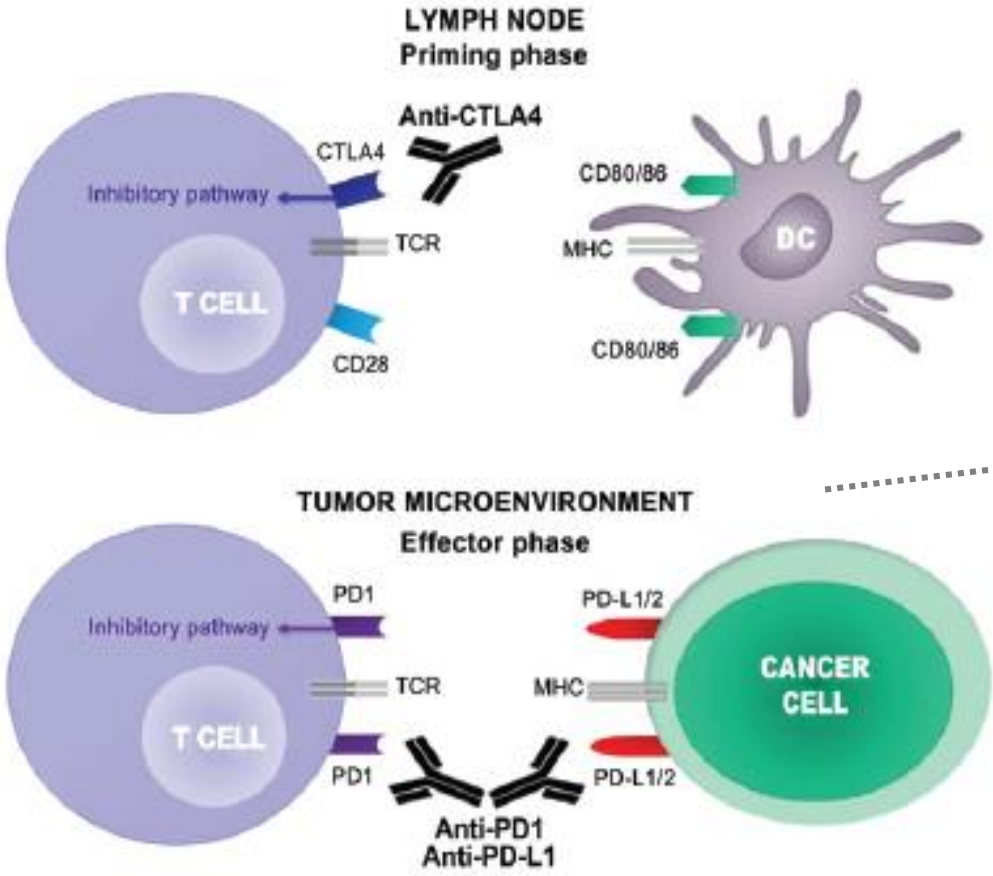
Types of Immunotherapy Used in Gynecologic Cancers and Current Approvals

Nora Disis
University of Washington
Fred Hutchinson Cancer Research Center
ndisis@uw.edu

Disclosures

- Fees for Non CE Services: SITC, PER
- Contracted Research: Pfizer, EMD Serono, Bavarian Nordisk, Precigen, Epithany, Veanna
- Other: Editor-in-Chief, JAMA Oncology
- Ownership Interest Greater Than 5 Percent: Epithany

Immune checkpoint inhibitors in gynecologic malignancy



Stucci et al, Onc Lett, 2017

Not FDA Approved

Ipilimumab

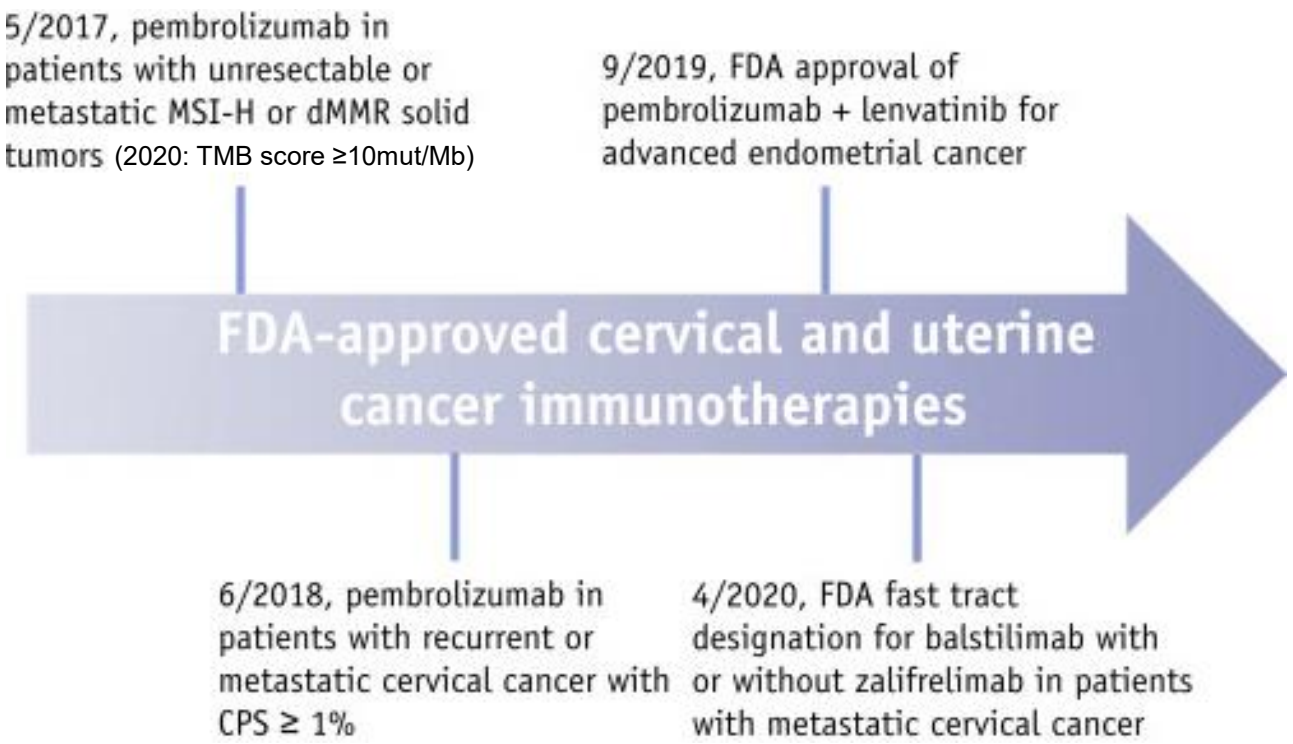
FDA Approved

Immune Checkpoint Inhibitor	Molecular Target	Gynecological Malignancies
Pembrolizumab	PD-1	Endometrial, ovarian and cervical cancer
Cemiplimab	PD-1	Cervical cancer
Nivolumab	PD-1	Ovarian cancer
Durvalumab	PD-L1	Ovarian cancer
Avelumab	PD-L1	Endometrial and ovarian cancer
Atezolizumab	PD-L1	Cervical cancer

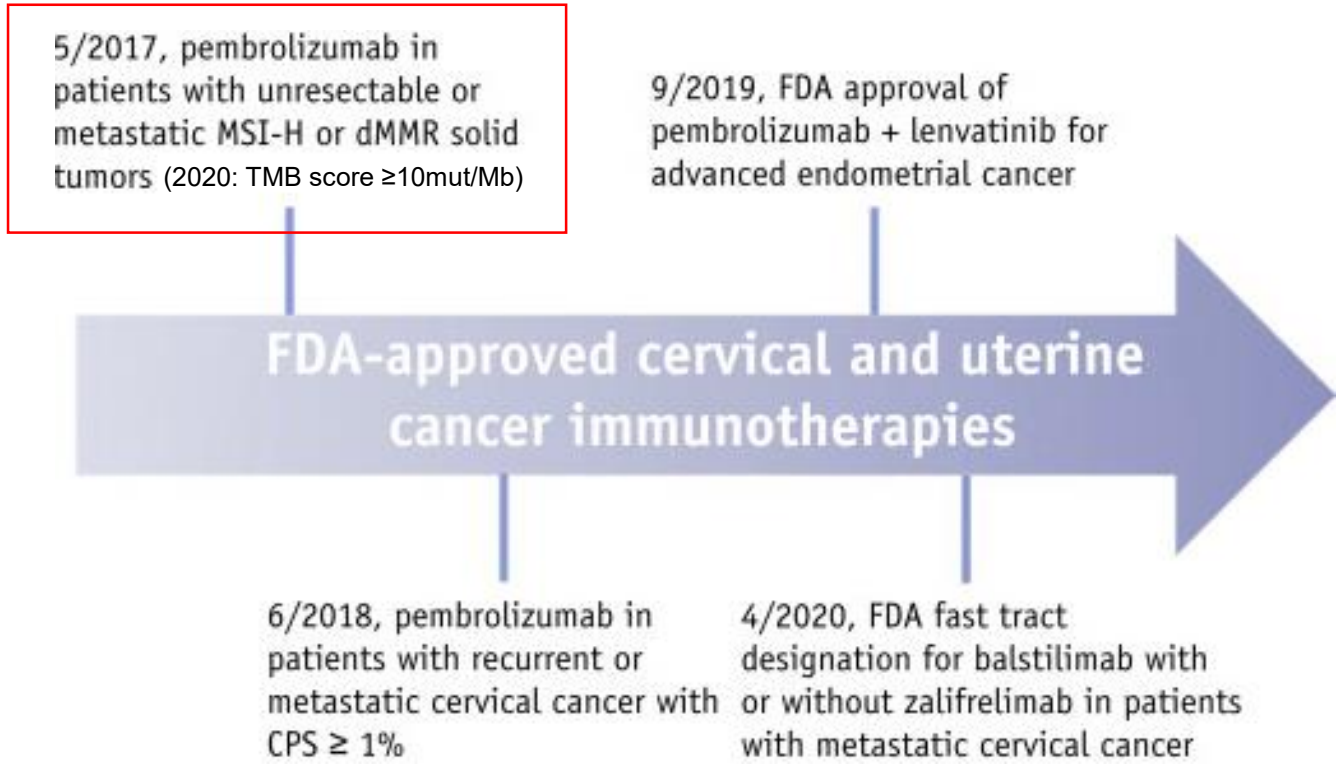
They are usually administered in combination to standard chemotherapy or other experimental agents. PD-L1 = programmed cell death protein 1 ligand, PD-1 = programmed cell death protein 1

Russo et al, KJR, 2021

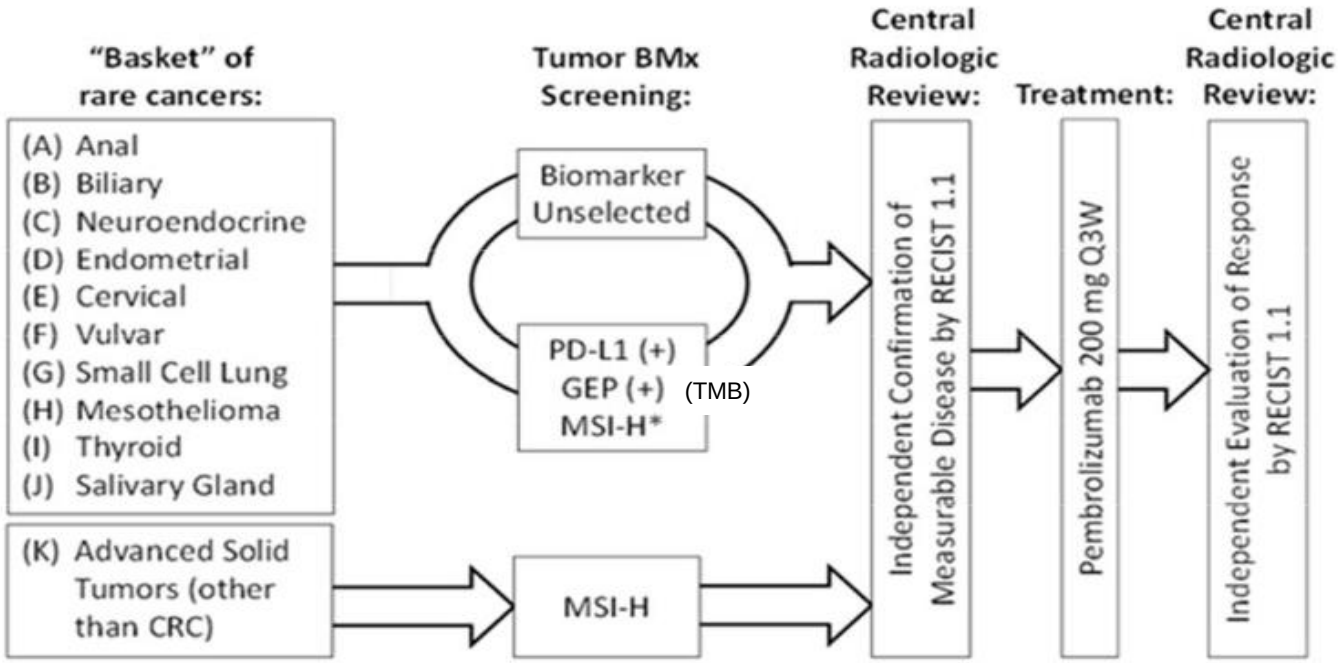
FDA approval timeline



FDA approval timeline

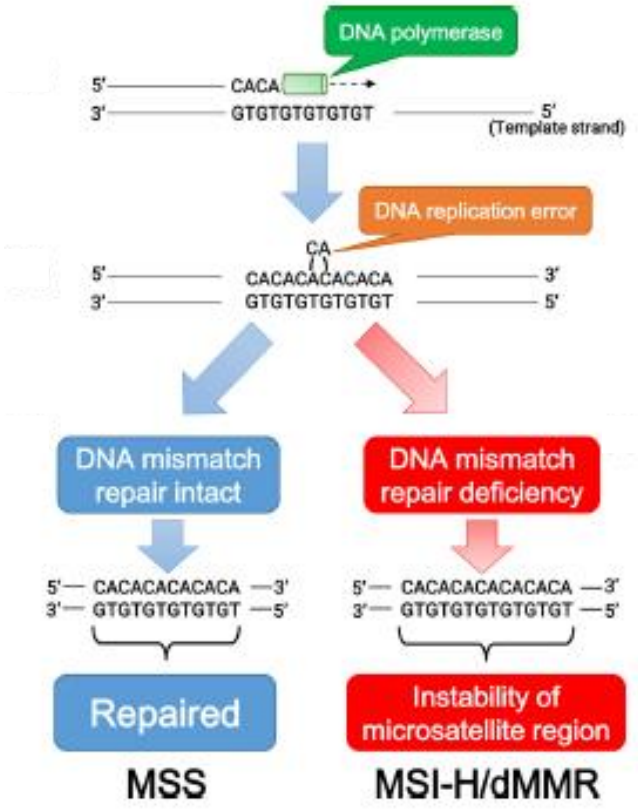


Keynote biomarker enrichment trial



KEYNOTE 158

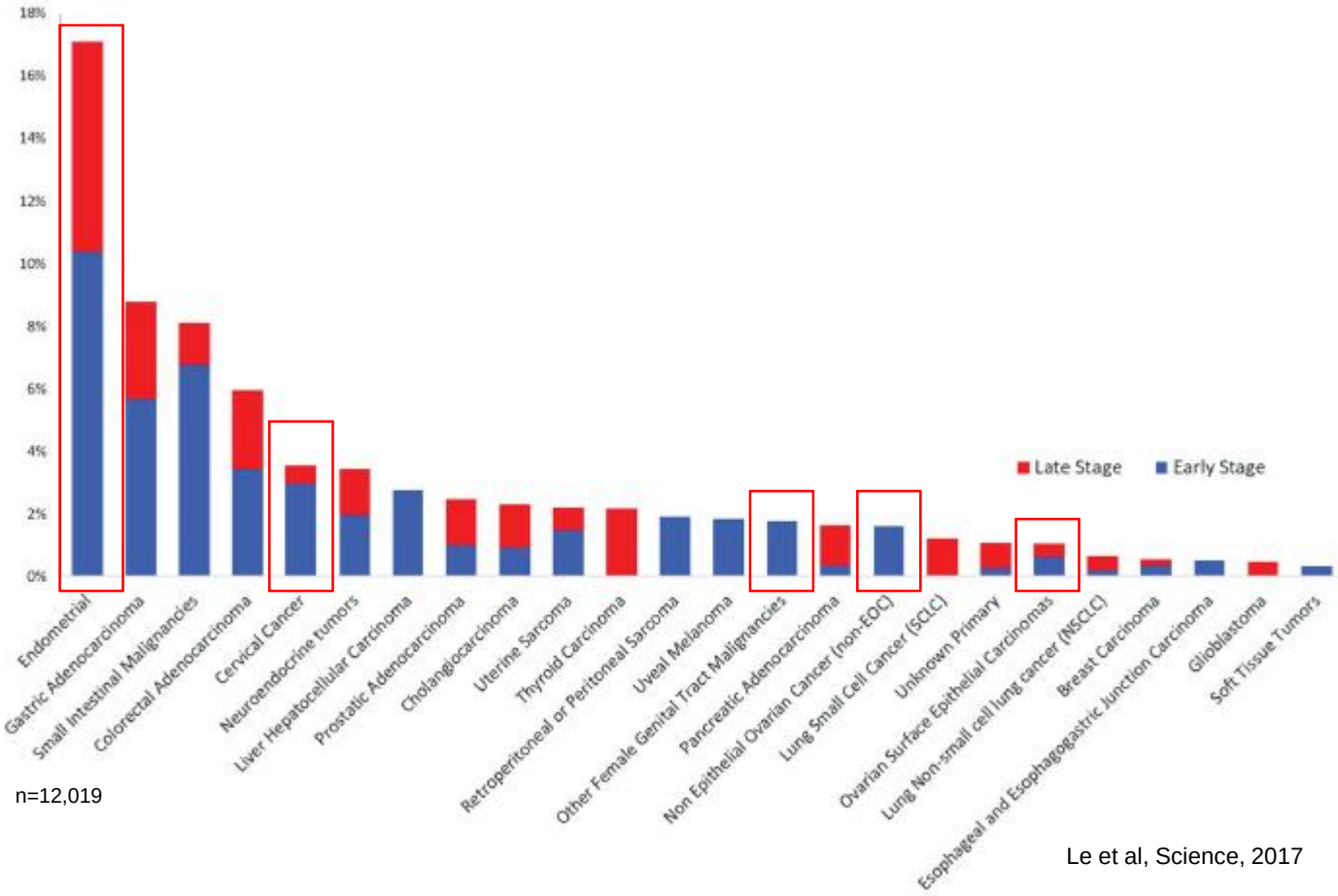
Biomarker based treatment: dMMR and MSI^{high}



Microsatellite stable

Microsatellite instability high
Mismatch repair deficiency

Eso et al, J Gastroenterol, 2019

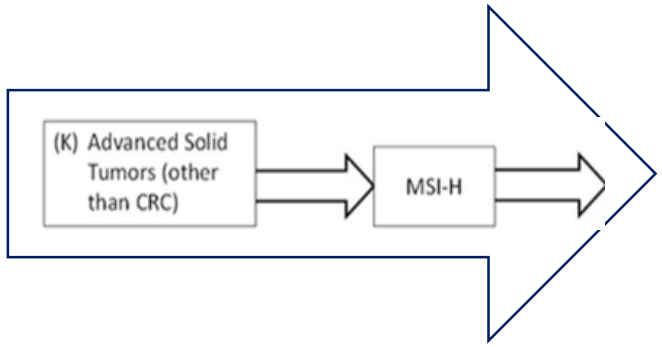


n=12,019

Le et al, Science, 2017

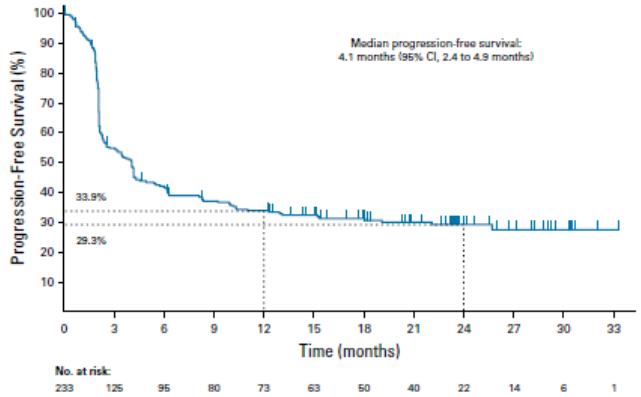
Single agent pembrolizumab in advanced recurrent MSI-H/dMMR gynecologic malignancies

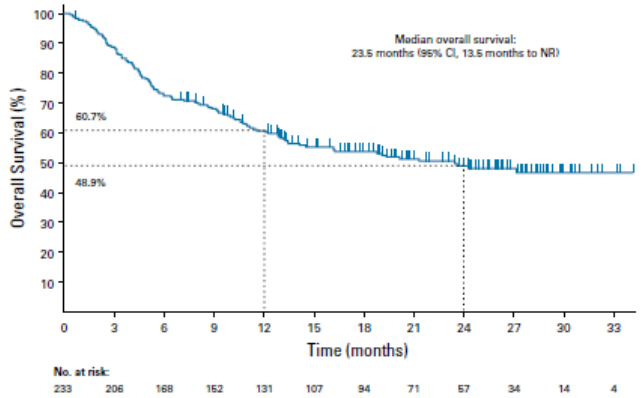
KEYNOTE 158: Biomarker Enrichment



MSI-H/dMMR
Non-colorectal
Advanced/progressive
Pembrolizumab 200mg q 3 weeks
2 years or until progression

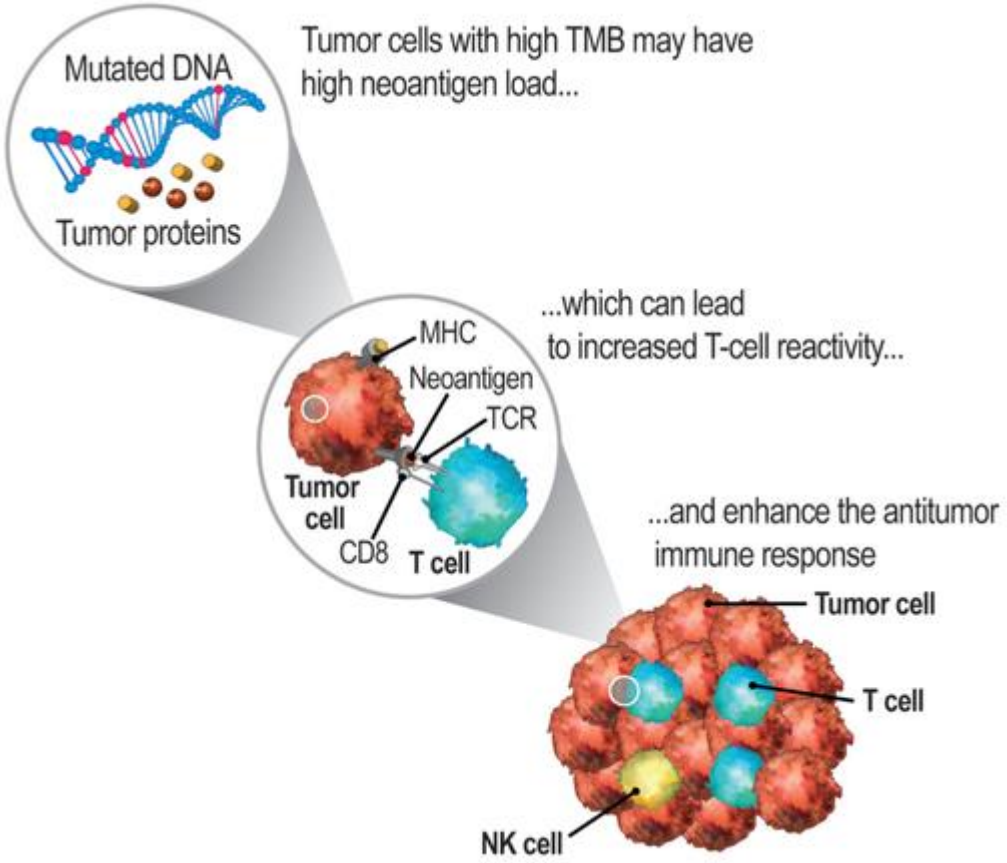
Cancer type of primary diagnosis	n=233	CR	PR
Endometrial	49 (21.0)	16%	41%
Gastric	24 (10.3)		
Cholangiocarcinoma	22 (9.4)		
Pancreatic	22 (9.4)		
Small intestine	19 (8.2)		
Ovarian	15 (6.4)	20%	13%
Brain	13 (5.6)		
Sarcoma	9 (3.9)		
Neuroendocrine tumor	7 (3.0)		
Cervical	6 (2.6)		
Prostate	6 (2.6)		
Adrenocortical	5 (2.1)		
Breast	5 (2.1)		
Thyroid	5 (2.1)		
Urothelial	5 (2.1)		
Mesothelioma	4 (1.7)		
Small-cell lung cancer	4 (1.7)		
Renal	3 (1.3)		
Salivary	2 (0.9)		
Anal	1 (0.4)		
Head and neck squamous cell carcinoma	1 (0.4)		
Nasopharyngeal	1 (0.4)		
Retroperitoneal	1 (0.4)		
Testicular	1 (0.4)		
Tonsil	1 (0.4)		
Vaginal	1 (0.4)		
Vulvar	1 (0.4)		



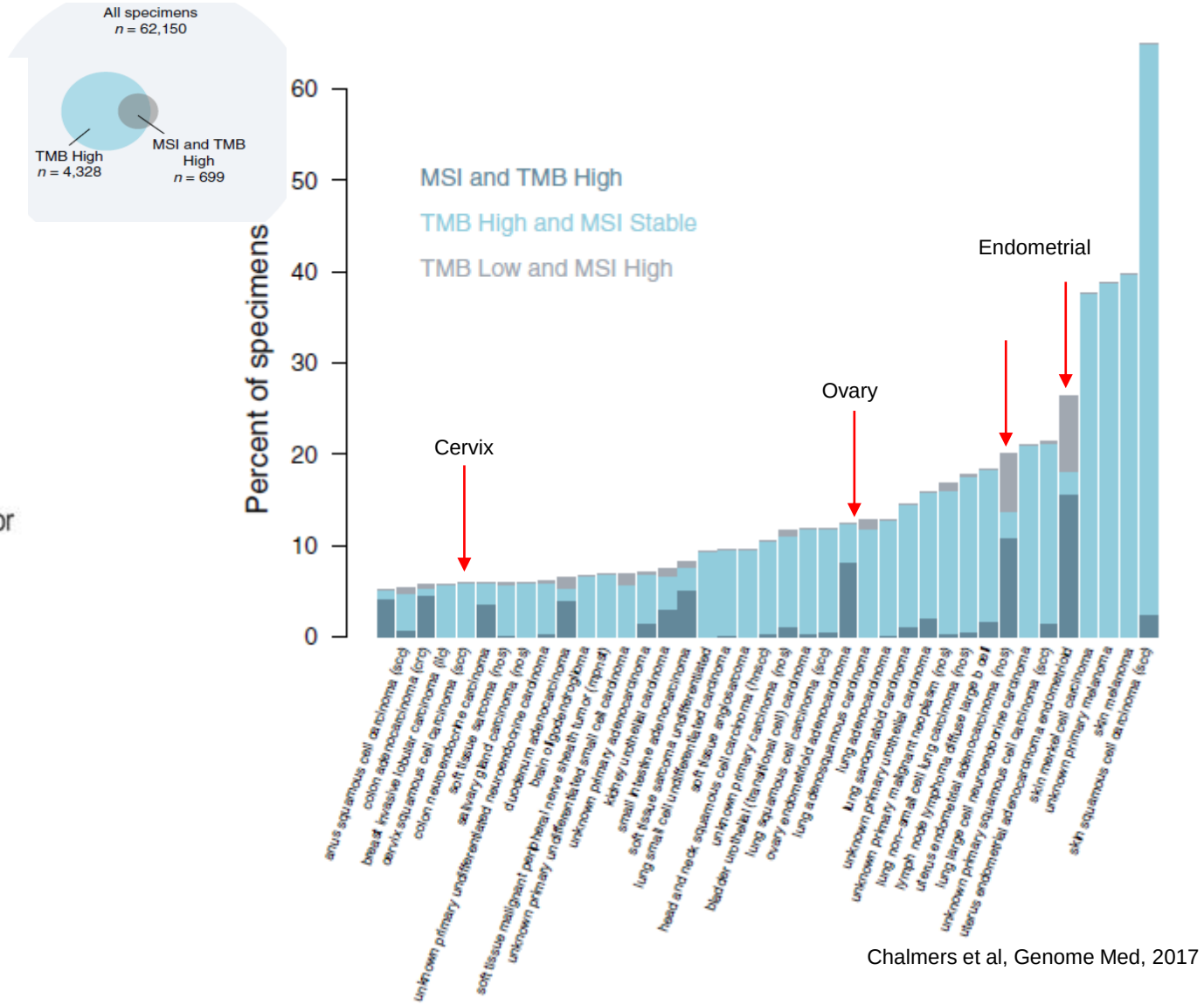


Marabelle et al, JCO, 2019

Biomarker based treatment: TMB



Stenzinger et al, Gene Chrom Ca, 2019



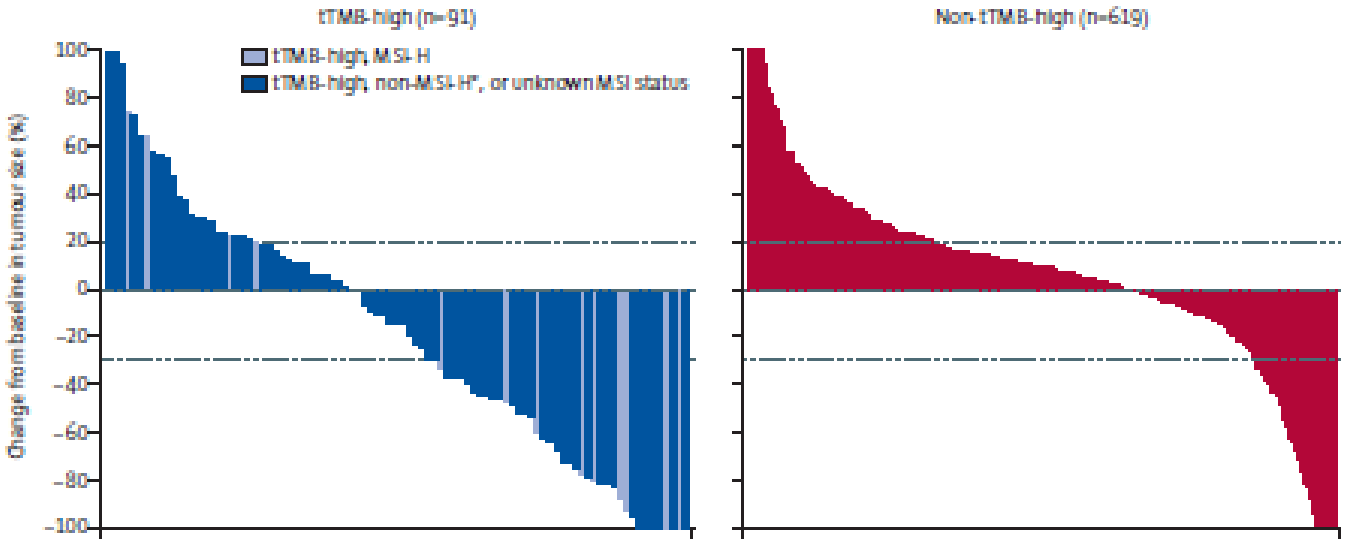
Chalmers et al, Genome Med, 2017

Single agent pembrolizumab in advanced recurrent gynecologic malignancies with TMB score ≥ 10mut/Mb

	tTMB-high (n=102)	tTMB-high (excluding MSI-H; n=81)*	Non-tTMB-high (n=688)
Best response			
Complete response	4 (4%)	3 (4%)	11 (2%)
Partial response	26 (25%)	20 (25%)	32 (5%)
Stable disease	14 (14%)	11 (14%)	227 (33%)
Non-complete response or non-progressive disease†	0	0	3 (<1%)
Progressive disease	48 (47%)	38 (47%)	349 (51%)
Not evaluable‡	1 (1%)	1 (1%)	13 (2%)
Not assessed§	9 (9%)	8 (10%)	53 (8%)
Objective response rate	29% (21–39)	28% (19–40)	6% (5–8)

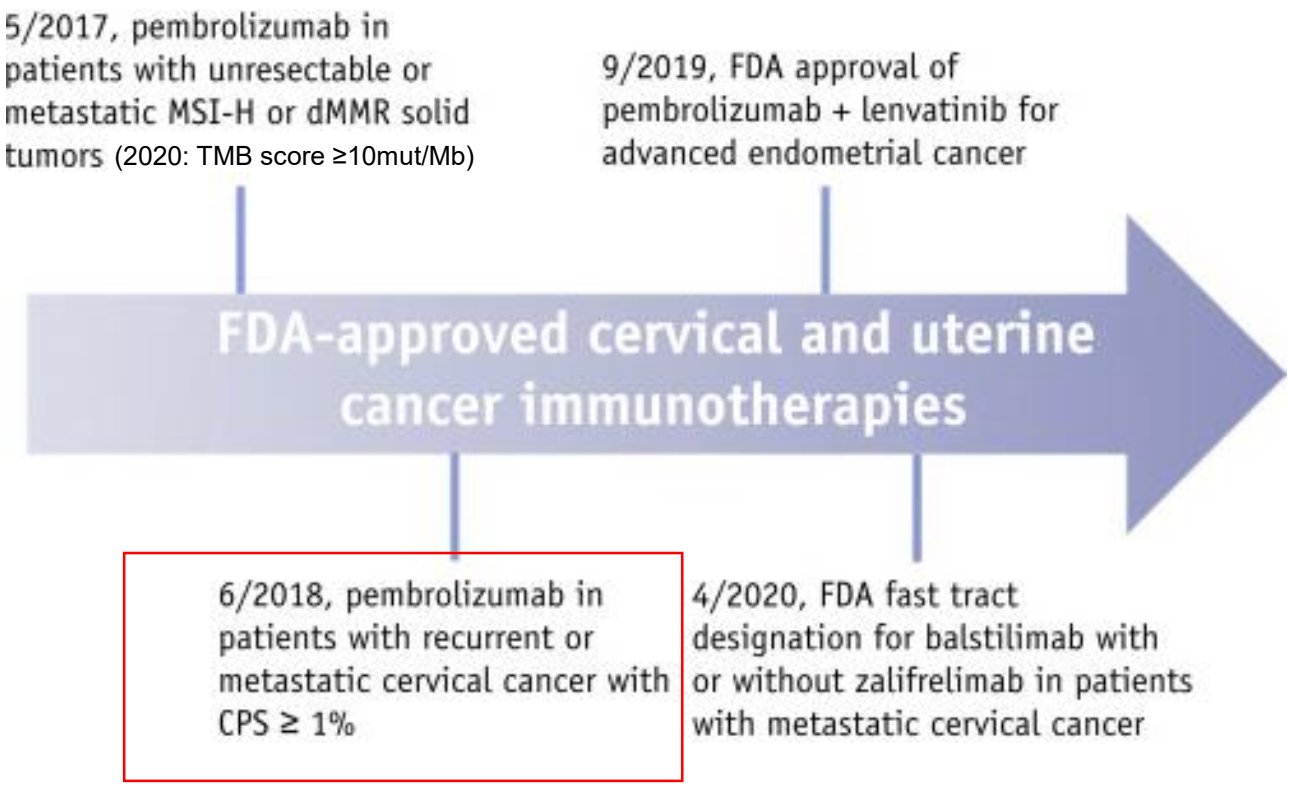
Data are n (%) or % (95% CI). MSI-H=high microsatellite instability. RECIST=Response Evaluation Criteria in Solid Tumors. tTMB-high=high tissue tumour mutational burden. *Excludes 14 patients who were MSI-high and seven additional patients who had missing MSI status. †Patients without measurable disease per central review at baseline who did not have a complete response or progressive disease. ‡Patients who did not have a post-baseline imaging assessment evaluable for response. §Patients who did not have post-baseline imaging.

Table 2: Objective response (per RECIST version 1.1), assessed by independent central review in the efficacy population

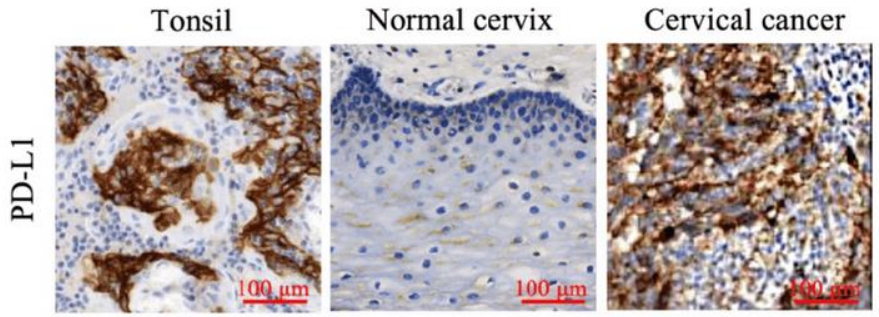


Marabelle et al, Lancet Oncol, 2020

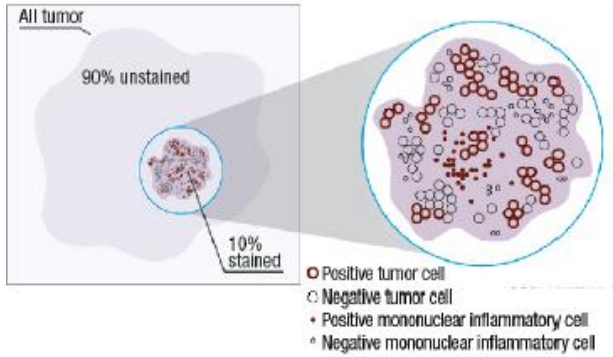
FDA approval timeline



Biomarker based treatment: PD-L1



Combined Positive Score



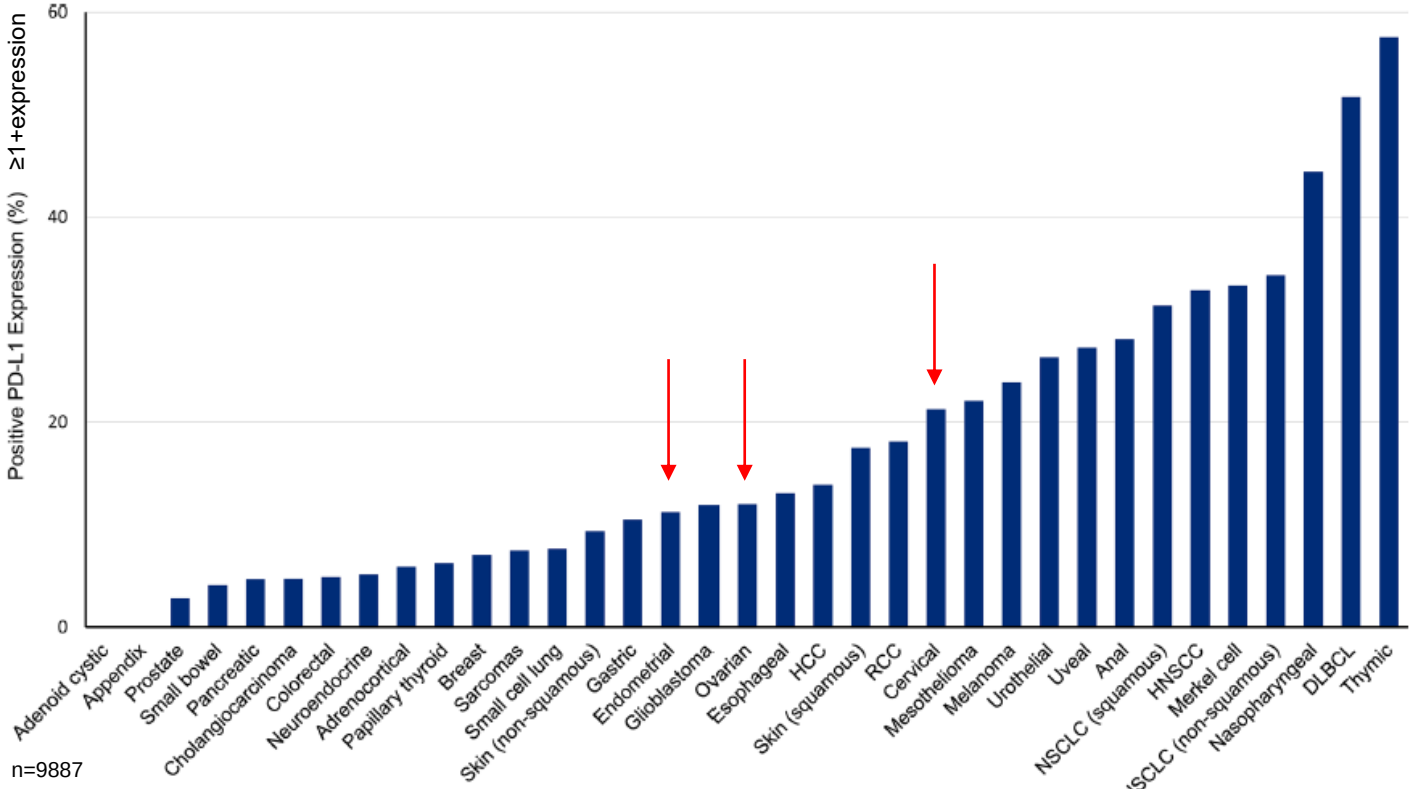
In the stained area, 50 of 100 tumor cells are PD-L1 positive, and there are 34 PD-L1-positive mononuclear inflammatory cells (MIC).

Combined positive score:

$$\frac{84 \text{ positive cells}}{100 \text{ tumor cells}} \times 100 \cong 80$$

10% of 80 = 8
Specimen is PD-L1 positive.

https://www.captodayonline.com



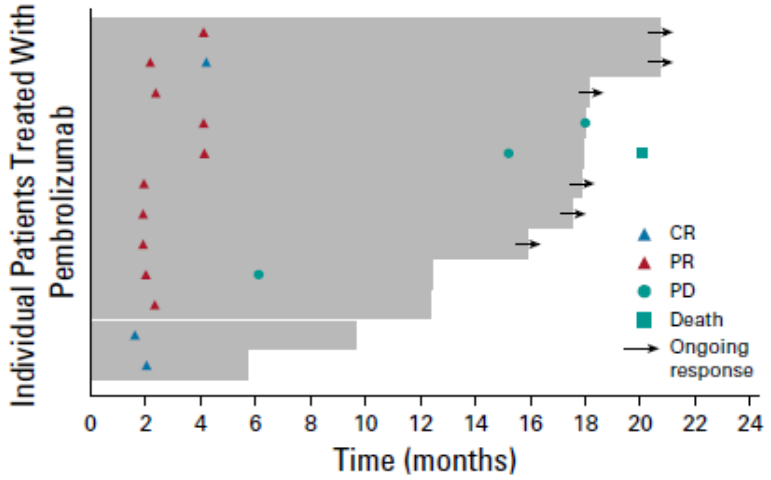
n=9887

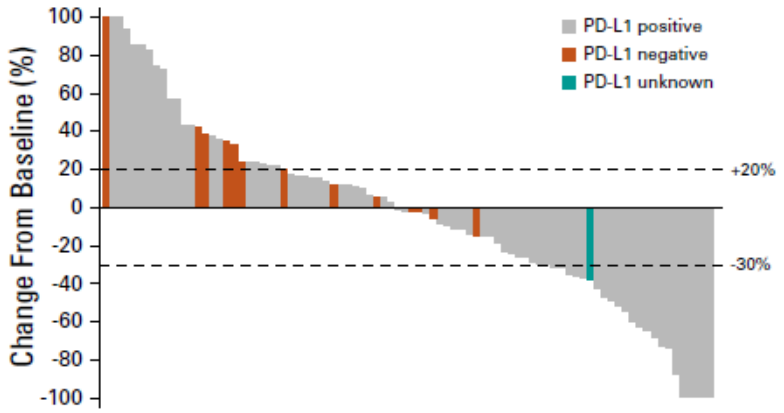
Yarchoan et al, JCI insight, 2019

Single agent pembrolizumab in advanced recurrent PD-L1 positive cervical cancer

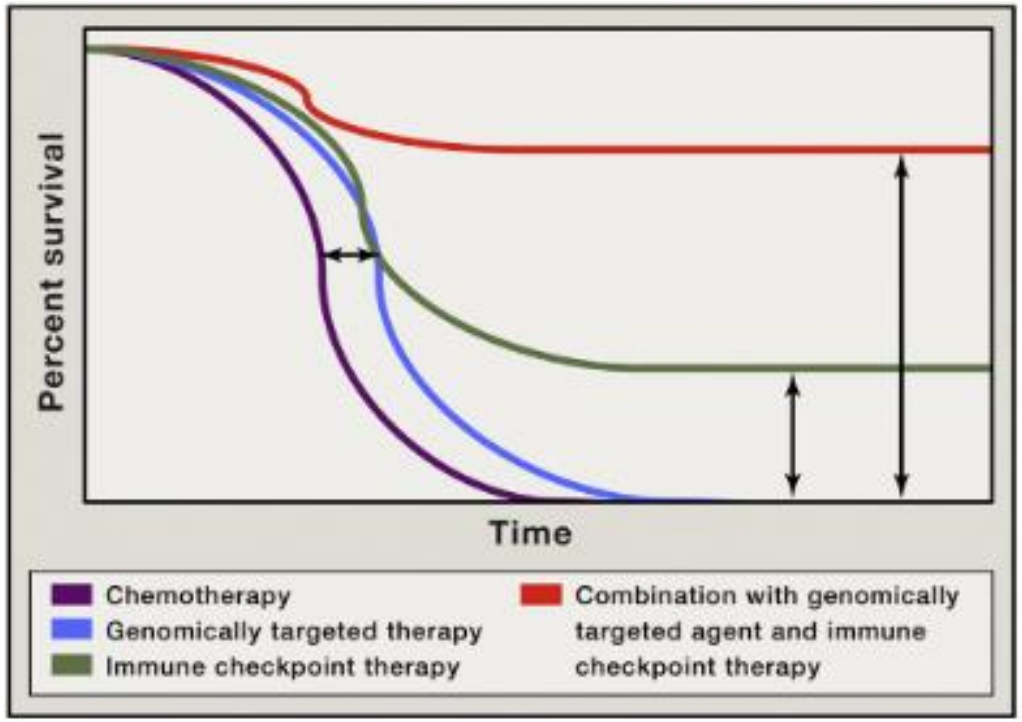
Antitumor Activity	Total Population (N = 98)*	PD-L1–Positive Population		PD-L1–Negative Population (n = 15)
		Total (n = 82)	Previously Treated (n = 77)†	
ORR	12 (12.2)	12 (14.6)	11 (14.3)	0 (0.0)
95% CI	6.5 to 20.4	7.8 to 24.2	7.4 to 24.1	0.0 to 21.8
DCR	30 (30.6)	27 (32.9)	24 (31.2)	3 (20.0)
95% CI	21.7 to 40.7	22.9 to 44.2	21.2 to 42.7	4.3 to 48.1
Best overall response				
CR	3 (3.1)	3 (3.7)	2 (2.6)	0 (0.0)
PR	9 (9.2)	9 (11.0)	9 (11.7)	0 (0.0)
SD	18 (18.4)	15 (18.3)	13 (16.9)	3 (20.0)
Progressive disease	55 (56.1)	44 (53.7)	42 (54.5)	10 (66.7)
Not able to be evaluated‡	5 (5.1)	4 (4.9)	4 (5.2)	1 (6.7)
Not able to be assessed§	8 (8.2)	7 (8.5)	7 (9.1)	1 (6.7)

Chung et al, JCO, 2019



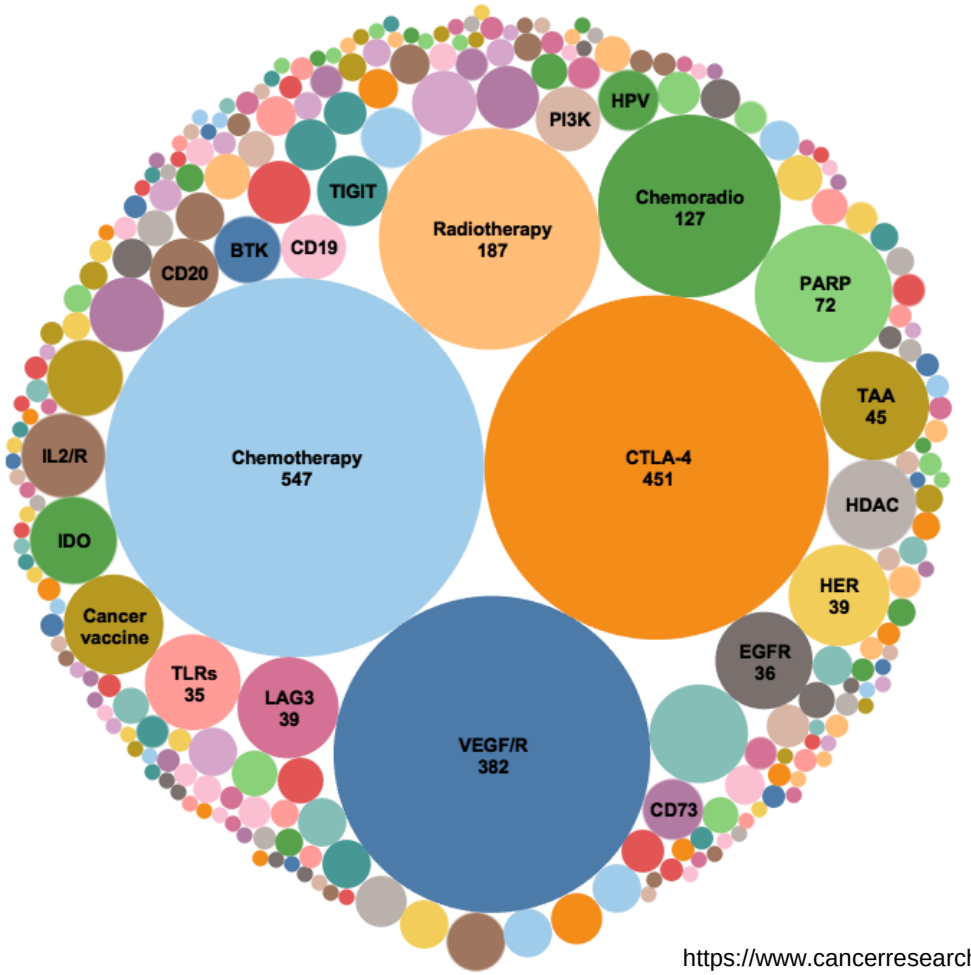


Combination regimens with immune checkpoint inhibitors and chemotherapy and targeted agents



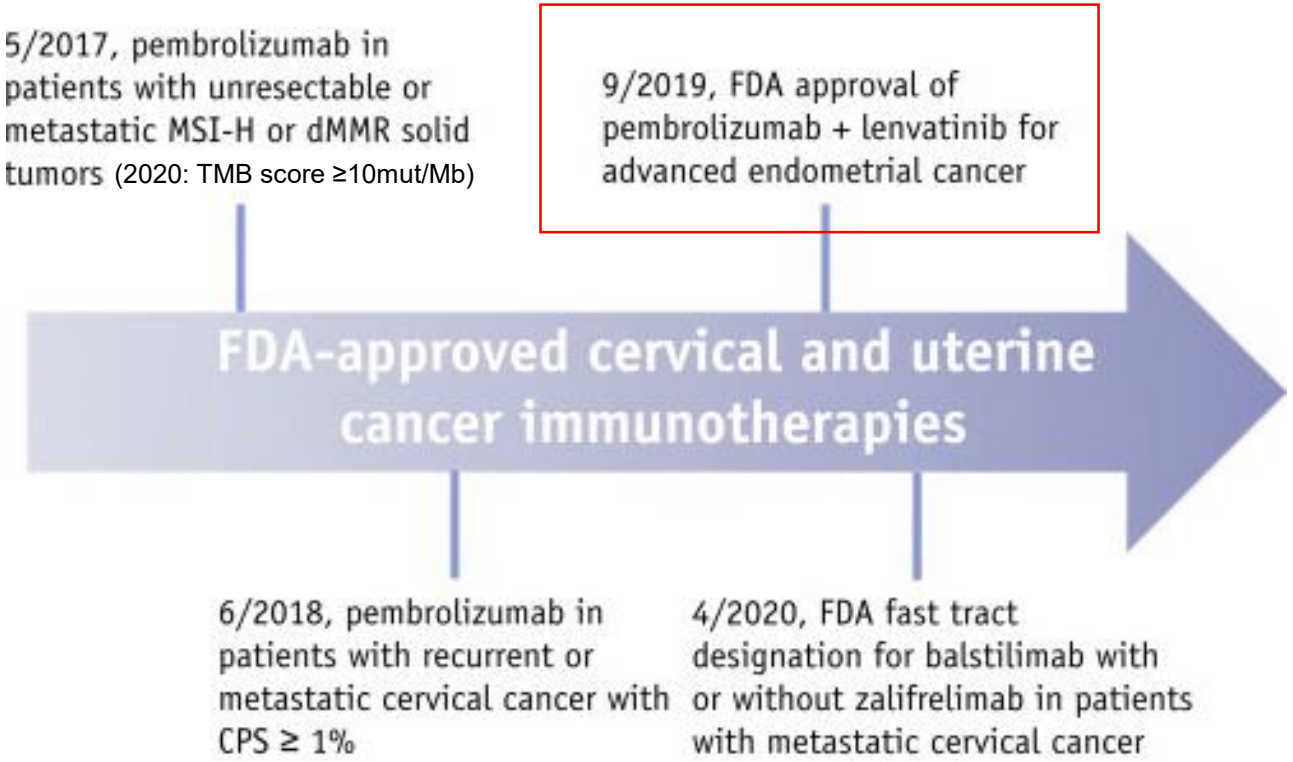
Sharma et al Cell, 2015

2020: ICI combinations in clinical trials



https://www.cancerresearch.org/

FDA approval timeline



Pembrolizumab and lenvatinib in advanced NON-MSI^{high} or dMMR^{+} endometrial cancer

KEYNOTE 775

Key eligibility criteria
- Advanced, metastatic, or recurrent endometrial cancer
- Measurable disease by BICR
- 1 Prior platinum-based CT[a]
- ECOG PS 0-1
- Tissue available for MMR testing

Stratification factors

MMR status (pMMR vs dMMR) and further stratification within pMMR by:
- Region (R1: Europe, USA, Canada, Australia, New Zealand, and Israel, vs R2: rest of the world)
- ECOG PS (0 vs 1)
- Prior history of pelvic radiation (Y vs N)

R (1:1)

Lenvatinib 20 mg PO QD + **Pembrolizumab**[b] 200 mg IV Q3W

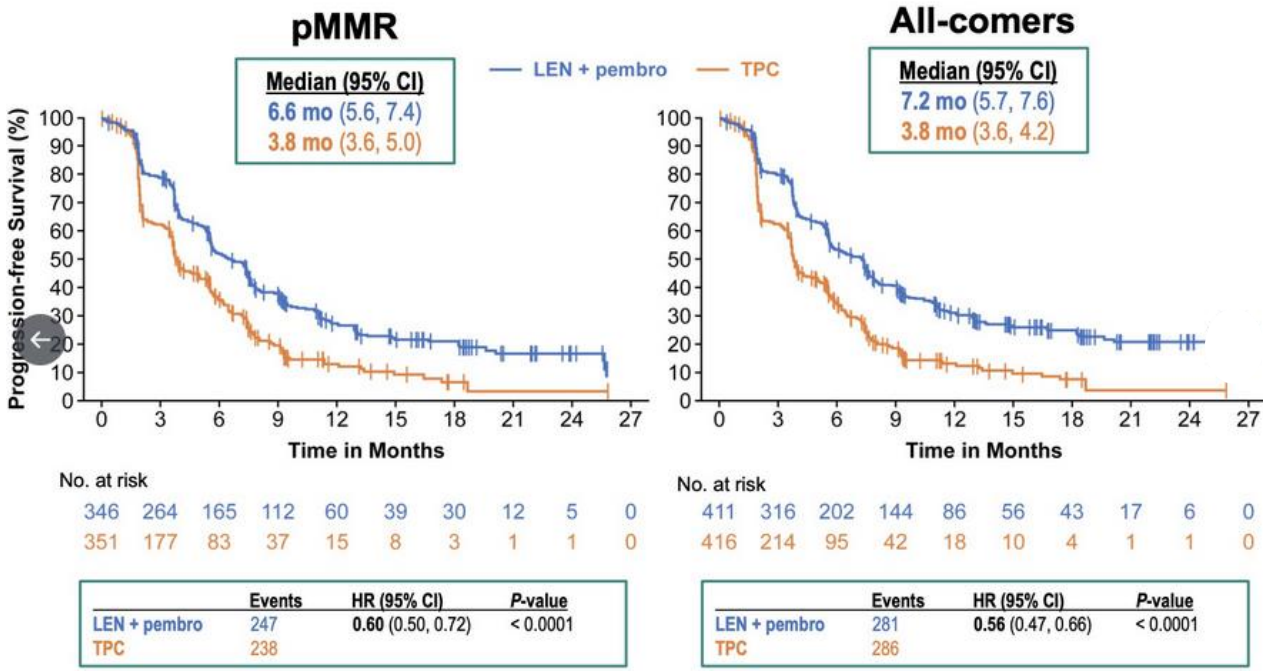
Treat until progression or unacceptable toxicity

Doxorubicin 60 mg/m^2 IV Q3W[c] or **Paclitaxel** 80 mg/m^2 IV QW (3 weeks on/1 week off)

Primary endpoints
- PFS by BICR
- Overall survival

Secondary endpoints
- ORR
- HRQoL
- Pharmacokinetics
- Safety

Key exploratory endpoint
- Duration of response



[a]By BICR per Response Evaluation Criteria in Solid Tumors version 1.1.

Dr. Makker, SGO, 2021

Similar results seen with overall survival

Pembrolizumab with chemotherapy or bevacizumab as front line therapy in advanced cervical cancer (CPS≥1)

Key Eligibility Criteria

- Persistent, recurrent, or metastatic cervical cancer not amenable to curative treatment
- No prior systemic chemotherapy (prior radiotherapy and chemoradiotherapy permitted)
- ECOG PS 0 or 1

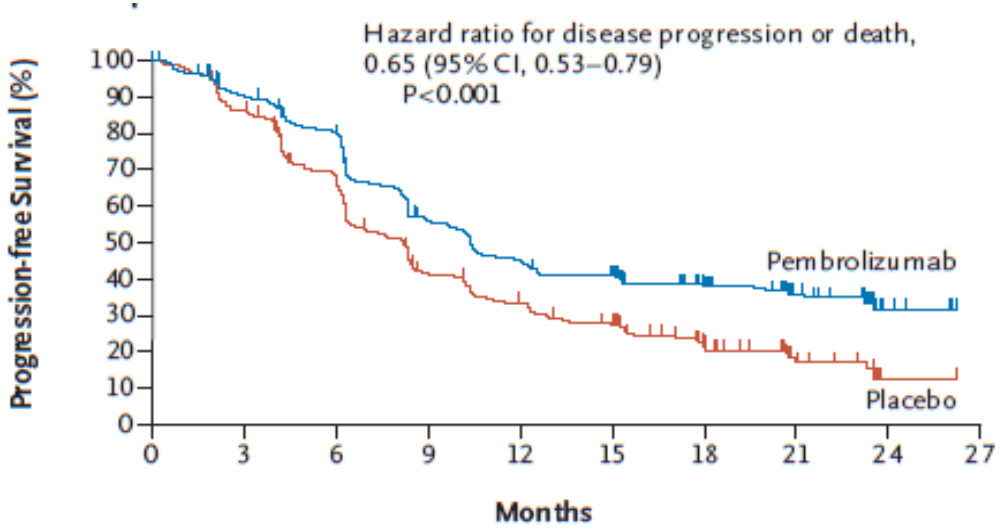
R 1:1

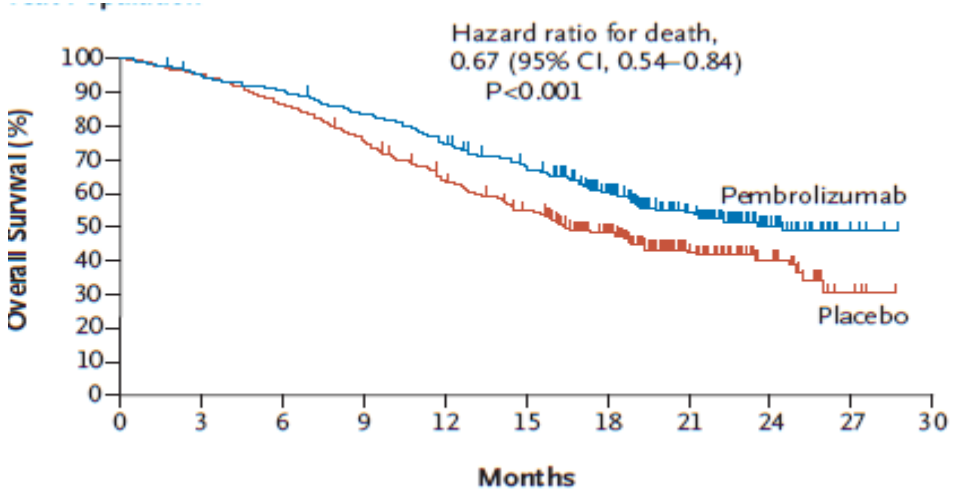
Pembrolizumab 200 mg IV Q3W
for up to 35 cycles
+
Paclitaxel + Cisplatin or Carboplatin IV Q3W
for up to 6 cycles[a]
±
Bevacizumab 15 mg/kg IV Q3W

Placebo IV Q3W
for up to 35 cycles
+
Paclitaxel + Cisplatin or Carboplatin IV Q3W
for up to 6 cycles[a]
±
Bevacizumab 15 mg/kg IV Q3W

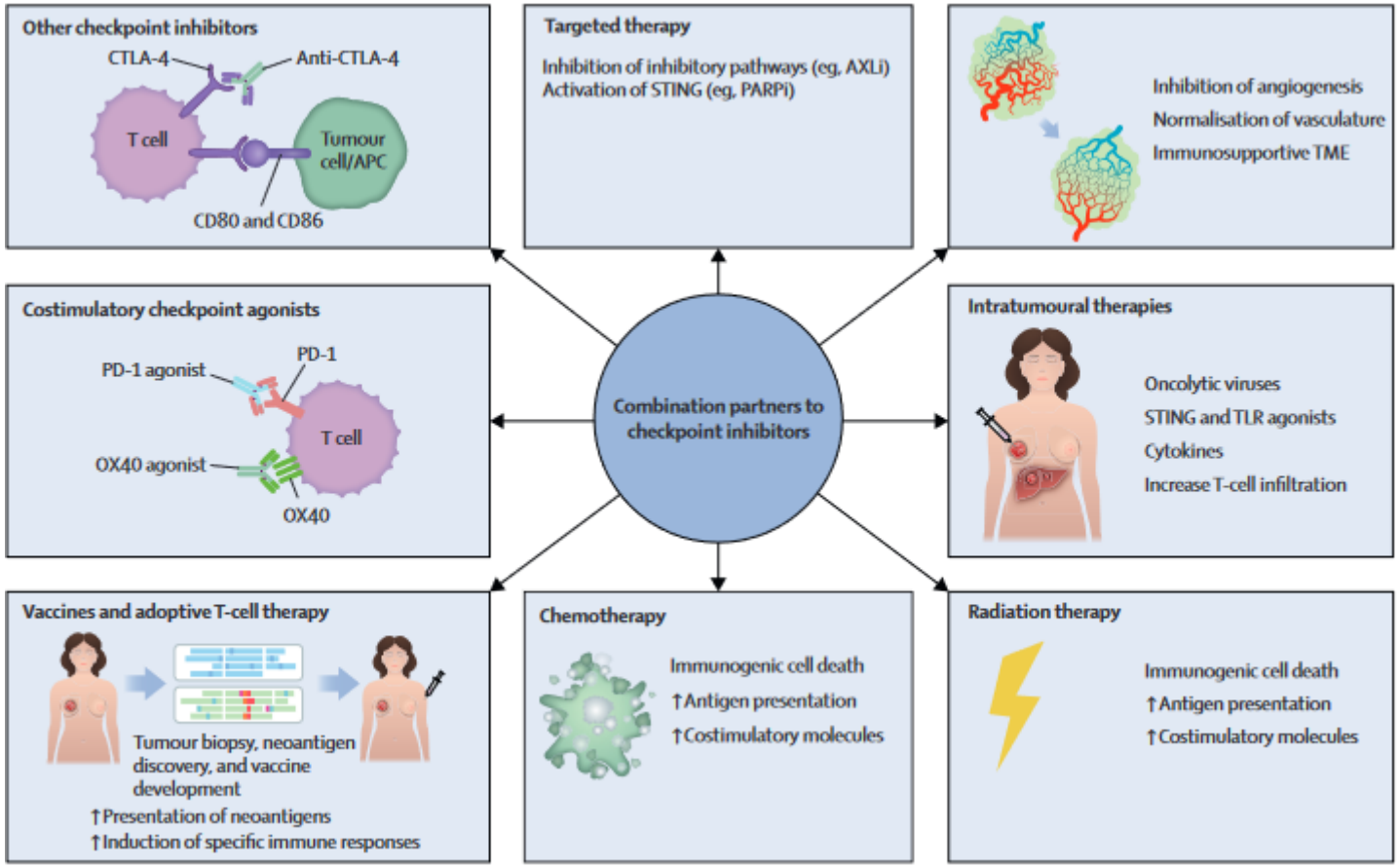
Keynote 826

Columbo et al, NEJM, 2021
Schema from Dr. Leslie Randall





Immunotherapy for gynecologic cancers: just the beginning…



Meric-Bernstam et al, Lancet, 2021