Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Breast & Gynecologic Cancers

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AAEM American Academy of Emergency Medicine — Champion of the Emergency Physician

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

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Disclosures

- Consulting Fees: Pfizer, BMS, Spectrum, Lilly, BeyondSpring, Novartis, Coherus, Amgen, Seagen, Merck, Coherus.
- Contracted Research: Pfizer, Amgen
- I will be discussing non-FDA approved indications during my presentation.

Outline

- Breast cancer
  - Approvals
  - In the pipeline
  - Biomarkers and immunotherapy responsiveness

Immunotherapy in breast cancer

- Standard-of-care treatment usually involves surgery, chemotherapy, radiation
- Application of immunotherapy is still in early stages

Estimated new cases

Female		
Breast	276,480	30%
Lung & bronchus	112,520	12%
Colon & rectum	69,650	8%
Uterine corpus	65,620	7%
Thyroid	40,170	4%
Melanoma of the skin	40,160	4%
Non-Hodgkin lymphoma	34,860	4%
Kidney & renal pelvis	28,230	3%
Pancreas	27,200	3%
Leukemia	25,060	3%
All sites	**912,930**	

Estimated deaths

Female		
Lung & bronchus	63,220	22%
Breast	42,170	15%
Colon & rectum	24,570	9%
Pancreas	22,410	8%
Ovary	13,940	5%
Uterine corpus	12,590	4%
Liver & intrahepatic bile duct	10,140	4%
Leukemia	9,680	3%
Non-Hodgkin lymphoma	8,480	3%
Brain & other nervous system	7,830	3%
All sites	**285,360**	

American Cancer Society 2020.

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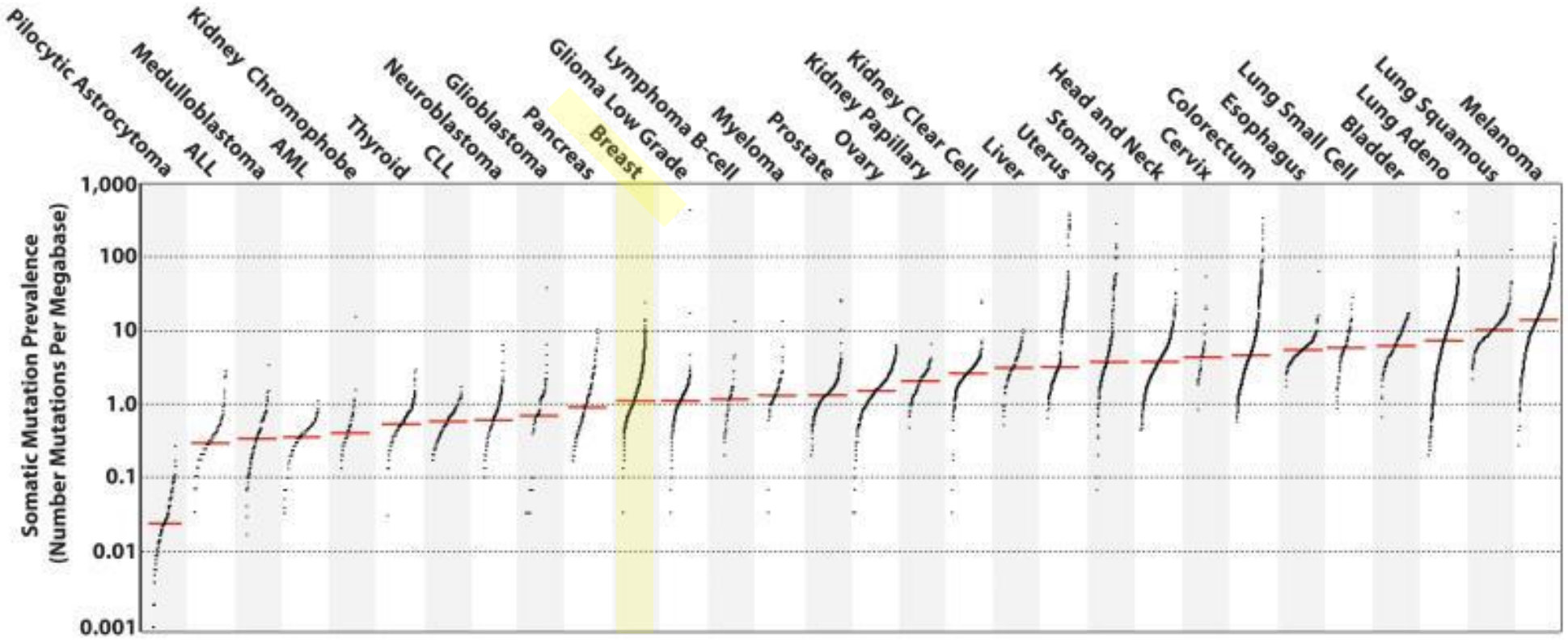
Immunotherapy in breast and gynecologic cancers



Alexandrov, Nature 2013.

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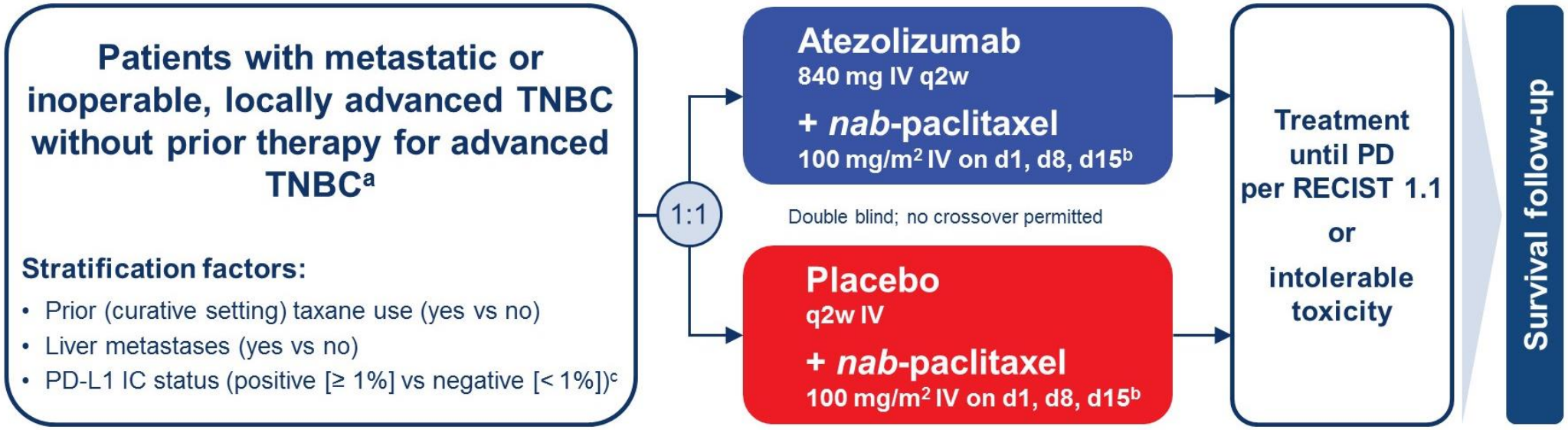
Current approvals in breast cancer

Checkpoint inhibitor	Approved	Indication	Dose
Pembrolizumab	2017	MSI-H/dMMR **advanced cancer** with progression on previous treatment	200 mg Q3W or 400 mg Q6W
Atezolizumab + nab-paclitaxel or paclitaxel protein-bound	2019	Advanced/Metastatic **TNBC** with PD-L1 ≥1% immune cells	840 mg atezolizumab Q2W + 100 mg/m^2 nab-paclitaxel on days 1, 8, 15
Pembrolizumab	2020	TMB-high **solid tumors** with progression on prior treatment	200 mg Q3W or 400 mg Q6W
Pembrolizumab + chemotherapy	2020	Advanced/Metastatic **TNBC** with CPS score >10%	200 mg Q3W or 400 mg Q6W
Antibody-drug conjugate	**Approved**	**Indication**	**Dose**
Ado-trastuzumab emtansine	2019	Adjuvant treatment of **HER2-positive** early breast cancer	3.6 mg/kg Q3W
Fam-trastuzumab deruxtecan-nxki	2019	Unresectable/metastatic **HER2-positive** breast cancer after 2+ HER2 regimens	5.4 mg/kg Q3W
Sacituzumab govitecan	2020	Metastatic **TNBC** after two previous therapies	10mg/kg on D1&D8 of 21-day cycle

Clinical Data – IMpassion130 PD-L1+ TNBC

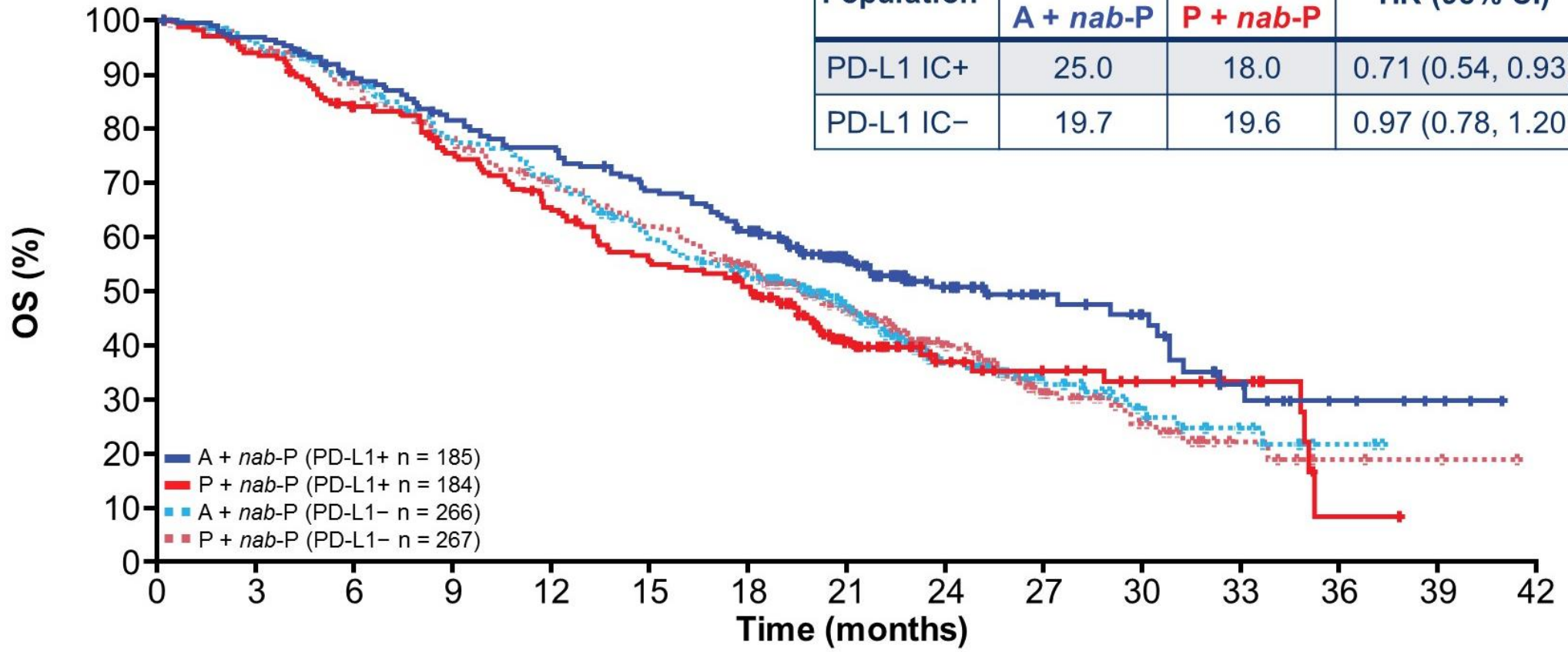


- Co-primary endpoints in ITT and PD-L1 IC+: PFS and OS[d]
- Pre-specified hierarchical testing of OS in ITT and, if significant, in PD-L1 IC+ patients
- In both treatment arms, 41% of patients were PD-L1 IC+

Schmid, ASCO 2019.

Clinical Data – IMpassion130 PD-L1+ TNBC

Population	Median OS, mo		HR (95% CI)
	A + *nab*-P	P + *nab*-P	
PD-L1 IC+	25.0	18.0	0.71 (0.54, 0.93)
PD-L1 IC−	19.7	19.6	0.97 (0.78, 1.20)



Schmid, ASCO 2019.

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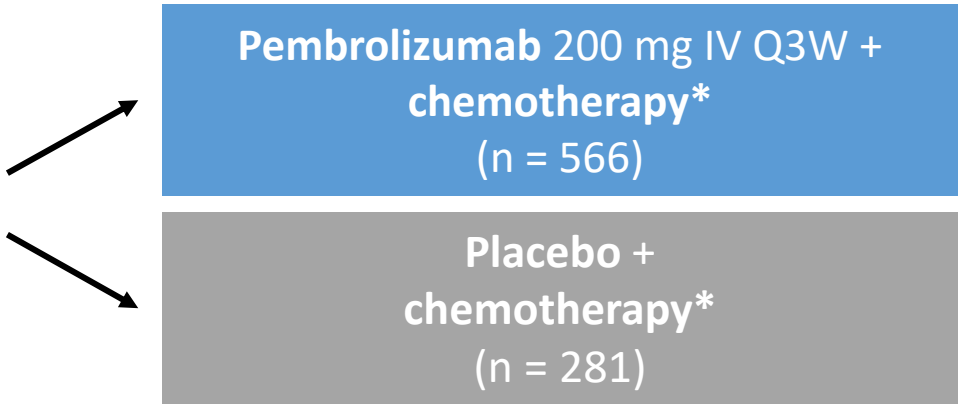
KEYNOTE-355: Study Design

- Randomized, double-blind, multicenter phase III trial

Stratified by chemotherapy (taxane vs gem/carbo); PD-L1 tumor expression (CPS > 1 vs < 1); previous Tx with same class of chemotherapy for EBC (Y vs N)

Adults with previously untreated locally recurrent inoperable or metastatic TNBC; completed curative intent Tx ≥ 6 mos before first recurrence
(N = 847)



Until progression, toxicity, or completion of 35 cycles of pembrolizumab/placebo

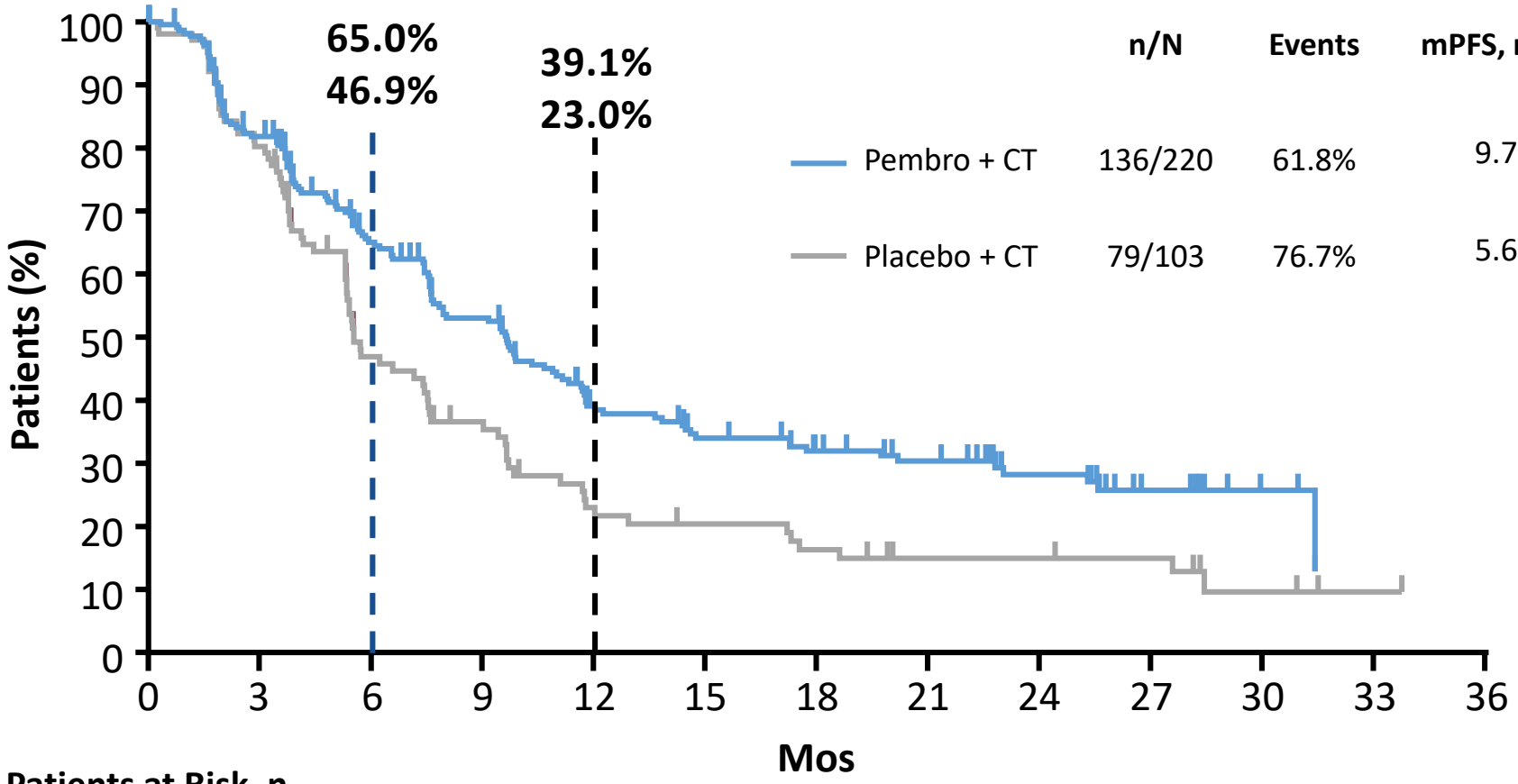
***Investigator's choice of chemotherapy:**

- **Nab-paclitaxel** 100 mg/m^2 IV on Days 1, 8, 15 of 28-day cycle
- **Paclitaxel** 90 mg/m^2 IV on Days 1, 8, 15 of 28-day cycle
- **Gem** 1000 mg/m^2 + carbo AUC 2 on Days 1, 8 of 21-day cycle

- Primary endpoints: PFS and OS (PD-L1 CPS ≥ 10, PD-L1 CPS ≥ 1, and ITT)
- Secondary endpoints: ORR, DoR, DCR, safety

Cortes. ASCO 2020. Abstr 1000.

KEYNOTE-355: PFS in PD-L1 CPS ≥ 10 Population



	n/N	Events	mPFS, mos	HR (95% CI)	*P* value (1-sided)
Pembro + CT	136/220	61.8%	9.7	0.65 (0.49-0.86)	.0012
Placebo + CT	79/103	76.7%	5.6		

Patients at Risk, n

220	173	122	96	63	52	44	37	25	12	5	0	0
103	80	41	30	18	15	12	8	8	7	3	1	0

Cortes. ASCO 2020. Abstr 1000.

San Antonio Breast Cancer Symposium®, December 8-12, 2020

ASCENT

ASCENT: A Phase 3 Confirmatory Study of Sacituzumab Govitecan in Refractory/Relapsed mTNBC

Metastatic TNBC
(per ASCO/CAP)
≥2 chemotherapies for advanced disease
[no upper limit; 1 of the required prior regimens could be progression occurred within a 12-month period after completion of (neo)adjuvant therapy]
N=529

NCT02574455

R 1:1

Sacituzumab Govitecan (SG)
10 mg/kg IV
days 1 & 8, every 21-day cycle
(n=267)

Treatment of Physician's Choice (TPC)*
(n=262)

Continue treatment until progression or unacceptable toxicity

Endpoints

Primary
- PFS†

Secondary
- PFS for the full population‡
- OS, ORR, DOR, TTR, safety

Exploratory
- **Biomarkers**

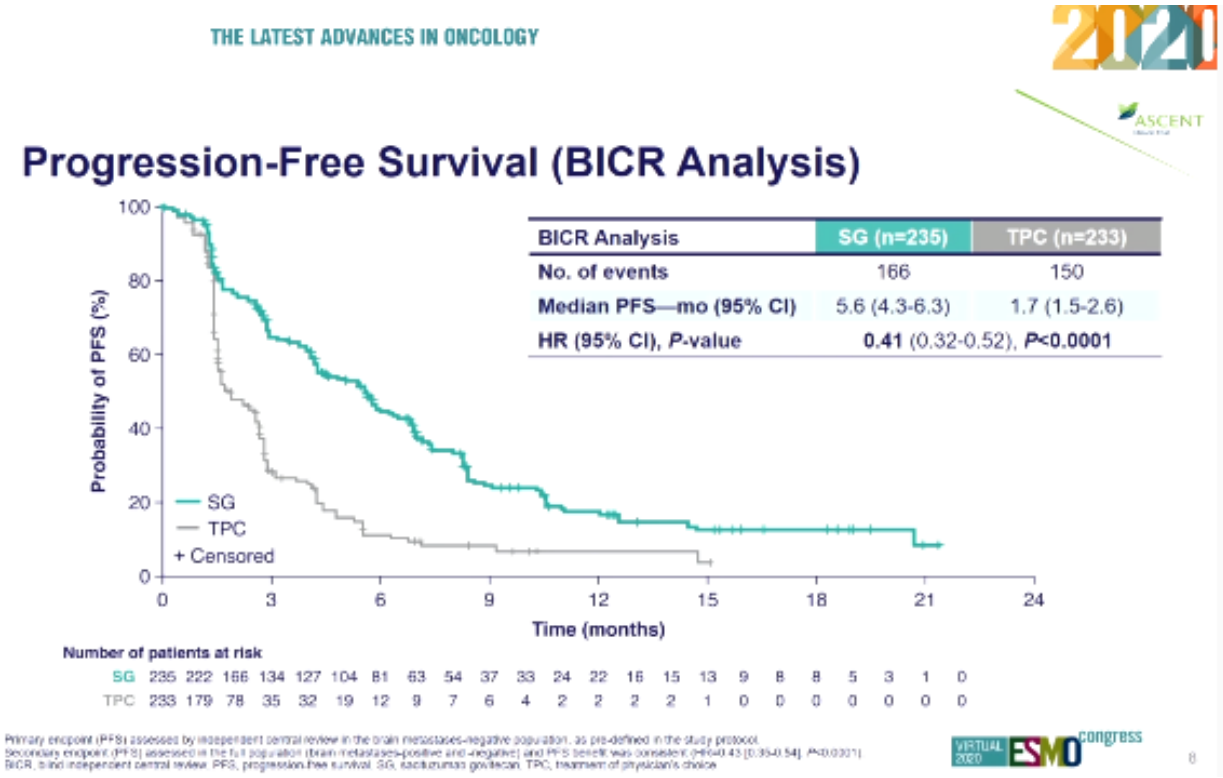
Data cutoff: March 11, 2020

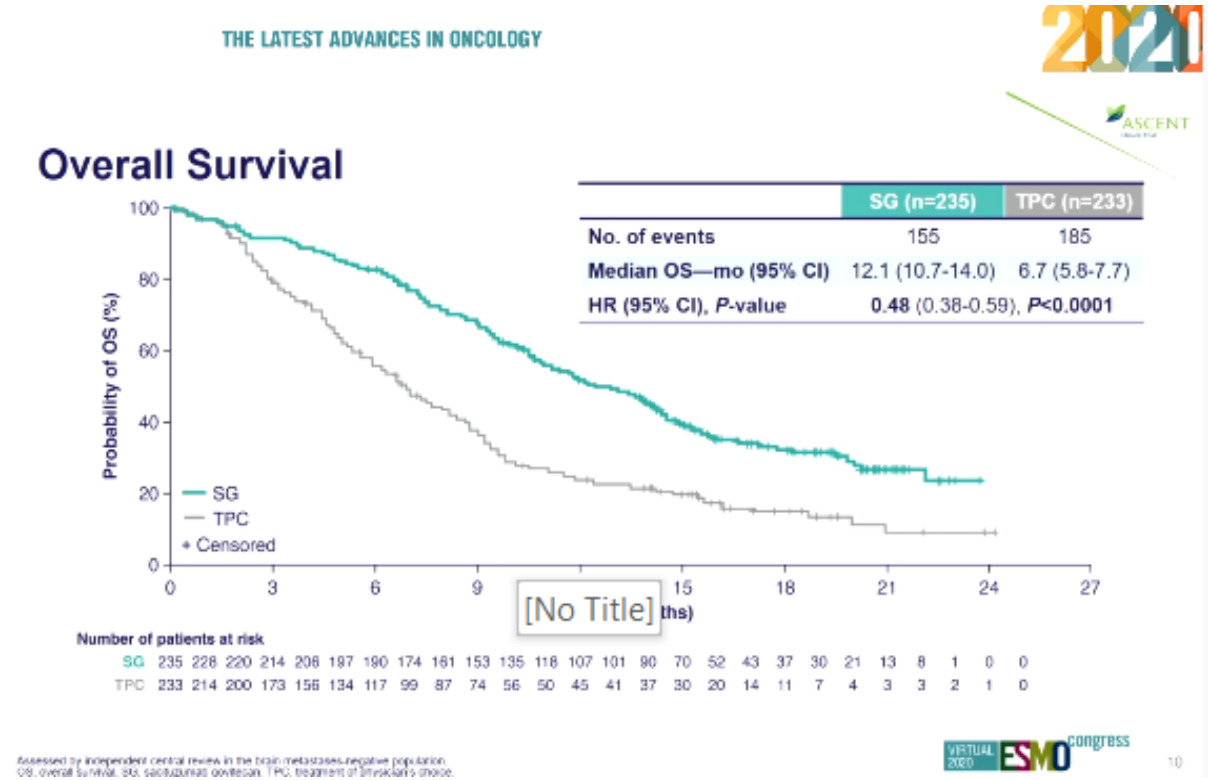
Stratification factors
- Number of prior chemotherapies (2-3 vs >3)
- Geographic region (North America vs Europe)
- Presence/absence of known brain metastases (yes/no)

We report the exploratory biomarker analysis in the brain metastases-negative (Brain Mets-Negative) population

*TPC: eribulin, vinorelbine, gemcitabine, or capecitabine. †PFS measured by an independent, centralized, and blinded group of radiology experts who assessed tumor response using RECIST 1.1 criteria in patients without brain metastasis. ‡The full population includes all randomized patients (with and without brain metastases). Baseline brain MRI only required for patients with known brain metastasis.
ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; DOR, duration of response; DSMC, Data Safety Monitoring Committee; IV, intravenous; mTNBC, metastatic triple-negative breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response.
National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT02574455.

Sacituzumab govitecan in TNBC





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KATHERINE: Trastuzumab Emtansine vs Trastuzumab as Adjuvant Therapy for HER2+ EBC

- International, randomized, open-label phase III study

Stratified by clinical stage, HR status, single vs dual neoadjuvant HER2-targeted therapy, pathologic nodal status after neoadjuvant therapy

Patients with HER2+ EBC (cT1-4/N0-3/M0) who had residual invasive disease in breast or axillary nodes after neoadjuvant chemotherapy plus HER2-targeted therapy* at surgery
(N = 1486)

→ T-DM1† 3.6 mg/kg IV Q3W x 14 cycles (n = 743)

→ Trastuzumab 6 mg/kg IV Q3W x 14 cycles (n = 743)

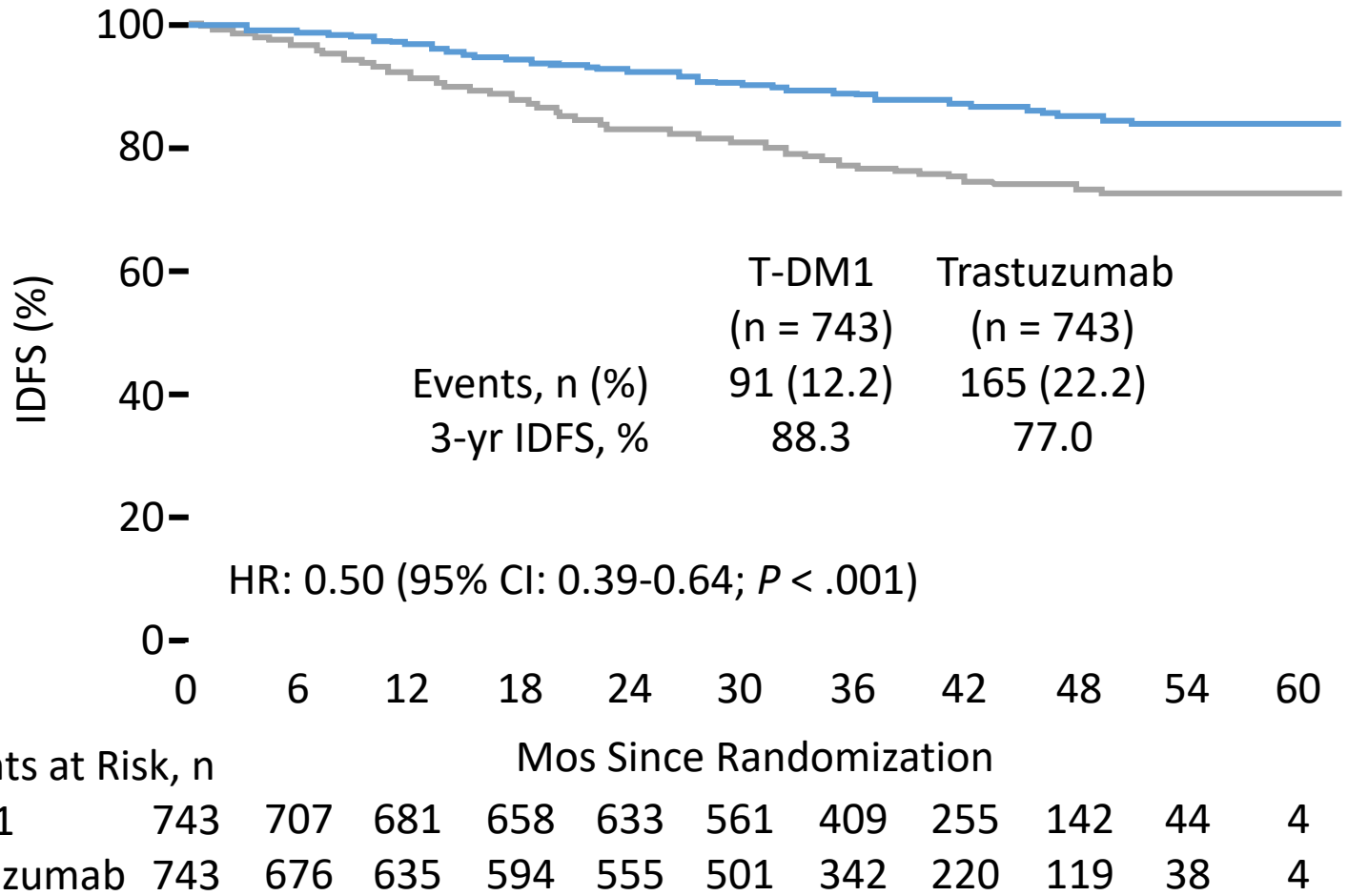
Randomization occurred within 12 wks of surgery; radiotherapy and/or endocrine therapy given per local standards. *Minimum of 9 wks taxane and trastuzumab. †Patients who d/c T-DM1 for toxicity allowed to switch to trastuzumab to complete 14 cycles.

Primary endpoint: IDFS

Secondary endpoints: distant recurrence-free survival, OS, safety

Geyer. SABCS 2018. Abstr GS1-10. von Minckwitz. NEJM. 2019;380:617.

KATHERINE: IDFS



First IDFS Event, %	T-DM1	T
Any	12.2	22.2
Distant recurrence	10.5*	15.9†
Locoregional recurrence	1.1	4.6
Contralateral breast cancer	0.4	1.3
Death without prior event	0.3	0.4

CNS events: *5.9% vs †4.3%.

von Minckwitz. NEJM. 2019;380:617.

In the Pipeline

- Immune checkpoint inhibitors + chemotherapy as neoadjuvant/adjuvant therapy for TNBC
- Immune checkpoint inhibitors + anti-HER2 agents for HER2+
- PARP inhibitors and ICIs
- Combination Immunotherapy
- Antibody Drug Conjugates
  - Margetuximab for HER2+
  - Trastuzumab Deruxtecan for HER2 low+
  - Trastuzumab Duocarmazine for HER2+

Biomarkers and immunotherapy responsiveness in breast cancers

- Potential markers of responsiveness include:
  - PD-L1
  - Tumor infiltrating lymphocytes
  - Mutational signatures

FDA-approved biomarkers only include:
- PD-L1+ by SP142
- PD-L1+ by CPS score, 22C3
- TMB 10 or more
- MSI high

ADDITIONAL TARGETED THERAPIES AND ASSOCIATED BIOMARKER TESTING FOR RECURRENT OR STAGE IV (M1) DISEASE

Biomarkers Associated with FDA-Approved Therapies					
Breast Cancer Subtype	**Biomarker**	**Detection**	**FDA-Approved Agents**	**NCCN Category of Evidence**	**NCCN Category of Preference**
Any[a]	*BRCA1* mutation *BRCA2* mutation	Germline sequencing	Olaparib Talazoparib	Category 1 Category 1	Preferred Preferred
HR-positive/ HER2-negative[b]	*PIK3CA* mutation	PCR (blood or tissue block if blood negative), molecular panel testing	Alpelisib + fulvestrant[d]	Category 1	Preferred second-line therapy
HR-negative/ HER2-negative[c]	PD-L1 expression • Threshold for positivity: ≥1% on tumor-infiltrating immune cells	IHC	Atezolizumab + albumin-bound paclitaxel	Category 2A	Preferred
Any	*NTRK* fusion	FISH, NGS, PCR (tissue block)	Larotrectinib[e] Entrectinib[e]	Category 2A Category 2A	Useful in certain circumstances[e] Useful in certain circumstances[e]
Any	MSI-H/dMMR	IHC, PCR (tissue block)	Pembrolizumab[f]	Category 2A	Useful in certain circumstances[f]

NCCN Guidelines.

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Case Study

- 52 yo F presents with a palpable mass in the left breast, measuring 4 x 3.5 cm on imaging, with palpable lymph node. Clinical Stage IIB ER-, PR-, HER2+ Breast Cancer
- Receives adjuvant docetaxel, carboplatin, trastuzumab and pertuzumab (TCHP) chemotherapy x 6 cycles with a complete clinical and partial pathologic response at lumpectomy and sentinel lymph node evaluation (ypT1B, ypN0).
- What are the next steps for systemic adjuvant therapy?

Case Study: Question #1

1. Continue trastuzumab and pertuzumab to complete a year of therapy
2. Continue trastuzumab only to complete a year of therapy
3. Switch to ado-trastuzumab emtansine to complete a year of therapy
4. No further therapy

Case study, continued

- She switches to ado-trastuzumab emtansine and completes a year of therapy
- 14 months later, she recurs in liver and lung. Biopsy shows ER-PR-HER2+ MBC. She receives paclitaxel, trastuzumab and pertuzumab with stable disease for 7 months, then progresses
- She then receives tucatinib, capecitabine and trastuzumab for 4 months and progresses
- What is your next treatment choice?

Case Study, Question #2

1. Switch to trastuzumab and lapatinib
2. No further therapy
3. Switch to ado-trastuzumab emtansine
4. Switch to trastuzumab deruxtecan
5. Switch to trastuzumab + vinorelbine

Case study, continued

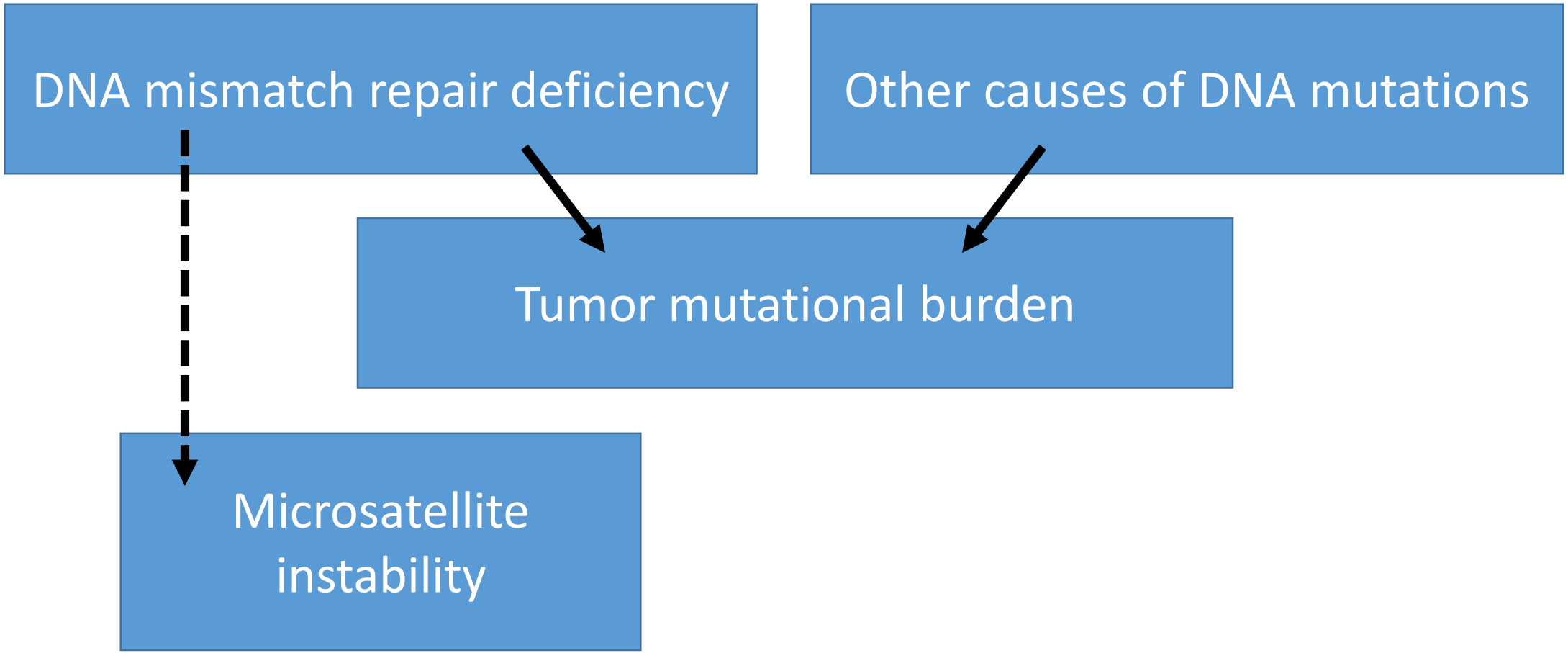
- She switches to trastuzumab deruxtecan and is in ongoing reponse at 10+ months

Immunotherapy for the Treatment of Microsatellite Instability or Tumor Mutational Burden – High Cancers

A few definitions

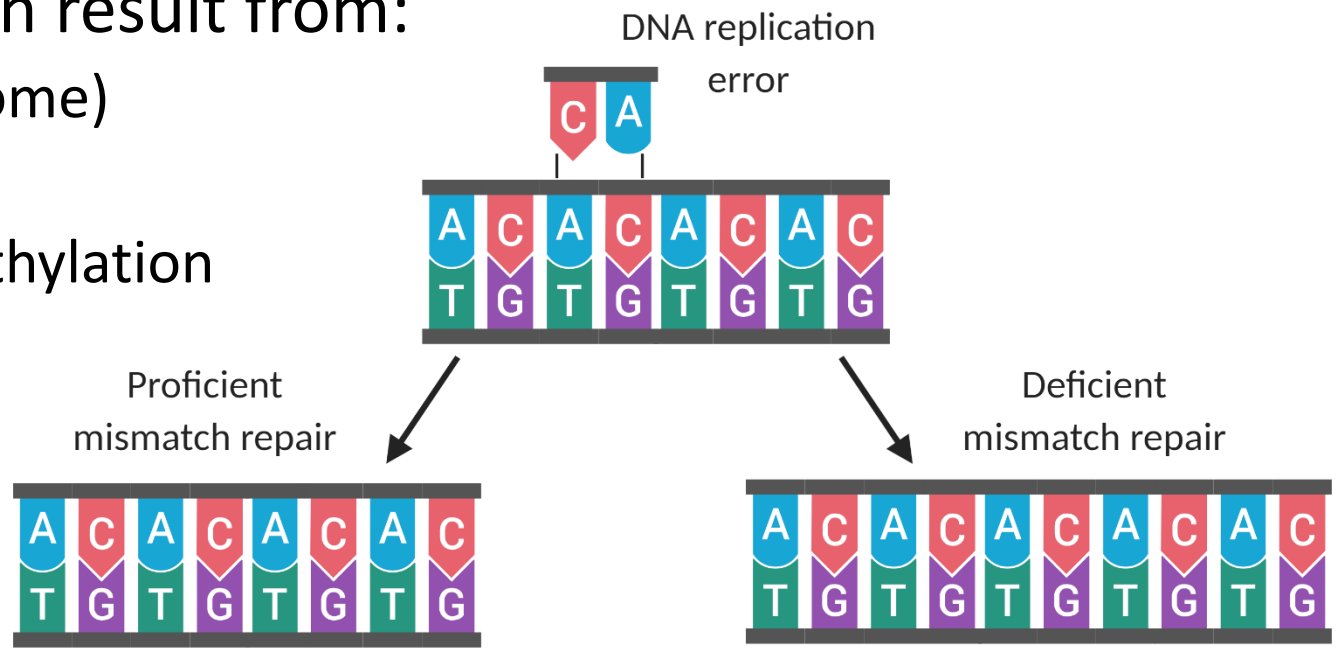
- **DNA mismatch repair deficiency:** Sub-optimal cell machinery for fixing mistakes made during DNA replication.
- **Microsatellite instability:** The number of repeated DNA bases in a microsatellite changes during DNA copying. The presence of MSI is phenotypic evidence that DNA mismatch repair is not functioning properly.
- **Tumor mutational burden:** The number of mutations in a cancer's genome

A few definitions



DNA mismatch repair

- MMR dysfunction can be caused by mutations in genes that code for MMR proteins (MLH1, MSH2, MSH6, PMS2)
- Mutations in MMR proteins can result from:
  - Hereditary causes (Lynch syndrome)
  - Somatic mutations
  - Silencing through promoter methylation



Somatic mutation: *an alteration in DNA that occurs after birth; can occur in any non-germline cell*

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Microsatellite Instability

Microsatellites are stretches of DNA with a repetitive sequence of nucleotides and are susceptible to acquiring errors when defective MMR genes are present.

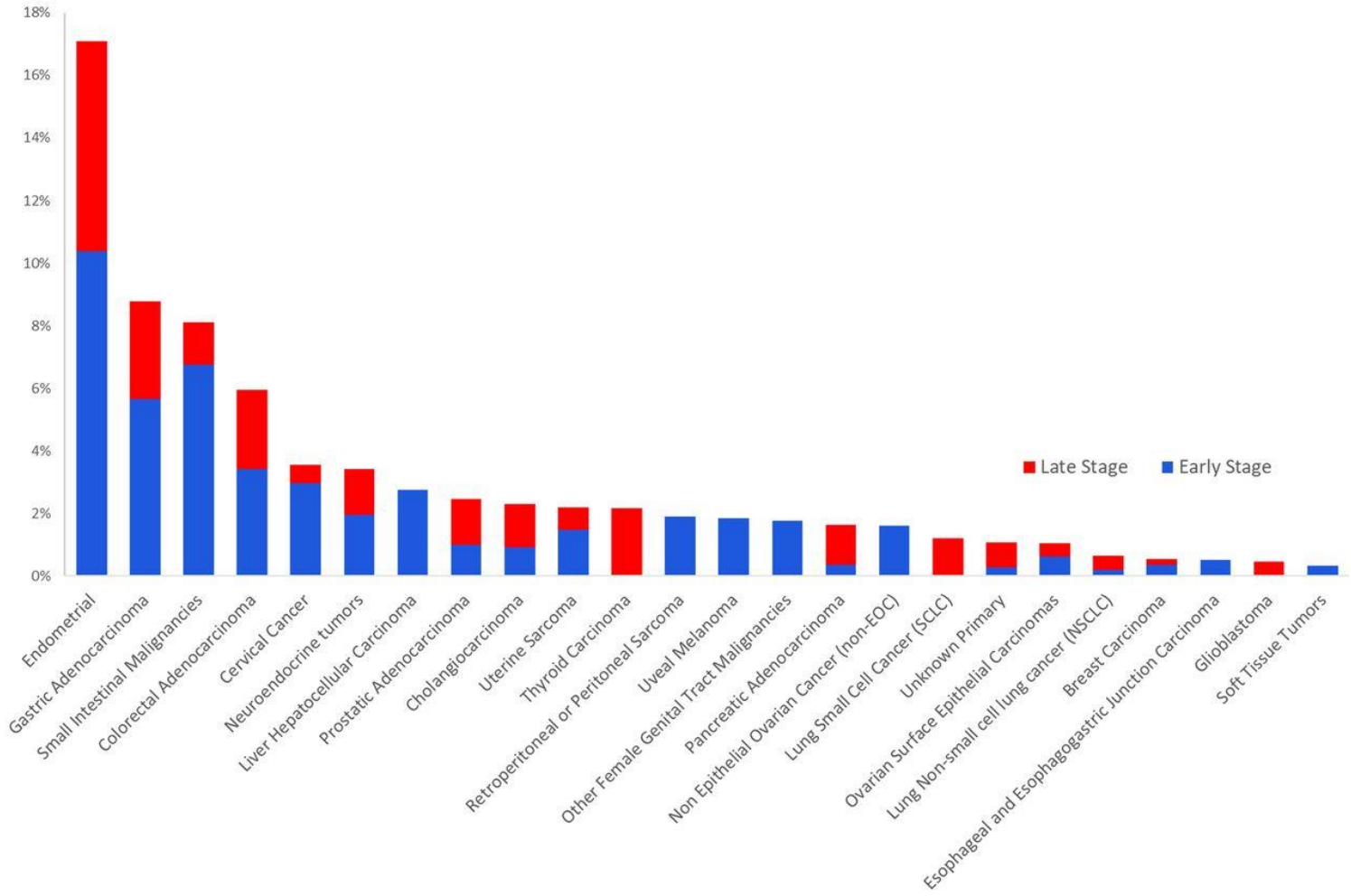
Method to measure MSI/MMR	What is measured?
Polymerase chain reaction (PCR)	5 targeted mononucleotide loci in the cancer DNA
Immunohistochemical staining (IHC)	Presence or absence of MMR proteins in sample
Next-generation sequencing (NGS)	Compares microsatellite sequences to matched normal or consensus sequence

Tumor mutational burden

TMB is a measure of the somatic mutations per area of a tumor's genome, reported in mutations/megabase (mut/Mb).

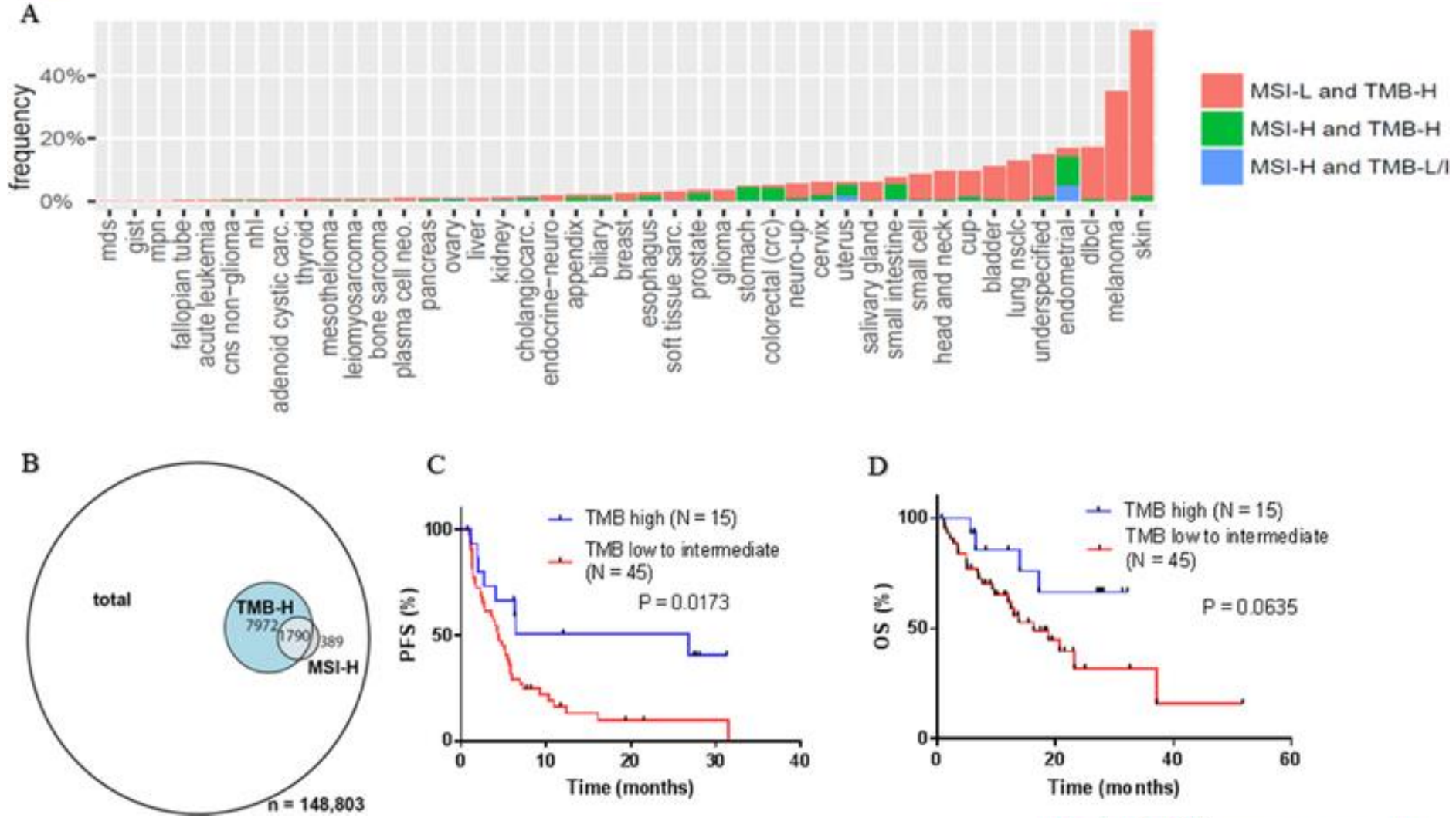
Method to measure TMB	What is measured?
Whole-exome sequencing (WES)	Sequencing all the protein-encoding regions of a tumor's DNA
Targeted panels	Sequencing of smaller portions of tumor's DNA

Many tumors are MSI-high or MMR-deficient



Le, Science 2017.

Relationship between TMB and MSI



Goodman, Cancer Immunol Res 2019.

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FDA-approved immunotherapies for MSI-high or TMB-high populations

	Drug	Indication	Dose
Tissue-agnostic	Pembrolizumab	Adult/pediatric patients with unresectable/metastatic **MSI-H or dMMR solid tumors** with progression on other treatment	Adults: 200 mg Q3W or 400 mg Q6W Pediatric: 2 mg/kg (up to 200 mg) Q3W
	Pembrolizumab	Adult/pediatric patients with unresectable/metastatic **TMB-high solid tumors** with progression on other treatment	Adults: 200 mg Q3W or 400 mg Q6W Pediatric: 2 mg/kg (up to 200 mg) Q3W
Colorectal cancer	Nivolumab	Patients >12 yr with **MSI-H/dMMR metastatic CRC** with progression after fluoropyrimidine, oxaliplatin, and irinotecan	≥40 kg: 240 mg Q2W or 480 mg Q4W <40 kg: 3 mg/kg Q2W
	Ipilimumab + nivolumab	Patients >12 yr with **MSI-H/dMMR metastatic CRC** with progression after fluoropyrimidine, oxaliplatin, and irinotecan	≥40 kg: 3 mg/kg nivolumab + 1 mg/kg ipilimumab Q3W for 4 doses, Then nivolumab 240 mg Q2W or 480 mg Q4W
	Pembrolizumab	**MSI-H or dMMR colorectal cancer** with progression after fluoropyrimidine, oxaliplatin, and irinotecan Or First-line treatment of **MSI-H or dMMR colorectal cancer**	Adults: 200 mg Q3W or 400 mg Q6W Pediatric: 2 mg/kg (up to 200 mg) Q3W

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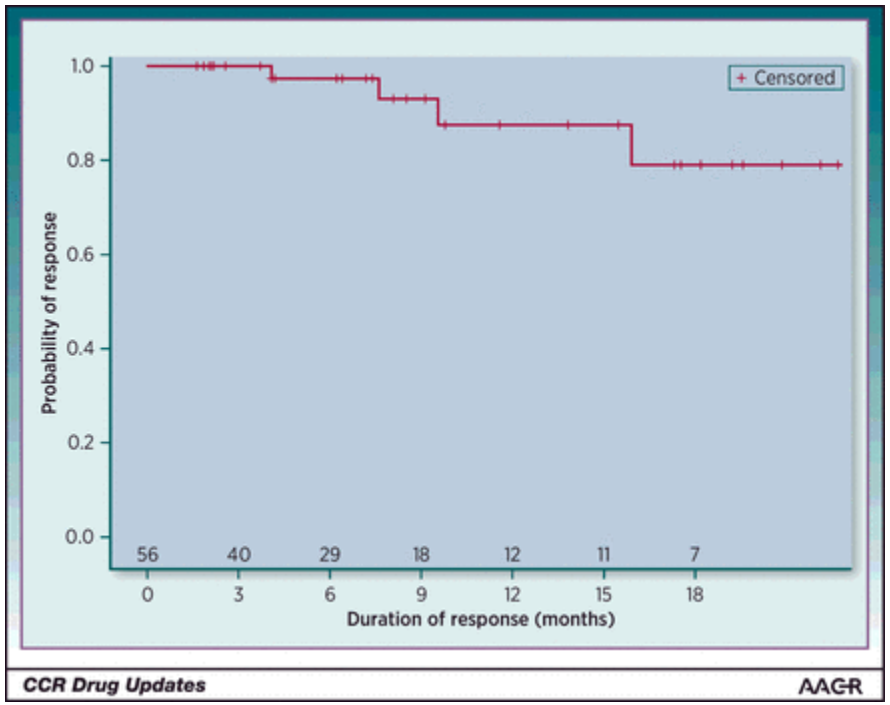
Pembrolizumab in MSI-high cancers

Trial	Study population
KEYNOTE-016	Colorectal cancer Non-colorectal cancer
KEYNOTE-164	Colorectal cancer
KEYNOTE-012	Retrospectively identified, PD-L1+ cancers
KEYNOTE-028	Retrospectively identified, PD-L1+ cancers
KEYNOTE-158	Non-colorectal cancers

All studies combined:
ORR: 39.6%
CR rate: 7%
78% of responses lasted ≥ 6 mo.



Marcus, Clin Cancer Res 2019.

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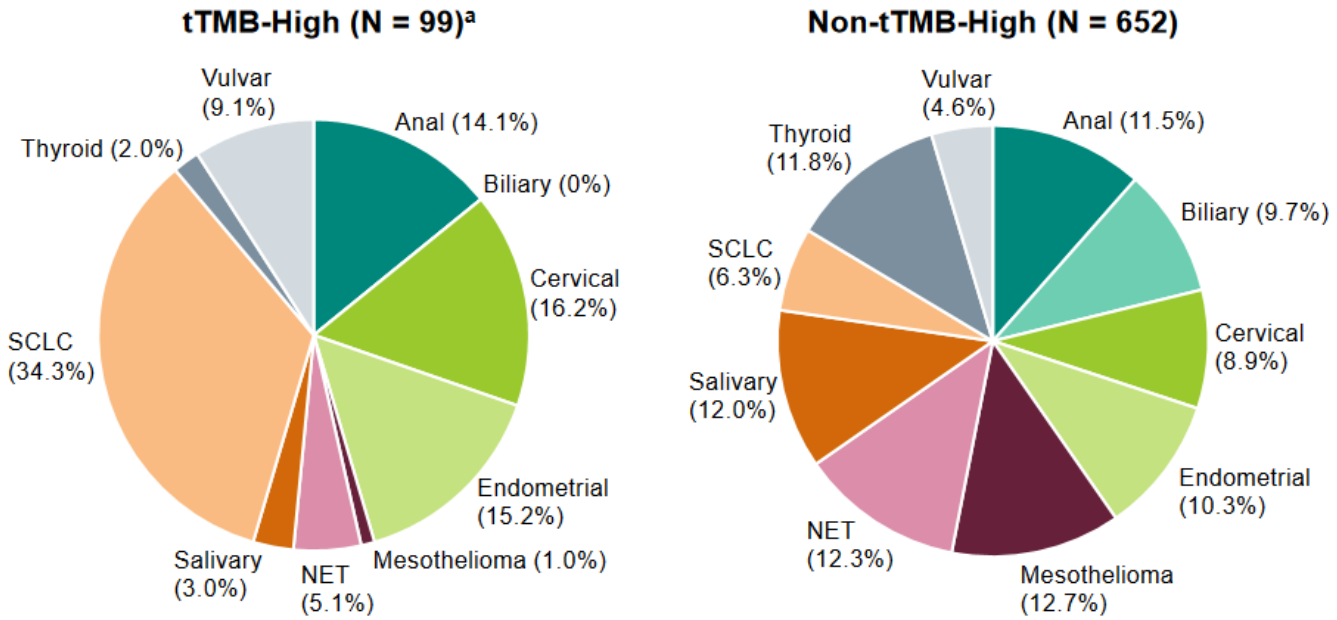
Pembrolizumab in TMB-high tumors

- Retrospective (but planned) analysis of KEYNOTE-158
- 13% of patients on the trial had TMB-high tumors (≥10 mut/Mb)



Marabelle, ESMO 2019

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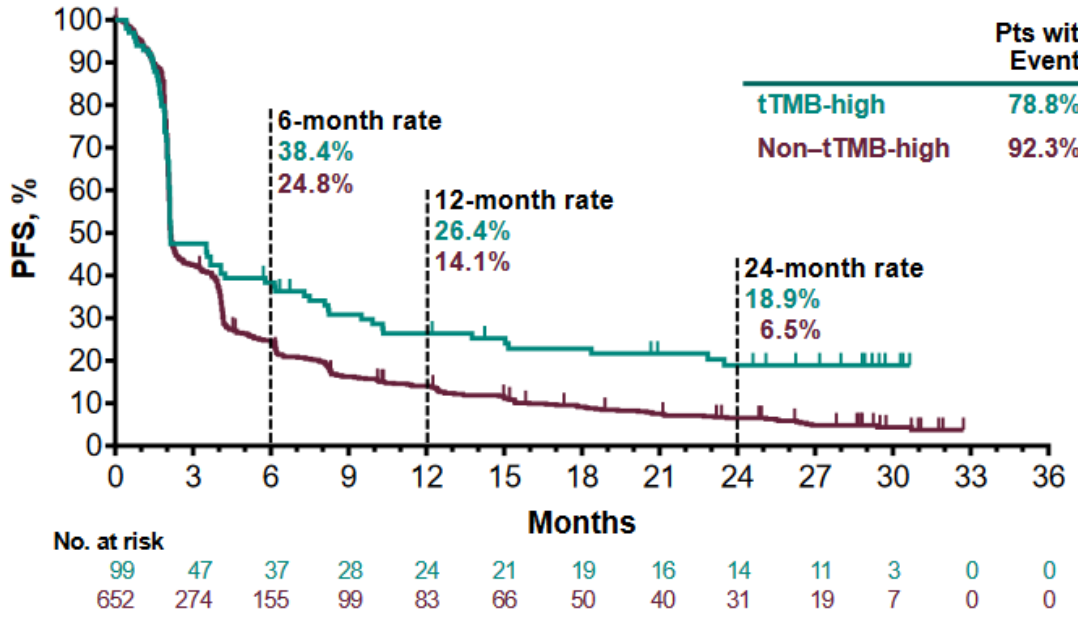
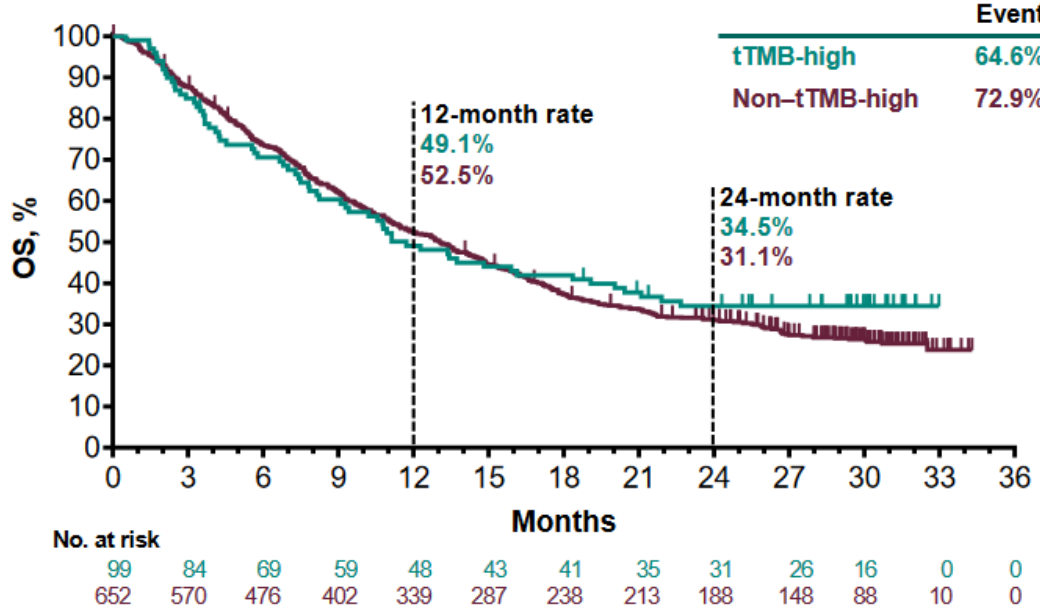
Pembrolizumab in TMB-high tumors



	Pts with Event	Median (95% CI), mo
tTMB-high	78.8%	2.1 (2.1-4.1)
Non–tTMB-high	92.3%	2.1 (2.1-2.3)



	Pts with Event	Median (95% CI), mo
tTMB-high	64.6%	11.7 (8.2-19.1)
Non–tTMB-high	72.9%	13.0 (11.5-14.6)

Marabelle, ESMO 2019

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Future Directions

- No standard companion diagnostic test for all approvals – subjectivity of interpreting results; lack of consistency
- Not every clinic has access to these resources for measuring MSI/MMR/TMB (PCR, IHC, NGS) – may limit who can use the treatment
- Laid the groundwork for future biomarker-related drug approvals