Research To Practice

February 18, 2023

Charlotte, NC

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Discussion Question

How are you incorporating anti-PD-1/PD-L1 antibodies into the management of microsatellite instability-high/mismatch repair-deficient advanced endometrial cancer? How do you choose between pembrolizumab and dostarlimab for these patients?

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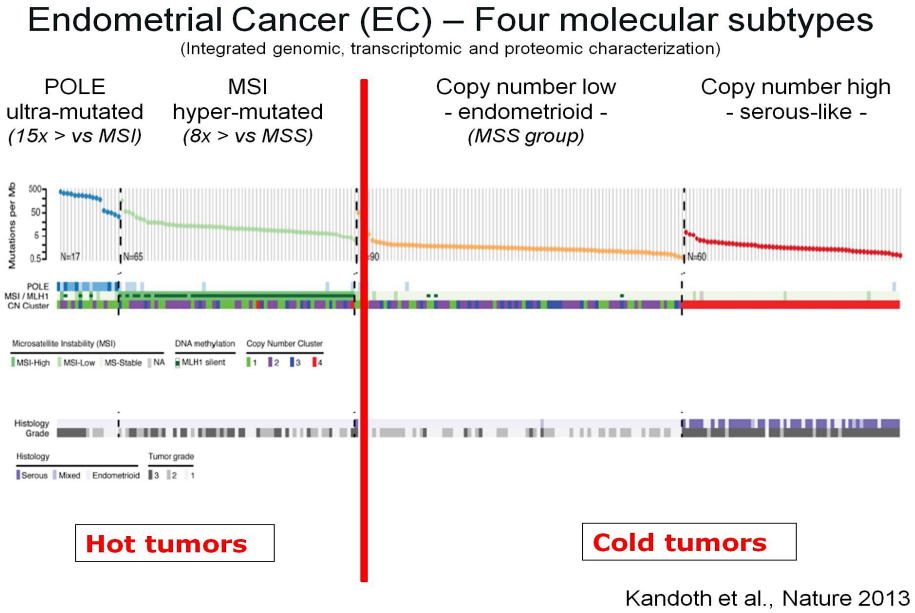
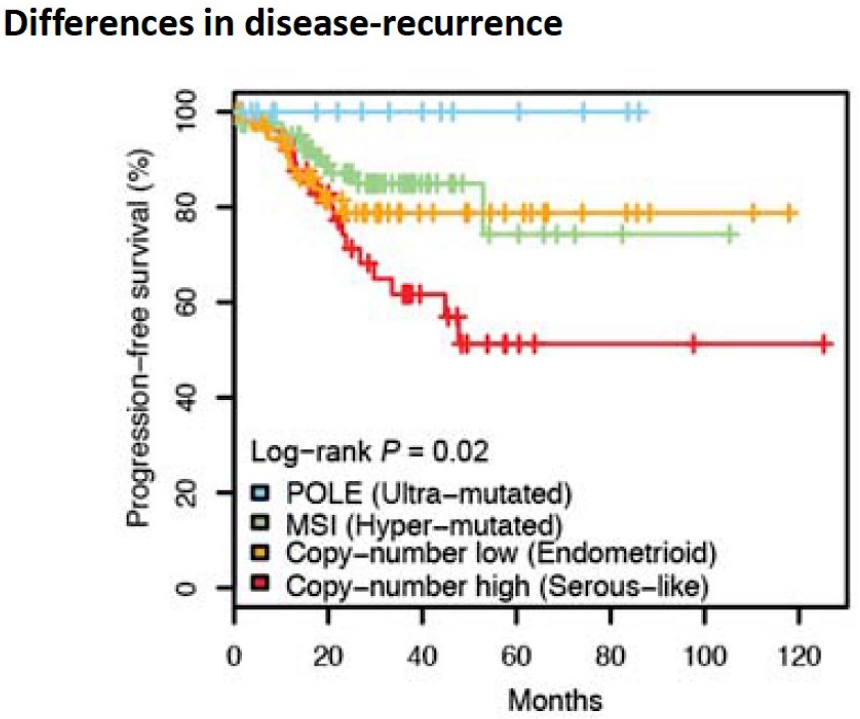
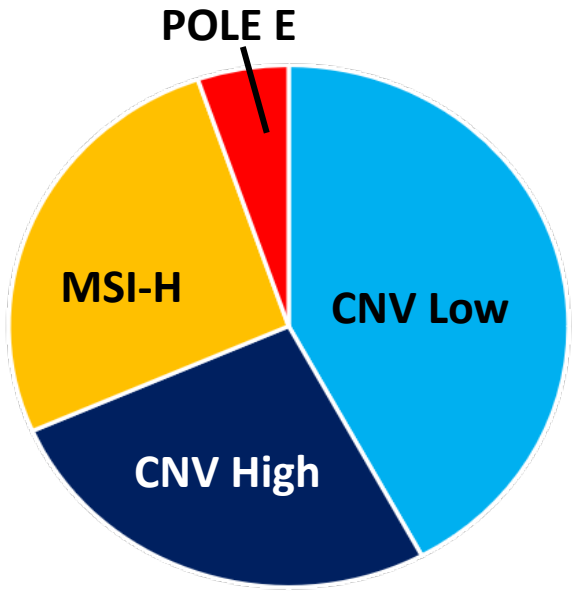
How does MSI-H/dMMR fit into Endometrial Cancer?



Kandoth et al., Nature 2013

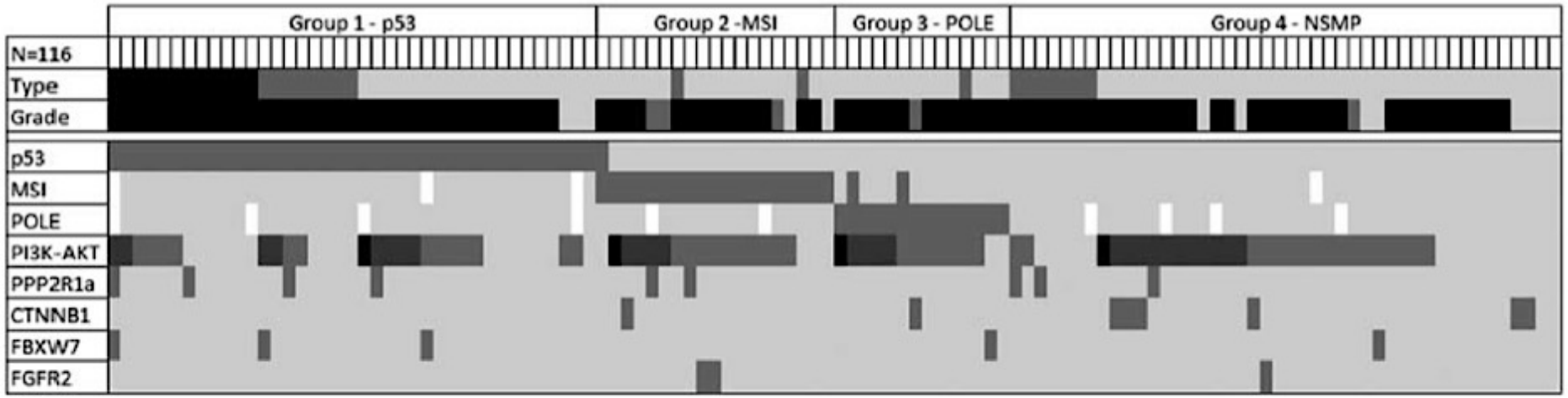


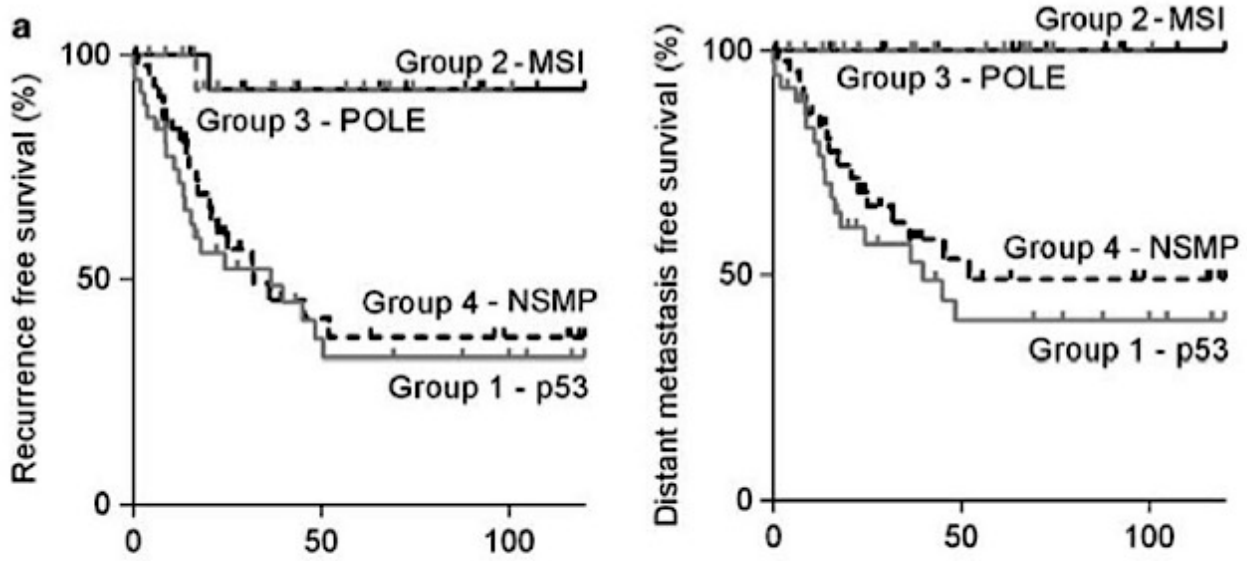


Nature. 2013;497(7447):67-73

Courtesy of Michael J. Birrer

Confirmation of TCGA Molecular subgroups

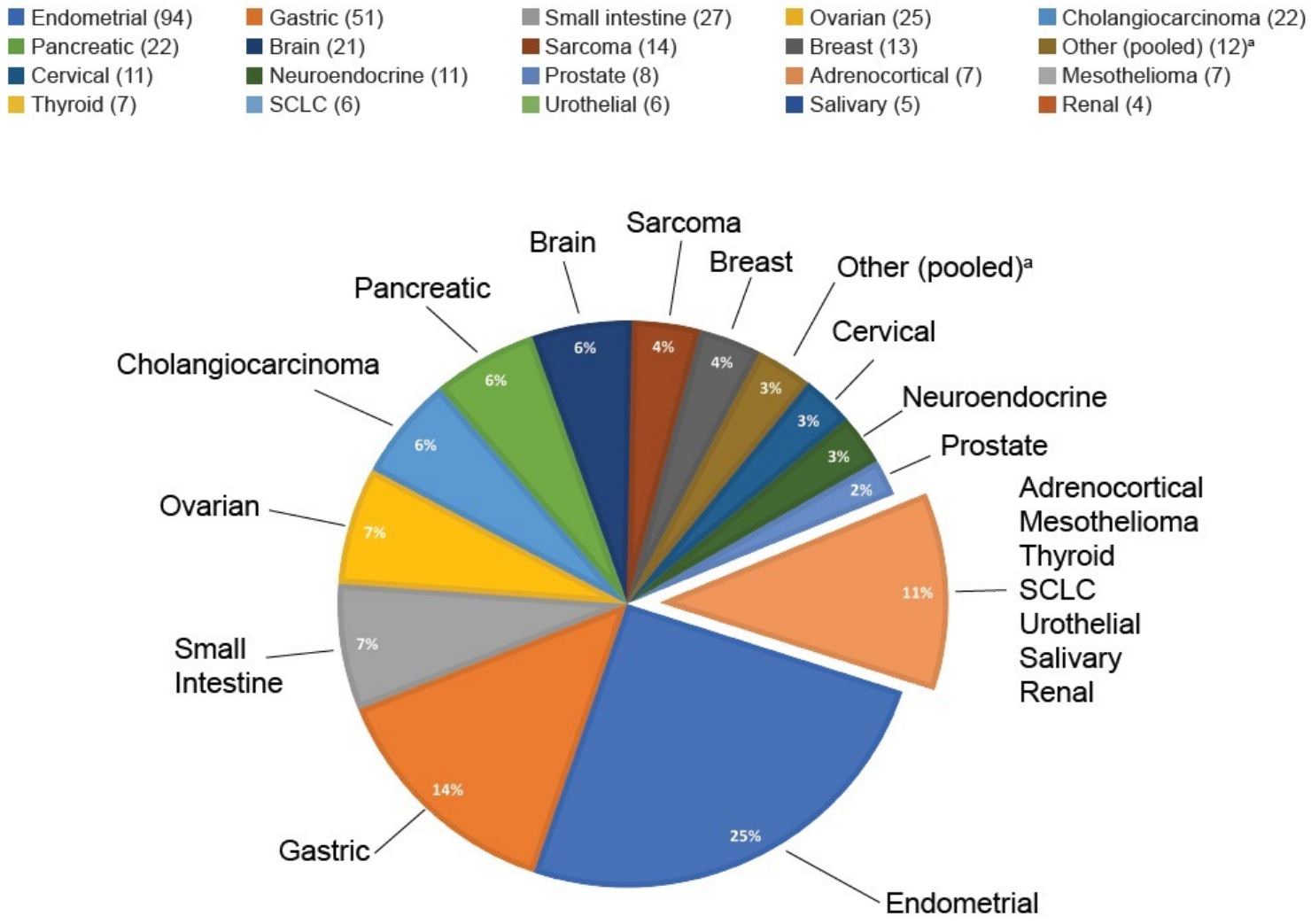




Stelloo et al, *EMBO Molecular Medicine*, 2015, doi: 10.15252

Courtesy of Michael J. Birrer

KEYNOTE-158: It Changed Everything for MSI-H Tumors



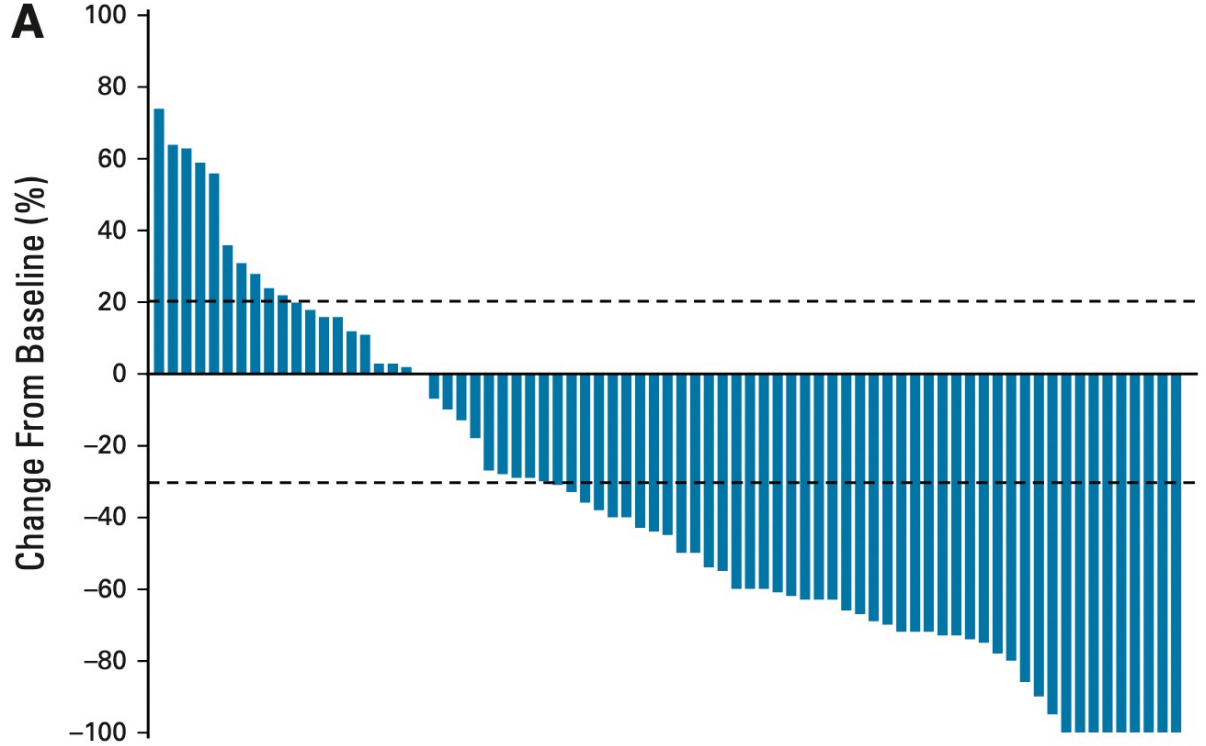
Maio M et al. ESMO 2022;Abstract 113P.

Courtesy of Michael J. Birrer

KEYNOTE-158: It Changed Everything for MSI-H Tumors

Pembrolizumab in Patients With Microsatellite Instability–High Advanced Endometrial Cancer: Results From the KEYNOTE-158 Study

David M. O'Malley, MD[1]; Giovanni Mendonca Bariani, MD[2]; Philippe A. Cassier, MD[3]; Aurelien Marabelle, MD, PhD[4]; Aaron R. Hansen, MBBS[5]; Ana De Jesus Acosta, MD[6]; Wilson H. Miller Jr, MD, PhD[7,8]; Tamar Safra, MD[9,10]; Antoine Italiano, MD, PhD[11,12]; Linda Mileshkin, MBBS[13]; Lei Xu, PhD[14]; Fan Jin, MD[14]; Kevin Norwood, MD[14]; and Michele Maio, MD[1]

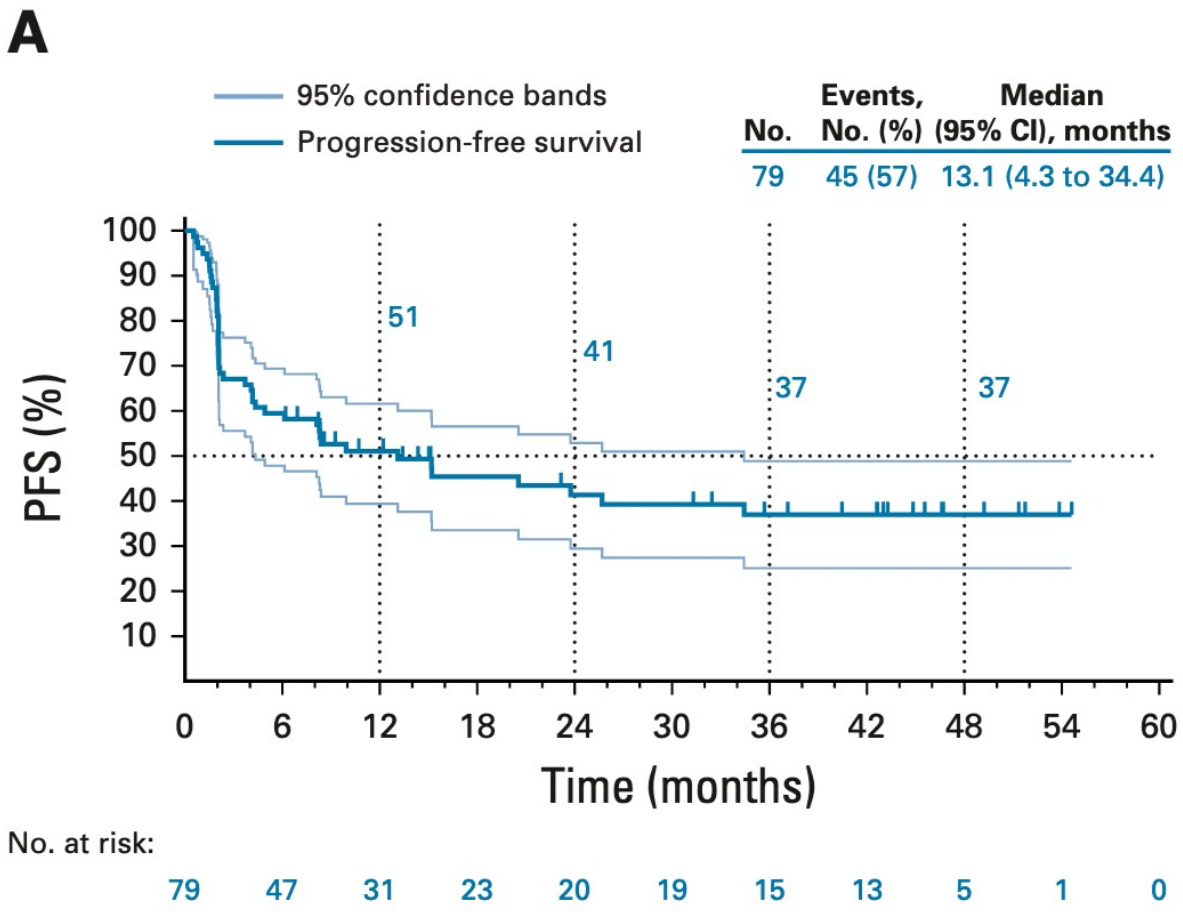


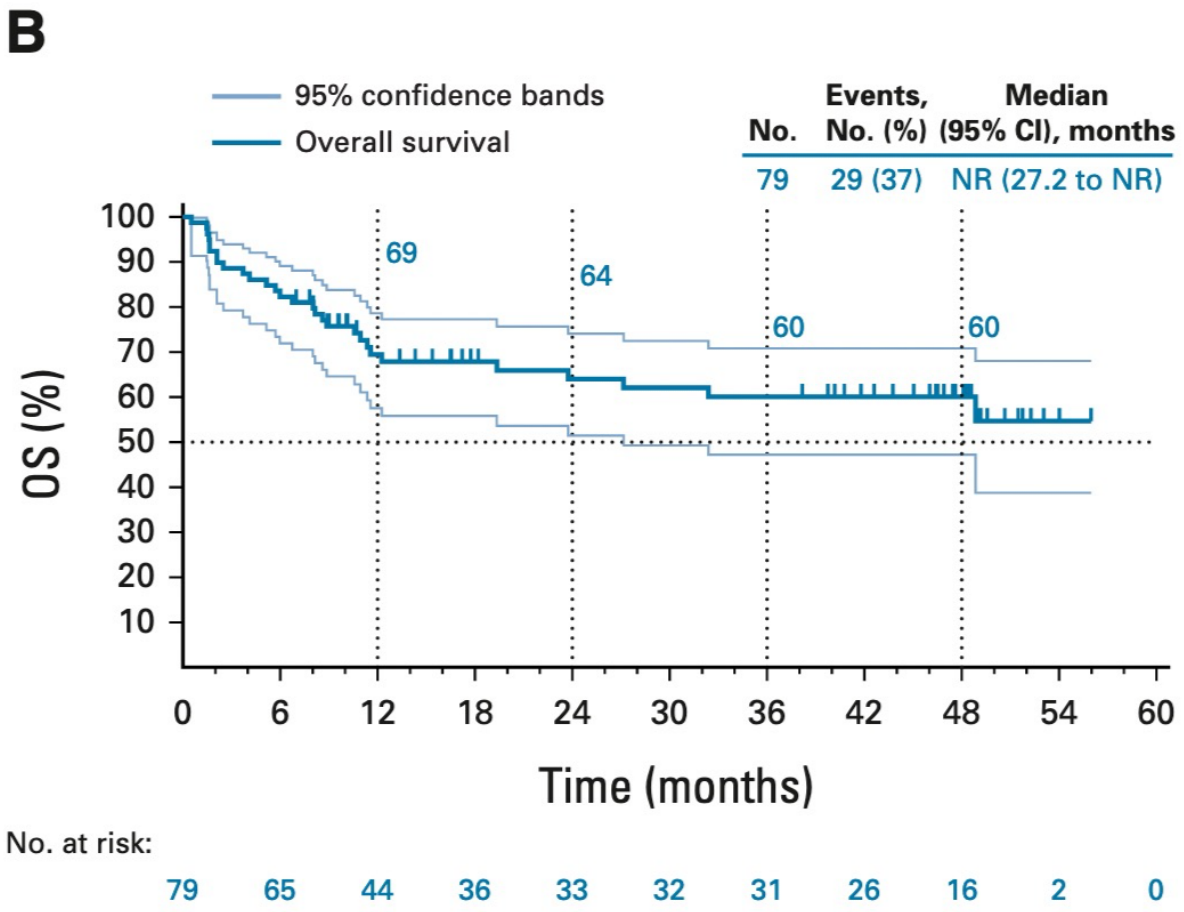
Among 79 patients in the efficacy analysis population, 48% (95% CI, 37 to 60) had an objective response as determined by independent central radiologic review, including 11 patients (14%) with CR and 27 (34%) with PR

O'Malley et. al, *Journal of Clinical Oncology* 2022; 40:7, 752-761.

Courtesy of Michael J. Birrer

Keynote 158 – Longer Follow-up data





O'Malley et. al, *Journal of Clinical Oncology* 2022; 40:7, 752-761

Courtesy of Michael J. Birrer

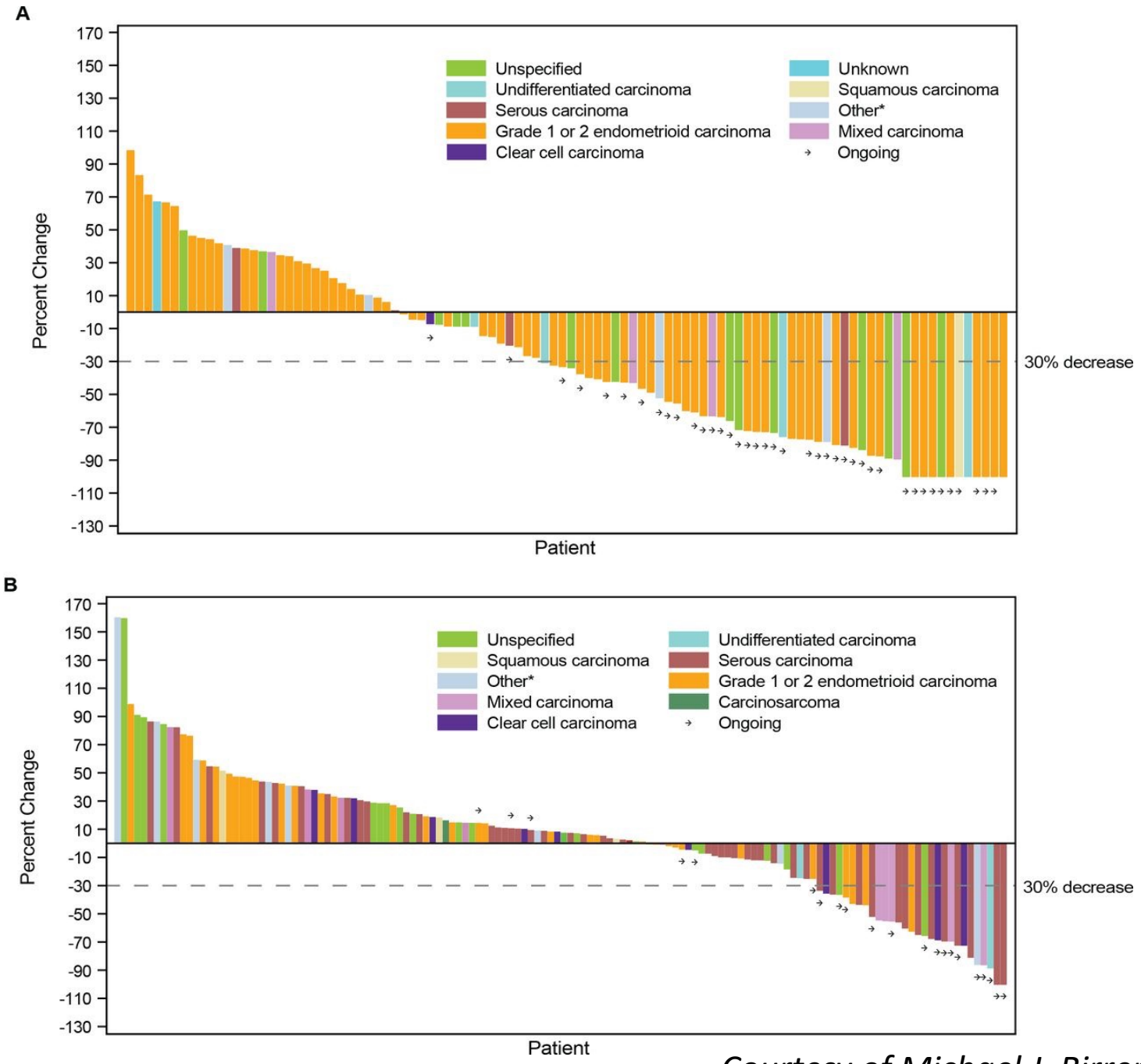
Role of IO in Endometrial Cancer

- All patients with advance stage disease should have MMR testing
- MMR testing is usually IHC for MLH1, MHL2, MSH6 and PMS2 done locally or commercially
- MMR testing can be MSI using 5 microsatellites and scored high or low
- Recurrent or metastatic disease - IO for MSI-H or dMMR - **category 1** (NCCN 2023)
- Phase III NRG-GY018: Pembrolizumab/chemo improves PFS, regardless of MMR status in Stage III-IV or recurrent disease
- Remember the Ruby Trial (moving IO earlier) – early report is that the trial is positive

Courtesy of Michael J. Birrer

Garnet Trial

- Anti-PD1 therapy (dostarlimab) in recurrent/ metastatic endometrial cancer
- Single ARM phase 1 with expansion cohorts
- Large numbers of dMMR (A) and MMRp (B)



Oaknin A et al. ASCO 2022;Abstract 5509.

Courtesy of Michael J. Birrer

Dealer's Choice?

Pembrolizumab

- Longest in clinical use
- Used in many tumors
- High affinity for target
- Dosing at Q6 weeks
- Typical autoimmune toxicities
- Category 1 first line

versus

Dostarlimab

- Only anti-PD1 tested for Q6 weeks
- Used in many tumors
- High affinity for target
- Dosing at Q6 weeks (first)
- Typical autoimmune toxicities
- Category 1 second line

Courtesy of Michael J. Birrer

Discussion Question

How are you incorporating pembrolizumab/lenvatinib into the management of microsatellite-stable advanced endometrial cancer?

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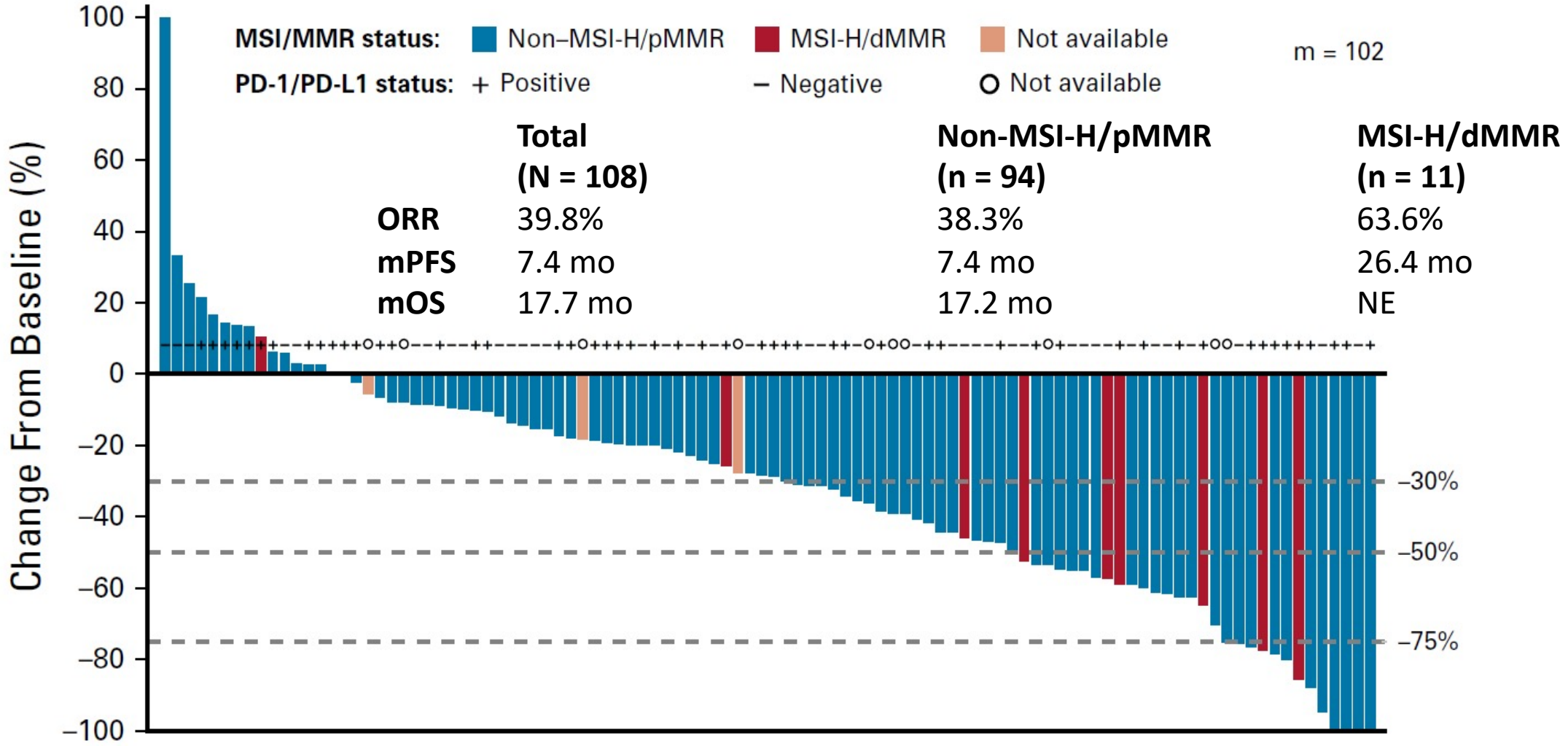
Phase I/II KEYNOTE-146: Lenvatinib Plus Pembrolizumab in Patients with Advanced Endometrial Cancer



	Total (N = 108)	Non-MSI-H/pMMR (n = 94)	MSI-H/dMMR (n = 11)
ORR	39.8%	38.3%	63.6%
mPFS	7.4 mo	7.4 mo	26.4 mo
mOS	17.7 mo	17.2 mo	NE

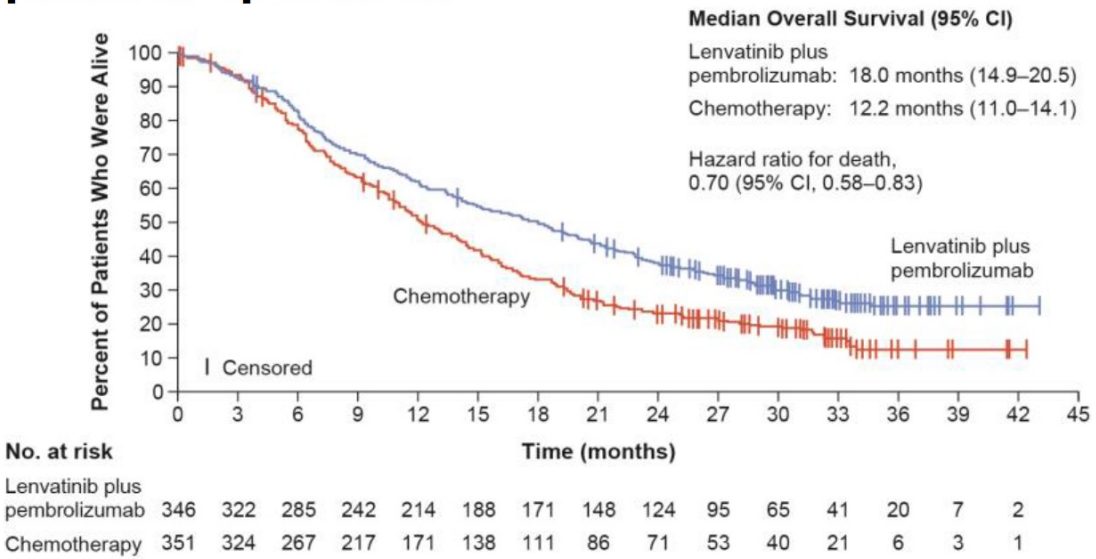
Makker V et al. *J Clin Oncol.* 2020;38:2981-2992; *J Clin Oncol* 2023;41:974-979.

Courtesy of Michael J. Birrer

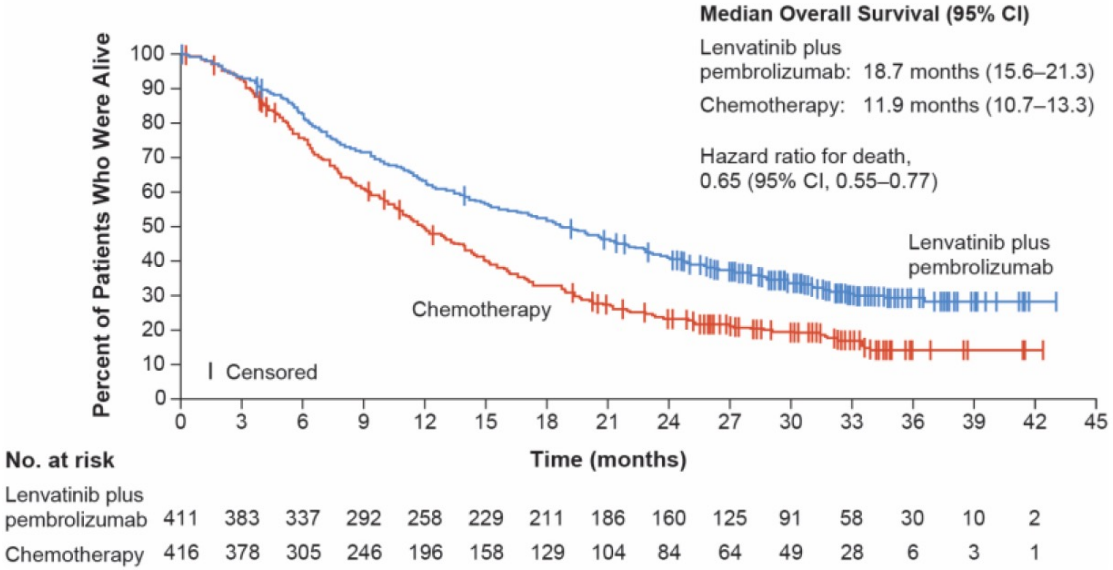
Lenvatinib Plus Pembrolizumab in Patients with Advanced Endometrial Cancer

- Keynote 775 Trial
- Randomized Phase III trial in recurrent endometrial cancer testing len/pem versus SOC chemotherapy

pMMR Population



All-Comer Population



Makker V et al. ESMO 2022; Abstract 525MO.

Courtesy of Michael J. Birrer

What is the role for Lenvatinib/Pembrolizumab for Endometrial Cancer

- Lenvatinib/Pembrolizumab is the standard of care for recurrent/metastatic endometrial **MMRp** patients (first line - Category 1 NCCN)
- The early phase trial showed ORR of approximately 50% with a clinical benefit rate of approximately 75%
- Keynote 775 showed both a PFS and OS advantage for Lenvatinib/Pembrolizumab over standard of care chemotherapy

Courtesy of Michael J. Birrer

Discussion Question

How do you monitor for and manage common adverse events associated with pembrolizumab/lenvatinib in patients with endometrial cancer? How do you approach initial dosing of lenvatinib?

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What about toxicity?

Preferred Term[a]	LEN + pembro (n = 406)		Chemotherapy (n = 388)	
	Any grade	Grade ≥ 3[b]	Any grade	Grade ≥ 3[b]
TEAEs, n (%)	405 (99.8)	366 (90.1)	386 (99.5)	286 (73.7)
Hypertension	264 (65.0)	159 (39.2)	20 (5.2)	10 (2.6)
Hypothyroidism	239 (58.9)	6 (1.5)	3 (0.8)	0 (0.0)
Diarrhea	226 (55.7)	33 (8.1)	79 (20.4)	8 (2.1)
Nausea	210 (51.7)	14 (3.4)	180 (46.4)	5 (1.3)
Decreased appetite	189 (46.6)	31 (7.6)	83 (21.4)	2 (0.5)
Vomiting	153 (37.7)	12 (3.0)	82 (21.1)	10 (2.6)
Weight decreased	144 (35.5)	44 (10.8)	23 (5.9)	1 (0.3)
Fatigue	138 (34.0)	22 (5.4)	107 (27.6)	12 (3.1)
Arthralgia	131 (32.3)	7 (1.7)	31 (8.0)	0 (0.0)
Proteinuria	124 (30.5)	21 (5.2)	13 (3.4)	1 (0.3)
Treatment-related TEAEs, n (%)[c]	395 (97.3)	320 (78.8)	364 (93.8)	233 (60.1)
Adverse events of special interest (for pembro), n (%)[d]	279 (68.7)	54 (13.3)	17 (4.4)	1 (0.3)
Clinically significant adverse events (for LEN), n (%)[d]	386 (95.1)	227 (55.9)	149 (38.4)	51 (13.1)
Dose interruption due to TEAE[e]	292 (71.9)	---	110 (28.4)	---
Dose reduction due to TEAE[f]	273 (67.2)	---	49 (12.6)	---
Treatment discontinuation due to TEAE[g]	159 (39.2)	---	31 (8.0)	---
Discontinuation of LEN	145 (35.7)	---	---	---
Discontinuation of pembro	90 (22.2)	---	---	---
Discontinuation of both LEN and pembro	65 (16.0)	---	---	---

Courtesy of Michael J. Birrer

How does one manage Lenvatinib/Pembrolizumab dosing and toxicity?

- FDA approved starting dose 20mg PO QD
- Final average final dose for Len in combination is 14mg PO
- Aggressive dose reduction is sometimes needed
- Hypertension occurs early (within 3 days) but can be controlled (consider prescriptions before starting)
- Diarrhea is of lower grade and manageable
- Fatigue is difficult and requires dose reduction
- Remember the importance of NPs and regular communication

Courtesy of Michael J. Birrer

Discussion Question

What do you make of recently presented findings with up-front maintenance selinexor for patients with metastatic endometrial cancer? Are there currently any situations in which you would use this strategy outside of a clinical trial?

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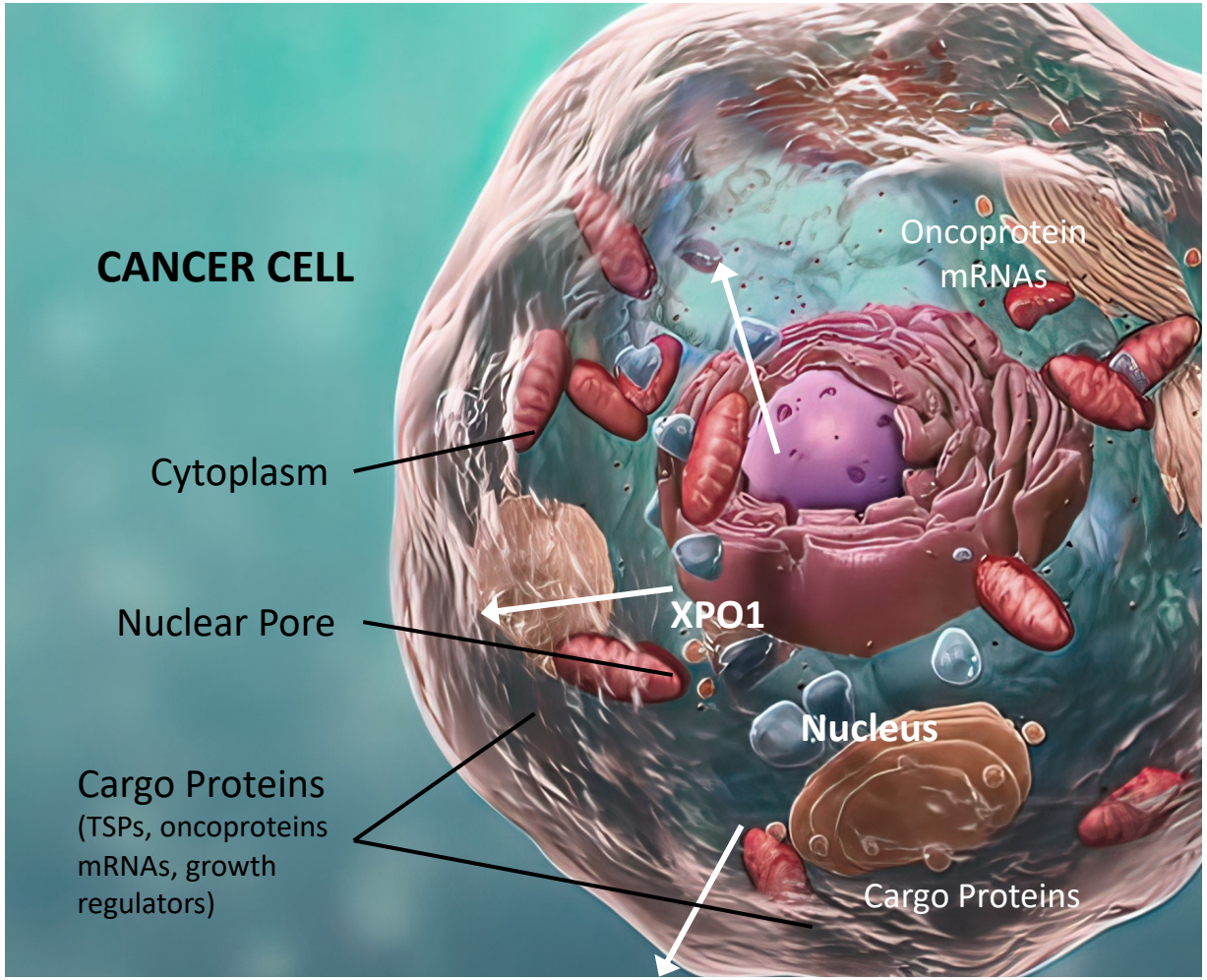
Selinexor: New and Novel Therapeutic Agent



- Selinexor is an oral selective inhibitor of XPO1 mediated nuclear export
- XPO1 exports tumor suppressor proteins including p53
- This leads to the accumulation of nuclear p53 which is wild type will lead to apoptosis

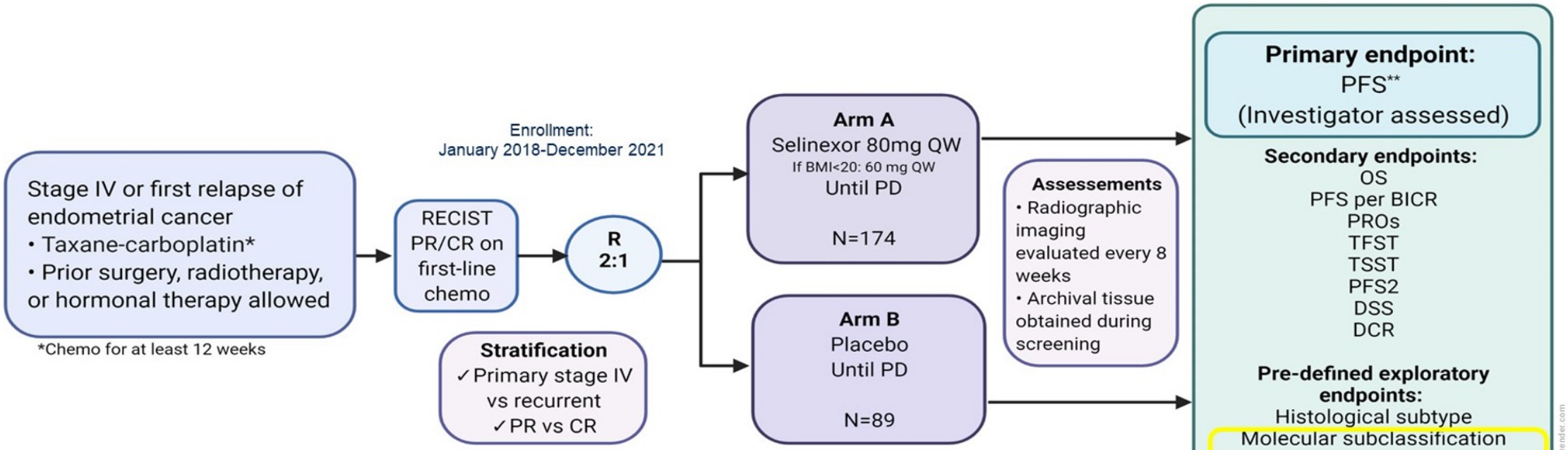
Courtesy of Michael J. Birrer

Selinexor

- Selinexor prolonged progression-free survival compared to placebo in patients with advanced or recurrent endometrial cancer
- Exploratory subgroup analysis identified p53 wild-type as a predictor of the efficacy
- Benefit for p53 wild type was seen across MMS and Copy Number Low patients

Courtesy of Michael J. Birrer

SIENDO Phase III Study Design



**140 PFS events needed to provide 80% power to detect a hazard ratio of 0.6 (median PFS 4.5 months for placebo and 7.5 months for selinexor) with a one-sided alpha of 0.025 and 2:1 randomization ratio favoring selinexor.

***Assessed by DNA sequencing and IHC

Data cutoff: January 18, 2022

Makker V et al. ASCO 2022;Abstract 5511.

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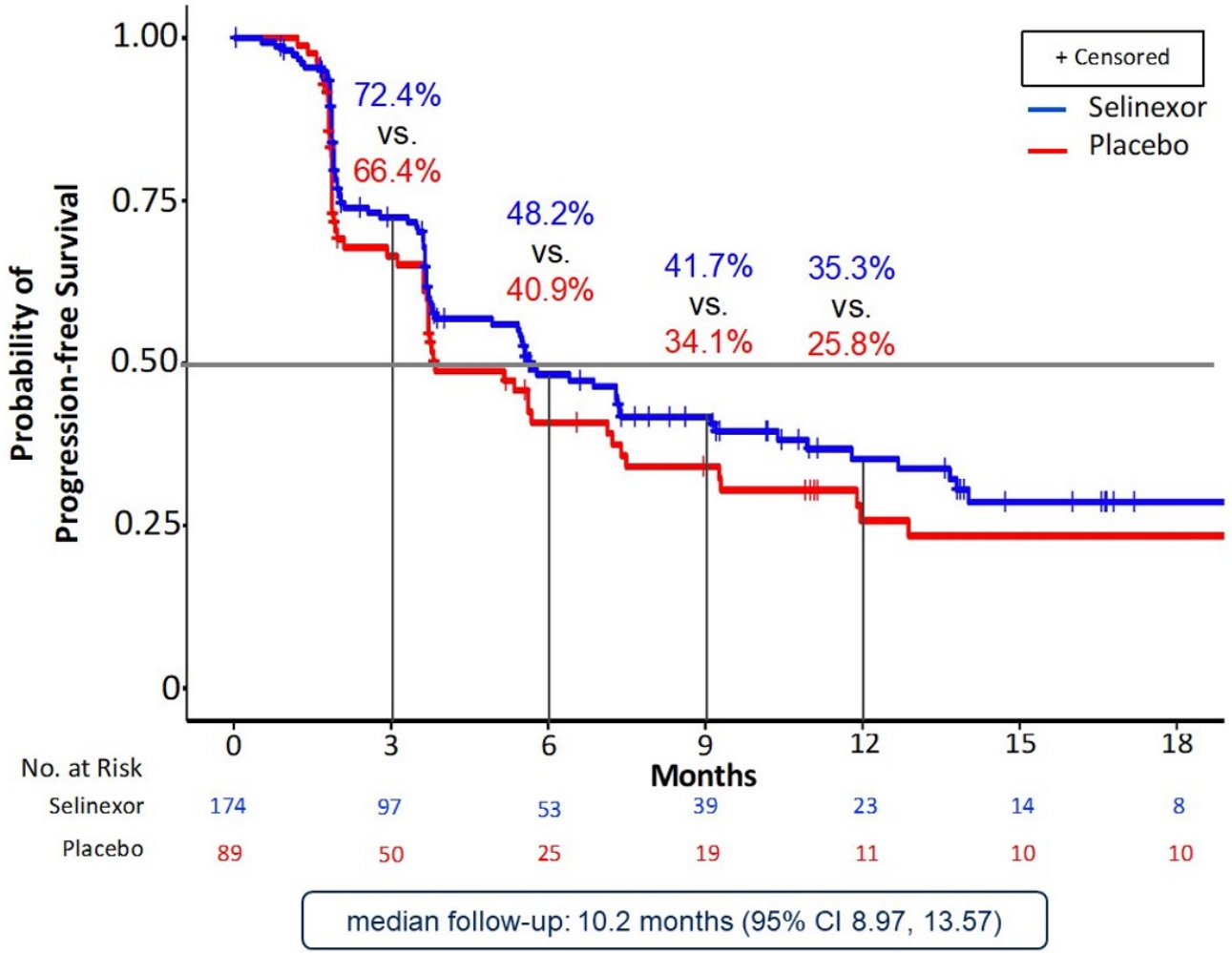
SIENDO Primary Endpoint: PFS in the Intent-to-Treat Population



Median PFS

Selinexor (n=174): 5.7 mo (95% CI 3.81-9.20)

Placebo (n=89): 3.8 mo (95% CI 3.68-7.39)

Audited* (by electronic case report form)

HR = 0.705 (95% CI 0.499-0.996)

One-sided P value = 0.024

Unaudited* (by interactive response technology)

HR = 0.76 (95% CI 0.543-1.076)

One-sided P value = 0.063

*In 7 patients (2.7% of 263), the stratification factor of CR/PR was incorrect and was corrected by the Investigators prior to database lock and unblinding. The statistical analysis was validated by the independent ENGOT statistician and approved by the IDMC.

CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival

Makker V et al. ASCO 2022;Abstract 5511.

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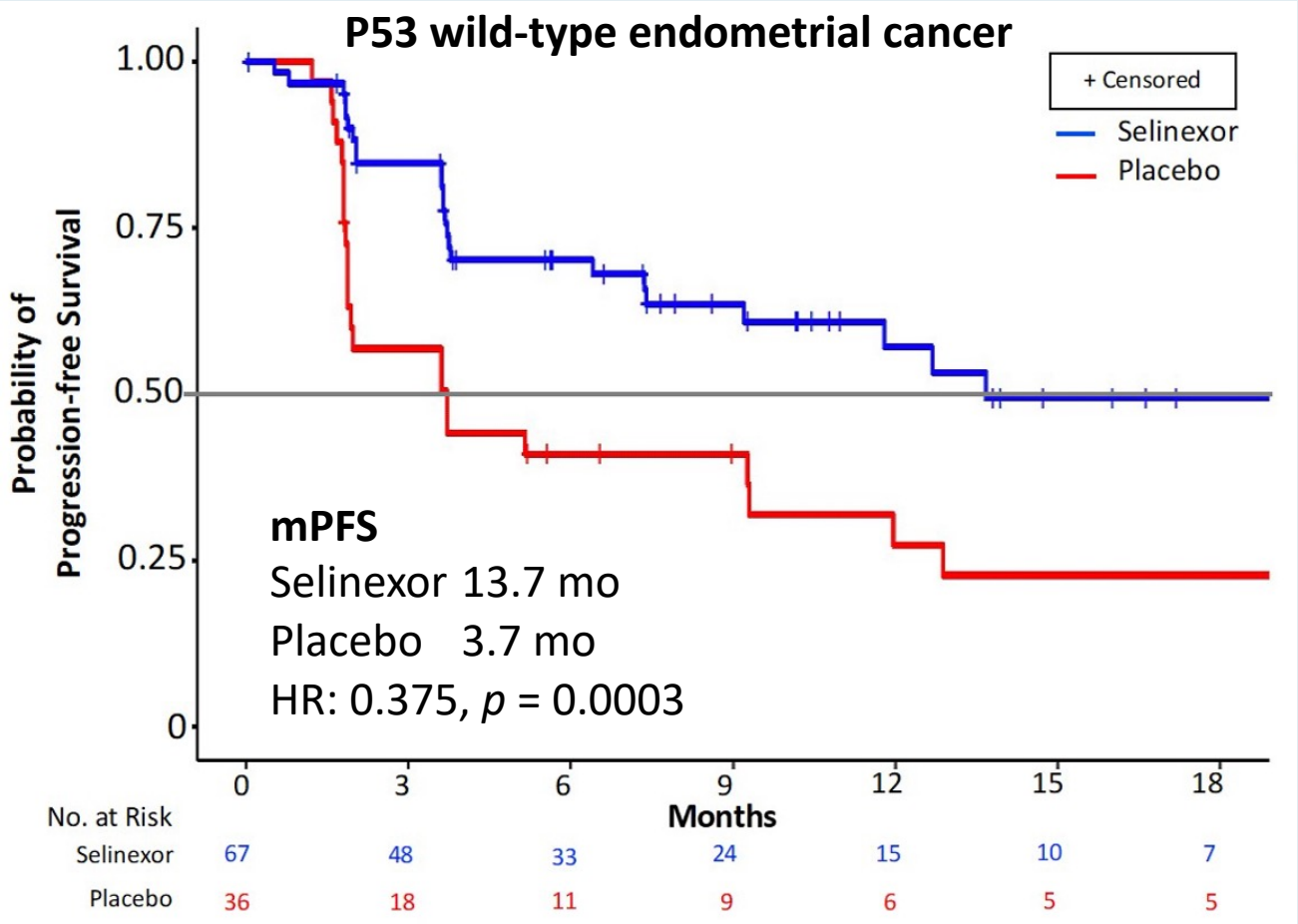
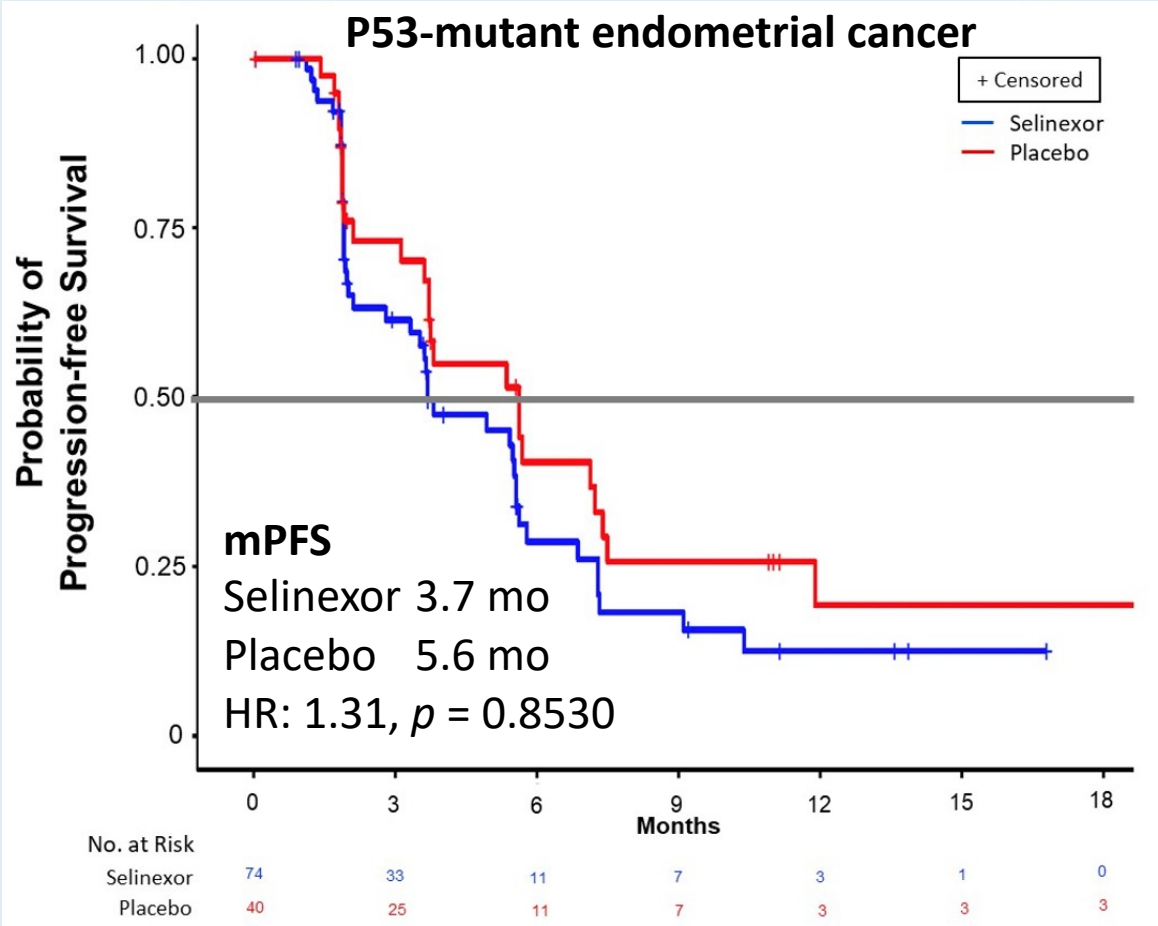
SIENDO: PFS by p53 Status





mPFS = median progression-free survival

Makker V et al. ASCO 2022;Abstract 5511.

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Discussion Question

How are you currently approaching up-front therapy for your patients with metastatic cervical cancer?

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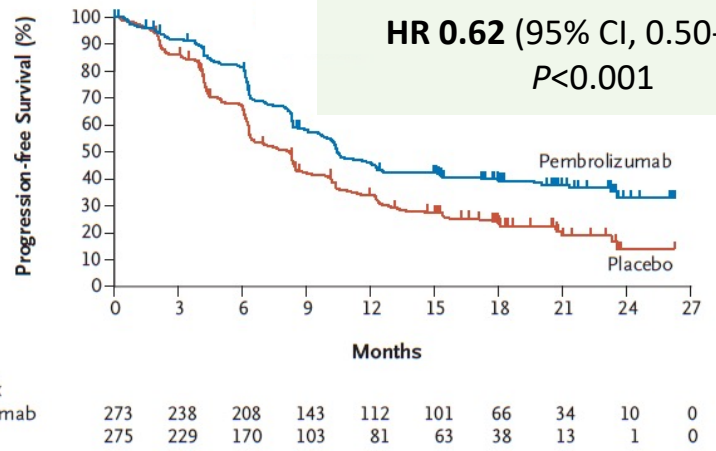
The Upfront Treatment of Metastatic Cervical Cancer A Changing Landscape

- In 2021 Pembrolizumab approved for treatment of PL1 pos metastatic/recurrent cervical cancer
- Keynote 826 randomized patients to GOG240 (bevacizumab MD choice) plus pembrolizumab or placebo
- Pembrolizumab use resulted in a prolongation of PFS (10.4 versus 8.2 months HR .62 P< .001) and OS
- OS at 24 months was 53% (Pembrolizumab) versus 41.7 (placebo) HR .64 p < .001)

Courtesy of Michael J. Birrer

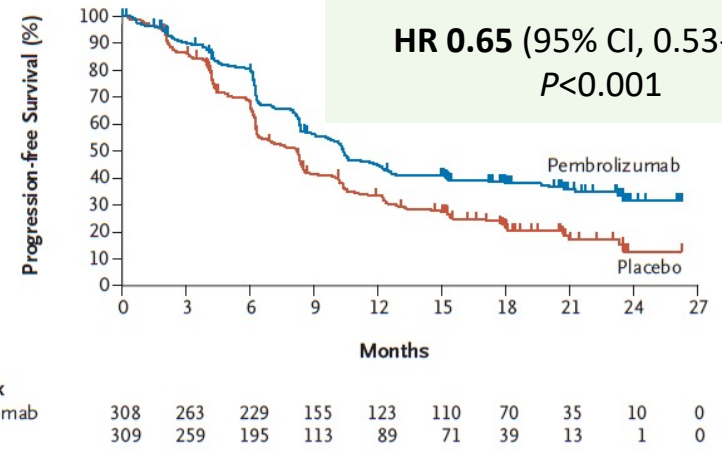
KEYNOTE 826: PFS

PD-L1 CPS ≥1 Population



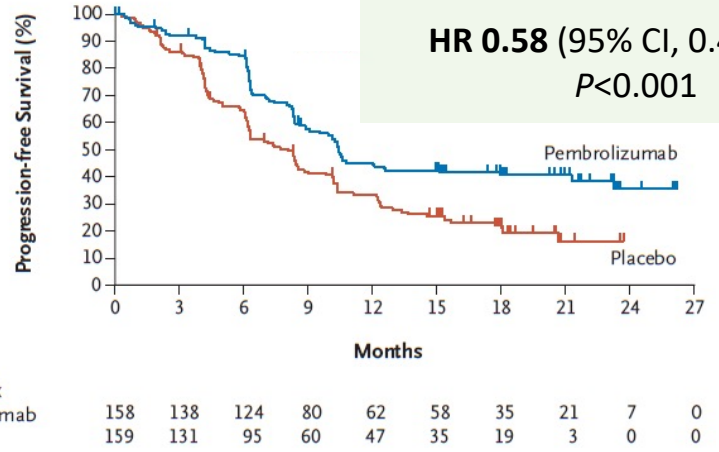
HR 0.62 (95% CI, 0.50-0.77)
P<0.001

ITT Population



HR 0.65 (95% CI, 0.53-0.79)
P<0.001

PD-L1 CPS ≥10 Population



HR 0.58 (95% CI, 0.44-0.77)
P<0.001

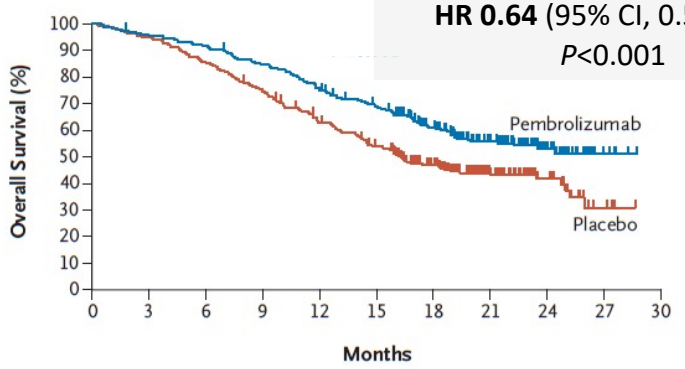
Colombo N, et al. *N Engl J Med.* 2021;385(20):1856-1867.

Courtesy of Michael J. Birrer

KEYNOTE 826: OS

PD-L1 CPS ≥1 Population

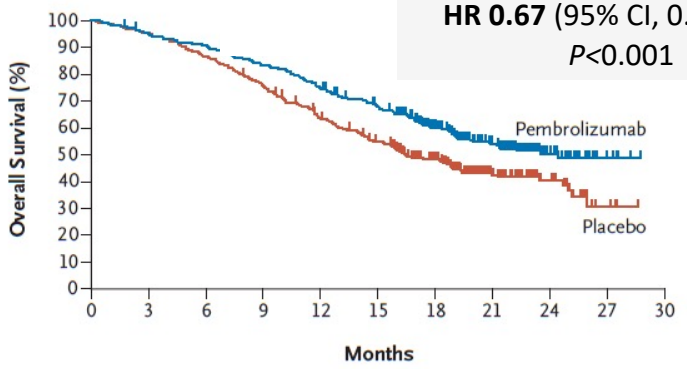
HR 0.64 (95% CI, 0.50-0.81)
P<0.001



No. at Risk											
Pembrolizumab	273	260	250	229	204	181	132	82	34	6	0
Placebo	275	261	235	206	168	140	100	55	25	4	0

ITT Population

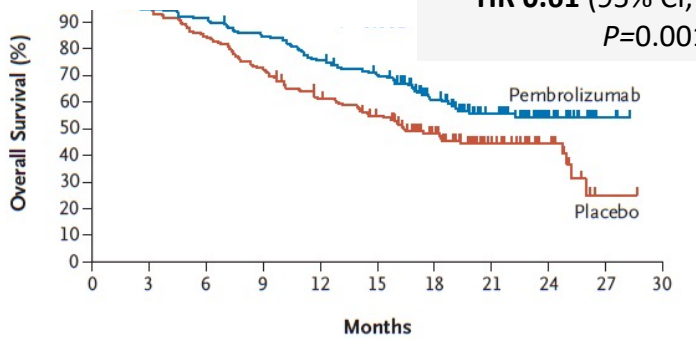
HR 0.67 (95% CI, 0.54-0.84)
P<0.001



No. at Risk											
Pembrolizumab	308	291	277	254	228	201	145	89	36	6	0
Placebo	309	295	268	234	191	160	116	60	28	4	0

PD-L1 CPS ≥10 Population

HR 0.61 (95% CI, 0.44-0.84)
P=0.001



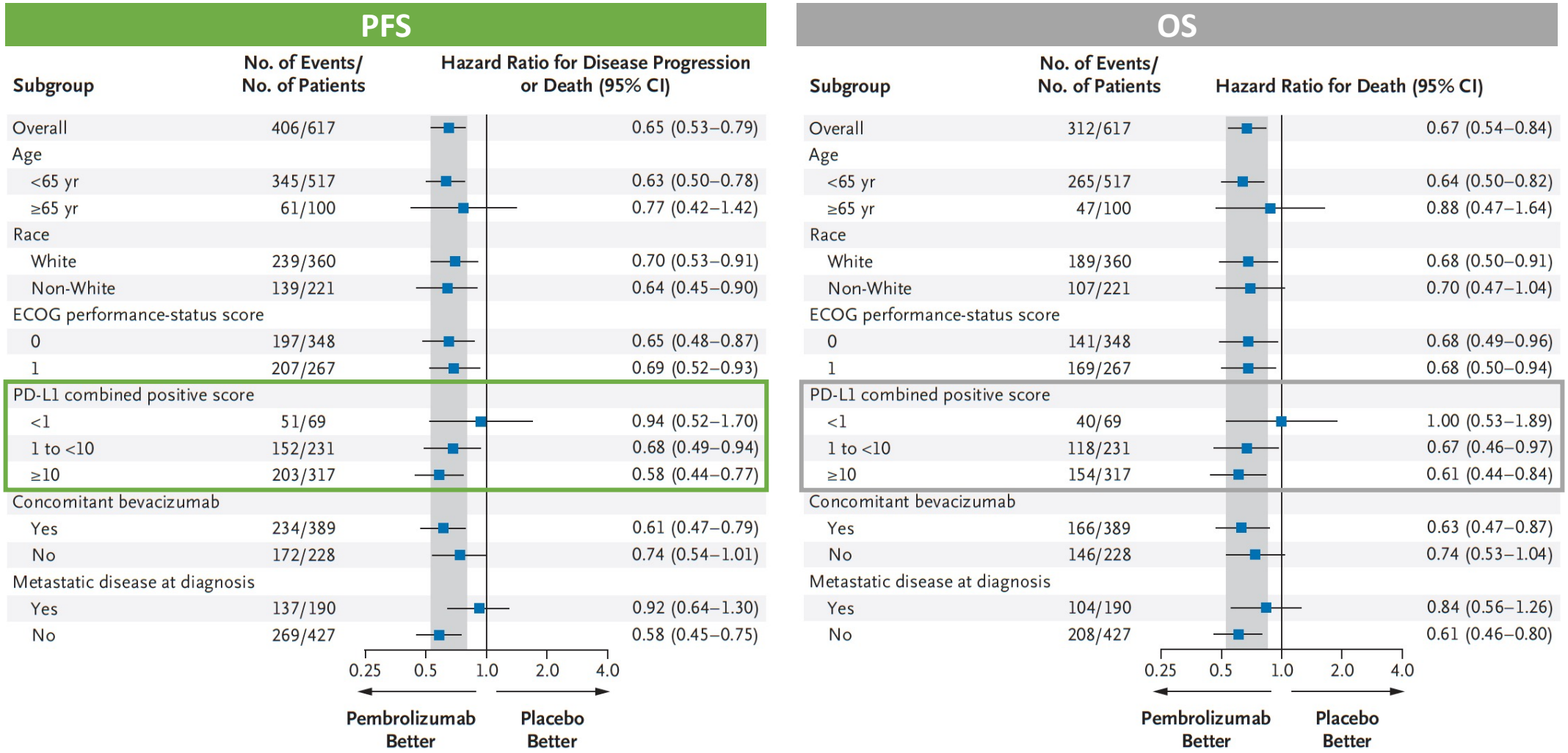
No. at Risk											
Pembrolizumab	158	149	144	132	118	106	76	46	21	3	0
Placebo	159	151	135	116	95	81	56	31	15	1	0

Pembrolizumab group mOS (ITT):
24.4 months

Colombo N, et al. *N Engl J Med.* 2021;385(20):1856-1867.

Courtesy of Michael J. Birrer

KEYNOTE 826: ITT Population Subgroup Analysis



Colombo N, et al. *N Engl J Med.* 2021;385(20):1856-1867.

Courtesy of Michael J. Birrer

The Upfront Treatment of Metastatic Cervical Cancer

- All tumors are typed for PDL1 expression (primary versus recurrent)
- PDL1 expression (CPS>1) are treated with Pembrolizumab containing regimen (GOG240 +/- bevacizumab)
- PDL1 negative patients are treated with GOG240 or if possible Tisotumab vedotin (indication is after chemotherapy)
- PDL1 negative patients who progress after GOG240 should get Tisotumab vedotin