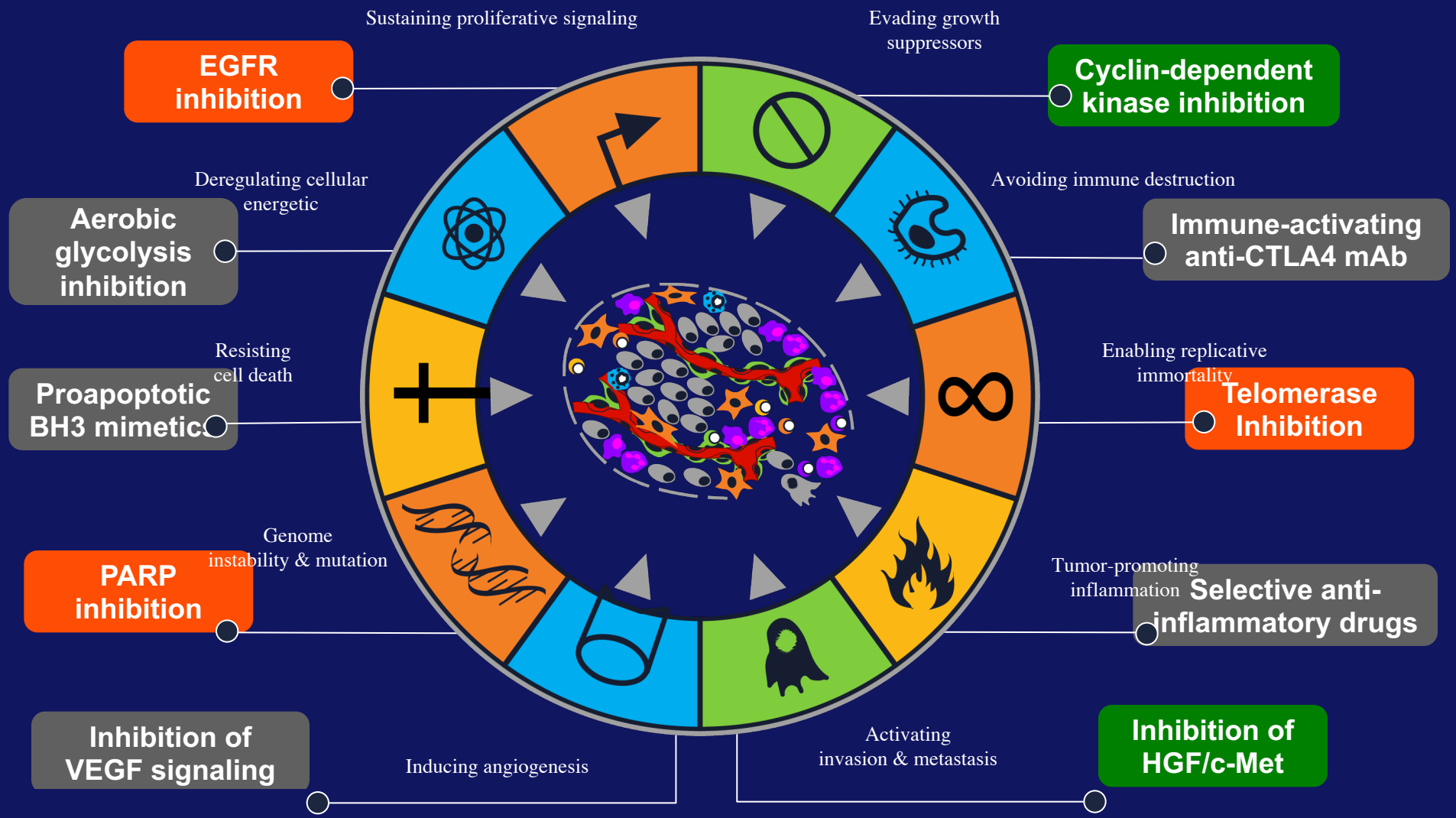
Immunotherapies in Gynecologic Malignancies

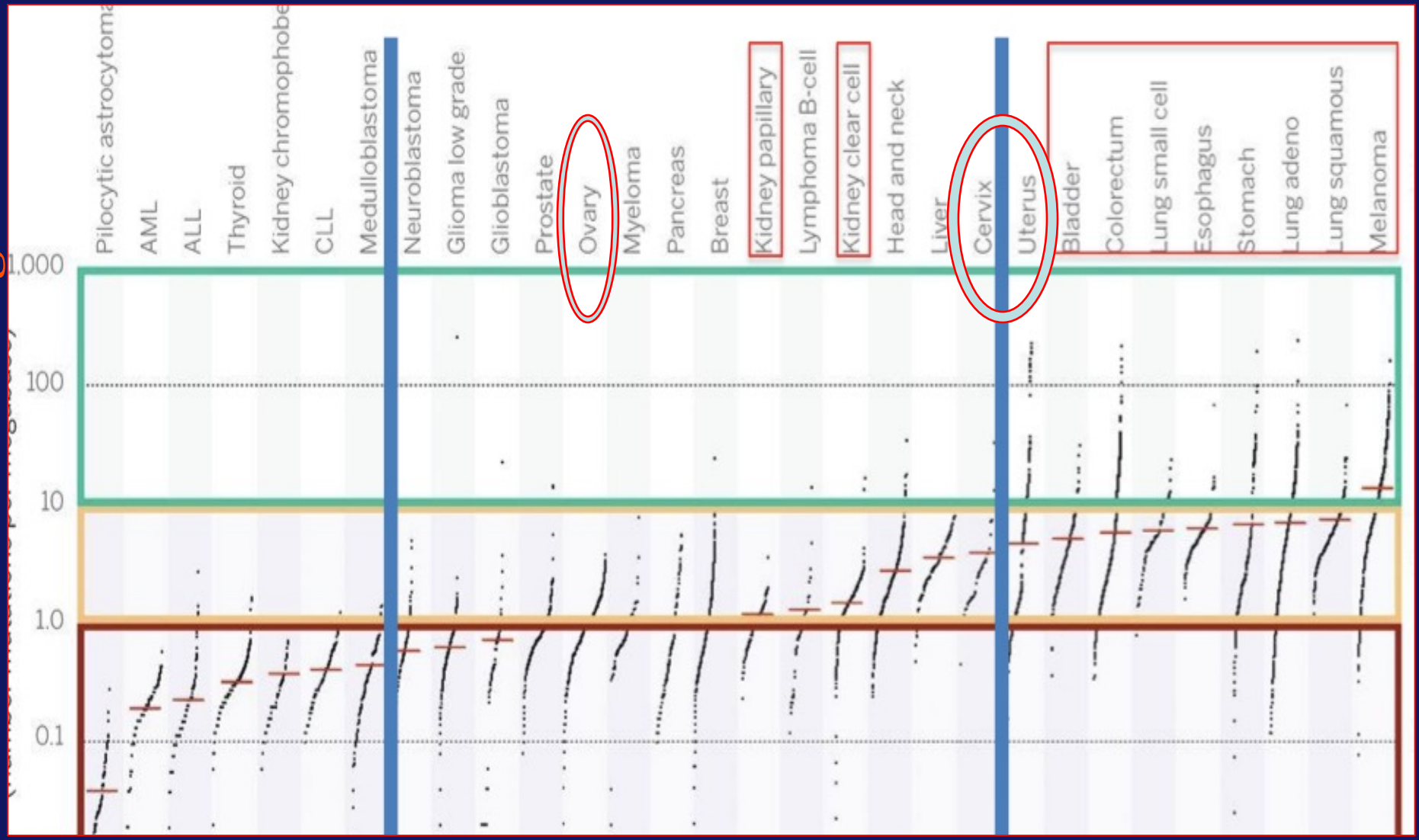
Thomas J. Herzog, MD
Paul & Carolyn Flory Professor
Deputy Director, UC Cancer Institute
Vice Chair Quality & Safety, Dept Ob/Gyn
University of Cincinnati

Strategies Targeting Hallmarks of Cancer



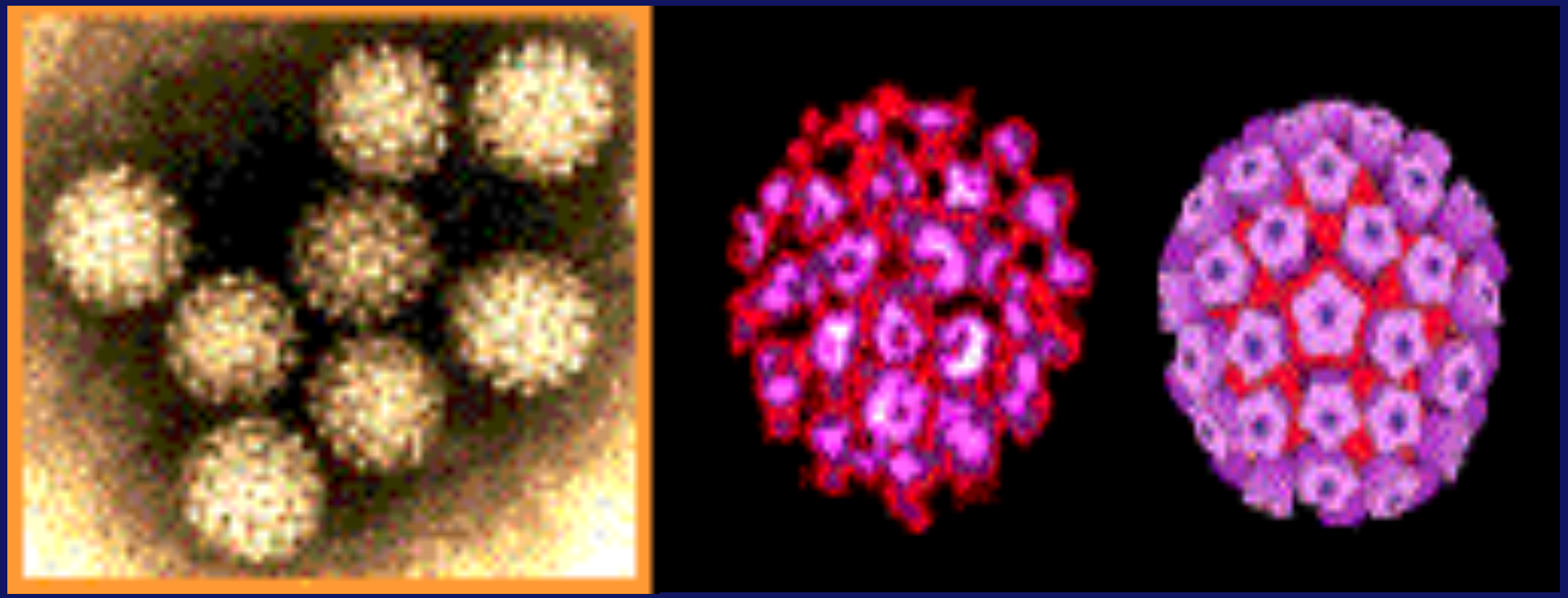
Hanahan and Weinberg. Cell. 2011;144(5):646-74.

Frequency of Somatic Mutations Across Tumor Types



Schumacher TN and Schreiber RD, *Science*, 2015

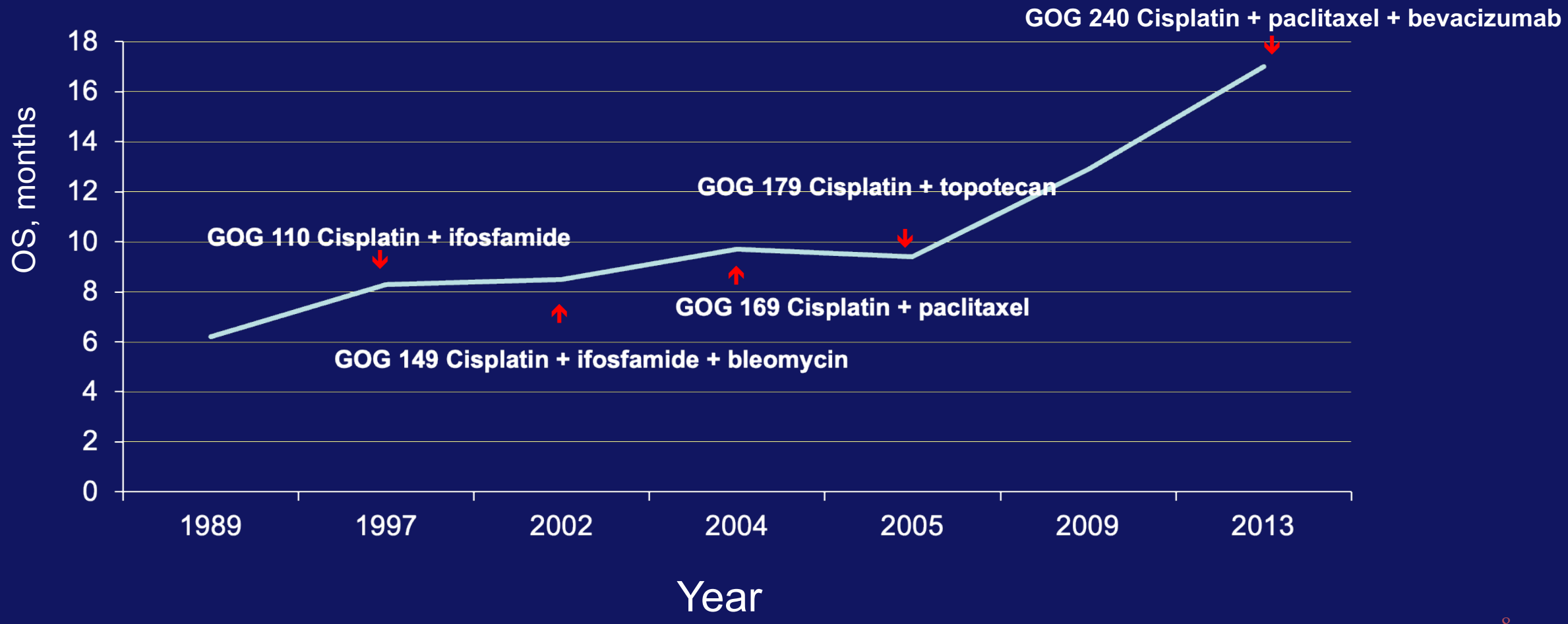
Cervical Cancer Immunotherapy



HPV Non enveloped Icosahedral DNA Virus

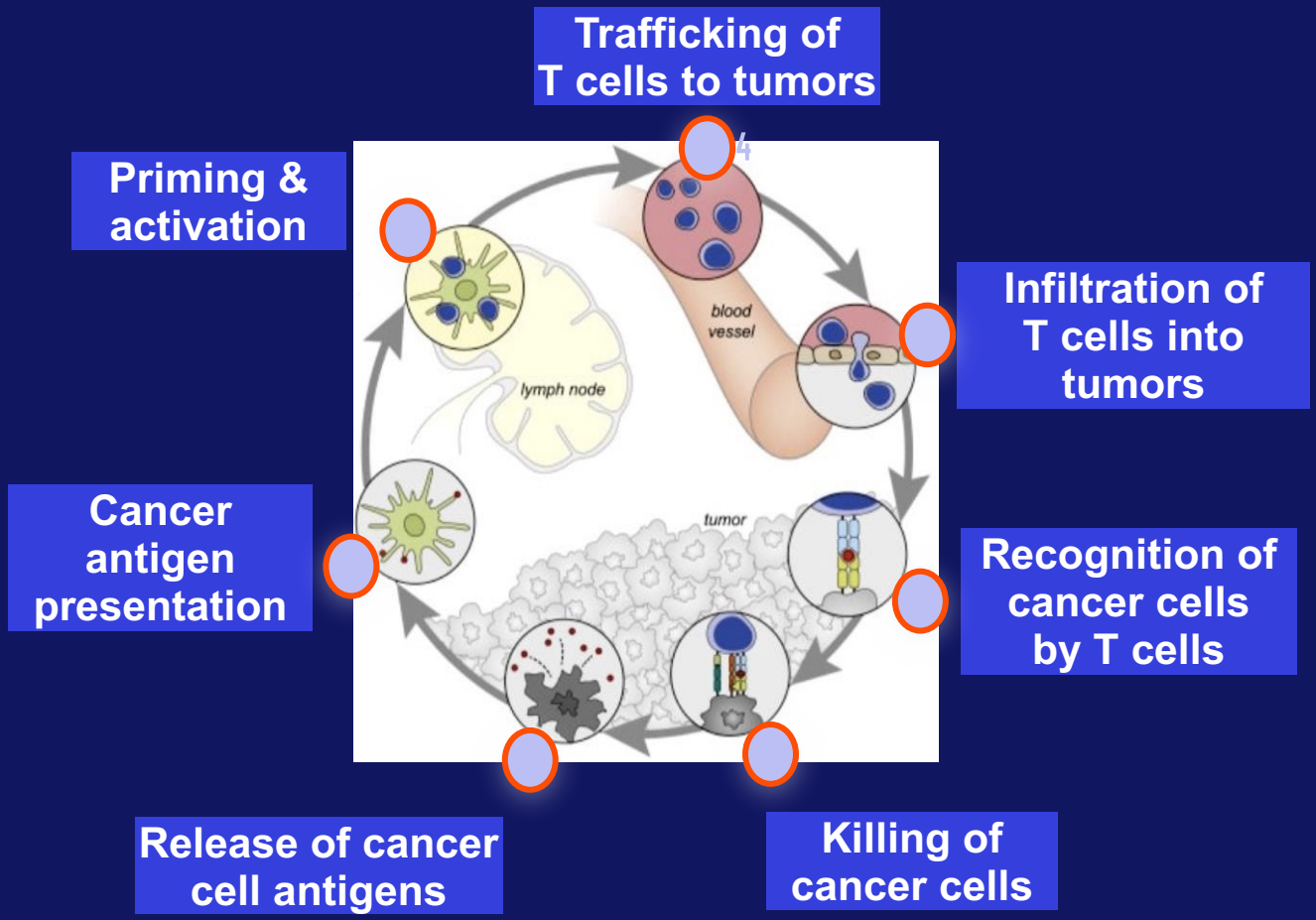
Improving OS in Recurrent or Metastatic Cervical Cancer

How Do We Move Forward?



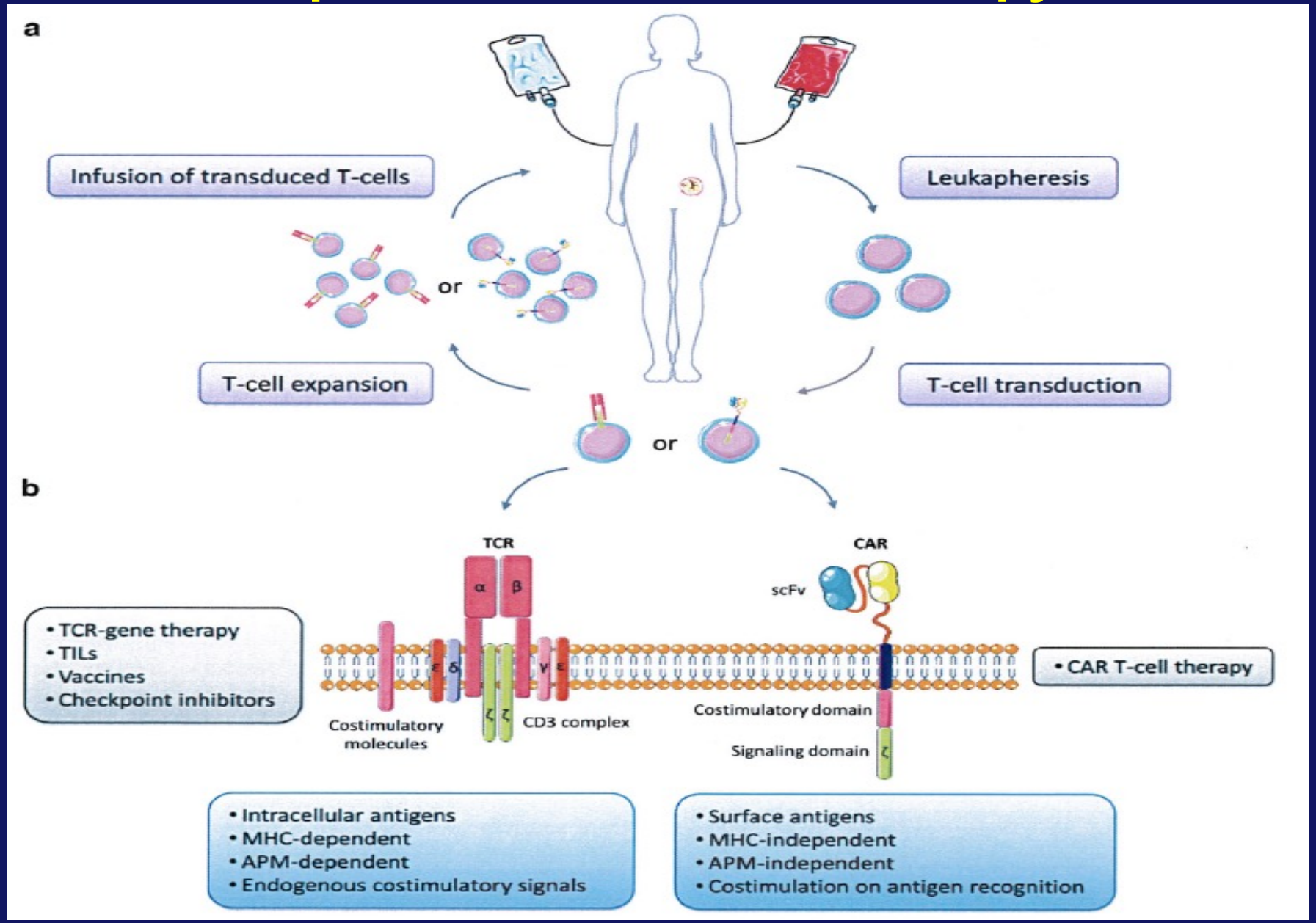
Rationale for Immunotherapy

- **TCGA data**
  - Amplifications in PD-L1/L2
    - Correlates with key immune cytolytic effectors
    - Can limit protective immunity
- **Immunotherapy**
  - PD-1/L1 inhibition
    - Promotes T-cell activation against tumors
  - CTLA-4 inhibition
    - Enhances tumor-specific CD8+ T-cell responses



1. Cancer Genome Atlas Research Network. *Nature.* 2017;543:378-84. 2. Chen DS, et al. *Immunity.* 2013;39:1-10.

Adoptive T-cell Transfer Therapy



Hinrichs CS, et al. *J Clin Oncol*. 2014;32(5s): Abstract LBA3008.

Rodriguez-Garcia A et al Gyn Onc 2017

Cervical Cancers & Checkpoint Blockade

	Lheureux et al.[1]	KEYNOTE-028[2]	KEYNOTE-158[3] (Cohort E)[b]	Checkmate 358[4]
Phase	2	1b	2	1/2
Population	Metastatic or recurrent cervical cancer with progression after prior platinum chemotherapy	PD-L1+ advanced cervical squamous cell cancers after failure of prior systemic therapy	Advanced cervical cancer with progression on or intolerance to ≥1 line of prior therapy, PD-L1+ (CPS ≥1)	HPV-associated tumors, including recurrent or metastatic cx, vaginal, vulvar cancers
Patients, n	42[a]	24	77[d]	24
Treatment	Ipilimumab	Pembrolizumab	Pembrolizumab	Nivolumab
ORR	8.8%[c]	12.5%[c]	14.3%	ITT: 20.8%[c] Cervical ca pts: 26.3%
DCR, %	32.3	25.0	—	70.8
mDOR	—	19.3 wk	NR (range: 4.1–18.6+ mo)	NR
PFS	mPFS: 2.5 mo	6-mo PFS: 13.0%	—	mPFS: 5.5 mo
OS	—	6-mo OS: 66.7%	—	NR
Safety	Manageable toxicities	≥Gr 3 TRAEs: 20.8%	Serious AEs: 39%	Gr 3/4 TRAEs: 12.5%
Follow-up	—	48.9 wk	11.7 mo	31 wk

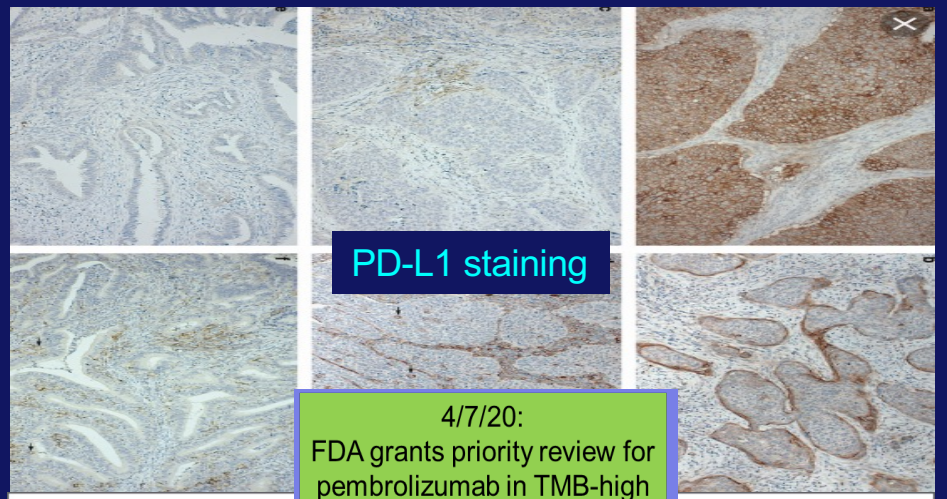
[a] 34 evaluable for efficacy. [b] trial led to the approval of pembrolizumab for treatment of patients with cervical cancer. [c] Primary endpoint.
[d] Cohort E = 98 pts, but pembrolizumab label includes data for response in 77 patients whose tumors expressed PD-L1.

CPS, combined positive score; DCR, disease control rate; ITT, intent to treat; mDOR, median duration of response;; NR, not reached; ORR, overall response rate;; PD-L1, programmed death ligand 1;; TRAE, treatment-related adverse event.

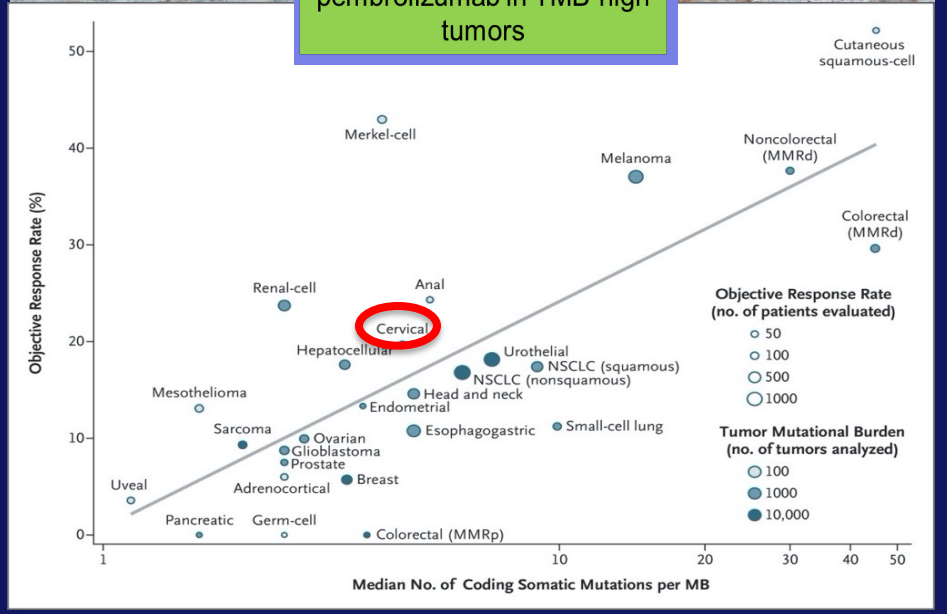
1. Lheureux S, et al. Presented at ASCO Annual Meeting, 2015. Abstract 3061. **2.** Frenel JS, et al. Presented at ASCO Annual Meeting, 2016. Abstract 5515. **3.** Pembrolizumab package insert. Merck & Co, Inc; December 2018. **4.** Hollebecque A, et al. Presented at ASCO Annual Meeting, 2017. Abstract 5504.

Immunotherapy biomarkers

- **PD-L1 expression**
  - ~60% in cervix ca
- **Combined positive score (CPS)**
  - Ratio of the # of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) to all tumor cells
  - CPS ≥1% used for cervical cancer
- **Tumor mutational burden (TMB)-high** status = ~6%
- **Microsatellite Instability (MSI)**
  - Ranges from 2.6% to 14%



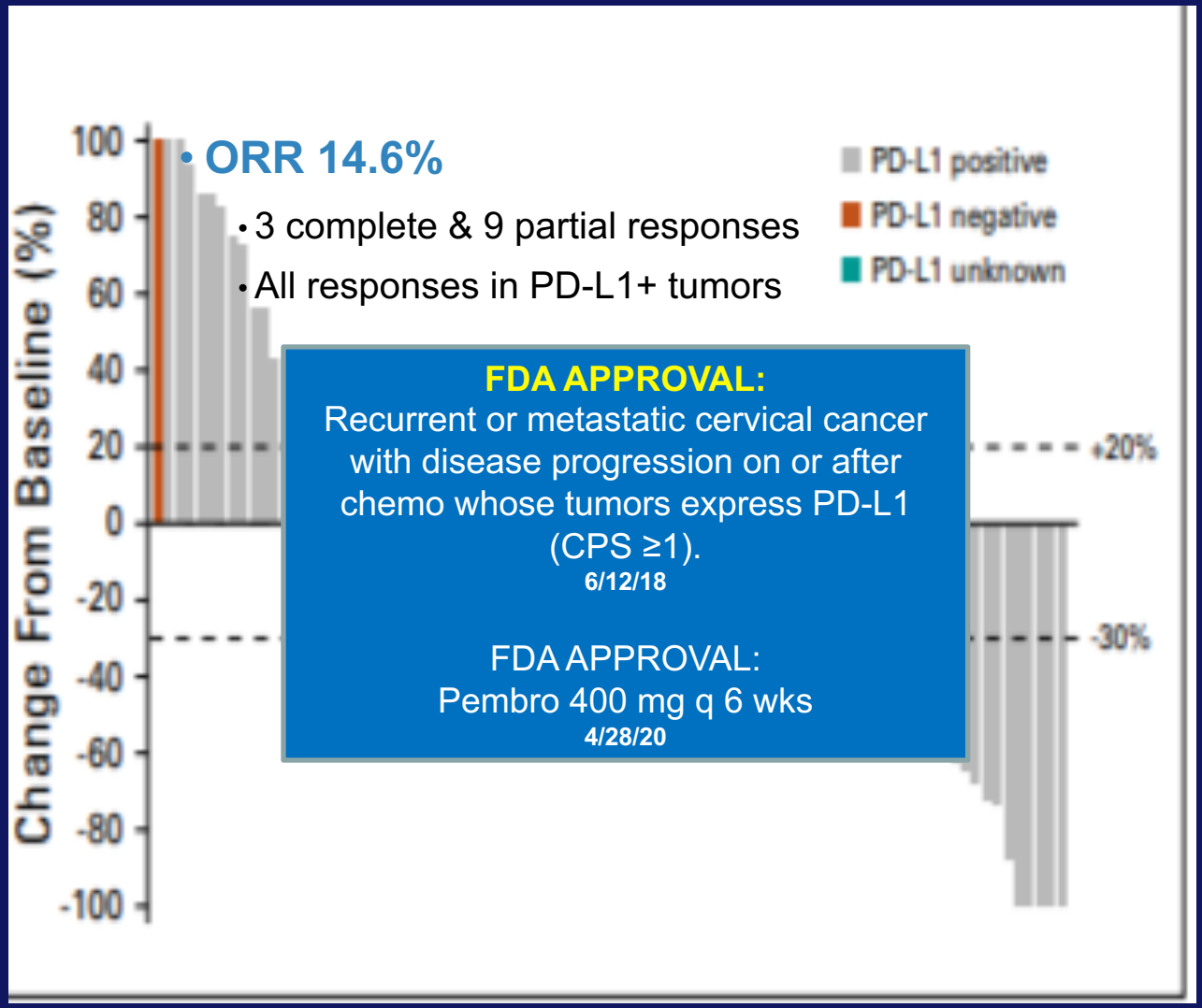
4/7/20:
FDA grants priority review for pembrolizumab in TMB-high tumors



Meng Y. J Cancer 2018. Enwere E. Mod Pathol 2017. Zhang L. N Engl J Med 2003. Yarchoan M. N Engl J Med 2017. Kulangara K. Arch Pathol Lab Med 2019. Chung TK. Gynecol Obstet Invest 2001. Bonneville R. JCO Precis Oncol 2017.

KEYNOTE 158: Pembrolizumab

- **Phase II study: 98 patients**
  - 200 mg IV q 3 wks
  - 79% with prior systemic Rx
  - 83.7% with PD-L1 expression
- Well-tolerated (12% with G3/4 events)
- 91% had DoR ≥ 6 mos
- Med OS: 9.4 mos
- Med OS in PD-L1+: 11 mos
- 12-mo OS in PD-L1+ = 47.3%



Chung HC. J Clin Oncol 2019.

CheckMate 358: Nivolumab & Ipilimumab

Endpoint	A: Nivo (3 mg/kg)+Ipil (1mg/kg)			B: Nivo (1 mg/kg)+Ipil (3mg/kg)	
	No prior treatment	Prior treatment		No prior treatment	Prior treatment
ORR	31.6%	23.1%		45.8%	36.4%
Clinical benefit rate	63.2%	53.8%		70.8%	72.7%
Median PFS	13.8	3.6		8.5	5.8
12-month PFS	52.6%	17.9%		43.5%	38.1%
OS	Not reached	10.3		Not reached	25.4
12-month OS	83.5%	37.5%		89.7%	78.0%
PD-L1 negative	33.3%	9.1%		0%	57.1%
PD-L1 positive	30.8%	40.0%		36.4%	16.7%
GI toxicity	36%			56%	
Discontinuation	18%			33%	

Naumann RW. ESMO 2019.

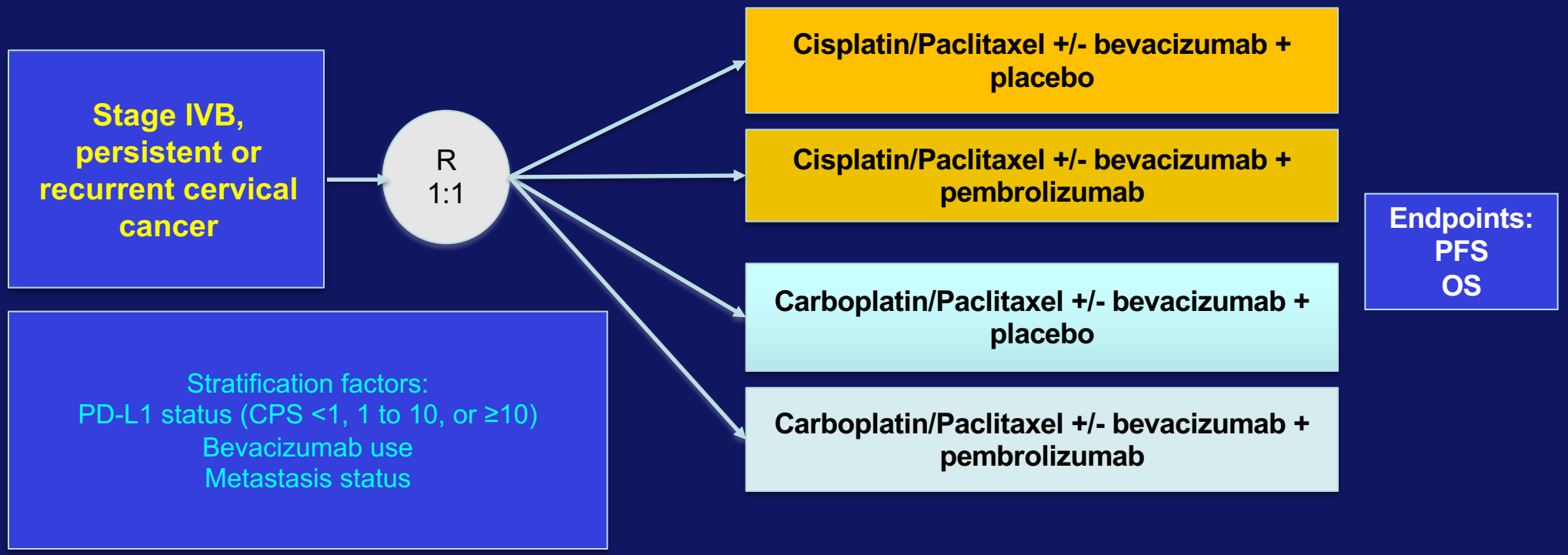
Balstilimab +/- Zalifremilab

Efficacy	Balstilimab	Balstilimab +/- Zalifremilab
ORR	14%	22%
CR	2%	6%
PR	12%	16%
Median DOR	15.4	Not reached
PD-L1 positive	19% (19/99)	27% (21/79)
PD-L1 negative	10% (4/42)	11% (4/36)
PD-L1 unknown	0% (0/19)	21% (6/28)

O'Malley DM. ESMO 2020

KEYNOTE 826: Pembrolizumab

- **Randomized Ph 3 Pembrolizumab in front line therapy**



Colombo N, et al. *N Engl J Med*. 2021. doi:10.1056/NEJMoa2112435

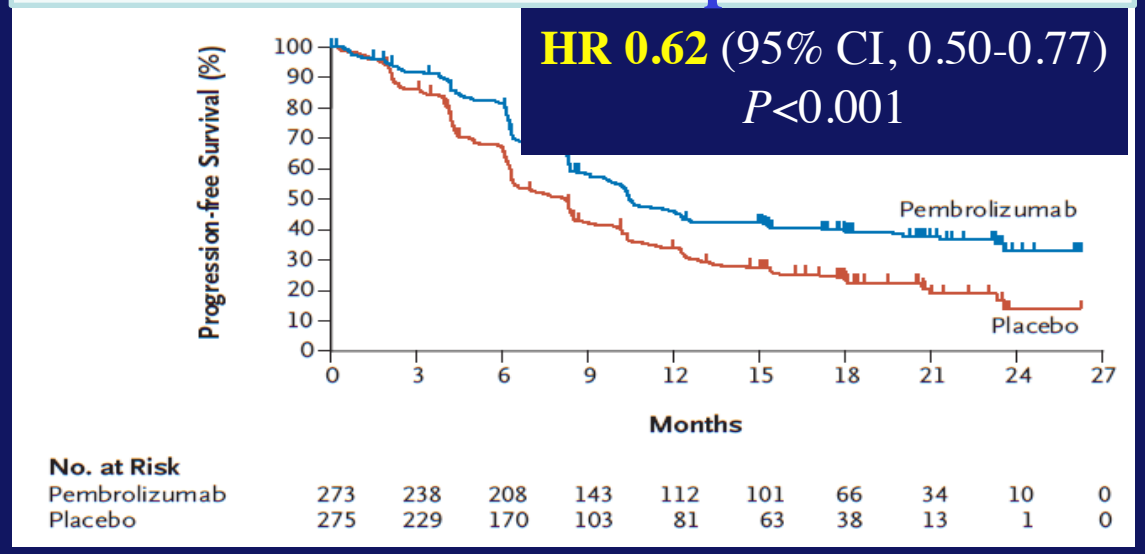
KEYNOTE 826 Demographics

	Pembrolizumab group (n=308)	Placebo group (n=309)
Age, median (range), y	51 (25-82)	50 (22-79)
ECOG PS 1, No. (%)	128 (42)	139 (45)
SCC, No. (%)	235 (76)	211 (68)
PD-L1 CPS, No. (%)		
<1	35 (11)	34 (11)
1 to <10	115 (37)	116 (38)
≥10	158 (51)	159 (51)
Bev during trial	196 (64%)	193 (62%)

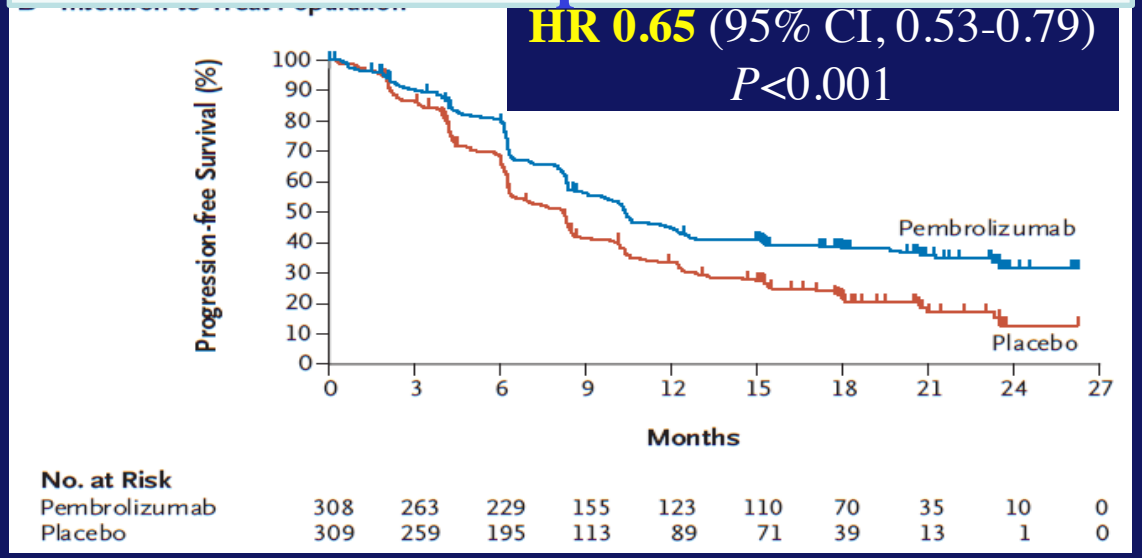
Colombo N, et al. *N Engl J Med*. 2021. doi:10.1056/NEJMoa2112435

KEYNOTE 826: PFS

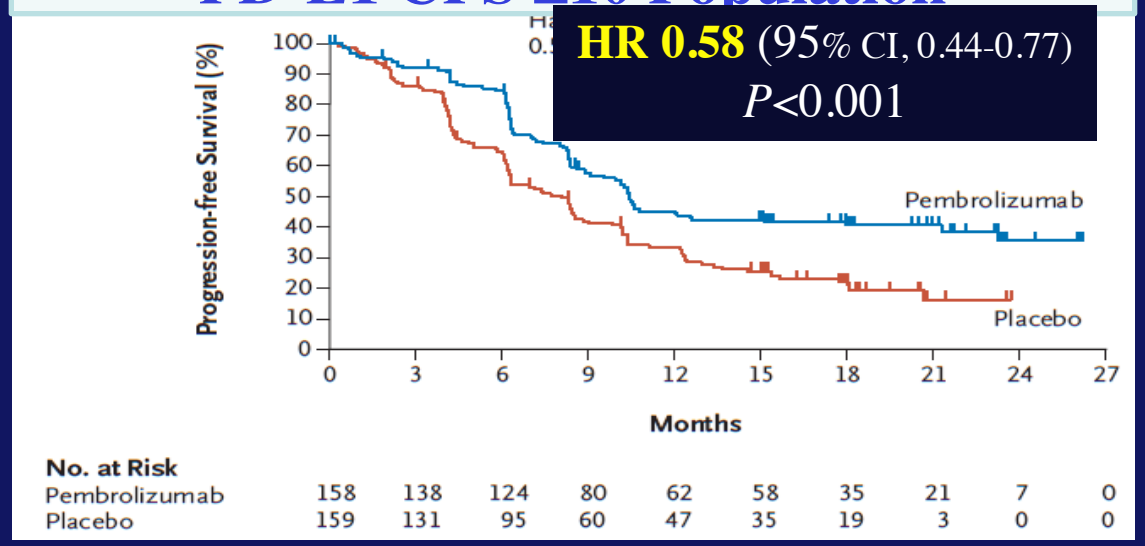
PD-L1 CPS ≥1 Population



ITT Population



PD-L1 CPS ≥10 Population

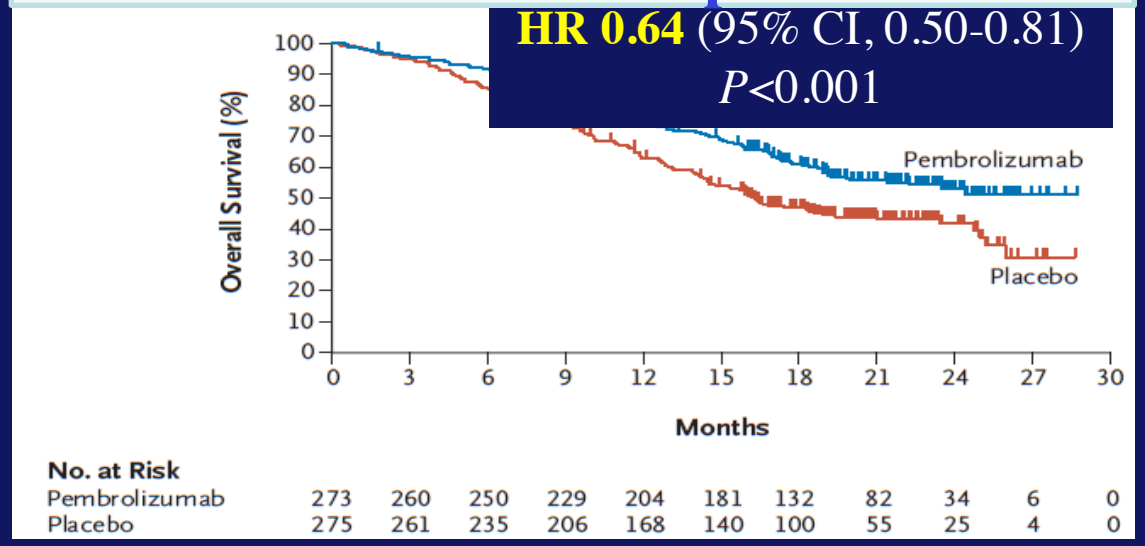


CPS < 1+ was 11% in both cohorts

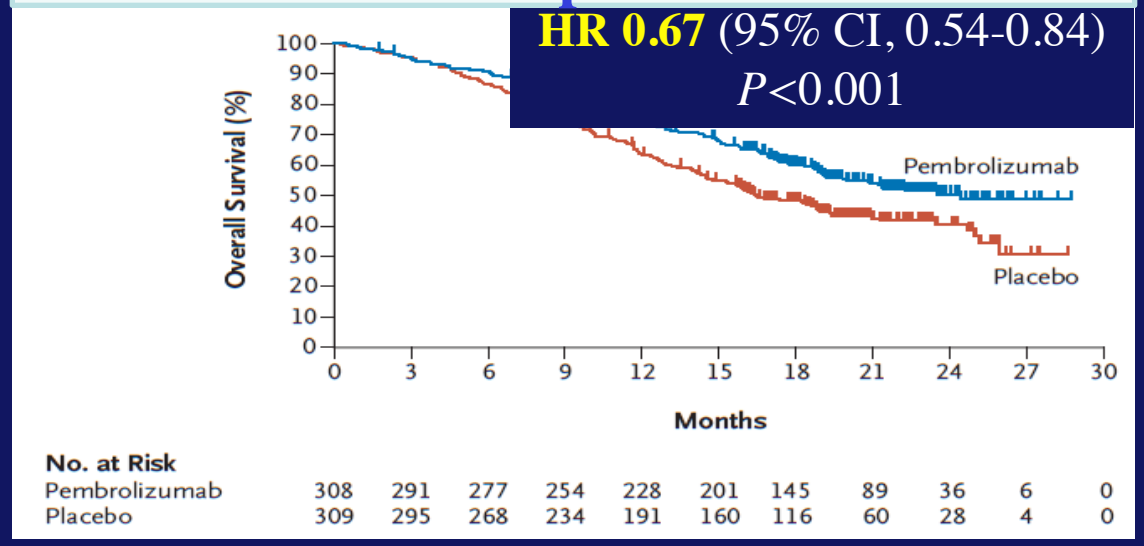
Colombo N, et al. *N Engl J Med*. 2021. doi:10.1056/NEJMoa2112435

KEYNOTE 826: OS

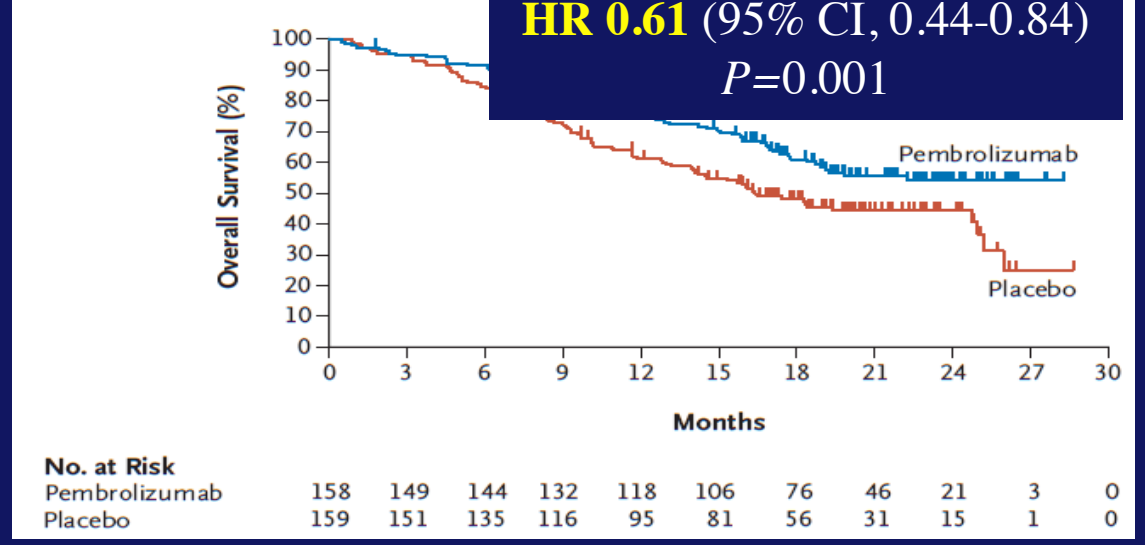
PD-L1 CPS ≥1 Population



ITT Population



PD-L1 CPS ≥10 Population



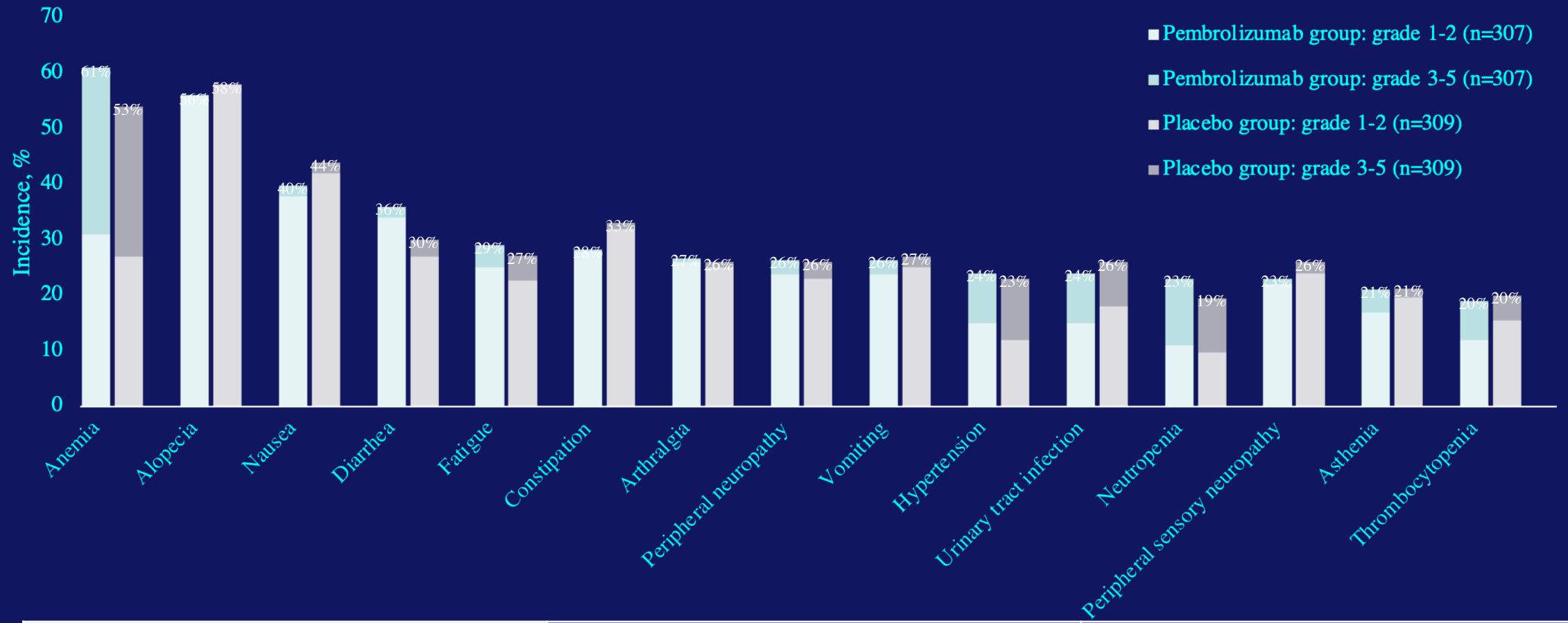
Pembrolizumab cohort mOS (ITT): 24.4 months

FDA approved 10/13/2021 in combination with chemotherapy, with or without bevacizumab, for pts with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥1)

Colombo N, et al. *N Engl J Med*. 2021.

KEYNOTE 826: Adverse Events

Adverse Events of Any Cause With an Incidence ≥20% in Either Group



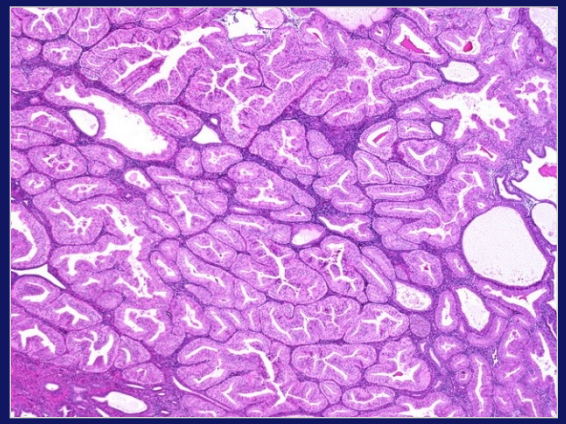
	Pembrolizumab group (n=307)		Placebo group (n=309)	
	Any grade	Grade 3-5	Any grade	Grade 3-5
Potentially immune-mediated AEs,	**33.9**	**11.4**	**15.2**	**2.9**

Colombo N, et al. *N Engl J Med*. 2021. doi:10.1056/NEJMoa2112435

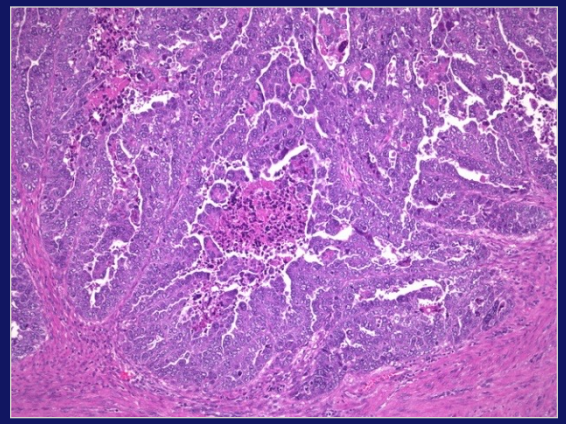
ENDOMETRIAL CANCER

Endometrial Cancer Classified According to Histologic Characteristics[1,2]

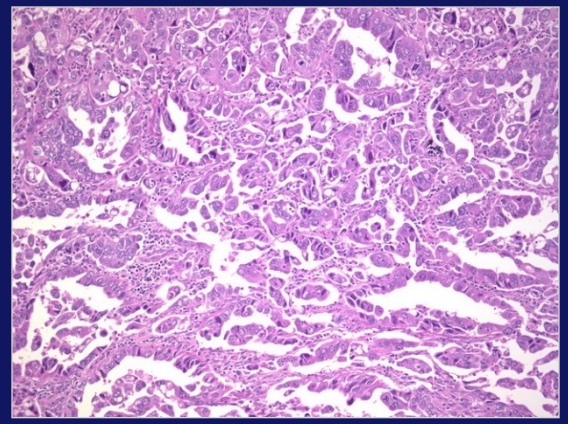
- The most common histologic subtypes are endometrioid, papillary serous, & clear cell carcinoma[1]



Endometrioid adenocarcinoma (low grade)[a]



Papillary serous adenocarcinoma



Clear cell carcinoma

Type I

Type II

Images reproduced from WebPathology. webpathology.com.

[a]Although less common (10%-19%), high-grade endometrioid carcinomas have an aggressive disease course and unfavorable prognosis similar to type II tumors[1,3]

1. Murali R et al. *Lancet Oncol*. 2014;15:e268-e278. 2. Morice P et al. *Lancet*. 2016;387:1094-1108. 3. Buhtoiarova TN et al. *Am J Clin Pathol*. 2016;145:8-21

Endometrial Cancer: Molecular Subtypes

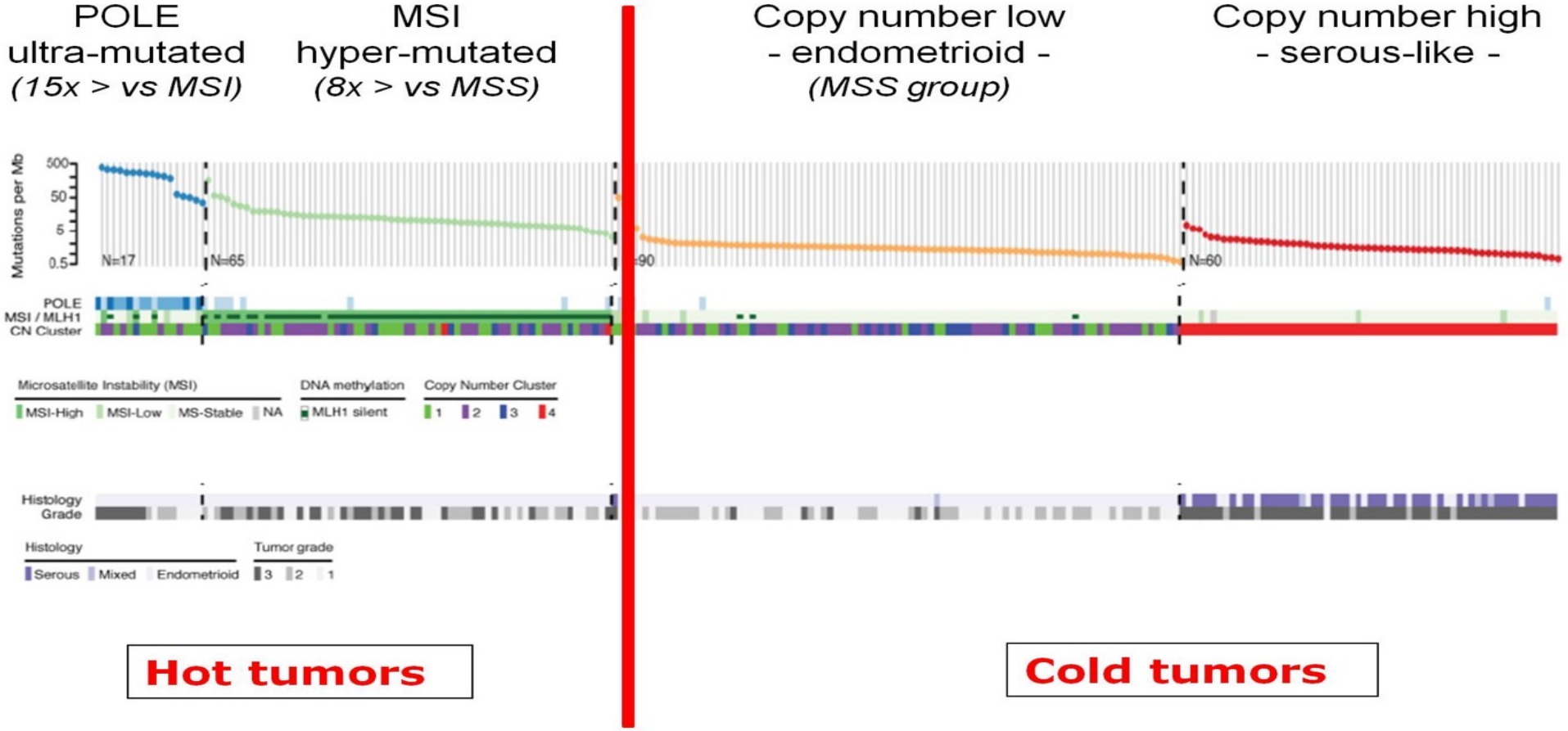
An integrated genomic analysis by The Cancer Genome Atlas (TCGA) network classified endometrioid endometrial cancers into 4 categories[1]

***POLE* ultramutated**	• Ultra-high somatic mutation frequency; MSS; frequent mutations in the exonuclease domain of *POLE*; high ASNS and CCNB1 expression • Represents ~4% of endometrioid tumors* • Best prognosis • Overtreating?
MSI hypermutated	• High mutation rate and few copy number alterations; high rate of *MLH1* promoter methylation; high phospho-AKT; low PTEN expression; frequent *PIK3CA* and *PIK3R1* mutations co-occurring with *PTEN* mutations • Represents ~39% of endometrioid tumors*†
Copy-number low‡	• High frequency of mutations in *CTNNB1*, *KRAS*, *SOX17*; frequent *PIK3CA* and *PIK3R1* mutations co-occurring with *PTEN* mutations; elevated levels of progesterone receptor and RAD50 expression • Represents ~49% of endometrioid tumors*
Copy-number high‡	• Greatest transcriptional activity; frequent *TP53* mutations; decreased levels of phospho-AKT; mutually exclusive *PIK3CA*, *PIK3R1*, and *PTEN* mutations • Represents ~9% of endometrioid tumors* • Worst prognosis • Undertrearting?

G Getz *et al*. *Nature* **497**, 67-73 (2013) doi:10.1038/nature12113

Endometrial Cancer (EC) – Four molecular subtypes

(Integrated genomic, transcriptomic and proteomic characterization)



Kandoth et al., Nature 2013

GOG 210 Endometrioid (Cosgrove 2018)

Incidence: 49% CNS, 4% POLE mutant, 39% MMR deficient, 8% copy number altered (CNA).
Cancer-specific mortality: 5%=CNS ; 2.6% =POLE tumors; 7.6%=MMR deficient tumors; 19% with CNA tumors.

A Genomics-Based Approach Has Identified 4 Distinct Molecular Subgroups of Endometrial Cancer[1,2]

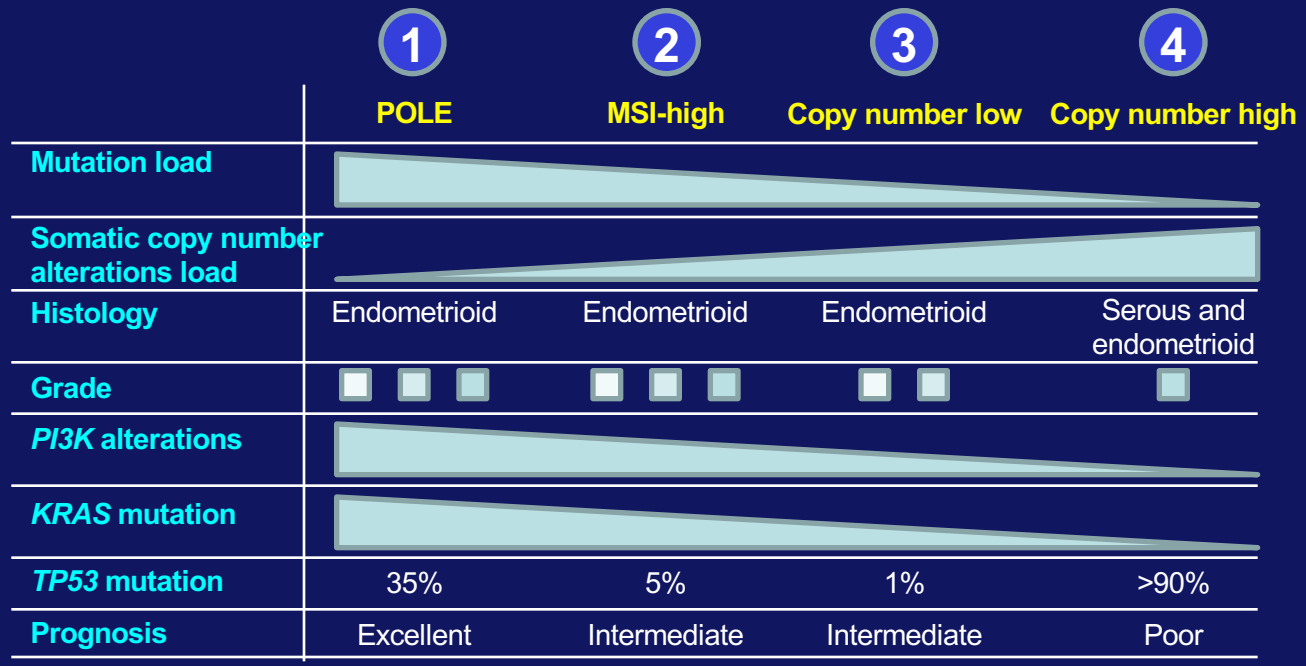


Image adapted from Morice P et al. *Lancet*. 2016;387(10023):1094-1108.

POLE & MSI-high groups have high tumor mutational load & are often characterized by high TILs and a high expression of immune checkpoints[3]

MSI, microsatellite instability; POLE, polymerase epsilon; TILs, tumor-infiltrating lymphocytes.

1. Cancer Genome Atlas Research Network et al. *Nature*. 2013;497:67-73. 2. Morice P et al. *Lancet*. 2016;387:1094-1108. 3. Mittica G et al. *Oncotarget*. 2017;8:90532-90544.

FDA News Release

FDA approves first cancer treatment for any solid tumor with a specific genetic feature

For Immediate Release May 23, 2017

Pembro in MSI-H

Release

The U.S. Food and Drug Administration today granted accelerated approval to a treatment for patients whose cancers have a specific genetic feature (biomarker). This is the first time the agency has approved a cancer treatment based on a common biomarker rather than the location in the body where the tumor originated.

Keytruda (pembrolizumab) is indicated for the treatment of adult and pediatric patients with unresectable or metastatic solid tumors that have been identified as having a biomarker referred to as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). This indication covers patients with solid tumors that have

Inquiries

Media

Angela Stark
301-796-0397

Consumers

888-INFO-FDA

Related Information

- FDA: Office of Hematology and Oncology Products
- FDA: Approved Drugs: Questions and Answers
- FDA: Fast Track, Breakthrough Therapy, Accelerated Approval, and Priority Review

FDA approves pembrolizumab for advanced endometrial carcinoma

On March 21, 2022, the Food and Drug Administration approved pembrolizumab (Keytruda, Merck), as a single agent, for patients with advanced endometrial carcinoma that is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and who are not candidates for curative surgery or radiation.

Endometrial Cancer: Immunotherapy Agents of Interest

	Keynote-158	KEYNOTE-028[2]	NCT01375842[3]	Makker ESMO[4]	GARNET[5]	Makker ASCO 19
Phase / type	1/2 : **HOT**	1b **COLD**	1a: **COLD**	1b/2 mostly **COLD**	Both **HOT** & **COLD**	RP2 mostly **COLD**
Population	Previously treated dMMR-recurrent or persistent EC	Previously treated locally advanced or metastatic PD-L1+ EC	Recurrent EC	Advanced EC	Previously treated recurrent/advanced EC	Previous treated EC[b]
Patients, n	49	24	15	54	125	27/26
Treatment	**Pembrolizumab**	**Pembrolizumab**	**Atezolizumab**	**Pembrolizumab + lenvatinib**	**Dostarlimab**	**Durva +- Treme**
ORR, %	**57**	**13.0[a]**	**13**	**36.7**	**49 MSI+ /20 MSS**	--
DCR, %	73	26.0	27	—	--	—
DOR	NR (3-27)	—	—	NR	NR	NR
mPFS	26 mo	1.8 mo	1.7 mo	10.1 mo	—	—
mOS	12-mo OS= 73%	NR	9.6 mo	—	—	—
Safety summary	16% Gr >3	Gr ≥3 TRAEs: 16.7%	Any TRAE: 47%	Gr ≥3 TRAEs: 59%	Gr ≥3 TRAEs: 11.4%	--
Median follow-up	9.1 mo	76.2 wk	Min: 11.2 mo	>12.0 mo	—	—

1. O'Malley, et al. Presented at ESMO 2019; 2. Ott PA, et al. *J Clin Oncol*. 2017;35(22):2535-2341; 3. Fleming GF, et al. Presented at ASCO Annual Meeting, 2017. Abstract 5585; 4. Makker V, et al. Presented at ESMO Annual Meeting, 2019; 5. Oaknin A, et al. Presented at SGO, 2019.

“Biomarker” Guided Therapy in Endometrial Cancer

- **MMR deficient & MSI-H population**
  - Harbor hundreds to thousands of somatic mutations that encode potential neoantigens and are thus immunogenic
- **Phase II Keynote 158 Study** (27 independent tumor types)
  - Endometrial (n=49), gastric (n=24), cholangiocarcinoma and pancreatic cancer most common
  - In the entire cohort: ORR 34.3%, (95% CI, 28.3% to 40.8%). Median PFS 4.1 months (95% CI, 2.4 to 4.9 months) and median OS 23.5 months (95% CI, 13.5 months to not reached).

TABLE 3. Antitumor Activity for Tumor Types With Greatest Enrollment

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)	–

Marabelle A, et al. J Clin Oncol, 2019

Single Agent IO in "biomarker" Selected Endometrial Cancer Populations (dMMR)

- Response to single agent IO in dMMR or MSI-high endometrial

Study & Drug	Patient Population	Outcome ORR
Keynote 158: Pembrolizumab (N=49)	Advanced stage or metastatic dMMR endometrial cancer	**57.1%**
PHAEDRA trial: Durvalumab (N=35 dMMR)	Advanced stage or metastatic endometrial cancer	**in dMMR: 43%**
GARNET study: Dostarlimab (N=70)	Previously treated, recurrent advanced stage endometrial cancer	**in dMMR: 45%**
Ph II Avelumab study (N= 15 dMMR)	Advanced stage or metastatic endometrial cancer	**26.7%**

Marabelle A, et al. J Clin Oncol, 2019
Antill PSK et al. J Clin Oncol 2019
Oaknin A et al. SGO virtual meeting 2020
Konstantinopoulos PA et al. J Clin Oncol 2019

Single Agent IO in "non-biomarker" Selected Endometrial Cancer Populations

Study & Drug	Patient Population	Outcome: ORR
Keynote 28: Pembrolizumab (N=24)	Advanced stage or metastatic PD-L1 + endometrial cancer	13%
PHAEDRA trial: Durvalumab (N=36 pMMR)	Advanced stage or metastatic endometrial cancer	in pMMR: 3%
GARNET study: Dostarlimab (N=94)	Previously treated, recurrent advanced stage endometrial cancer	in pMMR: 13%
Ph II Avelumab study (N= 16 pMMR)	Advanced stage or metastatic endometrial cancer	6%

** = updated data in the pMMR cohort has not been presented

Ott PA et al. J Clin Oncol 2017
Antill PSK et al. J Clin Oncol 2019
Oaknin A et al. Gynecol Oncol 2019
Konstantinopoulos PA et al. J Clin Oncol 2019

PD-L1 positive endometrial cancer is not approved indication of Pembrolizumab in China, Taiwan, Korea, Singapore, Philippine

Combination Checkpoint Inhibitor Studies in Advanced/Recurrent Endometrial Cancer

Checkpoint Inhibitors plus Anti-angiogenic Agents

KEYNOTE-146[1]

KEYNOTE-775 (Phase 3)[2]

ENGOT-en9/LEAP-001 (Phase 3)[3]

Pembrolizumab + Lenvatinib

NCT03367741:[4]

Nivolumab + Cabozantinib

Checkpoint Inhibitors plus Chemotherapy

NRG-GY018:[5]

Pembrolizumab + Paclitaxel/Carboplatin

AtTEnd/ENGOT-en7:[6]

Atezolizumab + Paclitaxel/Carboplatin

RUBY (ENGOT-EN6; GOG-3031):[7]

Dostarlimab + Chemotherapy

1. Makker V et al. *J Clin Oncol*. 2020;JCO1902627. 2. Clinicaltrials.gov. NCT03517449. Accessed: July 16, 2020. 3. Clincaltrials.gov. NCT03884101. Accessed: July 16, 2020. 4. Clinicaltrials.gov. NCT03367741. Accessed August 28, 2020. 5. Clinicaltrials.gov. NCT03914612. Accessed July 16, 2020. 6. Clinicaltrials.gov. NCT03603184. Accessed: July 16, 2020. 7. Clinicaltrials.gov. NCT03981796. Accessed: July 16, 2020.

Cold Tumors: Combination & Project ORBIS

U.S. FOOD & DRUG ADMINISTRATION

Simultaneous review decisions for pembrolizumab plus lenvatinib in Australia, Canada and US

Resources for Information on Approved Drugs

Hematology/Oncology (Cancer) Approvals & Safety Notifications

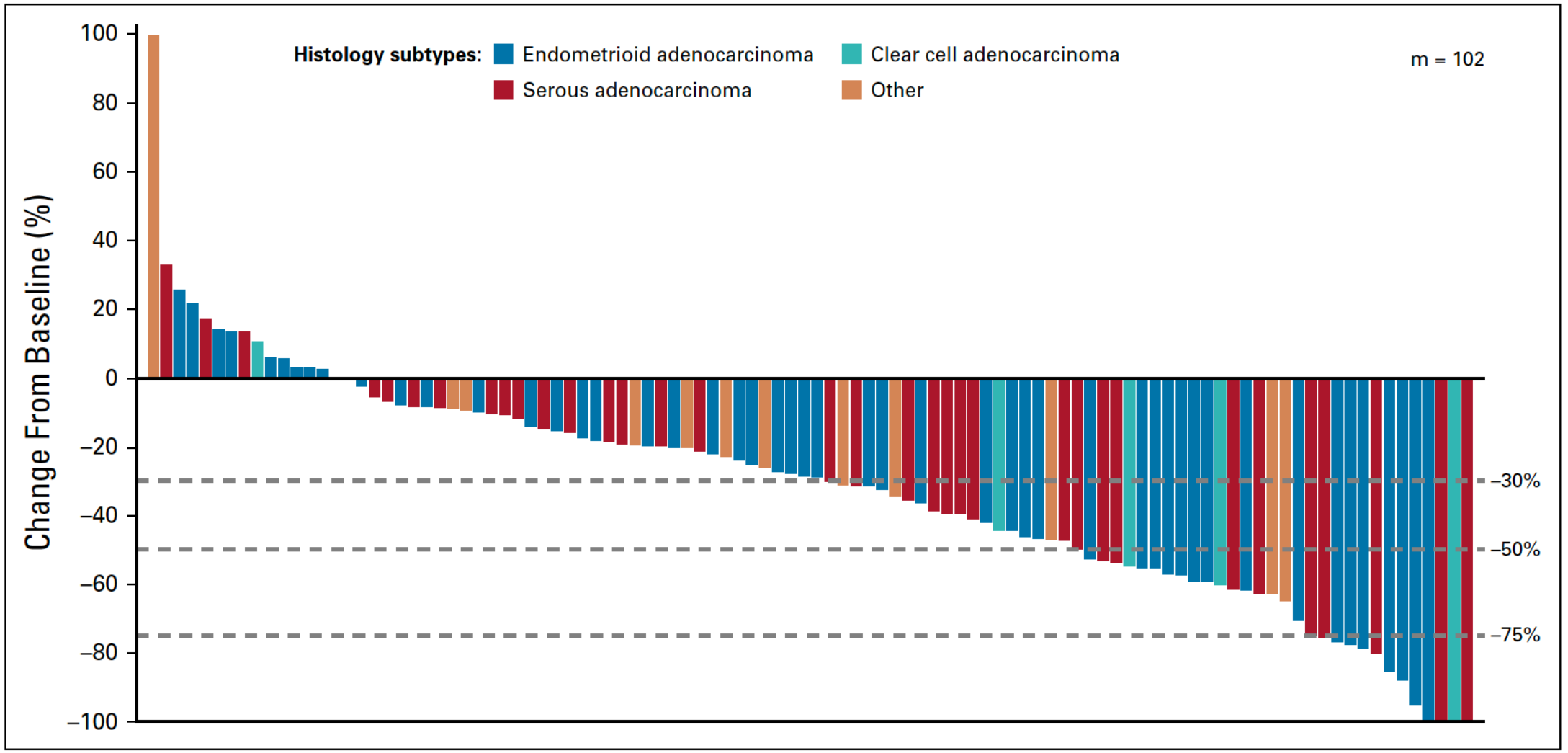
Drug Information Soundcast in Clinical Oncology (D.I.S.C.O.)

Approved Drug Products with

C[illegible] September 17, 2019[illegible]e Food and Drug Administration granted accelerated approval to the combination of pembrolizumab (KEYTRUDA, Merck) plus lenvatinib (LENVIMA, Eisai) for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) and who have disease progression following prior systemic therapy but are not candidates for curative surgery or radiation.

This review was conducted under Project Orbis, an initiative of the FDA Oncology Center of Excellence. Project Orbis provides a framework for concurrent submission and review of oncology drugs among international partners. The FDA, the Australian Therapeutic Goods Administration, and Health Canada collaborated on this review, allowing for simultaneous decisions in all three countries.

Pem/Len: Response by Histology



KEYNOTE-775: Ph 3 Pembrolizumab + Lenvatinib vs Chemotherapy in 2L EC[1,2]

Enrollment & Eligibility

- N = ~780 2L advanced, recurrent or metastatic EC patients; 1-2 prior Plat lines
  - Approximately 120 dMMR & 660 MMRp pts (need available archival tissue)
- Measurable disease (RECIST v1.1)
- ECOG PS ≤1
- Stratification factors:
  - dMMR vs MMRp
  - MMRp patients further stratified by ECOG PS, geographic region, and prior Hx of pelvic radiation(

R 1:1

- Physician's choice chemotherapy (doxorubicin or paclitaxel)
- Pembrolizumab 200 mg IV Q3W + lenvatinib 20 mg PO QD

Primary End Points

- PFS (BICR) & OS

Secondary End Points

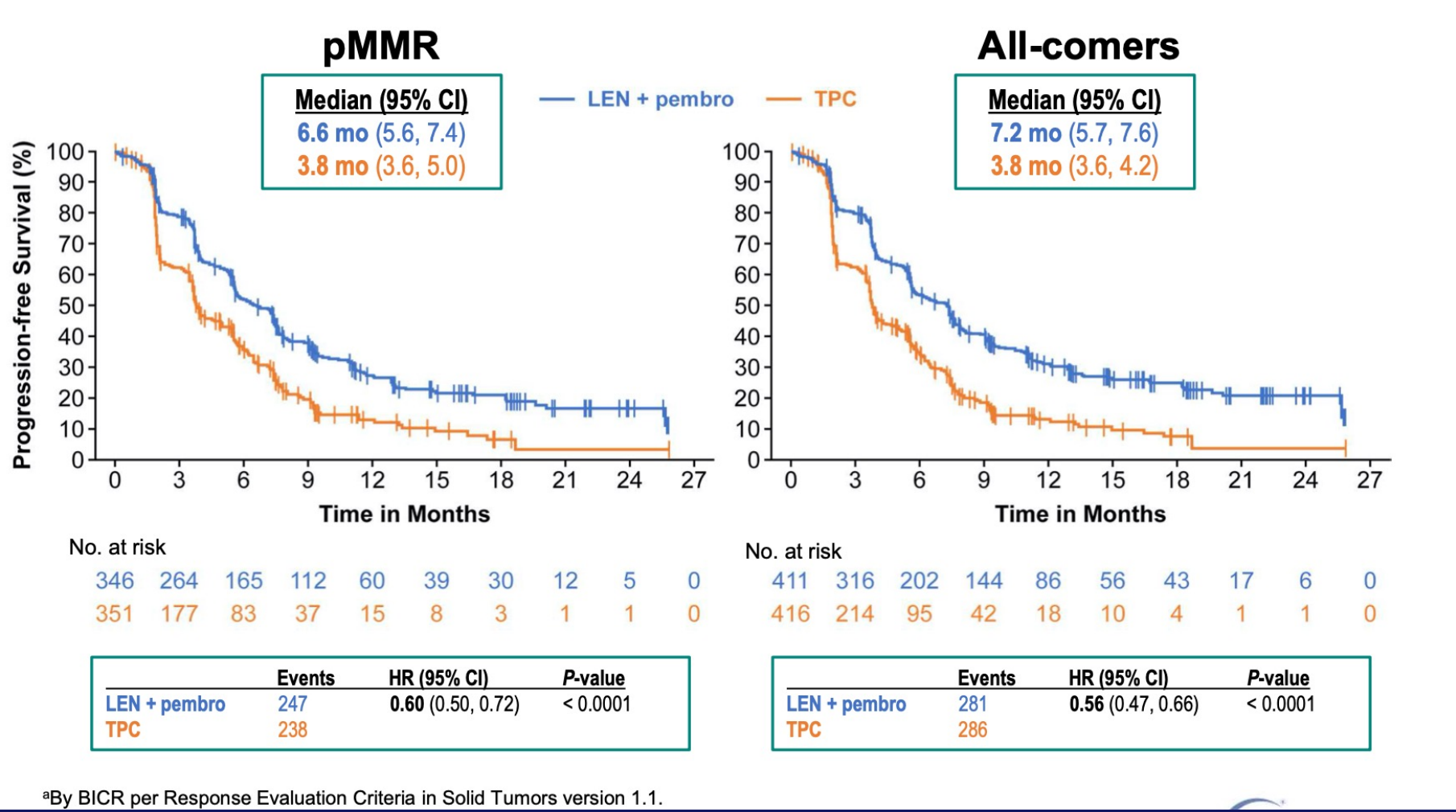
- ORR, HRQoL, safety & tolerability, PK

- Enrollment started in June 2018[2]

2L, second line; dMMR, deficient mismatch repair; EC, endometrial cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; IV, intravenous; MMRp, mismatch repair proficient; ORR, objective response rate; OS, overall survival; Q3W, every 3 weeks; QD, once daily; PFS, progression-free survival; PO, orally; PK, pharmacokinetics; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors.

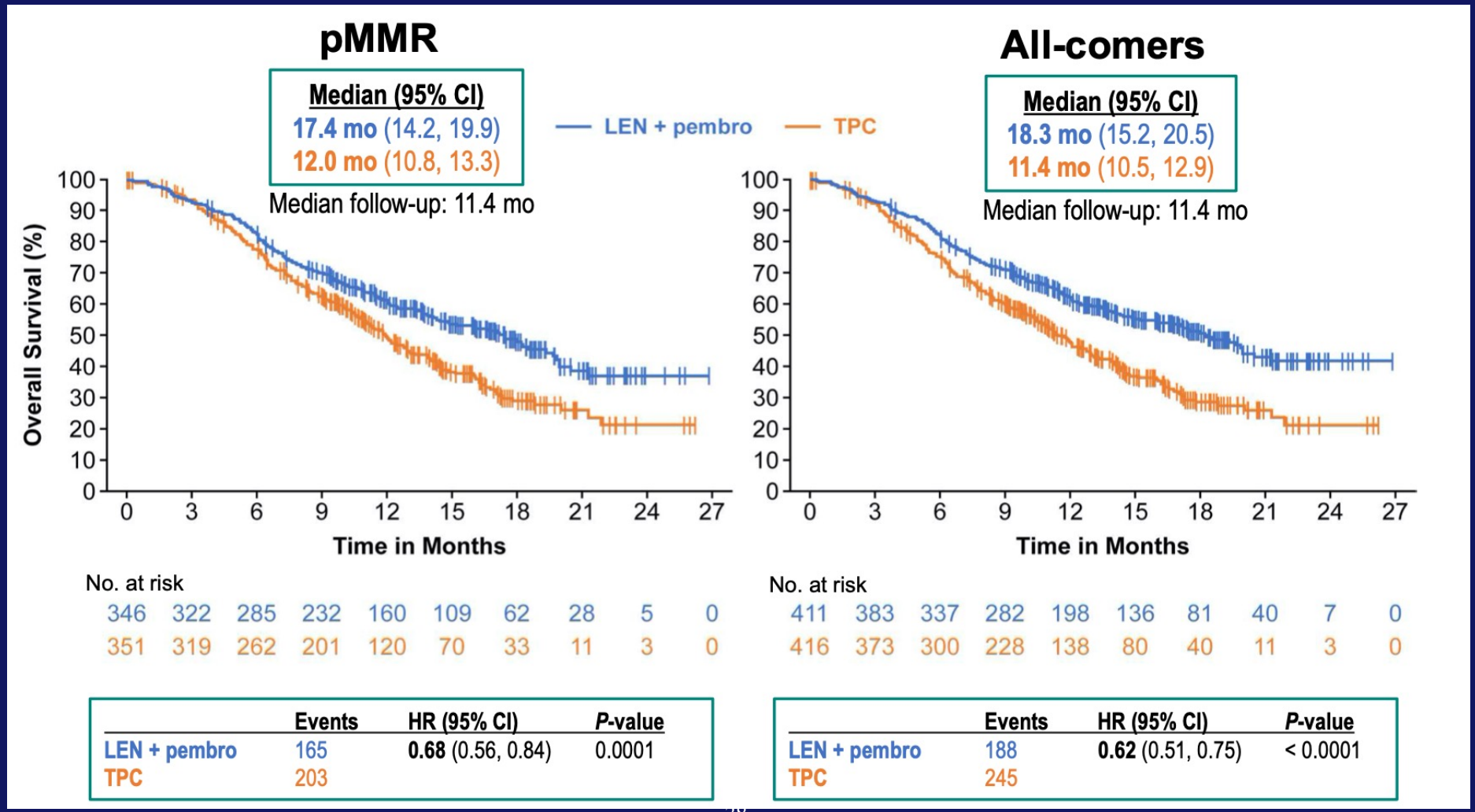
1. Makker V et al. *J Clin Oncol*. 2019:37(suppl):abstrTPS5607. 2. Clinicaltrials.gov. NCT03517449. Accessed July 16, 2020.

Combinatorial IO approach: Lenvatinib + Pembrolizumab Keynote 775 (NCT03517449)



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

Combinatorial IO approach: Lenvatinib + Pembrolizumab Keynote 775 (NCT03517449)



Endometrial Cancer: The Future

"Life can only be understood backwards, but it must be lived forwards" - **Søren Kierkegaard**

ENGOT-en9/LEAP-001: Ongoing Ph 3 Pembrolizumab + Lenvatinib in Newly Diagnosed EC[1,2]

Enrollment & Eligibility

- N = ~720 newly diagnosed stage III-IV or recurrent EC
- Stratification factors:
  - MMRp vs dMMR
  - MMRp further stratified by ECOG PS, measurable disease, and prior chemoradiation

Paclitaxel 175 mg/m^2 IV Q3W + Carboplatin AUC 6 IV Q3W

Pembrolizumab 200 mg IV Q3W + lenvatinib 20 mg PO QD

Primary End Points

- PFS and OS

Secondary End Points

- ORR, HRQoL, safety and tolerability, PK of lenvatinib

Exploratory End Points

- DOR, DCR, clinical benefit rate

- Enrollment started in April 2019 and is ongoing[1,2]
- Estimated primary completion date is April 2023[2]

AUC, area under the curve; DCR, disease control rate; dMMR, deficient mismatch repair; DOR, duration of response; EC, endometrial cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; IV, intravenous; MMRp, mismatch repair proficient; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PO, orally; Q3W, every 3 weeks; QD, once daily.

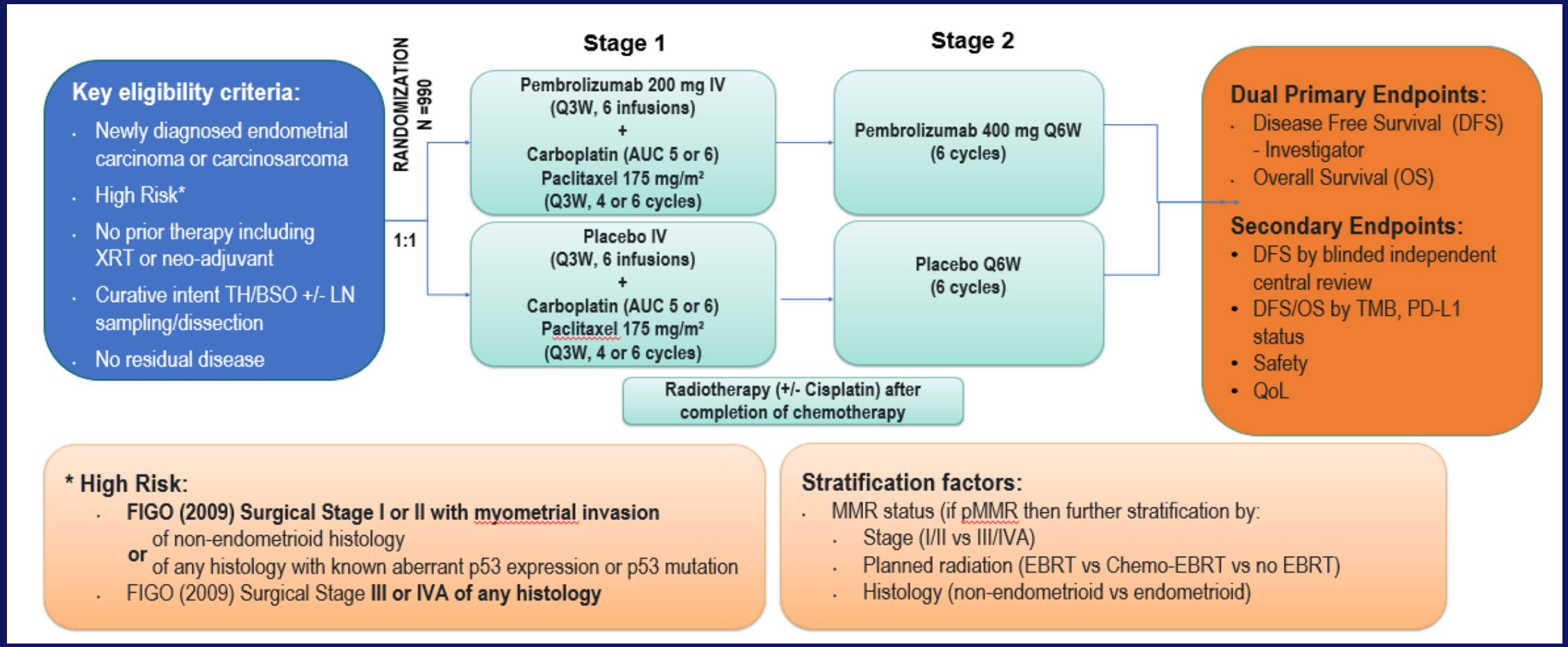
1. Marth C et al. *J Clin Oncol.* 2020;38(suppl):abstr. TPS6106. 2. Clincaltrials.gov. NCT03884101. Accessed July 16, 2020.

Endometrial Cancer: Active Trials: Adjuvant

Front-line Adjuvant PI: Slomovitz Co-PI: Barber	GOG-3053/ KEYNOTE-B21 NCT04634877	APh 3, Randomized, Double-Blind Study of Pembrolizumab vs Placebo in Combination With Adjuvant Chemotherapy With or Without Radiotherapy for Newly Diagnosed High-Risk Endometrial Cancer After Surgery With Curative Intent	Recruiting
Front–line Adjuvant PI: Backes	GY020	Testing the Addition of the Immunotherapy Drug, Pembrolizumab, to the Usual Radiation Treatment for Newly Diagnosed Early Stage High Intermediate Risk Endometrial Cancer	Recruiting

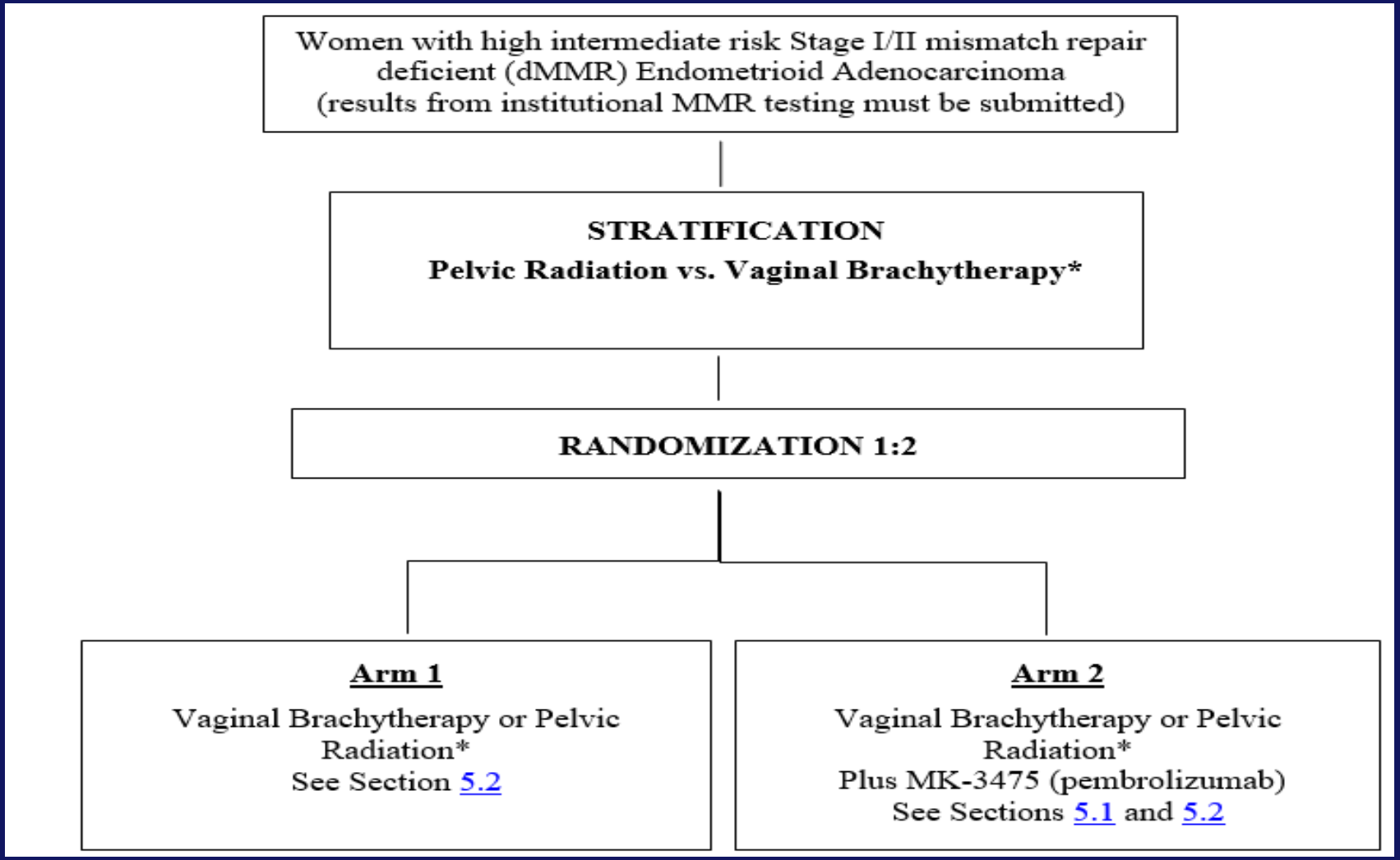
Ph 3, Randomized, Double-Blind Study of Pembrolizumab vs Placebo in Combo With Adjuvant Chemotherapy With or Without Radiotherapy for Newly Diagnosed High-Risk Endometrial Cancer After Surgery With Curative Intent

N=990
GOG Accrual: 69
GOG Activated Sites: 23
Primary Endpoint = DFS, OS
PI: Slomovitz, B, Barber, E
Site Selection Closed



NCT04634877

NRG-GY020



Note:

-Pts will receive standard vaginal brachytherapy.

-For patients with Stage IB grade 3 (≥ 50% myometrial invasion & grade 3) or Stage II, the treating physician may select pelvic external beam radiation (EBRT). This must be decided prior to randomization.

-All other patients will receive vaginal brachytherapy only.

Endometrial Cancer: 1st line Metastatic or Recurrent

Front-line, metastatic or recurrence PI: Powell *ENGOT led	GOG-3031/RUBY NCT03981796	A Phase 3, Randomized, Double-blind, Multicenter Study of Dostarlimab + Carboplatin-paclitaxel Vs Placebo + Carboplatin-paclitaxel in Patients With Recurrent or Primary Advanced Endometrial Cancer	Recruiting
Front-line, metastatic or recurrence PI: Westin Co-PI: Moore *GOG led	GOG-3041/DUO-E NCT04269200	A Randomised, Multicentre, Double-blind, Placebo-controlled, Phase III Study of First-line Carboplatin and Paclitaxel in Combination With Durvalumab, Followed by Maintenance Durvalumab With or Without Olaparib in Patients With Newly Diagnosed Advanced or Recurrent Endometrial Cancer	Recruiting
Front-line, metastatic or recurrent PI: Slomovitz, Backes *GOG led	GOG-3064/c93 NCT05173987	A Phase 3 Randomized, Open-label, Active-comparator Controlled Clinical Study of Pembrolizumab Versus Platinum Doublet Chemotherapy in Participants With Mismatch Repair Deficient (dMMR) Advanced or Recurrent Endometrial Carcinoma in the First-line Setting	Recruiting

Endometrial Cancer: 1st line Metastatic or Recurrent

Front-line, metastatic or recurrence PI: Marth	LEAP -001 NCT04865289	Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) Versus Chemotherapy for Endometrial Carcinoma (ENGOT-en9/MK-7902-001)	Active, not recruiting
Front-line, metastatic or recurrence	Attend NCT03603184	Phase III Double-blind Randomized Placebo Controlled Trial of Atezolizumab in Combination With Paclitaxel and Carboplatin in Women With Advanced/Recurrent Endometrial Cancer	Active, recruiting
Front-line, metastatic or recurrence PI: Eskander	NRG-GY-018 NCT03914612	Testing the Addition of the Immunotherapy Drug Pembrolizumab to the Usual Chemotherapy Treatment (Paclitaxel and Carboplatin) in Stage III-IV or Recurrent Endometrial Cancer	Recruiting

Endometrial Cancer: Active Trials 2nd Line

Recurrent, 2nd line, CPI pretreated or naive PI: Slomovitz Co-PI: Moxley	GOG-3038/POD1UM-204 NCT04463771	An Umbrella Study of INCMGA00012 Alone and in Combination with Other Therapies in Participants with Advanced or Metastatic Endometrial Cancer Who Have Progressed on or After Platinum-Based Chemotherapy	Recruiting Selection closed Sites: 23/30 Total: 40 (215) GOG:26
Recurrent, 2nd line PI: Huang Co-PI: Huang, Slomovitz	GOG-3039 NCT04393285	A Phase II Study of Abemaciclib in Combination with Letrozole in Advanced, Recurrent or Metastatic Endometrioid Endometrial Cancer	Recruiting Selection closed Sites: 19/25 Total: 5/50
Recurrent 2nd line, CPI naive PI: Slomovitz Co-PI: Moroney, Alvarez, Cantillo, Secord, LIu	AFT-50 EndoMap NCT04486352	A Phase IB/II Multi-Cohort Study of Targeted Agents With Atezolizumab for Patients With Recurrent or Persistent Endometrial Cancer	Not yet recruiting

OVARIAN CANCER

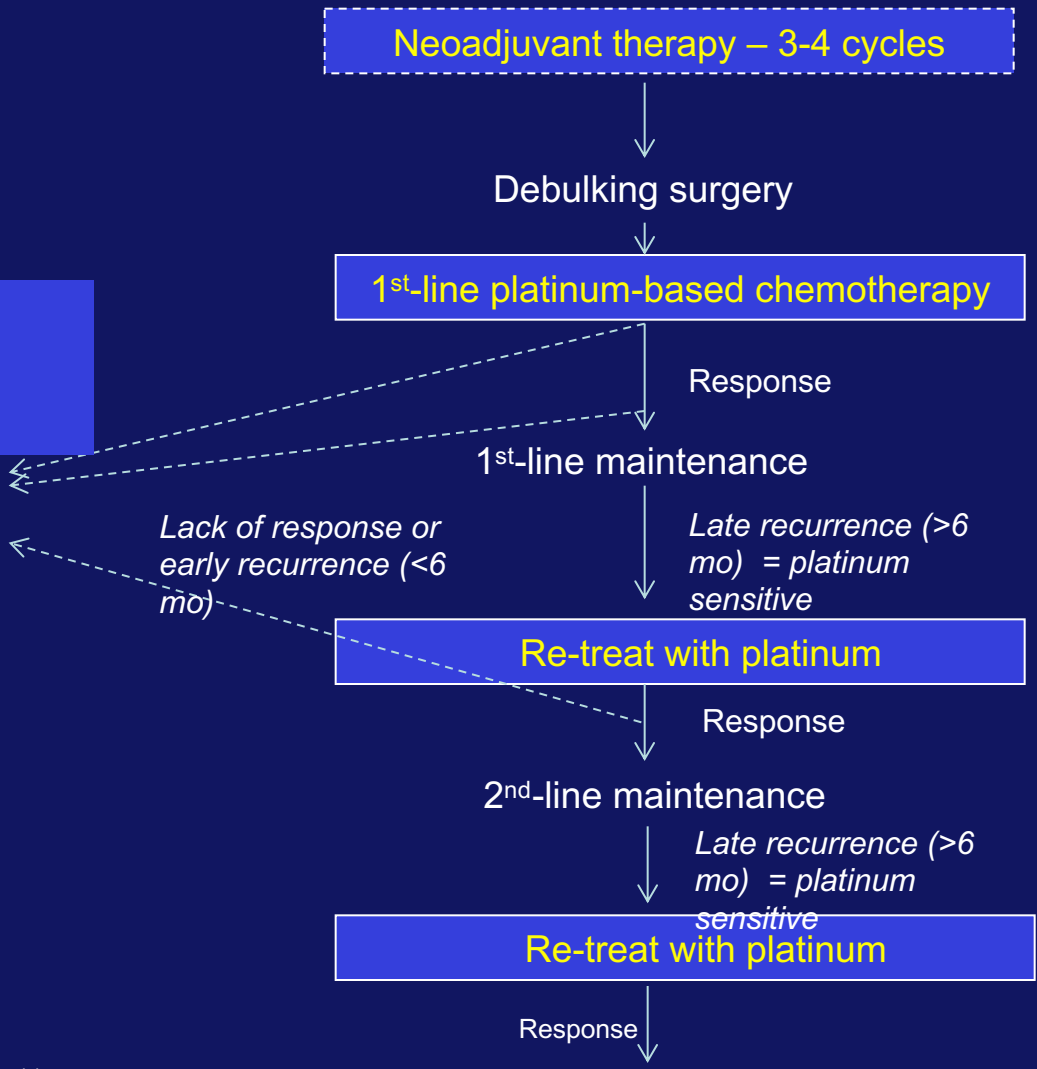
Ovarian Immune Checkpoint Inhibitors

	Ipilimumab[1]	Nivolumab[2]	Pembrolizumab[3]	Avelumab[4]
N	9	20	26	124
Patient population	Metastatic ovarian carcinoma	Platinum-resistant, post-taxane	Failure or inability to receive standard Tx; PD-L1+	Recurrent post-platinum
Prior therapies	NR	≥4: 55%	≥4: 80.8%	≥3: 65.3% (not including adjuvant)
PD-L1+ prevalence	NR	80% (IC 2/3)	100% (≥1% TC)	77% (≥1% TC)
Median follow-up	NR	11 months	NR	12.4 months
TRAE, any	22%	95%	69.2%	66.1%
TRAE, Gr 3+	NR	40%	3.8%	6.5%
ORR (95% CI)	**NR**	**15% (3.2-37.9)**	**11.5% (2.4-30.2)**	**9.7% (5.1-16.3)**
DCR (95% CI)	NR	45% (23-69)	34.6% (17-56)	54% (45-63)
mPFS	NR	3.5 months	NR	2.6 months
mOS	NR	20 months	NR	10.8 months

DCR, disease control rate; NR, not reached; TC, tumor cell; TRAE, treatment-related adverse event.

1. Hodi FS et al. *Proc Natl Acad Sci U S A*. 2008;105:3005-3010. 2. Hamanishi J et al. *J Clin Oncol*. 2015;33:4015-4022. Abstract 5510. 3. Varga A et al. Presented at ASCO 2015. 4. Disis ML et al. Presented at ASCO 2016. Abstract 5533.

Potential Impact of Immuno-Oncology Agents on Ovarian Cancer Treatment Paradigm



Frontline

- **JAVELIN Ovarian 100** (avelumab)
- Pembrolizumab + chemotherapy
- **IMaGyn50** atezolizumab

Resistant/ refractory

- **JAVELIN Ovarian 200** (avelumab)
- NRG GY-009 (atezolizumab)
- KEYNOTE 100 (pembrolizumab)
- Pembrolizumab + bevacizumab
- EORTC-1508 (atezolizumab)

Recurrent = PS = PS recurrence

- ATALANTE (atezolizumab)
- KEYNOTE 100 (pembrolizumab)
- Pembrolizumab + bevacizumab

PS, platinum sensitive.

1. NCCN guidelines. Version 1.2016. 2. Clinicaltrials.gov. Accessed October 11, 2016. 3.

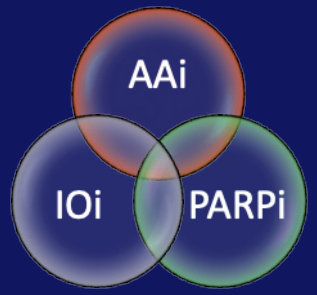
First-Line Ovarian Cancer Immuno Agents

First Line Treatment w/ Maintenance	First Line Switch Maintenance
JAVELIN100 (avelumab) – Negative Trial ImaGyn50/GOG-3015 (bev/atezolizumab) – Negative Trial	ATHENA/GOG-3020 rucaparib, nivolumab
FIRST niraparib/dostarlimab ± bevacizumab	
GOG-3036/ENGOT-ov43 olaparib/pembrolizumab ± bevacizumab	
GOG-3025/ENGOT-ov46 olaparib/durvalumab ± bevacizumab	
FLORA-5/GOG-3035 Oregovomab	

AAi: Angiogenesis inhibitor

IOi: PD-1/PD-L1 inhibitor

PARPi: PARP inhibitor



Conclusions

- Immune Oncology: exciting & extremely complex has literally exploded in past few years
- Identifying immune markers that more accurately predict response is critical
- Checkpoint blockade may unleash diverse antitumor T cell re-activities. MSI High is a universal target
- Can truly “cold” tumors be converted to “hot tumors?
- I/O therapies are now SOC in Cervical and Endometrial Cancers


Thank You!