Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

A Focus on Breast Cancer: Metastatic Breast Cancer

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Disclosures

- Consulting Fees: Novartis
- I will be discussing non-FDA approved indications during my presentation.

Agenda/Overview

- The winding road of immune checkpoint inhibitors in metastatic breast cancers
- Immune checkpoint inhibitor biomarkers beyond PDL1
  - High TMB, MSI-h/dMMR
- The future of immunotherapy for MBC

Agenda/Overview

- **The winding road of immune checkpoint inhibitors in metastatic breast cancers**

- Immune checkpoint inhibitor biomarkers beyond PDL1
  - High TMB, MSI-h/dMMR

- The future of immunotherapy for MBC

FDA-Approved ICIs in Metastatic Breast Cancer

Breast Cancer Specific

- ~~***Atezolizumab**** + *Nab-Paclitaxel in 1st line, metastatic TNBC*~~
- **Pembrolizumab** + Chemotherapy (nab-paclitaxel, paclitaxel or gemcitabine/carboplatin) in 1st line, metastatic TNBC

Not Breast Cancer Specific

- **Pembrolizumab*** in TMB-High (≥ 10 mutations/megabase)
- **Pembrolizumab*** in MSI-High or dMMR tumors

Reconciling metastatic TNBC ICI data

	KEYNOTE355	IMPASSION130	IMPASSION131
n (PD-L1+)	847 (332; 38%) PD-L1 22C3 CPS≥10	902 (369; 41%) PD-L1 SP142 ≥1%	943 (292; 45%) PD-L1 SP142 ≥1%
Treatment	(Paclitaxel or nab-paclitaxel or gemcitabine+carboplatin) + pembrolizumab (2:1)	Nab-paclitaxel + atezolizumab (1:1)	Paclitaxel + atezolizumab (2:1)
Proportion *de novo* MBC	30%	37%	28-30%
Prior taxane	45%	51%	51-53%
PD-L1+ PFS	5.6mo vs. 9.7mo HR 0.65 P=0.0012	5mo vs. 7.5mo HR 0.62 P<0.0001	5.7mo vs. 6mo HR 0.82 p=0.20
PD-L1+ OS benefit?	In PD-L1+ yes	In PD-L1+ yes; ITT no	No

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Adapted from Hope Rugo, ESMO 2020

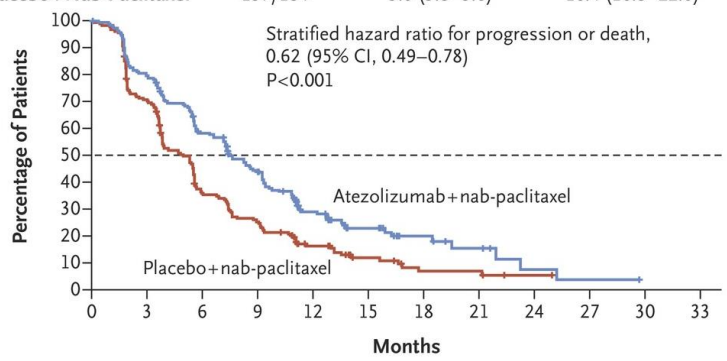
Reconciling metastatic TNBC ICI data

IMPASSION130: PFS

- Nab-Paclitaxel: Positive study

B Progression-free Survival in the PD-L1–Positive Subgroup

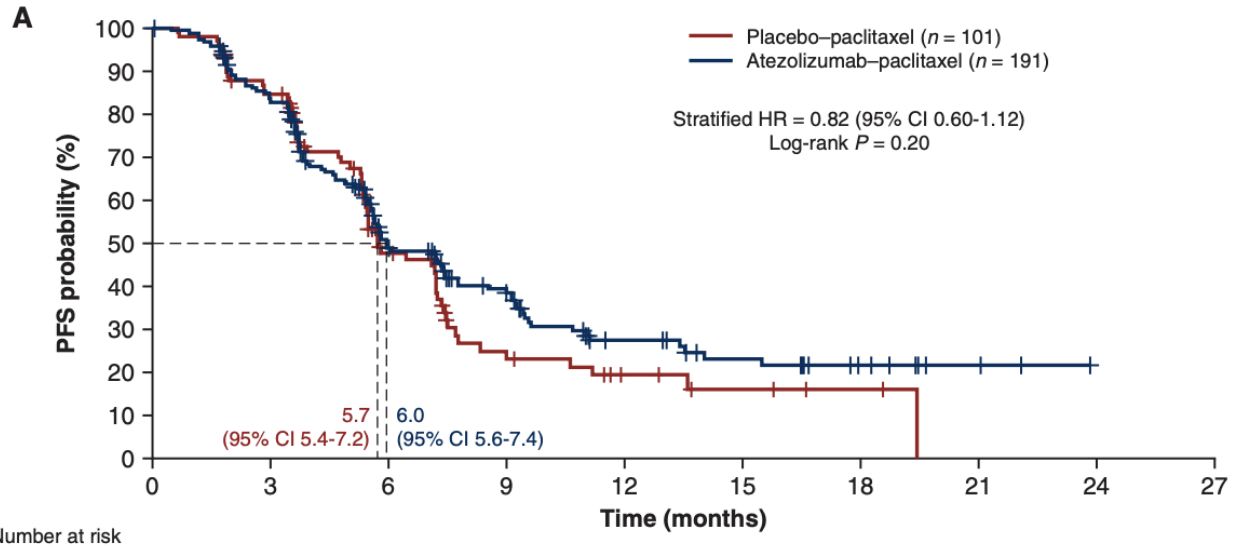
	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)	1-Yr Rate of Progression-free Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	138/185	7.5 (6.7–9.2)	29.1 (22.2–36.1)
Placebo+Nab-Paclitaxel	157/184	5.0 (3.8–5.6)	16.4 (10.8–22.0)



No. at Risk												
Atezolizumab+ nab-paclitaxel	185	146	104	75	38	19	10	6	2	1	NE	NE
Placebo+ nab-paclitaxel	184	127	62	44	22	11	5	5	1	NE	NE	NE

IMPASSION131: PFS

- Paclitaxel: Negative study



Number at risk										
Placebo–paclitaxel	101	81	33	14	7	4	2	0	0	0
Atezolizumab–paclitaxel	191	152	69	44	22	15	8	3	0	0

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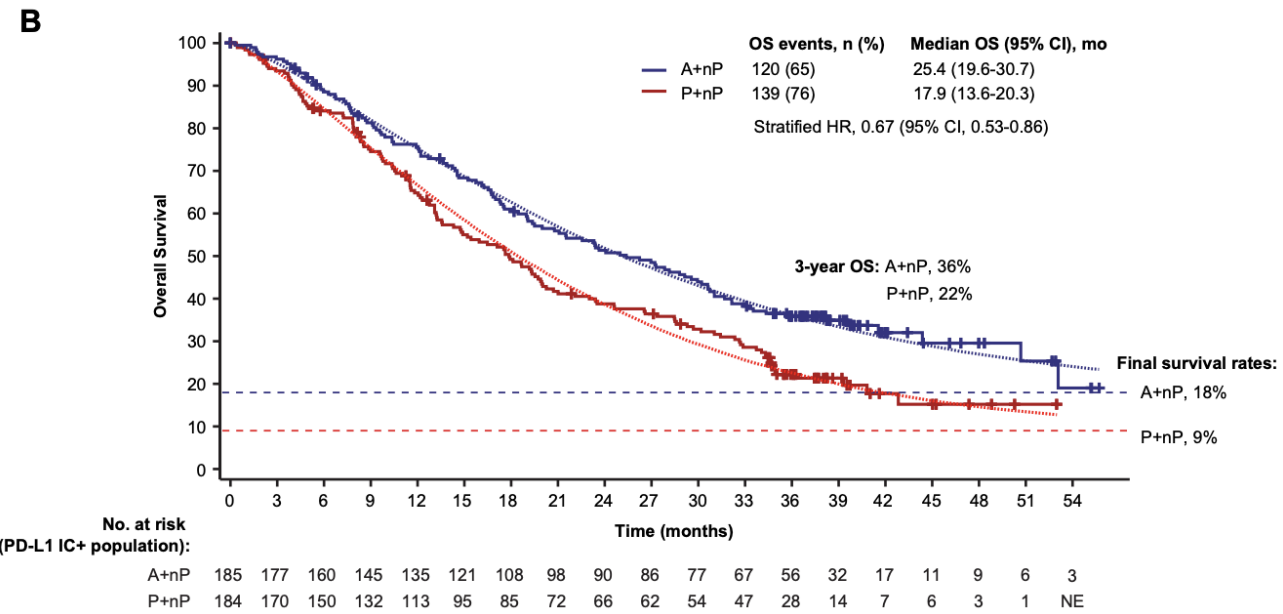
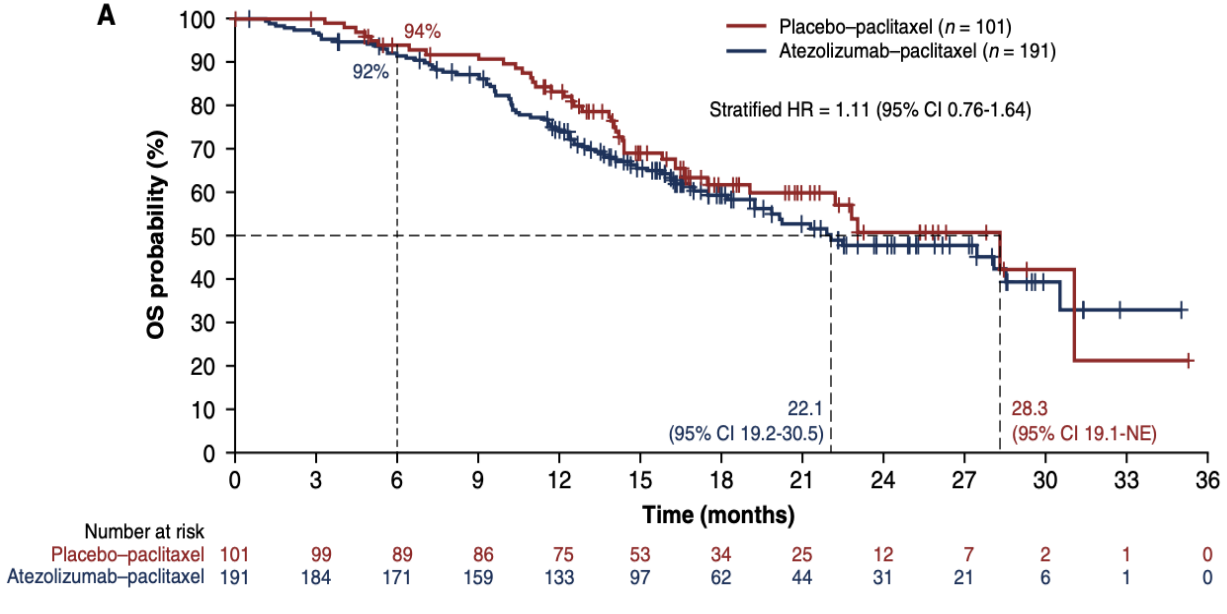
Schmid NEJM 2018; Miles Ann Onc 2021

Reconciling metastatic TNBC ICI data

IMPASSION130: OS (PD-L1+)



IMPASSION131: OS (PD-L1+)



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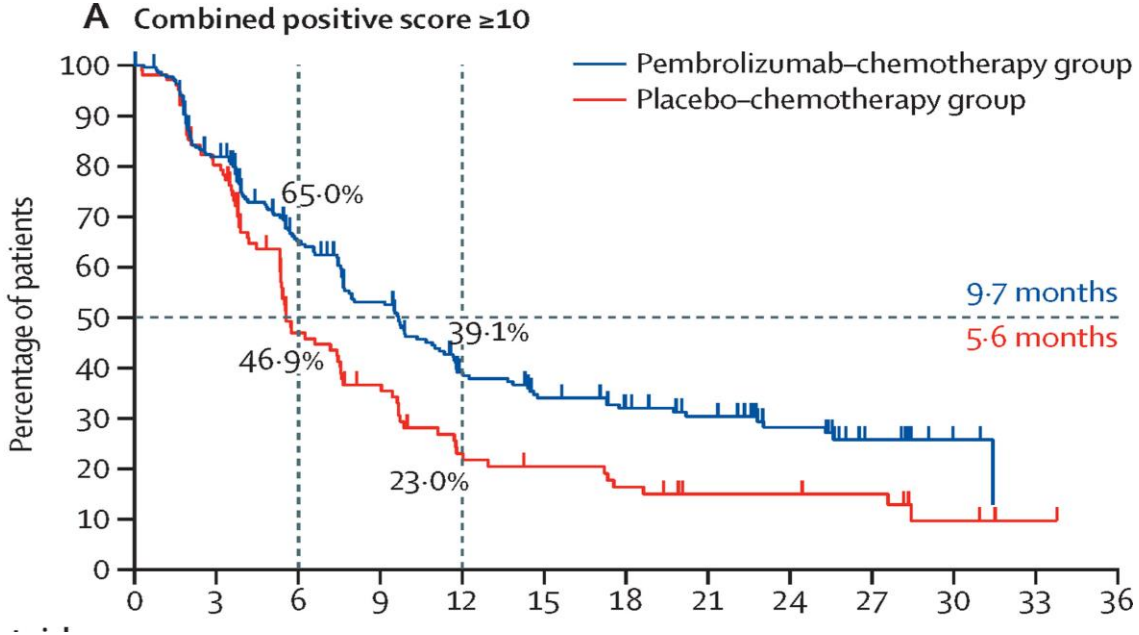
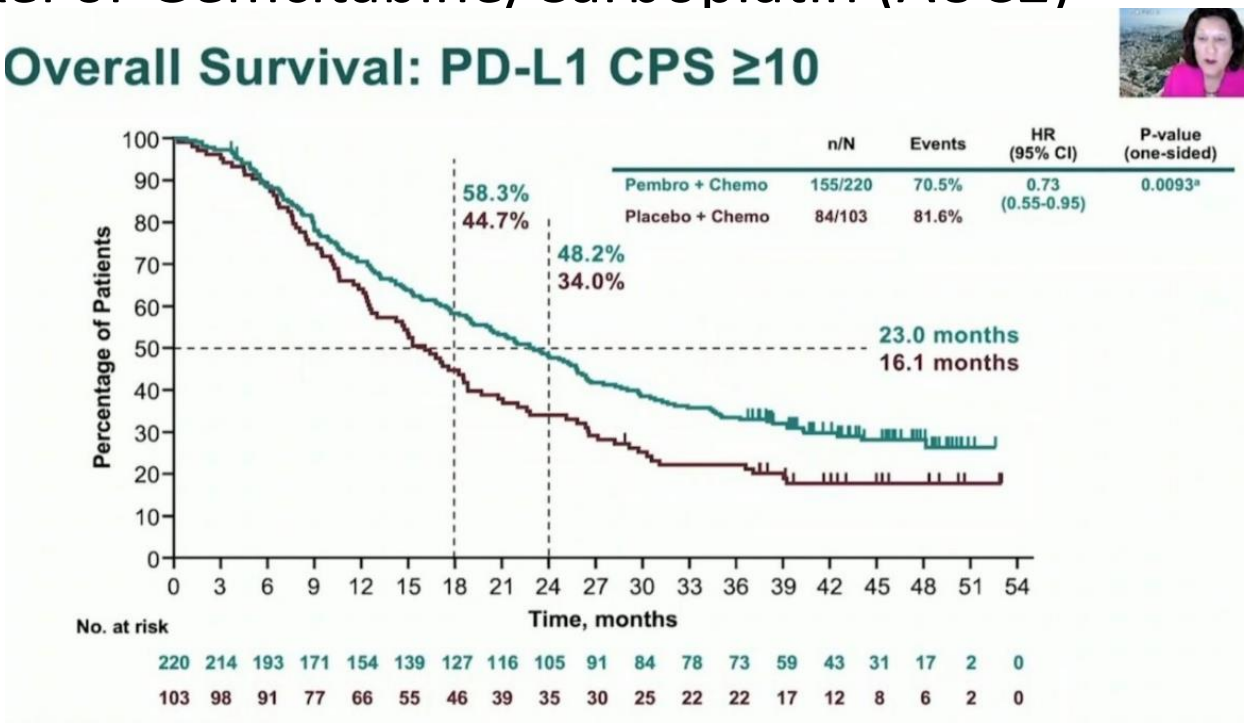
Emens *Ann Onc* 2021; Miles Ann Onc 2021

Reconciling metastatic TNBC ICI data: KEYNOTE-355

- 1L, mTNBC, randomized 2:1 (n = 847)
- Chemotherapy = Nab-Paclitaxel, Paclitaxel or Gemcitabine/Carboplatin (AUC2)





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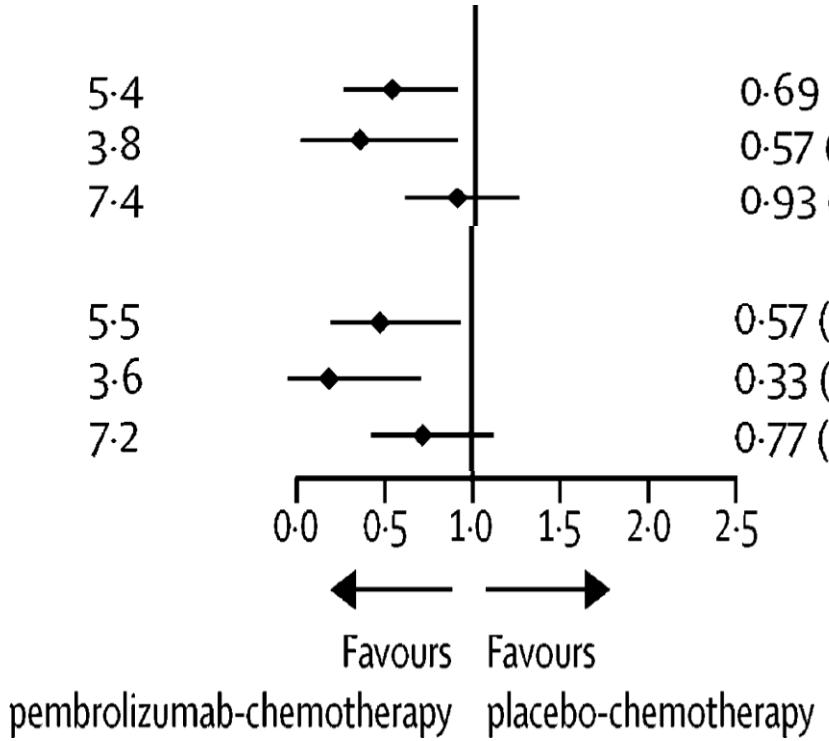
Cortes, J. Lancet. 2020; Rugo et al. 2021. ESMO Congress

Figure 3

Reconciling metastatic TNBC ICI data: KEYNOTE-355

ITT	**On-study chemotherapy**				
	Nab-paclitaxel	268	7·5	5·4	0·69 (0·51 to 0·93)
	Paclitaxel	114	8·0	3·8	0·57 (0·35 to 0·93)
	Gemcitabine-carboplatin	465	7·4	7·4	0·93 (0·74 to 1·16)
CPS ≥ 10	**On-study chemotherapy**				
	Nab-paclitaxel	99	9·9	5·5	0·57 (0·34 to 0·95)
	Paclitaxel	44	9·6	3·6	0·33 (0·14 to 0·76)
	Gemcitabine-carboplatin	180	8·0	7·2	0·77 (0·53 to 1·11)



Cortes, J. Lancet. 2020

PD-1/L1 Expression in Breast Cancer

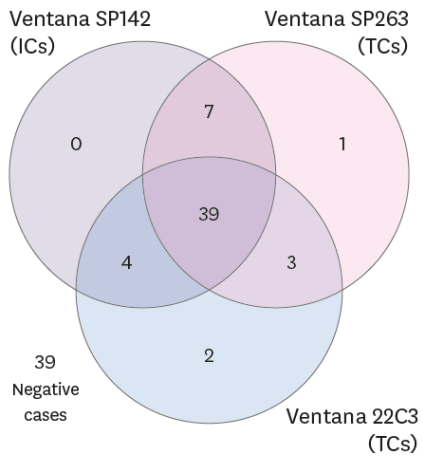
	Ventana PD-L1 (SP142)	Dako PD-L1 (22C3)
Approved for Companion Use	Atezolizumab in mTNBC	Pembrolizumab in mTNBC
PD-L1 Positive Definition	**≥ 1% on IC** *Tumor area, any staining*	**≥ 10 Combined Positive Score (CPS)** [% IC with any PD-L1 + % TC with membranous PD-L1] Total invasive TC

IC = immune cells
TC = tumor cells

95 Early Stage TNBC

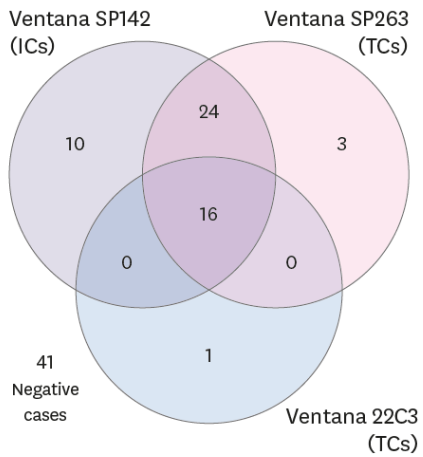
SP142 (≥ 1%) vs CPS ≥ 1%

A

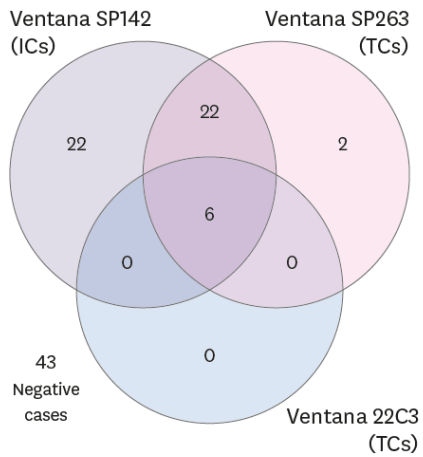


SP142 (≥ 1%) vs CPS ≥ 5%

B



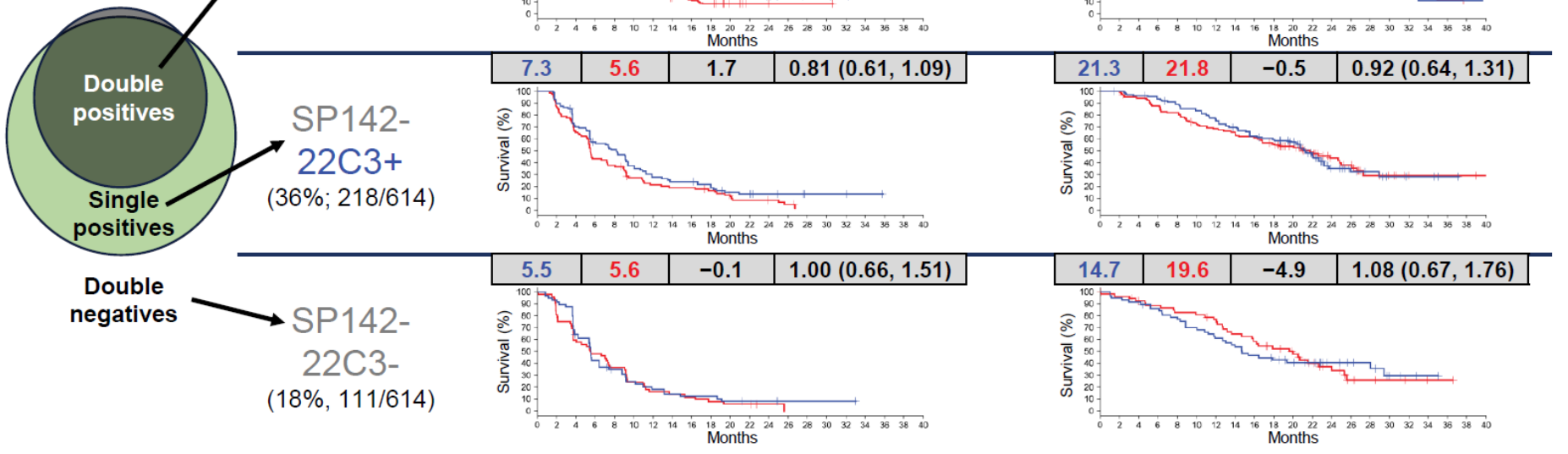
SP142 (≥ 1%) vs CPS ≥ 10%



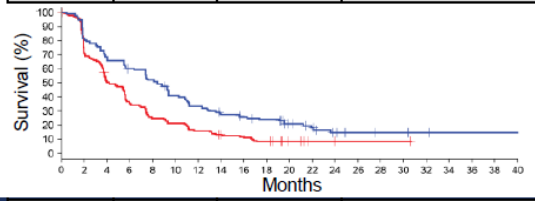
Emens et al. JITC. 2021.
Lee et al. J Breast Can. 2020.
Huang et al. Human Path. 2021.
https://www.accessdata.fda.gov/cdrh_docs/pdf16/p160002s009c.pdf
https://www.accessdata.fda.gov/cdrh_docs/pdf15/P150013S006c.pdf

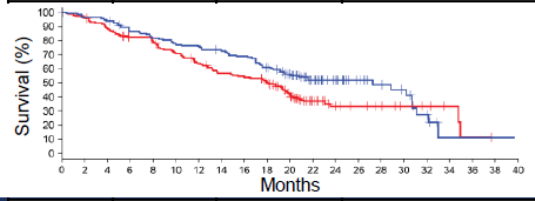
From Maggie Gatti-Mays

PD-1/L1 Expression in Breast Cancer



Population	PFS				OS			
	Median PFS, mo			HR (95% CI)	Median OS, mo			HR (95% CI)
	A + nP	P + nP	Δ		A + nP	P + nP	Δ	
SP142+ 22C3+ (45%; 279/614)	8.3	3.9	4.4	0.60 (0.46, 0.78)	27.3	18.0	9.3	0.71 (0.52, 0.98)
SP142- 22C3+ (36%; 218/614)	7.3	5.6	1.7	0.81 (0.61, 1.09)	21.3	21.8	−0.5	0.92 (0.64, 1.31)
SP142- 22C3- (18%, 111/614)	5.5	5.6	−0.1	1.00 (0.66, 1.51)	14.7	19.6	−4.9	1.08 (0.67, 1.76)





Double positive: SP142 IC ≥ 1%, 22C3 CPS ≥ 1; single positive: SP142 IC < 1%, 22C3 CPS ≥ 1; double negative: SP142 IC < 1%, 22C3 CPS < 1.
HR adjusted for prior taxanes, presence of liver metastases, age and ECOG PS.

Rugo et al. Abstract 6571
IMpassion130 PD-L1 IHC
https://bit.ly/30OmOqz

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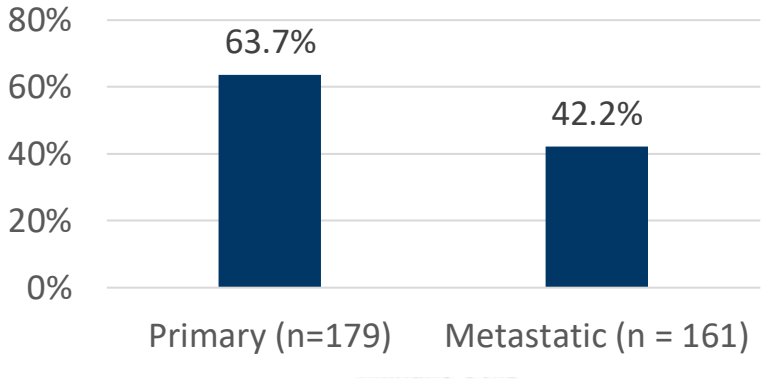
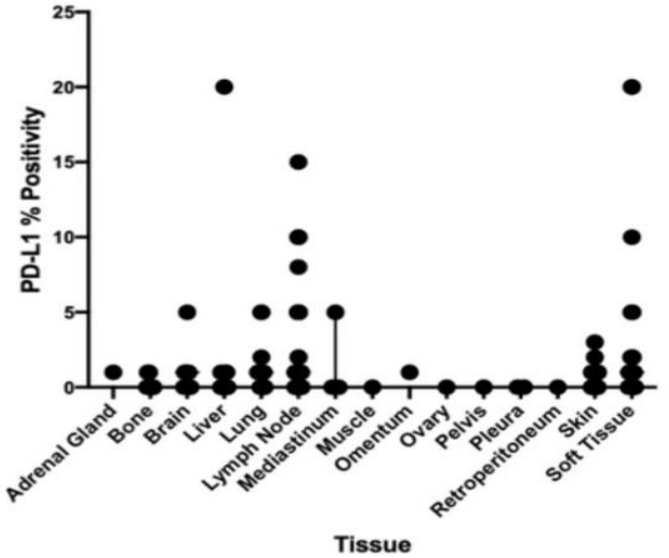
PD-1/L1 Expression in Breast Cancer

- **The Specimen Site Matters for PD-L1+**
  - Primary breast tumors > metastatic tumors
    - Metastatic tumors have fewer ICs, decrease immune activation markers
  - Varying PD-L1+ among metastatic sites
    - Highest in lung, soft tissue, lymph nodes
    - Lowest in liver *("immunologic graveyard")*
    - Limited use in bone *[PD-L1 assays are NOT validated on decalcified bone] and FNA aspirates*





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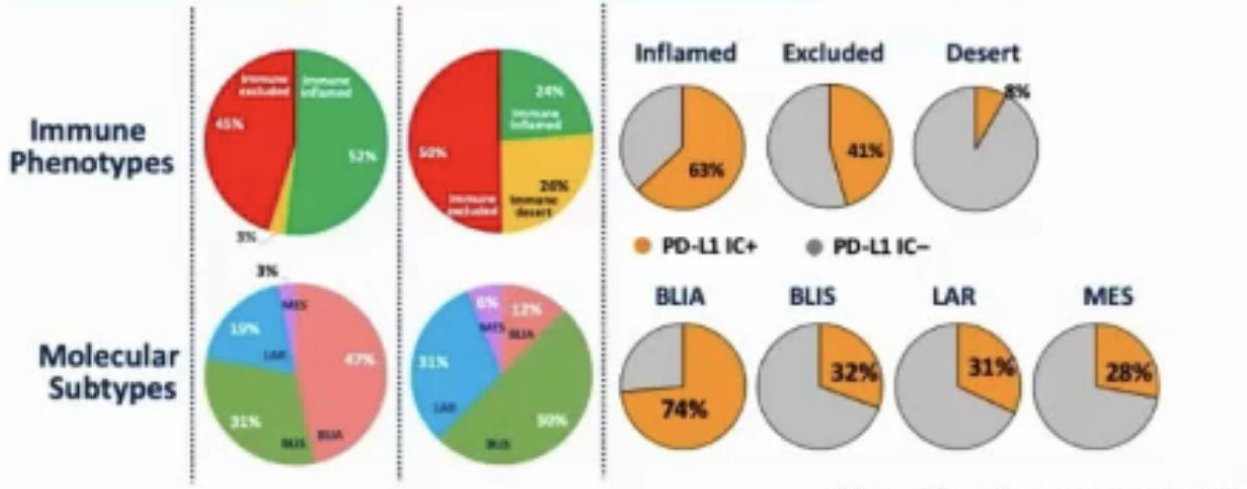
Rozenblitz et al. JITC. 2020.; Emens et al. JITC. 2021.

From Maggie Gatti-Mays

Immune vs. Other Biomarkers

	Impassion 130		Keynote 355	
	PD-L1+	PD-L1-	PD-L1+	PD-L1-
PFS	0.62 (0.45-0.78)	0.94 (0.78-1.13)	0.65 (0.49-0.86)	0.94 (0.76-1.16)
OS	0.67 (0.53-0.86)	1.02 (0.84-1.24)	0.73 (0.55-0.95)	1.04 (0.85-1.26)



Adapted from Emens LA. ASCO 2021

Take Home Points

- PD-L1+ benefit across studies
- Distribution varies within subtypes
- PD-L1+ tumors present
  - Across immune phenotypes
  - Across molecular subtypes

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Peter Schmid; SABCS 2021

Reconciling metastatic TNBC ICI data

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PD-L1+ OS benefit?	In PD-L1+ yes	In PD-L1+ yes; ITT no	No

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Adapted from Hope Rugo, ESMO 2020

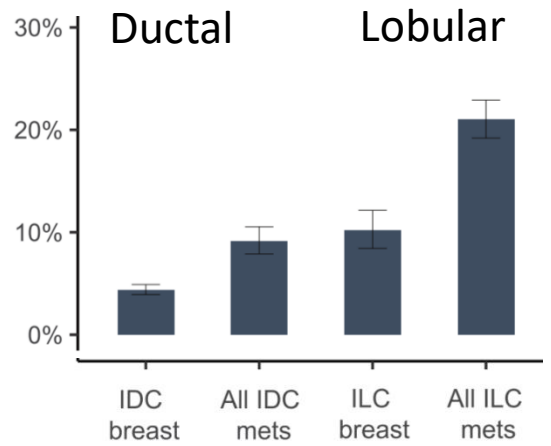
Agenda/Overview

- The winding road of immune checkpoint inhibitors in metastatic breast cancers
- **Immune checkpoint inhibitor biomarkers beyond PDL1**
  - **High TMB, MSI-h/dMMR**
- The future of immunotherapy for MBC

High TMB: Is it <u>really</u> a biomarker for breast cancer?

Foundation Medicine database
N=5739 samples

	ER+, HER2-	HER2+	Triple-negative	Lobular	Inflammatory	Metaplastic	Mucinous	Papillary
	Tumor Mutational Burden (TMB)							
Median TMB (mut/Mb)	2.6	3.5	3.5	2.6	2.5	2.6	1.7	3.5
TMB ≥ 10	7%	9%	7%	15%	10%	5%	6%	0%
TMB ≥ 20	2%	2%	2%	6%	3%	2%	3%	0%



Israel, SABCS 2020 | Sokol, SABCS 2020

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High TMB: Is it really a biomarker for breast cancer?

Clinical Trial Name	KEYNOTE-158
Patient Population	Previously treated, solid tumors that had a high number of mutations, defined as 10 mutations/megabase or more (~5% of all breast cancers)
# Patients on Trial	233 patients in efficacy cohort (5/233 breast cancer)

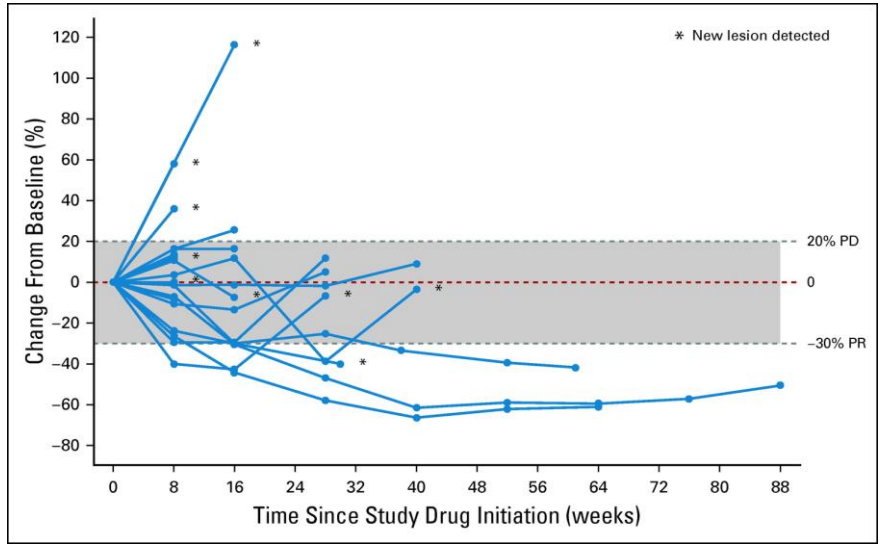
When Pembrolizumab (Keytruda) was used in patients with high mutational burden vs low…	
Was cancer better controlled (**improved response rate**)?	**YES*** (29% vs 6%)
Did patients live longer (improved OS)?	NO (11.7 vs 12.8 months)

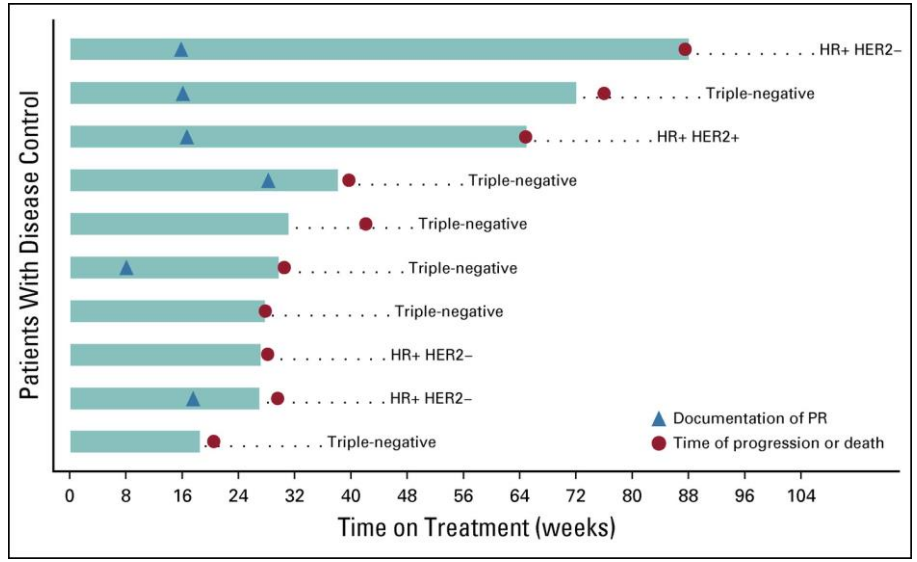
From Maggie Gatti-Mays

Thomas et al. OncoImmunology. 2018.; Barroso-Sousa et al. Ann Onc. 2020.; Marabelle et al. 2020. Lancet Oncoll Emens et al. JITC. 2021.

High TMB: Is it really a biomarker for breast cancer?

- **TAPUR Study (Ph2 basket study)**
  - 28 patients with metastatic breast cancer [TNBC = 13 (46%), HR+/HER2- = 12 (43%)]
  - **TMB: median 13 mut/Mb** (range 9 to 37 mut/Mb); PD-L1 status unknown
  - **Disease Control Rate 37%, ORR 21%** with median PFS = 10.6 weeks





From Maggie Gatti-Mays

High TMB: Is it really a biomarker for breast cancer?

NIMBUS

Eligibility:

- Metastatic HER2- breast cancer
- 0-3 lines of prior chemotherapy
- TMB ≥ 9 mut/Mb as assessed by a CLIA-approved cancer-gene panel
- Measurable disease by RECIST 1.1
- Mandatory research biopsy if tumor safely accessible
- No prior checkpoint inhibition

REGISTRATION

→ **Nivolumab 3 mg/kg Q2W**
+
Ipilimumab 1 mg/kg Q6W

1 cycle = 42 days (6 weeks)

→ **Duration of therapy**

Treatment until progression, unacceptable toxicity or up to 24 months

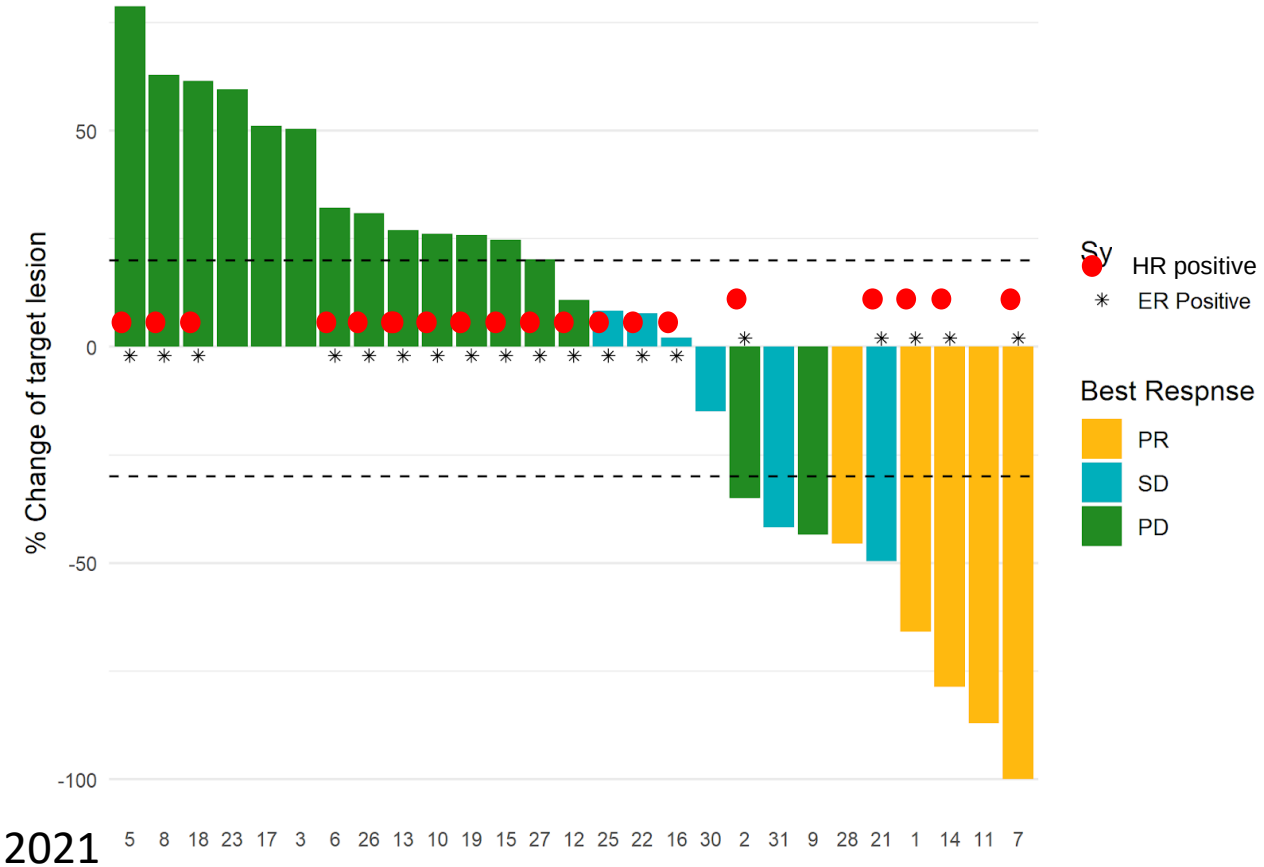
Tumor assessment: Imaging will be performed at baseline and Q6W for 24 weeks, and then Q9W.

Barroso-Sousa, et al SABCS 2021

High TMB: Is it really a biomarker for breast cancer?

NIMBUS: Objective Response Rate

Confirmed ORR, n (%)	5 (16.7%)
CR, n (%)	0
PR, n (%)	5 (16.7%)
SD, n (%)	6 (20%)
PD, n (%)	16 (53.3%)
Not evaluable, n (%)	3 (10%)
CBR, n (%)	5 (16.7%)

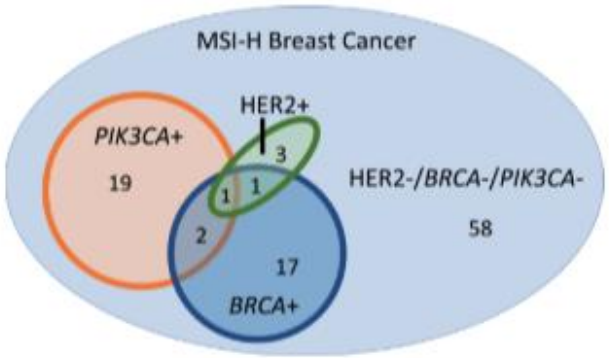


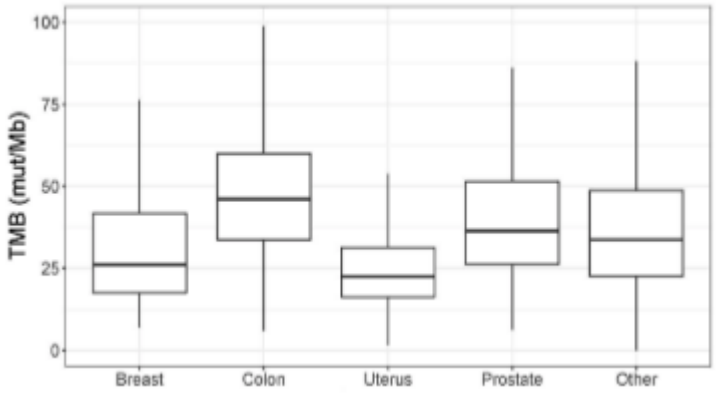
Barroso-Sousa, et al SABCS 2021

MSI-H: Is it <u>really</u> a biomarker for breast cancer?

Therapeutic Considerations in Microsatellite Instability High (MSI- H) Breast Cancers (BC) Identified by Comprehensive Genomic Profiling (CGP)

- FoundationMedicine: 29,160 breast cancer cases
  - MSI status determined at 95-114 loci
- **102 MSI-H** (<u>0.35%</u>) – **<u>RARE</u>**
  - Enriched among gBRCA1/2 mutation carı
  - Tend to have high TMB





MSI-H: Is it really a biomarker for breast cancer?

Clinical Trial Name	KEYNOTE-158
Patient Population	Previously treated, solid tumors that histologically/cytologically confirmed MSI-H/dMMR
# Patients on Trial	233 patients in efficacy cohort (5/233 breast cancer)
FDA Approval Status	Accelerated Approval (2020)

When Pembrolizumab (Keytruda) was used in patients with MSI-H/dMMR…	
Response rate	**34.3%**
Progression-free survival	4.1 mo
Overall survival	23.1 mo

***statistically significant**
****** Few breast cancer patients included**

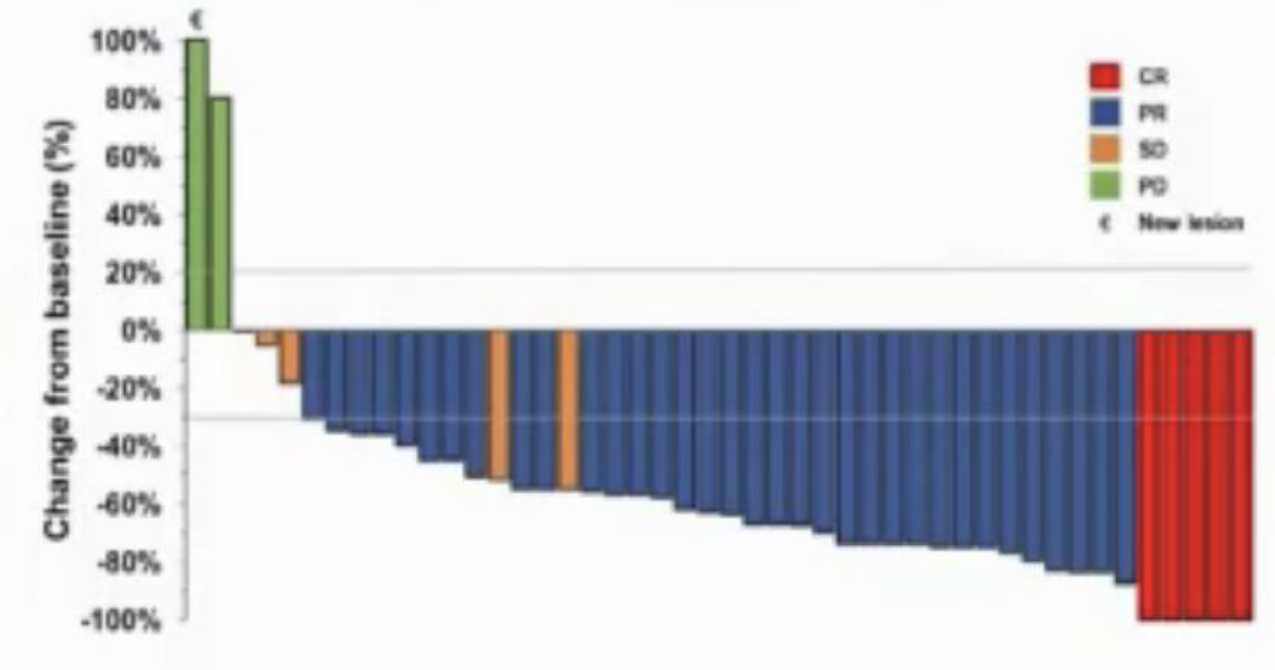
Thomas et al. OncoImmunology. 2018.; Barroso-Sousa et al. Ann Onc. 2020.; Marabelle et al. 2020. Lancet Oncoll Emens et al. JITC. 2021.

Agenda/Overview

- The winding road of immune checkpoint inhibitors in metastatic breast cancers
- Immune checkpoint inhibitor biomarkers beyond PDL1
  - High TMB, MSI-h/dMMR
- **The future of immunotherapy for MBC**

Will VEGF agents return? FEATURE-C-PLUS

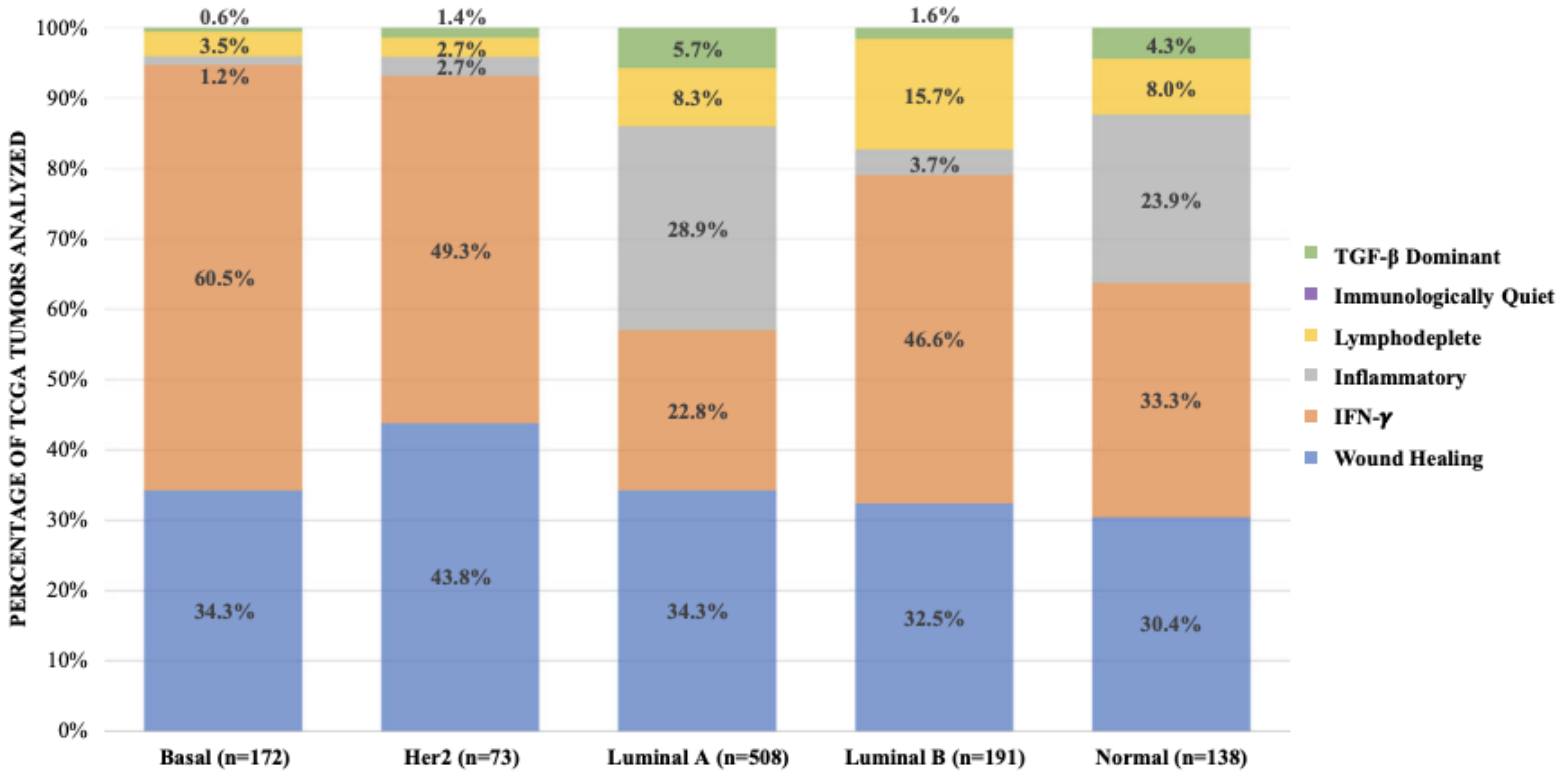
- Famitinib (anti-VEGFR2) + camrelizumab (anti-PD1) + nab-paclitaxel
- Phase 2 trial (n=48)
- ORR: 81.3% (10.9% CR)
- PFS: 60.2% at 9 mo



Shao ASCO 2021

What about non-TNBC MBC subsets? (HER2+ +/- ER+)

- Lower ICI response rates
  - Distinct TIME
- Combinations or sequencing therapy to activate a 'cold' TIME
  - CDK4/6i induction of IFN
  - Leveraging HER2 mAb ADCC
- Host factors?



Gatti-Mays et al *npj Breast Cancer* 2019

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Conclusions

- The winding road of immune checkpoint inhibitors in metastatic breast cancers
  - **Only breast-specific ICI approval for MBC is pembro for TNBC that is PD-L1 22C3 CPS≥10**
- Immune checkpoint inhibitor biomarkers beyond PDL1
  - **High TMB, MSI-h/dMMR: Pan-cancer approvals – rare but more than we think?**
- The future of immunotherapy for MBC
  - **Great interest in modulating the TIME – where will this go?**

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Thank you!