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Non-PD-1/L1 Immunotherapy Targets and Agents in Advanced NSCLC

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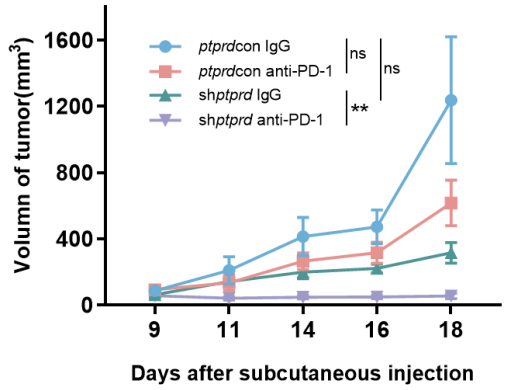
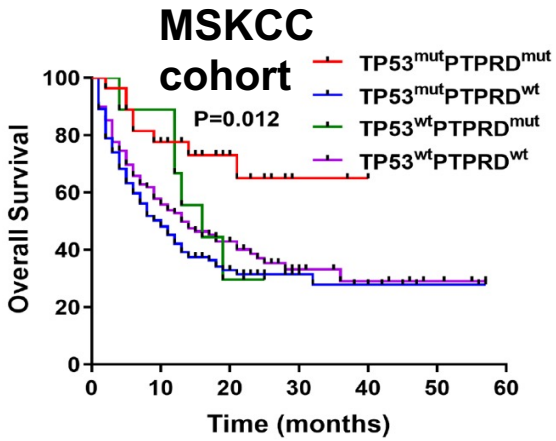
OA18.03 X. Cai et al. Surfaceome of TP53-Mutant NSCLC Reveals a Distinct Subtype with Immunotherapy Vulnerability, Characterized by Co-occurring PTPRD Mutant.

TP53/PTPRD knock-down mice more sensitive to anti-PD-1



Survival benefit from co mutant NSCLC from ICI



Background

- Protein Tyrosine Phosphatase Receptor type D (PTPRD) is a membrane receptor that regulates signal transduction pathways

- PTPRD-mutant lung cancer has increased tumour mutation burden (TMB) and immunotherapy (ICI) responsiveness

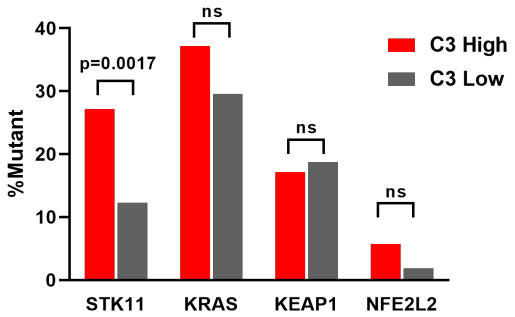
Clinical implications

- Co-mutant NSCLC maybe more sensitive to ICI

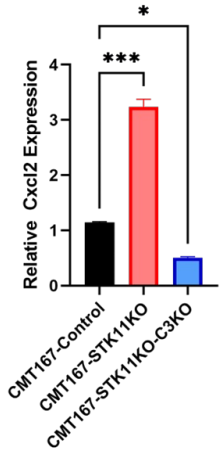
- Inhibiting wild type PTPRD in TP53-mutated lung cancer is a potential new drug target in lung cancer, to use concurrently with ICI therapies.

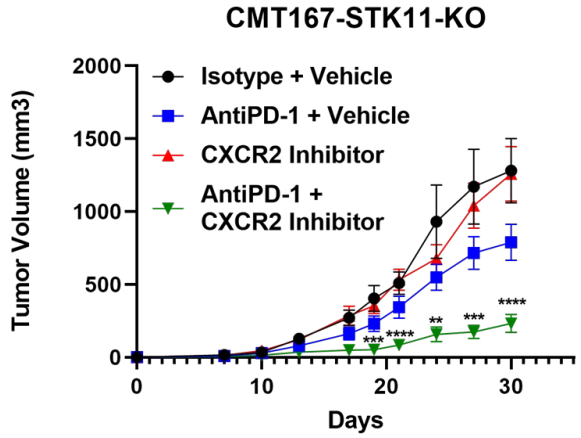
OA 18.04 E. Yau et al. Tumor-Derived Complement C3 as a Therapeutic Target in STK11 Mutant Non-Small Cell Lung Cancer.

High C3 expression in STK11-mutant tumors (TCGA) associated with poor survival



Treatment with CXCR2 inhibitor restored sensitivity of STK11-KO tumors to anti-PD-1.





Background

- STK11 (LKB1) controls AMP-activated protein kinases (cell metabolism, cell polarity, apoptosis, DNA damage response)

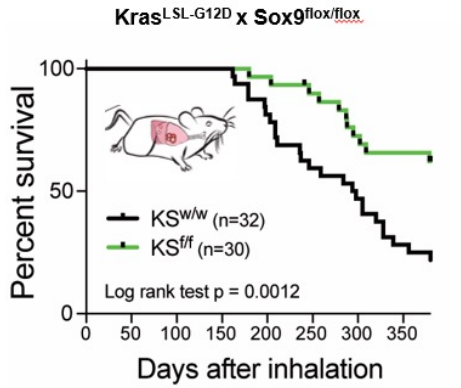
- STK11 mutation is an adverse predictor of ICI therapy benefits in lung cancer.

Clinical significance

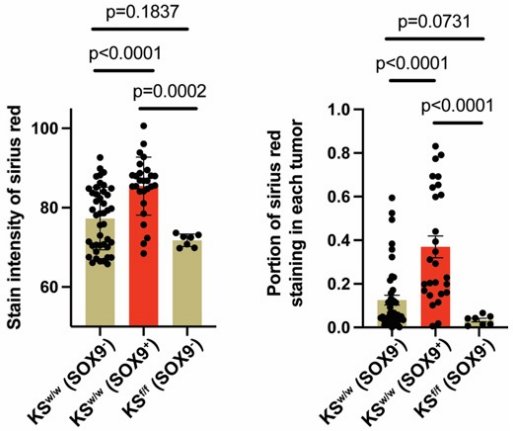
- Targeting C3 or CXCR2 (IL8 receptor) in STK11-mutated cancers may increase ICI sensitivity

OA 18.06 S.R. Pine et al. SOX9 Drives KRAS-Induced Lung Adenocarcinoma Progression Through Suppression of Anti-Tumor Immunity.

SOX9 loss promotes survival in KRAS G12D mutant NSCLC



Sox9 Suppresses Anti-tumor Immunity Through Increasing Tumor Stiffness (Increase collagen production)



Background

-SOX9 mutations are rare in lung cancer (1%) but over-expression is common (20-32% TCGA)

-SOX9 over-expression promotes EMT through several signaling pathways, such as EGFR, Wnt/β-cat.

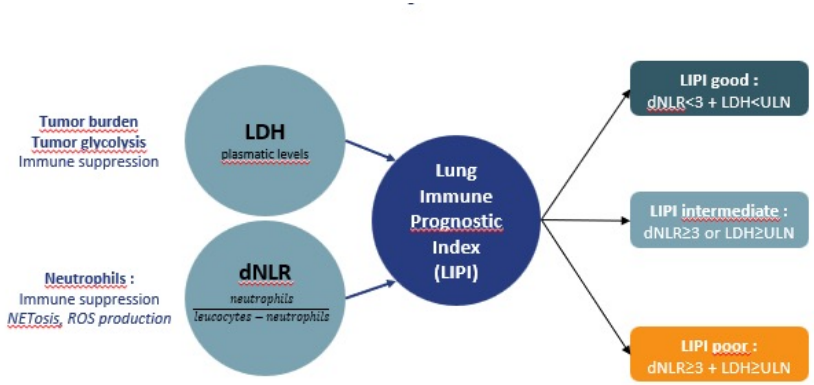
Clinical significance

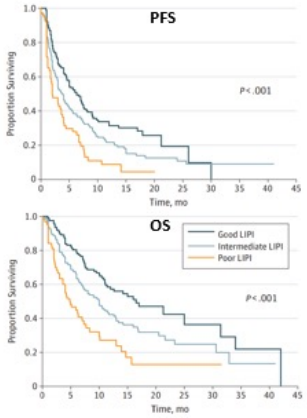
- Testing for SOX9 overexpression (by IHC or by RNA analysis) may predict resistance to immunotherapy

- Inhibiting SOX9 could be therapeutic target to potentiate immunotherapy

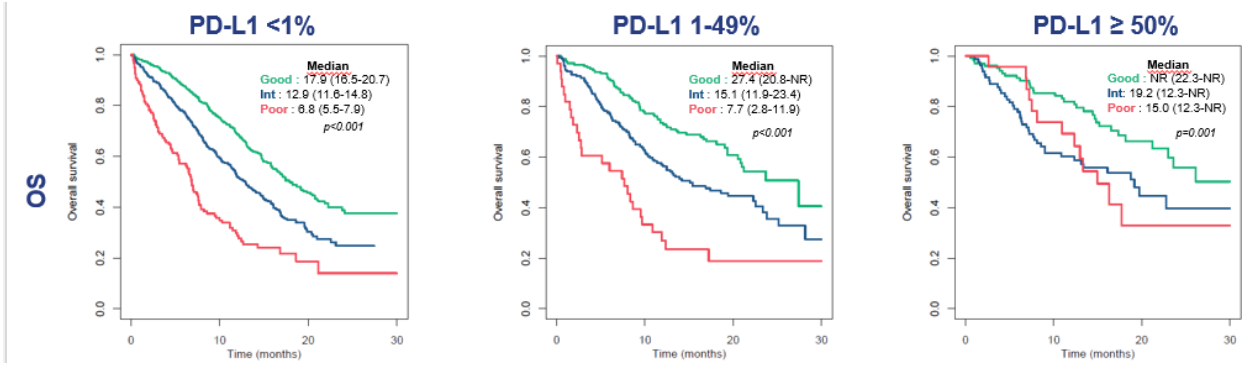
OA 15.05 Lung Immune Prognostic Index (LIPI) predicts outcomes from upfront chemotherapy + immunotherapy +/- antiangiogenic in advanced NSCLC – Roulleaux Dugage et al.

LIPI predicts survival from immunotherapy in NSCLC





Independent predictor from PD-L1



Background

Neutrophil/Lymphocyte ratio has been shown to be prognostic of immunotherapy response

LDH is prognostic in many tumor typies

Clinical significance

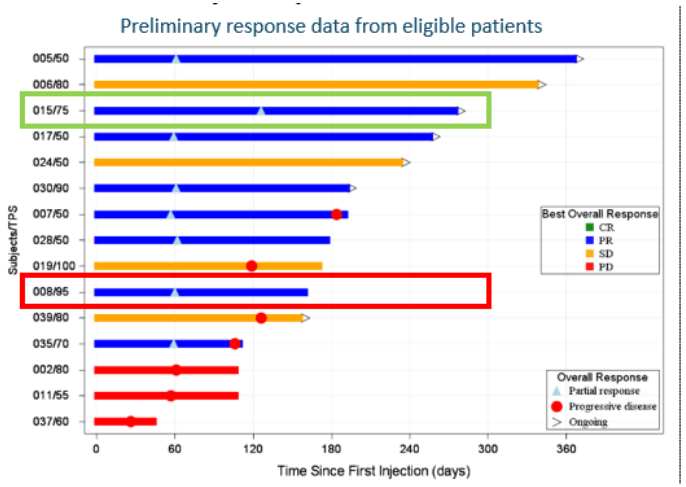
Using LIPI (NLR and LDH) may help estimate outcome for patients treated with immunotherapy

MA 15.09Phase 2 trial of IO102-IO103 vaccine plus pembrolizumab: preliminary results for the first-line treatment of lung adenocarcinoma IOB-022 / KN-D38: Jonathan Riess

Interim efficacy analysis: n = 15 with ≥2 cycles and either ≥2 post-baseline tumor assessments or discontinued

Best overall response	n = 15
ORR 95% CI	**8 (53.3%)** [26.6, 78.7]
PR	8 (53.3%)
SD	4 (26.7%)
PD	3 (20.0%)

Median duration of exposure to IO102-IO103 = 15 weeks (min-max 0–52)



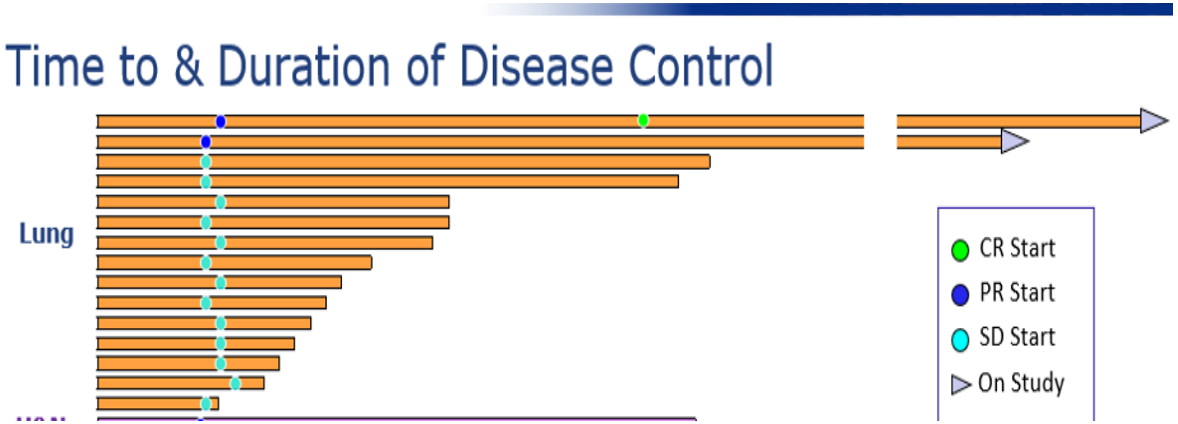
Background

IO102-IO203 vaccine: Anti-IDO and PD-1 vaccine subcutaneous injection to stimulate T cells + Pembrolizumab

First line PD-L1 >50% NSCLC

Clinical significance

More pts needed to see if vaccine improves response rate beyond immunotherapy alone in first line population



- To date, two subjects with NSCLC (1CR and 1PR) remain on therapy for **2.8 and 2.3 years,** respectively

Background

SIGLEC-15: Immunosuppressive cell surface receptor on T cells and tumor cells

PD-1/L1 Refractory NSCLC

NC318- S-15 antibody +/- pembro

Clinical significance

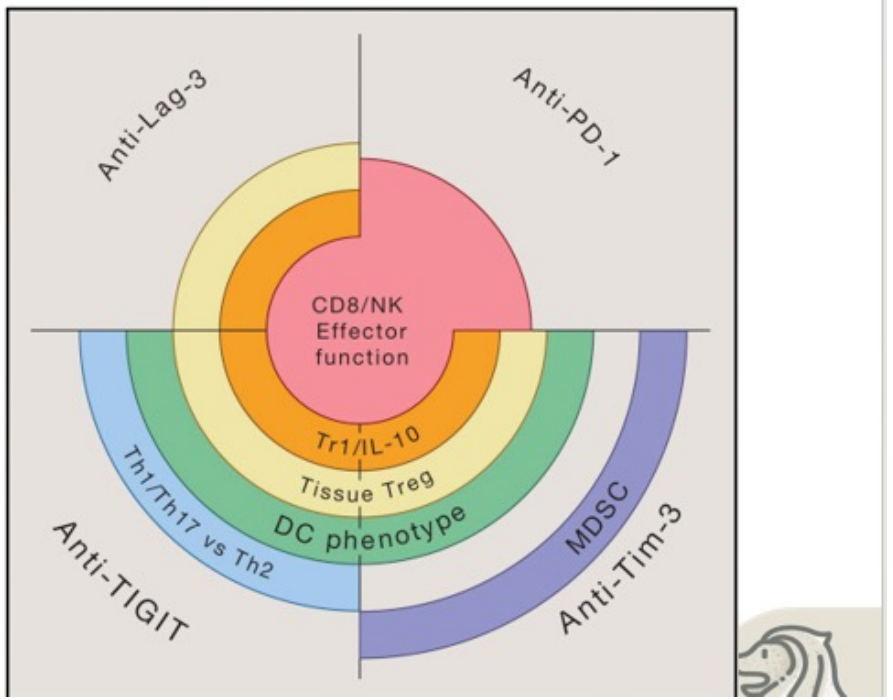
Durable response in immune refractory patients unusual; support expansion in this group and development of predictive biomarkers of response

ES 39.03: Emerging Strategies – Combinations with Newer Immune Checkpoint Targets- TIGIT, LAG3, TIM3

Dr Puey Ling CHIA
MBBS, M.Med, MRCP, FRACP, PhD
Department of Medical Oncology
Tan Tock Seng Hospital, Singapore

Why Anti-Lag-3, anti-TIGIT, anti-TIM3 should not be used as monotherapy:

- Although all checkpoint receptor blockades have some effect on CD8+ T cell and NK cell effector function, the effect of PD-1 blockade is proportionally larger than that of Lag-3, Tim-3, or TIGIT blockade alone.
- Further insights to the specialized functions of these ICI targets will allow is to best optimize the combinational strategies with existing therapies



ES39.04 Immunotherapy Beyond Immune Checkpoints (Vaccines, Cytokines, Etc)

Edward Garon
David Geffen School of Medicine at UCLA
USA

- Vaccines and cytokines are not validated targets in lung cancer
- New delivery mechanisms (e.g. mRNA) has increased enthusiasm regarding vaccines against selected antigens
- Personalized antigens are conceptually interesting, but have been limited by logistical challenges
- Early enthusiasm from early phase studies of cytokines (with PD-1 inhibition) has been difficult to replicate in larger studies
- Engineering approaches have potential to enhance efficacy and limit toxicity of immunostimulatory cytokines

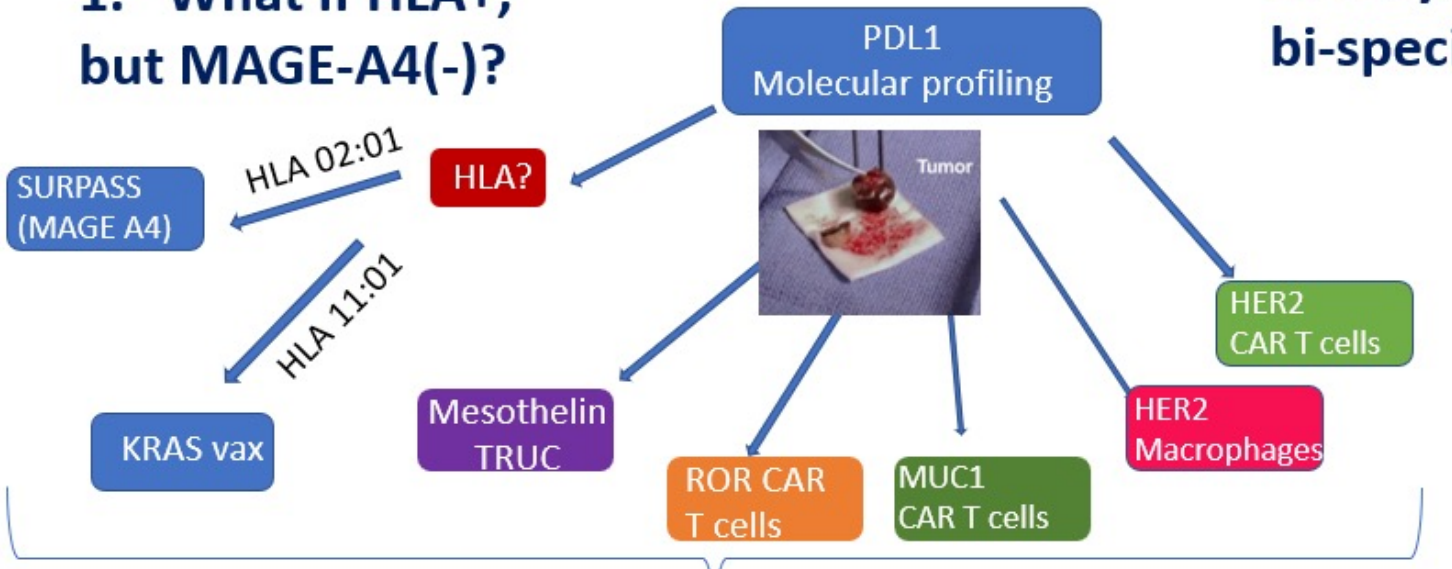
ES39.05: Cellular Therapy in NSCLC: Challenges and Opportunities

Melissa L. Johnson
Sarah Cannon Research Institute
USA

Identifying pts for Cell Therapy is Tough

1. What if HLA+, but MAGE-A4(-)?

3. Maybe I'll just pick a bi-specific instead....



2. Which Tumor Antigen to Target If You Can't Target Them All?

Conclusions

- The immunobiology of NSCLC is becoming better understood and probably unique to each tumor – genomic profiling and labs may inform chance of response
- The results of large trials anti-LAG3, TIGIT, and multitargeted TKIs are awaited
- Vaccine strategies, cellular therapy with TILs, and transgenic T cell therapy may help overcome immunologically “cold” tumors