A Conversation with the Investigators: Endometrial and Cervical Cancers

Monday, July 26, 2021
5:00 PM – 6:00 PM ET

Faculty

Mansoor Raza Mirza, MD
David M O'Malley, MD
Angeles Alvarez Secord, MD, MHSc

Moderator

Neil Love, MD

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Faculty

Mansoor Raza Mirza, MD
Medical Director
Nordic Society of Gynaecological Oncology – Clinical Trial Unit
Chairman, European Network of Gynaecological Trial Groups
Faculty Member, European Society of Gynaecological Oncology
Chief Oncologist
Copenhagen University Hospital
Copenhagen, Denmark

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Professor
Division Director, Gynecologic Oncology
Co-Director, Gynecologic Oncology Phase I Program
The Ohio State University and The James Cancer Center
Columbus, Ohio

Angeles Alvarez Secord, MD, MHSc
Professor of Obstetrics and
Gynecologist, Gynecologic Oncology
Director of Gynecologic Oncology
Clinical Trials
Duke Cancer Institute
Durham, North Carolina

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

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Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, Clovis Oncology, Eisai Inc, GlaxoSmithKline, ImmunoGen Inc and Merck.

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Dr Love — Disclosures

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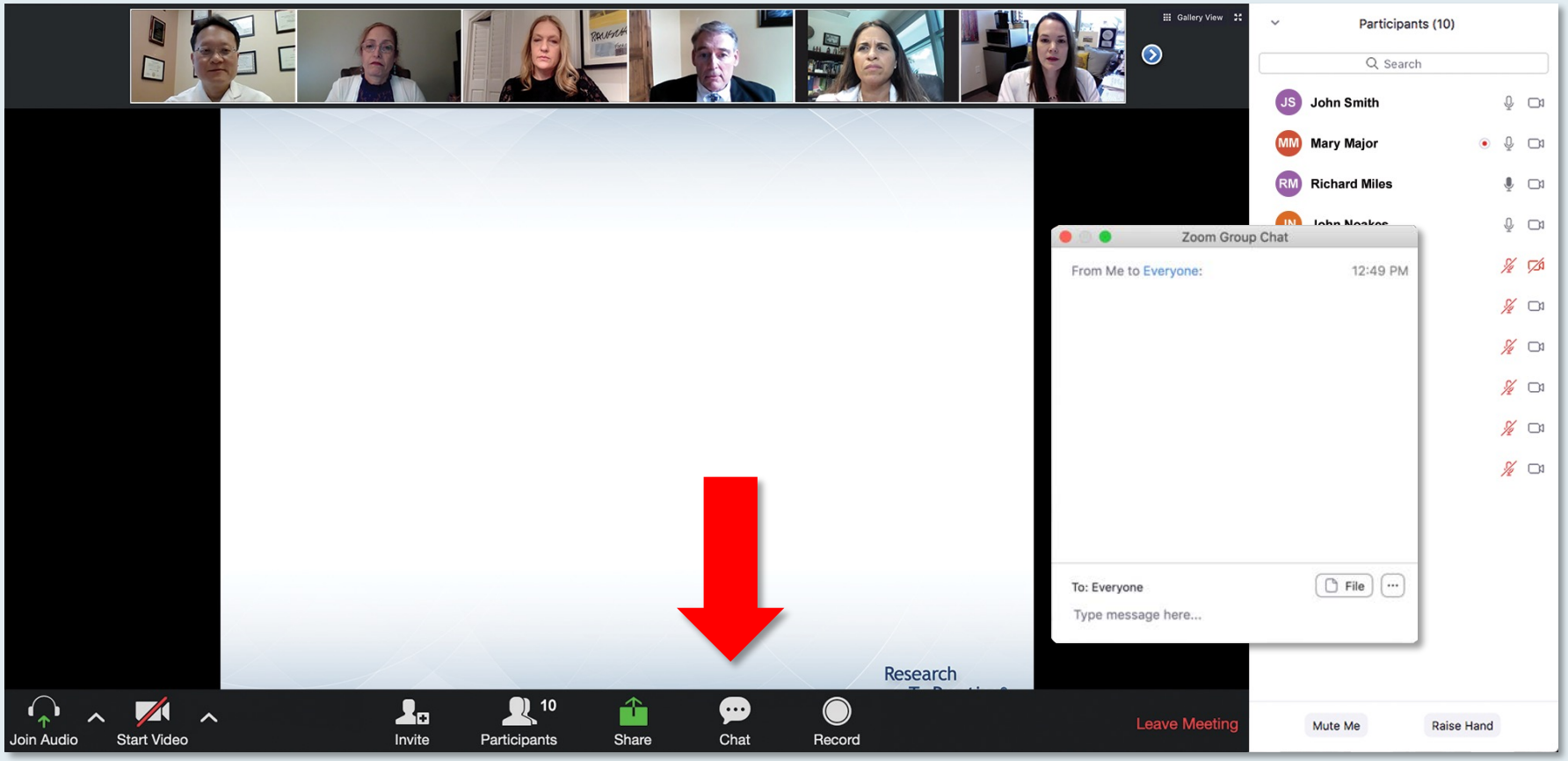

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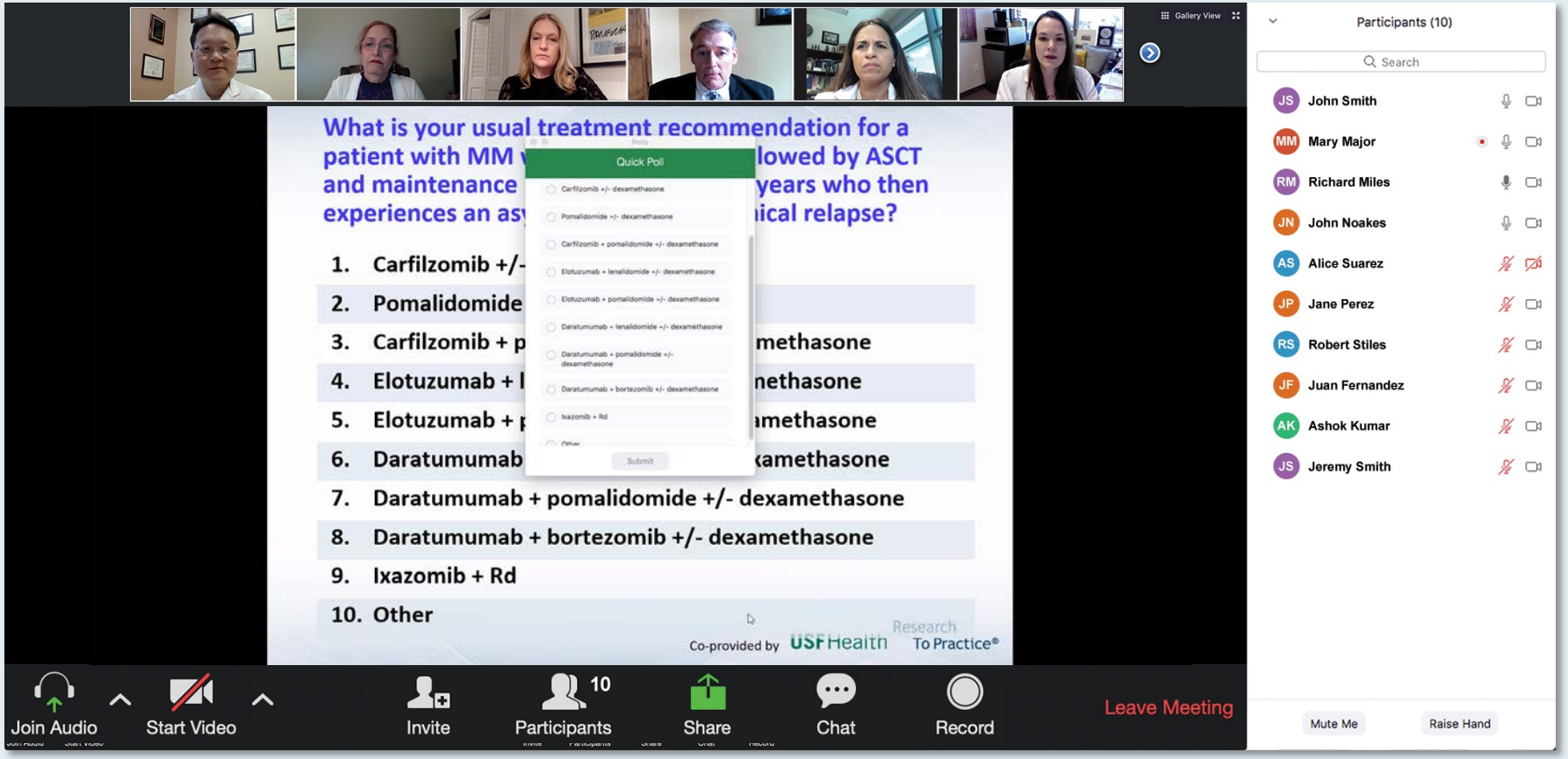
Familiarizing Yourself with the Zoom Interface

How to answer poll questions



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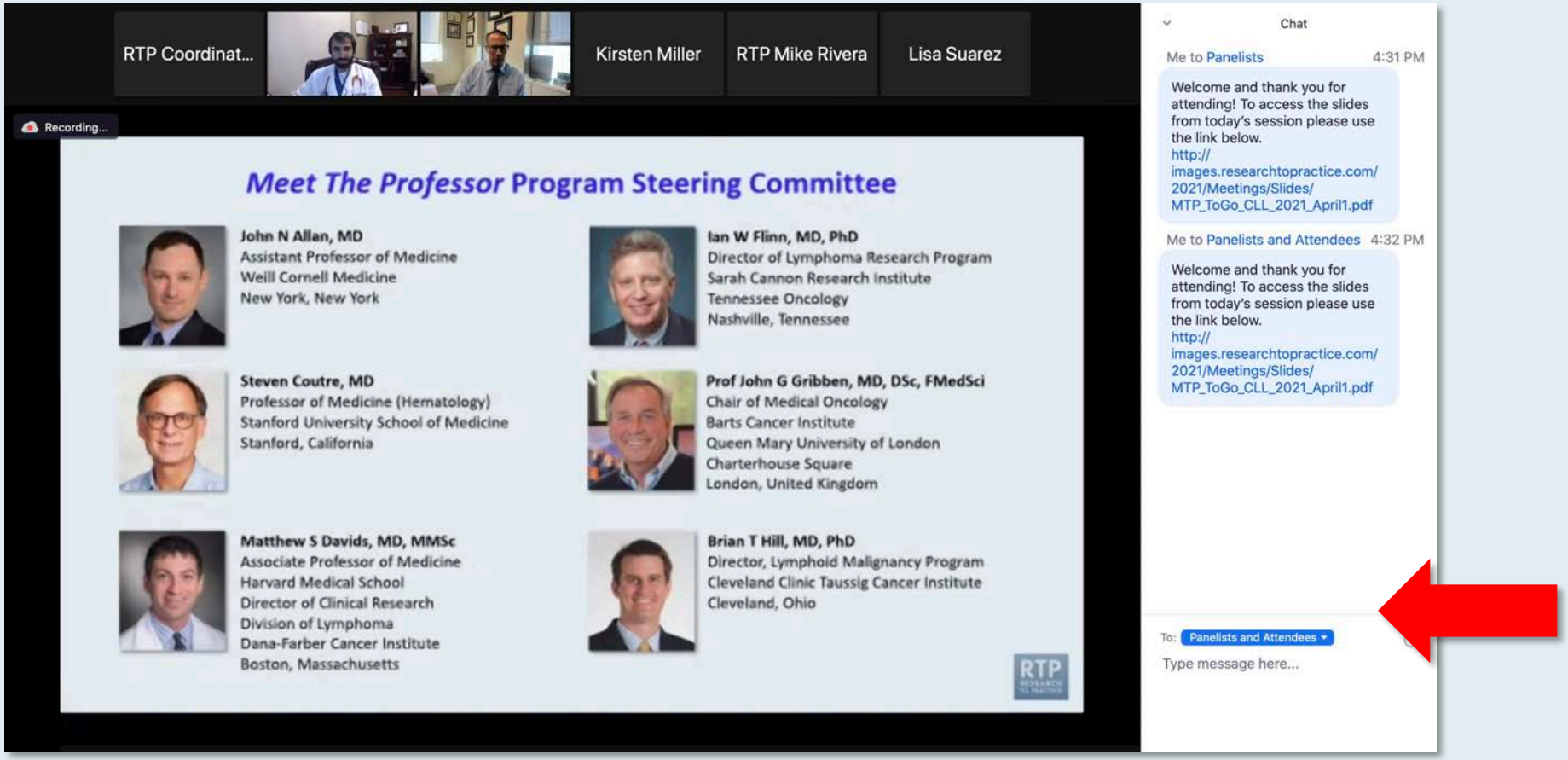
Expand chat submission box



Drag the white line above the submission box up to create more space for your message.

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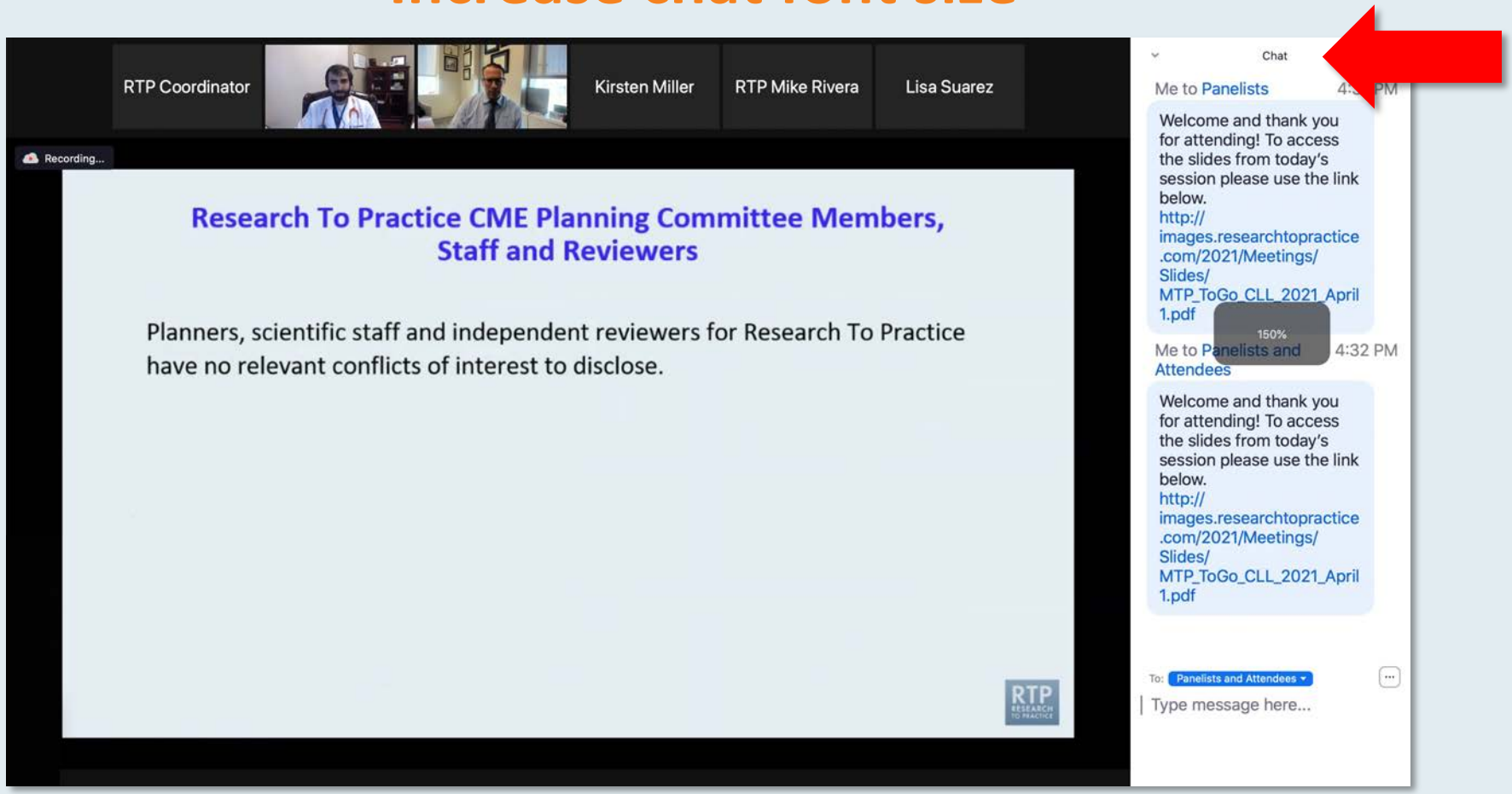
Increase chat font size



Press Command (for Mac) or Control (for PC) and the + symbol.
You may do this as many times as you need for readability.

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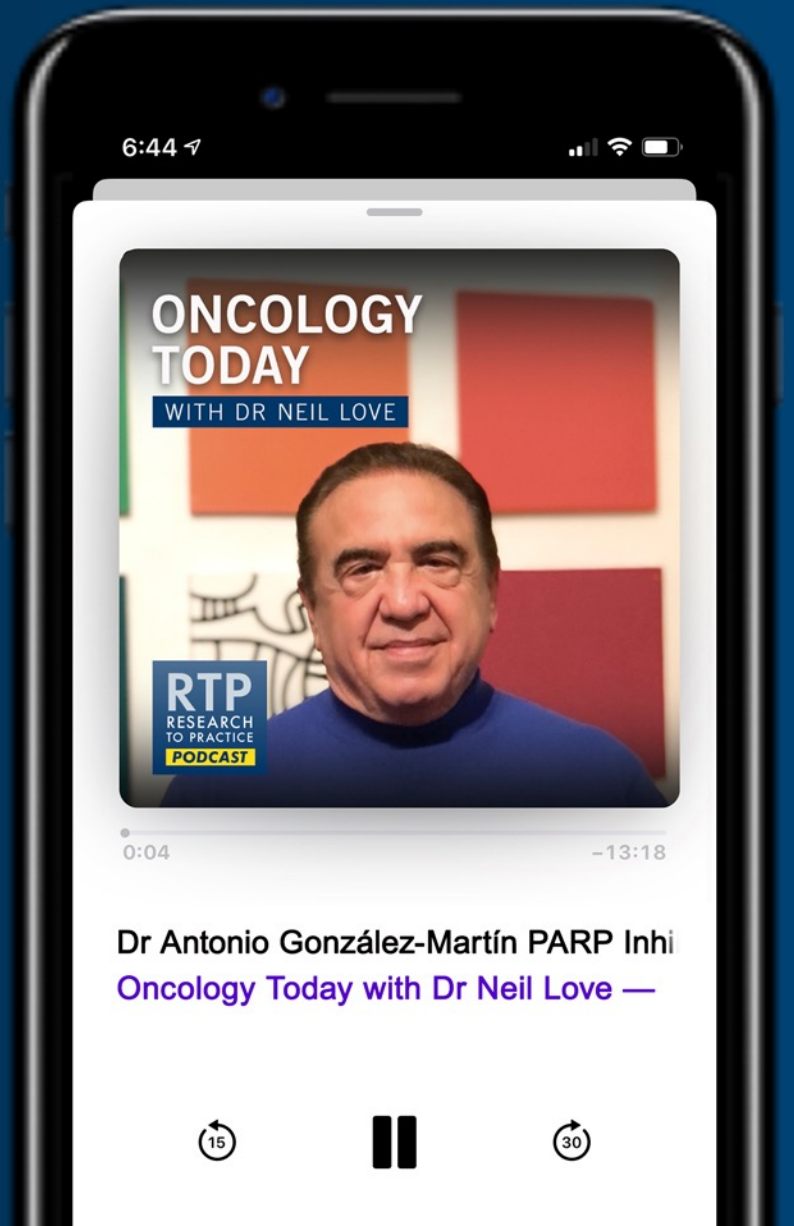

7 Exciting CME/MOC Events You Do Not Want to Miss

A Live Webinar Series Held in Conjunction with the 2021 ASCO Annual Meeting

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Zofia Piotrowska, MD, MHS
Gregory J Riely, MD, PhD

Moderator

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David R Spigel, MD
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Consensus or Controversy? Clinical Investigator Perspectives on the Current and Future Management of Mantle Cell, Diffuse Large B-Cell and Hodgkin Lymphoma

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5:00 PM – 6:00 PM ET

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Craig Moskowitz, MD
Laurie H Sehn, MD, MPH

Moderator

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Consensus or Controversy? Clinical Investigator Perspectives on the Current and Future Management of Colorectal and Gastroesophageal Cancers

Tuesday, August 3, 2021
5:00 PM – 6:30 PM ET

Faculty

Chloe E Atreya, MD, PhD
Dustin Deming, MD
Eric Van Cutsem, MD, PhD
Zev Wainberg, MD, MSc

Moderator

Neil Love, MD

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Kim A Reiss Binder, MD
Eileen M O'Reilly, MD
Philip A Philip, MD, PhD, FRCP

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Three Exciting Educational Events Held in Conjunction with the 2021 Pan Pacific Lymphoma Conference

In Partnership with the University of Nebraska Medical Center

Expert Second Opinion — Acute Myeloid Leukemia and Myelodysplastic Syndromes

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 2-3 business days.

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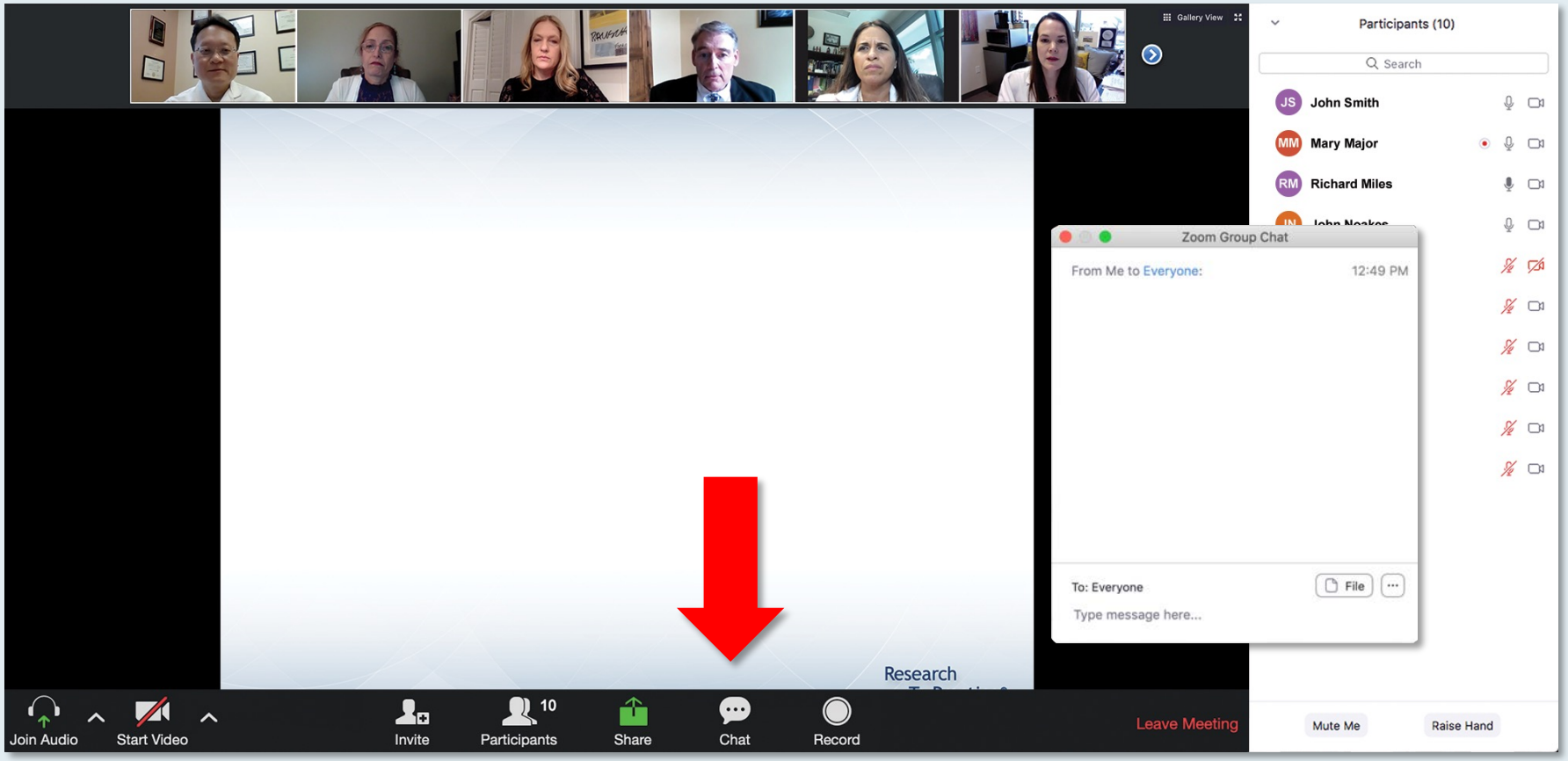

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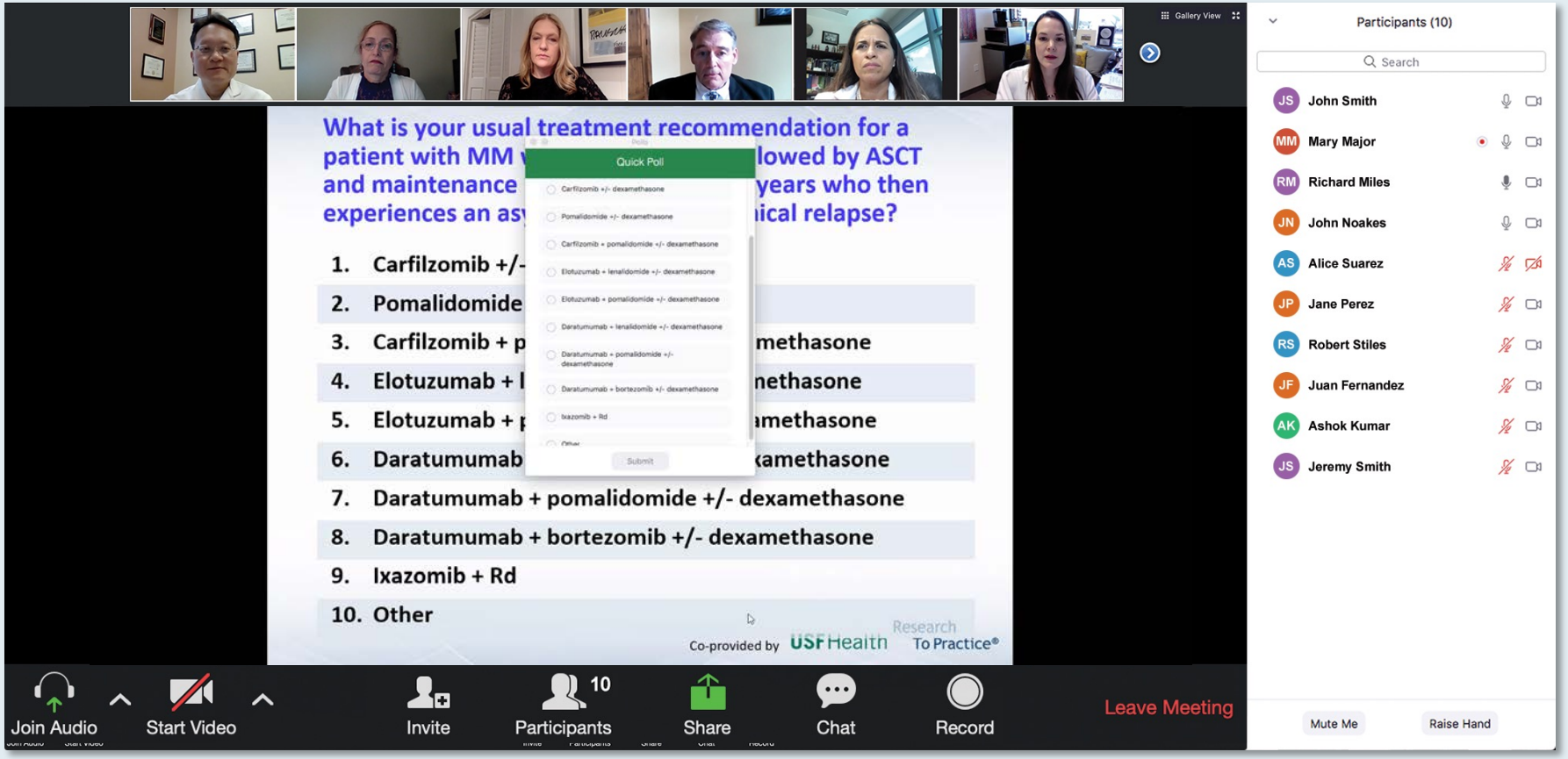

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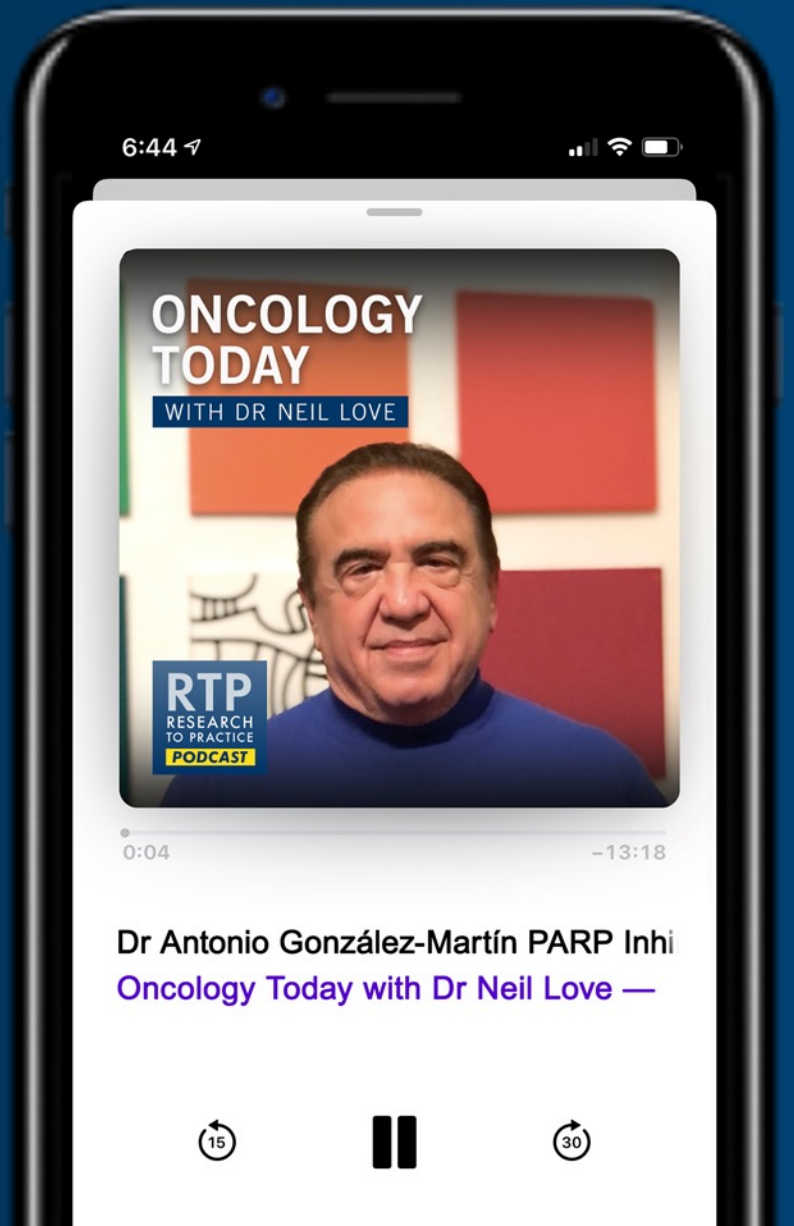

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ASCO 2021 Endometrial and Cervical Cancers Presentation Library

Contemporary Biomarker Assessment in Advanced Endometrial Cancer (EC) and Cervical Cancer (CC)

Mansoor Raza Mirza, MD

Download Slides

Current Treatment Planning for Patients with Advanced EC

David M O'Malley, MD

Download Slides

Selection of Therapy for Patients with Advanced CC

Angeles Alvarez Secord, MD, MHSc

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Agenda

Module 1: Current Treatment Planning for Patients with Advanced Endometrial Cancer (EC)

- Biomarker assessment in advanced EC; incidence of MSI-H/dMMR and current indications for testing
- KEYNOTE-775: Pembrolizumab + lenvatinib for recurrent EC; recent FDA approval
- GARNET: Dostarlimab for patients with MSI-H/dMMR and microsatellite-stable tumors
- Ongoing Phase III trials of anti-PD-1/PD-L1-based therapies for recurrent or primary advanced EC
- Faculty cases

Module 2: Selection of Therapy for Patients with Advanced Cervical Cancer (CC)

- Rationale for investigation of immunotherapy in advanced CC
  - Correlation between PD-L1 expression and response to anti-PD-1/PD-L1 antibodies
- KEYNOTE-158: Pembrolizumab monotherapy for metastatic CC
- EMPOWER-Cervical 1: Cemiplimab for patients with platinum-refractory CC
- Ongoing evaluations of anti-PD-1/PD-L1 antibodies + chemotherapy or chemoradiation therapy (CRT)
- Investigational agents and strategies for advanced CC (eg, balstilimab/zalifrelimab, tisotumab vedotin)
- OUTBACK: Addition of adjuvant chemotherapy after CRT as primary treatment for locally advanced CC
- Faculty cases

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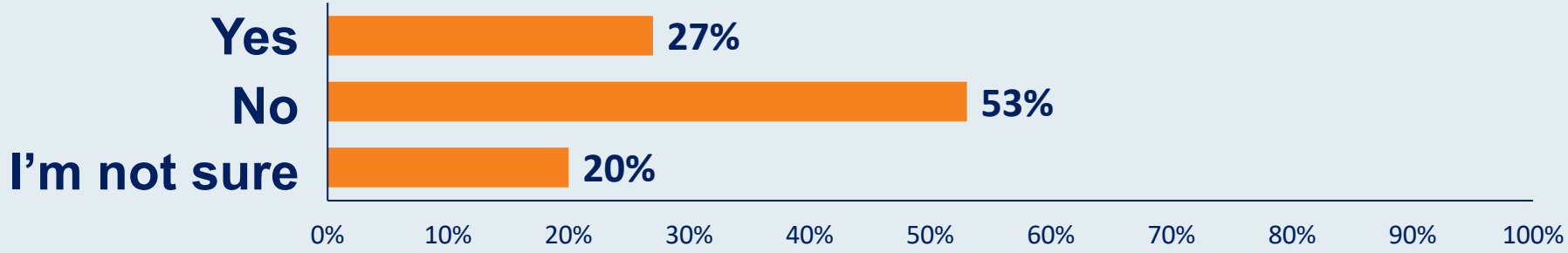
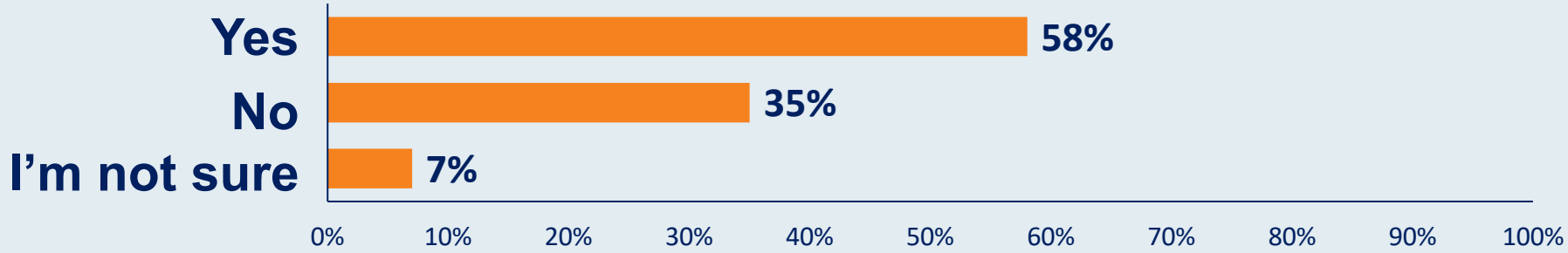
Regulatory and reimbursement issues aside, in which of the following situations would you likely recommend an anti-PD-1/PD-L1 antibody to a patient with MSI-high endometrial cancer?

Adjuvant therapy for a patient at high risk for recurrence



First-line treatment of metastatic disease



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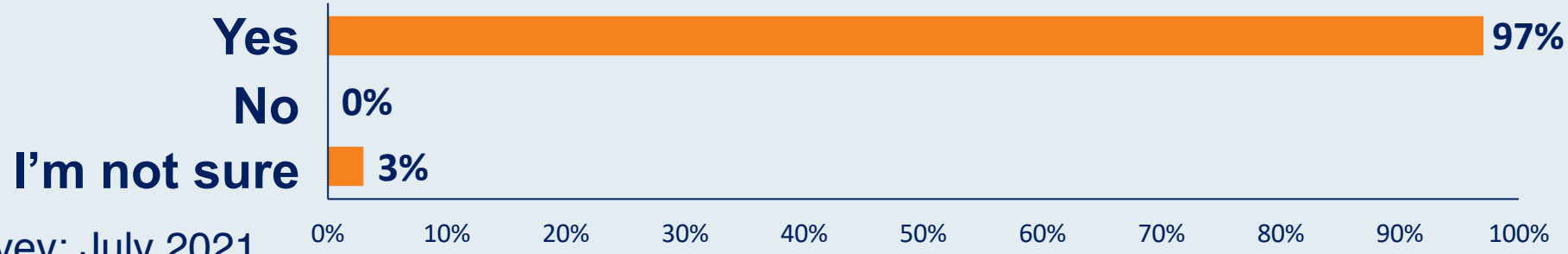

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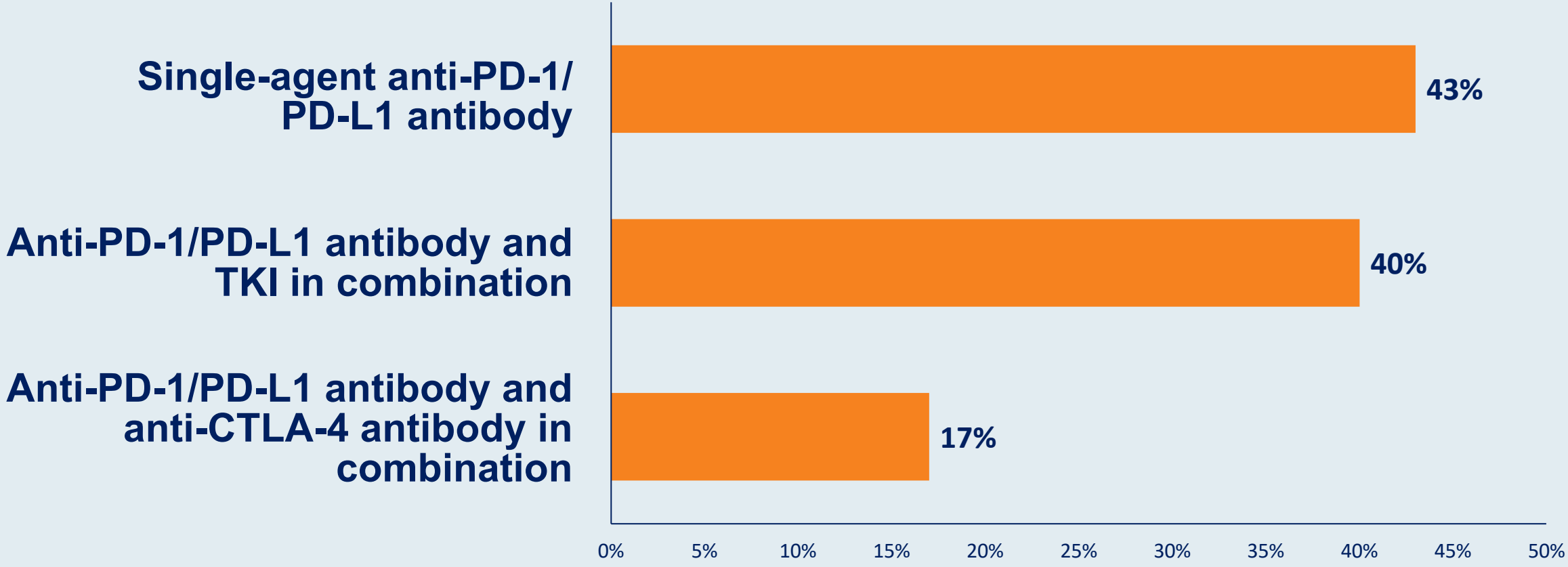
For a younger patient with MSI-high metastatic endometrial cancer, which approach to immunotherapy would you most likely use?



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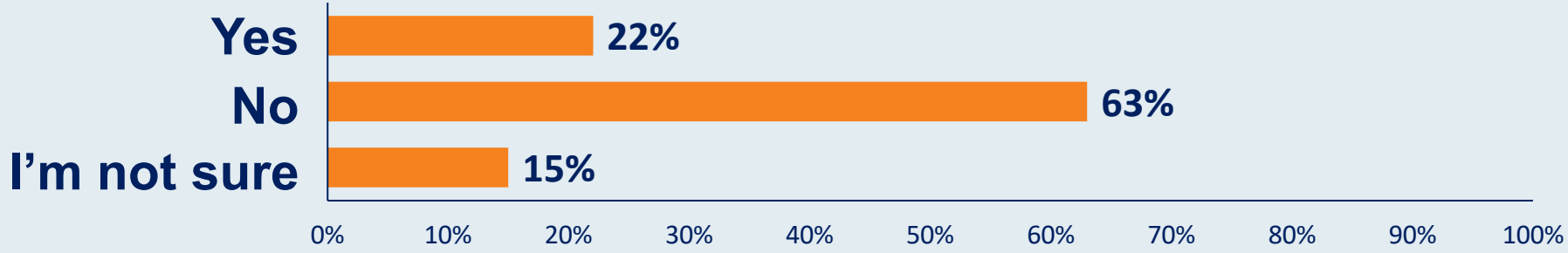
Regulatory and reimbursement issues aside, in which of the following situations would you likely recommend lenvatinib/pembrolizumab to a patient with microsatellite stable (MSS) endometrial cancer?

Adjuvant therapy for a patient at high risk for recurrence



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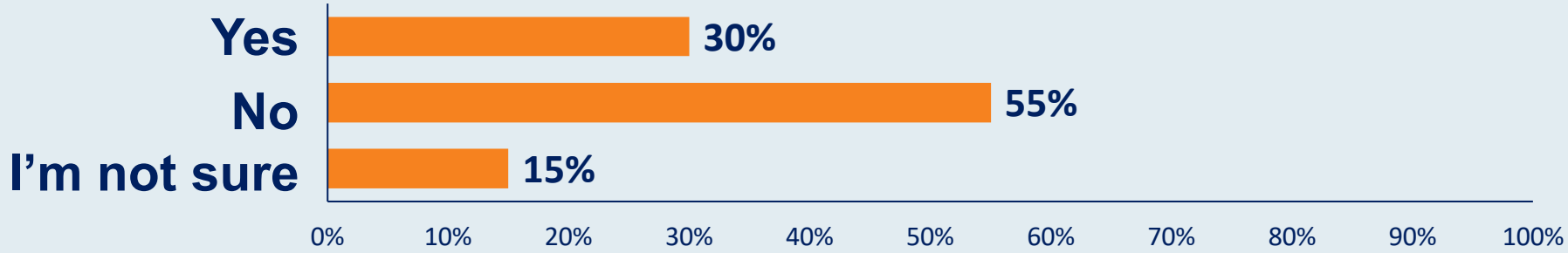

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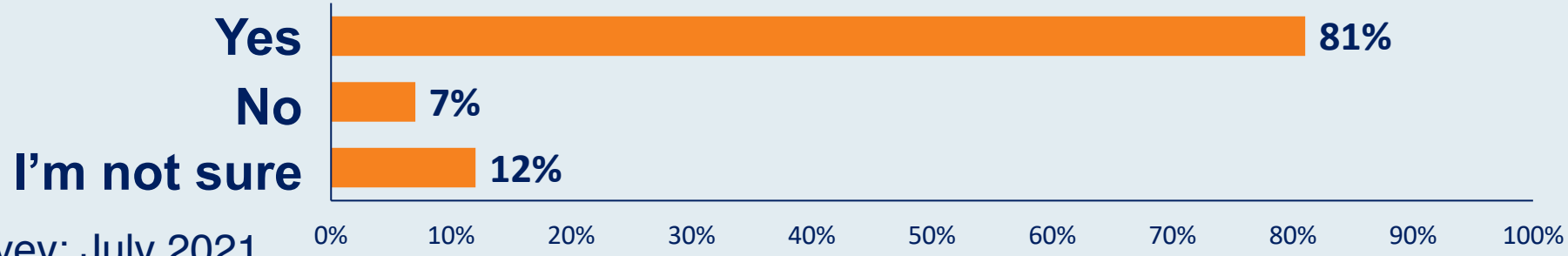

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MMR and MSI

Mutations resulting from dMMR frequently occur at microsatellites[1]

MMR protein ➔ IHC	MSI ➔ molecular biology[2]
Mismatch repair protein complexes (*MLH1+PMS2* and *MSH2+MSH6*) detect and correct mistakes during DNA replication[2]	**Consensus definition:** MSI is a condition of genetic hypermutability[2]
Absence or loss of function of one the 4 MMR proteins = mismatch repair-deficient (dMMR)[1,2]	MSI is characterised by clustering of mutations in microsatellites typically consisting of repeat length alterations[2]
dMMR is the cause of MSI-H[1,2]	The presence of MSI represents phenotypic evidence that MMR is not functioning normally (dMMR)[2]

MSI-H provides phenotypic evidence of dMMR, and so MSI-H and dMMR are seen as biologically the same population[2]

- The term dMMR/MSI-H is used to refer to the group of patients with mismatch repair deficiency
- The term MMRp/MSS is used to refer to the group of patients who are mismatch repair-proficient

dMMR, mismatch repair-deficient; DNA, deoxyribonucleic acid; IHC, immunohistochemistry; *MLH1*, mutL homolog 1; MMR, mismatch repair; *MSH2*, mutS homolog 2; *MSH6*, mutS homolog 6; MSI, microsatellite instability; MSI-H, microsatellite instability-high; MSS, microsatellite stable; MMRp, mismatch repair-proficient; *PMS2*, postmeiotic segregation increased 2

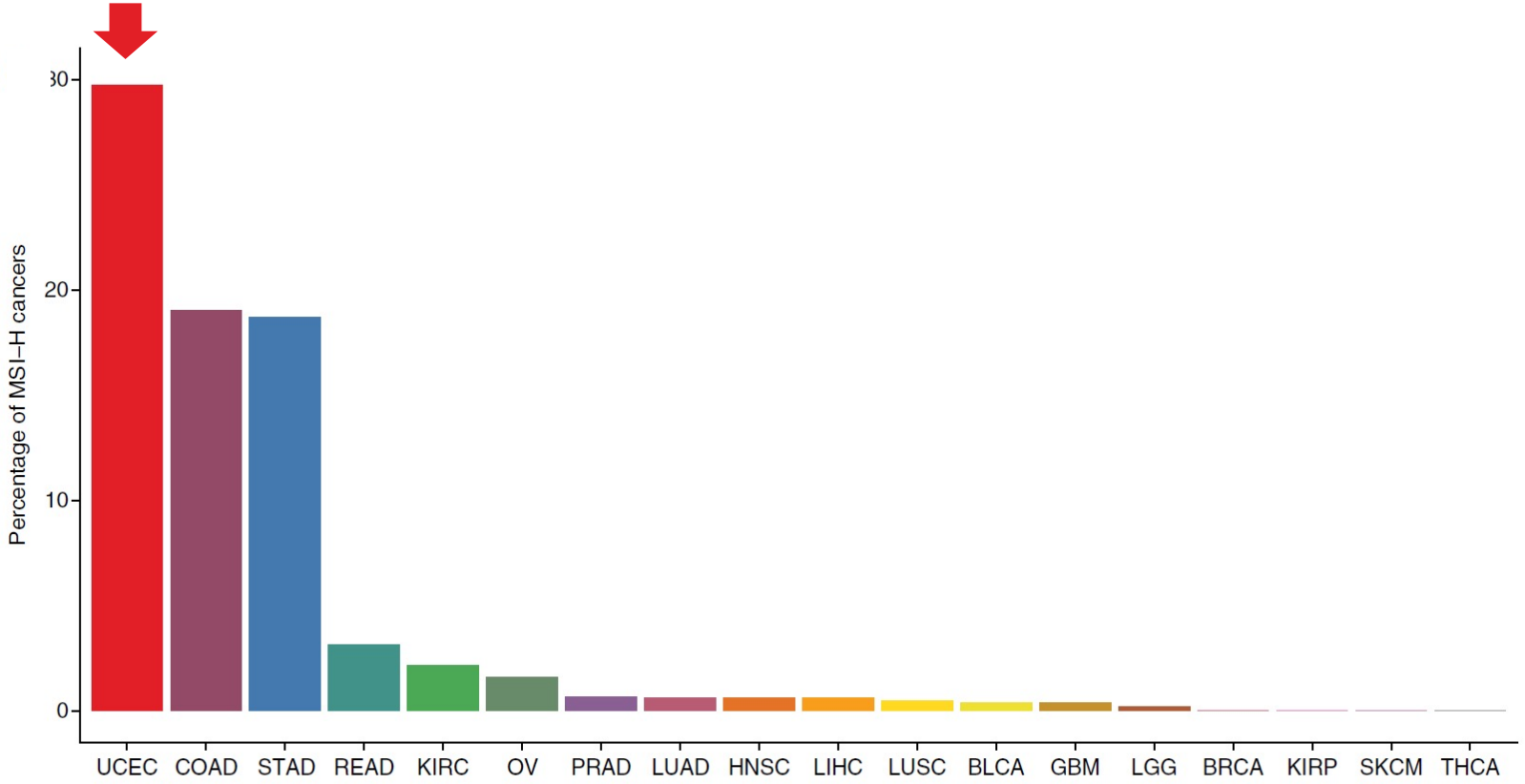
1. Kloor M, et al. *Trends Cancer.* 2016;2:121-133. 2. Luchini C, et al. *Ann Oncol.* 2019;30:1232-1243.

Courtesy of Mansoor Raza Mirza, MD

MSI/dMMR

Incidence in endometrial cancer

EC can be classified as microsatellite stable (MSS; 70–75%) or microsatellite instability-high (MSI-H; 25–30%)



BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; COAD, colon adenocarcinoma; dMMR, mismatch repair-deficient; EC, endometrial cancer; GBM, glioblastoma multiforme; HNSC, head and neck squamous cell carcinoma; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LGG, brain lower grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MSI, microsatellite instability; MSI-H, microsatellite instability-high; MSS, microsatellite stable; OV, ovarian serous cystadenocarcinoma; PRAD, prostate adenocarcinoma; READ, rectal adenocarcinoma; SKCM, skin cutaneous melanoma; STAD, stomach adenocarcinoma; THCA, thyroid carcinoma; UCEC, uterine corpus endometrial carcinoma.

Hause RJ, et al. ***Nat Med.*** **2016;22(11):1342–1350.**

Courtesy of Mansoor Raza Mirza, MD

Recommendations for MSI testing in the framework of immunotherapy

Table 1. Summary table of recommendations for MSI testing in the framework of immunotherapy and comments from the ESMO TR and PM WG consensus panel

Recommendation A: immunohistochemistry	The first test of choice is IHC, using antibodies recognising the four MMR proteins: MLH1, MSH2, MSH6 and PMS2.
Coefficient of agreement: strong (8.7)	
Main comment: MMR proteins form heterodimers; for a correct IHC interpretation, the consensus panel highlights that mutations in MLH1 are associated with IHC loss of both MLH1 and PMS2, while mutations in MSH2 are associated with IHC loss of both MSH2 and MSH6. There exist isolated losses of PMS2, MSH2 or MSH6, this strengthening the recommendation to use all four antibodies.	
Recommendation B: polymerase chain reaction	In case of doubt of IHC, confirmatory molecular analysis is mandatory. The first-line of molecular analysis is represented by PCR. It can be carried out using two possible panels: (i) a panel with two mononucleotide (BAT-25 and BAT-26) and three dinucleotide (D5S346, D2S123 and D17S250) repeats and (ii) a panel with five poly-A mononucleotide repeats (BAT-25, BAT-26, NR-21, NR-24, NR-27). The five poly-A panel is the recommended panel given its higher sensitivity and specificity.
Coefficient of agreement: strong (8.6)	
Main comment: both the suggested panels have been and are being used to assess MSI in clinical trials. Molecular tests guarantee the highest values of specificity and sensitivity in MSI testing.	
Recommendation C: next-generation sequencing	NGS represents another type of molecular tests to assess MSI. Its main advantages are represented by the possibilities of coupling MSI analysis with the determination of tumour mutational burden (TMB).
Coefficient of agreement: very strong (9.0)	
Main comment: NGS should be carried out only in selected centres devoted to these techniques.	

Coefficient of agreement ranges from 0 = totally disagree, to 10 = totally agree.
IHC, immunohistochemistry; PCR, polymerase-chain reaction; NGS, next-generation sequencing.

IHC, immunohistochemistry; *MSH2*, mutS homolog 2; *MSH6*, mutS homolog 6; MSI, microsatellite instability; PCR, polymerase-chain reaction; *PMS2*, postmeiotic segregation increased 2; NGS, next-generation sequencing

Luchini C, et al. *Ann Oncol.* 2019;30:1232-1243.

Courtesy of Mansoor Raza Mirza, MD

Immunotherapy in Endometrial Cancer

ORR in dMMR patients

Study	Drug	N	Patient selection	ORR (%)
KEYNOTE-158[1]	Pembrolizumab	49	Advanced/metastatic dMMR	57%
GARNET[2]	Dostarlimab	103	Previously treated Recurrent/advanced dMMR	45%
PHAEDRA[3]	Durvalumab	35	Advanced/metastatic dMMR	43%
NCT02912572[4]	Avelumab	15	Advanced/metastatic dMMR	27%
KEYNOTE-145[5]	Pembrolizumab + lenvatinib	15	Previously treated Recurrent/advanced dMMR	64%
KEYNOTE-775[6]	Pembrolizumab + lenvatinib	65	Previously treated Recurrent/advanced dMMR	Not known

dMMR, mismatch repair-deficient; ORR, overall response rate

1. Marabelle A, et al. *J Clin Oncol.* 2020;38(1):1-10; 2. Oaknin A, et al. Presented at European Society for Medical Oncology Virtual Congress 2020; 3. Antill YC, et al. *J Clin Oncol.* 2019;37(15_suppl):5501;
4. Konstantinopoulos PA, et al. *J Clin Oncol*. 2019;37(30):2786-2794; 5. Makker V, et al. *J Clin Oncol.* 2020;38(26):2981–2992; 6. Makker V, et al. Presented at Society for Gynecologic Oncology Virtual Annual Meeting 2021.

Courtesy of Mansoor Raza Mirza, MD

Immunotherapy in Endometrial Cancer

ORR in MMRp patients

Study	Drug	N	Patient selection	ORR (%)
KEYNOTE-158[1]	Pembrolizumab	107	Previously treated Recurrent/advanced MMRp	11%
GARNET[2]	Dostarlimab	142	Previously treated Recurrent/advanced MMRp	13%
PHAEDRA[3]	Durvalumab	36	Advanced/metastatic MMRp	3%
NCT02912572[4]	Avelumab	16	Advanced/metastatic MMRp	6%
KEYNOTE-145[5]	Pembrolizumab + lenvatinib	94	Previously treated Recurrent/advanced MMRp	36%
KEYNOTE-775[6]	Pembrolizumab + lenvatinib	346	Previously treated Recurrent/advanced MMRp	30%

MMRp, mismatch repair-proficient; ORR, overall response rate

1. Marabelle A, et al. *J Clin Oncol.* 2020;38(1):1-10; 2. Oaknin A, et al. Presented at European Society for Medical Oncology Virtual Congress 2020; 3. Antill YC, et al. *J Clin Oncol.* 2019;37(15_suppl):5501;
4. Konstantinopoulos PA, et al. *J Clin Oncol.* 2019;37(30):2786-2794; 5. Makker V, et al. *J Clin Oncol.* 2020;38(26):2981-2992; 6. Makker V, et al. Presented at Society for Gynecologic Oncology Virtual Annual Meeting 2021.

Courtesy of Mansoor Raza Mirza, MD

KEYNOTE-775

	pMMR		All-comers	
	LEN + pembro	TPC	LEN + pembro	TPC
Patients, n	346	351	411	416
Objective response rate, % (95% CI)	30.3 (25.5–35.5)	15.1 (11.5–19.3)	31.9 (27.4–36.6)	14.7 (11.4–18.4)
Difference vs TPC, %	15.2	--	17.2	--
P-value	< 0.0001		< 0.0001	
Best overall response, %				
Complete response	5.2	2.6	6.6	2.6
Partial response	25.1	12.5	25.3	12.0
Stable disease	48.6	39.6	47.0	40.1
Progressive disease	15.6	30.8	14.8	29.6
Not evaluable / assessed	0.6 / 4.9	2.0 / 12.5	1.2 / 5.1	1.9 / 13.7
Median duration of response (range), months	9.2 (1.6[a]–23.7[a])	5.7 (0.0[a]–24.2[a])	14.4 (1.6[a]–23.7[a])	5.7 (0.0[a]–24.2[a])
Median time to response (range), months	2.1 (1.5–9.4)	3.5 (1.0–7.4)	2.1 (1.5–16.3)	2.1 (1.0–7.4)

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KEYNOTE-775

	pMMR		All-comers	
	LEN + pembro	TPC	LEN + pembro	TPC
Patients, n	346	351	411	416
Objective response rate, % (95% CI)	30.3 (25.5–35.5)	15.1 (11.5–19.3)	31.9 (27.4–36.6)	14.7 (11.4–18.4)
Difference vs TPC, %	15.2		17.2	

July 21, 2021 – FDA grants regular approval to pembrolizumab plus lenvatinib for patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation

Stable disease	48.6	39.6	47.0	40.1
Progressive disease	15.6	30.8	14.8	29.6
Not evaluable / assessed	0.6 / 4.9	2.0 / 12.5	1.2 / 5.1	1.9 / 13.7
Median duration of response (range), months	9.2 (1.6[a]–23.7[a])	5.7 (0.0[a]–24.2[a])	14.4 (1.6[a]–23.7[a])	5.7 (0.0[a]–24.2[a])
Median time to response (range), months	2.1 (1.5–9.4)	3.5 (1.0–7.4)	2.1 (1.5–16.3)	2.1 (1.0–7.4)

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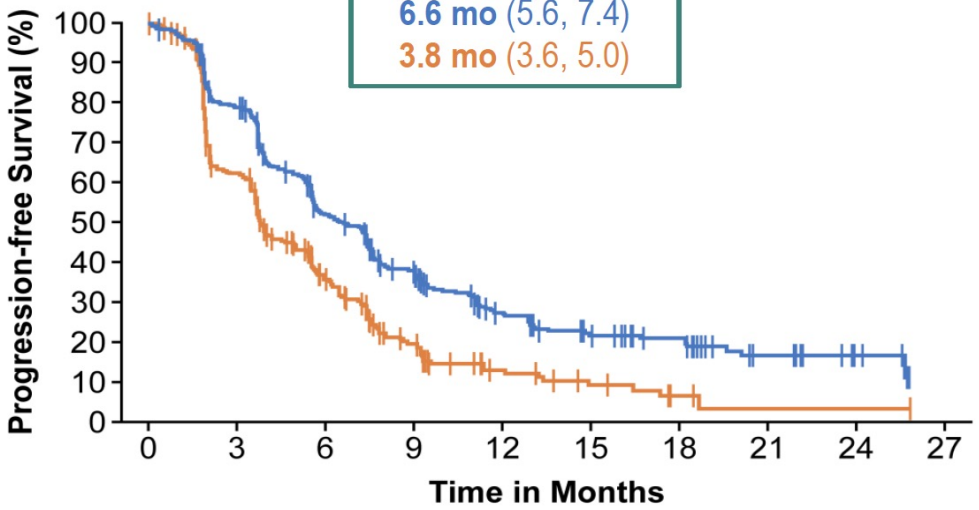
Progression-free Survival[a]

KEYNOTE-775

pMMR

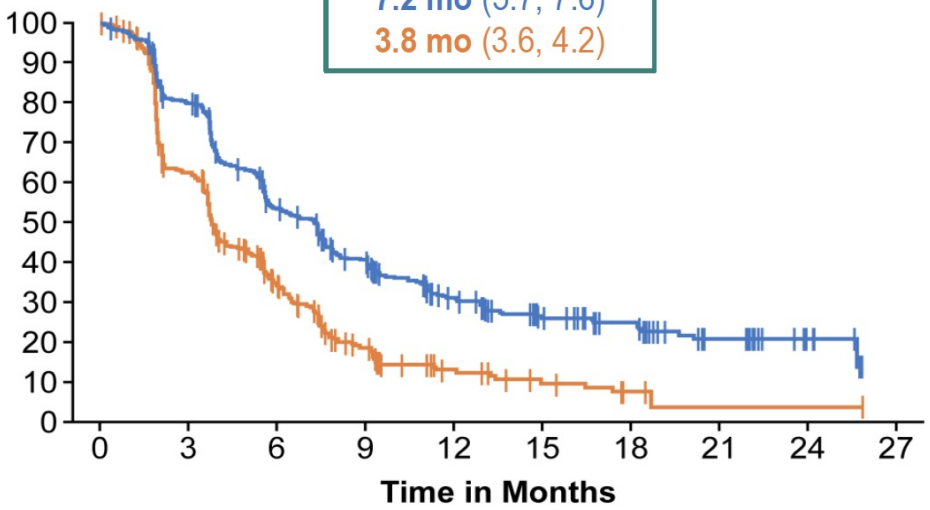


No. at risk

346	264	165	112	60	39	30	12	5	0
351	177	83	37	15	8	3	1	1	0

	Events	HR (95% CI)	*P*-value
LEN + pembro	247	**0.60** (0.50, 0.72)	< 0.0001
TPC	238		

All-comers



No. at risk

411	316	202	144	86	56	43	17	6	0
416	214	95	42	18	10	4	1	1	0

	Events	HR (95% CI)	*P*-value
LEN + pembro	281	**0.56** (0.47, 0.66)	< 0.0001
TPC	286		

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Courtesy of David M O'Malley, MD

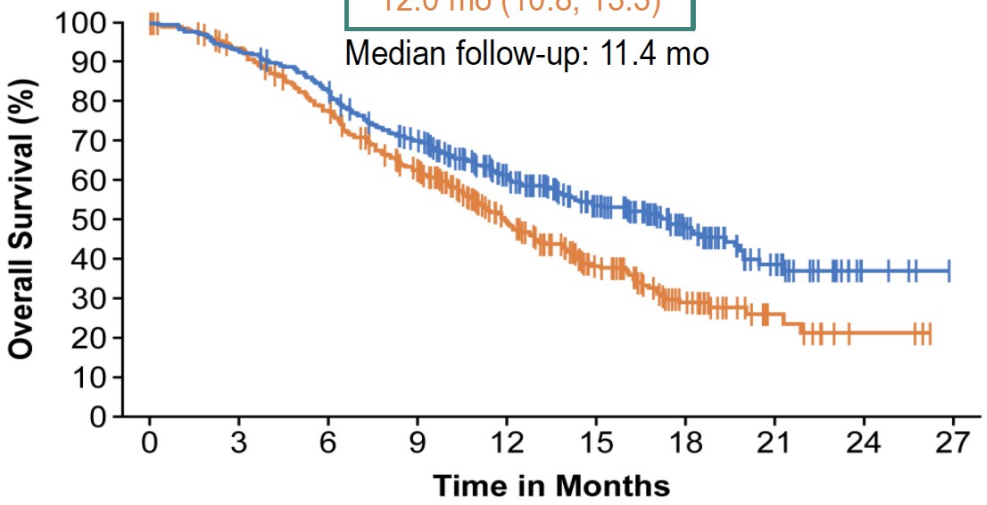
Overall Survival

KEYNOTE-775

pMMR

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

Median follow-up: 11.4 mo



No. at risk

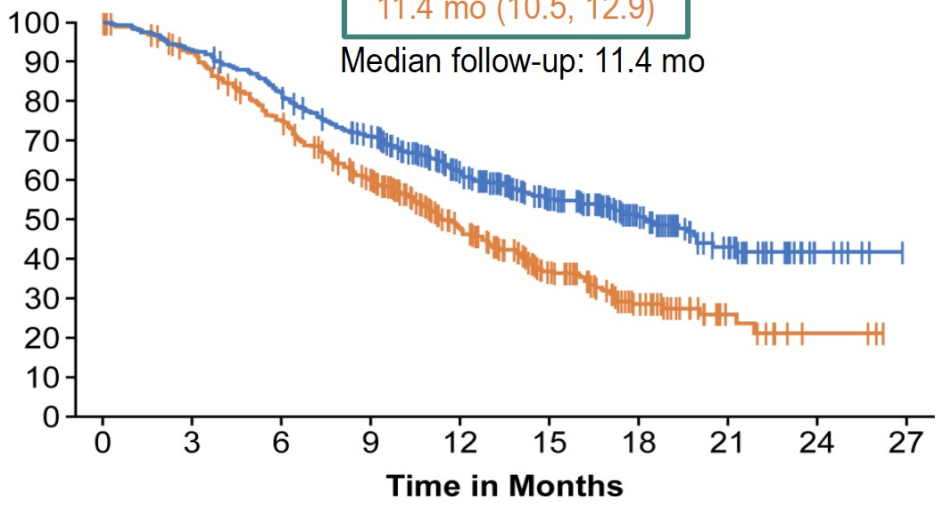
346	322	285	232	160	109	62	28	5	0
351	319	262	201	120	70	33	11	3	0

	Events	HR (95% CI)	*P*-value
LEN + pembro	165	**0.68** (0.56, 0.84)	0.0001
TPC	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
LEN + pembro	188	**0.62** (0.51, 0.75)	< 0.0001
TPC	245		

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Courtesy of David M O'Malley, MD

Treatment Exposure, Safety, and Discontinuation in All-comers

KEYNOTE-775

	LEN + pembro (n = 406)	TPC (n = 388)
Median duration of treatment (range), days	231 (1–817)	104.5 (1–785)
Patients with any TEAEs, %	99.8	99.5
Grade ≥ 3	88.9	72.7
Patients with any TEAEs leading to dose reductions, %[a]	66.5	12.9
Patients with any-grade TEAEs leading to interruption, %[b]	69.2	27.1
LEN[c]	58.6	--
Pembro[c]	50.0	--
LEN + pembro	30.8	--
Patients with any-grade TEAEs leading to discontinuation, %[b]	33.0	8.0
LEN[c]	30.8	--
Pembro[c]	18.7	--
LEN + pembro	14.0	--

[a]Includes LEN only or TPC. [b]Includes LEN or pembro or LEN + pembro or TPC. [c]Regardless of action taken with the other drug in the combination arm.
TEAE, treatment-emergent adverse event.

Makker et al, SGO Annual Meeting 2021

GARNET: Dostarlimab for MSI-H/dMMR and Microsatellite-Stable EC

Primary Endpoint Analysis

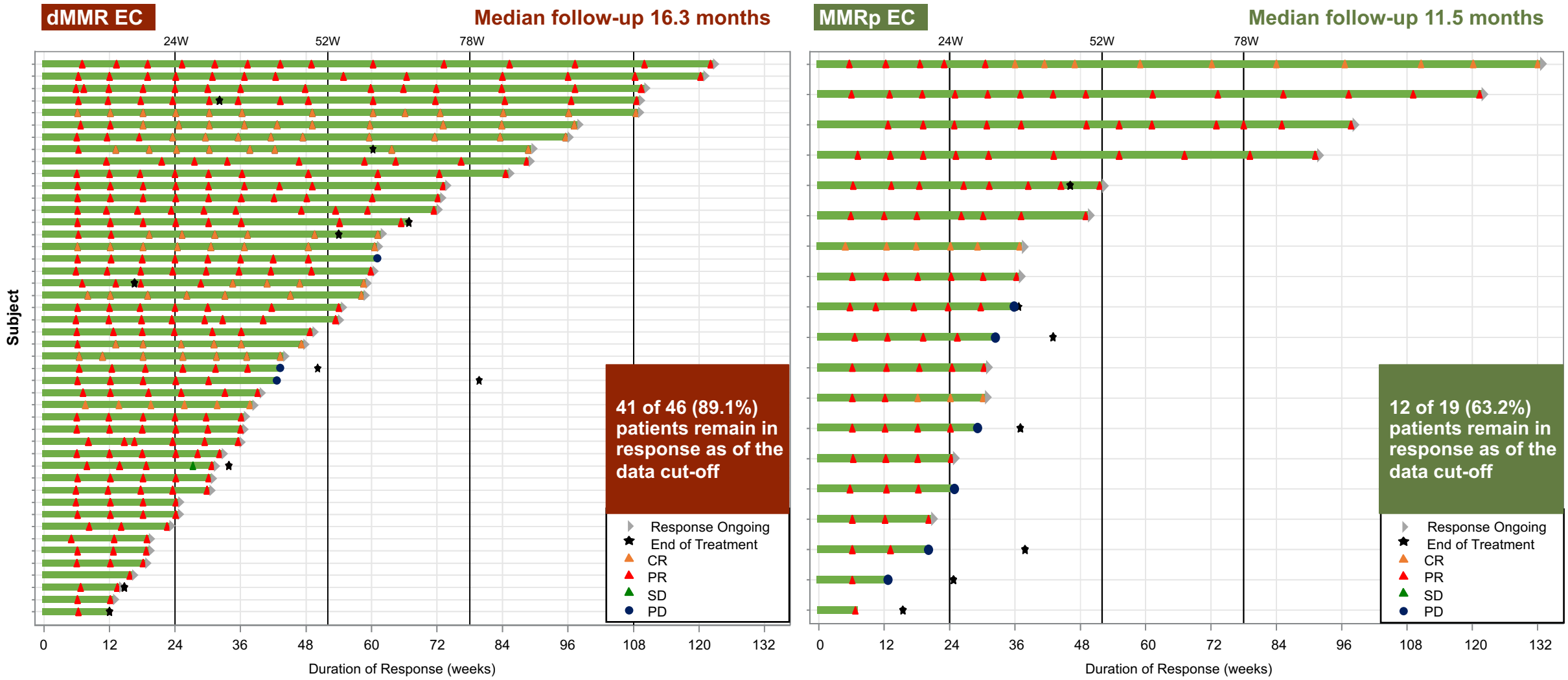
ORR was 44.7% in patients with dMMR EC, and 13.4% in patients with MMRp EC

Variable	dMMR EC, n=103	MMRp EC, n=142
Median follow-up time, mo	**16.3**	**11.5**
Objective response rate*, n (%, 95% CI)	**46 (44.7%, 34.9–54.8)**	**19 (13.4%, 8.3–20.1)**
Complete response, n (%)	11 (10.7)	3 (2.1)
Partial response, n (%)	35 (34.0)	16 (11.3)
Stable disease, n (%)	13 (12.6)	31 (21.8)
Progressive disease, n (%)	39 (37.9)	77 (54.2)
Not evaluable, n (%)	3 (2.9)	0
Not done, n (%)	2 (1.9)	15 (10.6)
Disease control rate†, n (%, 95% CI)	**59 (57.3%, 47.2–67.0)**	**50 (35.2%, 27.4–43.7)**
Response ongoing, n (%)	**41 (89.1)**	**12 (63.2)**
Median duration of response, (range) mo	**Not reached (2.63–28.09+)**	**Not reached (1.54+–30.36+)**
Kaplan–Meier estimated probability of remaining in response		
at 6 mo, %	97.8	83.0
at 12 mo, %	90.6	61.3
at 18 mo, %	79.2	61.3

ESMO 2020: Ana Oaknin, Lucy Gilbert, Anna V. Tinker, Renaud Sabatier, Valentina Boni, David M. O'Malley, Sharad Ghamande, Linda Duska, Prafull Ghatage, Wei Guo, Ellie Im, Bhavana Pothuri

Courtesy of David M O'Malley, MD

GARNET: Primary Endpoint Analysis
DoR



Data cut-off date March 1, 2020. CR, complete response; dMMR, mismatch mutation repair deficient; EC, endometrial cancer; MMRp, mismatch mutation repair proficient; PD, progressive disease; PR, partial response; SD, stable disease.

Oaknin A, et al. Presented at European Society for Medical Oncology Virtual Congress 2020.

Courtesy of Mansoor Raza Mirza, MD

Case Presentation – Dr Mirza: A 62-year-old woman with Stage IIIC endometrial cancer

- *December 2019: 62 yr old patient is diagnosed with endometrial cancer*
- *Pre-op PETCT revealed intra-abdominal spread and para-aortic nodal involvement*
- *Upfront surgery (complete resection)*
- *Histology report: endometrial cancer; serous adenocarcinoma; p53mut, MSS; ER neg; FIGO stage 3C*

- *Adjuvant carboplatin-paclitaxel x 6*

- *December 2020: Relapse with lung metastases after 5 months treatment-free interval*
- *Co-morbidity: well-controlled hypertension, well-controlled NIDDM*
- *Performance status: 0*

Courtesy of Mansoor Raza Mirza, MD

Case Presentation – Dr Mirza: A 62-year-old woman with Stage IIIC endometrial cancer (continued)

- *December 2019: 62 yr old patient is diagnosed of endometrial cancer*
- *Pre-op PETCT revealed intraabdominal spread and para-aortic nodal involvement*
- *Upfront surgery (complete resection)*
- *Histology report: endometrial cancer; serous adenocarcinoma; p53mut, MSS; ER neg; FIGO stage 3C*

- *Adjuvant carboplatin-paclitaxel x 6*

- *December 2020: Relapse with lung metastases after 5 months treatment-free interval*
- *Co-morbidity: well-controlled hypertension, well-controlled NIDDM*
- *Performance status: 0*

- Patient started on lenvatinib + pembrolizumab
  - *Pause of lenvatinib at day 14 due to diarrhoea*
  - *Lenvatinib resumed after one week with dose reduction (14mg daily)*

  Patient continues on treatment and is in complete response now at 6 months (CT evaluation)

Courtesy of Mansoor Raza Mirza, MD

Case Presentation – Dr Mirza: A 68-year-old woman with MSI-H Stage IIIC endometrial cancer

- *June 2019: 68 yr old patient, diagnosed with endometrial cancer.*
- *Preop PET-CT revealed para-aortic nodal spread*

- *Upfront surgery (complete resection)*
- *Histopathology: endometrioid adenocarcinoma; ER pos; p53wt, MSI-H; FIGO stage 3C*

- *Adjuvant carboplatin-paclitaxel x 6*

- *March 2021: Relapse with liver metastases*
- *Performance status: 0*
- *Co-morbidity: well-controlled hypertension*

Courtesy of Mansoor Raza Mirza, MD

Case Presentation – Dr Mirza: A 68-year-old woman with MSI-H Stage IIIC endometrial cancer (continued)

- *June 2019: 68 yr old patient, diagnosed of endometrial cancer.*
- *Preop PET-CT revealed para-aortic nodal spread*

- *Upfront surgery (complete resection)*
- *Histopathology: endometrioid adenocarcinoma; ER pos; p53wt, MSI-H; FIGO stage 3C*

- *Adjuvant carboplatin-paclitaxel x 6*

- *March 2021: Relapse with liver metastases*
- *Performance status: 0*
- *Co-morbidity: well-controlled hypertension*

- Patient is started on dostarlimab
- *No toxicity so far!*

- *Patient continues on dostarlimab and is in partial remission (CT evaluation)*

Courtesy of Mansoor Raza Mirza, MD

Case Presentation – Dr O'Malley: A woman in her 70s with MSI-high endometrial cancer

- A woman in her 70's presented with recurrent Stage IIIC2, Grade 3 endometrial cancer underwent robotic hyst/bso and lymph node debulking (25/36 lymph nodes were positive). Received 6 cycles of carboplatin/paclitaxel followed by radiation (pelvic and aortic). Approximately 3 years later had vaginal cuff recurrence where she underwent 6 cycles of carboplatin/paclitaxel followed by vaginal cuff brachytherapy. One year later she presented with multifocal recurrence (lung). Treated on clinical trial with pembrolizumab for 11 months. She was removed for hepatitis after a CR. She is without disease 4 years after stopping therapy. She was found to be MSI-high.

Agenda

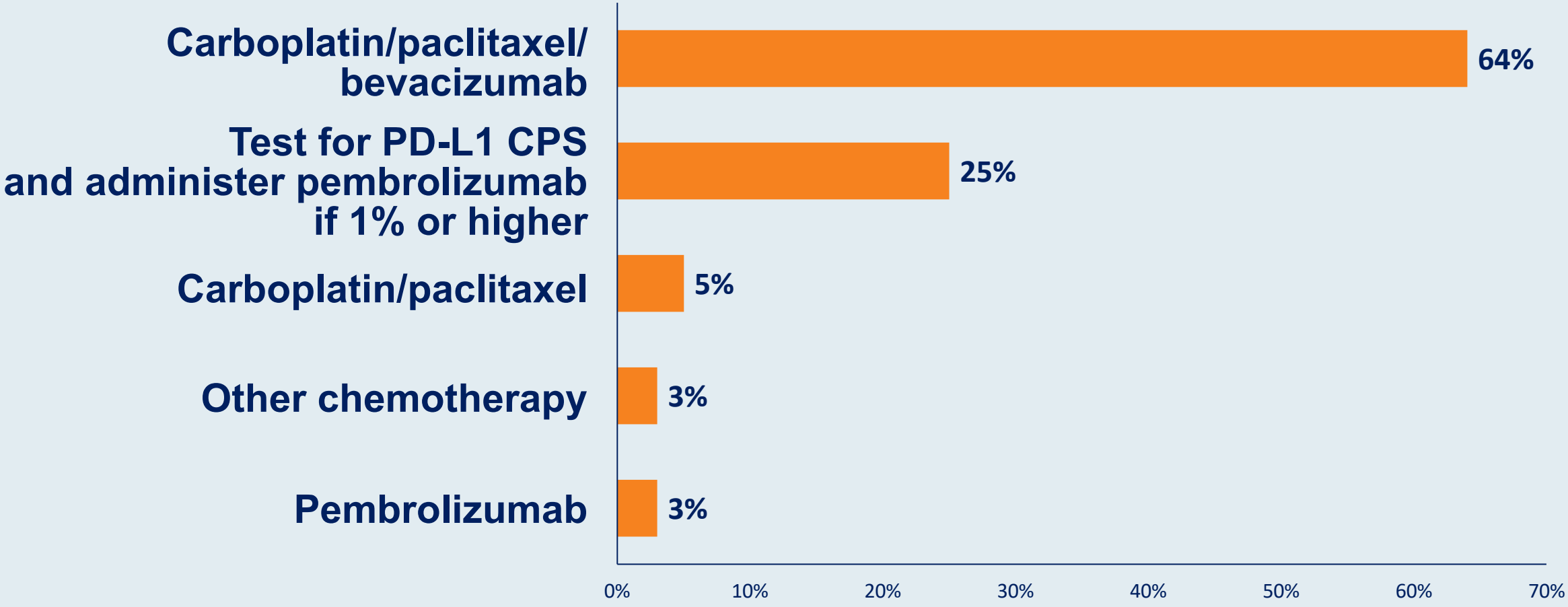
Module 1: Current Treatment Planning for Patients with Advanced Endometrial Cancer (EC)

- Biomarker assessment in advanced EC; incidence of MSI-H/dMMR and current indications for testing
- KEYNOTE-775: Pembrolizumab + lenvatinib for recurrent EC; recent FDA approval
- GARNET: Dostarlimab for patients with MSI-H/dMMR and microsatellite-stable tumors
- Ongoing Phase III trials of anti-PD-1/PD-L1-based therapies for recurrent or primary advanced EC
- Faculty cases

Module 2: Selection of Therapy for Patients with Advanced Cervical Cancer (CC)

- Rationale for investigation of immunotherapy in advanced CC
  - Correlation between PD-L1 expression and response to anti-PD-1/PD-L1 antibodies
- KEYNOTE-158: Pembrolizumab monotherapy for metastatic CC
- EMPOWER-Cervical 1: Cemiplimab for patients with platinum-refractory CC
- Ongoing evaluations of anti-PD-1/PD-L1 antibodies + chemotherapy or chemoradiation therapy (CRT)
- Investigational agents and strategies for advanced CC (eg, balstilimab/zalifrelimab, tisotumab vedotin)
- OUTBACK: Addition of adjuvant chemotherapy after CRT as primary treatment for locally advanced CC
- Faculty cases

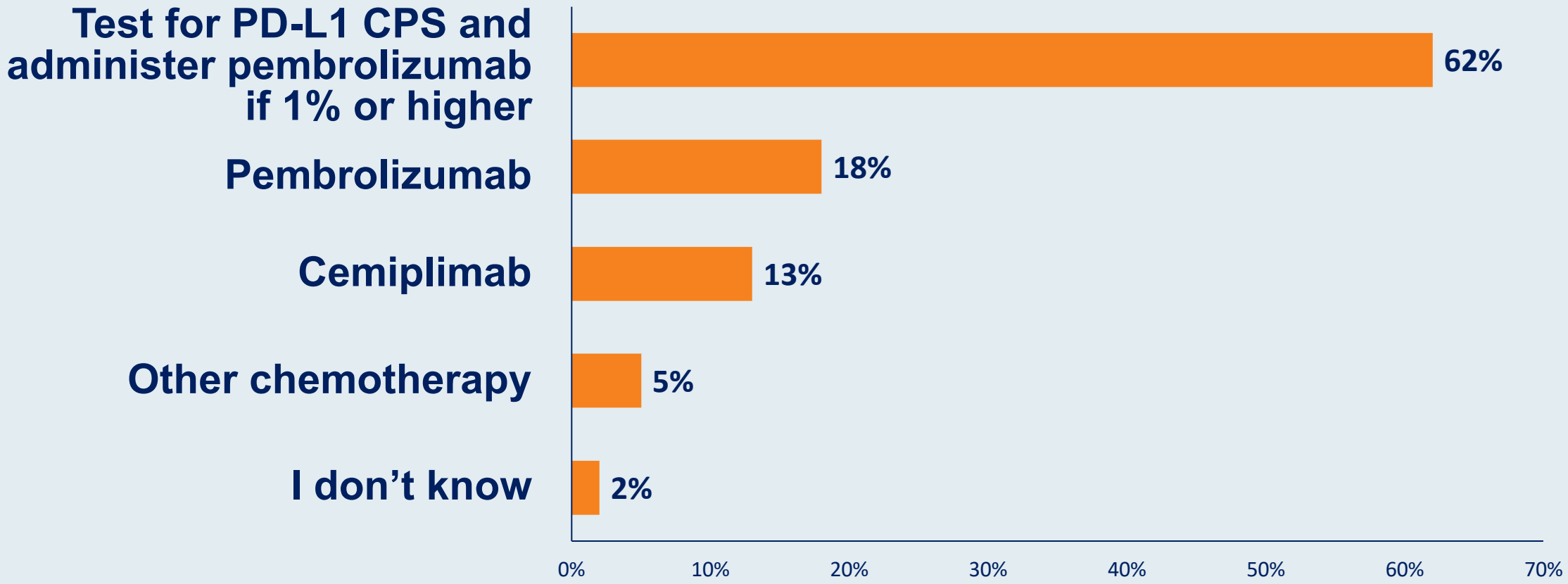
In general, what would be your preferred first-line therapy for a patient with MSS metastatic cervical cancer who experienced relapse 12 months after receiving cisplatin-based chemoradiation therapy for Stage IIIB disease?



Premeeting survey: July 2021

RTP RESEARCH TO PRACTICE

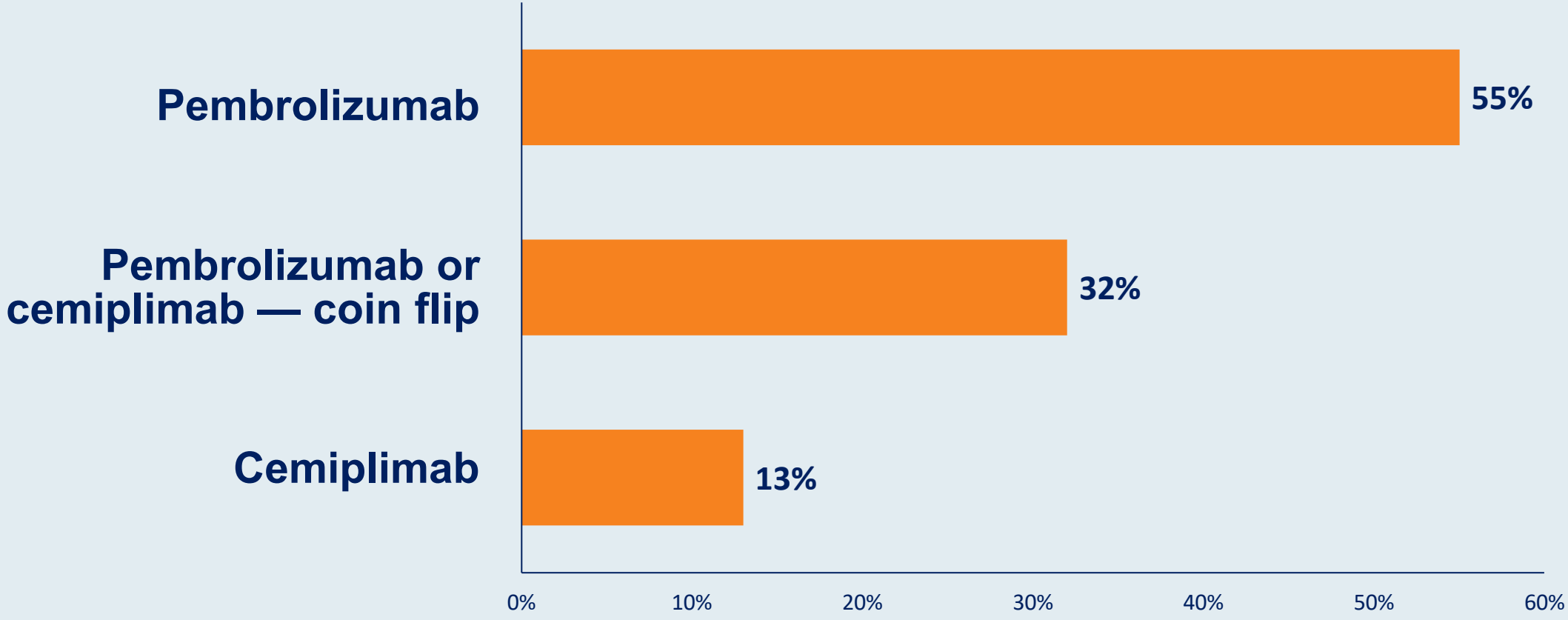
Regulatory and reimbursement issues aside, in general, what would be your preferred second-line therapy for a patient with MSS metastatic cervical cancer who experiences disease progression on carboplatin/paclitaxel/bevacizumab?



Premeeting survey: July 2021

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, what is your preferred anti-PD-1 antibody for the treatment of MSS metastatic cervical cancer with disease progression on carboplatin/paclitaxel/bevacizumab?

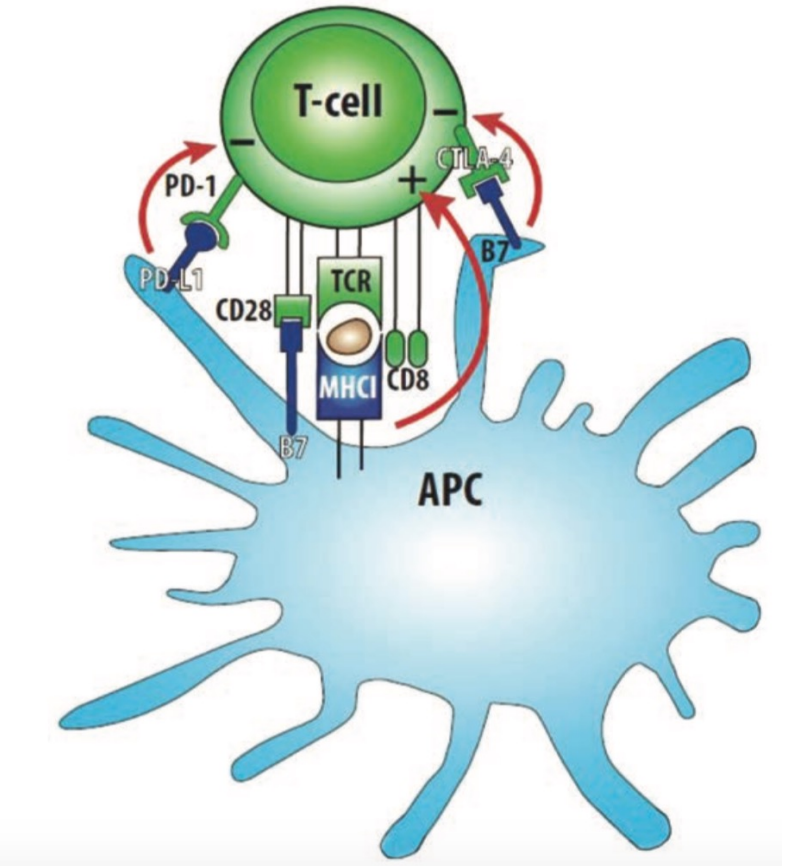


Premeeting survey: July 2021

RTP RESEARCH TO PRACTICE

Rationale to Pursue Immunotherapy in Cervical Cancer

- T cells play a central role in the control of viral infections and prevention of virus-associated tumors
- CC is the consequence of persistent infection by oncogenic HPV subtypes (e.g. 16 and 18)
- The immune response to viral infection depends on:
  - Presentation of viral antigen to specific T cells by APC: Interaction of TCRs and tumor-specific antigens bound to MHC of APCs.
  - Interaction between costimulatory ligands on APCs (B7) and their receptors on T cells (CD28)
  - Inflammatory cytokine signals
- On top, previous steps are **regulated by a complex of activating (CD28) and inhibitory signals (CTLA-4; PD-1).**
- In the setting of HPV infection, acquisition **of immunosuppressive mechanisms (or immune exhaustion/anergy**) leads to tumor immune evasion and development of invasive cancer.



TCRs: T-cell receptors; MHC: major histocompatibility complexes; APCs: Antigen-presenting cells

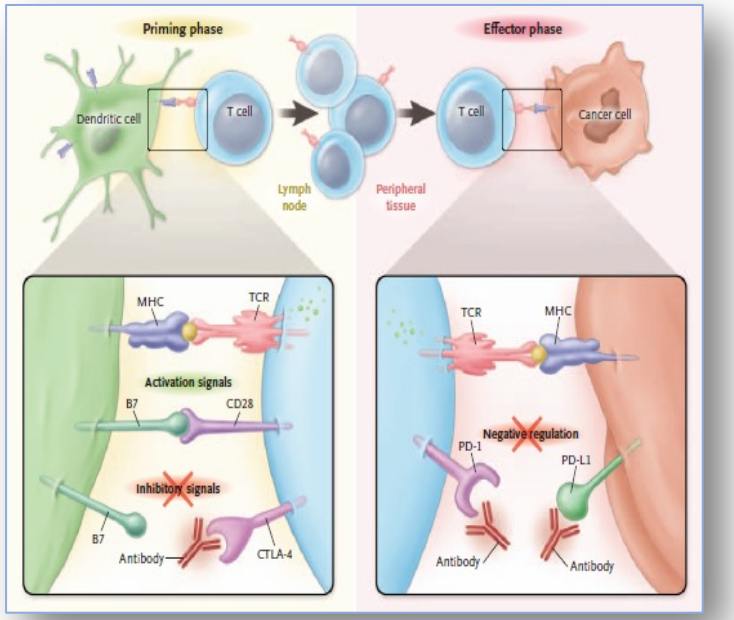
Dyer et al JNCCN; Volume 17 Number 1 January 2019

Courtesy of Mansoor Raza Mirza, MD

Rationale to Pursue Immunotherapy for Cervical Cancer: Mechanisms of Immune Inhibition: Checkpoints

Priming Phase (T-cell activation): CTLA-4

- **CTLA-4,** a ***negative co-stimulatory*** receptor, **binds to B7** ligands on APC with higher affinity than the CD28 (co-stimulatory receptor), suppressing the immune response.



Effector Phase (activated T cells): PD1-PD-L1 pathway

- **PD-1** is a ***negative co-stimulatory*** receptor mainly expressed on activated T cells which **bind to its ligands, PD-L1 and PD-L2** (on tumor cells and macrophages) inhibits effector T-cell function (T cells exhaustion).

- **PD-L1** (a solid biomarker of HPV infection) is **significantly up-regulated in CC:**
  - Squamous Cervical cancer between 54%-80% according to different series
  - Adenocarcinoma: 14%

Targeting CTLA-4 and/or the PD-1/PD-L1 pathway may be therapeutically effective and should be considered in the treatment of CC.

Keir ME et al. Ann Rev Immunol 2008; Pardoll DM. Nat Rev Cancer 2012; Liu C, et al. *Mol Med Rep* 2017;15:1063–1070; Mezache L, et al. *Mod Pathol* 2015;28:1594–1602; Heeren AM et al. *Mod Pathol.* 2016;29:753–763.

Courtesy of Mansoor Raza Mirza, MD

Pembrolizumab: KEYNOTE-158

US FDA Accelerated Approval of Pembrolizumab (June 12, 2018)

- Multicenter, non-randomized, open-label, multi-cohort trial
- Pembrolizumab 200 mg every 3 weeks until toxicity or progression
- Among the 98 patients in Cohort E, 77 (79%) had tumors that expressed PD-L1 with a CPS ≥ 1 and received at least one line of chemotherapy in the metastatic setting
  - 35% had one and 65% had ≥ two prior lines of therapy in the recurrent or metastatic setting.

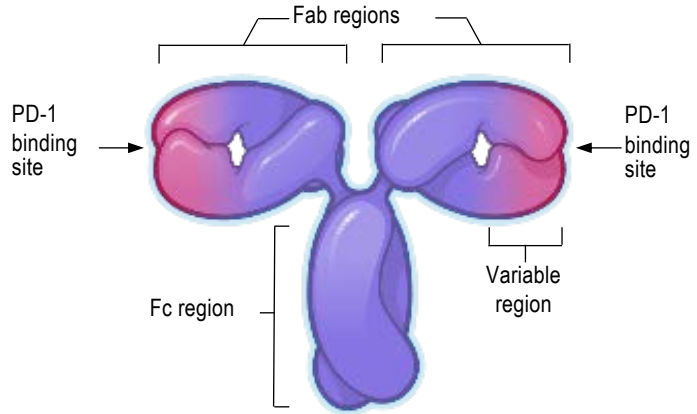
- ORR 14.3%
  - 2.6% had complete responses
  - All responses in PD-L1 positive tumors. ORR in patients with PD-L1+ tumors was 17.1%
  - 91% (10 of 11) of responders had ongoing response for 6 months or longer

Chung HC. J Clin Oncol 2019. Chung HC, et al. SGO Meeting 2021

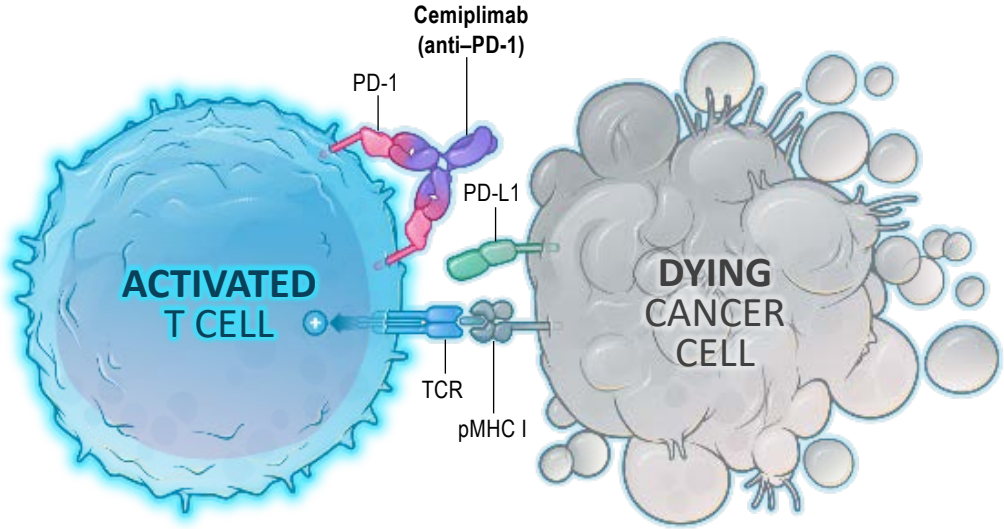
Courtesy of Angeles Alvarez Secord, MD, MHSc

CEMIPLIMAB

Cemiplimab Molecular Structure



Cemiplimab Mechanism of Action

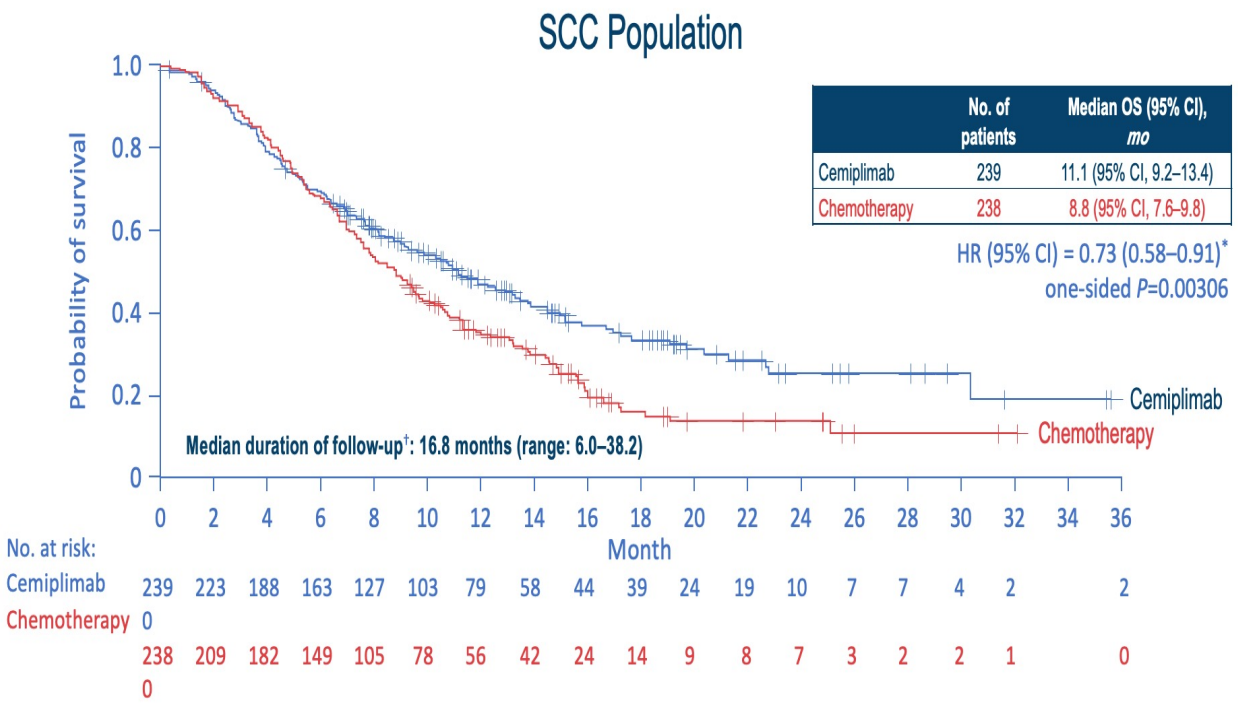


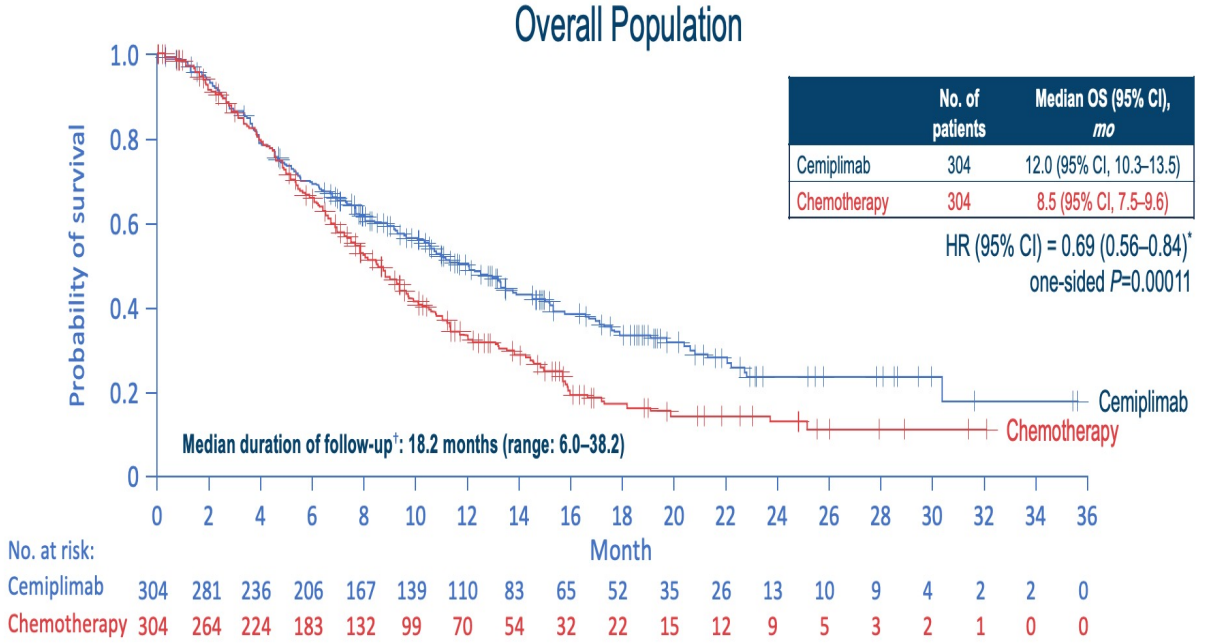
- High-affinity, humanised, hinge-stabilised IgG4 monoclonal antibody to the PD-1 receptor[1]
- Phase 1 R/M cervical cancer (n=20; Expansion Cohorts for monotherapy and cemiplimab + hfRT)[2]
  - Safety profile similar to that of other PD-1 inhibitors[2]
  - Monotherapy cohort: 10% ORR; 20% DCR; 11.2 m DoR[2]

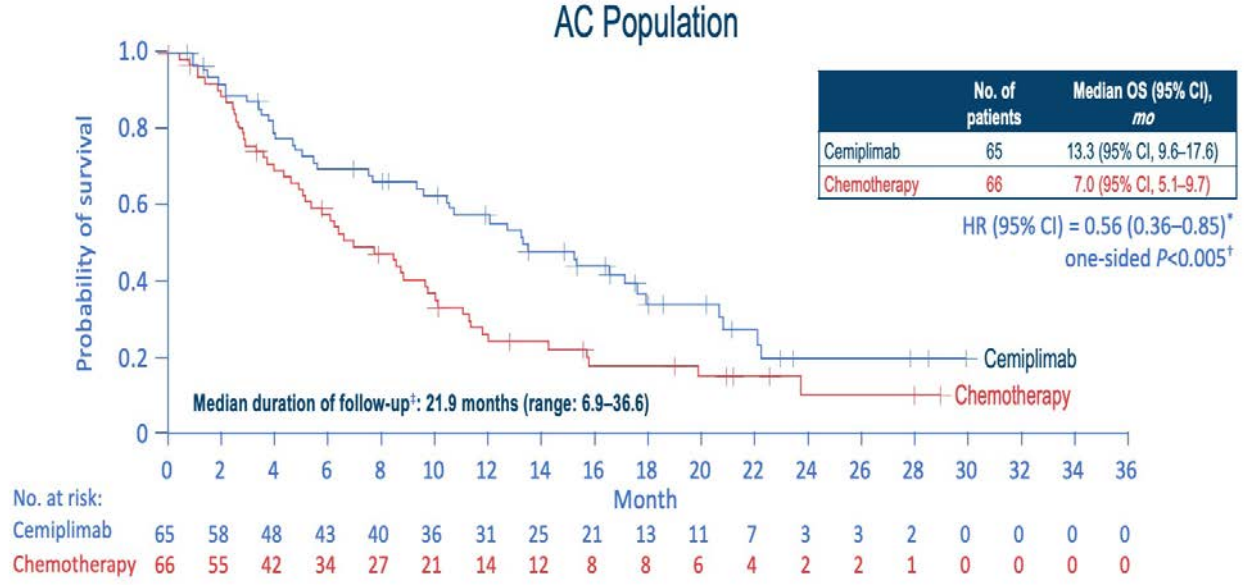
Burova E et al. *Mol Cancer Ther.* 2017;16:861–870. 2. Rischin D et al. *Gynecol Oncol.* 2020;159:322–328.

Courtesy of Angeles Alvarez Secord, MD, MHSc

EMPOWER-CERVICAL 1: Overall Survival with Cemiplimab







Presented by Tewari, K 2021

Courtesy of Angeles Alvarez Secord, MD, MHSc

EMPOWER-CERVICAL 1: OBJECTIVE RESPONSE RATE

By investigator assessment	Overall population	
	Cemiplimab (n=304)	Chemotherapy (n=304)
Response		
Objective response rate (ORR:CR+PR)	50 (16.4)	19 (6.3)
95% CI for ORR[a]	(12.5, 21.1)	(3.8, 9.6)
Best overall tumour response, n (%)		
Complete response (CR)[b]	10 (3.3)	3 (1.0)
Partial response (PR)[b]	40 (13.2)	16 (5.3)
Stable disease (SD)[c]	125 (41.1)	148 (48.7)
Progressive disease (PD)	105 (34.5)	88 (28.9)
Not evaluable (NE)	24 (7.9)	49 (16.1)
Stratified CMH test one-sided *P*-value[d]	0.00004	
Odds ratio (95% CI)[d]	2.984 (1.707, 5.215)	
KM estimated median DOR, months (95% CI)[e]	16.4 (12.4, NE)	6.9 (5.1, 7.7)
Median observed time to response, months (range)	2.7 (1.2–11.4)	1.6 (1.2–9.0)

- ORR of SCC population
  - Cemiplimab: 17.6% (95% CI: 13.0–23.0)
  - Chemotherapy: 6.7% (95% CI: 3.9–10.7)
- ORR of AC population
  - Cemiplimab: 12.3% (95% CI: 5.5–22.8)
  - Chemotherapy: 4.5% (95% CI: 0.9–12.7)

[a]Clopper-Person exact confidence interval (CI); [b]CR/PR must be confirmed by repeated assessments no less than 4 weeks apart; [c]SD criteria must be met at least once for a minimum duration of 4 weeks after first dose date; [d]One-sided *P*-value and odds ratio using geographic region and histology stratified Cochran-Mantel-Haenszel (CMH) test. Due to the low response rate in the chemotherapy arm, the results from CMH test should be interpreted with caution; [e]Based on patients with confirmed CR or PR.

Data cutoff date: 4 Jan 2021

Presented by Tewari, K 2021

Courtesy of Angeles Alvarez Secord, MD, MHSc

Trial	Design	1° endpoint
CALLA NCT03830866	CRT vs CRT + durvalumab + maintenance durvalumab (NO LONGER RECRUITING)	PFS
KEYNOTE-A18/GOG3047 NCT04221945	CRT vs CRT + pembrolizumab + maintenance pembrolizumab	PFS/OS
ATOMICC NCT03833479	CRT followed by NFT or maintenance dostarlimab (phase II)	PFS
KEYNOTE-826 NCT03635567	Cisplatin or carboplatin/paclitaxel +/- bev vs cisplatin or carboplatin/paclitaxel +/- bev + pembrolizumab (NO LONGER RECRUITING)	PFS/OS
FERMATA NCT03912415	C/T +/- bev vs C/T +/- bev + BCD-100	OS
BEATcc/GOG3030 NCT03556839	C/T/bev vs C/T/ bev + pembrolizumab	OS
innovaTV 301 NCT04697628	Tisotumab vedotin vs chemotherapy in recurrent or metastatic cervical cancer	OS

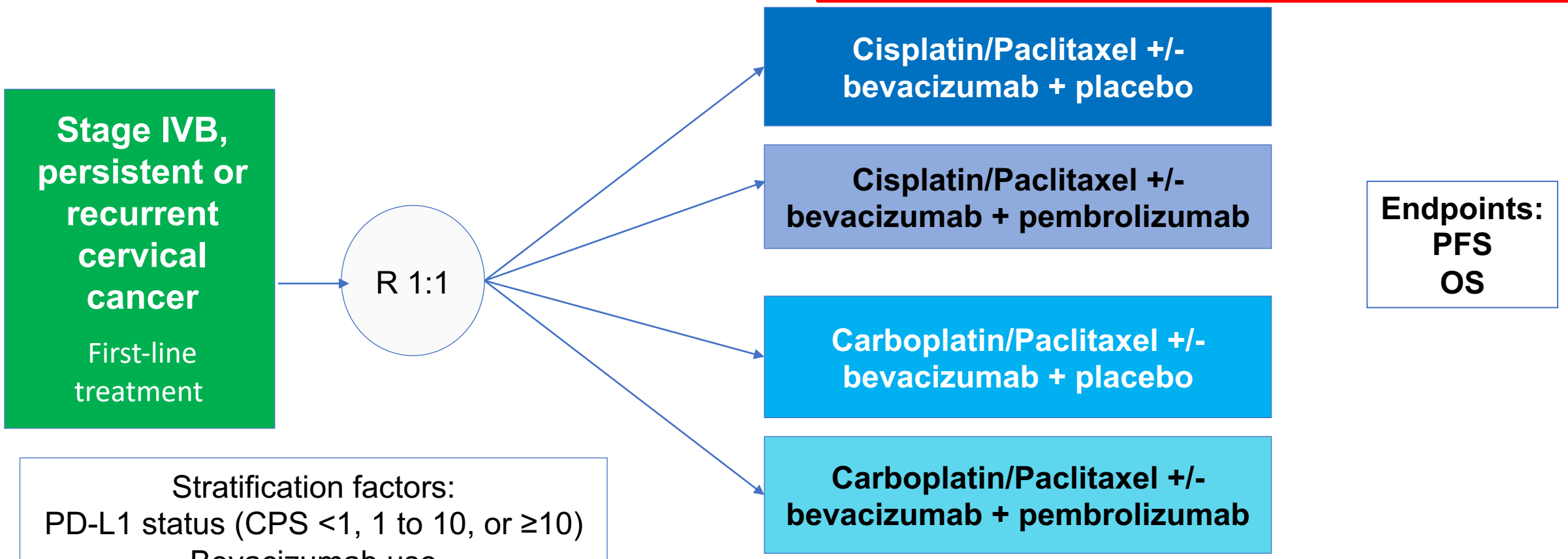
https://clinicaltrials.gov Accessed 06/18/2021

Courtesy of Angeles Alvarez Secord, MD, MHSc

KEYNOTE 826: Schema

Phase 3 KEYNOTE-826

Trial Met Dual Primary Endpoints of Overall Survival (OS) and Progression-Free Survival (PFS) in Patients With Persistent, Recurrent or Metastatic Cervical Cancer June 22, 2021 6:45 am ET



NCT03635567

Shapira-Frommer R. ASCO 2019.

Courtesy of Angeles Alvarez Secord, MD, MHSc

Balstilimab (PD-1 Inhibitor) +/- Zalifrelimab (CTLA-4 inhibitor)

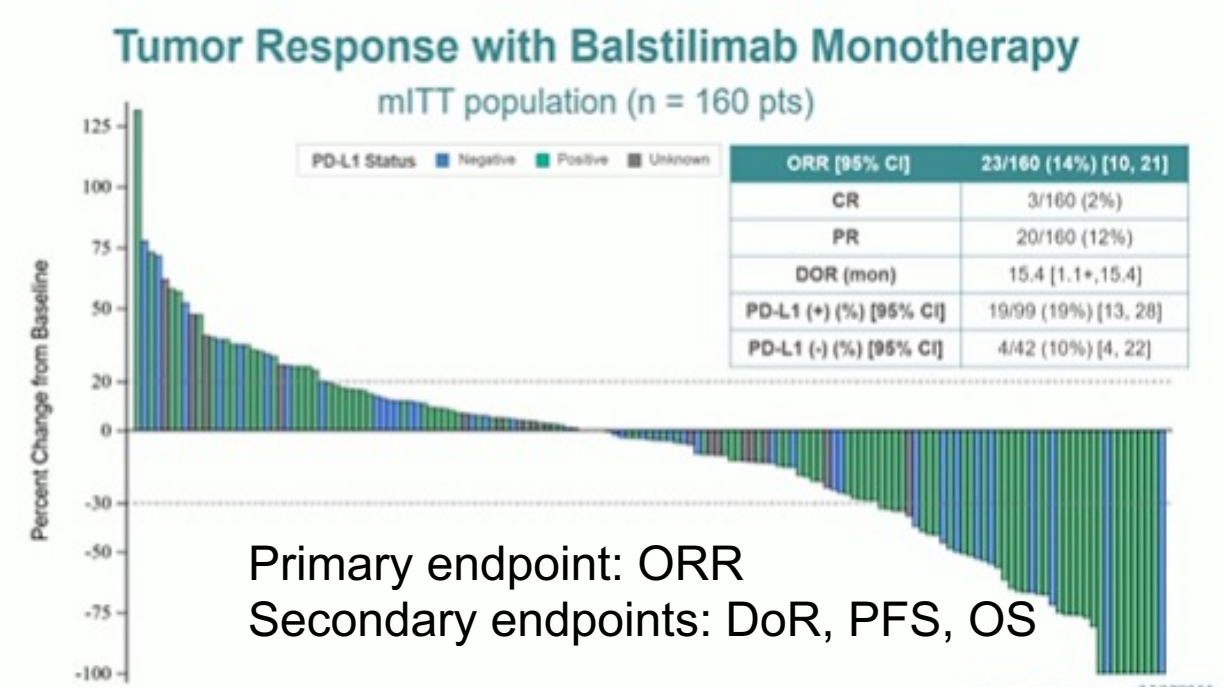
Balstilimab 3 mg/kg q2w

- 161 patients; 138 with prior chemo
  - 99% received only one prior line
  - 33% prior bevacizumab
- CPS≥1% in 61%
- All grade immune AEs: 30%
- Treatment discontinuation 13.7%

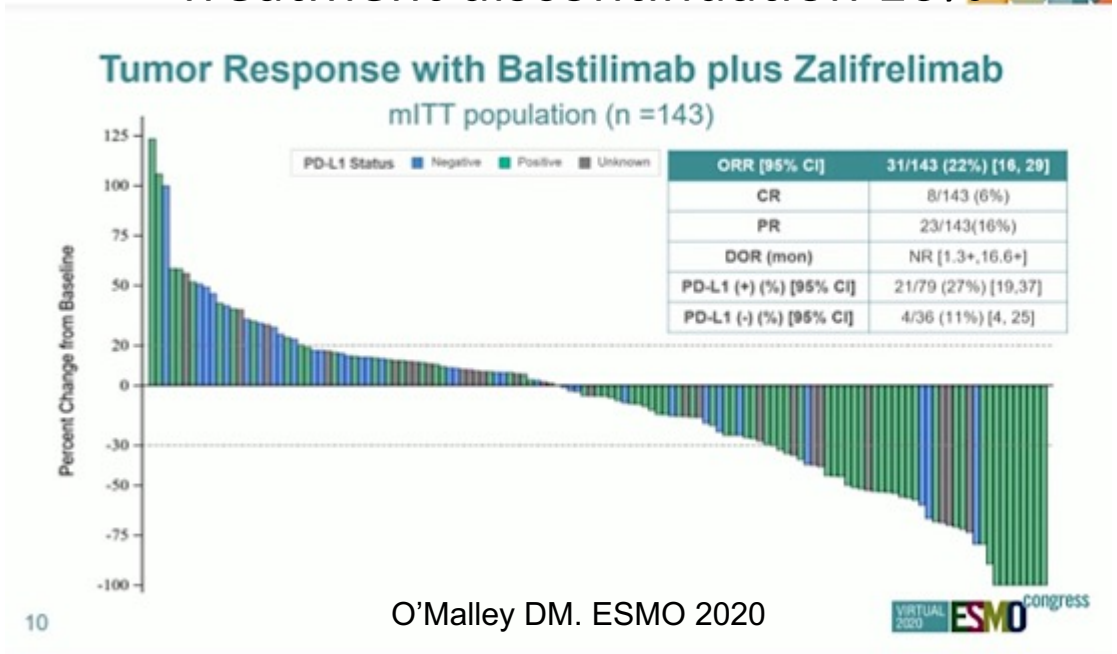
ORR: 14% vs 22%
DoR: 15.4 vs not reached

Balstilimab 3 mg/kg q2w + Zalifrelimab 1 mg/kg q6w

- 143 patients evaluable
  - 97% with one prior regimen
  - 37% with prior bevacizumab
- CPS ≥1% in 51%
- All grade immune AEs: 35%
- Treatment discontinuation 10%



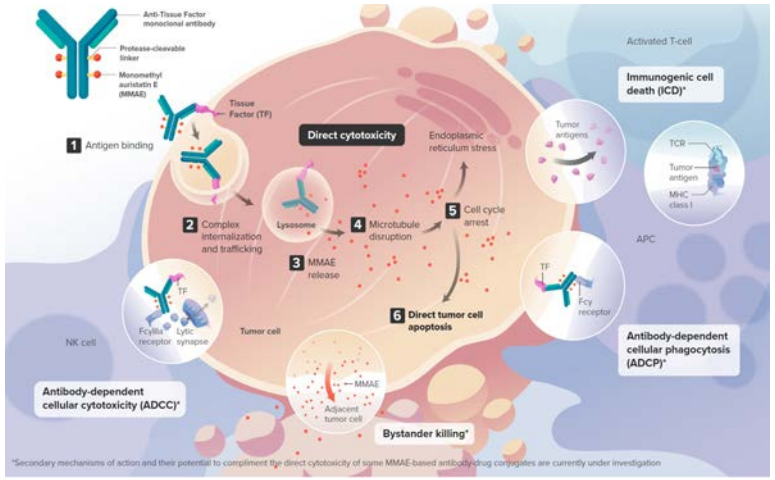
Primary endpoint: ORR
Secondary endpoints: DoR, PFS, OS



O'Malley DM. ESMO 2020

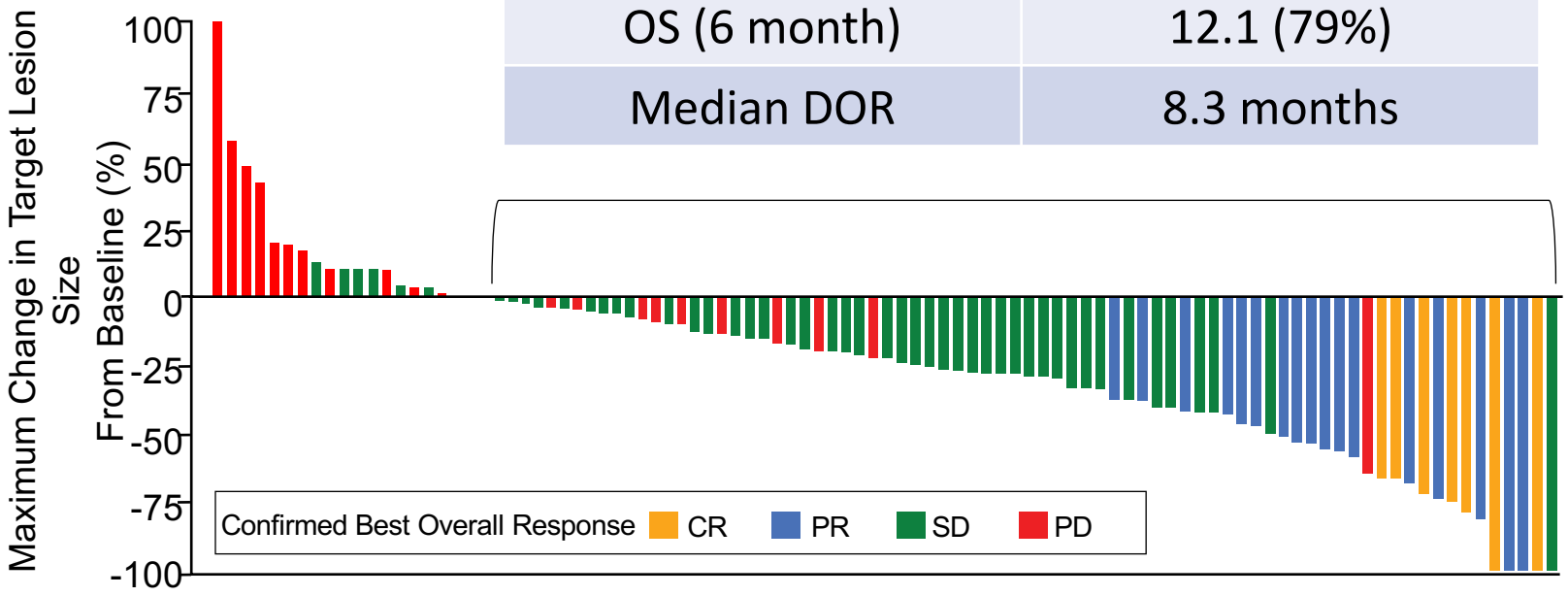
Courtesy of Angeles Alvarez Secord, MD, MHSc

Tisotumab Vedotin: InnovaTV 204



- Phase II: InnovaTV 204
  - Prior chemotherapy
    - 70% 1 prior
    - 30% 2 priors
  - 54% with prior chemoRT
  - 63% with prior bevacizumab
  - 56% did not respond to prior chemo regimen

Efficacy	Tisotumab
ORR	24%
CR	7%
PR	17%
SD	49%
PFS (6 month)	4.2 (34%)
OS (6 month)	12.1 (79%)
Median DOR	8.3 months



Most responses within first two cycles

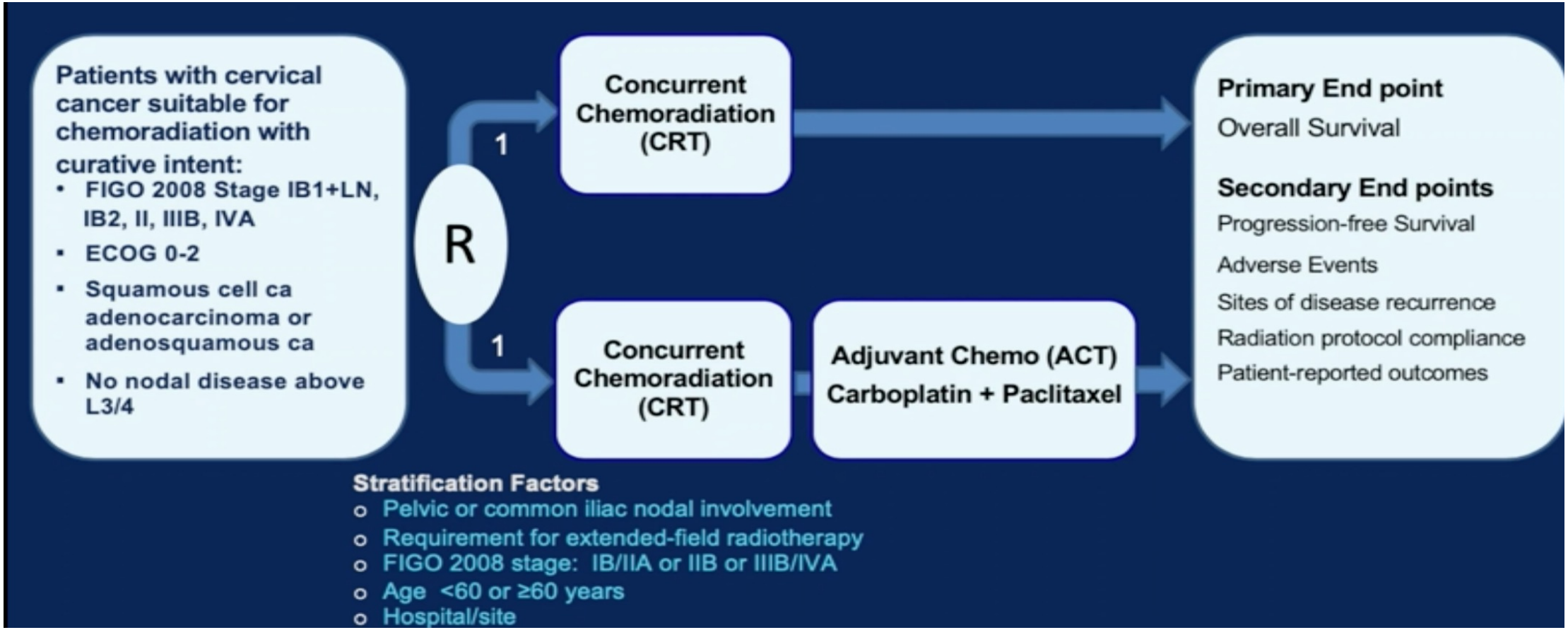
Adverse events: Alopecia, epistaxis, nausea, fatigue, ocular toxicity.
13% discontinuation rate

Coleman RL. Lancet 2021. Hong DS. Clin Cancer Res 2020.

Courtesy of Angeles Alvarez Secord, MD, MHSc

OUTBACK: Schema

Adjuvant chemotherapy following chemo-radiation as primary treatment for locally advanced cervical cancer compared to chemo-radiation alone: The randomised phase 3 OUTBACK Trial (ANZGOG 0902, RTOG 1174, NRG 0274)

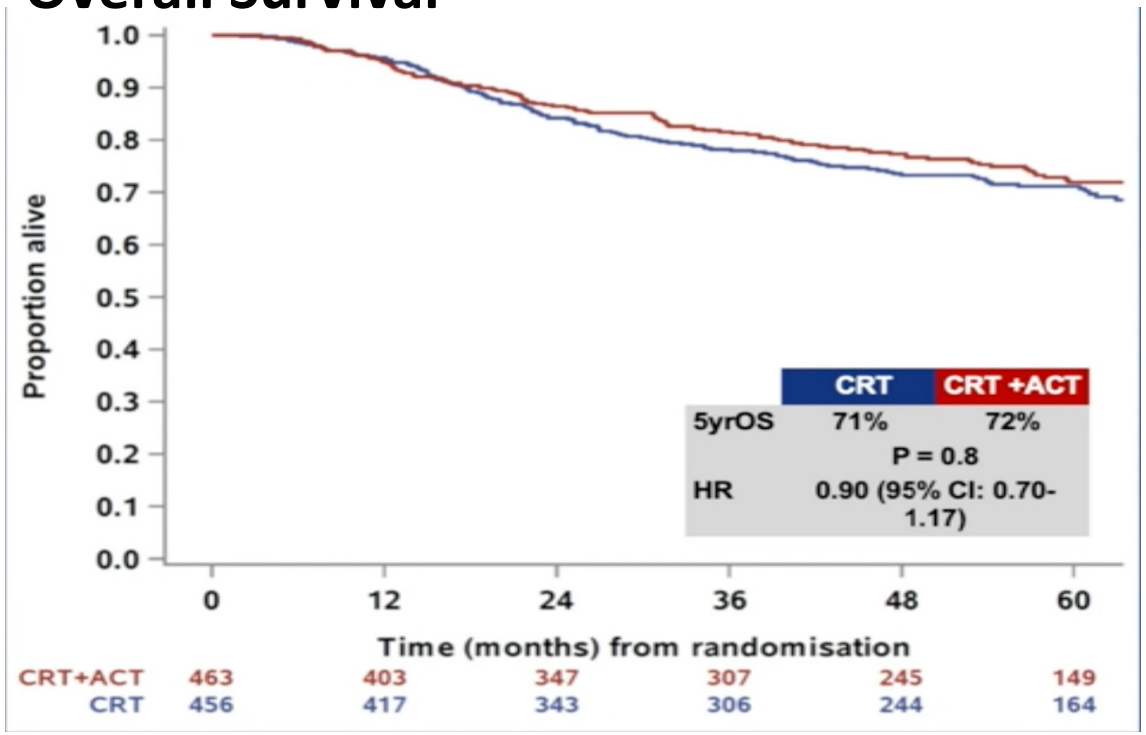


Mileshkin L ASCO 2021

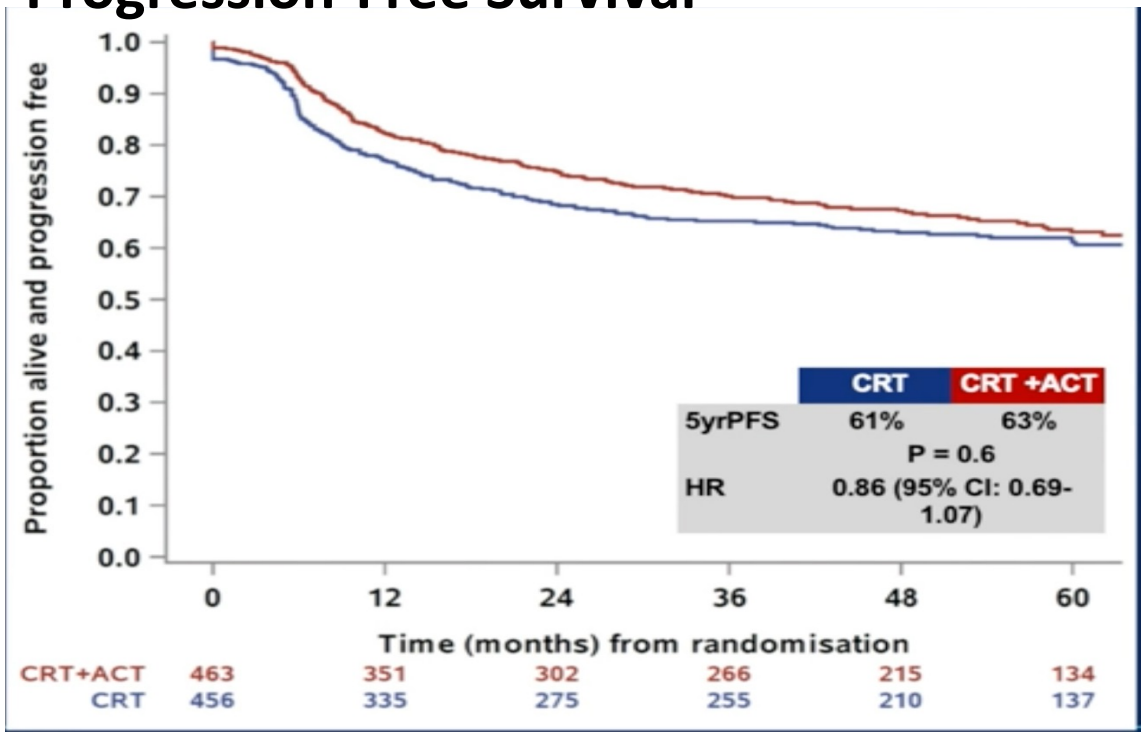
Courtesy of Angeles Alvarez Secord, MD, MHSc

OUTBACK: Survival Outcomes

Overall Survival



Progression-Free Survival



Sensitivity Analysis

	Rates at 5 years (%) CRT	CRT +ACT	Difference (95% CI)	P	Hazard ratios from Cox regressions (95% CI)	P	Interaction P
Overall survival							0.11
Completed CRT	71	74	+3.3 (-4 to 11)	0.37	0.81 (0.60-1.08)	0.15	
Did not complete CRT	73	64	-9.2 (-24 to 5)	0.21	1.32 (0.77-2.25)	0.32	
Progression-Free Survival							0.12
Completed CRT	62	66	+4.8 (-3 to 12)	0.22	0.78 (0.60-1.00)	0.05	
Did not complete CRT	60	51	-8.6 (-23 to 6)	0.26	1.16 (0.75-1.80)	0.49	

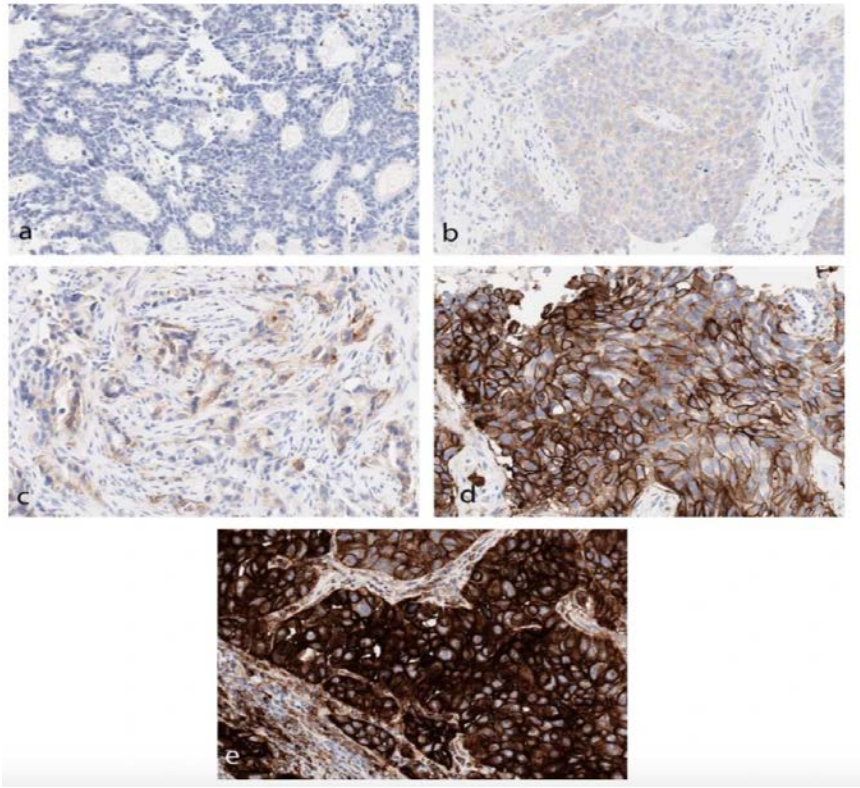
Mileshkin L ASCO 2021

Courtesy of Angeles Alvarez Secord, MD, MHSc

Case Presentation – Dr Secord: A 35-year-old woman with Stage IB cervical cancer

- 35 y.o. G1P1 with a h/o stage Ib invasive squamous cell carcinoma s/p RA radical hysterectomy, PA&PLND and oophoropexy and adjuvant CRT.
- 5 years later imaging revealed right middle lobe spiculated nodule with confirmed lung biopsy c/w recurrent squamous cell carcinoma
- Treated carboplatin/paclitaxel/bevacizumab but discontinued due to dose-limiting cytopenia.
- She presented for a second opinion. CT imaging demonstrated progressive disease with new lung nodules, pleural effusion, and metastatic disease to the ribs.
    - PD-L1 > 1% lung biopsy.

PD-L1 staining



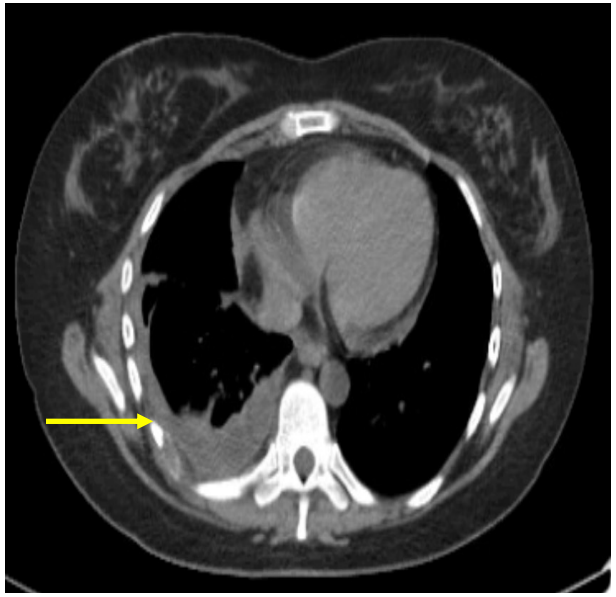
- Combined positive score (CPS)
    - Number of PD-L1 staining cells (tumor cells + immune cells ie. lymphocytes, macrophages) to all tumor cells
    - CPS ≥ 1% used for cervical cancer
- Tumor proportion score (TPS)
    - Ratio of the number of PD-L1 expressing tumor cells to that of all tumor cells

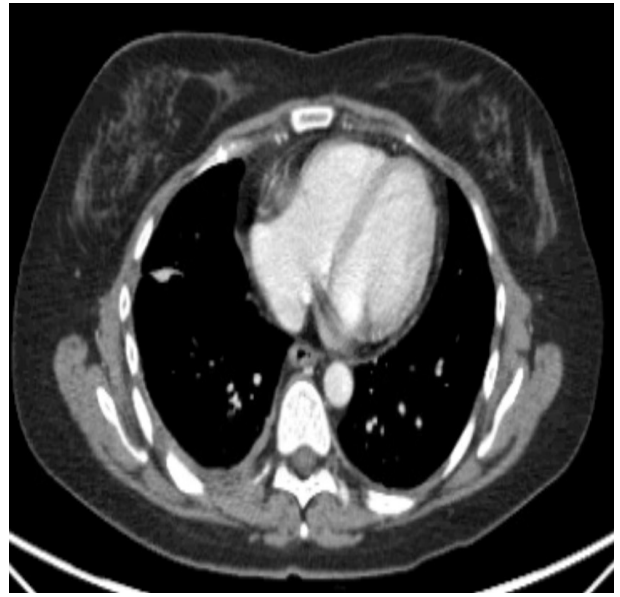
O'Malley EP, Modern Pathology 2019

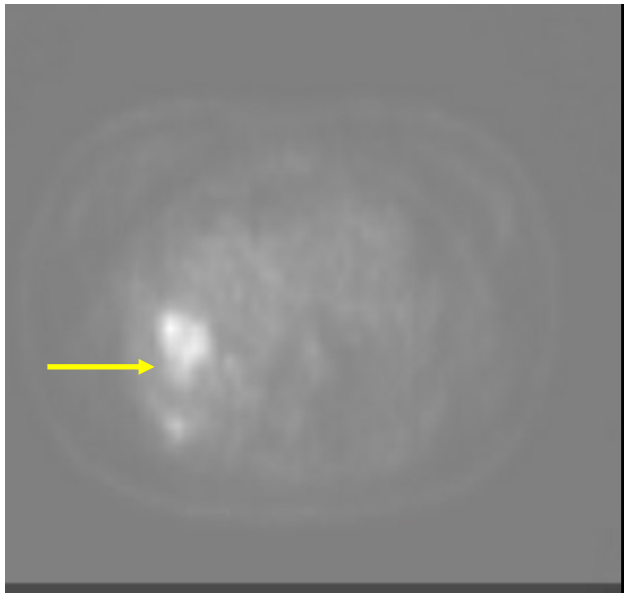
Courtesy of Angeles Alvarez Secord, MD, MHSc

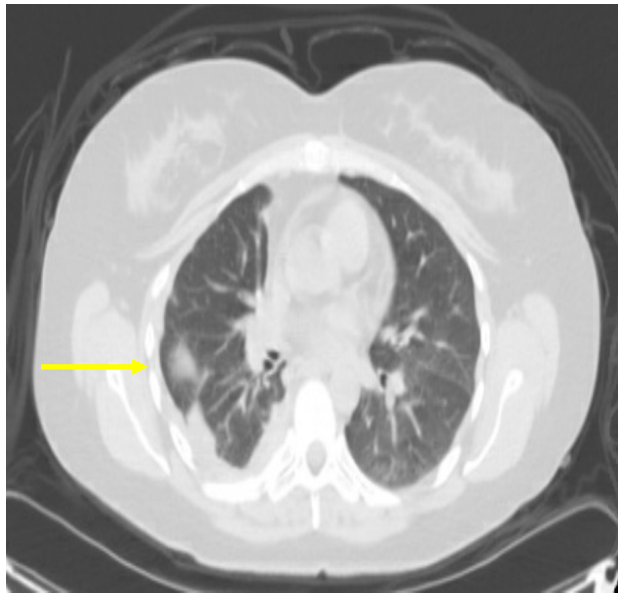
Case Presentation – Dr Secord: A 35-year-old woman with Stage IB cervical cancer (continued)

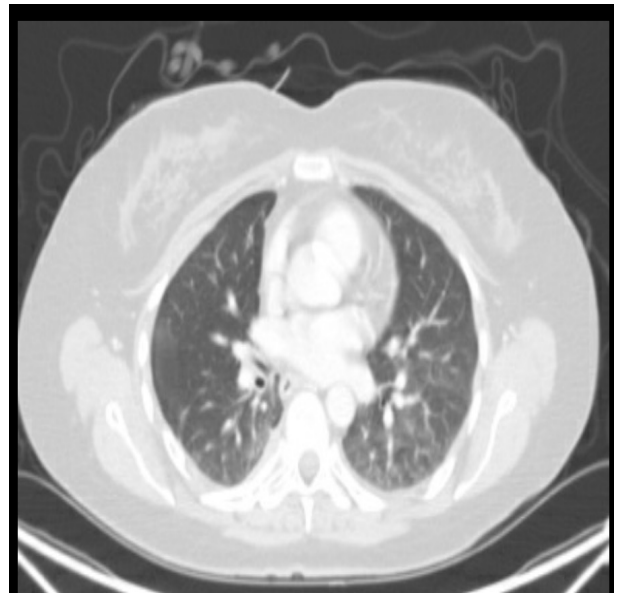
Pembrolizumab started. Repeat imaging after 3 months showed resolution of disease in the pleura and one lung nodule.







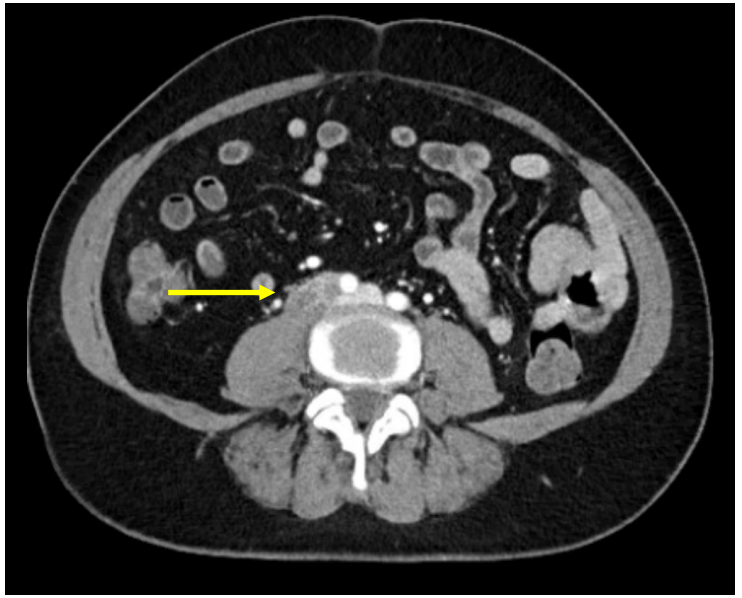


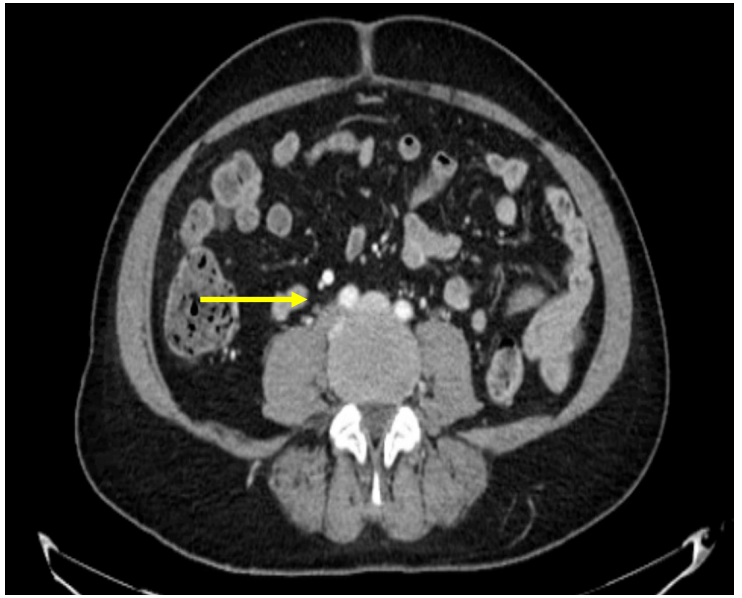


Courtesy of Angeles Alvarez Secord, MD, MHSc

Case Presentation – Dr Secord: A 45-year-old with metastatic cervical cancer

- 45 y.o. diagnosed with metastatic invasive squamous cell of the cervix with invasion of the uterus, lower vagina, urethra, pelvic lymph nodes, left ischium, bilateral inguinal lymphadenopathy.
- s/p palliative XRT to left ischial metastases and carboplatin/paclitaxel/bevacizumab x 8 cycles with excellent PR and near resolution of disease.
- CT c/a/p: Interval enlargement of a retroperitoneal lymph node ~3 cm
- Tumor testing: PD-L1 90% (positive)
- Goals of care reviewed and treatment options discussed.
- Cycle 1 pembrolizumab 400 mg IV q 6 weeks initiated.
- CT scan after 2 cycles demonstrated significant decreased adenopathy.
- Tolerating therapy well.





Courtesy of Angeles Alvarez Secord, MD, MHSc

Faculty Cases Appendix

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Case Presentation – Dr Mirza: A 44-year-old woman with Stage IIB cervical cancer

- *December 2017: 44 yrs old patient is diagnosed of FIGO IIB cervical cancer*
- *Initial workup including PETCT and MRI revealed pelvic disease (involving para cervical space with one PET positive pelvic node (right side). No extra-pelvic spread.*
- *Histology report: squamous cell carcinoma, HPV positive.*

- *No co-morbidity*
- *Heavy smoker*

- *Patient received External Beam Radiotherapy followed by brachytherapy with concomitant wkly cisplatin.*
- *Complete clinical remission and on PET-CT three months post treatment*

Courtesy of Mansoor Raza Mirza, MD

Case Presentation – Dr Mirza: A 44-year-old woman with Stage IIB cervical cancer (continued)

- *December 2017: 44 yrs old patient is diagnosed of FIGO IIB cervical cancer*
- *Initial workup including PETCT and MRI revealed pelvic disease (involving para cervical space with one PET positive pelvic node (right side). No extra-pelvic spread.*
- *Histology report: squamous cell carcinoma, HPV positive.*
- *No co-morbidity*
- *Heavy smoker*

- *Patient received External Beam Radiotherapy followed by brachytherapy with concomitant wkly cisplatin.*
- *Complete clinical remission and on PET-CT three months post treatment*

- *January 2020: multiple liver metastasis on CT scan.*
- *No >grade 1 late side effects of radiation therapy*
- *Normal EDTA*
- *No co-morbidity*
- *Performance status: 0*
- *Patient started on cisplatin-paclitaxel-bevacizumab*
- *Complete remission after 3 courses*
- *Paclitaxel dropped after 6 courses (neurotoxicity); cisplatin dropped after 8 courses (nephrotoxicity)*

Courtesy of Mansoor Raza Mirza, MD

Case Presentation – Dr Mirza: A 44-year-old woman with Stage IIB cervical cancer (continued)

- *December 2017: 44 yrs old patient is diagnosed of FIGO IIB cervical cancer*
- *Initial workup including PETCT and MRI revealed pelvic disease (involving para cervical space with one PET positive pelvic node (right side). No extra-pelvic spread.*
- *Histology report: squamous cell carcinoma, HPV positive.*
- *No co-morbidity*
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- *Patient received External Beam Radiotherapy followed by brachytherapy with concomitant wkly cisplatin.*
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- *Patient started on cisplatin-paclitaxel-bevacizumab*
- *Complete remission after 3 courses*
- *Paclitaxel dropped after 6 courses (neurotoxicity); cisplatin dropped after 8 courses (nephrotoxicity)*

- *May 2021: Patient progress with liver metastases on bevacizumab*

Courtesy of Mansoor Raza Mirza, MD

Case Presentation – Dr Mirza: A 44-year-old woman with Stage IIB cervical cancer (continued)

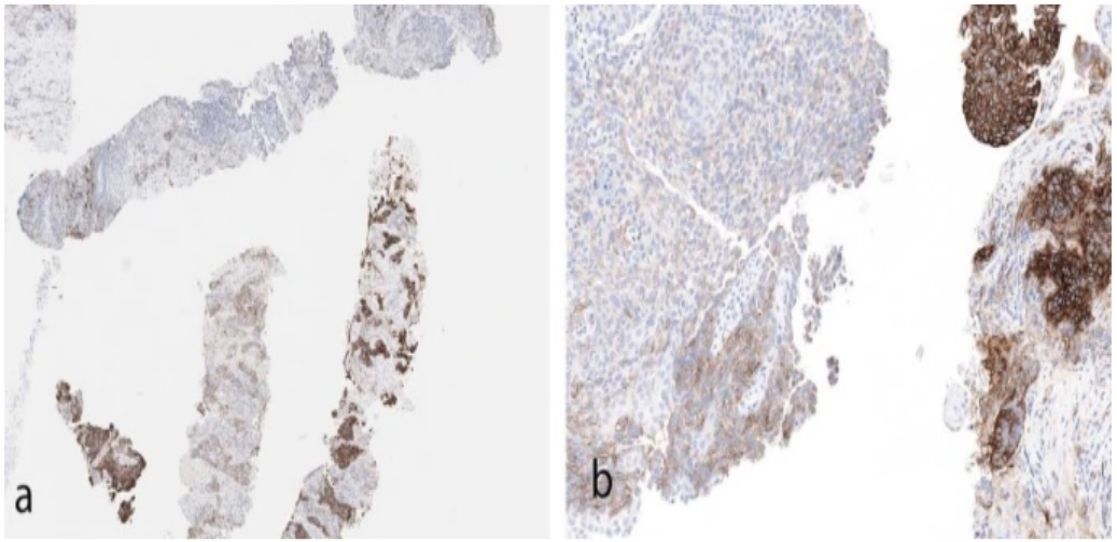
- *January 2020: multiple lever metastases on CT scan.*
- *No >grade 1 late side effects of radiation therapy*
- *Normal EDTA*
- *No co-morbidity*
- *Performance status: 0*
- *Patient started on cisplatin-paclitaxel-bevacizumab*
- *Complete remission after 3 courses*
- *Paclitaxel dropped after 6 courses (neurotoxicity); cisplatin dropped after 8 courses (nephrotoxicity)*
- *May 2021: Patient progress with liver metastases on bevacizumab*
- *PD-L1 positive*

- Patient is started on cemiplimab
- *No toxicity so far*
- *First tumour evaluation due end July*

Courtesy of Mansoor Raza Mirza, MD

Case Presentation – Dr Secord: A 31-year-old woman with recurrent cervical cancer

- 31 y.o. with h/o stage 1B1 adenocarcinoma of the cervix s/p RA-trachelectomy, cerclage, bilateral sentinel pelvic LND, R common iliac LND in 2015.
- 3 years later she was diagnosed with symptomatic bilateral pelvic masses. FNA of the pelvic masses revealed mucinous adenocarcinoma. She underwent XL, BSO, omentectomy. Final pathology consistent with recurrent cervical cancer.
- Initiated cisplatin/paclitaxel/ and bevacizumab added cycle 2. Achieved a CR and continued on maintenance bevacizumab after having a platin reaction and difficulty tolerating paclitaxel.
- After 5 months bevacizumab maintenance CT demonstrated peritoneal implants, pulmonary nodules, and adenopathy.
- Foundation Medicine testing: PD-L1 negative: *KRAS* mutation



Examples (**a**, **b**) of intratumoral variation in PD-L1 staining intensity from 0 to 3+ (22C3)

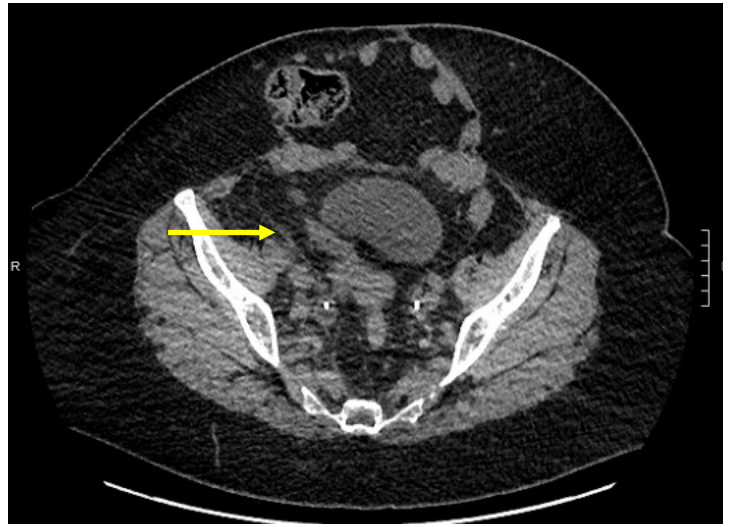
Courtesy of Angeles Alvarez Secord, MD, MHSc

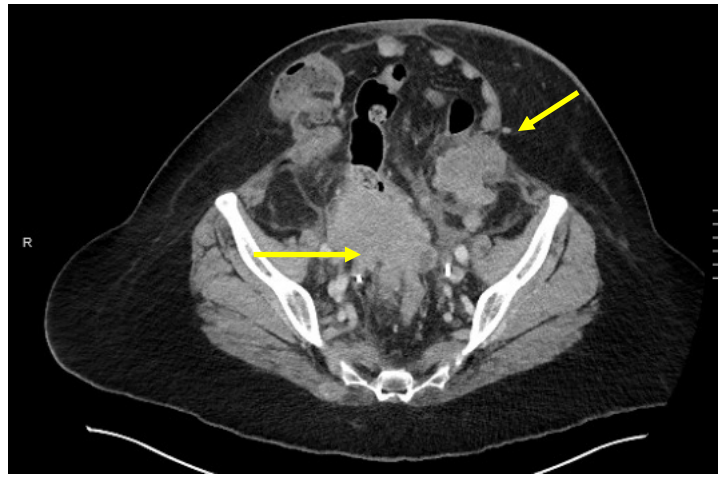
O'Malley EP, Modern Pathology 2019

Case Presentation – Dr Secord: A 31-year-old woman with recurrent cervical cancer (continued)

- Clinical trial with durvalumab + experimental agent. PD after initial cycle.
- Repeat A PD-L1 stain obtained at outside hospital demonstrated CPS>1. “This score is based on the presence of several aggregates of lymphocytes within the tumor showing membranous staining.”
- Initiated pemetrexed and folic acid and had sustained SD to PR. After 8 cycles diagnosed with PD
- Initiated Ipilimumab 3mg/kg /Nivolumab 1mg/kg for 2 cycles. PD
- CT scan: Increasing size of primary pelvic mass and extensive carcinomatosis and adenopathy
- Palliative radiation
- Initiated trametinib 1.5mg PO daily but discontinued after cycle #2 due to significant decrease in EF to 30%.
- Held drug 4 weeks and repeated ECHO but still not improved and trametinib discontinued.
- Goals of care discussion and transitioned to Hospice

CT scans on Ipilimumab/Nivolumab





Courtesy of Angeles Alvarez Secord, MD, MHSc

What General Medical Oncologists Want to Know About Targeted Therapy for Non-Small Cell Lung Cancer

Tuesday, July 27, 2021
5:00 PM – 6:00 PM ET

Faculty

Professor Solange Peters, MD, PhD
Zofia Piotrowska, MD, MHS
Gregory J Riely, MD, PhD

Moderator

Neil Love, MD

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 2-3 business days.

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