Memorial Sloan Kettering Cancer Center

SITC Updates: Uterus, Cervix and Vulva Cancer

Roisin O'Cearbhaill, MD

Clinical Director, Solid Tumor Malignancies, Cellular Therapy
Research Director, Gynecologic Medical Oncology,
Memorial Sloan Kettering Cancer Center

Memorial Sloan Kettering Cancer Center

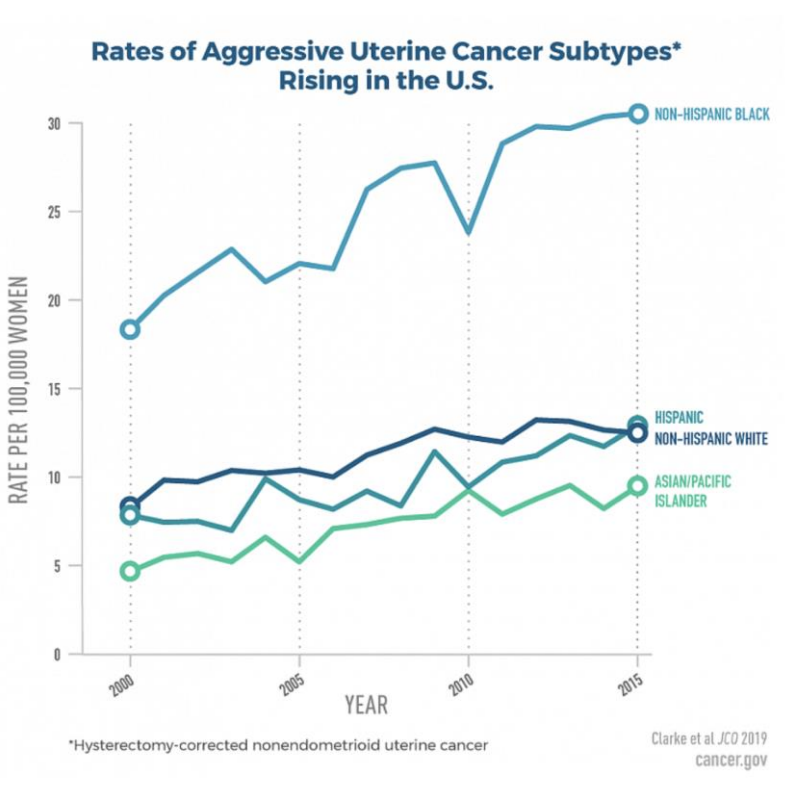
Disclosures

- Consulting Fees: GSK, Bayer, Regeneron, SeaGen, Fresenius Kabi, Carina Biotech and Curio.
- Other: (Speaker): GOG Foundation, Hitech Health, Curio

Memorial Sloan Kettering Cancer Center

Endometrial Cancer – Current Incidence and Outcomes

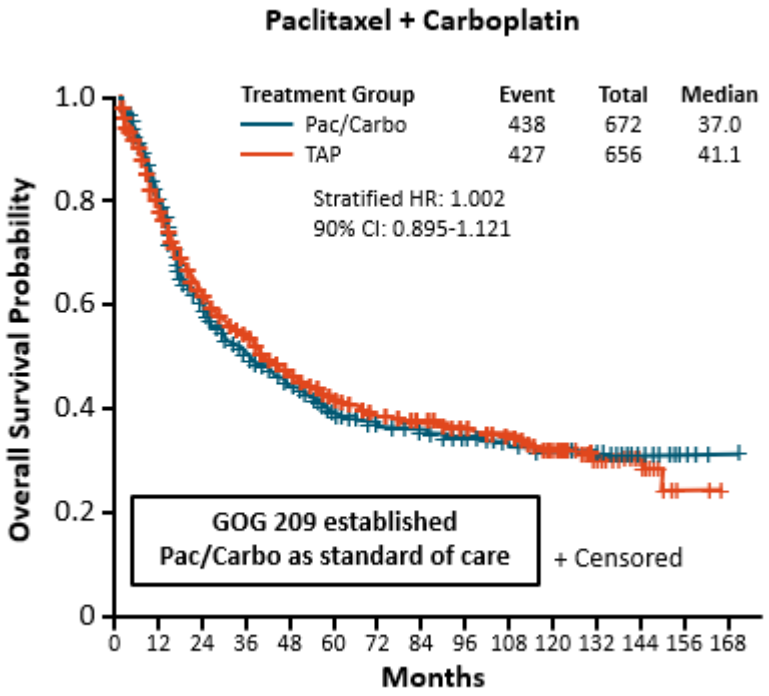
61,880+ cases		12,160+ deaths
50,000	Endometrioid	5,700
31,800	Gr1-2	2,820 (8.8%)
8,200	Gr3	2,890 (35%)
5,500	Serous	3,800 (69%)
1,400	Clear Cell	660 (47%)

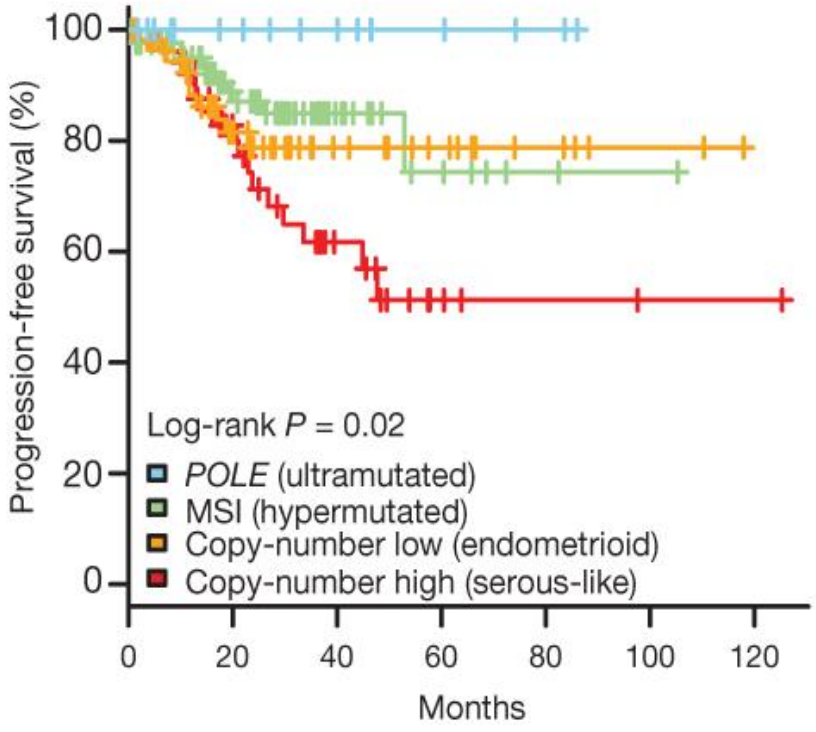


National Cancer Institute. SEER Cancer Stat Facts: Uterine Cancer.

Memorial Sloan Kettering Cancer Center

Endometrial Cancer- Current Status



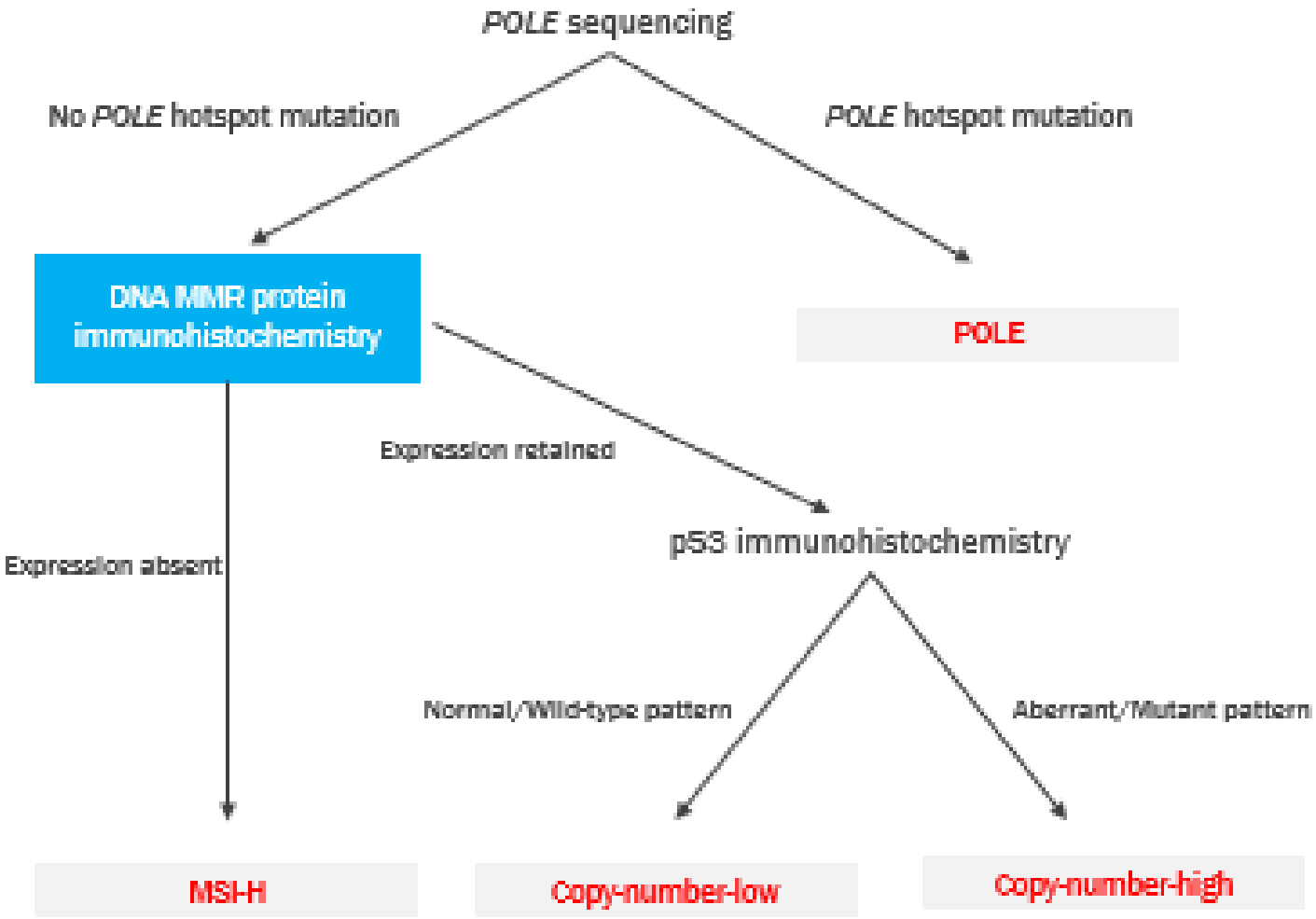


Miller DS, et al. *J Clin Oncol*. 2020;38:3841-3850.

Nature. 2013;497(7447):67-73

Memorial Sloan Kettering Cancer Center

Molecular Subtyping



Nature. 2013;497(7447):67-73

Memorial Sloan Kettering Cancer Center

NCCN Compendium: Category 1 and 2A

Cytotoxics

- Carboplatin/paclitaxel
- Carboplatin/paclitaxel/trastuzumab (HER2+ stage III/IV or recurrent serous carcinomas)
- Carboplatin/docetaxel
- Cisplatin/doxorubicin/paclitaxel
- Carboplatin/paclitaxel/bevacizumab
- Carboplatin
- Cisplatin
- Paclitaxel
- Doxorubicin
- Liposomal doxorubicin
- Topotecan

Targeted Agents

- Progestins
- Tamoxifen
- Aromatase inhibitors
- Megestrol/tamoxifen (alternating)
- Letrozole/everolimus (endometrioid adenocarcinomas)
- Bevacizumab
- Temsirolimus

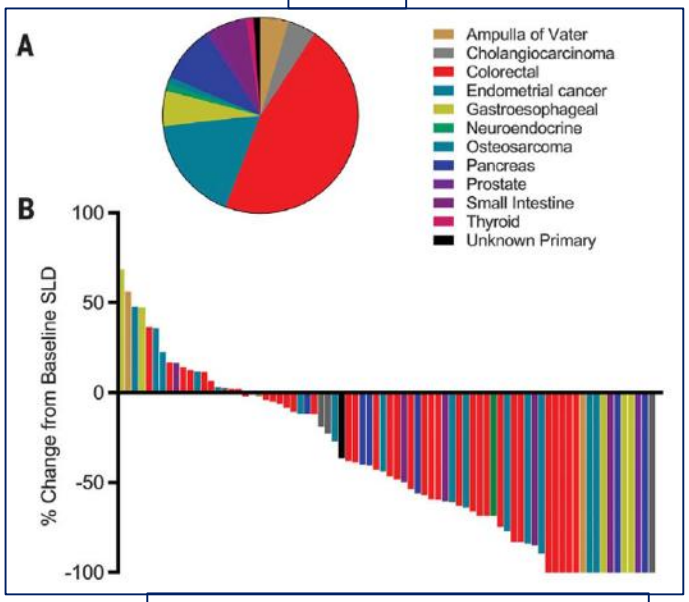
Immunotherapy

- Pembrolizumab (MMR-d/MSI-H)
- Nivolumab (MMR-d/MSI-H)
- Pembrolizumab/lenvatinib (MMR-p/MSS)
- Dostarlimab (MMR-d/MSI-H)

Memorial Sloan Kettering Cancer Center

Single Agent anti-PD1 responses in Endometrial Cancer

MSI

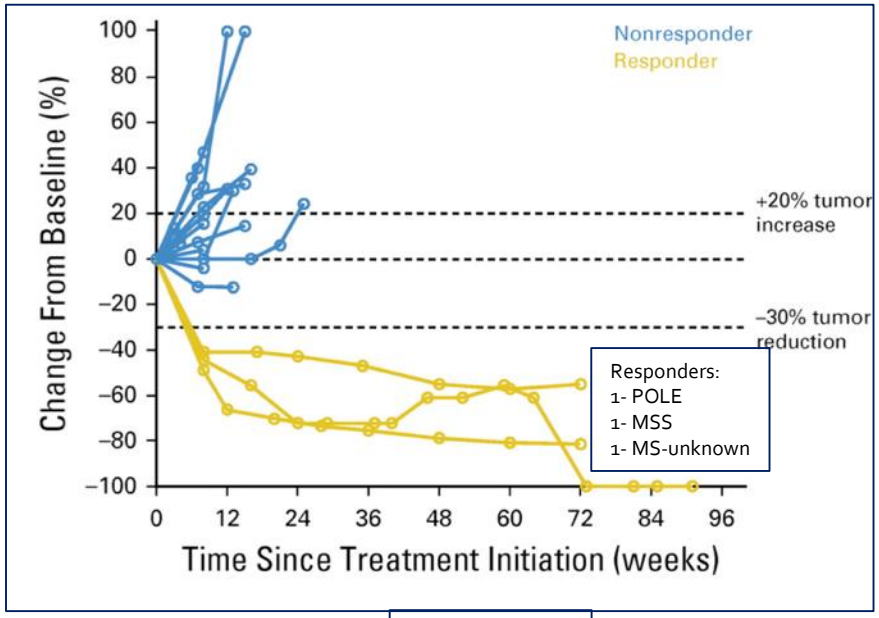


Endometrial cohort (n=15)
CR: 3 (20%)
PR: 5 (33%)
SD: 3 (20%)

ORR: 53%

Approved by FDA

Non-MSI Endometrial (PD-L1)+)



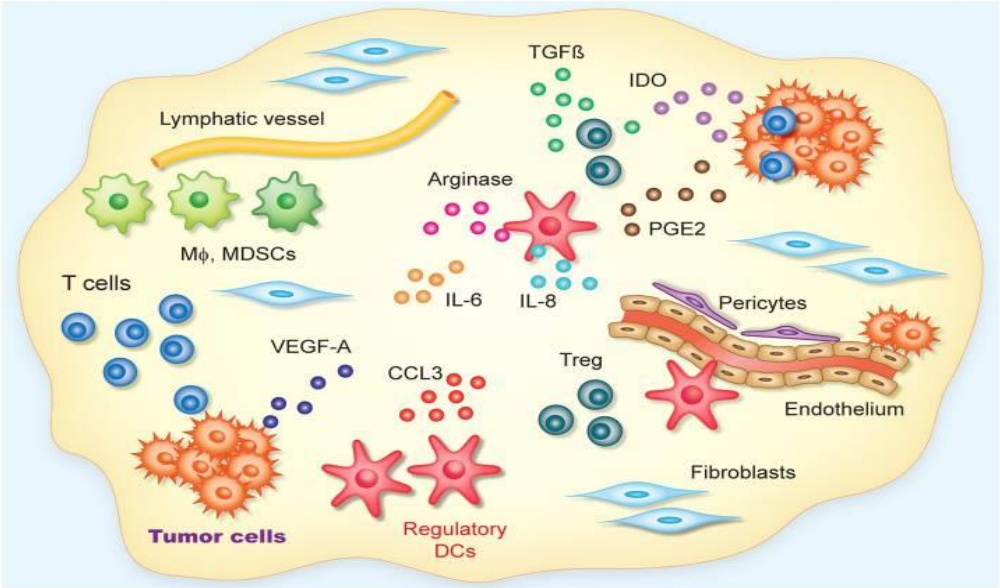
ORR 13%

Le D. et al., Science 2017; Ott et al., JCO 2017

Memorial Sloan Kettering Cancer Center

The Hostile Tumor Microenvironment

Multiple inhibitory factors that limit efficacy of immunotherapy



- Tregs
- MDSCs
- TAMs
- Expression of inhibitory ligands by tumor (PD-L1)
- Tumor secretion of T cell suppressive cytokines (TGF-β, IL-10)

Scarlett et al. Expert Rev Obstet Gynecol. 2012

Memorial Sloan Kettering Cancer Center

Currently Approved Immunotherapies for Recurrent Endometrial Carcinoma

	KEYNOTE-158[1,2]	KEYNOTE-146[3,4]	KEYNOTE-775[5]	GARNET[6,7]
Agent	Pembrolizumab	Pembrolizumab + Lenvatinib	Pembrolizumab + Lenvatinib	Dostarlimab
Population	Previously treated dMMR-recurrent or persistent EC	Previously treated metastatic endometrial cancer, MSI-H or dMMR +/-	Previously treated d-MMR advanced, recurrent or metastatic endometrial cancer	Previously treated recurrent/advanced EC
Patients, n	49	108	827 (all-comers)	125
Overall Response Rate, %	**57**	**41**	**31.9**	**49 $^{MSI+}$/20 MSS**
Disease control rate, %	73	--	--	--
Duration of response	NR (3-27)	21.2 (7.6-NE)	--	NR
Progression free survival (median)	26 mo	7.4 mo	7.2 mo	—
Overall survival (median)	12-mo OS= 73%	16.7 mo	18.3 mo	—
Adverse events	16% Gr >3	Gr ≥3 TRAEs: 66.9%	Gr ≥3 TRAEs: 88.9%	Gr ≥3 TRAEs: 11.4%
Median follow-up	9.1 mo	--	--	—

1. O'Malley ESMO 2019. Abstract 3394. 2. O'Malley. ESMO 2021. Oral Session 795MO. 3. Makker. SGO 2020. Abstract. SP02-10. 4. Makker. *JCO*. 2020; 38: 2981. 5. Makker V, et al. SGO 2021. Abstract 2. 6. Oaknin et al. ESMO 2020. Abstract LBA36. 7. Oaknin. ESMO 2021. ePoster 76P.

Memorial Sloan Kettering Cancer Center

KEYNOTE-158: Study Design

Pembrolizumab

Patients with unresectable or metastatic endometrial cancer with progression on or intolerance to standard therapy; ECOG PS 0 or 1;

Cohort D: endometrial cancer
Cohort K: non-colorectal, MSI-H/dMMR solid tumor

→ **Pembrolizumab 200 mg IV Q3W**

Up to 35 cycles or PD, unacceptable toxicity

Primary Endpoint	Overall Response Rate (ORR) by central RECIST
Secondary Endpoints	Progression-free survival (PFS), Overall survival (OS), Duration of Response (DoR) and Safety

O'Malley ESMO 2019. Abstract 3394; O'Malley. ESMO 2021. Oral Session 795MO.

Memorial Sloan Kettering Cancer Center

KEYNOTE-158: Antitumor Activity of Pembrolizumab in MSI-H Advanced EC

- Prospective, open-label phase II study in patients with MSI-H/dMMR solid tumors (N = 233)

Tumor Type	No.	CR, No.	PR, No.	ORR, % (95% CI)	Median PFS, Months (95% CI)	Median OS, Months (95% CI)	Median DOR, Months (range)
Endometrial	49	8	20	57.1 (42.2 to 71.2)	25.7 (4.9 to NR)	NR (27.2 to NR)	NR (2.9 to 27.0+)
Gastric	24	4	7	45.8 (25.6 to 67.2)	11.0 (2.1 to NR)	NR (7.2 to NR)	NR (6.3 to 28.4+)
Cholangiocarcinoma	22	2	7	40.9 (20.7 to 63.6)	4.2 (2.1 to NR)	24.3 (6.5 to NR)	NR (4.1+ to 24.9+)
Pancreatic	22	1	3	18.2 (5.2 to 40.3)	2.1 (1.9 to 3.4)	4.0 (2.1 to 9.8)	13.4 (8.1 to 16.0+)
Small intestine	19	3	5	42.1 (20.3 to 66.5)	9.2 (2.3 to NR)	NR (10.6 to NR)	NR (4.3+ to 31.3+)
Ovarian	15	3	2	33.3 (11.8 to 61.6)	2.3 (1.9 to 6.2)	NR (3.8 to NR)	NR (4.2 to 20.7+)
Brain	13	0	0	0.0 (0.0 to 24.7)	1.1 (0.7 to 2.1)	5.6 (1.5 to 16.2)	–

NOTE. Efficacy analyses included all patients who received at least one dose of pembrolizumab. Only confirmed responses are included. Response was assessed per RECIST version 1.1 by independent central radiologic review.

Abbreviations: +, no progressive disease by the time of last disease assessment; CR, complete response; DOR, duration of response; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

FDA Approval May 2017
First FDA approval based on a biomarker regardless of tumor type

Marabelle A, ..., Diaz LA Jr. J Clin Oncol. 2020 Jan 1;38(1):1-10

Memorial Sloan Kettering Cancer Center

KEYNOTE-146: Study Design Phase 1b/2

Pembrolizumab + Lenvatinib in Previously Treated Endometrial Cancer

Metastatic endometrial cancer, ECOG PS 0/1, ≤ 2 previous lines of therapy (N = 108)

- **Not MSI-H or dMMR** (n = 94)
- **MSI-H/dMMR** (n = 11)
- **MSI/MMR not available** (n = 3)

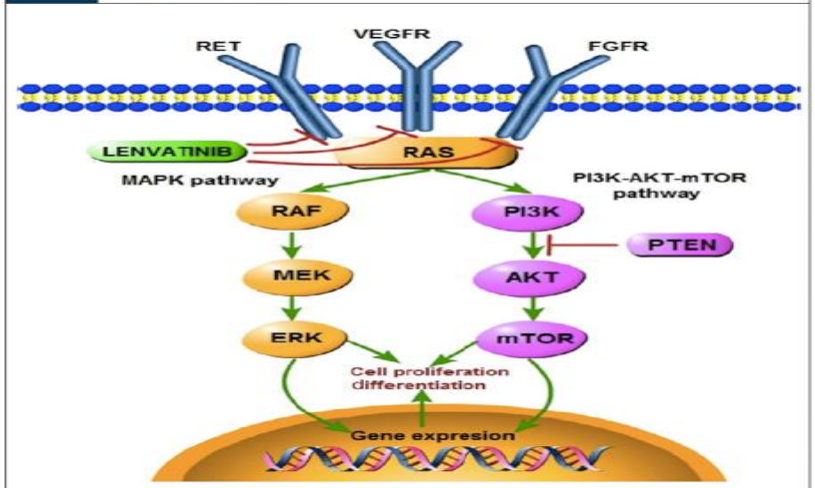
→ **Lenvatinib** 20 mg PO QD + **Pembrolizumab** 200 mg IV Q3W (up to 35 cycles)

- 49% PD-L1 +
- 37% had 2 prior lines of therapy

Primary Endpoint	Overall Response Rate (ORR)
Secondary Endpoints	Duration of Response (DoR), Disease Control Rate (DCR)

Makker. SGO 2020. Abstr. SP02-10; Makker. *JCO*. 2020; 38: 2981.

Figure Kinase signaling cascade involved in development of thyroid carcinomas and representing the two main pathways, MAPK and PI3K-AKT-mTOR.



Reprinted with permission from Stjepanovic N, Capdevila J. Multikinase inhibitors in the treatment of thyroid cancer: specific role of lenvatinib. *Biologics: Targets and Therapy*. 2014;8:129-139. ©2014. Permission conveyed through Copyright Clearance Center, Inc.

Memorial Sloan Kettering Cancer Center

KEYNOTE-146: Efficacy Summary

Pembrolizumab + Lenvatinib in Patients With Previously Treated EC

Investigator Assessment per irRECIST	Total (n = 108)	Not MSI-H or dMMR (n = 94)	MSI-H/dMMR (n = 11)
ORR_{WK24}, n (%)	41 (38.0)	34 (36.2)	7 (63.6)
ORR, n (%)	42 (38.9)	35 (37.2)	7 (63.6)
CR	8 (7.4)	7 (7.4)	1 (9.1)
PR	34 (31.5)	28 (29.8)	6 (54.5)
Median DoR, mos (95% CI)	21.2 (7.6-NE)	NE (7.4-NE)	21.2 (7.3-NE)
Median PFS, mos (95% CI)	7.4 (5.3-8.7)	7.4 (5.0-7.6)	18.8 (4.0-NE)
Median OS, mos (95% CI)	16.7 (15.0-NE)	16.4 (13.5-25.9)	NE (7.4-NE)

dMMR, deficient mismatch repair; DoR, duration of response; EC, endometrial cancer; irRECIST, immune-related Response Evaluation Criteria in Solid Tumors; MSI-H, microsatellite instability-high

Makker. *JCO*. 2020; 38: 2981.

Memorial Sloan Kettering Cancer Center

Keynote-775 Study Design

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:

- World Region
- ECOG PS (0 vs 1)
- Prior history of pelvic radiation (Yes vs No)

R (1:1)

Lenvatinib
20 mg PO QD
+
Pembrolizumab
200 mg IV Q3W

Doxorubicin
60 mg/m² IV Q3W
or
Paclitaxel
80 mg/m² IV QW
(3 weeks on/1 week off)

Treat until progression or unacceptable toxicity

Primary endpoints

- PFS by BICR
- Overall survival

Secondary endpoints

- ORR
- HRQoL
- Pharmacokinetics
- Safety

Key exploratory endpoint

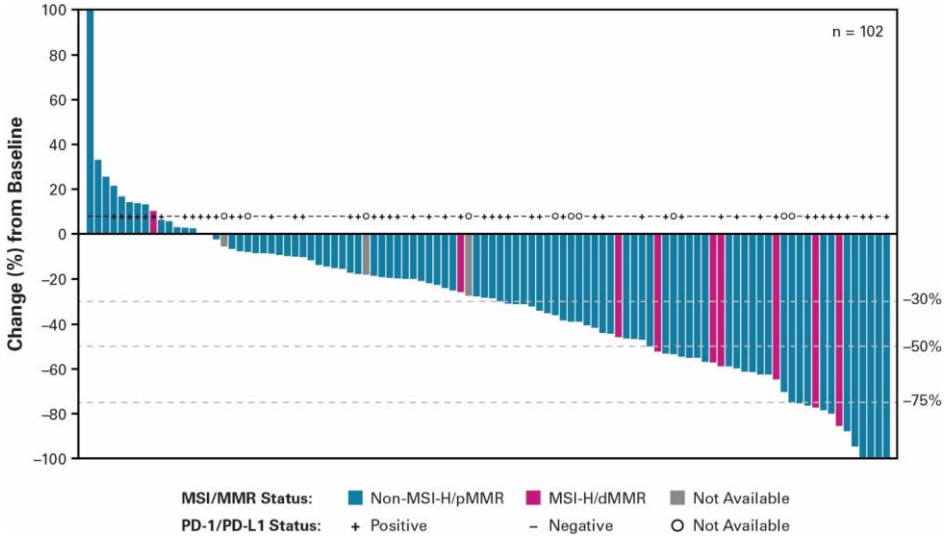
- Duration of response

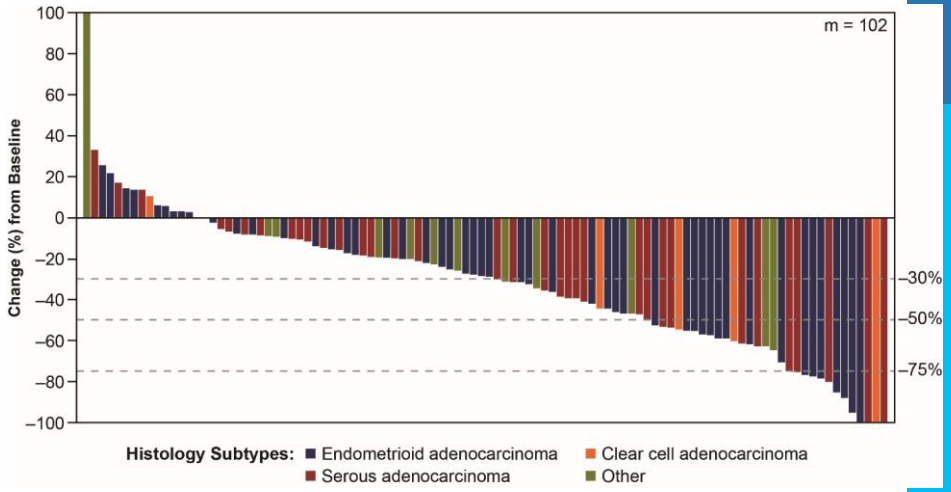
[a]up to 2 prior platinum-based CT regimens if 1 is given in the neoadjuvant or adjuvant treatment setting. BICR, blinded independent central review; pMMR, mismatch repair-proficient;

. **Makker V et al. *J Clin Oncol*. 2020;38:2981-2992.**

Memorial Sloan Kettering Cancer Center

Lenvatinib plus Pembrolizumab Previously Treated Endometrial Cancer





Treatment	pMMR	dMMR
ORR	37.2% (35/94)	63.6% (7/11)
DOR Median (95% CI)	NE (7.4–NE)	21.2 (7.3–NE)

FDA Accelerated Approval 2019
FDA Full Approval July 2021
for recurrent/advanced
endometrial cancer who are not MSI-H or dMMR

Makker V et al. Lancet Oncol. 2019 May;20(5):711-718 &J Clin Oncol. 2020 Sep 10;38(26):2981-2992

Memorial Sloan Kettering Cancer Center

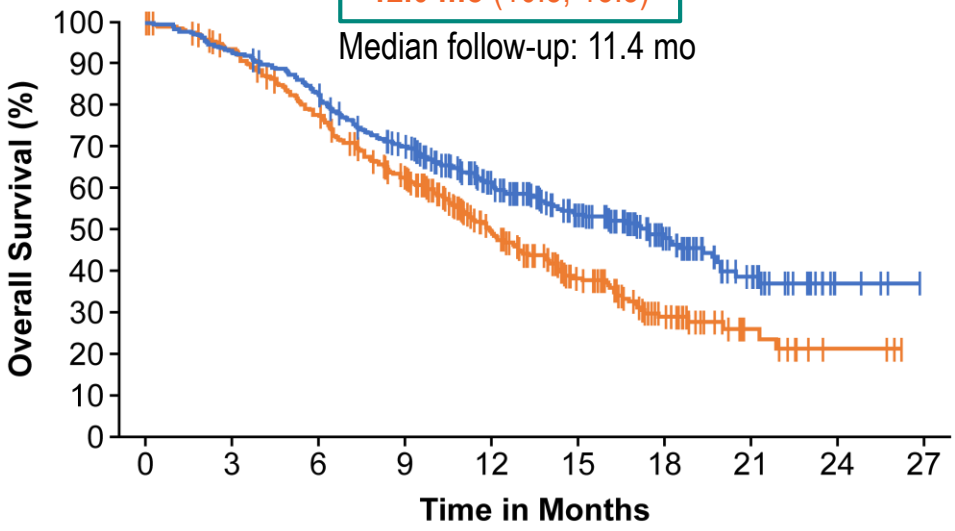
Overall Survival – Keynote 775

pMMR

Median (95% CI)
17.4 mo (14.2, 19.9)
12.0 mo (10.8, 13.3)

LEN + pembro — TPC

Median follow-up: 11.4 mo



No. at risk

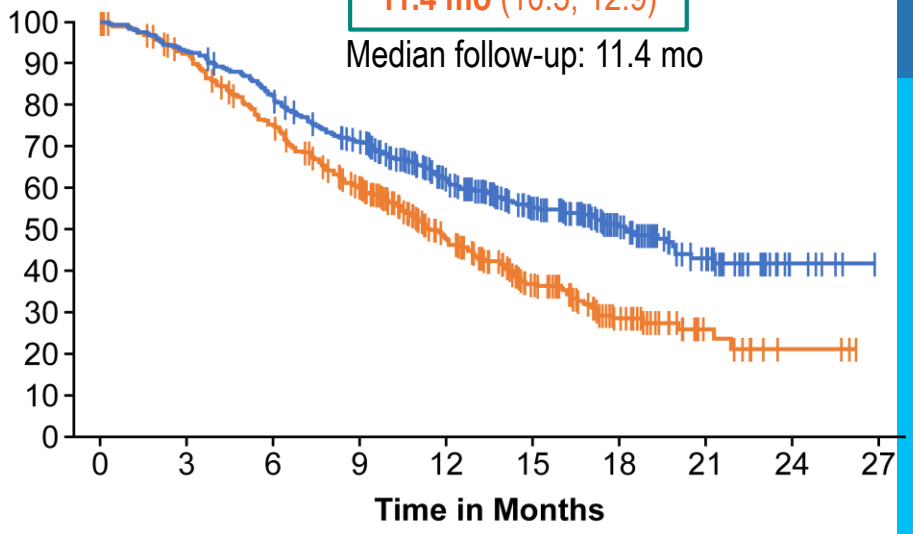
346	322	285	232	160	109	62	28	5	0
351	319	262	201	120	70	33	11	3	0

	Events	HR (95% CI)	*P*-value
Lenvatinib + pembro	165	**0.68** (0.56, 0.84)	0.0001
Chemotherapy	203		

All-comers

Median (95% CI)
18.3 mo (15.2, 20.5)
11.4 mo (10.5, 12.9)

Median follow-up: 11.4 mo



No. at risk

411	383	337	282	198	136	81	40	7	0
416	373	300	228	138	80	40	11	3	0

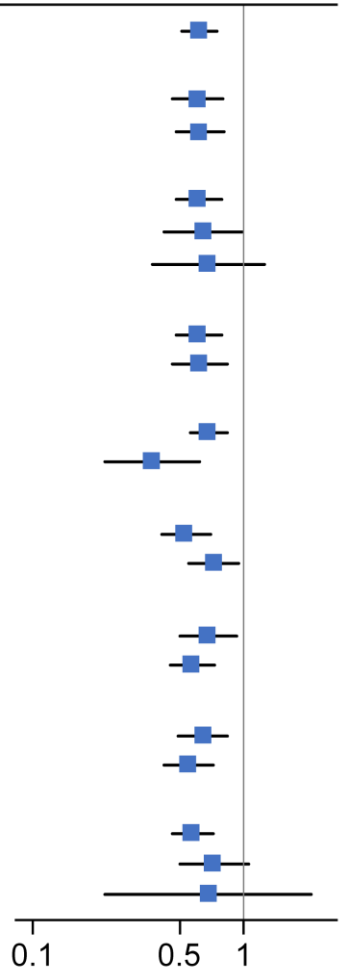
	Events	HR (95% CI)	*P*-value
Lenvatinib + pembro	188	**0.62** (0.51, 0.75)	< 0.0001
Chemotherapy	245		

Makker V, et al. SGO 2021.

Memorial Sloan Kettering Cancer Center

Overall Survival –Keynote 775 Subgroup Analyses: All-comers

	No. of Events/N	HR	95% CI
Overall	433/827	0.62	(0.51, 0.75)
Age Group			
< 65 years	205/410	0.61	(0.46, 0.80)
≥ 65 years	228/417	0.62	(0.48, 0.81)
Race			
White	258/507	0.61	(0.48, 0.79)
Asian	87/177	0.65	(0.42, 0.99)
Other	44/63	0.68	(0.37, 1.26)
Region			
Region 1	255/474	0.61	(0.48, 0.79)
Region 2	178/353	0.62	(0.46, 0.84)
MMR Status			
pMMR	368/697	0.68	(0.56, 0.84)
dMMR	65/130	0.37	(0.22, 0.62)
ECOG Status			
0	222/487	0.53	(0.41, 0.70)
1	210/339	0.73	(0.55, 0.95)
Prior History of Pelvic Radiation			
Yes	169/341	0.68	(0.50, 0.93)
No	264/486	0.57	(0.45, 0.73)
Histology			
Endometrioid	222/497	0.65	(0.49, 0.84)
Non-endometrioid	211/330	0.55	(0.42, 0.72)
Prior Lines of Therapy			
1	308/574	0.57	(0.46, 0.72)
2	112/229	0.72	(0.50, 1.06)
≥ 3	13/24	0.69	(0.22, 2.10)



Makker V, et al. SGO 2021.

Memorial Sloan Kettering Cancer Center

KEYNOTE-775: Adverse Events

2nd-line Pembrolizumab + lenvatinib vs chemotherapy in advanced EC

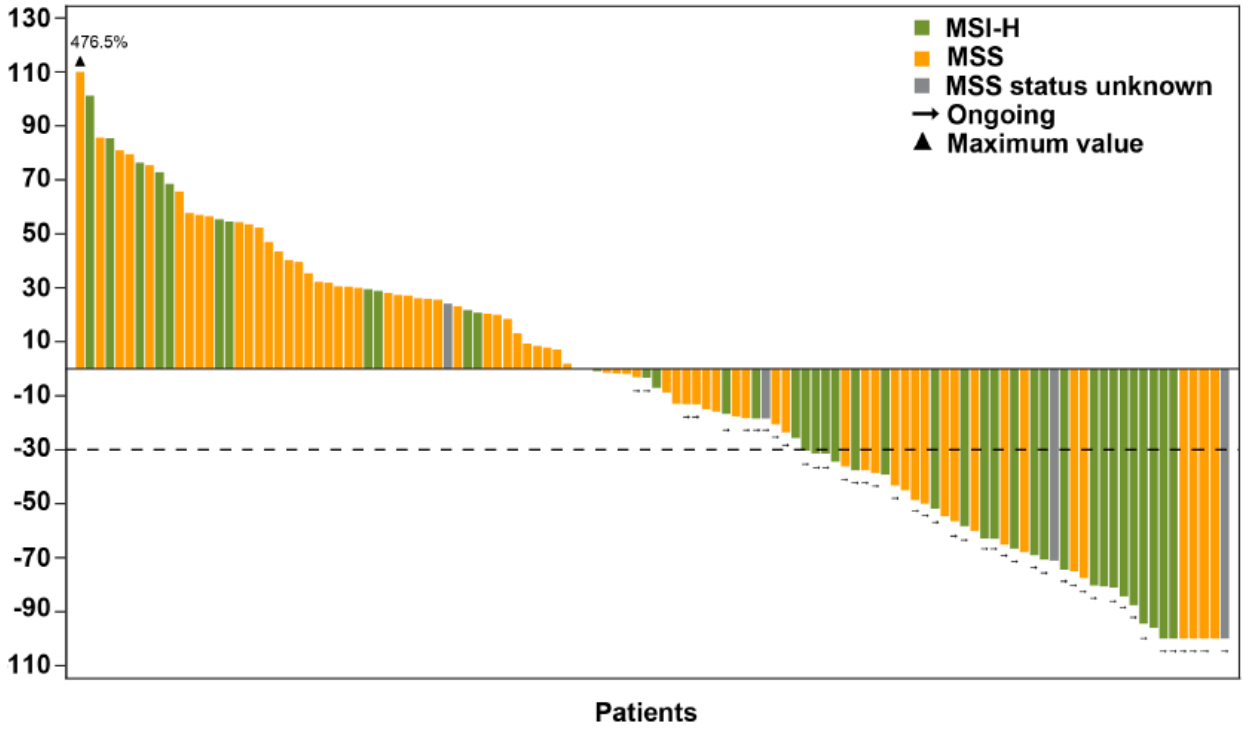
	Len + Pem (n=406)	Chemo (n=388)
Duration of treatment, median (range)	231 (1-817)	104.5 (1-785)
Patient with any TEAEs, %	99.8	99.5
Grade ≥3	88.9	72.7
Patients with any TEAEs leading to dose reductions, %	66.5	12.9
Patients with any-grade TEAEs leading to interruption, %	69.2	27.1
Lenvatinib	58.6	--
Pembrolizumab	50.0	--
Len + Pem	30.8	--
Patients with any-grade TEAEs leading to discontinuation, %	33.0	8.0
Lenvatinib	30.8	--
Pembrolizumab	18.7	--
Len + Pem	14.0	--

	Len + Pem (n=406)		Chemo (n=388)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Patient with any TEAEs, %	**99.8**	**88.9**	**99.5**	**72.7**
Hypertension	64.0	37.9	5.2	2.3
Hypothyroidism[e]	57.4	1.2	0.8	0.0
Diarrhea	54.2	7.6	20.1	2.1
Nausea	49.5	3.4	46.1	1.3
Decreased appetite	44.8	7.9	21.1	0.5
Vomiting	36.7	2.7	20.9	2.3
Weight decrease	34.0	10.3	5.7	0.3
Fatigue	33.0	5.2	27.6	3.1
Arthralgia	30.5	1.7	8.0	0.0
Proteinuria	28.8	5.4	2.8	0.3
Anemia	26.1	6.2	48.7	14.7
Constipation	25.9	0.7	24.7	0.5
Urinary tract infection	25.6	3.9	10.1	1.0
Headache	24.9	0.5	8.8	0.3
Asthenia	23.6	5.9	24.5	3.9
Neutropenia	7.4	1.7	33.8	25.8
Alopecia	5.4	0.0	30.9	0.5

Len, lenvatinib; Pem, pembrolizumab; TEAE, treatment-emergent adverse event; Chemo: treatment of physician's choice.
Makker V, et al. SGO 2021. Abstract 2.

Memorial Sloan Kettering Cancer Center

GARNET: Dostarlimab in MSI-H and MSS endometrial cancer



>50% reduction in total tumor burden in 85% of MSI-H and 69% of MSS responders

Oaknin et al., SGO 2019

Memorial Sloan Kettering Cancer Center

Phase I GARNET: Efficacy of Dostarlimab in dMMR Endometrial Cancer (updated)

	Cohort A1 dMMR EC (n = 103)
Median follow-up time, months	**20.4**
Confirmed responses, n	46
Objective response rate, %	44.7
(95% CI)	(34.9-54.8)
CR, n (%)	11 (10.7)
PR, n (%)	35 (34.0)
SD, n (%)	13 (12.6)
PD, n (%)	39 (37.9)
Not evaluable, n (%)	5 (4.9)
Disease control rate, %	**57.3**
(95% CI)	**(47.2-67.0)**
Median DoR, months (range)	**34.7**
	(2.63-35.78+)

FDA Approval April 2021
Dostarlimab accelerated approval for dMMR-recurrent/advanced endometrial cancer

FDA Approval August 2021
Approved for adult patients with dMMR recurrent or advanced solid tumors

Berton. ASCO 2021. Abstr 2564. NCT02715284.

Memorial Sloan Kettering Cancer Center

Cervical and Vulvar Cancer

Memorial Sloan Kettering Cancer Center

Evolving Landscape for Systemic Treatment in Cervical Cancer

- Cisplatin with radiation (CCRT) 1999
- Cisplatin + paclitaxel 1-L 2009
- Platinum + paclitaxel +/- bevacizumab 2014
- Carboplatin + Paclitaxel 2015
- Pembrolizumab 2018
  - Cemiplimab *2022* TBD
  - Balstilimab *2021* TBD
- Durvalumab with CCRT based on CALLA and pembrolizumab based on KN-A18 TBD
- Addition of pembrolizumab 1-L for PDL1+ based on KN-826 2021
- Tisotumab Vedotin 2021
- Adoptive T cell therapies TBD

Memorial Sloan Kettering Cancer Center

KEYNOTE-158 Phase II Basket Trial (Update): Pembrolizumab in Advanced Cervical Cancer

International, multicohort, open-label phase II study

Advanced cervical cancer that progressed on or was intolerant to ≥1 line of standard therapy; ECOG PS 0-1; (N = 98)

→ Pembrolizumab 200 mg Q3W →

For 2 yrs, unacceptable toxicity, PD

Primary endpoint: ORR

Prior interim analysis showed 12.2% ORR (0% ORR in PD-L1–negative tumors)

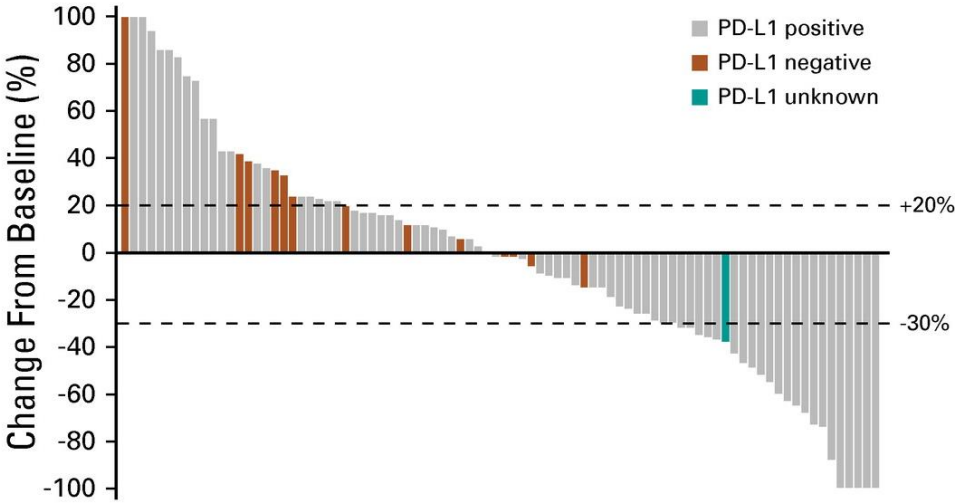
- Secondary endpoints: DoR, PFS, OS, safety

FDA Approval June 2018
Recurrent/metastatic cervical cancer PD-L1+ (CPS1 ≥1), MSI-H or dMMR status
(later approved for TMB>10)

1. Chung. JCO. 2019;37:1470. 2. Chung. SGO 2021. Abstr 41.

Memorial Sloan Kettering Cancer Center

PD-1 blockade in cervical cancer: Updated KEYNOTE 158 Pembrolizumab



Total (N=98)	PD-L1+ (N=82)	PD-L1- (N=15)
ORR	14 (17.1%)	0 (0%)

Pembrolizumab is FDA- approved for previously treated PD-L1+ cervical cancer

Median Duration of Response: not reached (range: 3.7-35.2+ months)

Chung et al., JCO 2019, Chung. SGO 2021. Abstr 41

Memorial Sloan Kettering Cancer Center

Patients were treated regardless of PD-L1 status

EMPOWER / GOG-3016: Single-agent PD-1 blockade (cemiplimab) vs. chemo in 2-L cervical cancer

Recurrent/metastatic cervical cancer
≥1 previous therapy;
enrollment regardless of PD-L1
ECOG PS 0/1
(N = 608)

→ Cemiplimab 350 mg IV Q3W

→ Investigator's choice chemotherapy

up to 96 wk or drug discontinuation

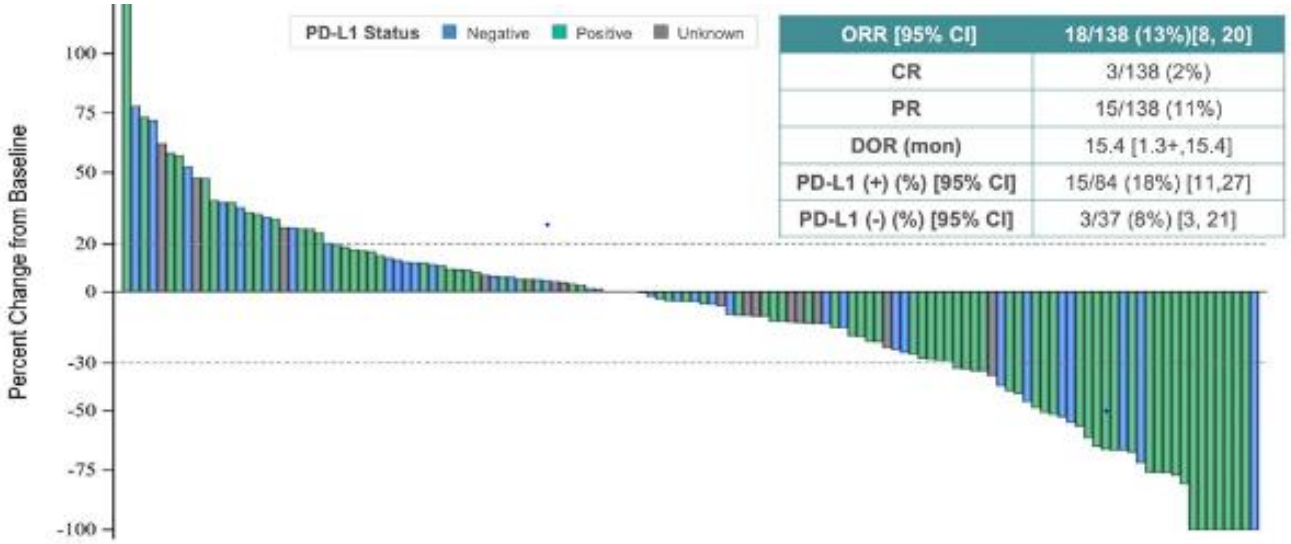
option for retreatment

	Chemotherapy	Cemiplimab	HR (95% CI)
OS	8.5 months	12 months	0.69 (0.56-0.8) p<0.001
OS (squamous)	8.8 months	11.1 months	0.73 (0.58-0.91) p=0.003
OS (adenocarcinoma)	7.0 months	13.3 months	0.56 (0.36-0.85) p<0.005

Tewari KS et al ESMO 2021

Memorial Sloan Kettering Cancer Center

Single-agent PD-1 blockade (Balstilimab) in 2-L cervical cancer



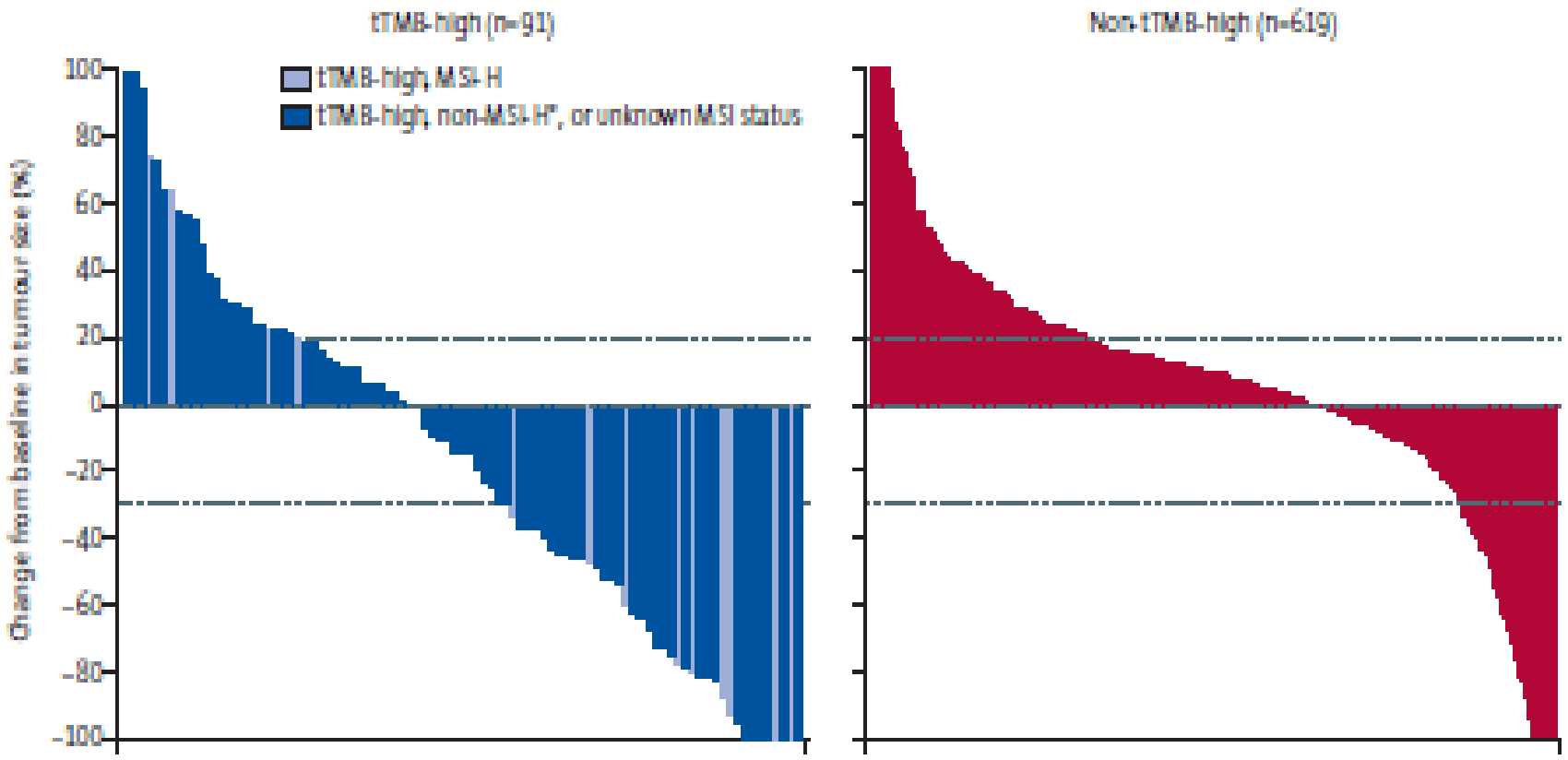
ORR [95% CI]	18/138 (13%)[8, 20]
CR	3/138 (2%)
PR	15/138 (11%)
DOR (mon)	15.4 [1.3+,15.4]
PD-L1 (+) (%) [95% CI]	15/84 (18%) [11,27]
PD-L1 (-) (%) [95% CI]	3/37 (8%) [3, 21]

The FDA has accepted the biologics license application for the anti-PD-1 balstilimab for recurrent of metastatic cervical cancer

O'Malley et al., ESMO 2020

Memorial Sloan Kettering Cancer Center

Pembrolizumab in advanced, recurrent gynecologic cancers with TMB score ≥ 10mut/Mb



Marabelle et al, Lancet Oncol, 2020

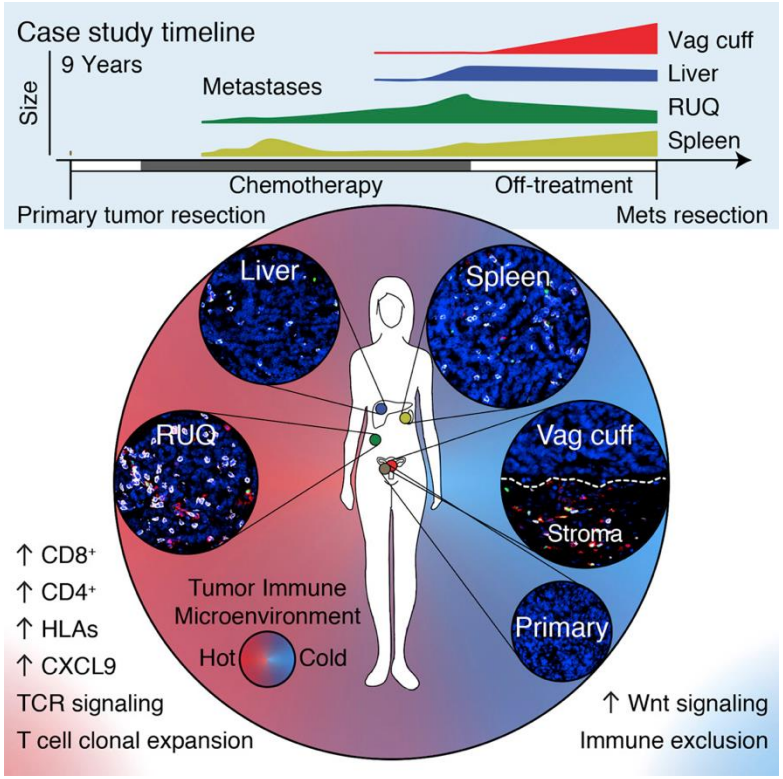
Memorial Sloan Kettering Cancer Center

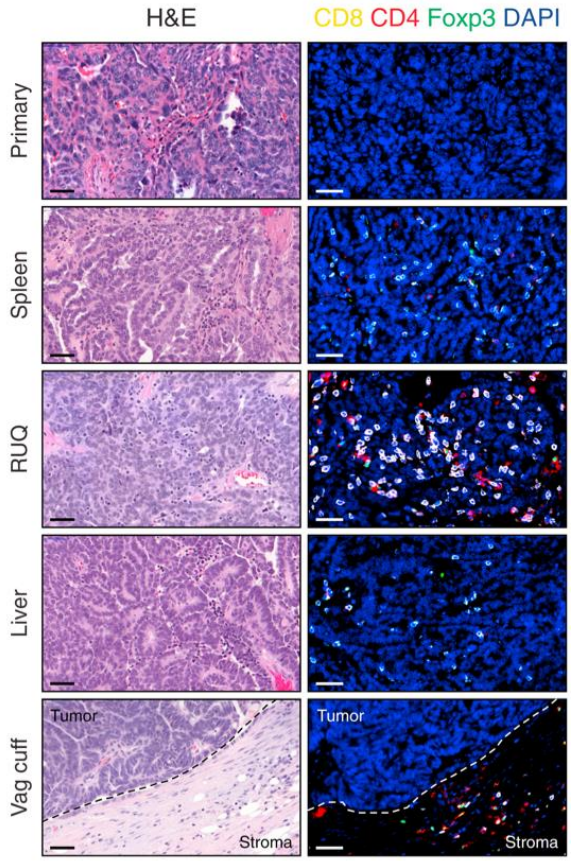
Cervical and Vulvar Cancer:

Immune checkpoint blockade Combinations

Memorial Sloan Kettering Cancer Center

Intra and Inter-tumor Heterogeneity can often be seen in Gynecologic Cancers
Different Tumor Microenvironments within the Same Patient

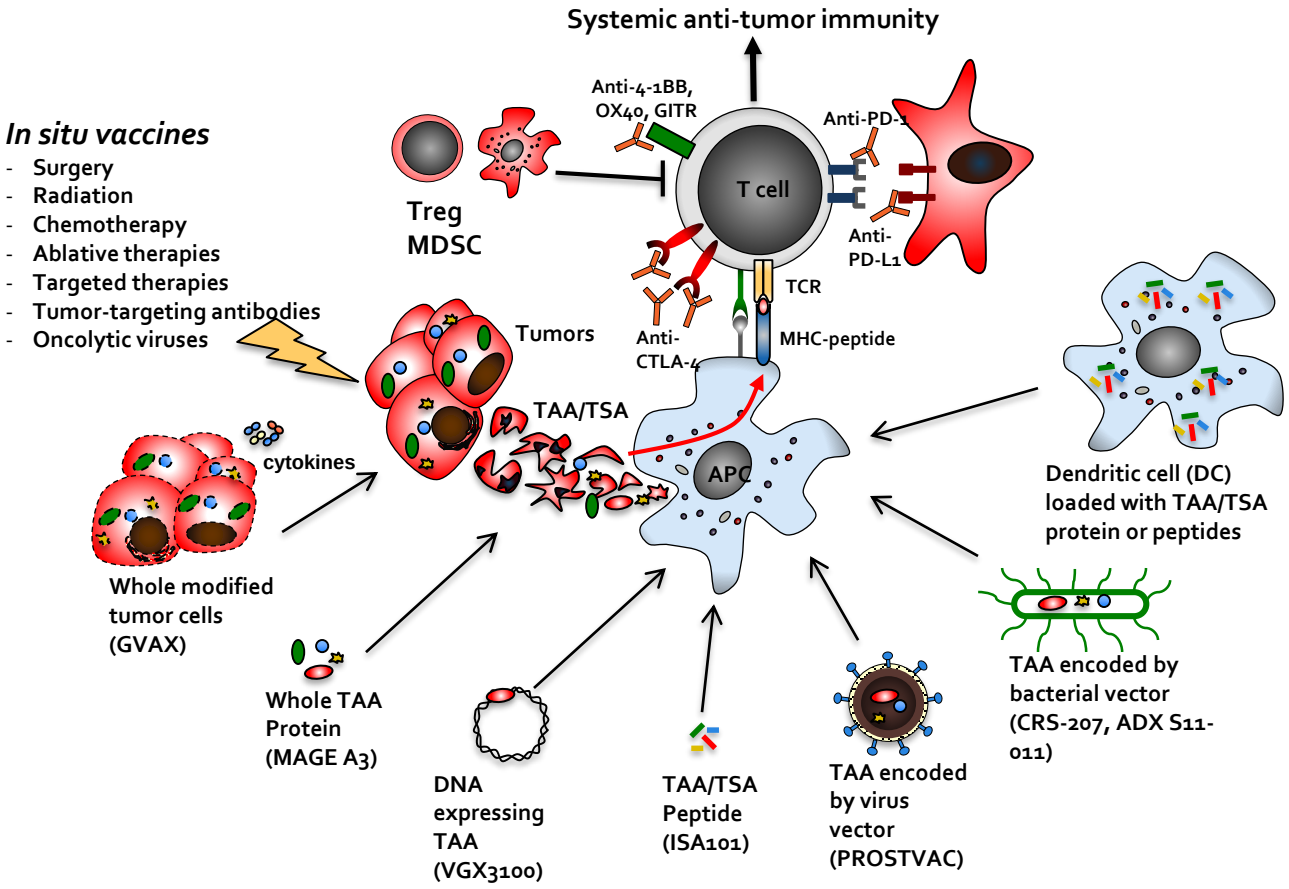




Jimenez-Sanchez et al., Cell 2017, Chen and Mellman, Nature 2017;

Memorial Sloan Kettering Cancer Center

Optimal immunotherapies likely requires combinations



Courtesy of Dmitriy Zamarin

Adapted from Bourla and Zamarin, *Oncology*. 30:59-66 (2016)

Memorial Sloan Kettering Cancer Center

Randomized phase III trials of combinations with immune checkpoint inhibitors

Locally advanced Disease

Trial	Agent (n)	Design	Stratification factors	Primary endpoint(s)
CALLA	Durvalumab (n=714)	2 arms 1:1 • Cisplatin + RT+ Durvalumab • Cisplatin + RT	• Stage	PFS
KEYNOTE-A18/ENGOT-cx11/GOG-3047	Pembrolizumab (n=980)	2 arms 1:1: • Cisplatin+RT+pembrolizumab • Cisplatin+RT	• Stage • Planned EBRT	PFS OS

Recurrent / Metastatic Disease

Trial	Agent (n)	Design	Stratification factors	Primary endpoint(s)
KEYNOTE-826 (NCT03635567)	Pembrolizumab (n=600)	2 arms 1:1: • Arm 1: Cisplatin + Paclitaxel + Pembrolizumab +/- Bevacizumab • Arm 2: Cisplatin + Paclitaxel +/- Bevacizumab	• Stage • +/-bev • PDL-L1 status	PFS OS
BEATcc (NCT 03556839)	Atezolizumab (n=404)	2 arms 1:1 • Arm 1: Cisplatin + Paclitaxel + Bevacizumab + Atezolizumab • Arm 2: Cisplatin + Paclitaxel + Bevacizumab	• -Prior CRT • Histology • Chemotherapy backbone: cisplatin v carboplatin	OS
FERMATA (NCT03912415)	BCD-100 (Prolgolimab) (n=316)	2 arms 1:1 • GOG 240 control (MD choice bev) • Prolgolimab + cisplatin + paclitaxel + /-bevacizumab	• -Stage • +/-bev • PDL-L1 status • Ethnicity	OS

Memorial Sloan Kettering Cancer Center

Randomized phase III trials of combinations of immune checkpoint inhibitors

Locally advanced Disease

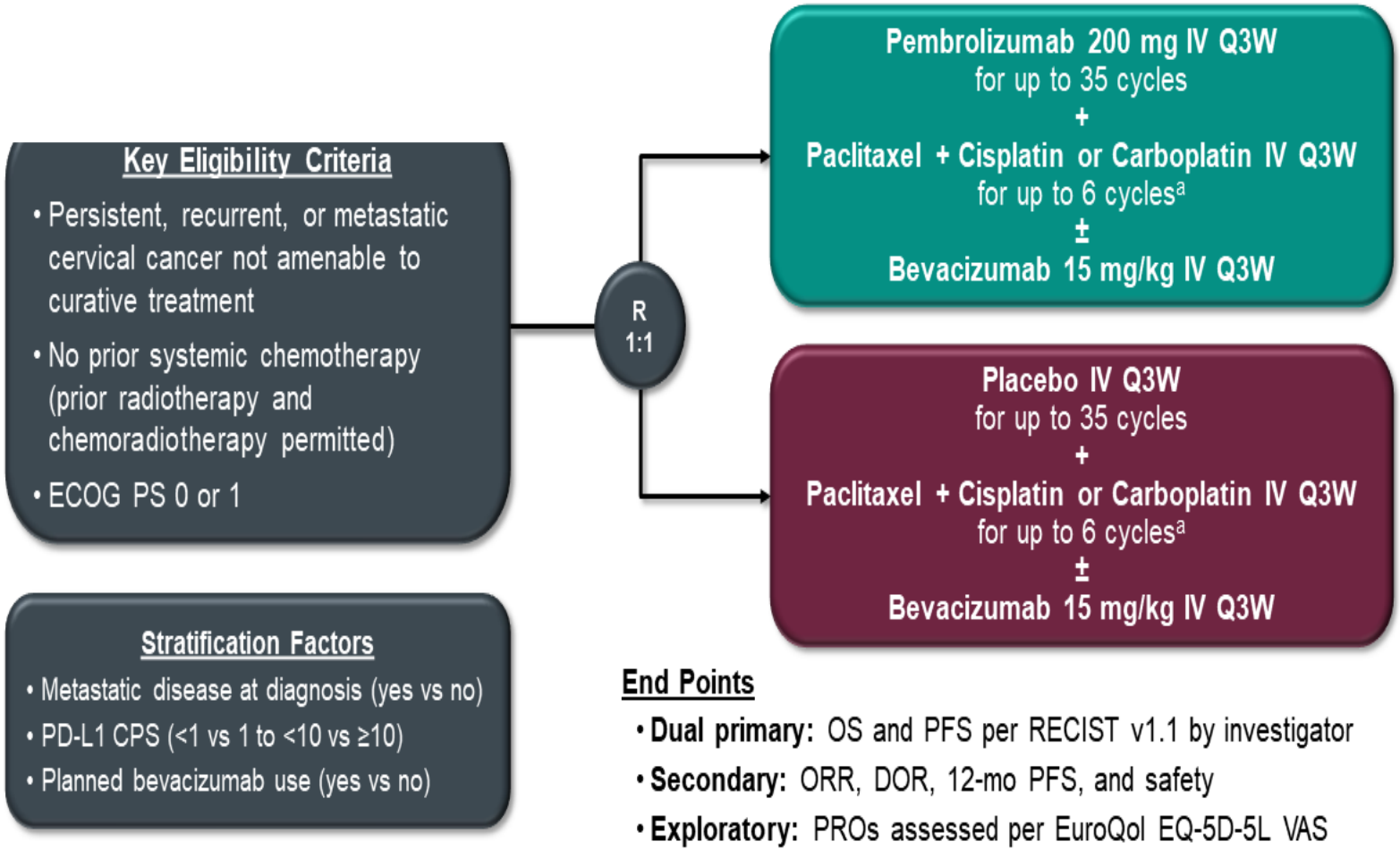
Trial	Agent (n)	Design	Stratification factors	Primary endpoint(s)
CALLA	Durvalumab (714)	2 arms 1:1 • Cisplatin + RT+ Durvalumab • Cisplatin + RT	• Stage	PFS
KEYNOTE-A18/ENGOT-cx11/GOG-3047	Pembrolizumab (980)	2 arms 1:1: • Cisplatin+RT+pembrolizumab • Cisplatin+RT	• Stage • Planned EBRT	PFS OS

Recurrent / Metastatic Disease

Trial	Agent (n)	Design	Stratification factors	Primary endpoint(s)
KEYNOTE-826 (NCT03635567)	Pembrolizumab (600)	2 arms 1:1: • Arm 1: Cisplatin + Paclitaxel + Pembrolizumab +/- Bevacizumab • Arm 2: Cisplatin + Paclitaxel +/- Bevacizumab	• Stage • +/-bev • PDL-L1 status	PFS OS **FDA approval October 2021**
BEATcc (NCT 03556839)	Atezolizumab (404	2 arm 1:1 • Arm 1: Cisplatin + Paclitaxel + Bevacizumab + Atezolizumab • Arm 2: Cisplatin + Paclitaxel + Bevacizumab	• -Prior CRT • Histology • Chemotherapy backbone: cisplatin v carboplatin	OS
FERMATA (NCT03912415)	BCD-100 (316)	2 arm 1:1 • GOG 240 control (MD choice bev) • BCD-100 + cisplatin + taxol + bev	• -Stage • +/-bev • PDL-L1 status • Ethnicity	OS

Memorial Sloan Kettering Cancer Center

KEYNOTE 826: Randomized, Double-blinded, Phase 3 Study

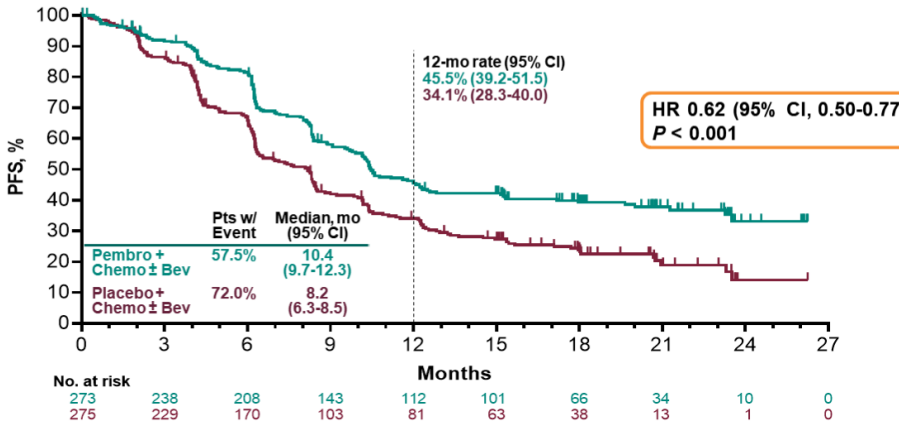


Colombo, et al NEJM 2021

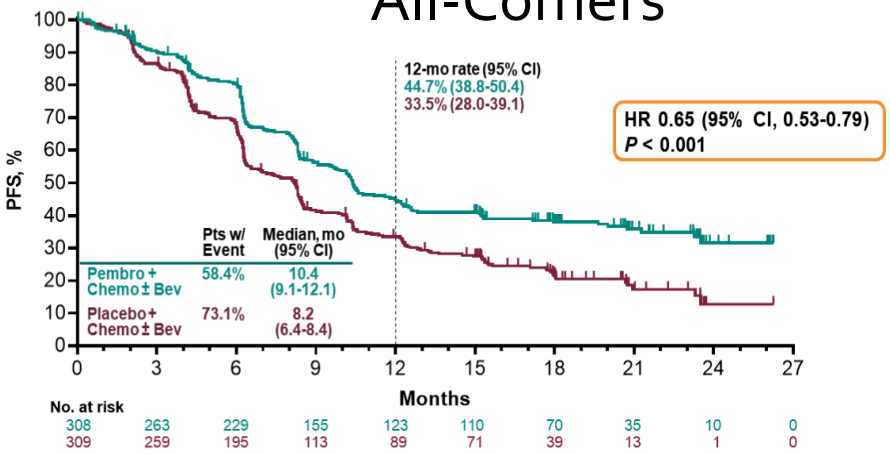
Memorial Sloan Kettering Cancer Center

KEYNOTE 826: Pembrolizumab plus Chemotherapy for Recurrent / Metastatic Cervical Cancer: Progression-Free Survival

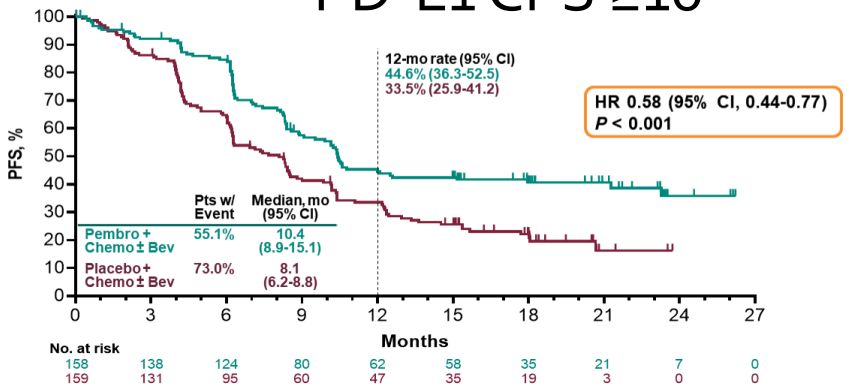
PD-L1 CPS ≥1

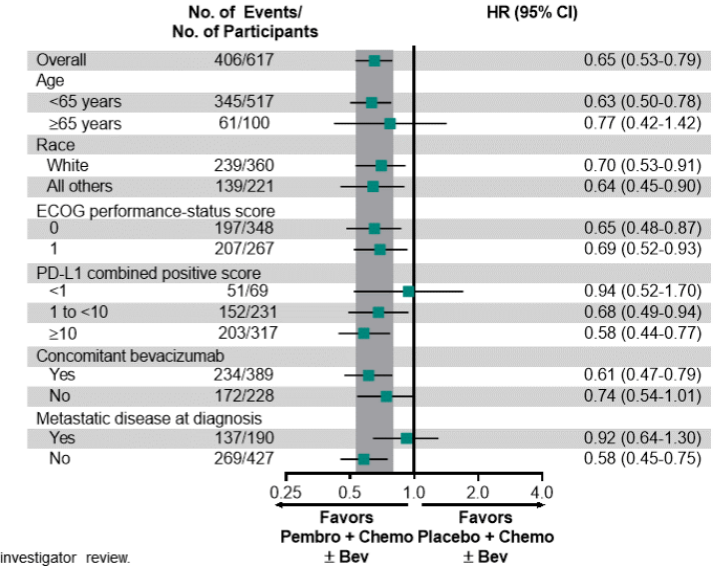


All-Comers



PD-L1 CPS ≥10





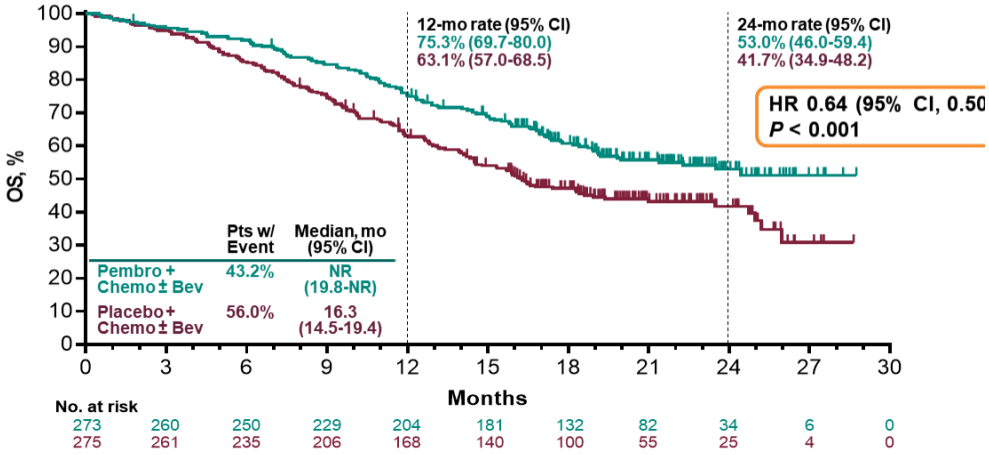
1.1 by investigator review.

Colombo, et al NEJM 2021

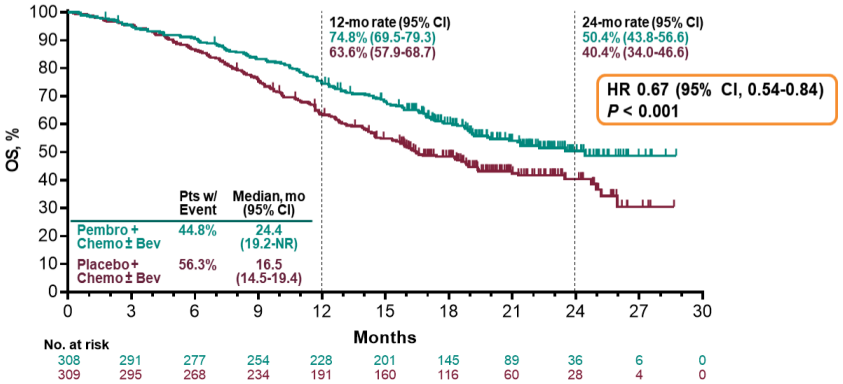
Memorial Sloan Kettering Cancer Center

KEYNOTE 826:– Overall Survival

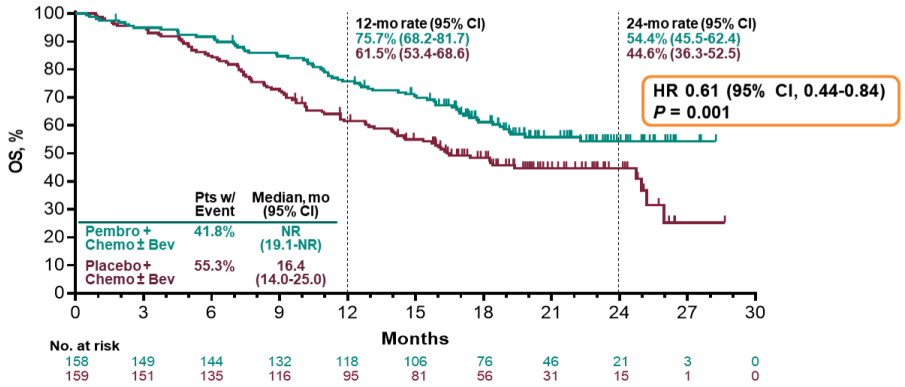
PD-L1 CPS ≥1

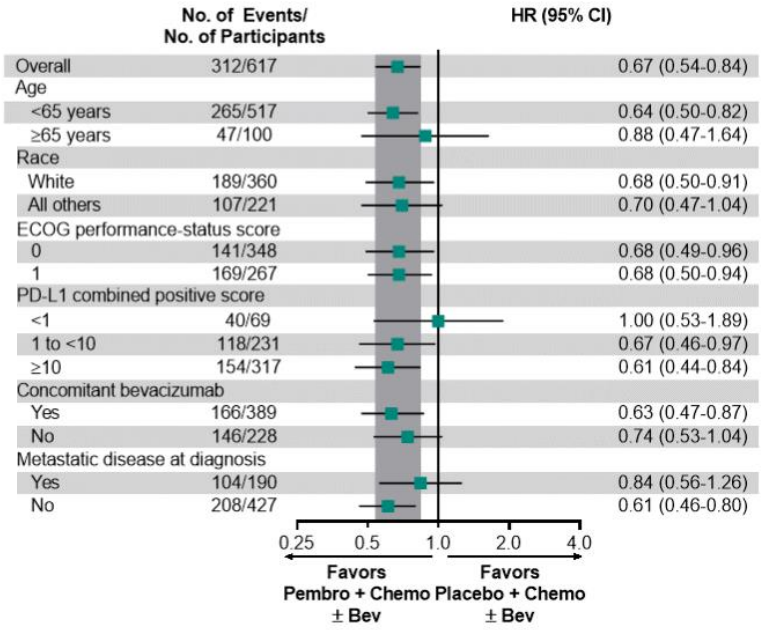


All-Comers



PD-L1 CPS ≥10





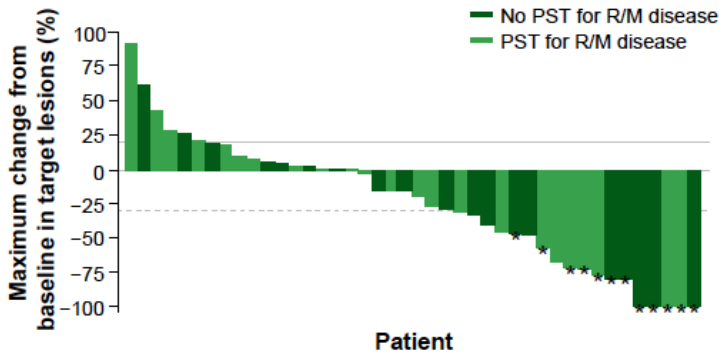
Colombo, et al NEJM 2021

Memorial Sloan Kettering Cancer Center

Combined CTLA-4 and PD-1 blockade in advanced cervical cancer (CHECKMATE 358, ipilimumab and nivolumab)

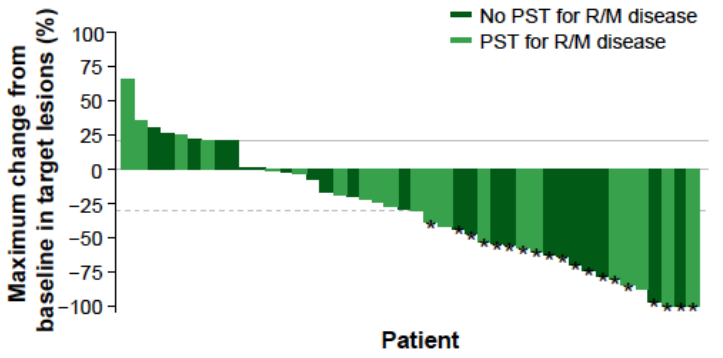
ORR: 31.6% (no PST)
ORR: 23.1% (+PST)

NIVO3+IPI1



ORR: 45.8% (no PST)
ORR: 36.4% (+PST)

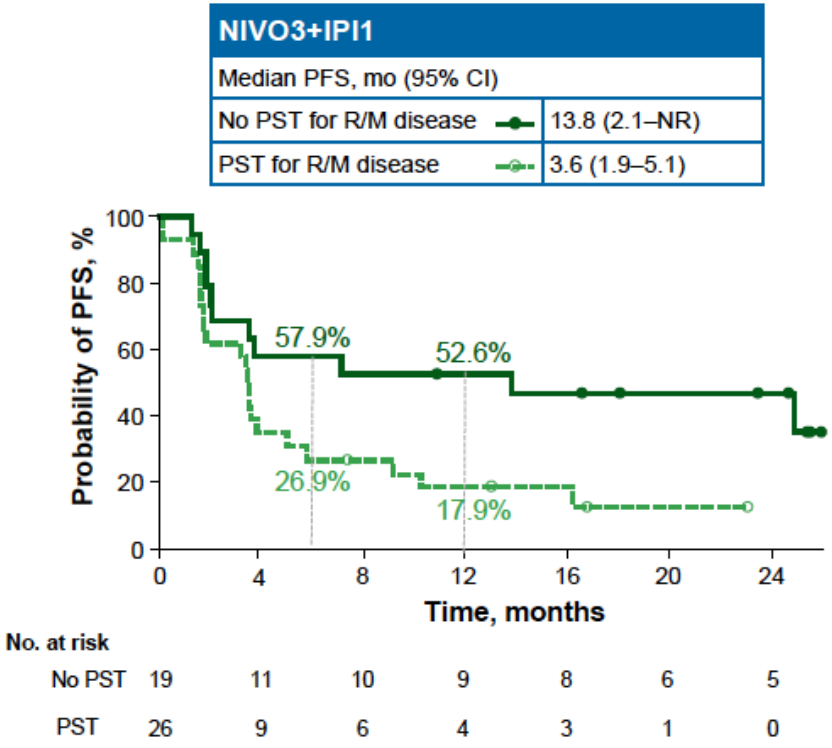
NIVO1+IPI3

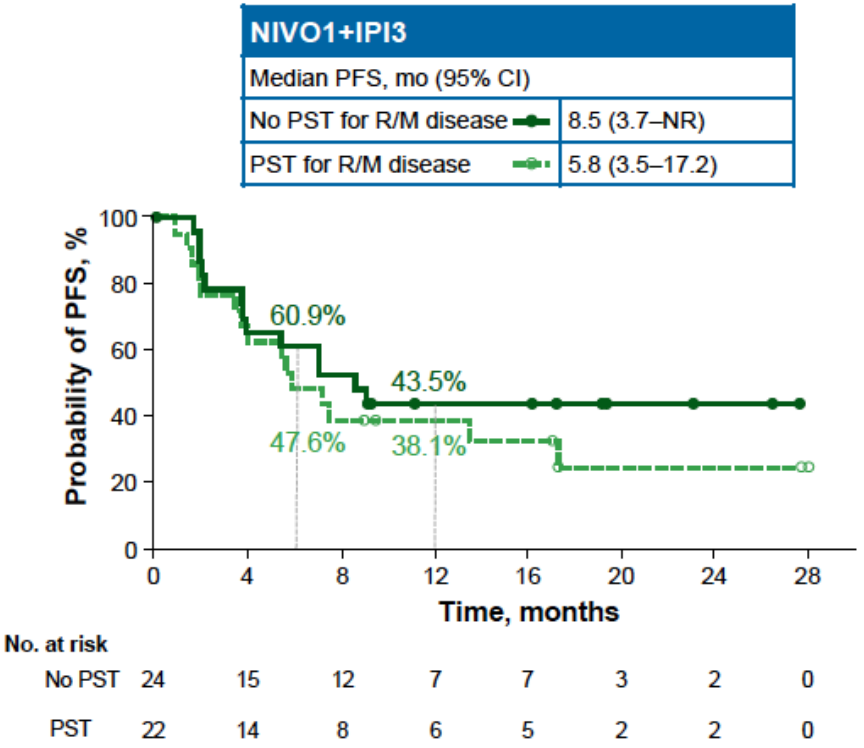


Presented by Ana Oaknin et al., ESMO 2019

Memorial Sloan Kettering Cancer Center

Combined CTLA-4 and PD-1 blockade in advanced cervical cancer CHECKMATE 358



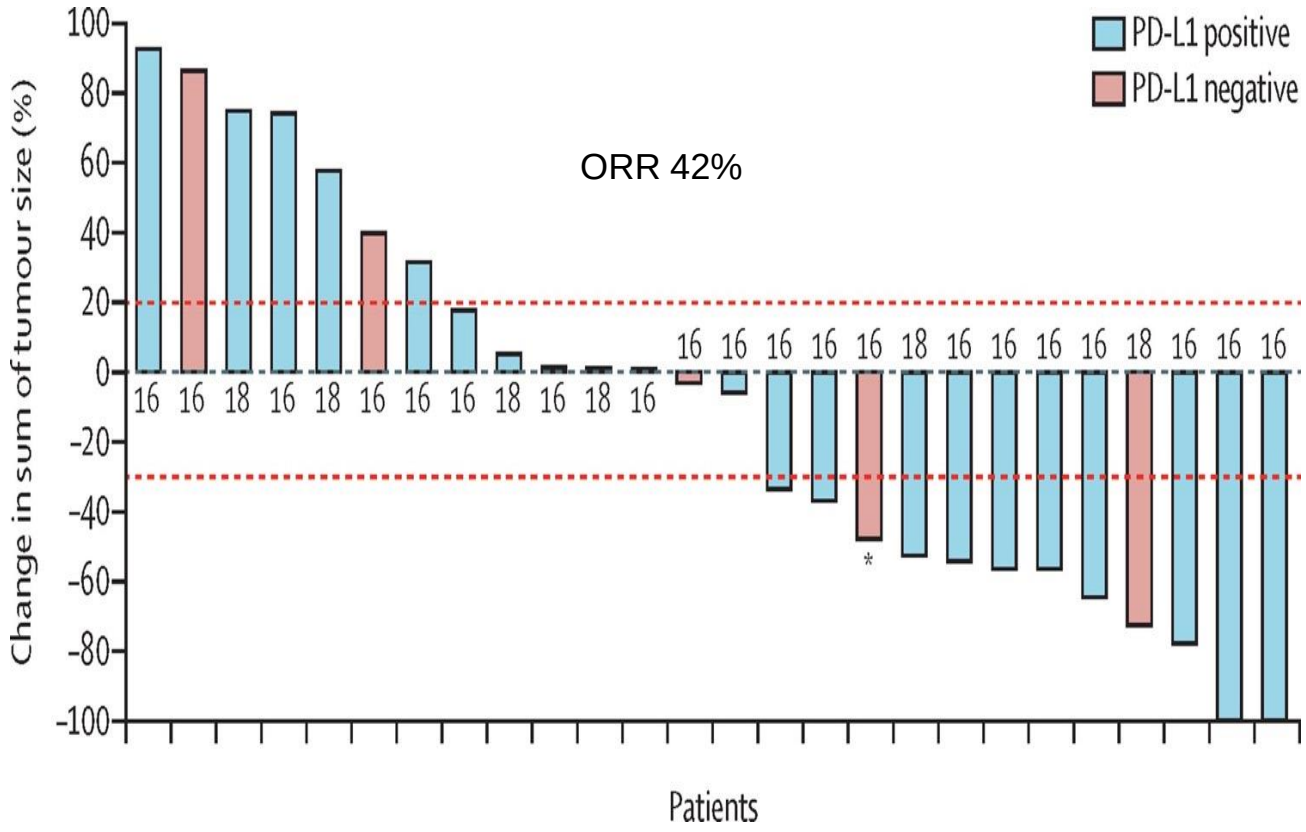


RW Naumanm and Ana Oaknin et al., ESMO 2019

Memorial Sloan Kettering Cancer Center

Combination of Pembrolizumab with HPV vaccine in advanced cervical cancer

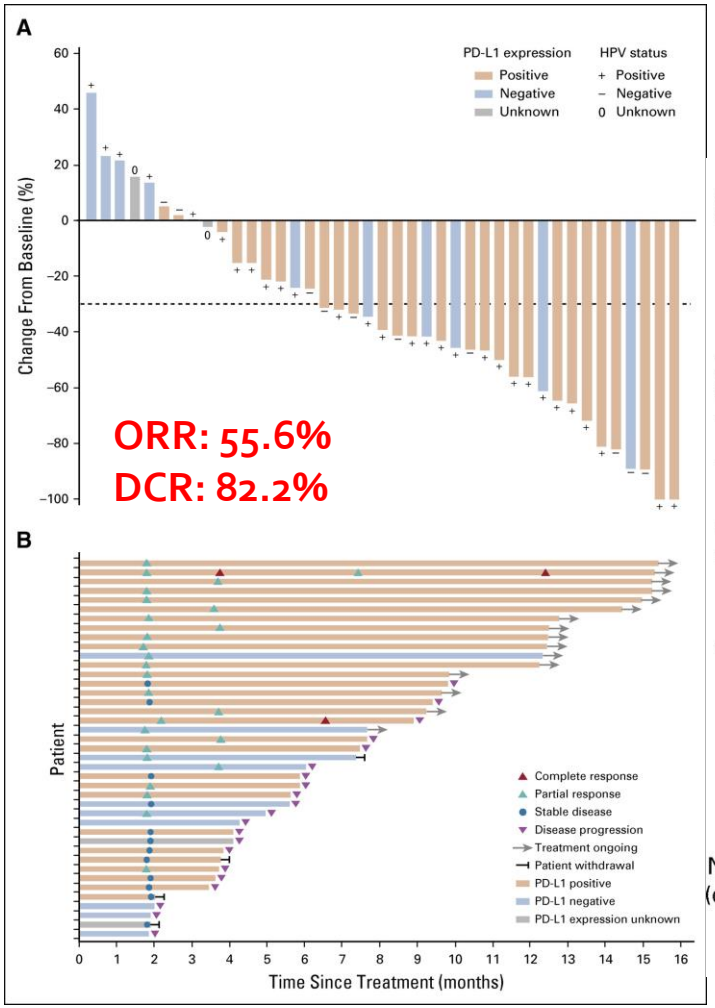
GX-188E (tirvalimogene teraplasmid): DNA-encoded vaccine against HPV 16 and HPV 18



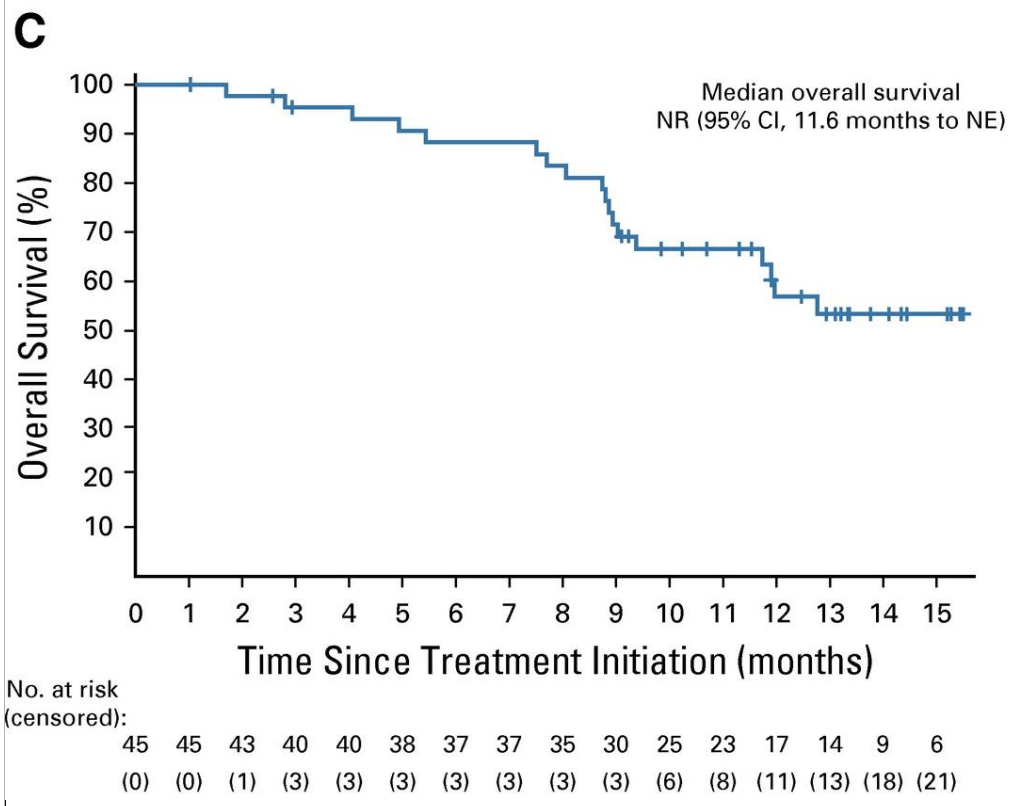
Youn et al., Lancet Oncology 2020

Memorial Sloan Kettering Cancer Center

Combinations of PD-1 blockade with targeted agents



Apatinib: VEGFR-targeted TKI
Camrelizumab: anti-PD-1



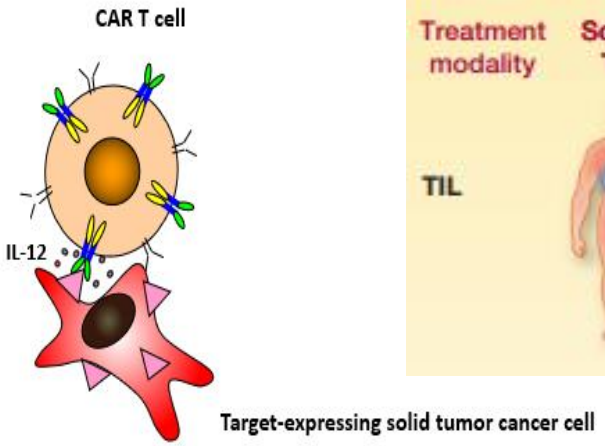
Lan C et al., J. Clin. Oncol. 2020; 38: 4095

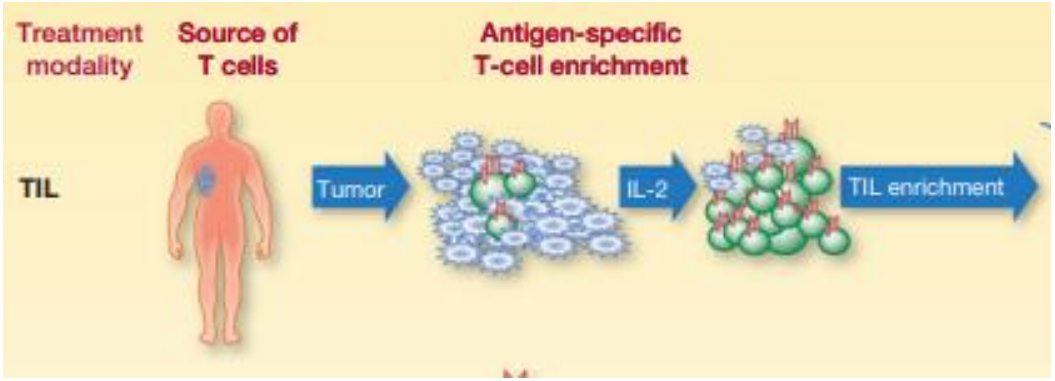
Memorial Sloan Kettering Cancer Center

Adoptive Cell Therapy

Isolation of T cells with genetic modification with aim to recognize and target tumor antigen

- **TCR gene modified T cells**
- **Tumor Infiltrating Lymphocytes**
- **Chimeric antigen receptor (CAR) modified T cells**



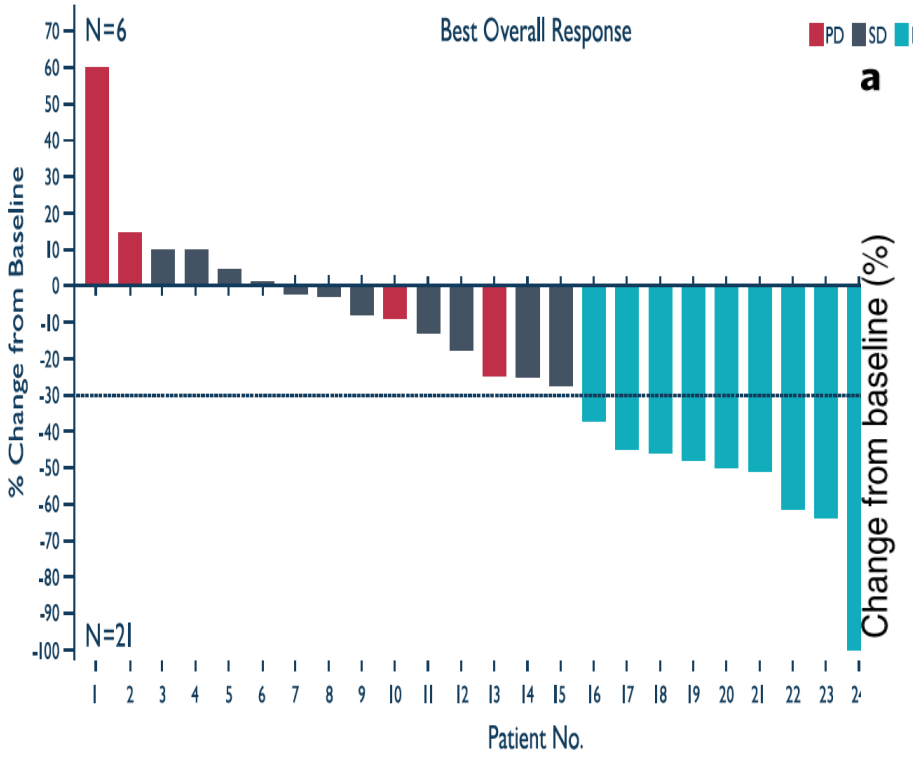


Yee C. Clin. Can. Res. 2013

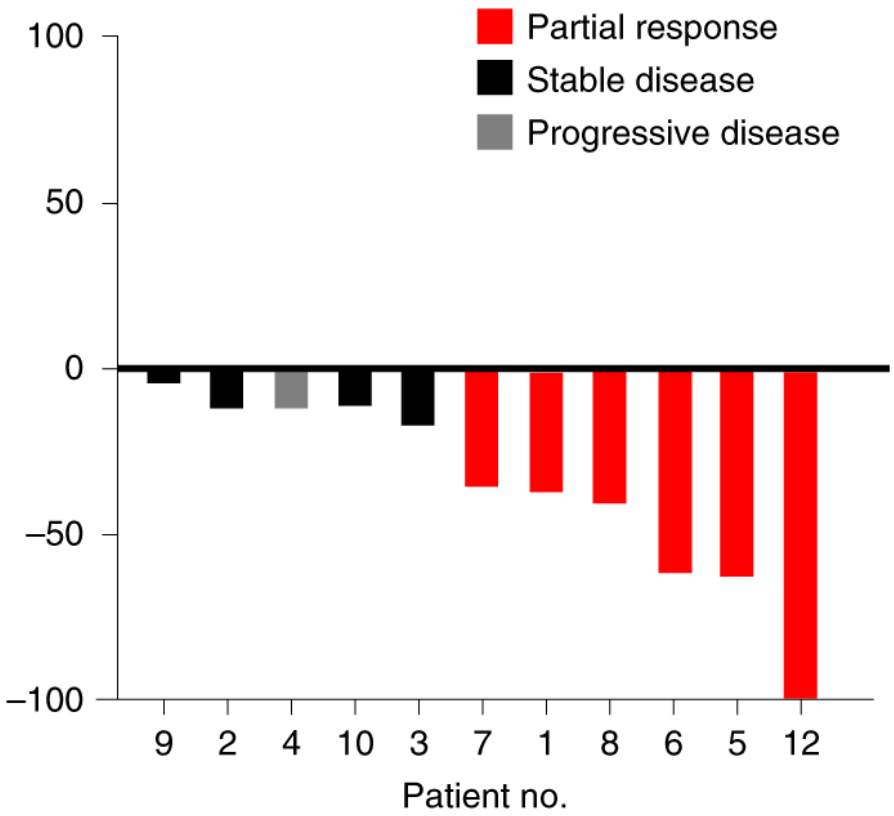
Memorial Sloan Kettering Cancer Center

Adoptive T cell therapies

TILs



T cells targeting HPV16 E7



Jazaeri et al., ASCO 2019,
Nagarsheth, … Hinrichs CS, Nat Med. 2021

Take Home Messages

- Immune checkpoint blockade is FDA approved for endometrial and cervical cancers
- Checkpoint blockade is promising in gynecologic cancers, but we still have a long way to go!
- Many barriers to overcome
- Frequent relapse: need to improve persistence and disease control
- Combination therapies will be a key to success: with other immunotherapies, targeted therapy, cellular therapies or chemotherapy in order to optimize the immune response, overcome a suppressive microenvironment and the challenges of intra- and inter-tumor heterogeneity