

Predictive markers for treatment with Immune checkpoint inhibitors - PD-L1 et al -

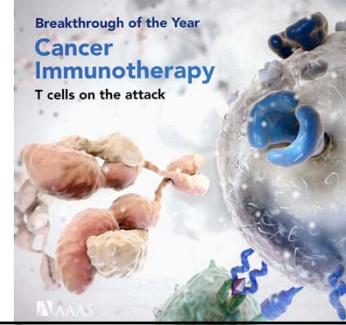
Lukas Bubendorf
Pathology



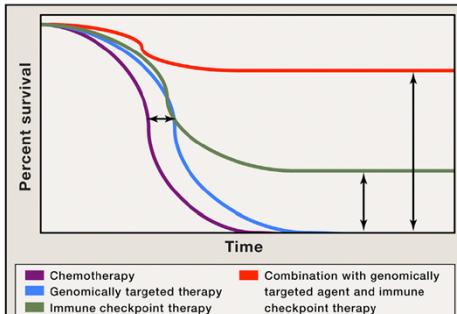
Science
26 December 2013 | 342

Breakthrough of the Year Cancer Immunotherapy

T cells on the attack

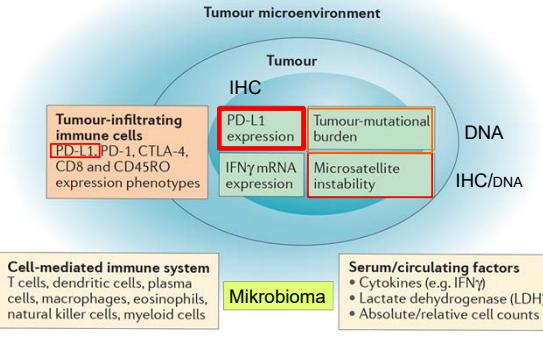


Improved overall survival as a result of combination therapy



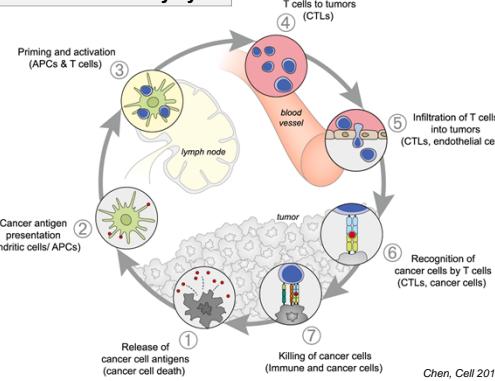
Sharma & Ellison, Cell 2015

Predictive biomarkers for the treatment with immune checkpoint inhibitors (ICI)



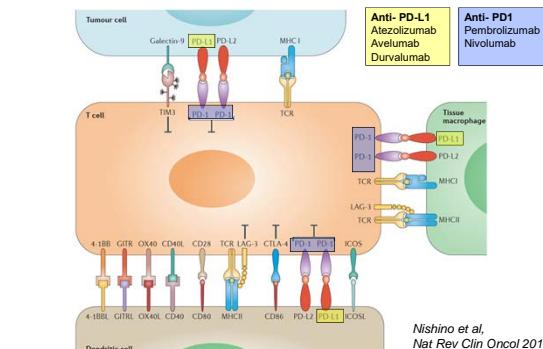
Nishino et al, Nat Rev Clin Oncol 2017

The cancer immunity cycle

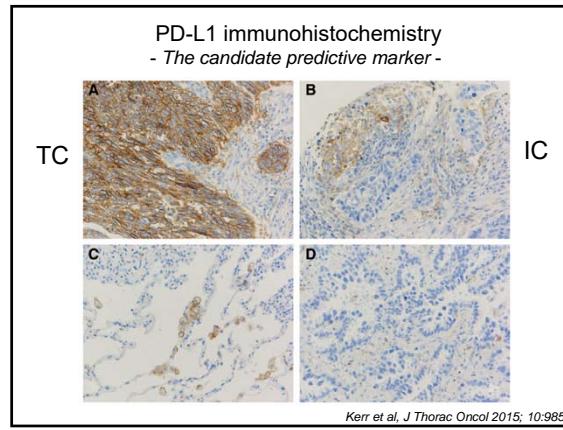
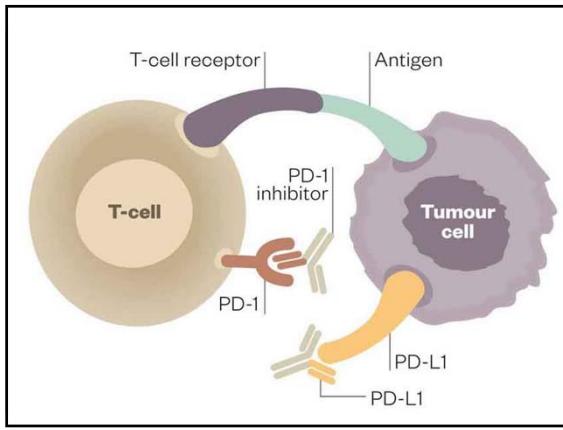


Chen, Cell 2013

Immune-checkpoint molecules regulating anti-tumor immune response



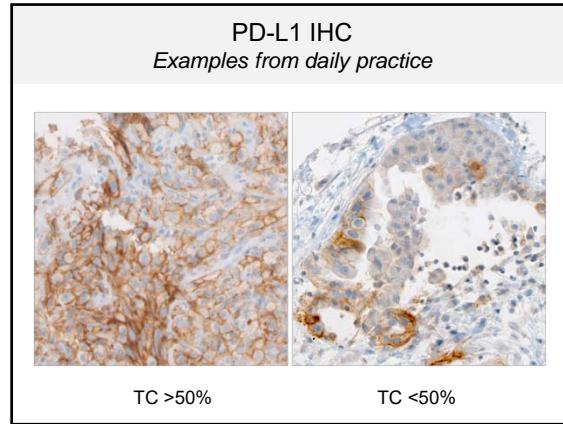
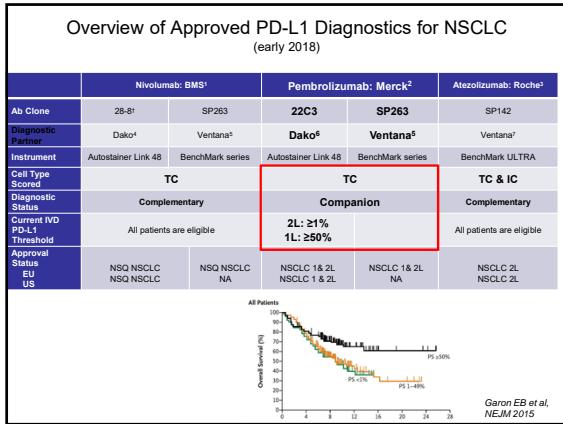
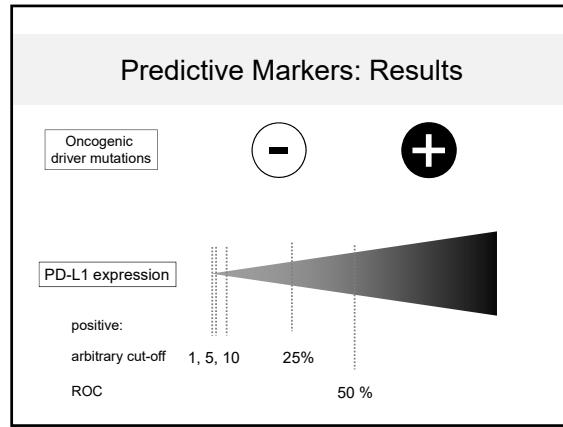
Nishino et al,
Nat Rev Clin Oncol 2017

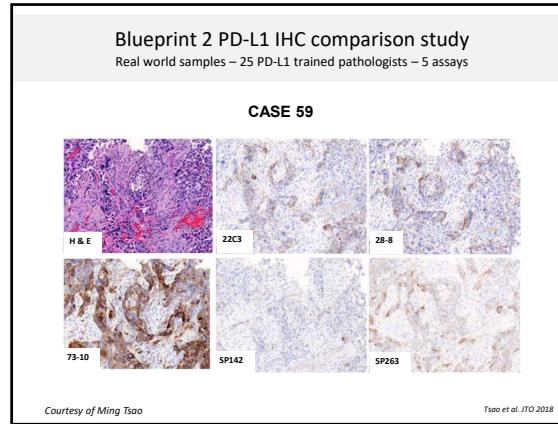
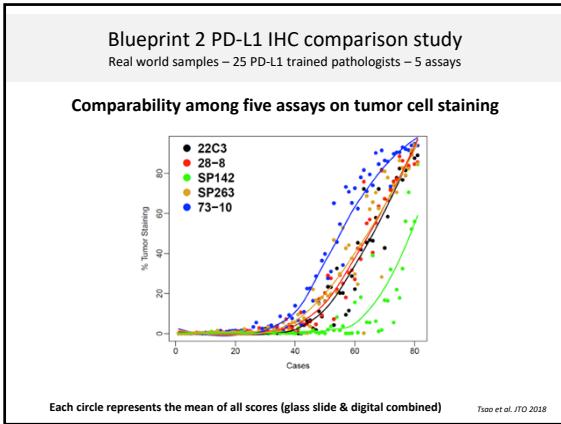
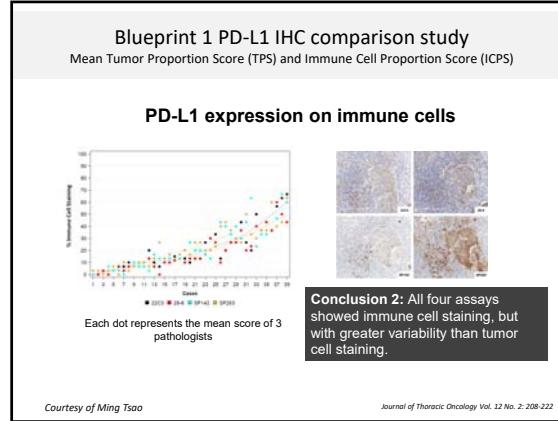
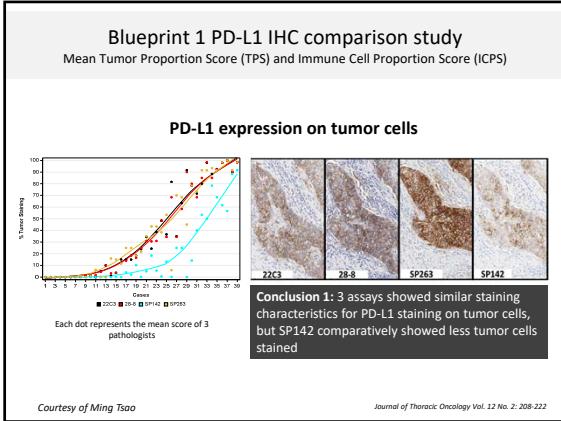
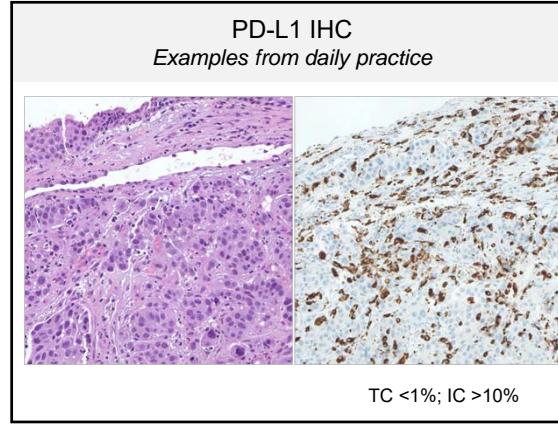
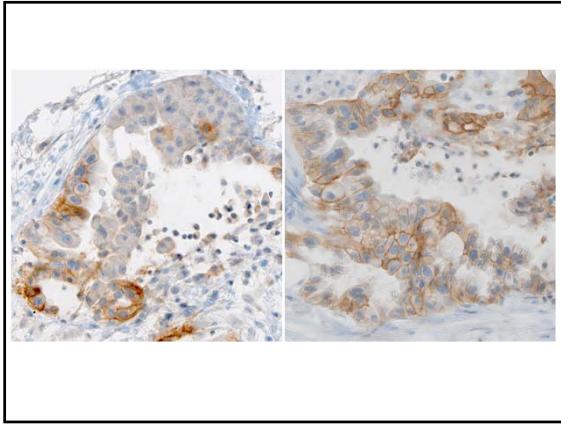


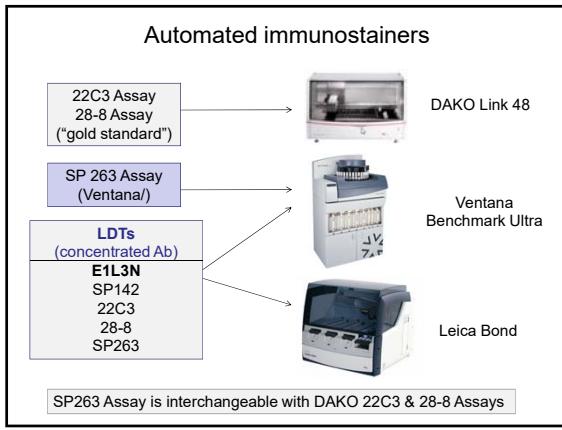
The dilemma of predictive PD-L1 IHC
5 drugs, each with its own PD-L1 IHC assay

Drug	Antibody	Platform	TC	IC
Nivolumab	28-8 clone	Dako	+	
Pembrolizumab	22C3 clone	Dako	+	
Atezolizumab	SP142 clone	Ventana	+	+
Durvalumab	SP263 clone	Ventana	+	
Avelumab	73-10 clone	Dako	+	

- 5 antibodies
- 2 immunostainer platforms
- Different cut-offs (<1%, 5%, 10%, 25%, 50%)
- Different scoring: Tumor cells +/- Immune cells



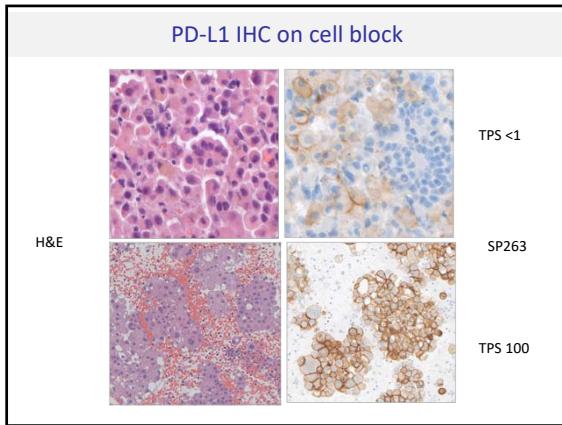




PD-L1 TC Immunohistochemistry
Cell block vs. histology

Publication	n	Assay	Platform	Concordance TPS ≥ 50%
Skov BG	86	28-8 pharmDx 22C3 pharmDx	ASL48 (Dako)	90% 94%
Heymann J	23	22C3 pharmDx	BM U (Ventana)	91%
Russel E	41	E1L3N LDT	ASL48 (Dako)	84% (same site)
Ilie M	70	22C3 LDTs	ASL48 (Dako) BM U (Ventana)	96%
Noll B	38	22C3 pharmDx	ASL48 (Dako)	89%

Skov & Skov, *Appl Immunohistochem Mol Morphol* 2017;25:452
Heymann JJ et al, *CCP* 2017
Ilie M et al, *CCP* 2018
Russel-Goldman E et al, *CCP* 2018



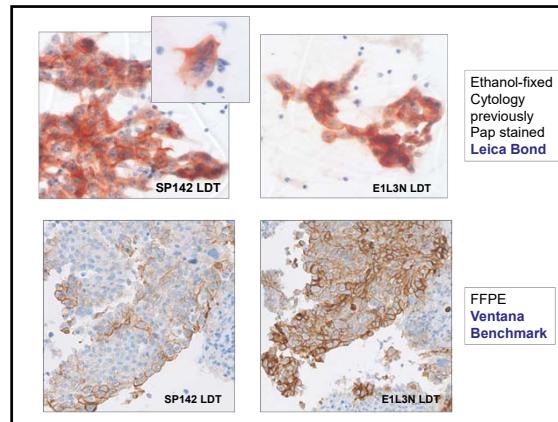
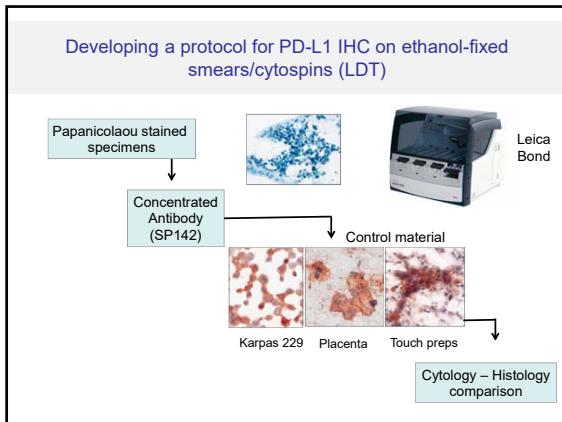
Cancer Cytopathology 2018

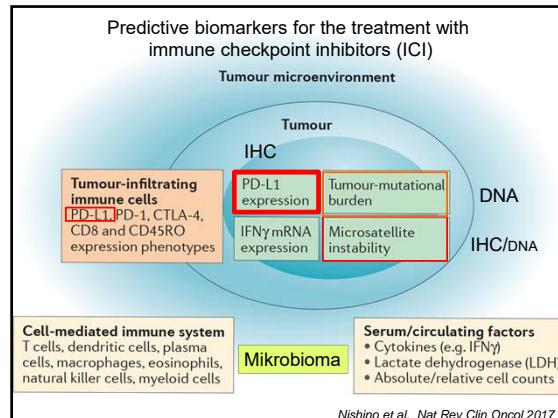
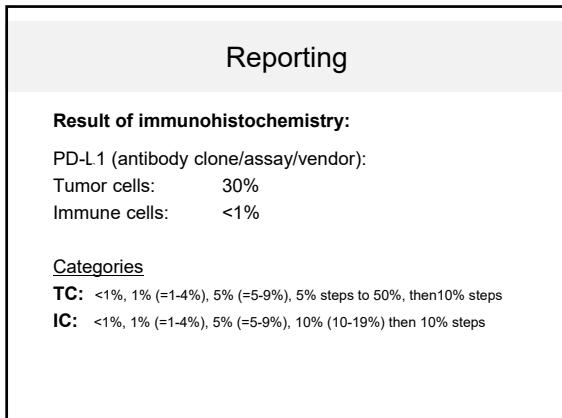
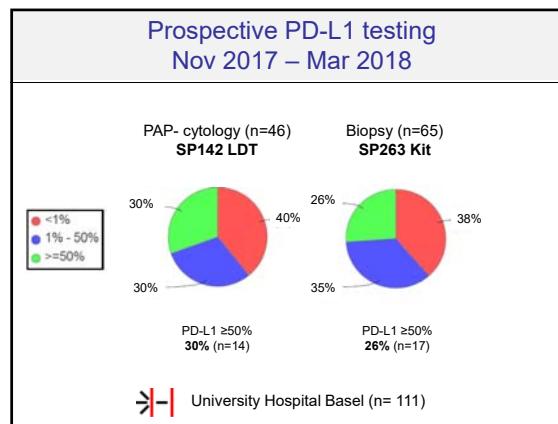
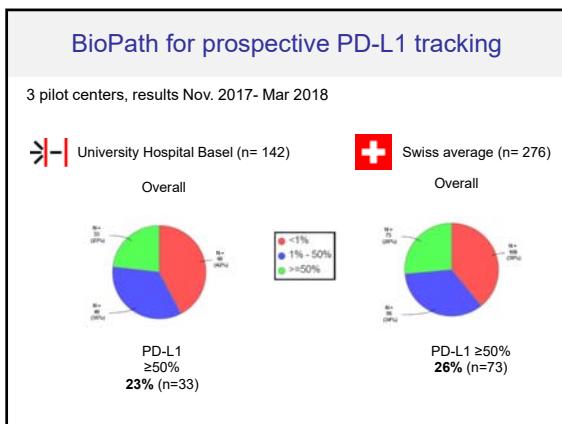
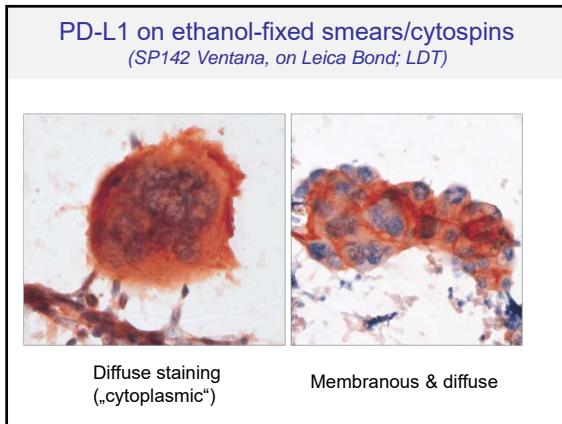
Programmed Death Ligand 1 Testing in Non-Small Cell Lung Carcinoma Cytology Cell Block and Aspirate Smear

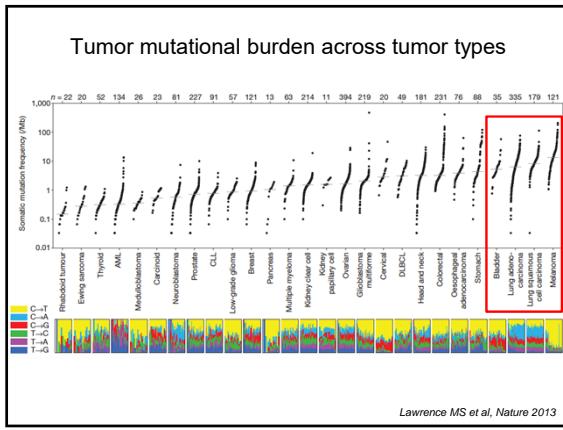
Preparations

Bryce Noll, MD; Wei-Lien Wang, MD; Yun Gong, MD; Jun Zhao, MD; Neda Kalhor, MD; Victor Prieto, MD, PhD; Gregg Staerkel, MD; and Sinchita Roy-Chowdhuri, MD, PhD

- Retrospective PD-L1 on PAP-stained cytology & matched Bx
- 22C3 pharmDx on Dako ASL48
 - Same protocol for PAP-stained cytology and FFPE CB and Bx
- Concordance TPS ≥ 50%:
 - PAP vs biopsy: 100% (37/37; 19 with TPS≥50)
 - CB vs biopsy: 89% (34/38; 14 with TPS≥50)

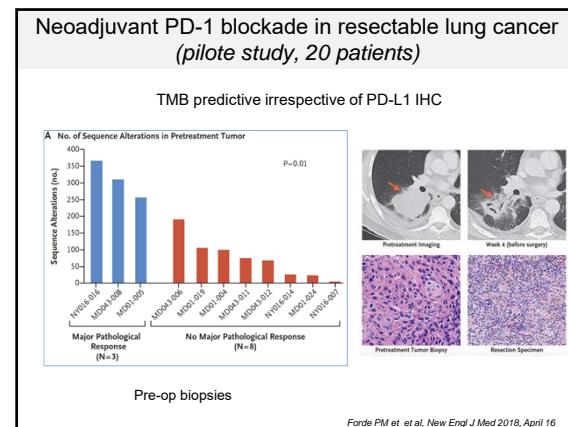
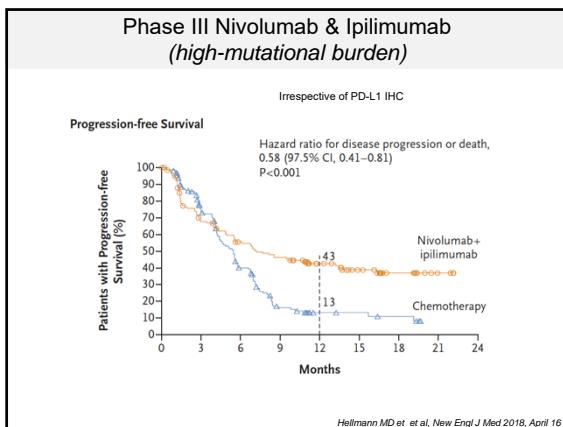
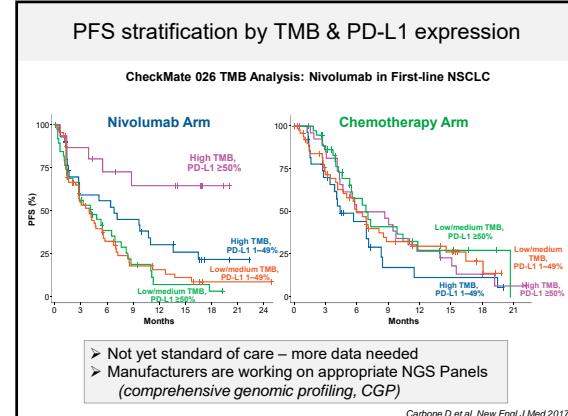
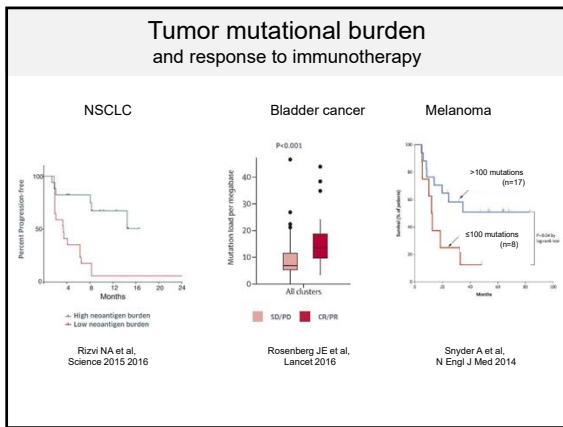






Mutational burden – the concept

- Checkpoint inhibitors are most efficient in tumors with high mutation load (i.e. melanoma & lung cancer)
- Many mutations → many neo-antigens
- Antigen recognition by immune system
- Enhanced efficacy of immune checkpoint inhibitors



Estimating tumor mutation burden using next-generation sequencing assay.

ThermoFisher

- Ion Torrent Sequencing Platform
- FFPE material
- PCR based target panel
- 409 known cancer genes
- 20ng input DNA

FOUNDATION ONE **FOUNDATION ONE Home**

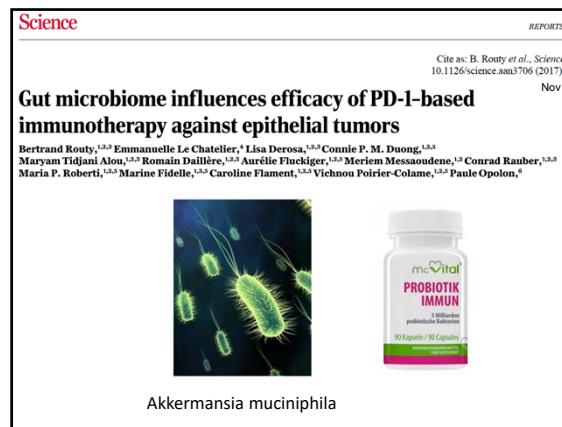
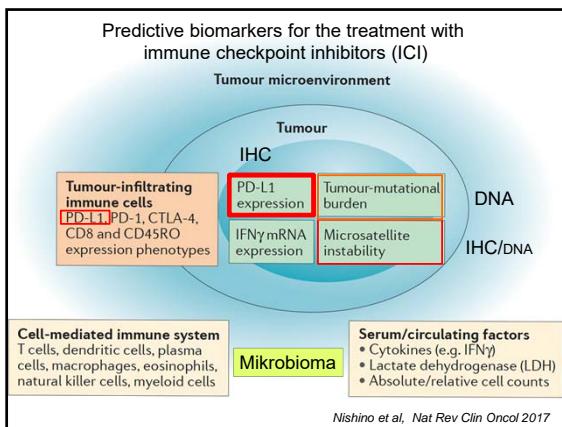
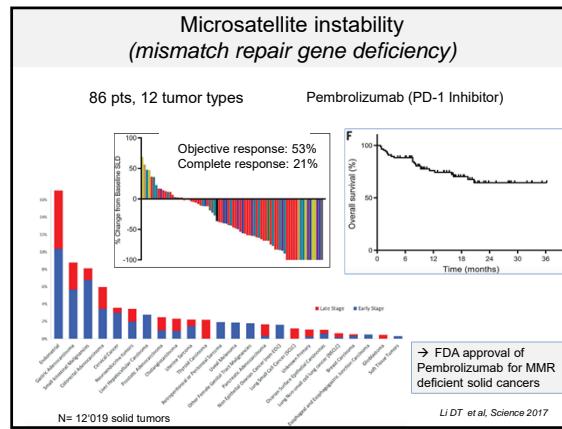
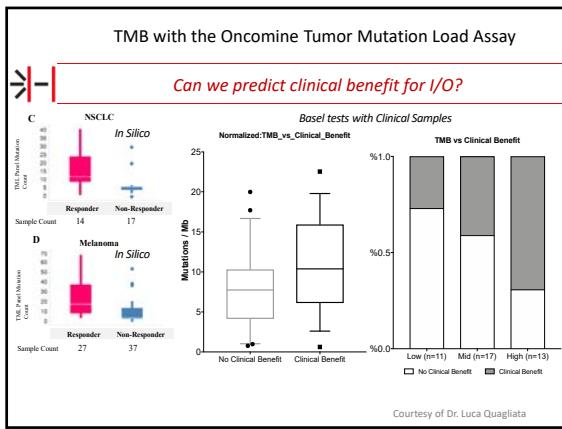
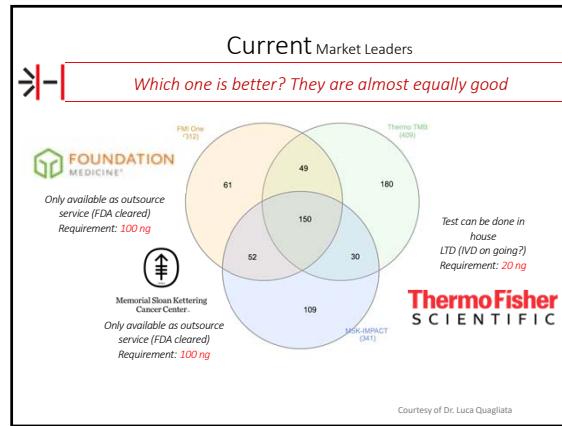
CANCER IMMUNOTHERAPY: WILL IT WORK FOR MY PATIENT?

Tumor Mutational Burden (TMB) is a validated, quantitative genomic biomarker associated with response to immunotherapy¹

Sub-category: Biomarkers and Correlative Studies from Immunotherapy Trials

Category: Developmental Therapeutics—Immunotherapy

Meeting: 2017 ASCO Annual Meeting abstr e14529



Conclusions

- PD-L1 IHC testing is reality.
- Role of the immune environment remains to be analyzed.
- Tumour mutational burden is entering routine practice.
- Mismatch repair deficiency (high TMB).
- Predictive testing also in an adjuvant and neo-adjuvant setting

