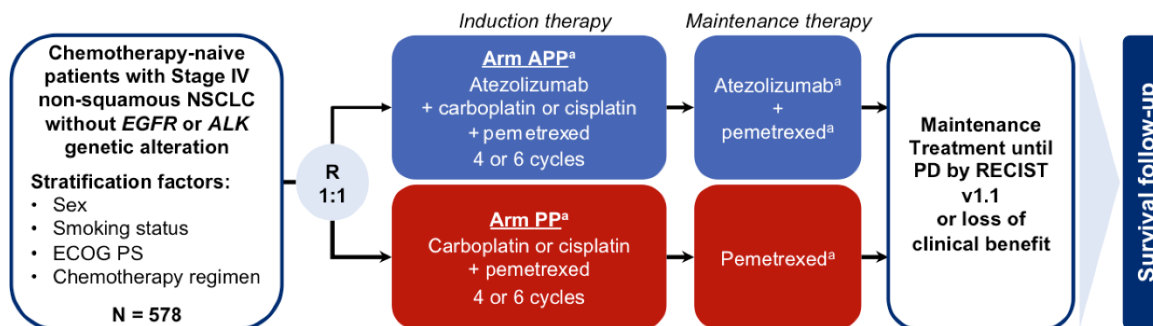


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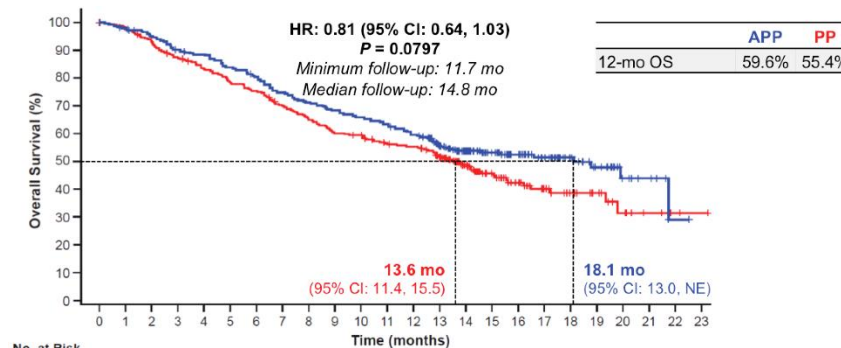
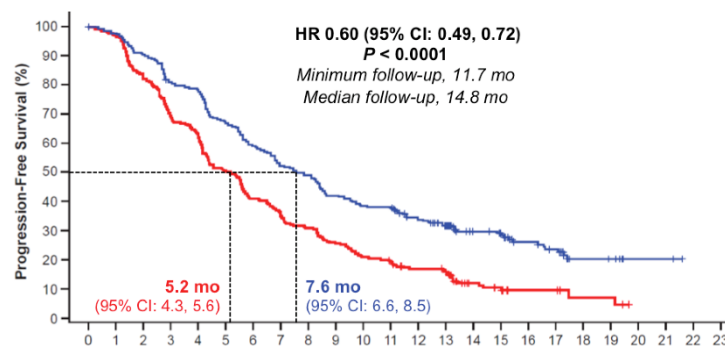
Biological Goal of Combinations with a Checkpoint Inhibitor

- Induce Ag-specific T cells (not present before): Vaccine, Release Ag with RT/targeted agent/chemoRx
- Provide more Ag-presenting cells
- Activation/Modulation of APC :Anti-CD40 +TLR, anti-VEGF?
- Drive T-cell expansion to expand pool of Ag-specific T cells :Cytokines, vaccines, co-stimulation (CD27, CD137, OX40, GITR, ICOS)
- Change a suppressive systemic (deviated) cytokine/other environment :Th1 cytokines, Anti-YKL-40, Reduce MICA/MICB,
- Remove other regulatory checkpoints/suppressive factors for T-cell activation/expansion in periphery (LN): CTLA-4,?
- **Drive T-cells into microenvironment:** CTLA-4, GITR, anti-VEGF, pro-inflammatory agents, targeted agents
- Expand/activate/change ratio of T-cells in microenvironment :Cytokines, vaccines, co-stimulation (CD27, CD137, OX40, GITR, ICOS)
- **Remove other checkpoints/ T-cell suppression in microenvironment:** Treg (CTLA-4), cytokines and anti-cytokines, Ido, arginase, multiple checkpoints (PD-1 pathway, other B7-H, KIR, HLA-G, CD200, TIm3, LAG3)
- Restore tumor Ag presentation
- **Transfer Engineered T Cells-CAR-T**
- **Problem→ Identifying the critical deficiency(ies) in individual patients**

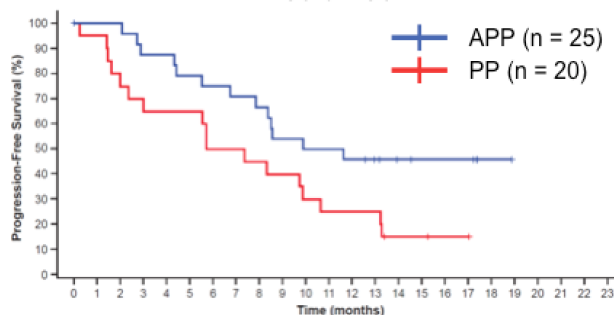
IMPower132: Atezolizumab+Platin+Pemetrexed



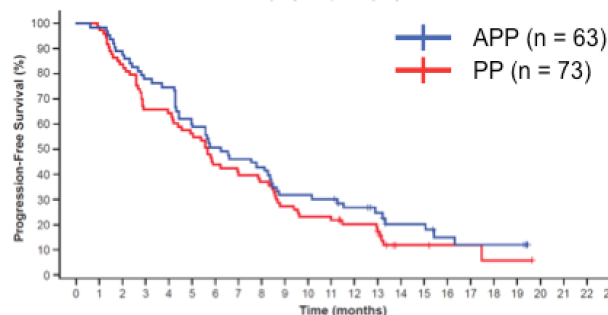
- Co-primary endpoints: INV-assessed PFS and OS
- Secondary endpoints: INV-assessed ORR and DOR, PRO and safety measures



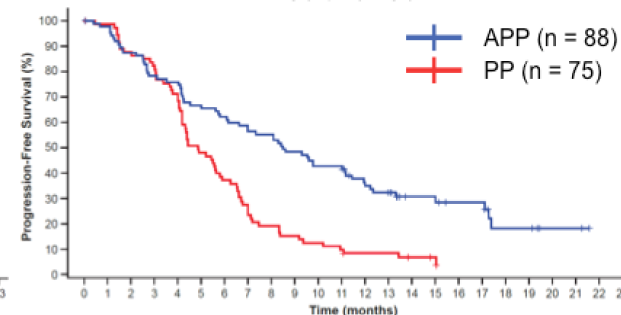
PD-L1 High TC3 or IC3



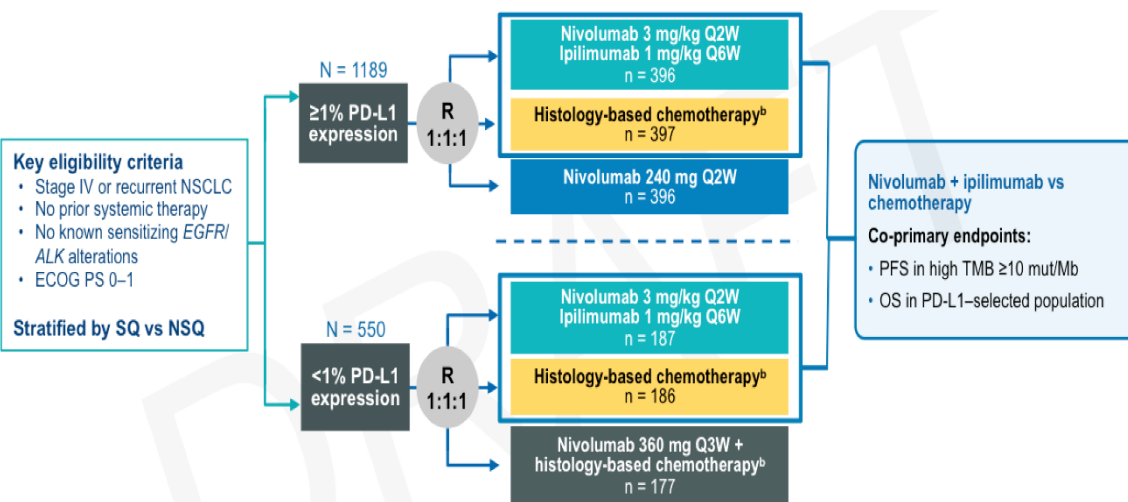
PD-L1 Low TC1/2 or IC1/2



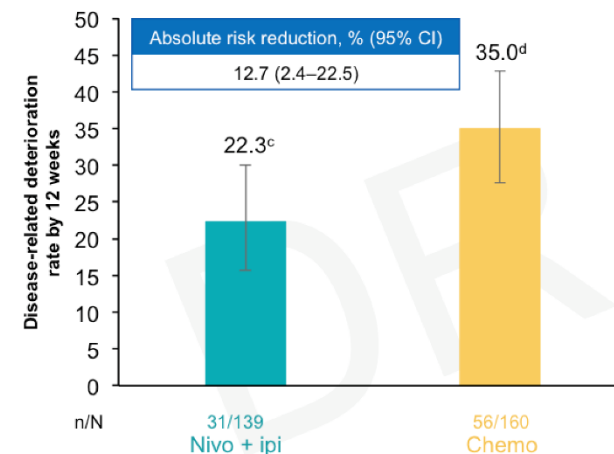
PD-L1 Negative TC0 and IC0



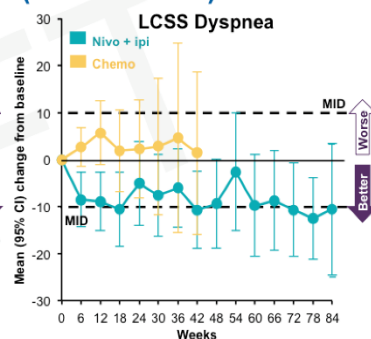
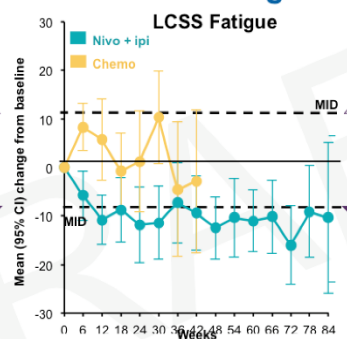
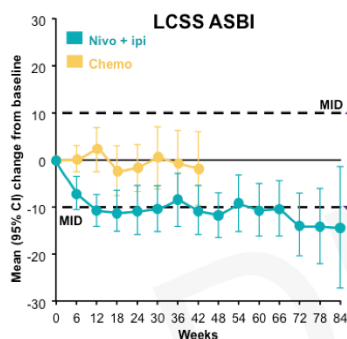
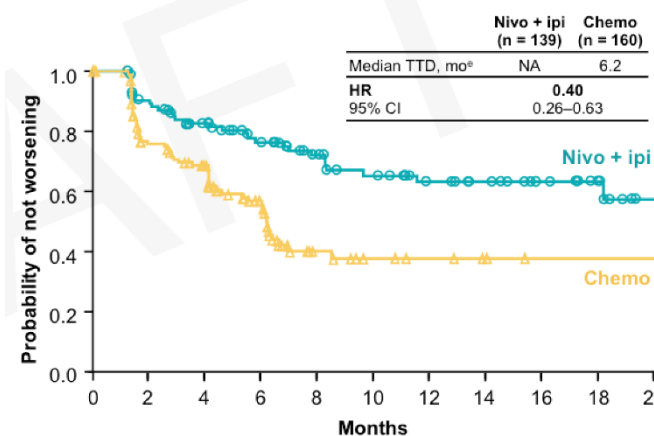
PROs in CheckMate 227



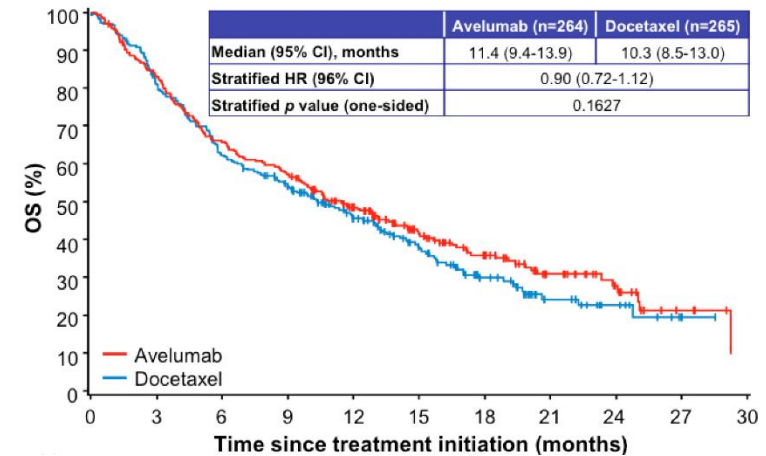
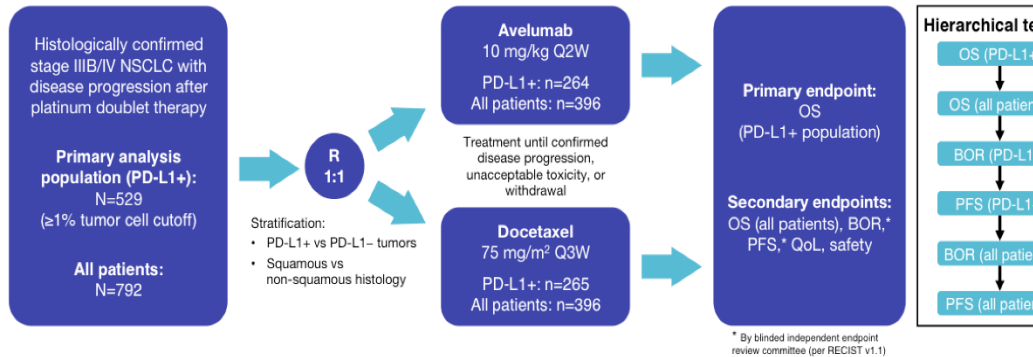
Proportion of patients with symptom deterioration on treatment or follow-up by Week 12



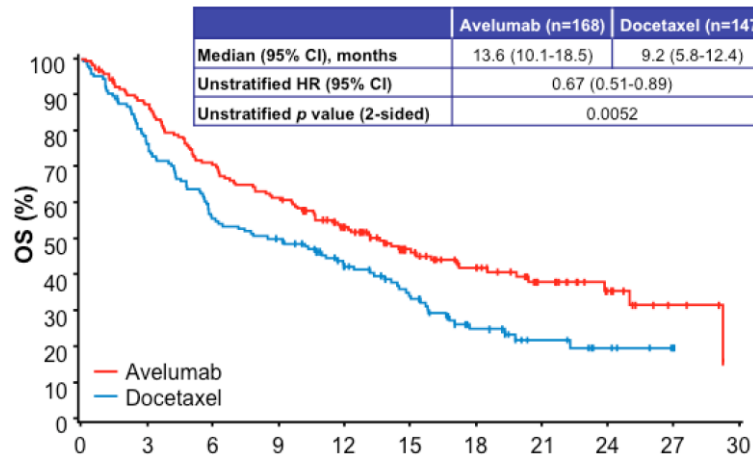
Time to first disease-related deterioration on treatment (common assessments) or follow-up



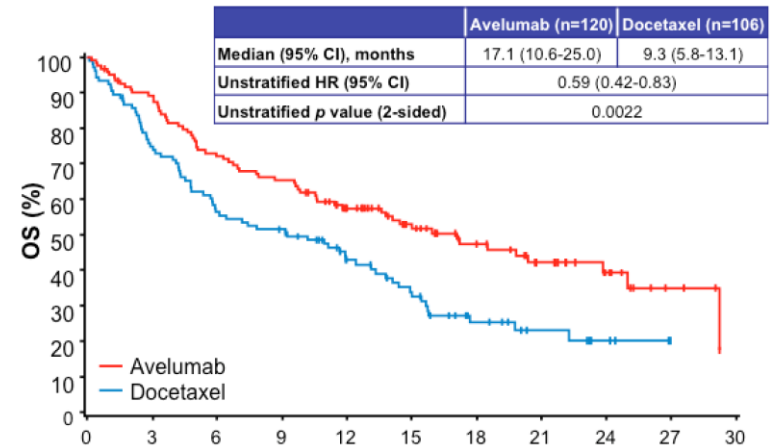
Avelumab vs Docetaxel pretreated JAVELIN Lung 200



≥50% PD-L1+



≥80% PD-L1+



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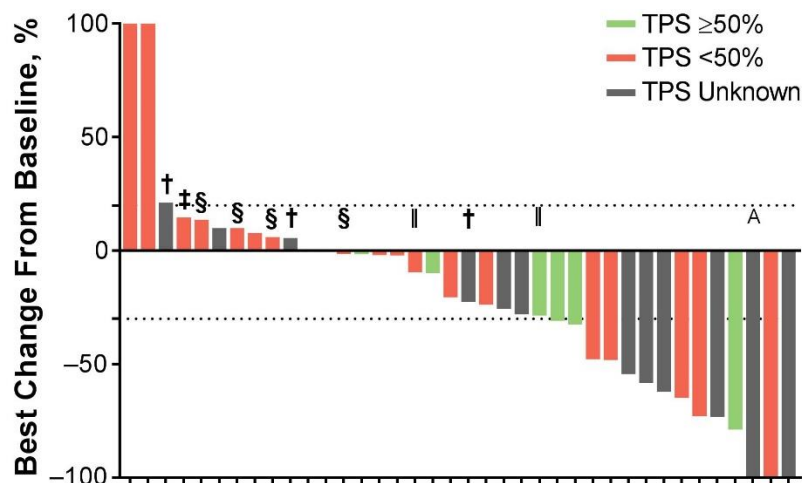


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Epacadostat Plus Pembrolizumab in Patients With Non-Small Cell Lung Cancer: Phase 1/2 Results From ECHO-202/KEYNOTE-037

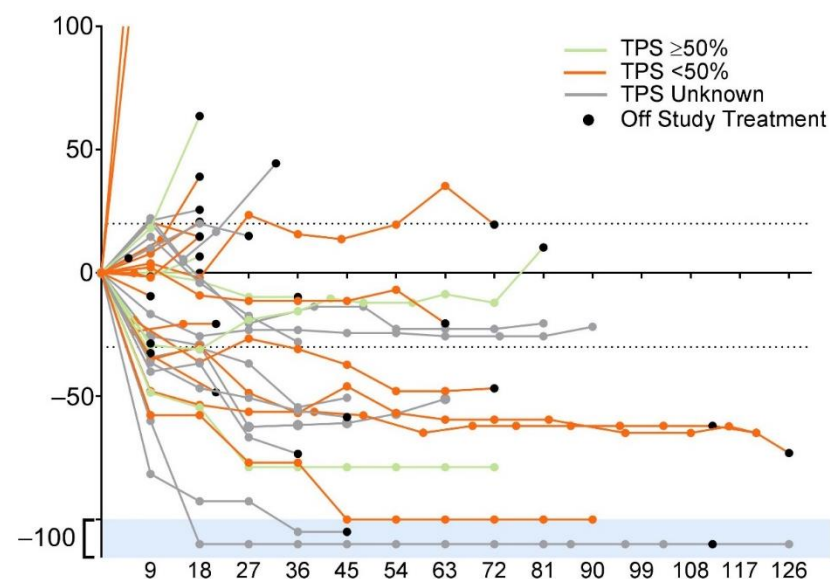
Key Eligibility Criteria

- Adult patients with stage IIIB, IV, or recurrent NSCLC were enrolled
- Phase 2 patients must have had progression after platinum-based chemotherapy and an appropriate TKI (for those with an *EGFR*-sensitizing mutation and *ALK* gene rearrangement)
- Baseline tumor biopsies were required
- Prior treatment with an immune checkpoint inhibitor or IDO inhibitor was not allowed



Treatment

- **Phase 1:** epacadostat (25 mg, 50 mg, 100 mg, or 300 mg) BID + pembrolizumab (2 mg/kg or 200 mg Q3W)
- **Phase 2 (RP2D):** epacadostat 100 mg BID + pembrolizumab 200 mg Q3W

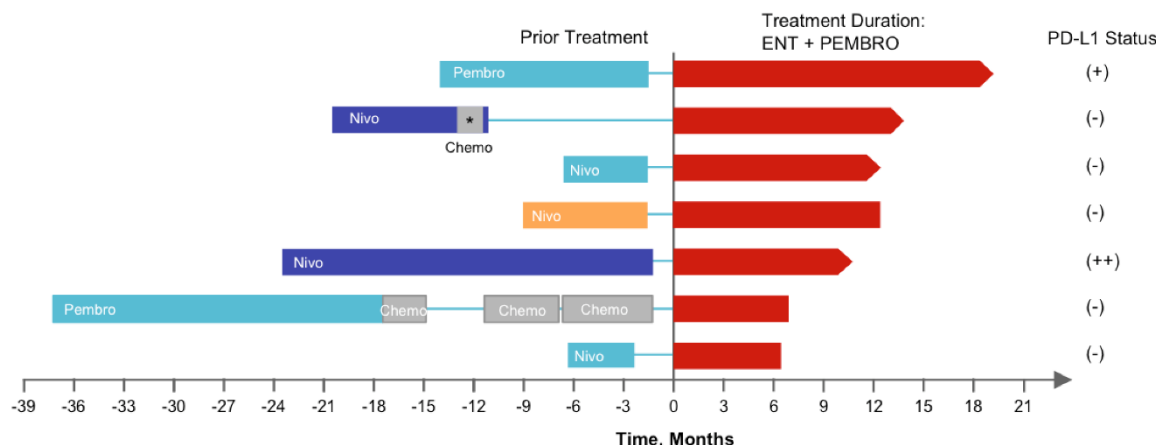
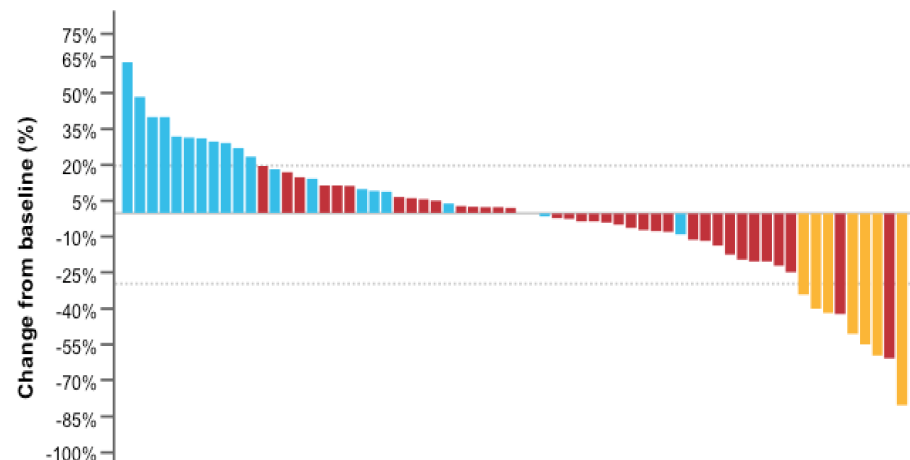
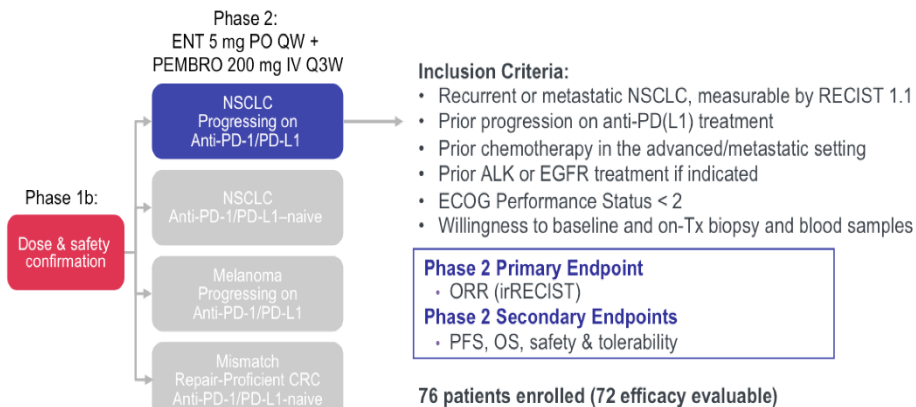


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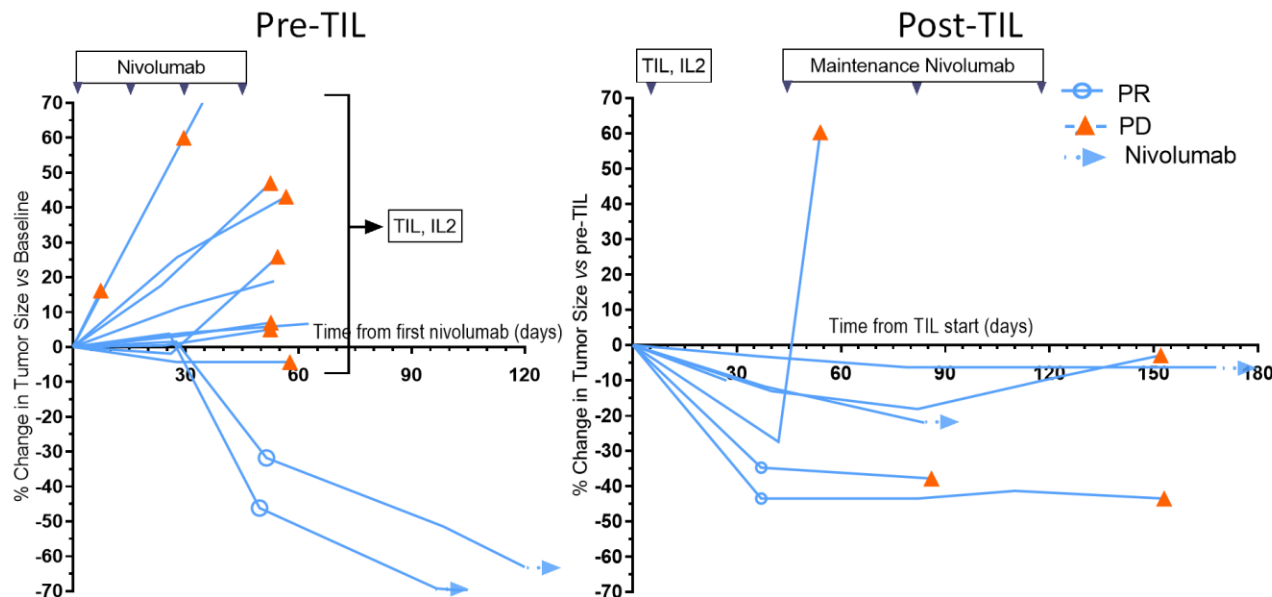
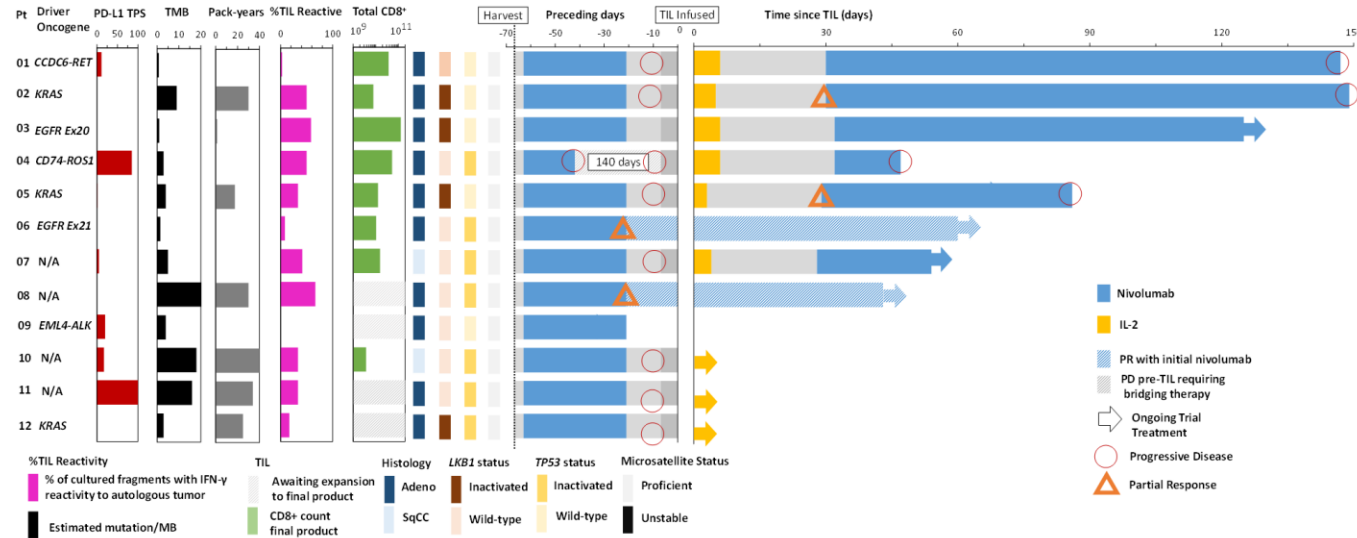
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Entinostat and Pembrolizumab ENCORE601

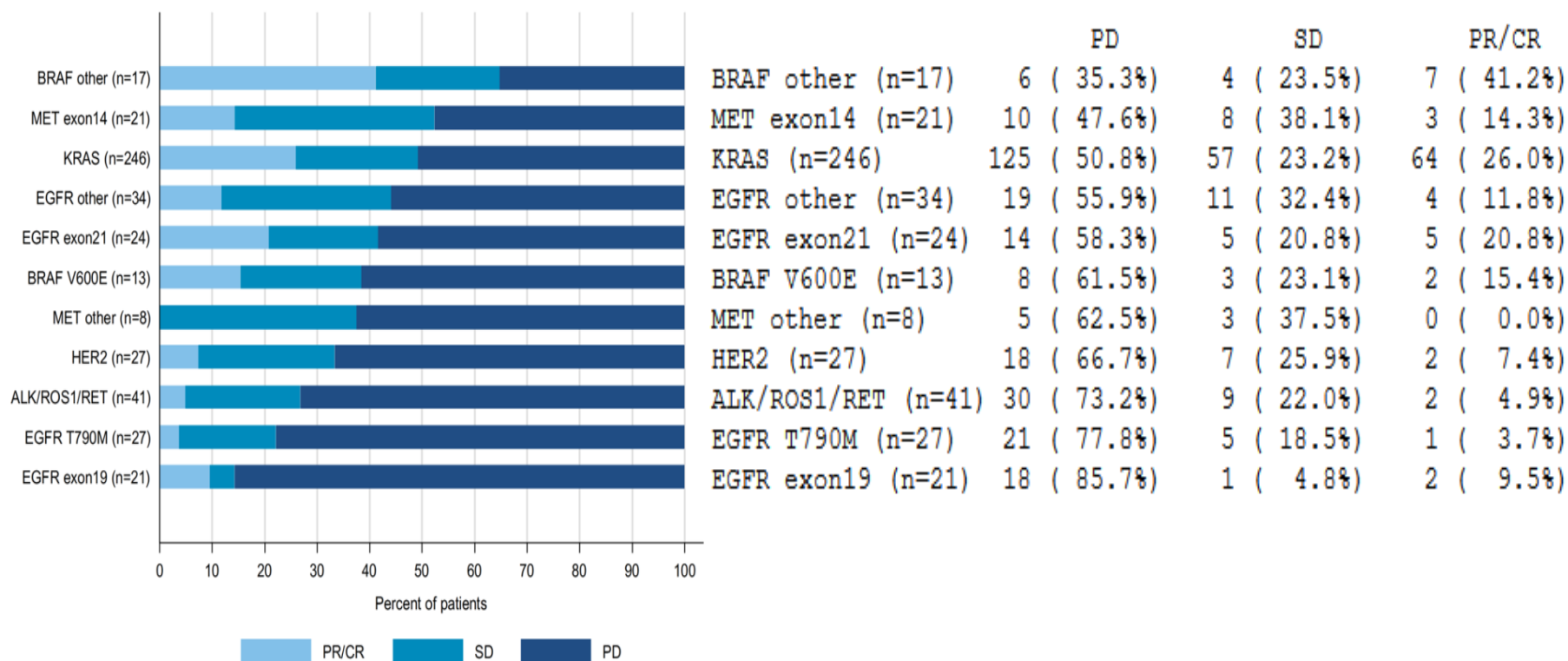


- Independent of pre-treatment PD-L1 expression and response to prior PD-1 blockade
- Predictors (higher levels of peripheral monocytes) and dynamics (suppressed MDSCs, increased CD8s) on

Adoptive TIL transfer in association with Nivolumab in PD



Molecular subtypes sorted by best response (RECIST1.1)



BLUEPRINT 2B



The Blueprint 2 team
28 IASLC investigators
15 countries
5 continents
STATISTICS: M. Pintilie (Toronto)

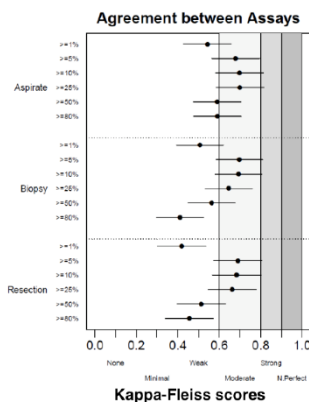
Blueprint 2A outcomes

1. Blueprint phase 2A involving real-life clinical lung cancer samples and 25 pathologists largely affirms the results of Blueprint phase 1
2. 22C3, 28-8 and SP263 are comparable, SP142 detects less, while 73-10 stains more PD-L1 positive tumor cells
3. PD-L1 scoring on digital images and glass slides show comparable reliability
4. Scoring of tumor cell PD-L1 expression by pathologists on tissue samples shows strong reliability
5. Scoring of immune cell PD-L1 expression remains challenging for pathologists, with poor reliability
6. Scoring of PD-L1 expression on cytology samples may have moderate reliability; this requires further confirmation

Materials (Blueprint phase 2B)

- **Thirty one triplet samples** (whole tissue block, core or forceps biopsy and FNA cell block) were prospectively collected from **routine clinical practice** of 11 pathologists (IASLC Pathology Committee members), using locally approved research protocols

	Histology of case material
Adenocarcinoma	17
Squamous cell carcinoma	12
Large cell	2
Total	31



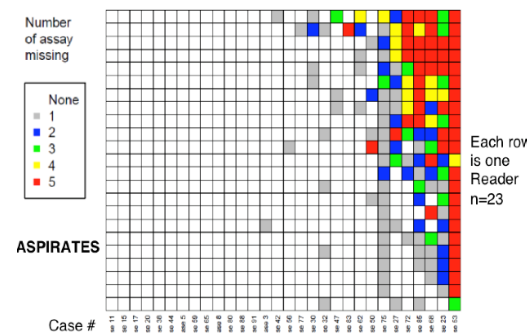
Good agreement between assays around specified cut points

Mean, Median values of TPS

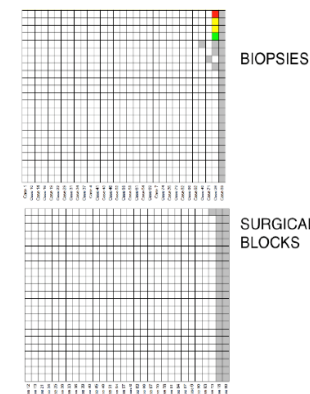
Assay	Aspirate (Mean,median)	Biopsy (Mean,median)	Resection (Mean,median)	Aspirate vs. Biopsy (p)	Aspirate vs. Resection (p)	Biopsy vs. Resection (p)
22C3	19.0, 0.9	18.2, 0.7	22.2, 0.5	0.31	0.90	0.26
28-8	21.6, 1.7	19.0, 0.9	21.6, 2.6	0.13	0.79	0.19
73-10	26.0, 2.4	25.3, 2.8	27.4, 3.3	0.86	0.18	0.41
SP142	5.2, 0	4.2, 0.04	6.8, 0.09	0.57	0.49	0.12
SP263	22.4, 1.5	23.7, 2.7	25.3, 4.2	0.18	0.031	0.25

The p-values are based on Wilcoxon signed-rank test.

Mean, median values differ between some assays but not between sample types



About 13% of aspirate reads not possible; ≤1% of others



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