HUMANITAS UNIVERSITY

HUMANITAS CANCER CENTER

12.35 SESSIONE 8

IMMUNOTERAPIA NEI TUMORI TRIPLO- NEGATIVI

Biomarkers predittivi nel carcinoma mammario metastatico

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ENETS

ESMO Designated Centers of Integrated Oncology and Palliative Care

OECI COMPREHENSIVE Cancer Centre

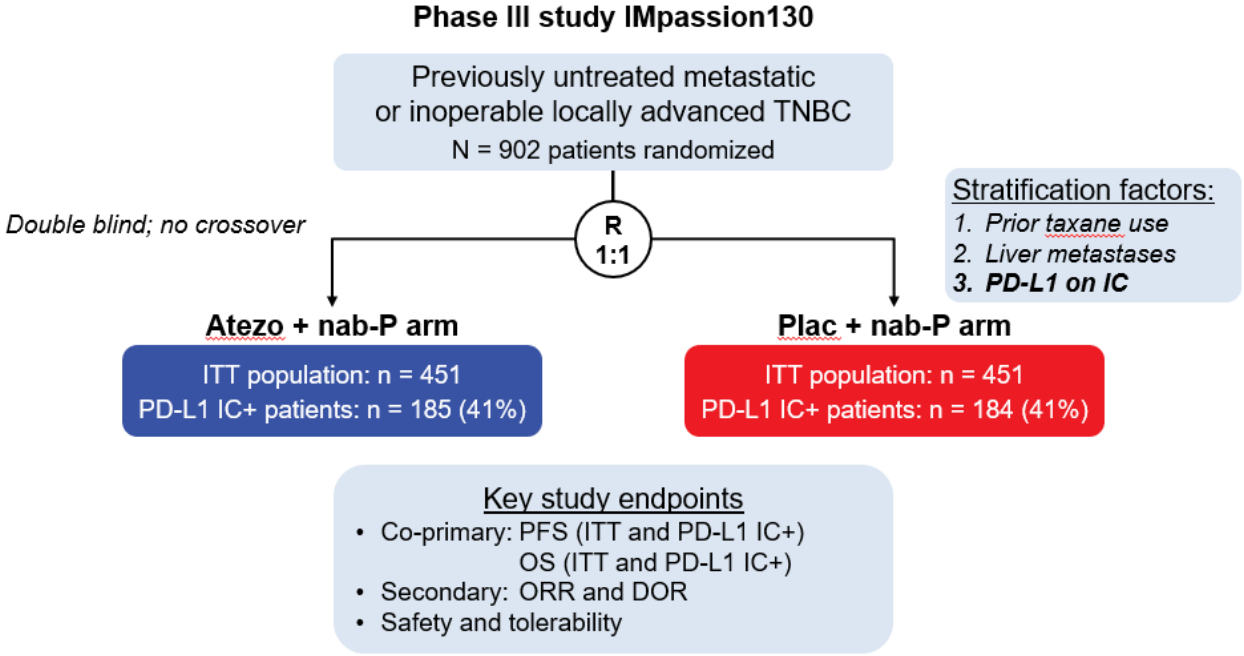
Disclosure information

Advisory board: Kyowa Kirin

Editorial board: Novartis

Consultant: EISAI

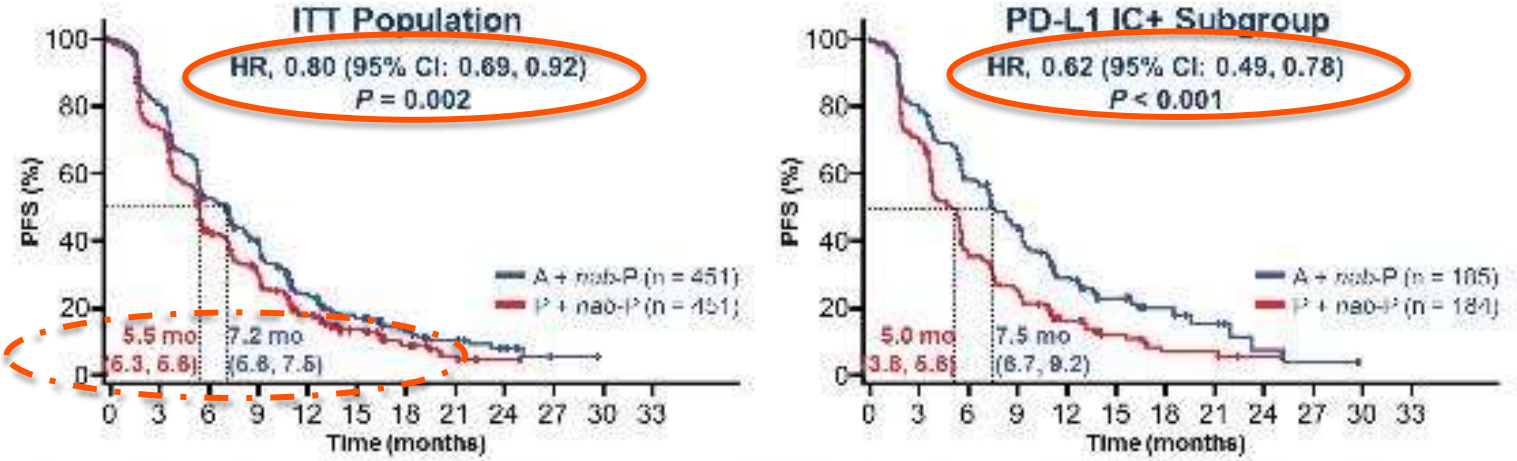
IMpassion130



- Pre-specified hierarchical testing of OS in ITT and, if significant, in PD-L1 IC+ patients
- In both treatment arms, 41% of patients were PD-L1 IC+

IMpassion130: primary PFS analysis

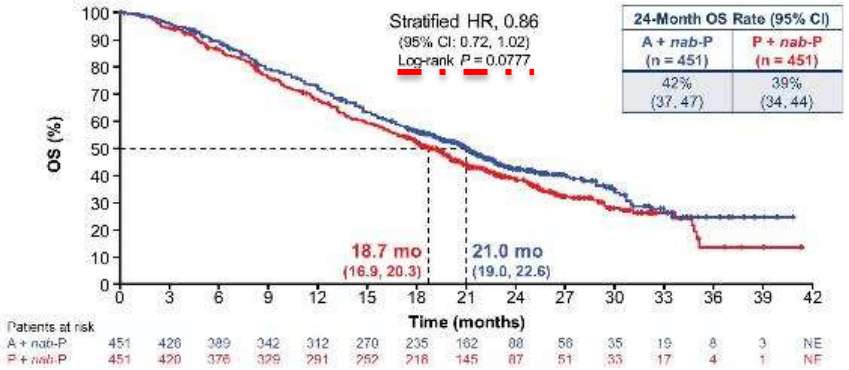
Primary PFS Analysis in the ITT and PD-L1 IC+ Subgroup



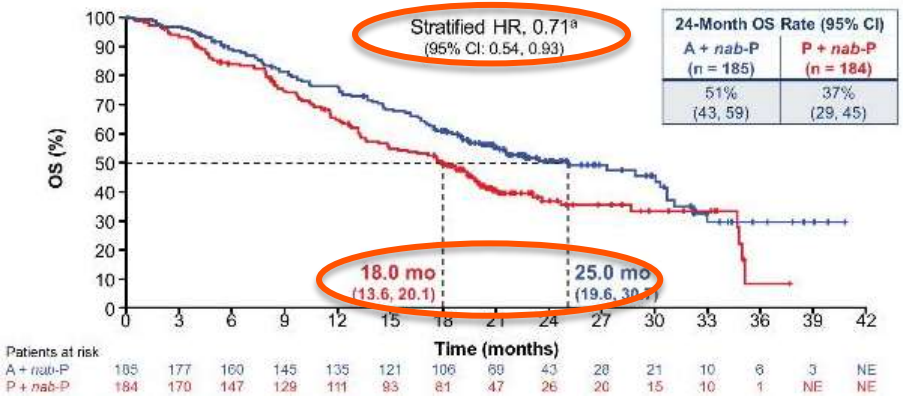
- PFS benefit driven by PD-L1 IC+ patients, as a treatment effect was not observed in PD-L1 IC− patients[1]
- Based on these data,[2] atezolizumab + *nab*-paclitaxel received accelerated approval by the FDA[3] and is recommended for patients with PD-L1 IC+ mTNBC in the NCCN[1] and AGO[5] guidelines

IMpassion130: second interim OS analysis

OS in ITT Population



OS in PD-L1+ Population

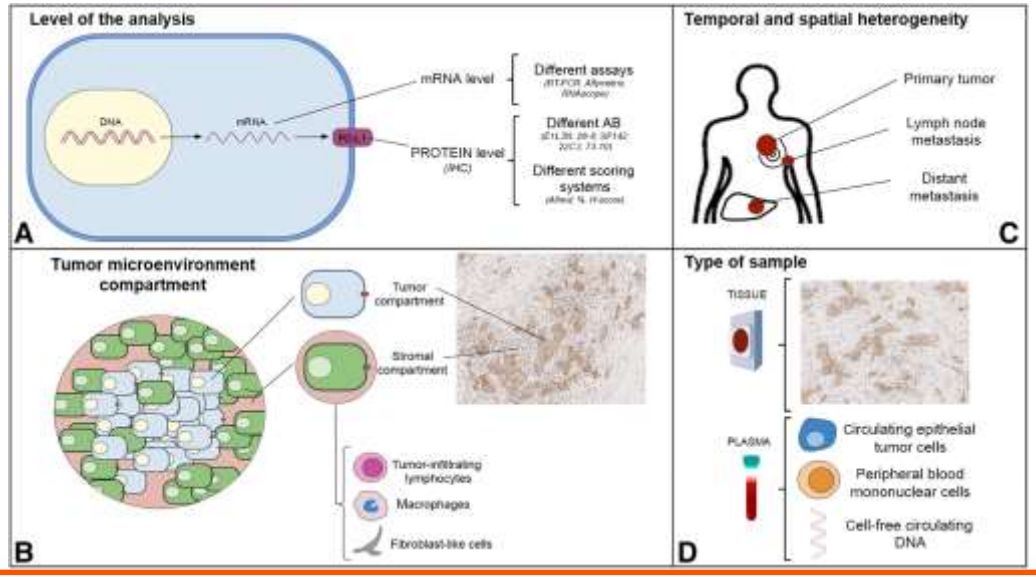


PD-L1 testing in breast cancer

The Oncologist®

Breast Cancer

Programmed Cell Death Ligand 1 in Breast Cancer: Technical Aspects, Prognostic Implications, and Predictive Value

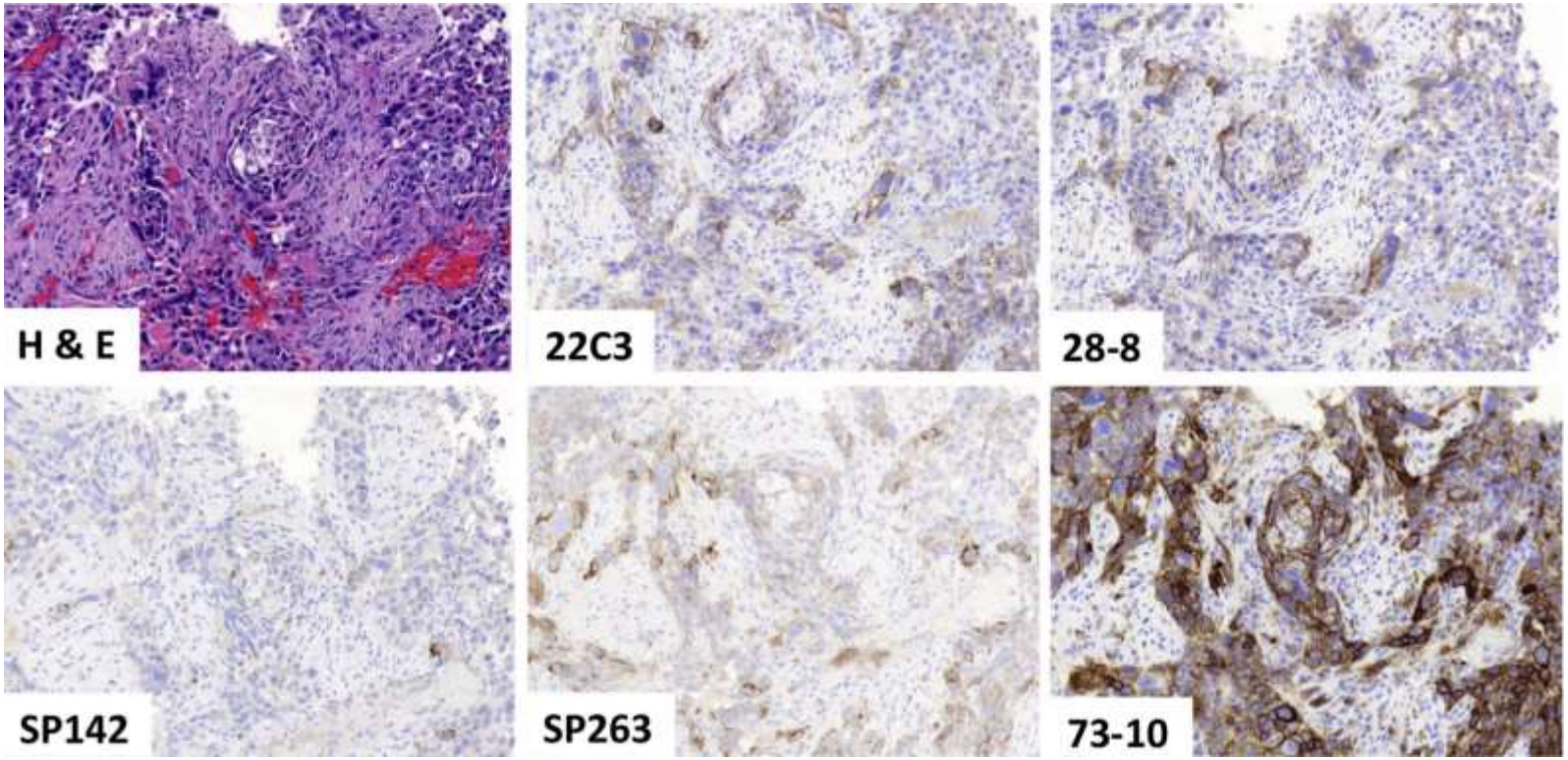


IMpassion130: biomarkers of clinical benefit

Expression of PD-L1 on tumor-infiltrating immune cells (IC) was predictive of benefit with atezolizumab plus *nab*-paclitaxel

- PD-L1 expression on IC was evaluated using the VENTANA PD-L1 SP142 IHC assay with a ≥ 1% cutoff
- The SP142 assay has been clinically validated and FDA-approved to identify patients with mTNBC for treatment with atezolizumab+ nab-paclitaxel
- Dako 22C3 and VENTANA SP263 are 2 other commercially available PD-L1 IHC assays approved for non-TNBC indications

PDL1 staining: five assays



BARCELONA 2019 ESMO congress

Performance of PD-L1 immunohistochemistry assays in unresectable locally advanced or metastatic triple-negative breast cancer: post hoc analysis of IMpassion130

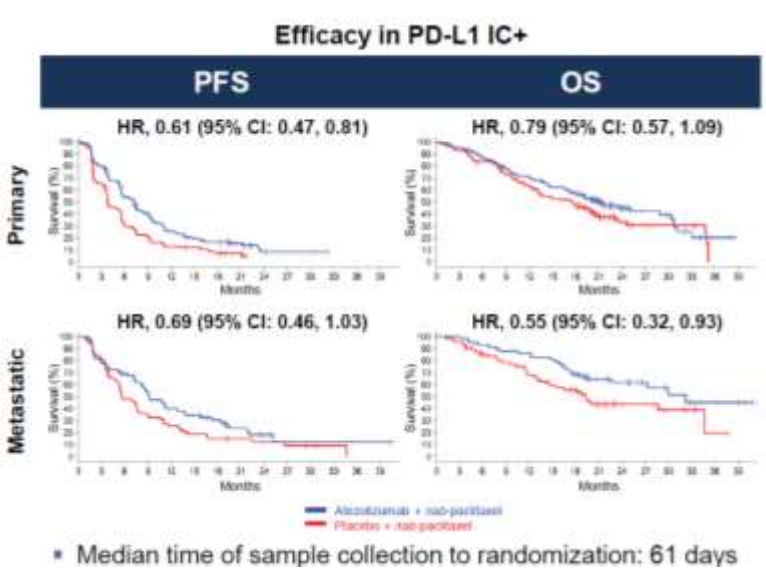
Hope S. Rugo,[1] Sherene Loi,[2] Sylvia Adams,[3] Peter Schmid,[4] Andreas Schneeweiss,[5] Carlos H. Barrios,[6] Hiroji Iwata,[7] Véronique Diéras,[8] Eric P. Winer,[9] Mark M. Kockx,[10] Dieter Peeters,[10] Stephen Y. Chui,[11] Jennifer C. Lin,[11] Anh Nguyen Duc,[11] Giuseppe Viale,[12] Luciana Molinero,[11] Leisha A. Emens[13]

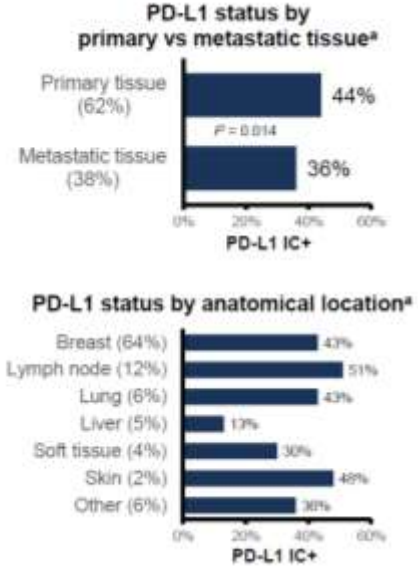
[1]University of California San Francisco Comprehensive Cancer Center, San Francisco, CA, USA; [2]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [3]NYU Langone Medical Center, New York, NY, USA; [4]Barts Cancer Institute, Queen Mary University London, London, UK; [5]University Hospital and German Cancer Research Center Heidelberg, Heidelberg, Germany; [6]Centro de Pesquisa Clínica, HSL, PUCRS, Porto Alegre, Brazil; [7]Aichi Cancer Center Hospital, Nagoya, Japan; [8]Department of Medical Oncology, Centre Eugène Marquis, Rennes, France; [9]Dana-Farber Cancer Institute, Boston, MA, USA; [10]HistoGeneX NV, Antwerp, Belgium; [11]Genentech, Inc., South San Francisco, CA, USA; [12]University of Milan, European Institute of Oncology IRCCS, Milan, Italy; [13]University of Pittsburgh Medical Center Hillman Cancer Center, Pittsburgh, PA, USA

esmo.org

Post hoc exploratory biomarker sub-study

- Clinical activity was observed in the SP142 PD-L1 IC+ subgroup, regardless of whether the sample was from the primary tumour or metastatic tissue

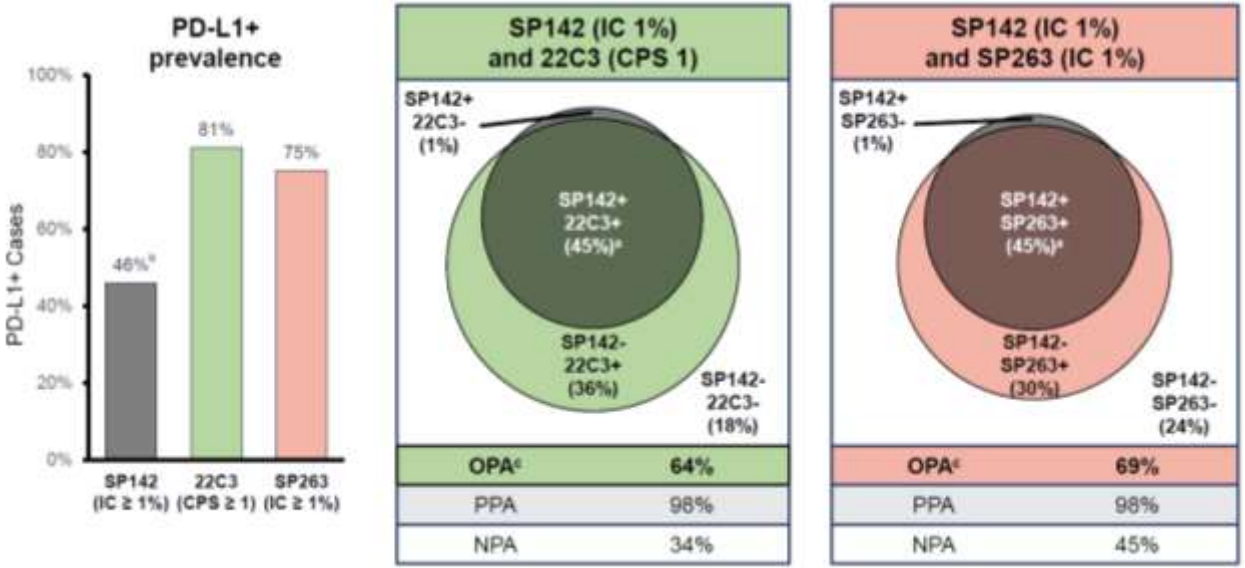




PD-L1 IHCs: prevalence and analytical concordance

The analytical concordance was < 90% → assays not equivalent:

- 22C3 (CPS ≥ 1) and SP263 (IC ≥ 1%) PD-L1 assays identified a larger patient population of which SP142+ (IC ≥ 1%) is a subgroup

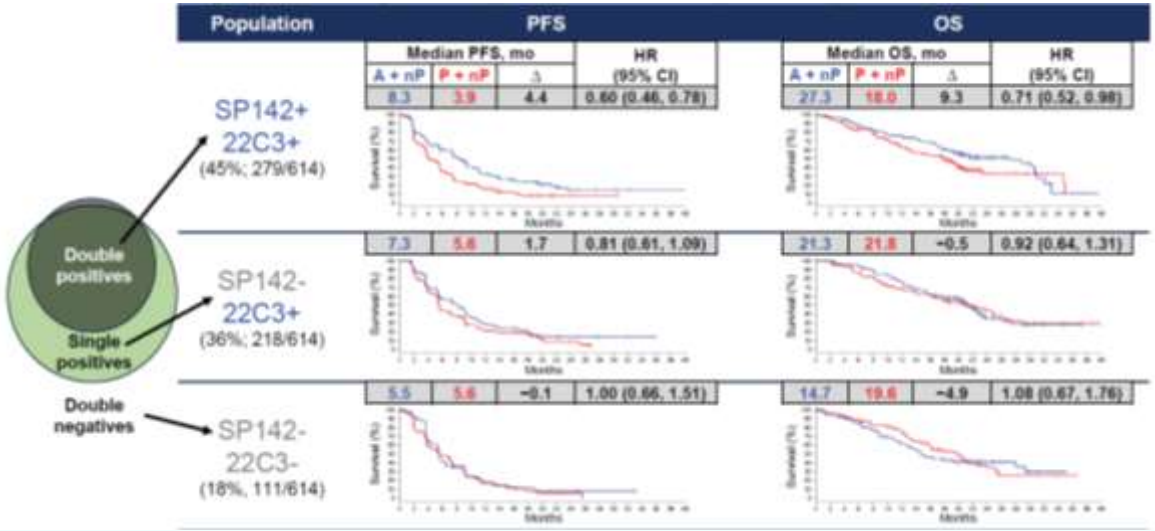


CPS, combined positive score; TC, tumour cells; IC, immune cells; Rugo HS et al, ESMO 2019

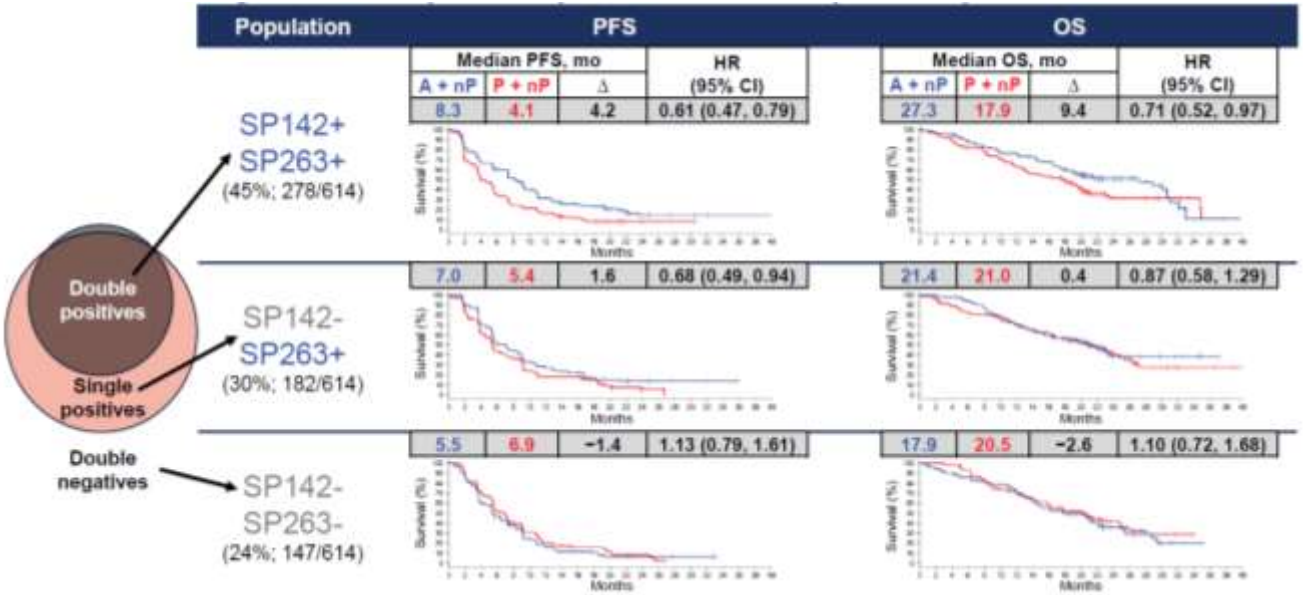
PD-L1 IHCs: clinical benefit

The clinical benefit in 22C3+ and SP263+ subgroups was driven by the SP142+ subgroup

−The SP142 assay identified patients with the smallest HR point estimates and longest median PFS and OS from atezolizumab + *nab*-paclitaxel

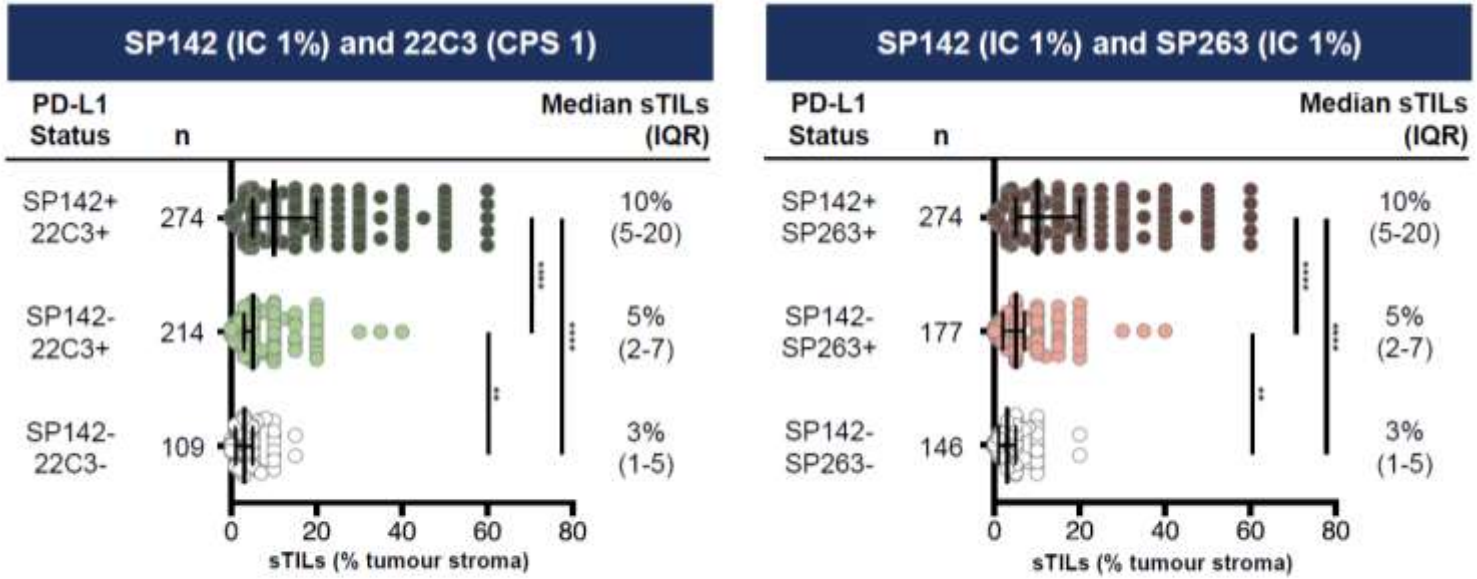


PD-L1 IHCs: clinical benefit



The SP142 assay at IC >1% cutoff is the approved diagnostic test used to identify patients with mTNBC most likely to benefit from the addition of atezolizumab to *nab*-paclitaxel

…and tumor-infiltrating CD8+ T cells?

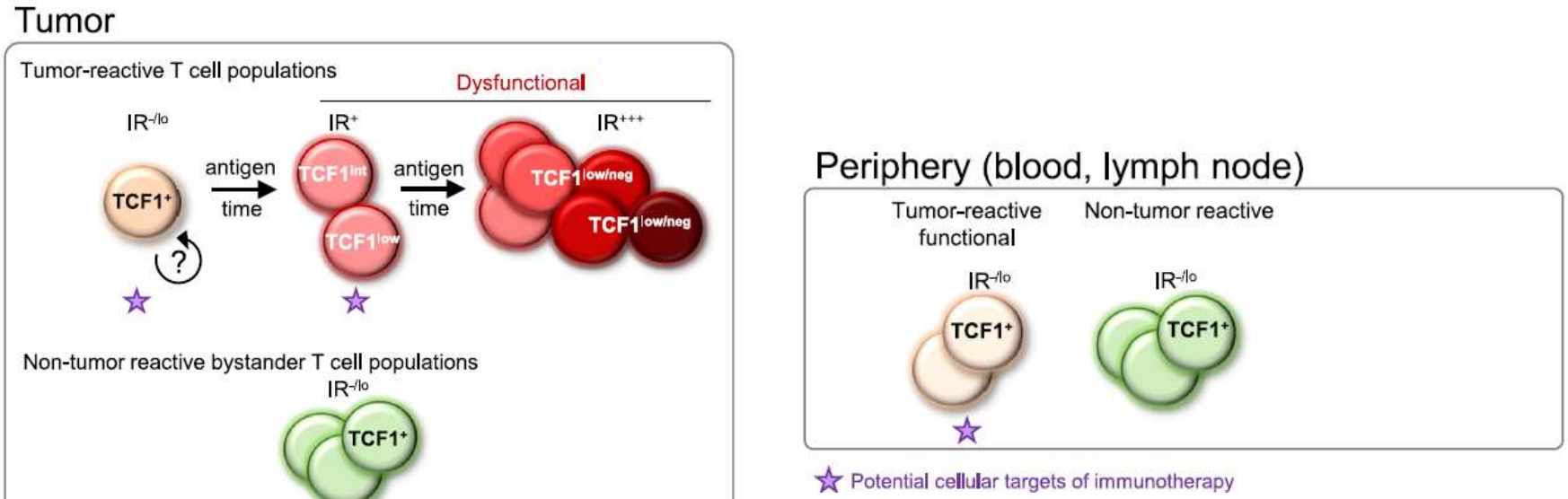


- Within the 22C3+ or SP263+ subgroups, SP142+ patients had numerically higher sTIL counts compared with SP142- patients

- TILs were predictive of ICI efficacy only in PD-L1-positive tumors

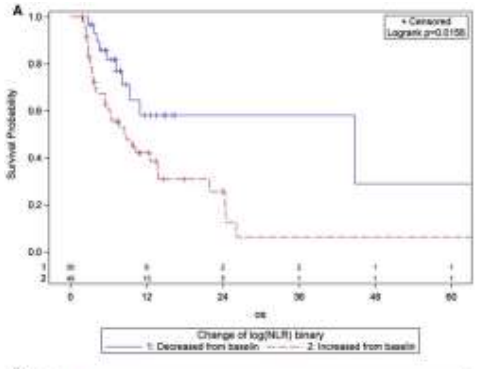
sTIL, stromal tumour-infiltrating lymphocyte.; Rugo HS et al, ESMO 2019

Heterogeneity of TILs populations

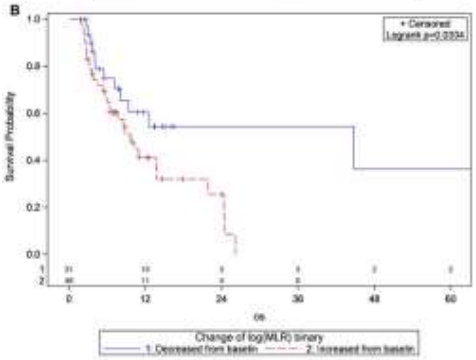


IR, inhibitory receptors; TCF, critical transcription factor

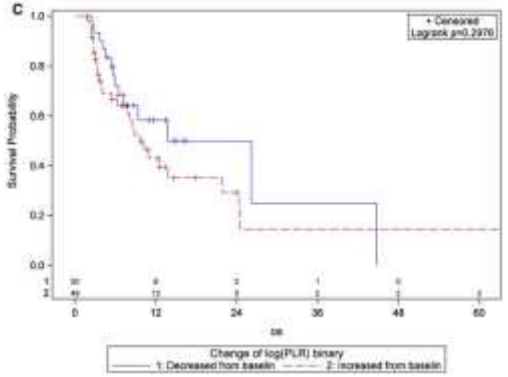
Peripheral Inflammatory Biomarkers



Neutrophil-to-lymphocyte ratio



Monocyte-to-lymphocyte ratio



Platelet-to-lymphocyte ratio

Baseline and early changes in NLR, MLR, and PLR values were strongly associated with clinical outcomes in patients who received IO-based treatment regimens on phase 1 trials.
Confirmation in a homogenous patient population treated on late-stage trials or outside of trial settings is warranted.

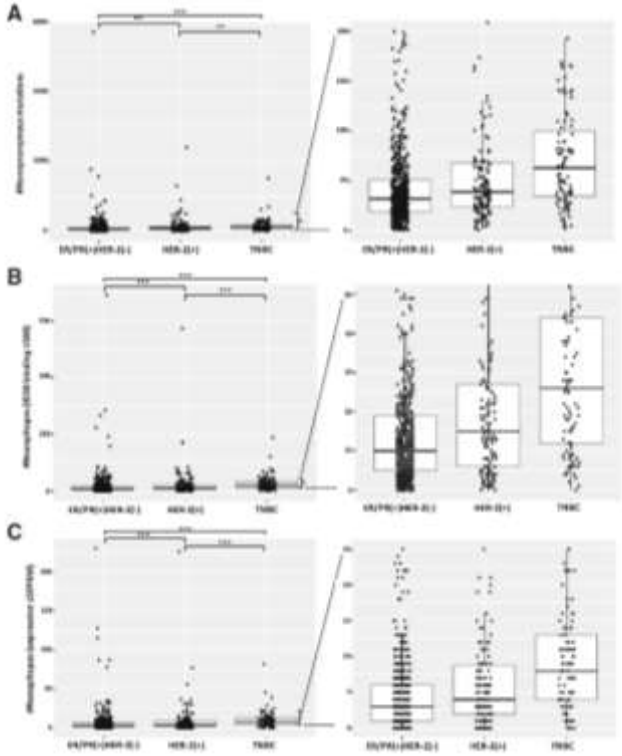
Bilen MA et al., Cancer 2019;125:127-134

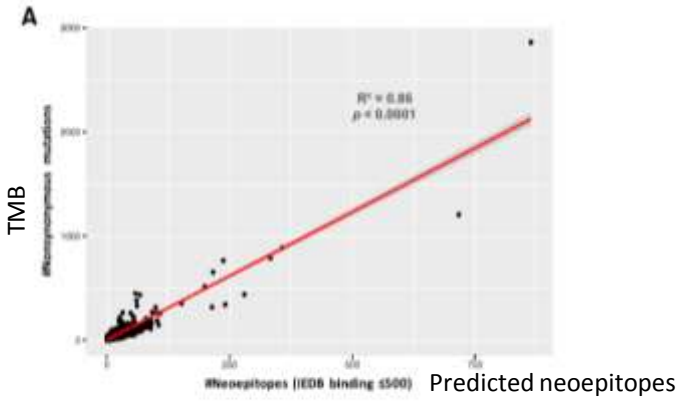
Tumor mutational burden and potential neoepitopes

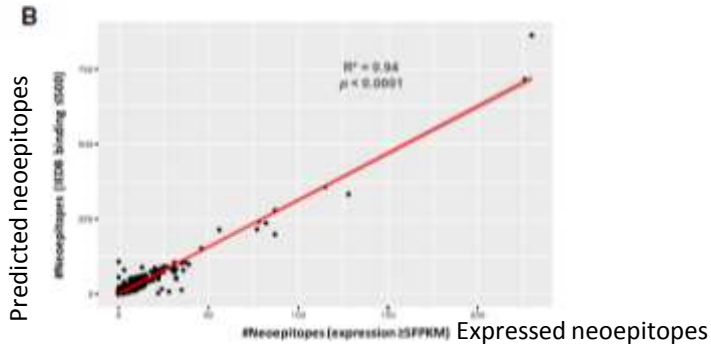
TMB

Predicted neoepitopes

Expressed neoepitopes







Narang P et al, BMC Cancer 2019;19:200

TMB and overall survival after immunotherapy

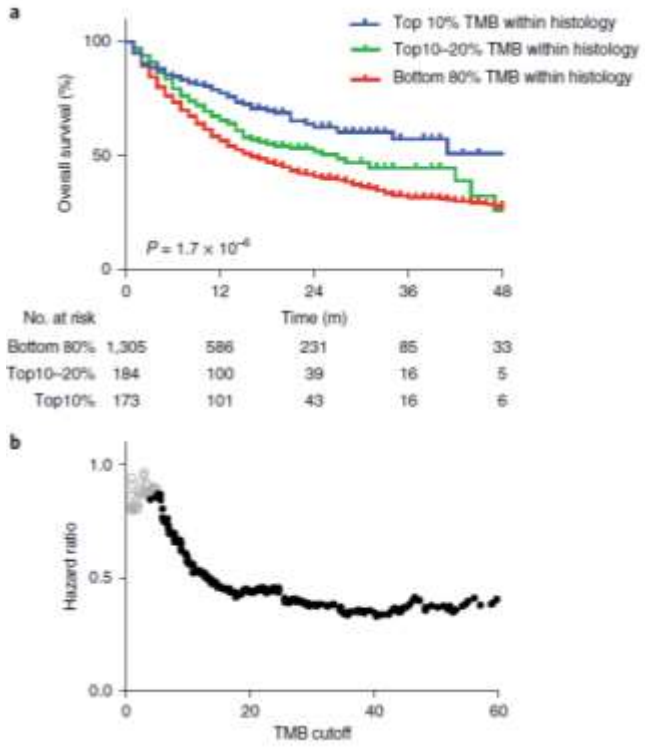
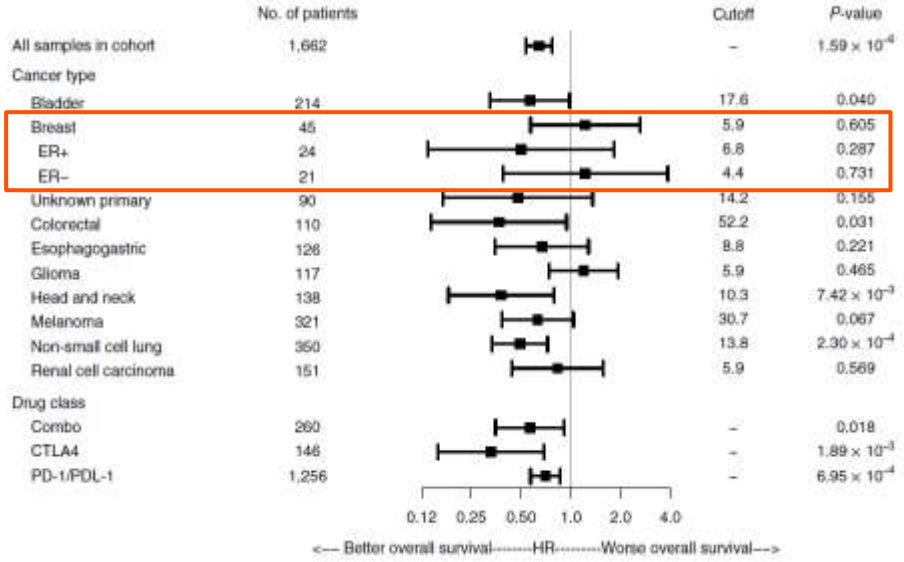


Table 1 | Multivariable analysis of factors associated with overall survival

	HR	95% CI	*P* value
Normalized mutation count			
Continuous	0.985	0.979–0.991	3.4×10^{-7}
Binary (top 20% of each histology)	0.61	0.508–0.733	1.3×10^{-7}



Samstein RM et al., Nature Genetics 2019; 51: 202-206

Multiomics Prediction of Response Rates to ICIs

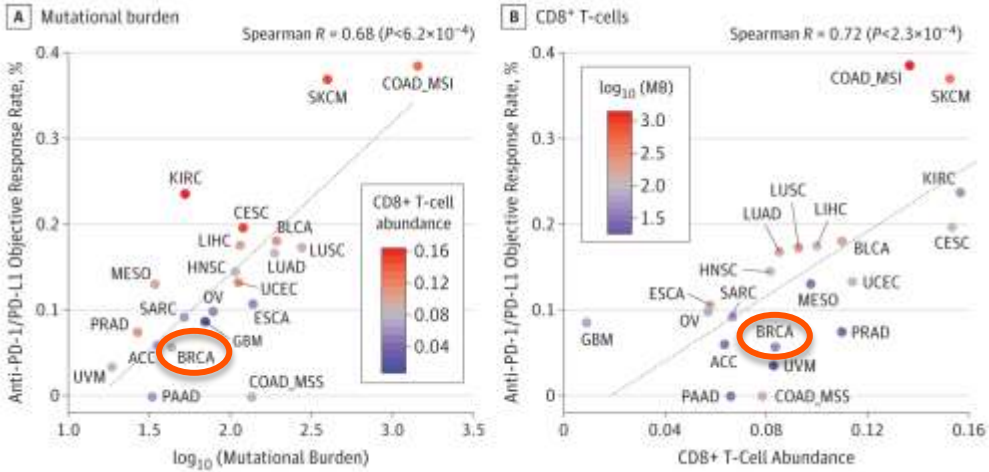
- Tumors containing comparably high mutational burden may exhibit variable responses, suggesting that **additional factors** may contribute to anti-PD-1/PD-L1 response
- Whole-exome and RNA sequencing of 7,187 patients from the publicly available Cancer Genome Atlas and the objective response rate (ORR) data of 21 cancer types obtained from a collection of clinical trials were analyzed

- Thirty-six variables of 3 distinct classes:

(1) tumor neoantigens,

(2) tumor microenvironment&inflammation,

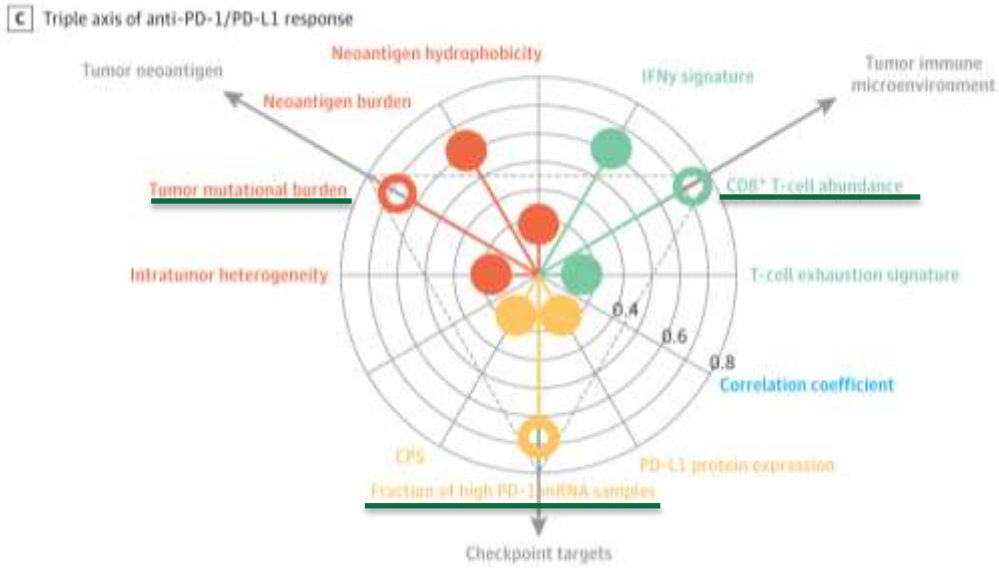
(3) checkpoint targets.



Lee JS et al., JAMA Oncol. Published online August 22, 2019. doi:10.1001/jamaoncol.2019.2311

Multiomics Prediction of Response Rates to ICIs

- Among 36 variables, **estimated CD8+ T-cell abundance** was the most predictive of the response to anti–PD-1/PD-L1 therapy across cancer types (Spearman R = 0.72; p < 2.3 × 10-4), followed by the **tumor mutational burden** (Spearman R = 0.68; p < 6.2 × 10-4), and the fraction of samples with **high PD1 gene expression** (Spearman R = 0.68; p < 6.9 × 10-4).

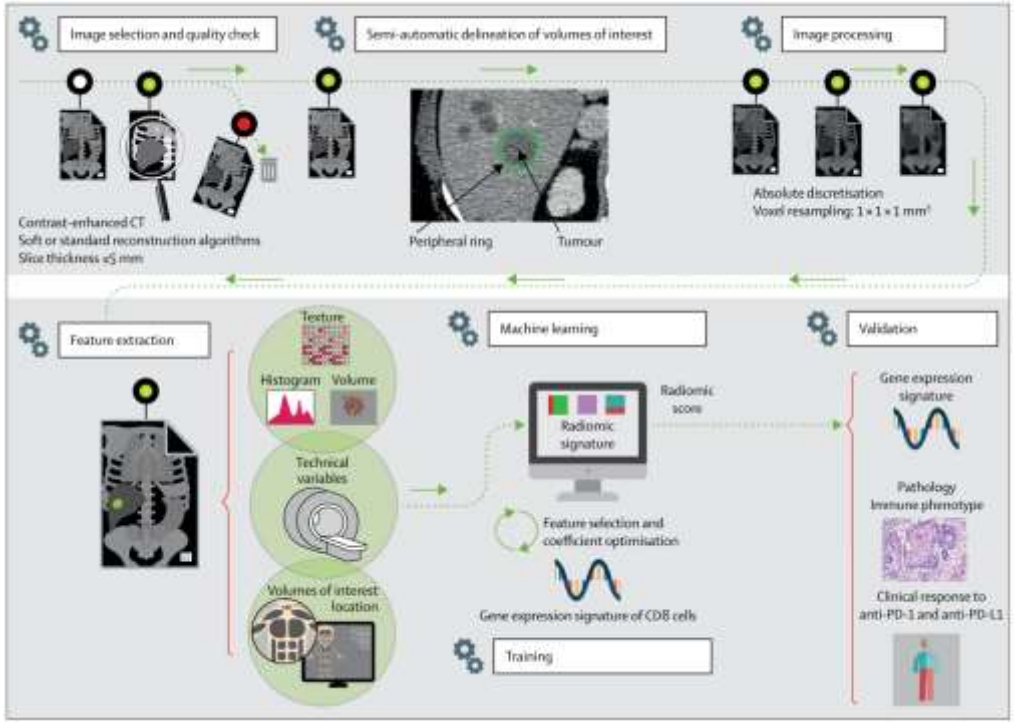


JAMA Network

Lee JS et al., JAMA Oncol. Published online August 22, 2019. doi:10.1001/jamaoncol.2019.2311

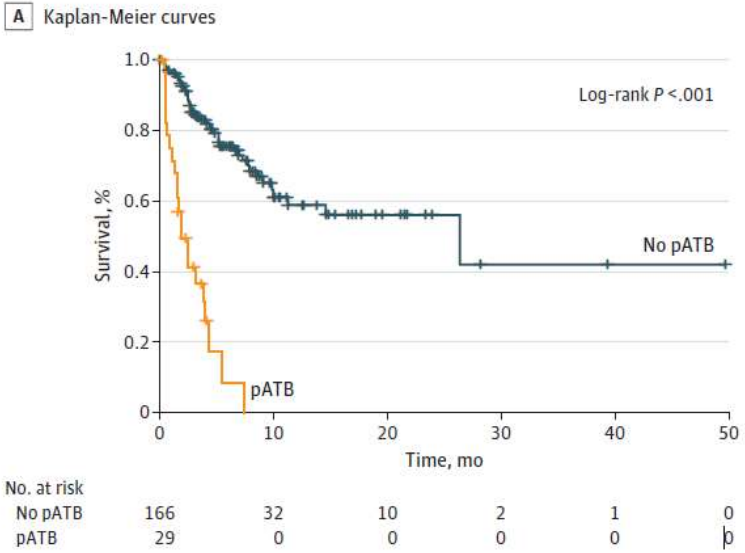
Machine learning: radiomic signature of CD8 cells

- Retrospective multicohort study of advanced solid tumors
- Aim: to develop a radiomic signature predictive of immunotherapy response by combining CT images and RNA seq data from tumor biopsies to estimate CD8 abundance
- Homogeneous and hypodense tumors and peripheral rings were associated with a high CD8 cell score
- High baseline radiomic score → higher proportion of patients responding to immunotherapy and improved OS



Sun R, et al. Lancet Oncol 2018

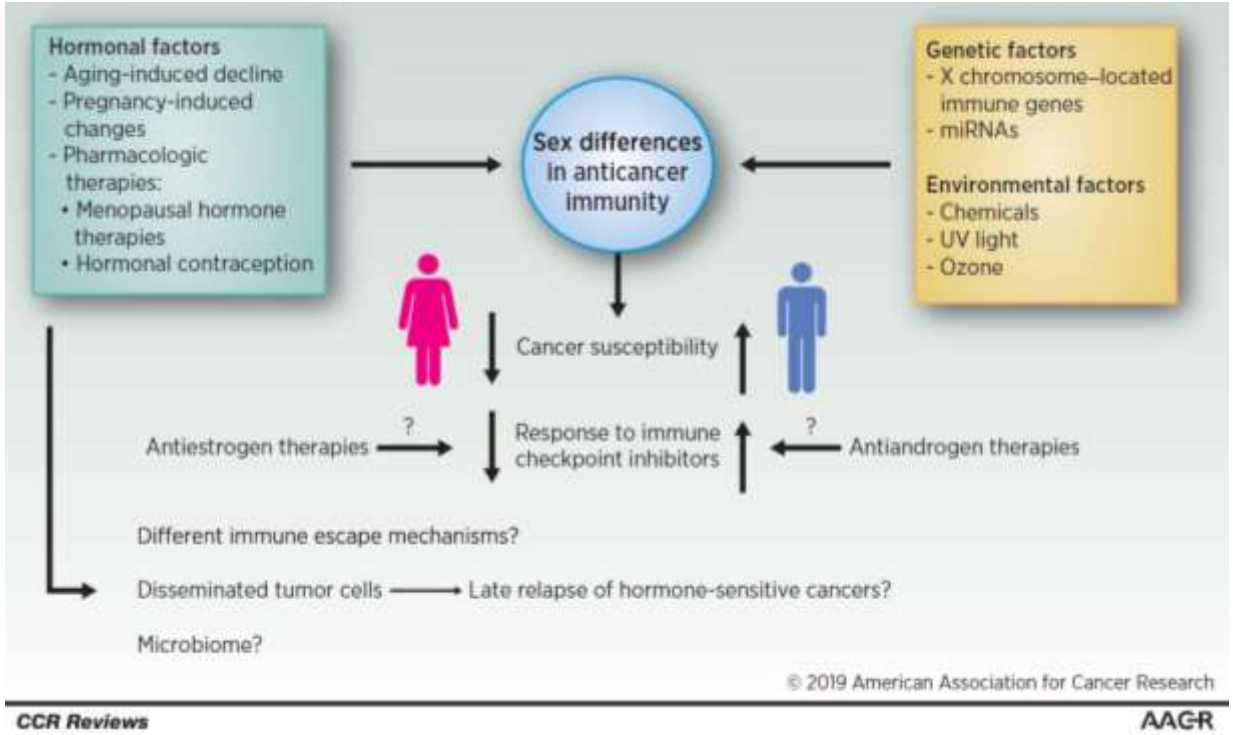
Association Between pATB Therapy and Survival and Response to ICIs



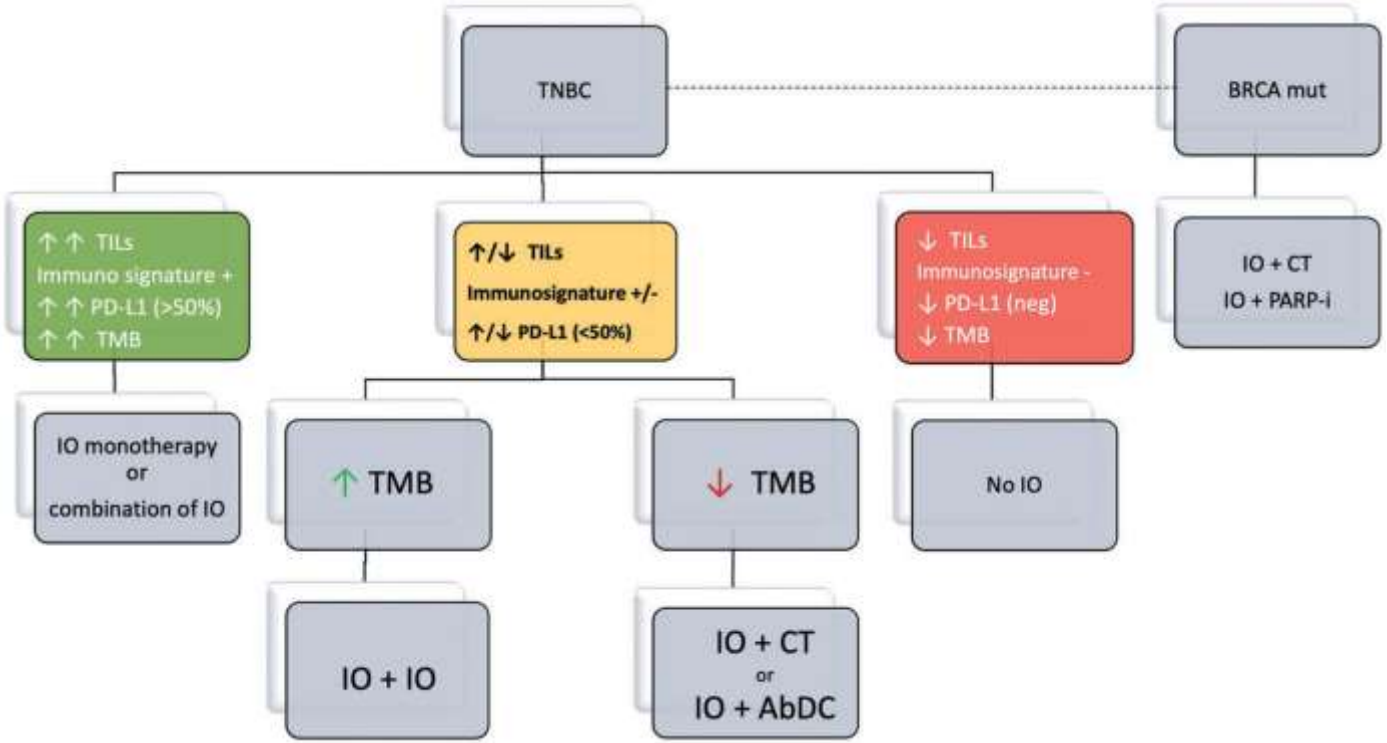
Kaplan-Meier curves illustrating the association of prior broad-spectrum antibiotic (pATB) therapy administered up to 30 days prior to immunotherapy with adverse survival in the study population (n = 196).

Pinato DJ et al, JAMA Oncology Published online September 12, 2019

Sex Hormones and Anticancer Immunity



Proposal for a precision immunotherapy trial strategy in mTNBC



Tarantino P and Curigliano G, Expert Opinion on Biological Therapy 2019;19(5):383-385

Conclusions

- PDL1 is only part of the story!
  - Multiple assays for PD-L1 (SP142, IC >1%)
- TILs
  - NLR, MLR, and PLR?
- TMB
- CD8+ T cell abundance
  - Radiomic biomarkers
- Concomitant medications
- Hormonal factors
- Integration of “omics” and clinical data to fully describe tumor behavior

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