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Immunotherapy in Breast Cancer: Biomarkers and Correlative Studies

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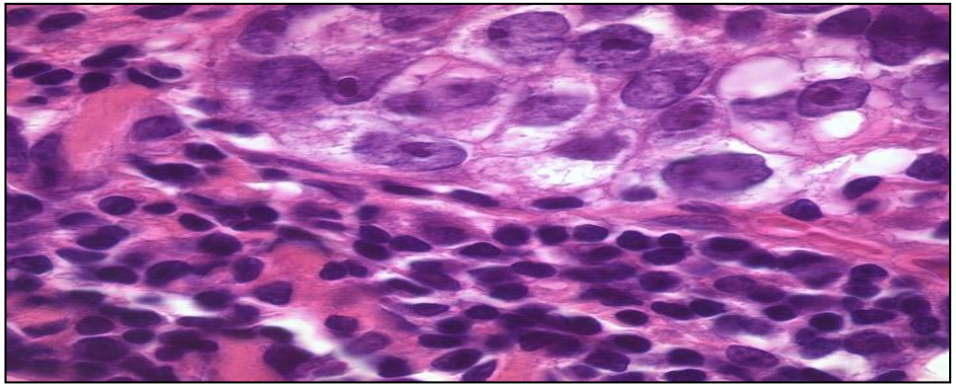
DISCLOSURE SLIDE

- Dr Francis
- Honoraria: AstraZeneca, Novartis
- Travel for lecture: Pfizer

Breast Cancer Immunotherapy: Biomarkers

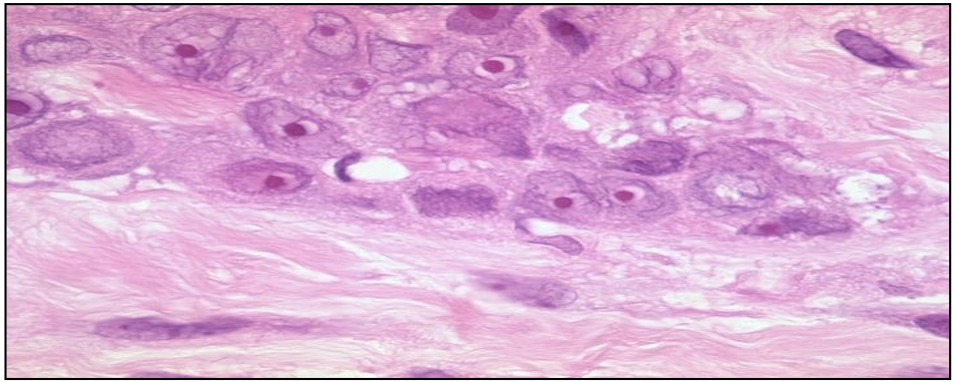
Biomarker examples from Tumour Biopsies
TILs Tumor Infiltrating Lymphocytes
PD-L1 Programmed Death-Ligand 1
MSI-H / **dMMR** Microsatellite Instability High / Mismatch Repair deficient
TMB Tumor Mutational Burden
CD8+ T cells (cytolytic)

Immune Landscape (pre-existing host immunity) Variable in Breast Cancers



High TILs

Tumor-infiltrating lymphocytes TILs in tumor stroma



No TILs

Which Breast Cancer Treatments use the Immune System to attack cancer cells ?

- Immune checkpoint inhibitors (PD-1 and PD-L1 inhibitors)
- Chemotherapy agents cause direct cell death but also engage the immune system to eradicate tumor cells. Dying cells release antigens that activate immune system.
- Trastuzumab blocks HER2 signalling but innate and adaptive immunity are also crucial for response

Galluzzi et al, Nat Rev Drug Discovery 2012

Park et al, Cancer Cell 2010

TILs Tumor Infiltrating Lymphocytes in Breast Cancer - a logical Immunotherapy Biomarker

- TILs are predominantly activated T cells
- TILs are evidence of baseline immunity
- These lymphocytes are trying to fight the cancer
- Quantity of TILs is important

TILs Tumor Infiltrating Lymphocytes in Breast Cancer - what do we know ?

- **Higher TILs strong favourable prognostic marker early stage TNBC treated adjuvant chemotherapy**

Loi et al, J Clin Oncol 2019

- **Higher TILs - predictive marker for neoadjuvant pCR and results in survival advantage in TNBC and HER2+**

Denkert et al, Lancet Oncol 2018

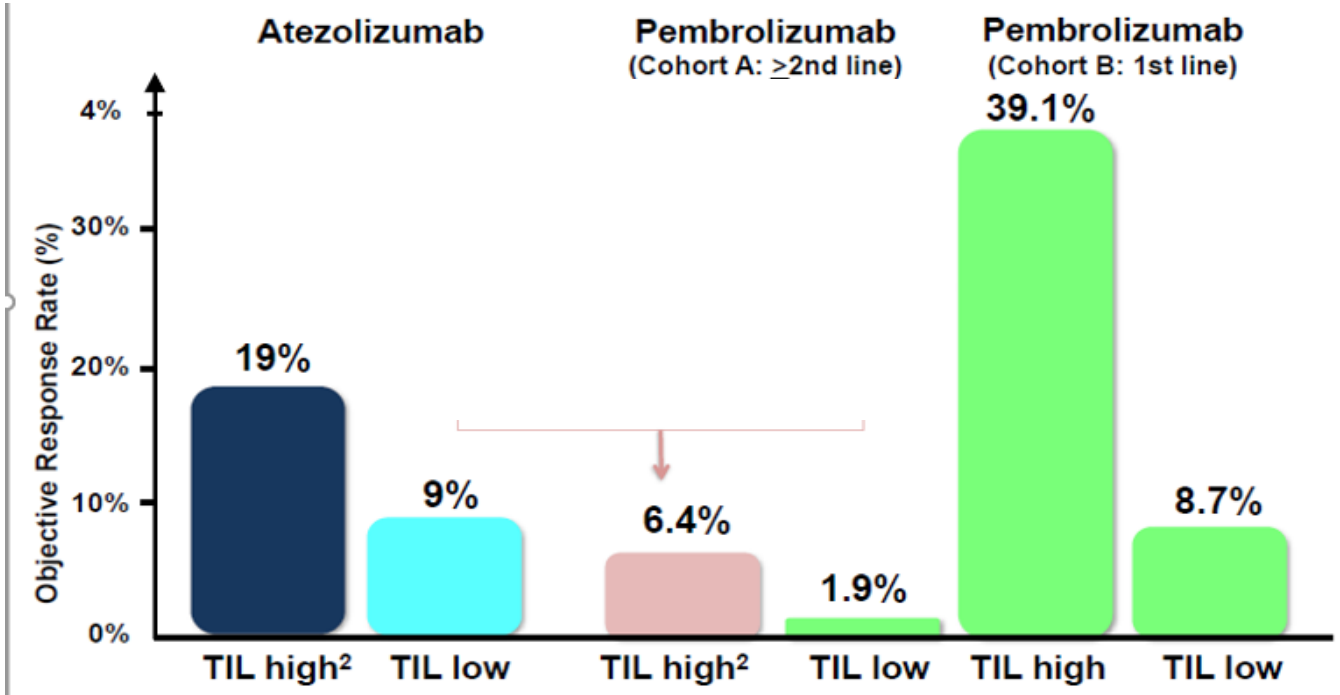
- **Higher TILs -improved overall survival in HER2+ MBC treated with chemo + trastuzumab + pertuzumab (Cleopatra trial)**

Luen et al, Lancet Oncol 2017

TILs Tumor Infiltrating Lymphocytes in Breast Cancer - a logical Immunotherapy Biomarker

- Fewer TILs in metastatic vs early stage biopsies – as disease advances, immune system more exhausted
- TILs may also vary according to metastatic site
- If some baseline TILs, then enhancing immunity with immunotherapy Rx could improve outcome

TILs: Immuno(mono)therapy response rates in mTNBC



Schmid P, et al. AACR 2017; Adams S, et al ASCO 2017, Loi, ESMO 2017

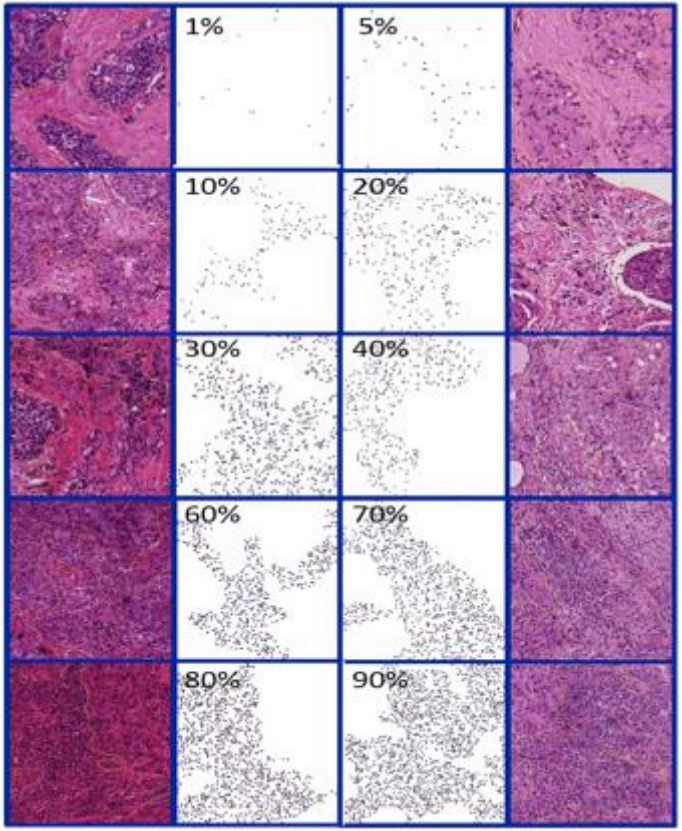
review

Annals of Oncology 00: 1–13, 2014
doi:10.1093/annonc/mdu450

The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014

- **Evaluate %TILs in the BC tumor stroma**

- **Training tool freely available online**
  - **www.tilsinbreastcancer.org**

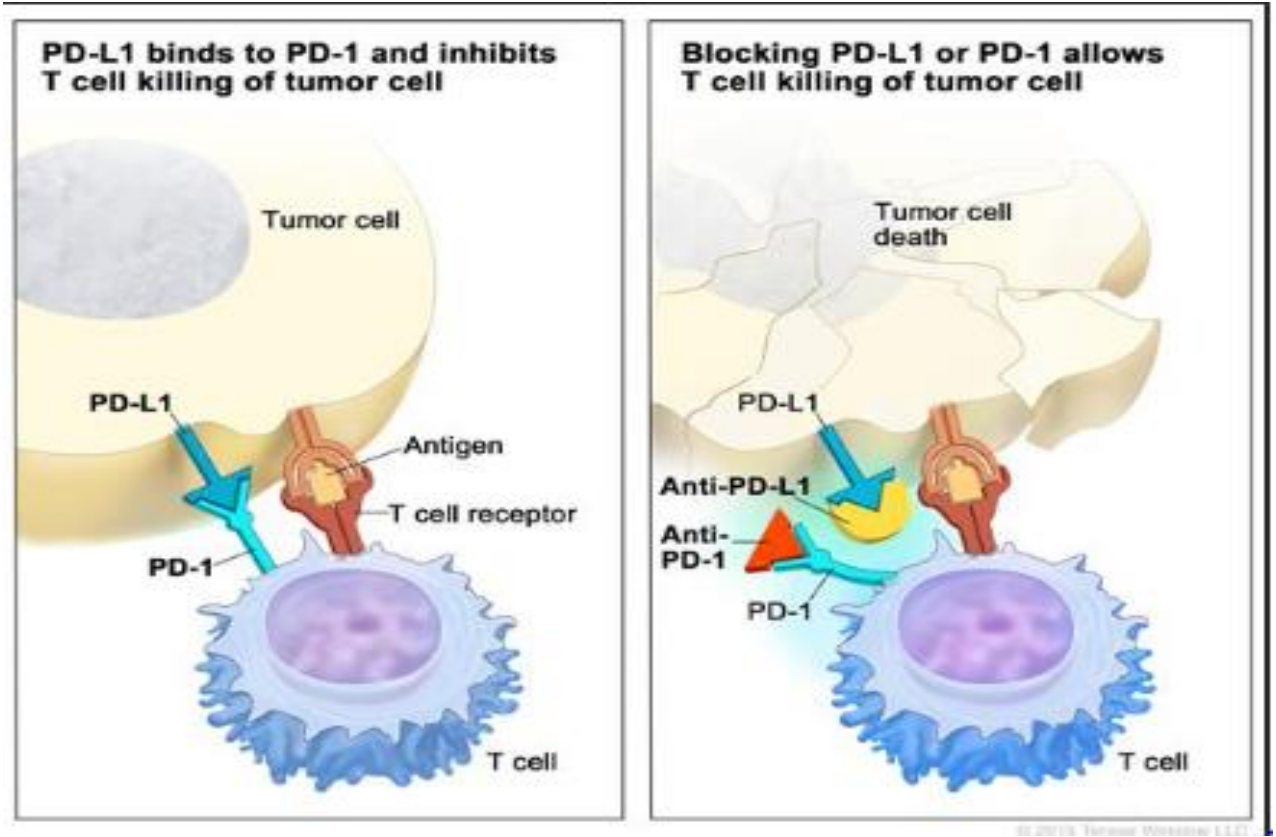


Salgado et al, Annals Oncol 2014
Denkert et al, Modern Pathology 2016

PD-L1 Programmed Death-Ligand 1

- The normal function of PD-L1 is to regulate the balance between tolerance and T-cell activation.
- PD-L1 is expressed on T-cells, B lymphocytes, dendritic cells and macrophages
- PD-L1 is expressed (upregulated) on tumor cells in range of cancers – helps evade immune destruction

Programmed Death-1 (PD-1) expressed on T cells
Programmed Death-Ligand 1 (PD-L1) may be expressed on tumor cells and help cells evade immune destruction



PD-L1 Programmed Death-Ligand 1

- In cancer, PD-L1 is both a therapeutic target and a biomarker
- PD-L1 is a new FDA biomarker for atezolizumab immunotherapy in metastatic TNBC (ie. PD-L1 stained tumor infiltrating immune cells covering $\geq$1% tumor area)
- In TNBC, PD-L1 is mainly expressed on tumor infiltrating immune cells

Immunotherapy Biomarker: Challenges with PD-L1

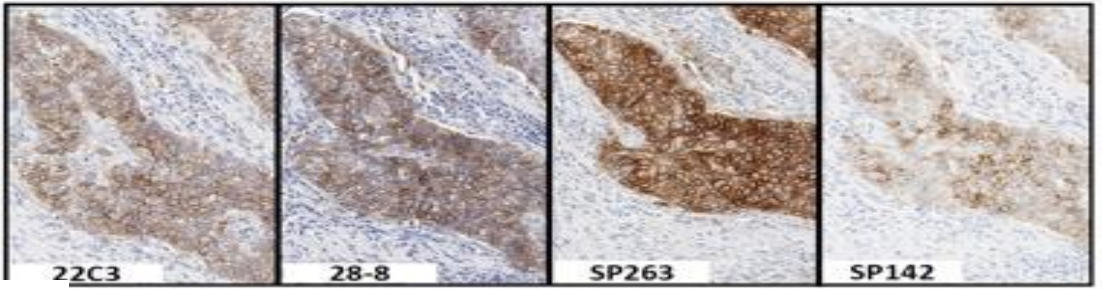
- PD-L1 expression identifies tumors with an increased chance of response to immunotherapy, however…
- Some patients with PD-L1 negative tumors have had durable responses to immunotherapy
- Not all with PD-L1 positive tumors respond
- Tumor biomarker biopsies were not always recent
- Poor standardisation - different assays, cut-offs
- Different scoring and cell type (tumor, immune)
- Problems with reproducibility

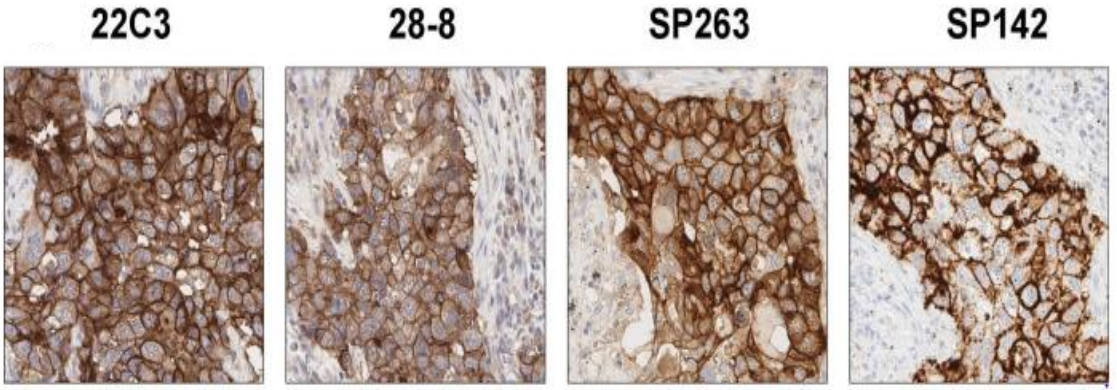
Different PD-L1 Immunohistochemistry Assays

PD-L1 IHC Assay	Checkpoint Inhibitor Trial Agent Tested	Pharma Company
Dako IHC 22C3	Pembrolizumab (Keynote trials)	Merck
Dako IHC 28-8	Nivolumab	BMS
Ventana IHC SP263	Durvalumab (GeparNeuvo trial)	AstraZeneca
Ventana IHC SP142	Atezolizumab (IMpassion 130 trial)	Roche-Genentech

Different PD-L1 Immunohistochemistry Assays

Example of PD-L1 Tumor Expression





PD-L1 positive Different IHC Scoring Systems

Tumor Proportion Score **TPS** (a percentage from 0-100)

PD-L1 positive Tumor Cells (**TC**)/all Tumor Cells x 100

Immune Cell (proportion) Score $IC_{\%}$

PD-L1 positive Immune Cells /all Immune Cells x 100

Combined Positive Score **CPS**

PD-L1 positive Tumor Cells + Immune Cells /all Tumor Cells x 100

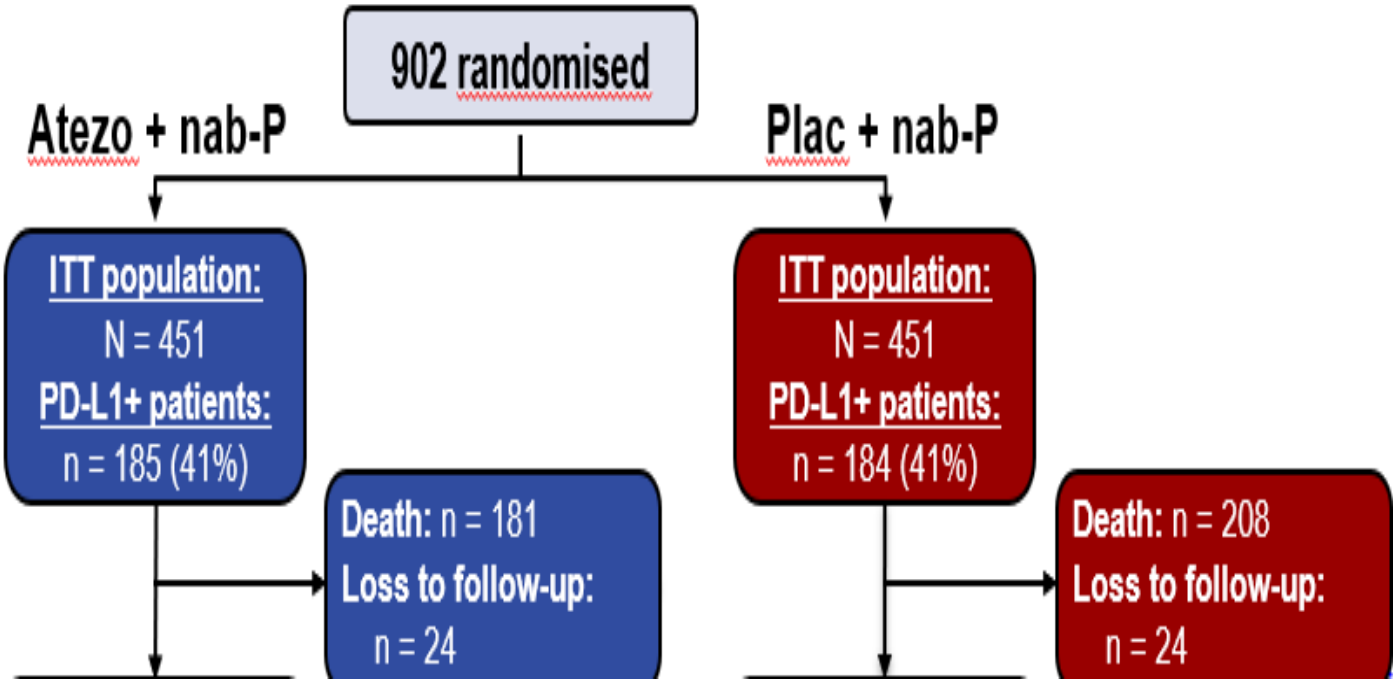
Immune Cell (area) Score IC_A

PD-L1 positive Immune Cell area/Tumor area x 100

(PD-L1 Positive Cut-off ≥1% IMpassion 130 Breast mTNBC Trial)

IMpassion 130 Trial – advanced/metastatic 1st line TNBC

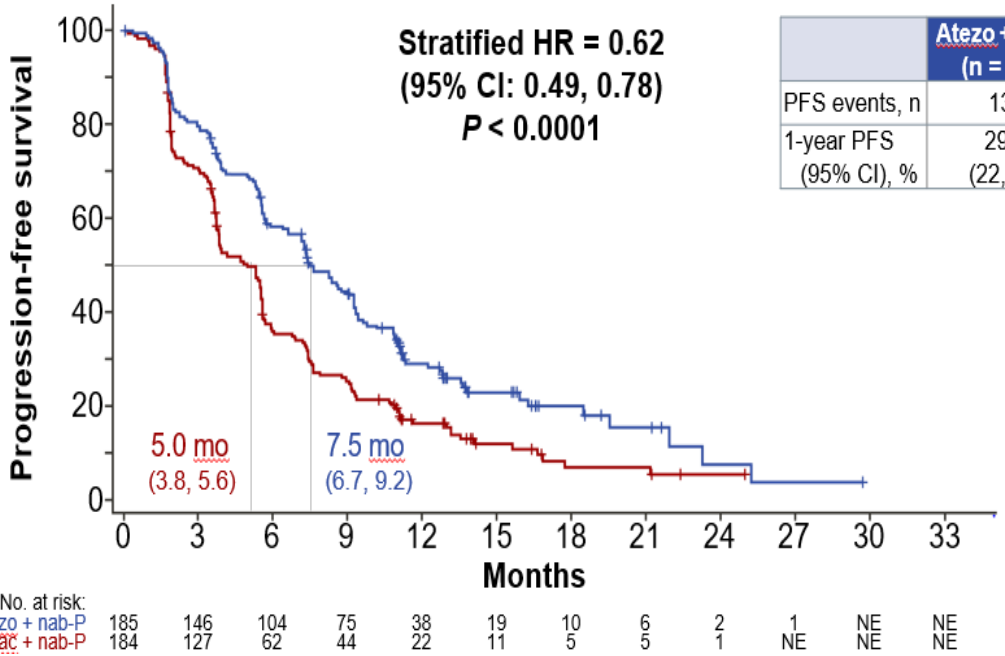
Testing addition of Atezolizumab (PD-L1 inhibitor) to chemo



Schmid et al ESMO 2018

IMpassion 130 Trial – advanced/metastatic 1st line TNBC

Primary PFS analysis: PD-L1+ population

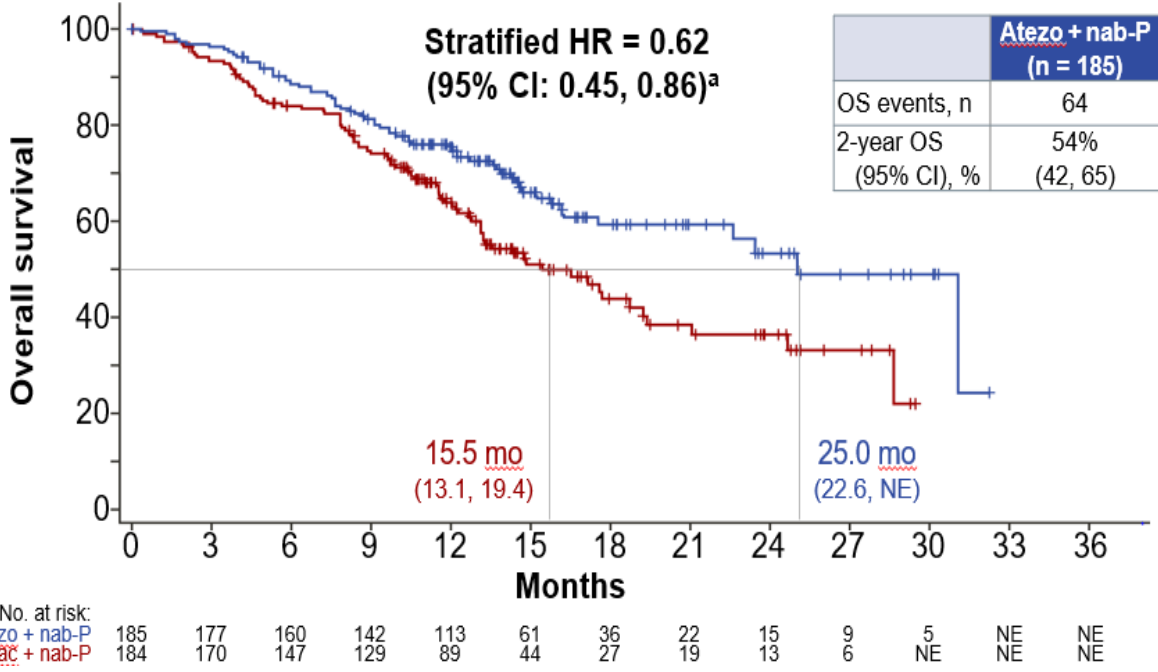


	Atezo + nab-P (n = 185)	Plac + nab-P (n = 184)
PFS events, n	138	157
1-year PFS (95% CI), %	29% (22, 36)	16% (11, 22)

Schmid et al ESMO 2018

IMpassion 130 Trial – advanced/metastatic 1st line TNBC

Interim OS analysis: PD-L1+ population

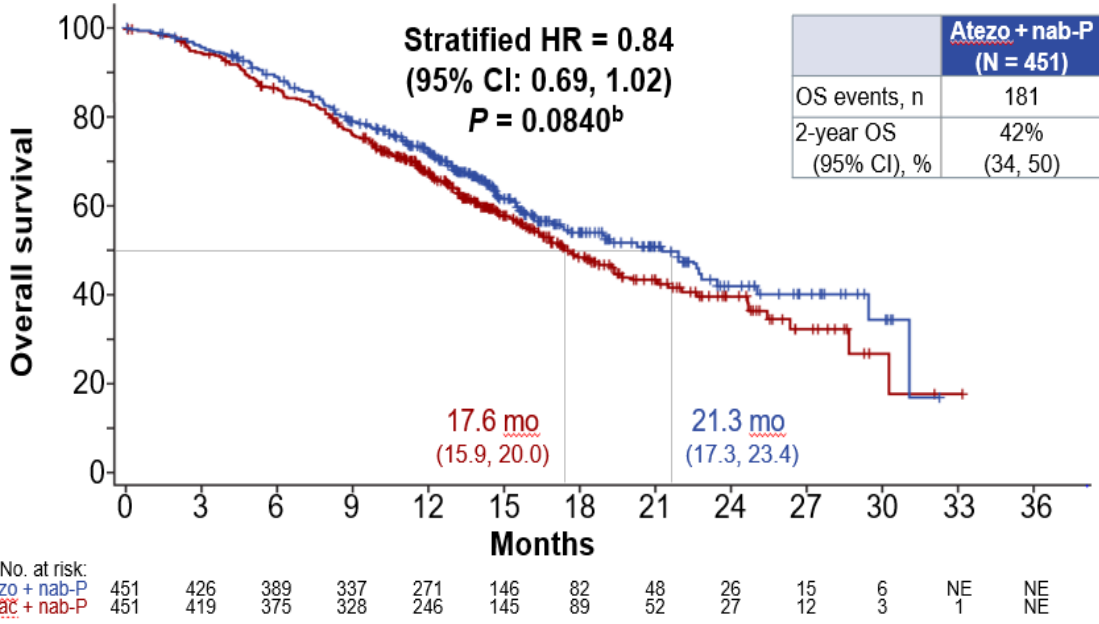


	Atezo + nab-P (n = 185)	Plac + nab-P (n = 184)
OS events, n	64	88
2-year OS (95% CI), %	54% (42, 65)	37% (26, 47)

Schmid et al ESMO 2018

IMpassion 130 Trial – advanced/metastatic 1st line TNBC

Interim OS analysis: ITT population[a]



	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
OS events, n	181	208
2-year OS (95% CI), %	42% (34, 50)	40% (33, 46)

Schmid et al ESMO 2018

Breast Cancer Immunotherapy Biomarkers

- Biomarkers to help predict response to immune checkpoint inhibitors are continuous biologic variables

- Selecting a continuous biomarker cut-point for a higher prevalence of biomarker positive patients (ie. PD-L1 or TILs ≥1%) reduces the response rate to therapy in cohort

- Selecting a continuous biomarker cut-point (threshold) for a higher response rate to therapy (ie. PD-L1 or TILs ≥10%) reduces the proportion of biomarker positive patients.

Evelhoch et al, Ann Oncol Oct 2018 (ESMO); 29 (Suppl 8): viii31: 99P

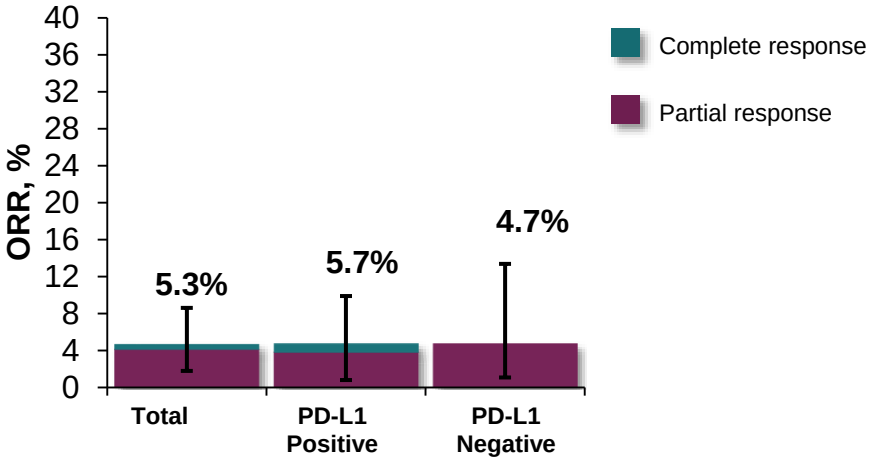
Cancer Immunotherapy

Biomarkers of response – biomarker positive frequency and relevant cut-points may be context specific

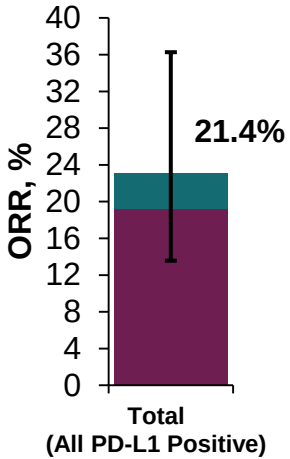
	Clinical Context
Type of Cancer	Breast vs. Melanoma vs. NSCLC
Subtype of Cancer	Breast: TNBC vs. HER2+ vs. Luminal
Disease Stage	Early Stage vs. Metastatic disease
Line of Therapy	1st line vs. 2nd line vs. later line metastatic
Tumor presence	Neoadjuvant (intact) vs. Adjuvant (resected)
Timing of sample	Pre-Rx (baseline) vs. On-Rx vs. Post-Rx
Types of therapy	Monotherapy vs. Combination
Assay technique	ie. IHC assay used, scoring system

KEYNOTE-086 Trial: Pembrolizumab in mTNBC

Cohort A (N = 170):
Previously Treated mTNBC, Any PD-L1 status



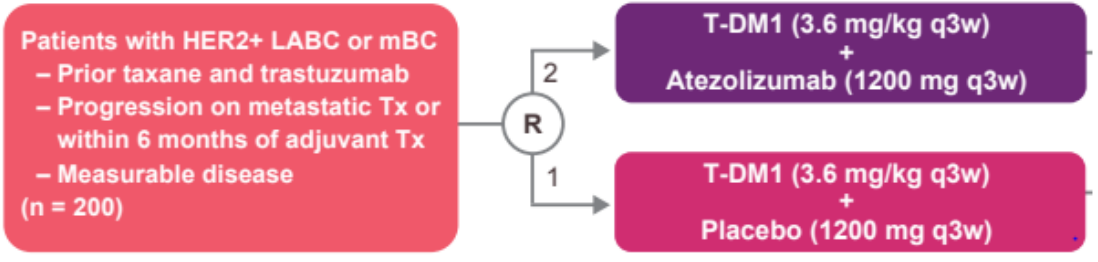
Cohort B (N = 84):
Untreated mTNBC, PD-L1 Positive



Data cutoff date: 10 Nov 2017.

Adams et al 2018

KATE2 Randomized Phase 2 Immunotherapy Trial Previously Treated Advanced HER2+ Breast Cancer



Stratification factors

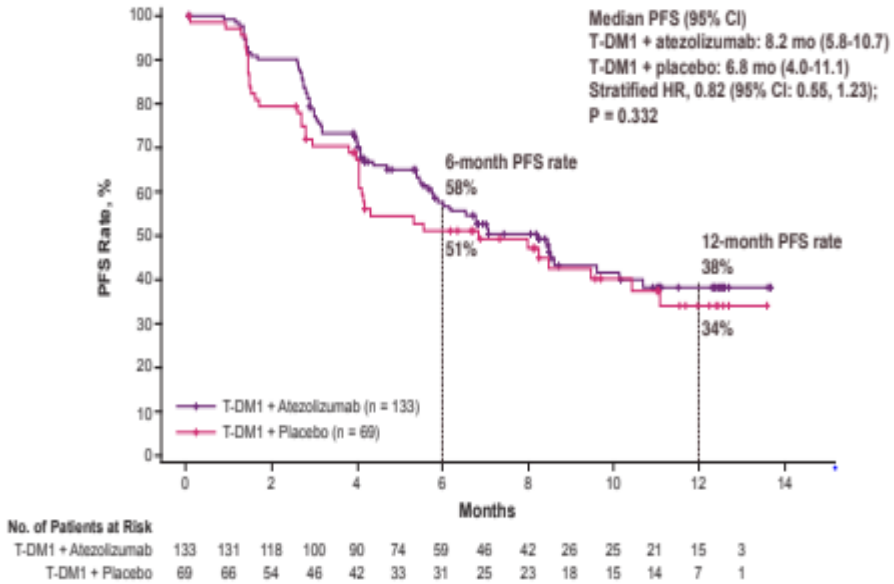
– Tumor PD-L1 status (IC0 vs IC1/2/3)
– World region (Western Europe vs US vs rest of world)
– Liver metastases (yes vs no)

Emens et al, SABCS 2018

Abstract #1253
Poster #PD3-01

KATE2 Immunotherapy HER2+ve Primary Endpoint

PFS in ITT Patients – no significant increase



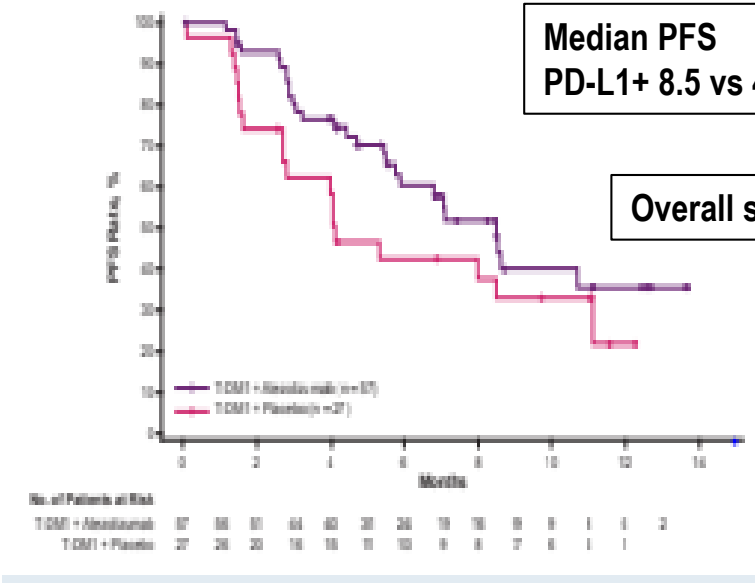
Overall survival data pending

Emens et al, SABCS 2018

Abstract #1253
Poster #PD3-01

KATE2 Immunotherapy HER2+ve: Atezolizumab

Significant increase in PFS for PD-L1+ tumors



Median PFS
PD-L1+ 8.5 vs 4.1 months

Overall survival data pending

Emens et al, SABCS 2018

Abstract #1253
Poster #PD3-01

PANACEA trial

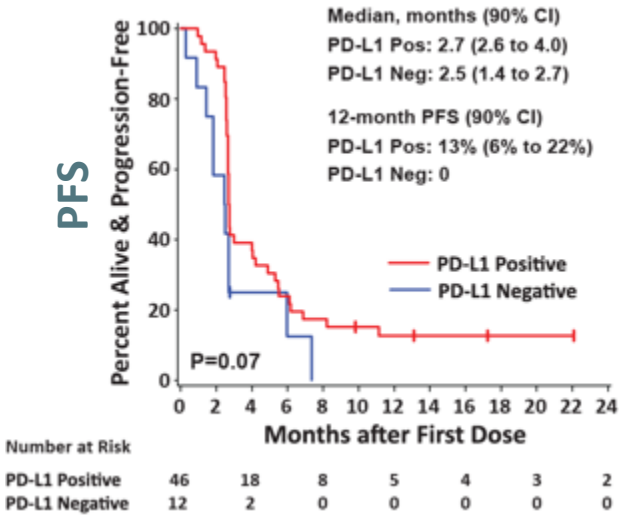
Phase Ib/II trial of Pembrolizumab in advanced, Trastuzumab-resistant, HER2-positive breast cancer

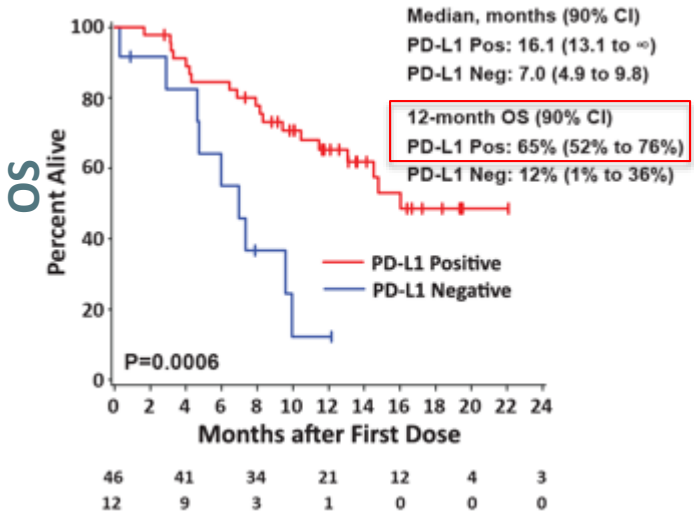
Single arm, signal seeking
Primary Endpoint was efficacy of the combination

Loi et al, Lancet Oncology 2018

PANACEA: HER2+ Pembrolizumab + Trastuzumab

PFS and Overall Survival by PD-L1 Status



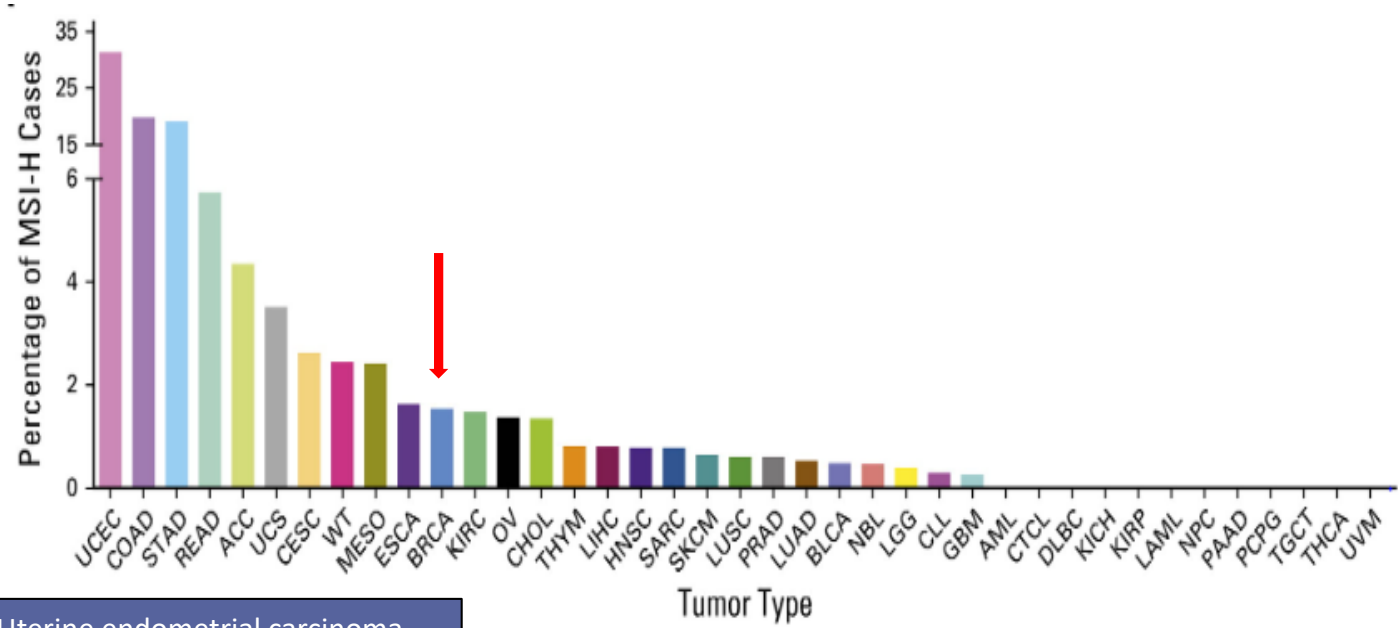


Loi et al, Lancet Oncology 2018

Microsatellite Instability-High MSI-H
Mismatch Repair Deficient dMMR

- Immunotherapy response biomarkers
- FDA granted accelerated approval of pembrolizumab (PD-1 inhibitor) for any MSI-H or dMMR progressive metastatic solid tumour
- Uncommon in metastatic breast cancer < 2% patients

Prevalence of MSI-High across multiple tumor types



Uterine endometrial carcinoma
Colon adenocarcinoma
Stomach adenocarcinoma
Rectal adenocarcinoma

Bonneville et al, J Precis Oncol 2017

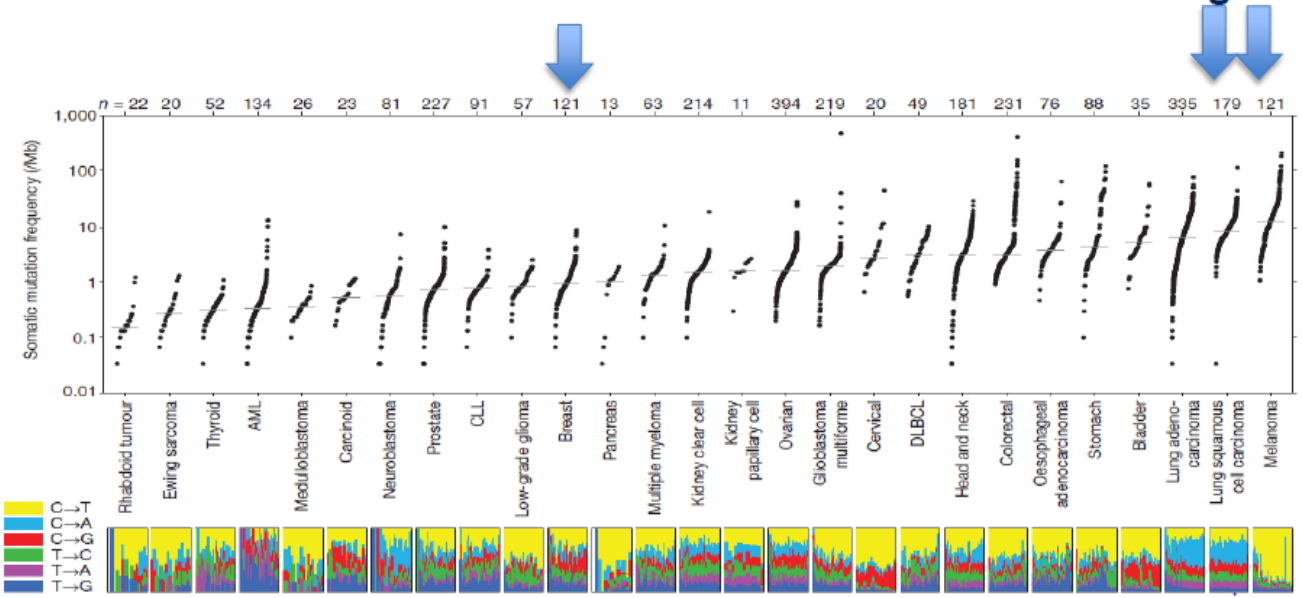
Mismatch Repair Deficient dMMR
Microsatellite Instability-High MSI-H

- dMMR tumor can be detected by loss IHC expression of one of MMR proteins - MLH1, MSH2, MSH6, PMS2
- Can be germline mutation (Lynch HNPCC syndrome), sporadic somatic mutations, methylation changes
- MSI-H can be detected by polymerase chain reaction (PCR) or large multigene NGS panel
- MSI-H tumors associated with increased TILs

Immunotherapy Biomarker: Tumor Mutational Burden

Toxins (UV light, smoking, HPV)

Mutational burden: somatic mutations could act as tumor antigens



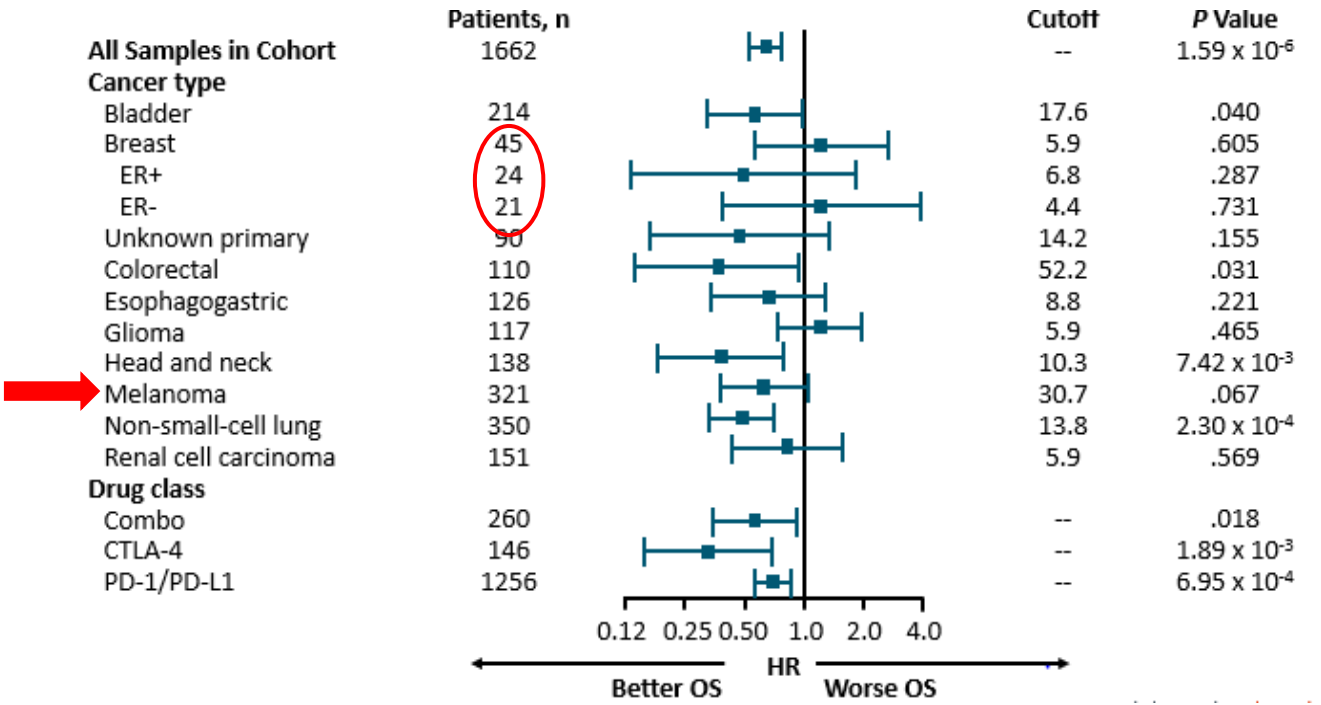
Lawrence et al, Nature 2013

High Tumor Mutational Burden (TMB)
Immunotherapy Biomarker

- High TMB useful biomarker in some types cancer (ie. frequently present and associated with responses to immune checkpoint inhibitors)
- Cut-off for high: > ? mutations per megabase (Mb)

- Little data to support high TMB as useful predictive immunotherapy biomarker in breast cancer
- Breast cancers do not typically have high TMB (with exception of gBRCA mutated or MSI tumors)

Association of higher TMB (top 20%) with overall survival after immune checkpoint inhibitor therapy



Samstein et al, Nat Genet 2019

Immunotherapy: Other Biomarkers Studied

Biomarkers obtained from blood / host
LDH (serum Lactate Dehydrogenase)
N/L ratio (peripheral blood Neutrophil-Lymphocyte ratio)
Gut Microbiome (faecal sample)
HLA Genotype
Others ? IL6, CRP, ctDNA, etc

Breast Cancer Immunotherapy:
Role Biomarker and Correlative Studies

- Aim to increase proportion of patients who benefit
- ? Avoid expense and toxicity in those who won't benefit
- Don't want to exclude patients who might benefit

- May be crucial to recognize benefit in a relevant subgroup of immunotherapy-treated patients in trials. Overall randomized ITT population may not have relevant benefit, but biomarker positive subgroup may have a clinically meaningful benefit

Acknowledgement – Prof Sherene Loi