Mansoor Raza Mirza

- Lecture

The Future Treatment of Endometrial Cancer

Mansoor Raza Mirza

Medical Director: **NSGO-CTU** (Nordic Society of Gynaecological Oncology)
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Chairman$_{2020\text{-}2022}$: **ENGOT** (European Network of Gynaecological Oncology Trials group)
Vice-President: **ESGO** (European Society of Gynaecological Oncology)

DECLARATION OF INTERESTS

Allarity Therapeutics, Advisory Board, Personal
Astra Zeneca, Advisory Board & Invited Speaker, Personal
Biocad, Advisory Board, Personal
Biontech, Advisory Board, Personal
Boehringer Ingelheim, Advisory Board, Personal
Clovis, Advisory Board, Personal
Daiichi-Sankyo, Advisory Board, Personal
Genmab, Advisory Board & Invited Speaker, Personal
GSK, Advisory Board & Invited Speaker, Personal
Immunogen, Advisory Board, Personal
Karyopharm, Advisory Board, Personal
Merck, Advisory Board, Personal
Mersana, Advisory Board & Invited Speaker, Personal
Novartis, Advisory Board, Personal
Regeneron, Advisory fee, Personal
Roche, Advisory Board, Personal
SeaGen, Advisory Board & Invited Speaker, Personal
Takeda, Advisory Board & Invited Speaker, Personal
Zailab, Advisory Board, Personal
Karyopharm, Member of Board of Directors, Stocks/Shares, Personal
Sera Prognostics, Member of Board of Directors, Stocks/Shares, Personal

No financial interest

Allarity, Research Grant, Institutional,
Apexigen, Research Grant, Institutional,
Astra Zeneca, Research Grant, Institutional,
Boehringer Ingelheim, Research Grant, Institutional
Clovis, Research Grant, Institutional
Deciphera, Trial Chair, Institutional,
GSK, Research Grant, Institutional,
Mersana, Trial Chair, Institutional,
Novartis, Research Grant, Institutional,
NuvationBio, Trial Chair, Institutional,
Ultimovacs, Research Grant, Institutional,

Background

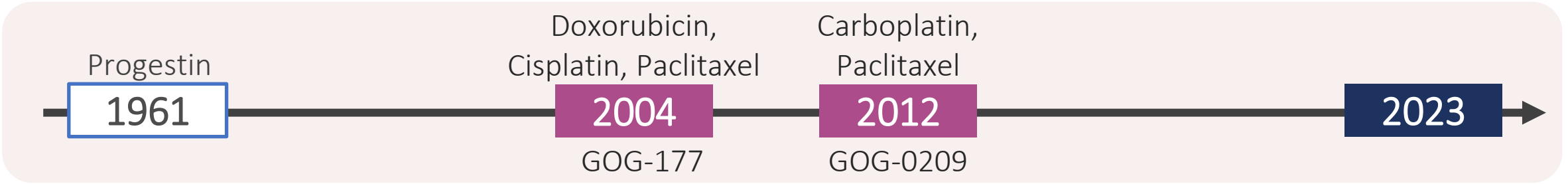
Endometrial cancer (EC) remains the only gynaecologic malignancy with a rising incidence and mortality.

While patients diagnosed at an early-stage (low-risk) have an excellent prognosis, those diagnosed at a late stage have a 5-year survival rate of only 17%.

Carboplatin/paclitaxel (CP) is standard of care for first-line treatment of primary advanced or recurrent EC; however long-term outcomes remain poor, with median OS <3 years

The molecular classification (TCGA) has boosted the development of targeted therapy in EC

Anti–PD-1 based therapy has transformed the management of EC post-platinum chemotherapy and in the first-line



Sung, H. et al.CA CancerJ. Clin. 71, 209–249 (2021); Colombo N, *et al*. *Ann Oncol* 2016; 27: 16–41; Bestvina CM & Fleming GF. *Oncologist* 2016; 21: 1250–1259; Concin N, *et al*. *Int J Gyn Cancer* 2021; 31: 12–39; Yang S, et al. *Discov Med.* 2011;12:205-212; Fleming GF, et al. *J Clin Oncol*. 2004;22:2159-2166; Oaknin A, et al. *J Immunother Cancer*. 2022;10(1):e003777; O'Malley DM, et al. *J Clin Oncol.* 2022;40(7):752-761; Makker V, et al. *N Engl J Med*. 2022;386:437-448; Miller DS, et al., *Gynecol Oncol*. 2012;125:771–773; Miller DS, et al., *J Clin Oncol*. 2020;38:3841-3850. Mirza MR. et al. NEJM March 27, 2023, DOI: 10.1056/NEJMoa2216334; Eskander RN. Et al. NEJM March 27, 2023 DOI: 10.1056/NEJMoa2302312

GOG0209: PFS & OS

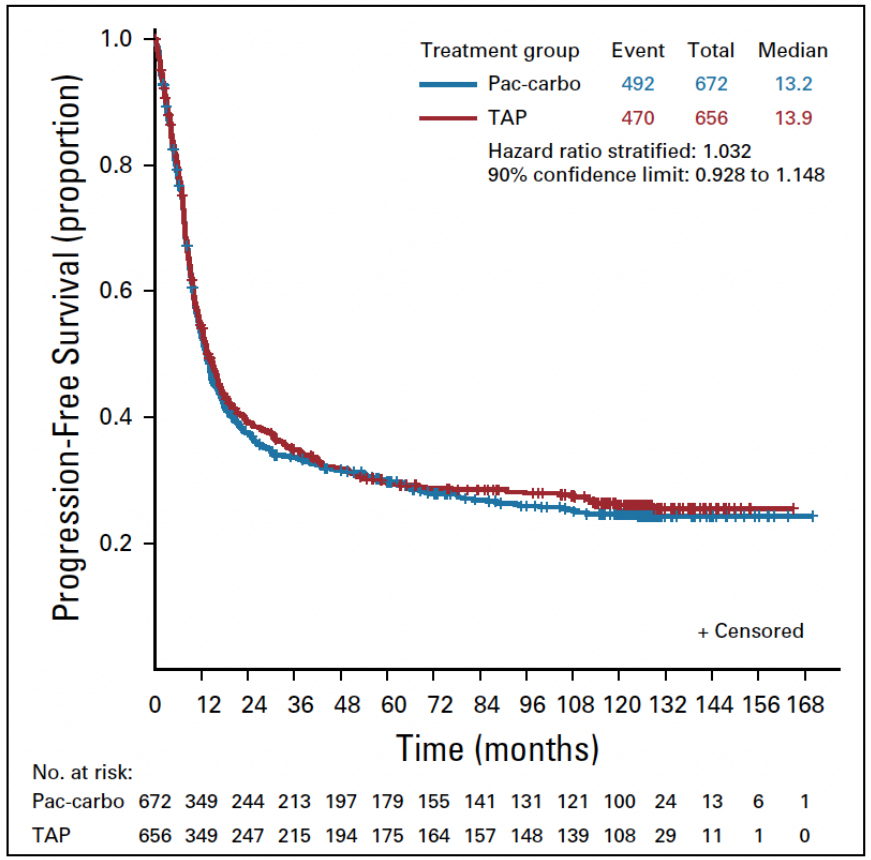


FIG 2. Updated progression-free survival time distribution by randomized treatment group. Carbo, carboplatin; pac, paclitaxel; TAP, paclitaxel-doxorubicin-cisplatin.

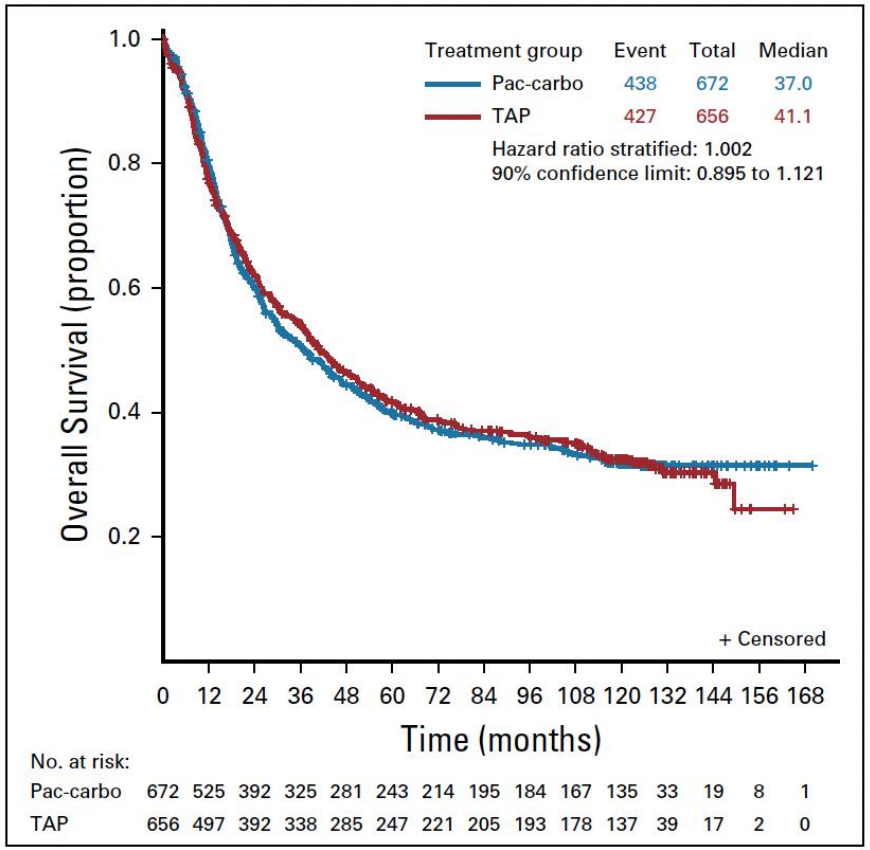


FIG 3. Updated overall survival time distribution by randomized treatment group. Carbo, carboplatin; pac, paclitaxel; TAP, paclitaxel-doxorubicin-cisplatin.

Miller DS et al. *J Clin Oncol.* 2020; 38(33): 3841-3850

Post Carboplatin-Paclitaxel:

Currently used chemotherapy agents in advanced or recurrent endometrial cancer have limited response rates

Agent	ORR (%)	mDOR (months)	mPFS (months)
Paclitaxel[1]	27.3	4.2	mOS: 10.3
Bevacizumab[2]	13.5	6	4.2
Ifosfamide[3]	12.5	3 to 4.9	5
Docetaxel[4]	7.7	NR	2.0
Topotecan[5]	9.0	4.5	NR
Ixabepilone[6]	12.0	5.8	2.9
Etoposide[7]	14	NR	4
Pegylated liposomal doxorubicin[8]	9.5	2.7	mOS: 8.2

mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; NR, not reached; ORR, overall response rate.

1. Lincoln S et al. *Gynecol Oncol*. 2003;88(3):277-271. 2. Aghajanian C et al. *J Clin Oncol.* 2011;29(16):2259-2265. 3. Barton C et al. *Cancer Chemother Pharmacol.* 1990;26(Suppl):S4-6. 4. Garcia AA et al. *Gynecol Oncol*. 2008;111(1):22-26. 5. Miller DS et al. *Gynecol Oncol*. 2002;87(3):247-251. 6. Muggia FM et al. *J Clin Oncol*. 2002;20(9):2360-2364. 7. Poplin EA et al. *Gynceol Oncol*.1999;74(3):432-435. 8. Dizon DS et al. *J Clin Oncol*. 2009;27(19):3104-3108.

Molecular profile of endometrial cancers

Histology	Endometrioid			Serous and high grade endometrioid	Carcinosarcoma	Clear cell
TCGA subtype	'POLE-ultramutated'	'MSI-hypermutated'	'MSS copy-number low'	'copy-number high serous-like'	NA	NA
Mutation load						
SCNA load						
Grade	1, 2, 3	1,2,3**	1,2	3	High	High
ER status	ER- ; ER+	ER+ ; ER-	ER+			
TP53 mutation	35%	low	low	>90%	60-90%	35%
PI3K alterations	PTEN M+ (94%) PIK3CA M+ (71%) PIK3R1 M+(65%)	PTEN M+ (75-85%) PIK3CA M+(50-55%) PIK3R1 M+(30-40%)		PTEN (11%) PIK3CA A+ (45%) PIK3CA M+ (35%) PIK3R1 M+ (12%)	PTEN M+ (19%) PIK3CA M+ (35%) PIK3CA A+ (14%)	PTEN loss (80%) PIK3CA (18%)
KRAS mutation	>50%	35%			17%	0%
Erbb alterations	0	low	low	ErbB2 A+ 30-40% (serous)	ErbB2 A+ (13%) ErbB3 A+/M+ (13%)	ErbB2 M+ (12%)
FGFR amplification or mutation	FGFR1 A+/M+ (7%) FGFR2 A+/M+ (13%) FGFR3 A+/M+ (5%)				FGFR3 A+ (20%)	
Wnt/βcatenin			CTNNB1 M+ (>50%)			
Other	ARID1A M+ (75%) PD1/PD-L1 overexpr. Mutation(s) in the exonuclease domain of the POLE gene	ARID1A M+(35-40%) PD1/PD-L1 overexpr.	ARID1A M+(35-40%)	PPP2R1A M+(20%) FBXW7 M+(20% of UC) HER-2 (25%)	ARID1A (25%) PPP2R1A (28%) FBXW7 M+(35%) CCNE1 A+ (42%) Sox17 A+ (25%)	ARID1A (25%) TERT promoter mutations

Modified from Morice et al, Lancet 2015

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Modified from Morice et al, Lancet 2015

Immune Checkpoint Inhibitors in Second+ lines

Avelumab

Humanized IgG1 monoclonal antibody that binds to the inhibitory immune checkpoint ligand PD-L1 on tumour cells and immune cells and blocks its interaction with the receptors PD-1 and B7.1

Durvalumab

Human IgG1 monoclonal antibody that binds to the inhibitory immune checkpoint ligand PD-L1 on tumour cells and immune cells and blocks its interaction with the receptors PD-1 and B7.1

Pembrolizumab

Humanized IgG4 monoclonal antibody that binds to the inhibitory immune checkpoint receptor PD-1 and blocks its interaction with the ligands PD-L1 and PD-L2

Dostarlimab

Humanized IgG4 monoclonal antibody that binds to the inhibitory immune checkpoint receptor PD-1 and blocks its interaction with the ligands PD-L1 and PD-L2

Pembrolizumab is approved:

- In the US and Europe
  - For patients with unresectable or metastatic, dMMR/MSI-H or TMB-H solid tumours that have progressed following prior treatment.
  - In combination with lenvatinib for the treatment of advanced or recurrent EC (only pMMR in US) in adults with disease progression following prior treatment with a platinum-containing therapy

Dostarlimab is approved:

- In the EU for dMMR/MSI-H advanced/recurrent endometrial cancer that have progressed on or following prior treatment
- In the US for adult patients dMMR recurrent or advanced solid tumours that have progressed on or following prior treatment

Konstantinopoulos PA, *et al*. *J Clin Oncol* 2019; 20: 2786−2794. Antill YC, *et al*. *J Immunother Cancer* 2021; **9**: e002255; .Marabelle A, *et al*. *J Clin Oncol* 2020; 38: 1–10. Oaknin A, *et al*. *JAMA Oncol* 2020; **6**: 1766−1772.KEYTRUDA US prescribing information 2021.; KEYTRUDA SmPC 2021; emperli SmPC 2021. Jemperli US prescribing information 2021.

Combination Approaches

Antiangiogenic Agents	Chemotherapy	PARP inhibitors
• Reduction in Treg activity • Reversal of immunosuppressive effects of VEGF • Improved T-cell trafficking and infiltration of CD8+ into the tumor bed	• Immunogenic cell death • Enhanced presentation of tumor specific antigens • Increased T-Cell activation by DC	• Enhanced DNA Damage with increased CD8+T Cells • Potential Synergistic antitumor activity partly mediated by STING pathway

Ciciola P, et al. J Clin Med. 2020; Bailly C, et al. NAR Cancer. 2020;Huang J.,et al. *Biochem and Biophy Res Comm*. 2015; 463:551-6; Sen et al. Cancer Discov 2019

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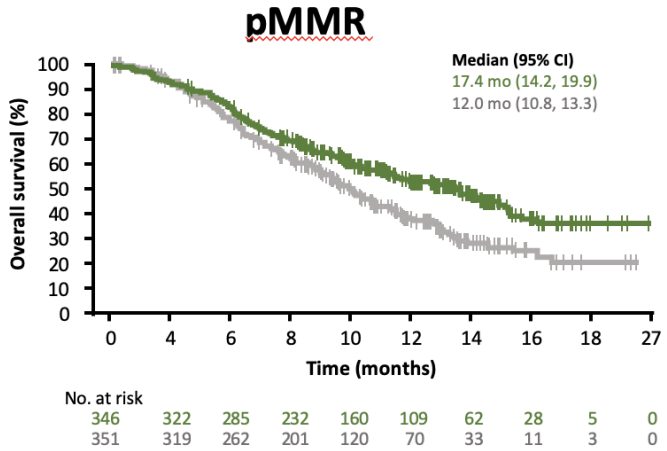
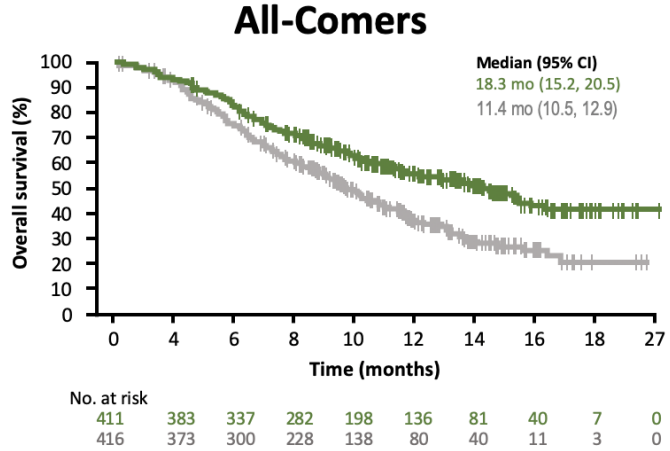
KEYNOTE-775: Primary End-Points

PFS in pMMR and All-Comers

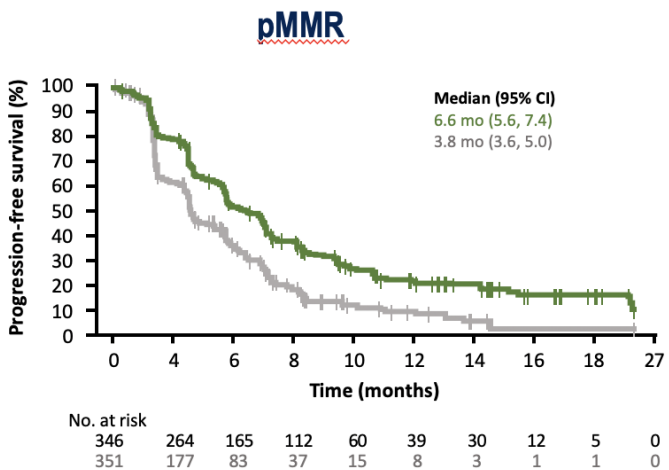


	Events	HR (95% CI)	p-value
LEN + pembro	165	0.68 (0.56, 0.84)	< 0.0001
TPC	203		

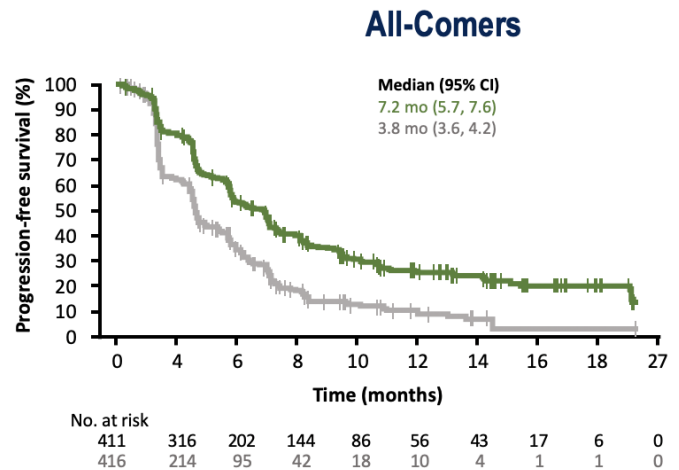


	Events	HR (95% CI)	p-value
LEN + pembro	188	0.62 (0.51, 0.75)	< 0.0001
TPC	245		

OS in pMMR and All-Comers



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



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

Makker V, *et al. N Engl J Med* 2022; 386: 437−448.

LEAP-001 | ENGOT-en9 (NCT03884101)

Phase 3 randomized, open-label, study of pembrolizumab (MK-3475) plus lenvatinib (E7080/MK-7902) versus chemotherapy for first-line treatment of advanced or recurrent EC (LEAP-001)[1,2]

Eligible patients:

- Newly diagnosed Stage III-IV or recurrent EC
- ECOG PS 0 or 1
- Prior adjuvant chemotherapy allowed if completed ≥6 months prior to enrollment

Stratification:

- MMRp vs dMMR
- MMRp further stratified by ECOG PS, measurable disease, and prior chemoradiation

R 1:1
N=875

Pembrolizumab 200 mg IV Q3W + lenvatinib 20 mg PO QD
(MMRp, n≈306; dMMR, n≈132)

Paclitaxel 175 mg/m^2 IV Q3W + Carboplatin AUC 6 IV Q3W
(MMRp, n≈306; dMMR, n≈132)

Primary endpoints: PFS (BICR), OS

Secondary endpoints: ORR, HRQOL, safety and tolerability

Exploratory endpoints: DOR, DCR, CBR

Status: Active, not recruiting

AUC, area under the curve; BICR, blinded independent central radiology review; CBR, clinical benefit rate; DCR, disease control rate; DOR, duration of response; 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; PFS, progression-free survival; PO, orally; Q3W, every 3 weeks; QD, once daily; R, randomization. [a]Treat until disease progression or unacceptable toxicity. Pembrolizumab must be stopped after 35 cycles, but lenvatinib may continue after stopping pembrolizumab. [b]Study will be fully enrolled when 612 patients with MMRp tumors and ~263 patients with dMMR tumors are recruited. [c]A lower starting dose of paclitaxel (135 mg/m^2) and carboplatin (AUC 5 mg/mL/min) may be administered to patients at risk of developing toxicities due to previous pelvic/spine radiation. An AUC of 5 mg/mL/min dose of carboplatin may be administered in accordance with local practice. [d]Patients may receive up to 7 cycles of paclitaxel/carboplatin; however, chemotherapy treatment beyond 7 cycles may be permitted (with the sponsors' approval) for patients who continue to derive clinical benefit.

1. National Library of Medicine. https://www.clinicaltrials.gov/ct2/show/NCT03884101. Accessed October 17, 2022. 2. Marth C et al. *Int J Gynecol Cancer.* 2022;32:92-100.

Combination Approaches

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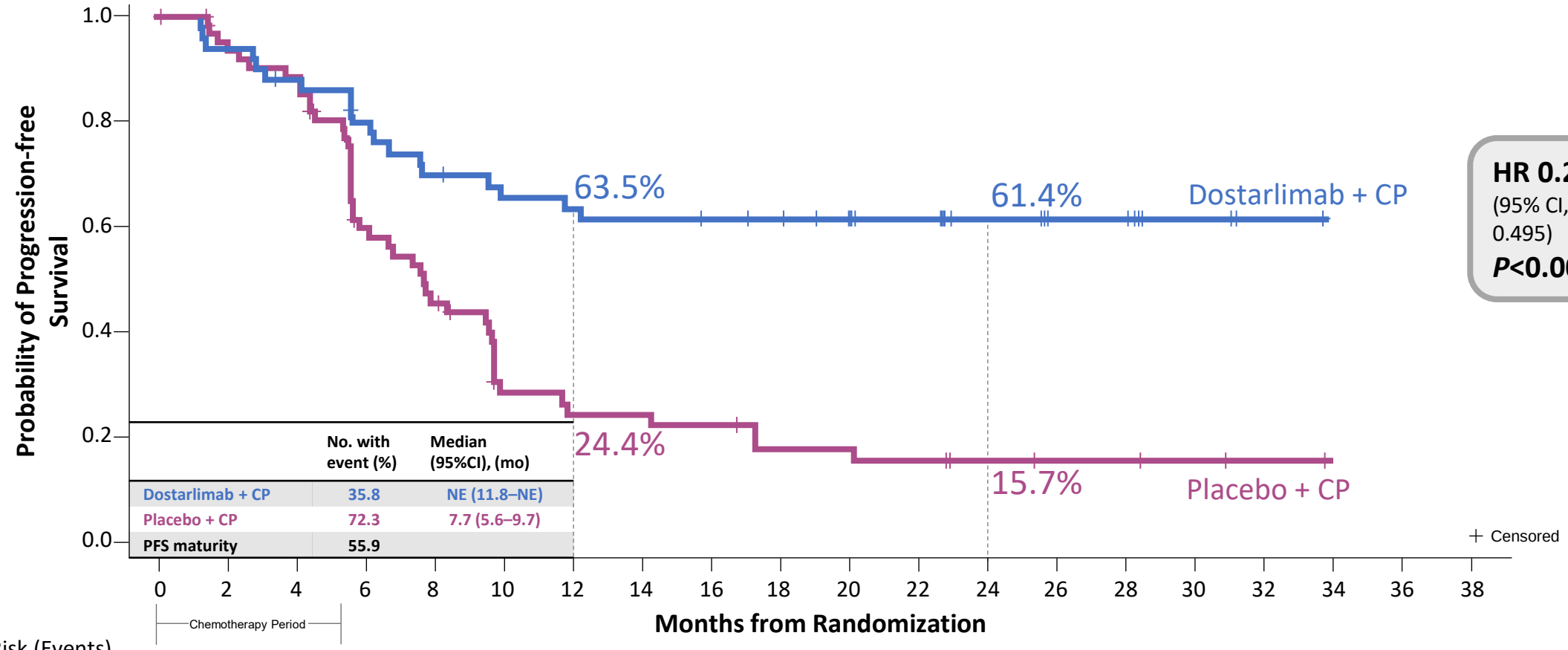
PRIMARY ENDPOINT: PFS IN dMMR/MSI-H POPULATION



HR 0.28
(95% CI, 0.162–0.495)
***P*<0.0001**

At Risk (Events)

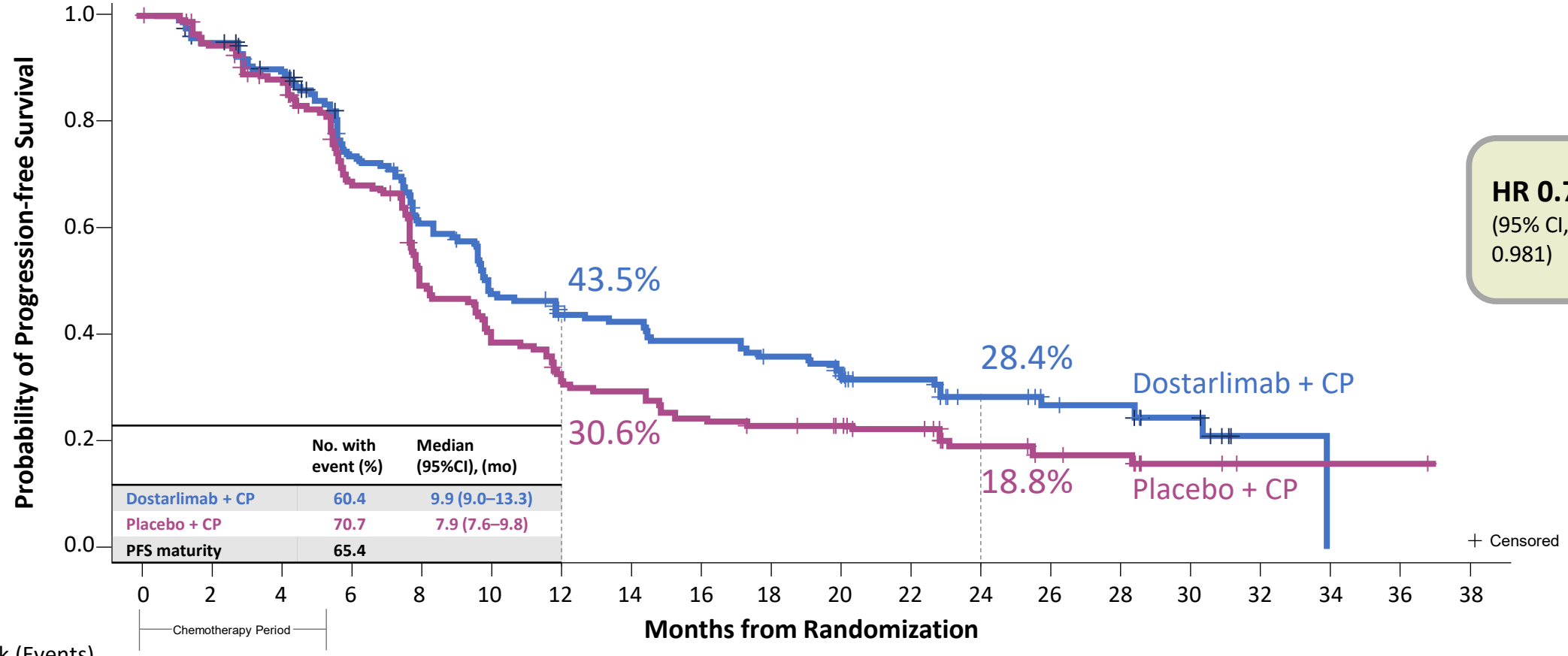
Dostarlimab + CP	53(0)	48(3)	44(6)	39(10)	34(15)	31(17)	30(18)	29(19)	28(19)	27(19)	25(19)	19(19)	13(19)	9(19)	9(19)	4(19)	1(19)	0(19)
Placebo + CP	65(0)	57(4)	54(7)	34(24)	26(32)	14(41)	12(43)	12(43)	11(44)	8(46)	8(46)	7(47)	4(47)	3(47)	3(47)	2(47)	1(47)	0(47)

Median duration of follow-up 24.79 months.

CP, carboplatin/paclitaxel; dMMR, mismatch repair deficient; HR, hazard ratio; MSI-H, microsatellite instability-high; NE, not estimable; PFS, progression-free survival.

Mirza MR, *et al. N Engl J Med, March 27, 2023*

PFS IN MMRp/MSS POPULATION



HR 0.76
(95% CI, 0.592–0.981)

At Risk (Events)

Dostarlimab + CP	192(0)	172(9)	153(19)	118(45)	96(65)	74(86)	64(92)	61(94)	56(99)	51(103)	41(108)	33(109)	21(112)	14(113)	13(113)	8(114)	1(115)	0(116)	
Placebo + CP	184(0)	162(10)	146(22)	110(53)	77(83)	60(100)	47(112)	45(114)	37(122)	34(124)	31(124)	25(125)	16(128)	11(129)	10(129)	3(130)	1(130)	1(130)	1(130)	0(130)

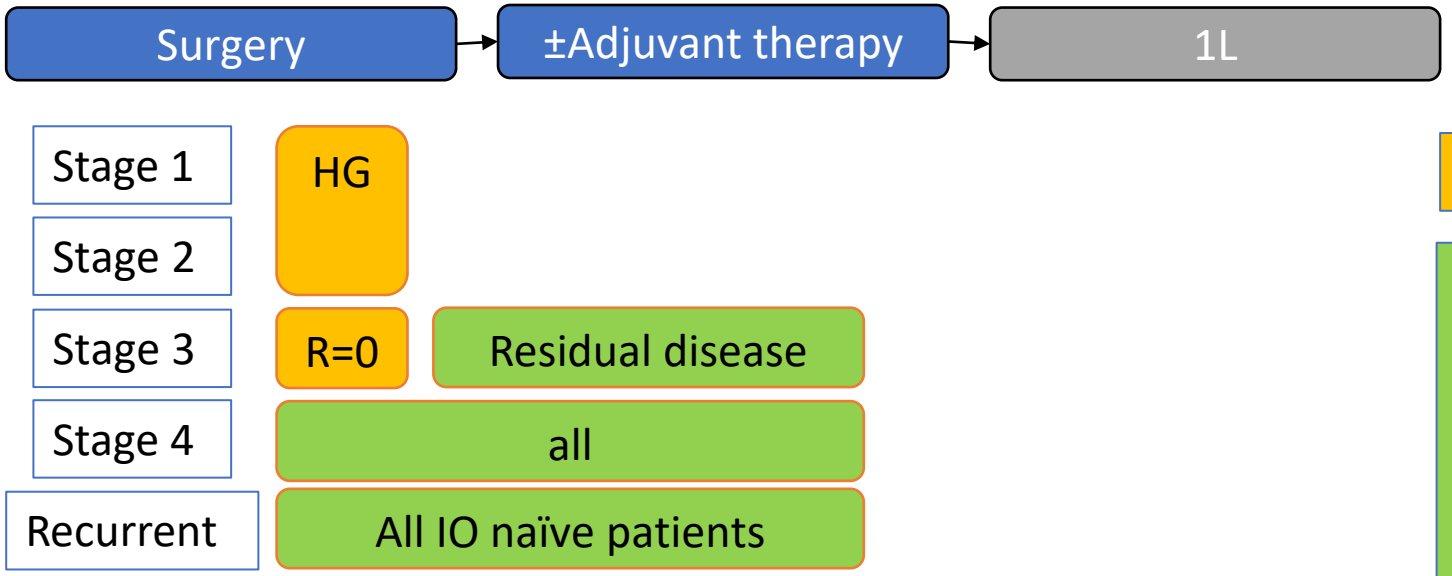
CP, carboplatin/paclitaxel; HR, hazard ratio; MMRp, mismatch repair proficient; MSS, microsatellite stable; PFS, progression-free survival.

Endometrial Cancer
Competitive Landscape of Phase III Immunotherapy Trials in First-Line

Name	EN6-RUBY	EN7-ATTEND	NRG018	EN-11	EN6-RUBY Part 2	DUO-E	EN9-LEAP-1	EN-15	EN-13 Domenica
Lead group Study chair	NSGO-CTU Mirza	MaNGO Colombo	NRG Eskander	BGOG Van Gorp	NSGO-CTU Mirza	GOG-F Westin	AGO-A Marth	MITO Lorusso	GINECO Joly
Investigational agent	Dostarlimab	Atezolizumab	Pembrolizumab	Pembrolizumab	Dostarlimab + Niraparib	Durvalumab + Olaparib	Pembrolizumab + Lenvatinib	Pembrolizumab	Dostarlimab
N	494	550	775	990	270	699	720	350	220
Concomitant	+	+	+	+	+	+	Pembro+Lenva vs. Chemotherapy	Pembrolizumab vs. Chemotherapy	Dostarlimab vs. Chemotherapy
Maintenance	+	+	+		+	+			
EU	+	+	-	+	+	+	+	+	+
US	+	-	+	+	+	+	+	+	-
Expected readout	**Reported NEJM 2023**	”ESMO23”	**Reported NEJM 2023**	”ESMO23”	Q2 2024	”ESMO23”	”ESMO23”	?	?

Endometrial Cancer

Competitive Landscape of Phase III Immunotherapy Trials in First-Line



ENGOT-EN11

ENGOT-EN6 RUBY
NRG018
ENGOT-EN7 ATTEND
LEAP1
DUO-E
RUBY Part 2

dMMR only:

ENGOT-EN15 (C93)
DOMENICA

Molecular profile of endometrial cancers

Histology	Endometrioid			Serous and high grade endometrioid	Carcinosarcoma	Clear cell
TCGA subtype	'POLE-ultramutated'	'MSI-hypermutated'	'MSS copy-number low'	'copy-number high serous-like'	NA	NA
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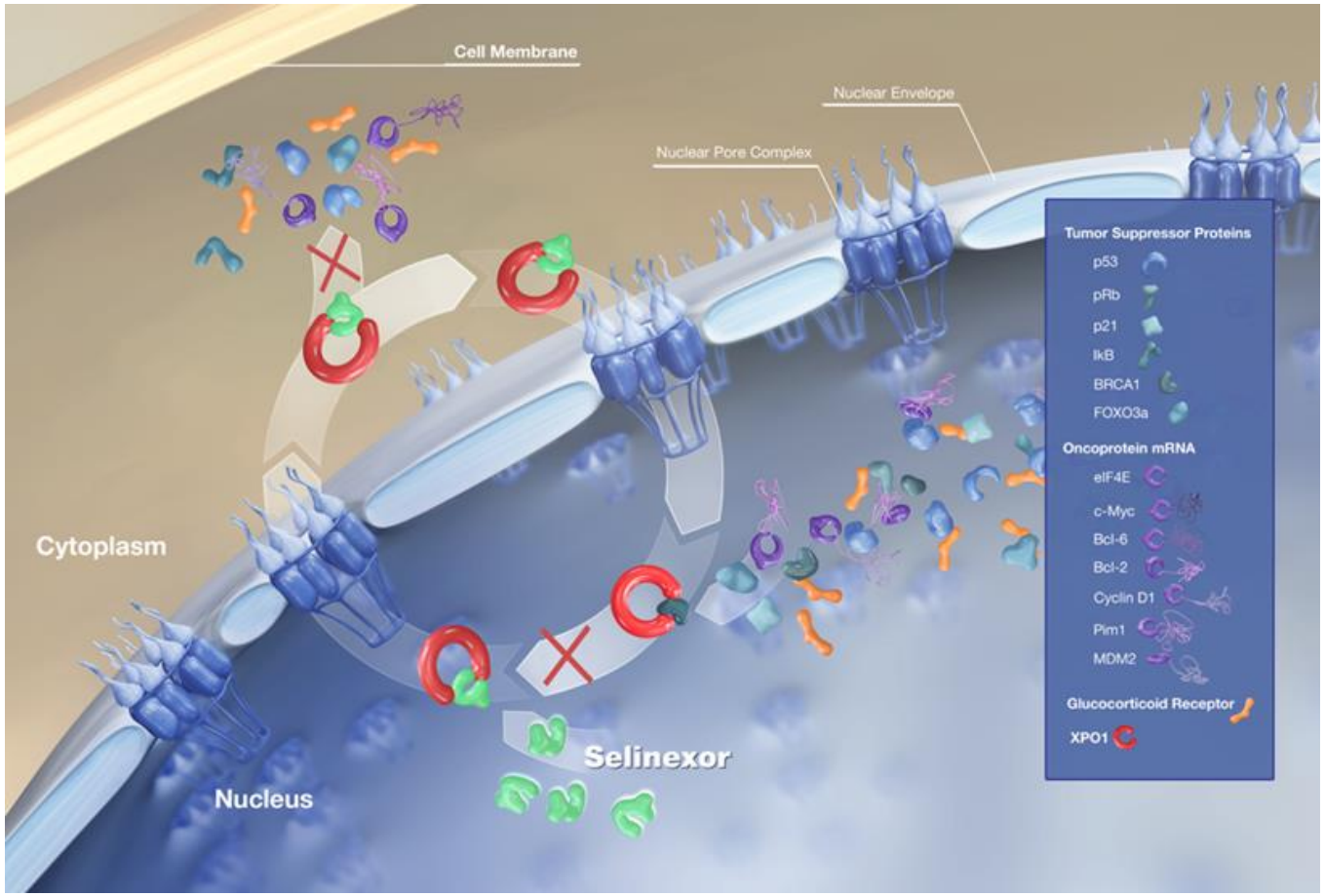
Modified from Morice et al, Lancet 2015

Selinexor: XPO1 inhibition



Exportin 1 (XPO1) is the major nuclear export protein for:[1]

- Tumor suppressor proteins (TSPs, e.g., p53, IkB, PTEN, and FOXO1)

Inhibition of XPO1 results in:[1]

- The increase in nuclear levels and activation of TSPs
- Reduction of oncoprotein levels

Selinexor is an oral selective XPO1 inhibitor

Preclinical data for selinexor:[2]

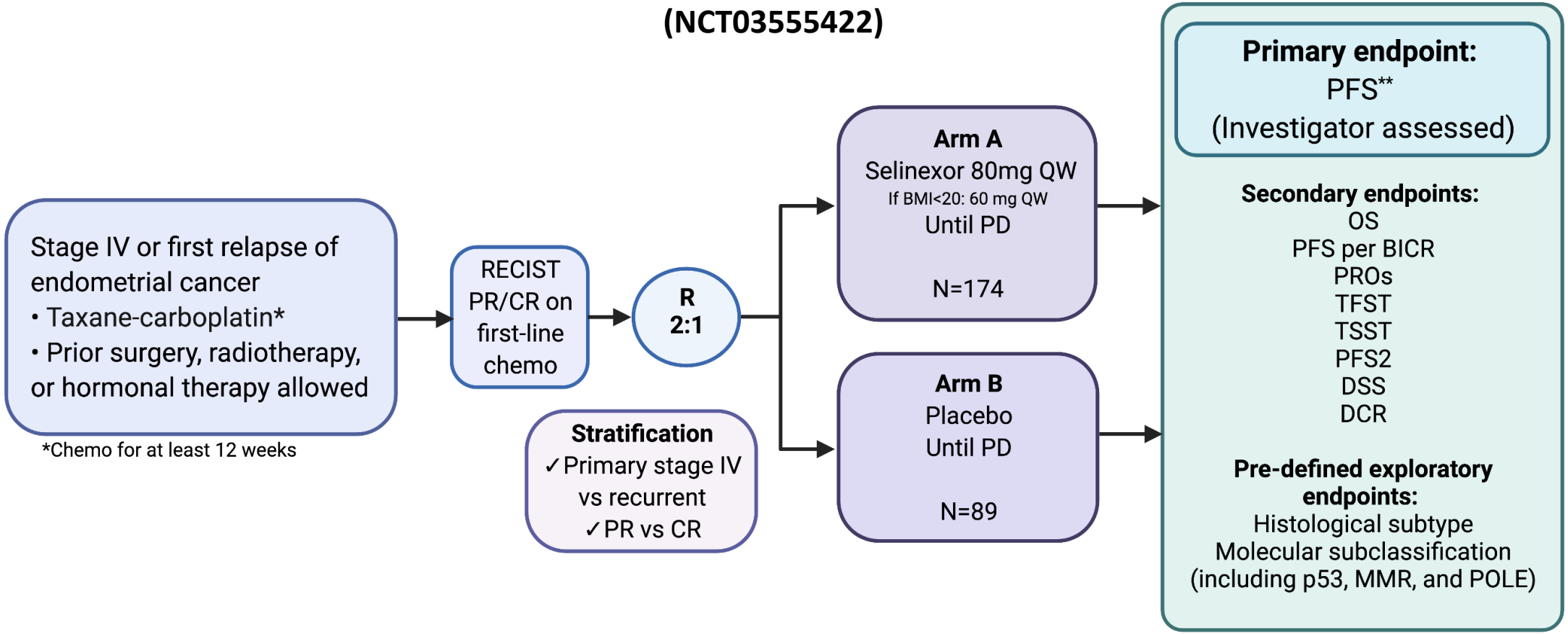
- Reactivates multiple TSPs, including p53 wild type, by preventing nuclear export

1. Fung HY, Chook YM. Atomic basis of CRM1-cargo recognition, release and inhibition. Semin Cancer Biol. 2014;27:52–61.
2. Tai YT, Landesman Y, Acharya C, et al. CRM1 inhibition induces tumor cell cytotoxicity and impairs osteoclastogenesis in multiple myeloma: molecular mechanisms and therapeutic implications. Leukemia. 2014;28(1):155–165.

Vergote…..Mirza et al ESMO VP 2021

Trial Design

Stage IV or first relapse of endometrial cancer endometrioid, serous, undifferentiated, or carcinosarcoma (NCT03555422)



**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.

BMI, body mass index; DCR, disease control rate; DSS, disease-specific survival; QW, once weekly; CR, complete response; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival on subsequent therapy; PR, partial response; PROs, patient-reported outcomes ; R, randomized; TFST, time to first subsequent therapy; TSST, time to second subsequent treatment

Vergote…..Mirza et al ESMO VP 2021
Vergote…..Mirza et al JCO 2023 in press

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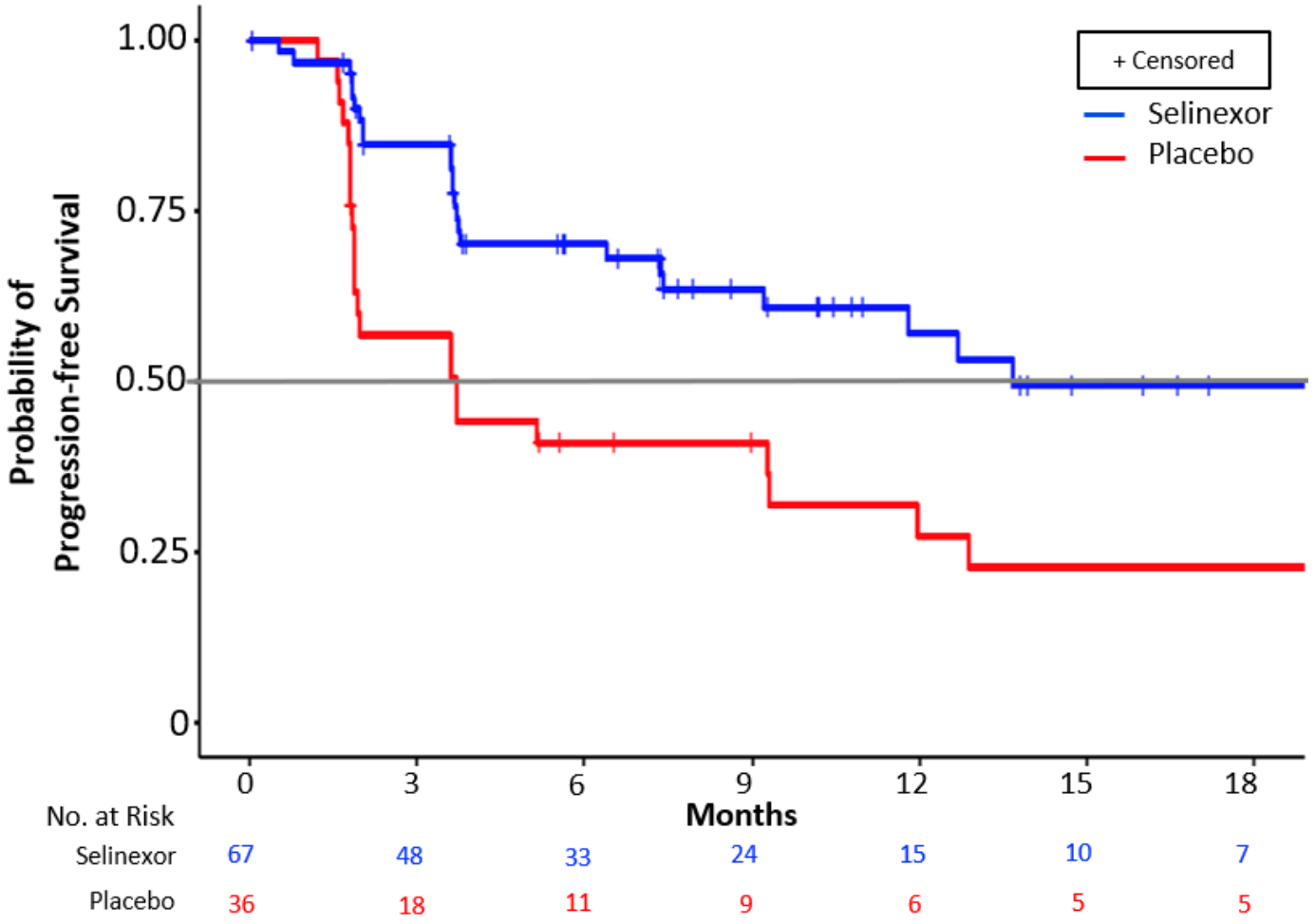
ENGOT-EN5/GOG-3055/SIENDO

SUBGROUP PFS: PATIENTS WITH WILD TYPE p53 EC

(BASED ON AUDITED STRATIFICATION FACTORS)



Median PFS

Selinexor (n=67): 13.7 mo (95% CI 9.20-NR)

Placebo (n=36): 3.7 mo (95% CI 1.87-12.88)

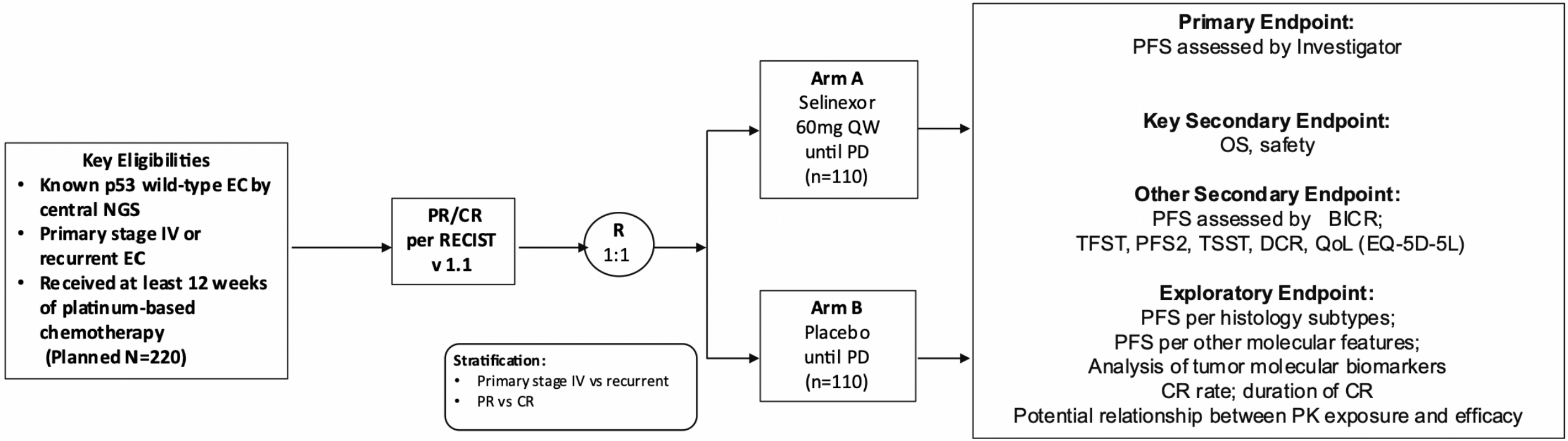
HR (audited) = 0.375 (95% CI 0.210-0.670)

One-sided nominal P value = 0.0003

Vergote…..Mirza et al ESMO VP 2021

Vergote…..Mirza et al JCO 2023 in press

ENGOT-EN20 / XPORT



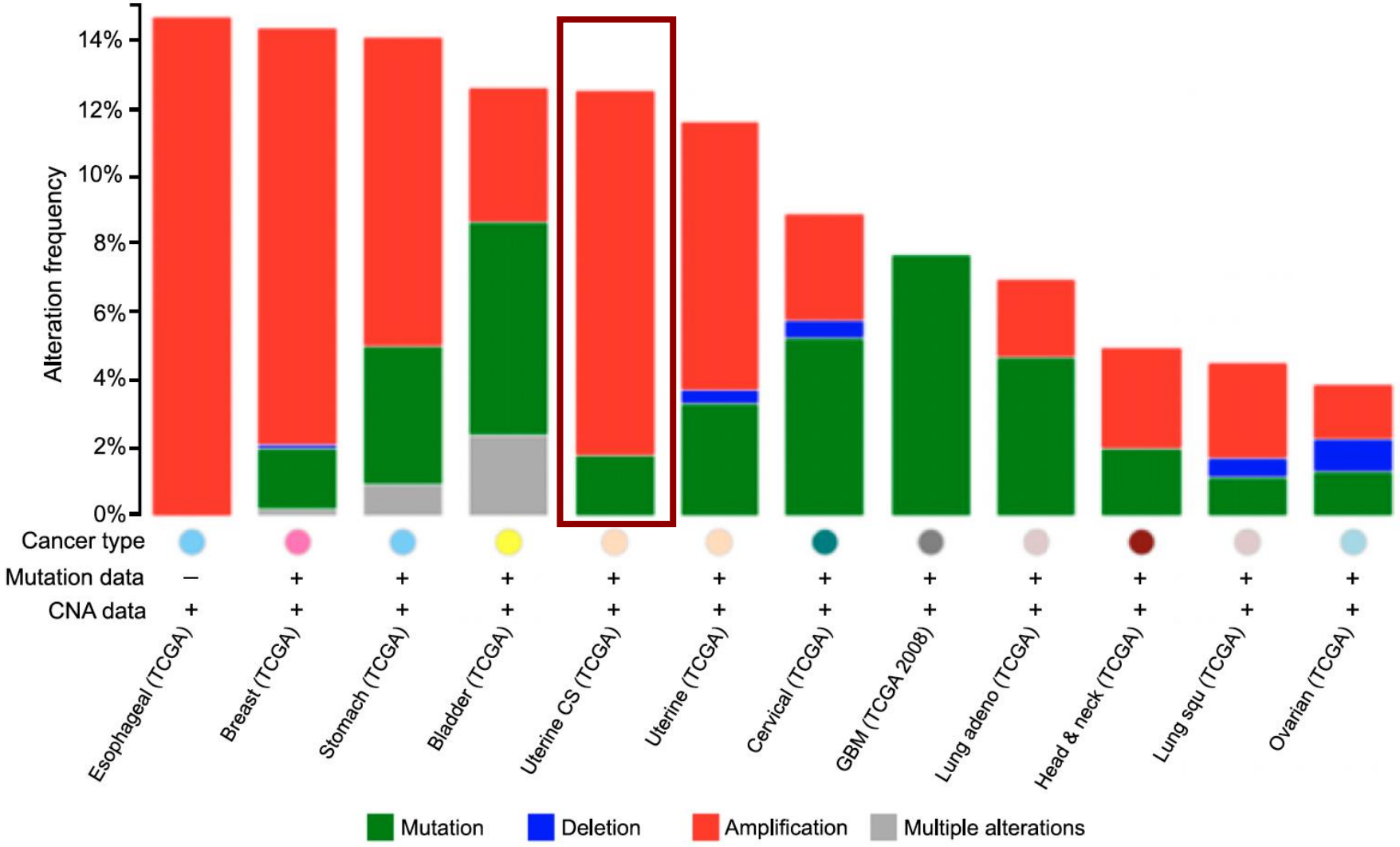
Vergote et al.

Molecular profile of endometrial cancers

Histology	Endometrioid			Serous and high grade endometrioid	Carcinosarcoma	Clear cell
TCGA subtype	'POLE-ultramutated'	'MSI-hypermutated'	'MSS copy-number low'	'copy-number high serous-like'	NA	NA
Mutation load						
SCNA load						
Grade	1, 2, 3	1,2,3**	1,2	3	High	High
ER status	ER- ; ER+	ER+ ; ER-	ER+			
TP53 mutation	35%	low	low	>90%	60-90%	35%
PI3K alterations	PTEN M+ (94%) PIK3CA M+ (71%) PIK3R1 M+(65%)	PTEN M+ (75-85%) PIK3CA M+(50-55%) PIK3R1 M+(30-40%)		PTEN (11%) PIK3CA A+ (45%) PIK3CA M+ (35%) PIK3R1 M+ (12%)	PTEN M+ (19%) PIK3CA M+ (35%) PIK3CA A+ (14%)	PTEN loss (80%) PIK3CA (18%)
KRAS mutation	>50%	35%			17%	0%
Erbb alterations	0	low	low	ErbB2 A+ 30-40% (serous)	ErbB2 A+ (13%) ErbB3 A+/M+ (13%)	ErbB2 M+ (12%)
FGFR amplification or mutation	FGFR1 A+/M+ (7%) FGFR2 A+/M+ (13%) FGFR3 A+/M+ (5%)				FGFR3 A+ (20%)	
Wnt/βcatenin			CTNNB1 M+ (>50%)			
Other	ARID1A M+ (75%) PD1/PD-L1 overexpr. Mutation(s) in the exonuclease domain of the POLE gene	ARID1A M+(35-40%) PD1/PD-L1 overexpr.	ARID1A M+(35-40%)	PPP2R1A M+(20%) FBXW7 M+(20% of UC) HER-2 (25%)	ARID1A (25%) PPP2R1A (28%) FBXW7 M+(35%) CCNE1 A+ (42%) Sox17 A+ (25%)	ARID1A (25%) TERT promoter mutations

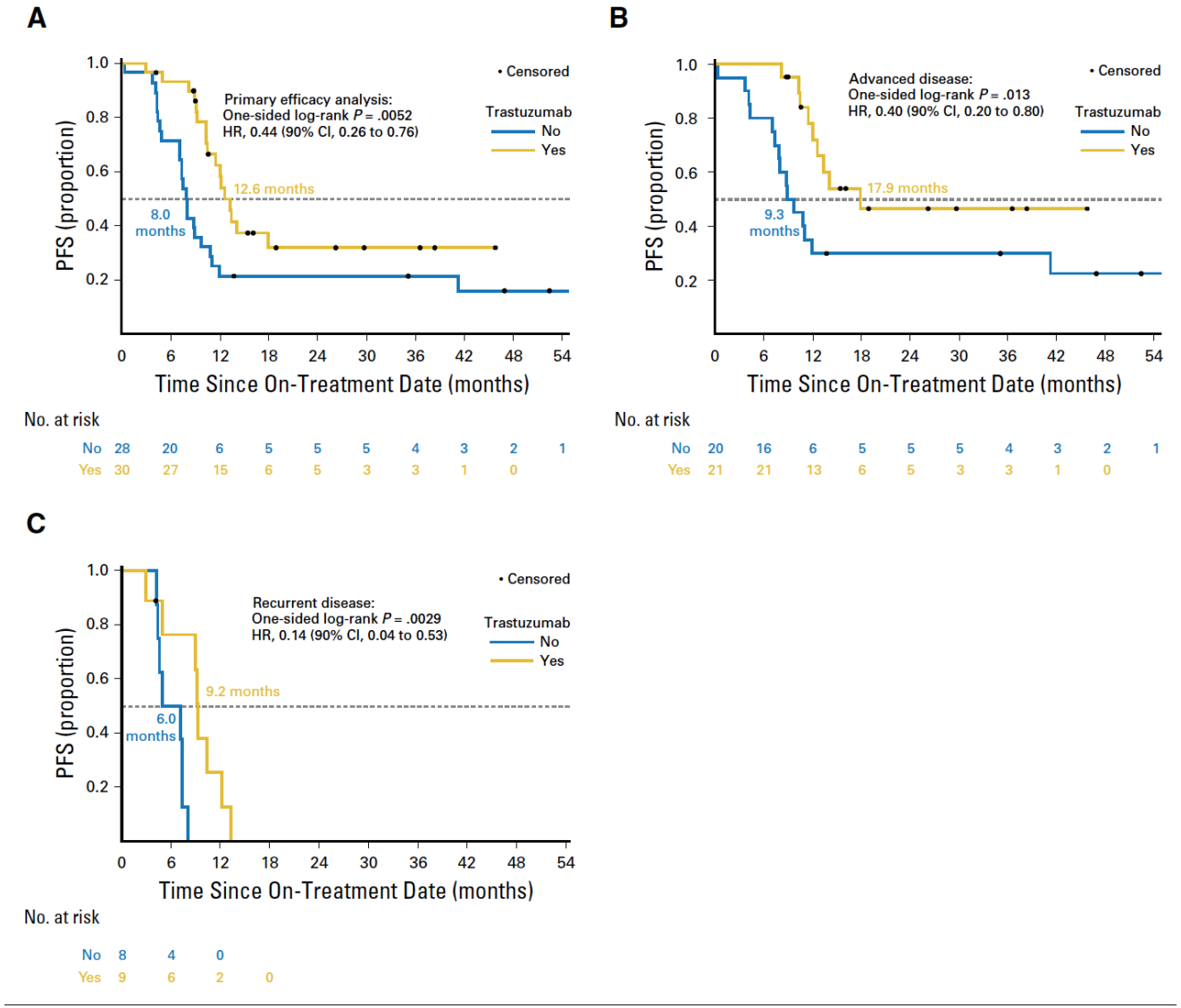
Modified from Morice et al, Lancet 2015

The TCGA analysis of HER2 mutation, deletion, and amplification across the 12 most common disease sites



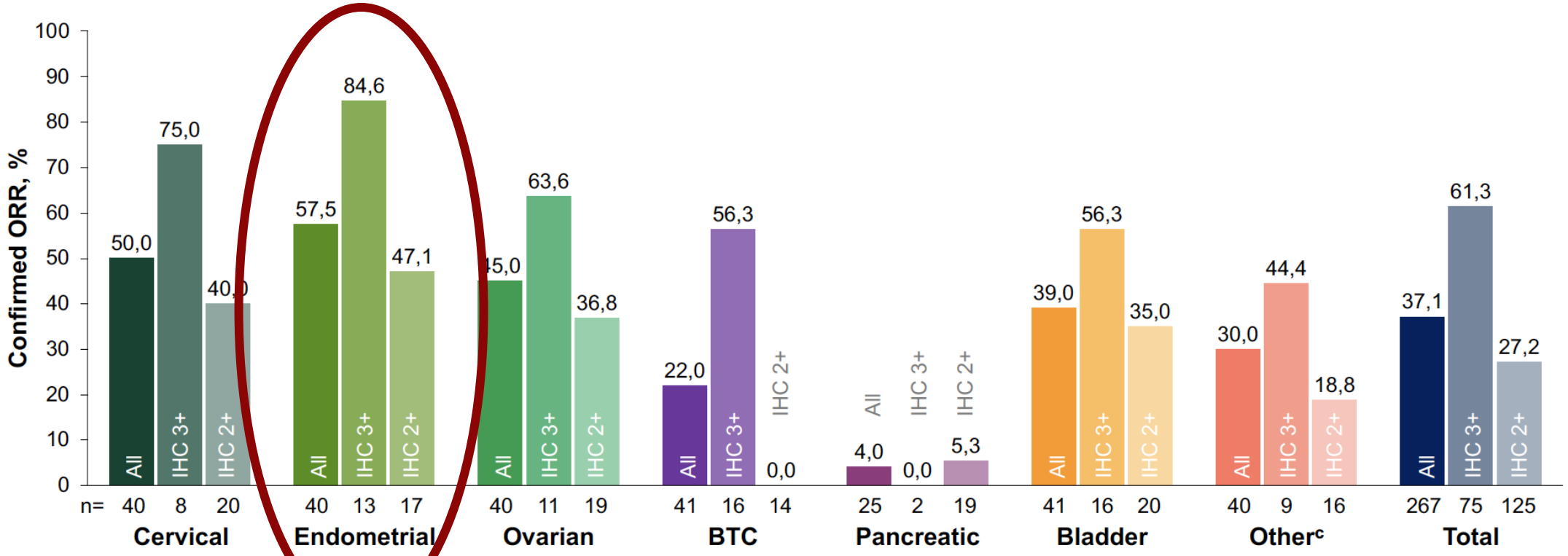
Gao J et al. Sci Signal 2013;6:pl1

Randomized Phase II Trial of Carboplatin-Paclitaxel Versus Carboplatin-Paclitaxel-Trastuzumab in Uterine Serous Carcinomas That Overexpress Human Epidermal Growth Factor Receptor 2/neu



Fader et al. J Clin Oncol 2018; 36:2044-2051.

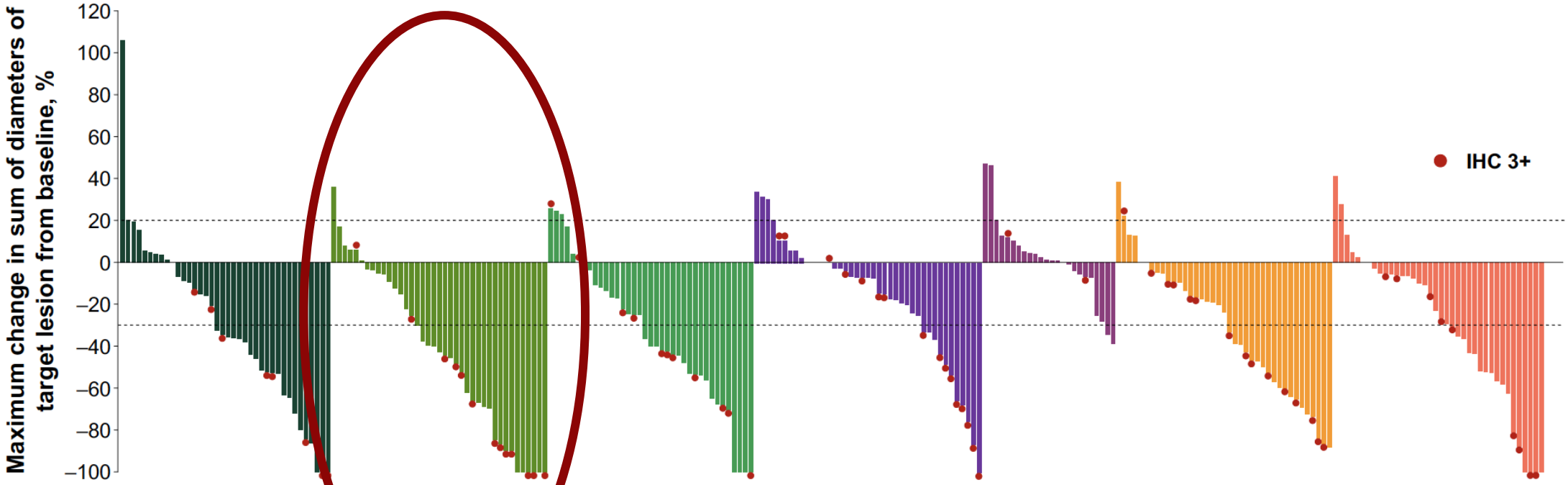
Objective Response Rate by HER2 status



	All patients (N=99)	IHC 3+ (n=46)	IHC 2+ (n=34)
Median DOR, months (95% CI)	11.8 (9.8–NE)	22.1 (9.3–NE)	9.8 (4.2–12.6)

Analysis of ORR was performed in patients who received ≥1 dose of T-DXd; all patients (n=267; including 67 patients with IHC 1+ [n=25], IHC 0 [n=30], or unknown IHC status [n=12] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=75) or IHC 2+ (n=125) status. Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd; all patients (n=99; including 19 patients with IHC 1+ [n=6], IHC 0 [n=9], or unknown IHC status [n=4] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=46) or IHC 2+ (n=34) status. [a]Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer.
BTC, biliary tract cancer; CI, confidence interval; DOR, duration of response; IHC, immunohistochemistry; NE, non-estimable; ORR, objective response rate.

Best Percentage Change in Target Lesion From Baseline



ORR in IHC 3+ n (%)	Cervical (n=8)	Endometrial (n=13)	Ovarian (n=11)	BTC (n=16)	Pancreatic (n=2)	Bladder (n=16)	Other[a] (n=9)
	6 (75.0)	11 (84.6)	7 (63.6)	9 (56.3)	0	9 (56.3)	4 (44.4)

Analyses were performed in patients who received ≥1 dose of T-DXd (n=267). Analysis of ORR in IHC 3+ was performed in patients with centrally confirmed HER2 status (n=75).
[a]Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer.
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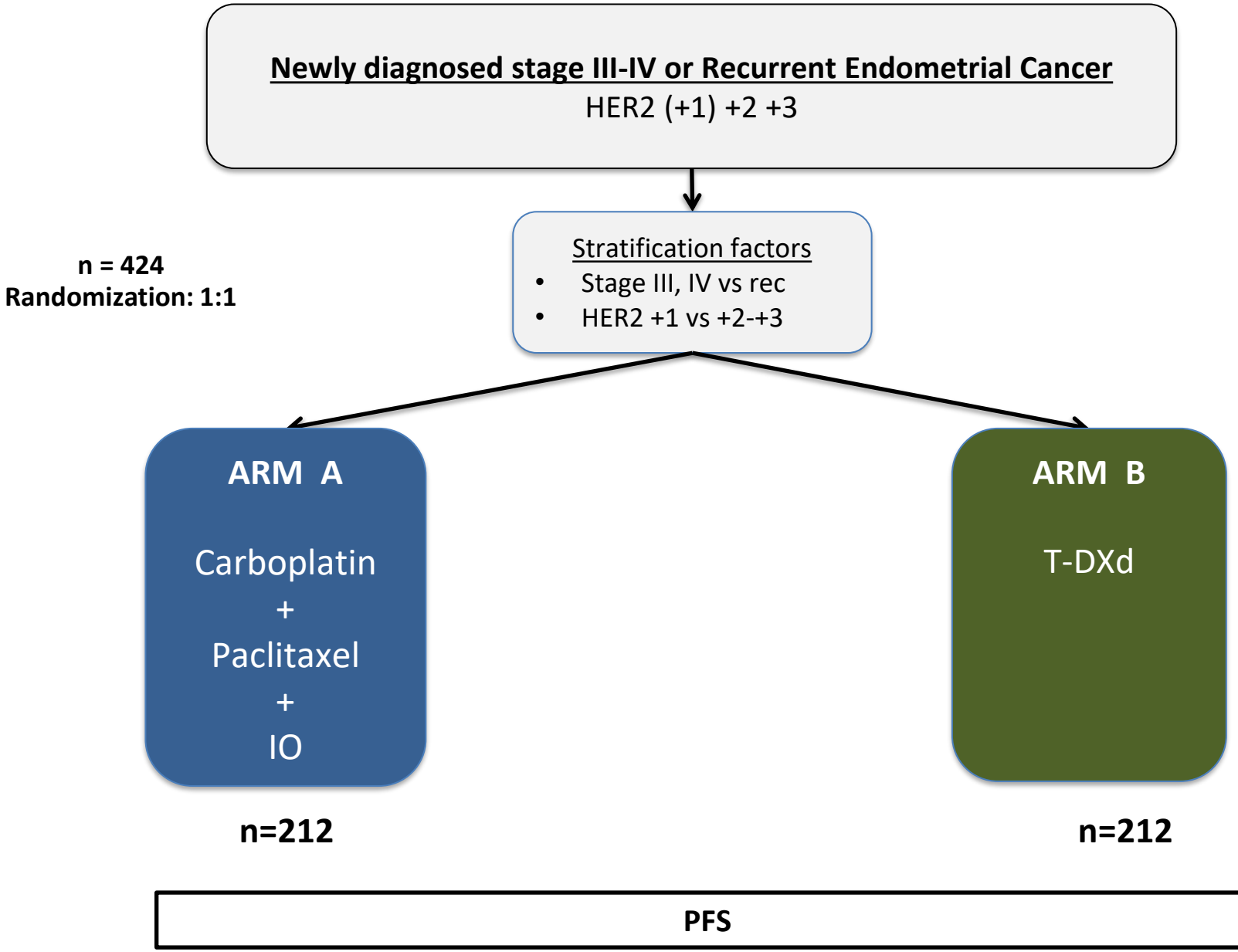
Study proposal

ENGOT-ENxx/T-DXd



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Modified from Morice et al, Lancet 2015

ENGOT-EN3 / NSGO-PALEO

ENGOT model A, sponsor NSGO-CTU, NCT02730429

- Measurable/evaluable endometrial cancer
- Primary stage 4 or relapsed disease
- ≥1 prior systemic therapy
- ER+ (≥10%) endometrioid adenocarcinoma
- ECOG PS 0/1
- No prior endocrine therapy except MPA and megestrol acetate
- No prior CDK inhibitor

1:1 randomisation

Placebo 125 mg days 1–21
Letrozole 2.5 mg days 1–28

Repeated every 28 days until progression

Palbociclib 125 mg days 1–21
Letrozole 2.5 mg days 1–28

Stratification:
- No. of prior lines (primary advanced disease vs 1st relapse vs ≥2 relapses)
- Measurable vs evaluable disease per RECIST
- Prior use of MPA/megestrol acetate

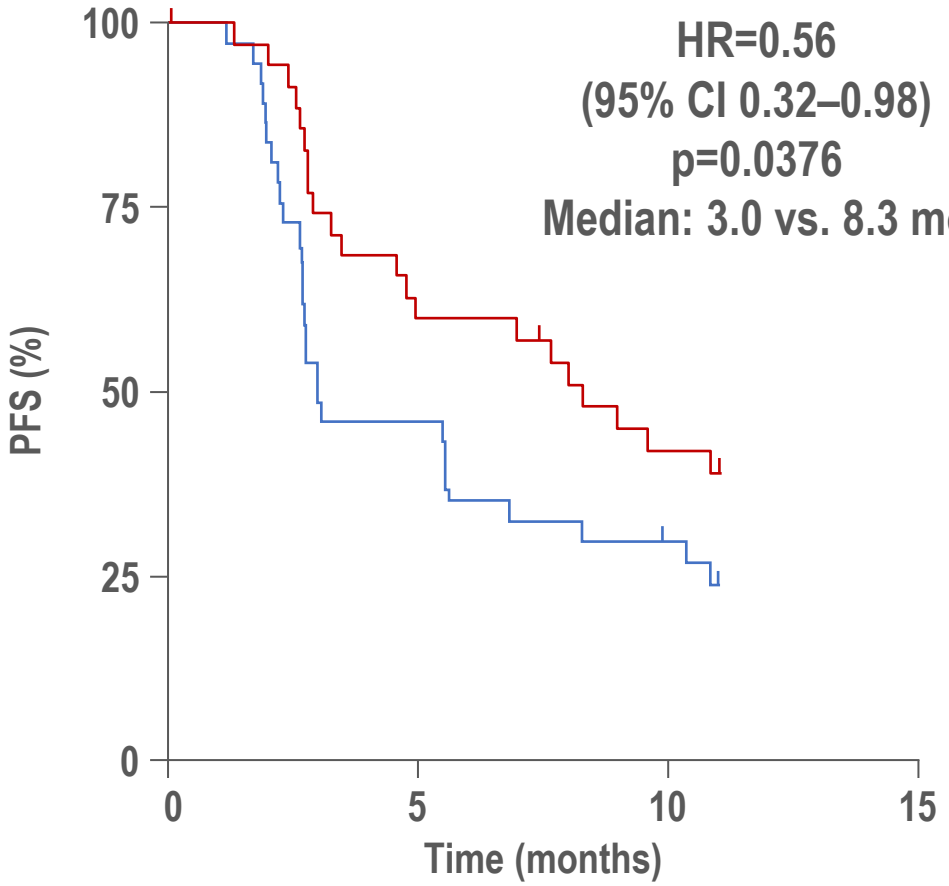
Primary endpoint: Investigator-assessed PFS (target HR 0.625, 80% power, 15% 1-sided α)
Secondary endpoints:
- PFS in subgroups
- Objective response rate, disease control rate, PFS2, overall survival
- PROs
- Safety and tolerability

HR = hazard ratio; MPA = medroxyprogesterone acetate; PROs = patient-reported outcomes

ENGOT-EN3 / NSGO-PALEO

Efficacy (ITT population)

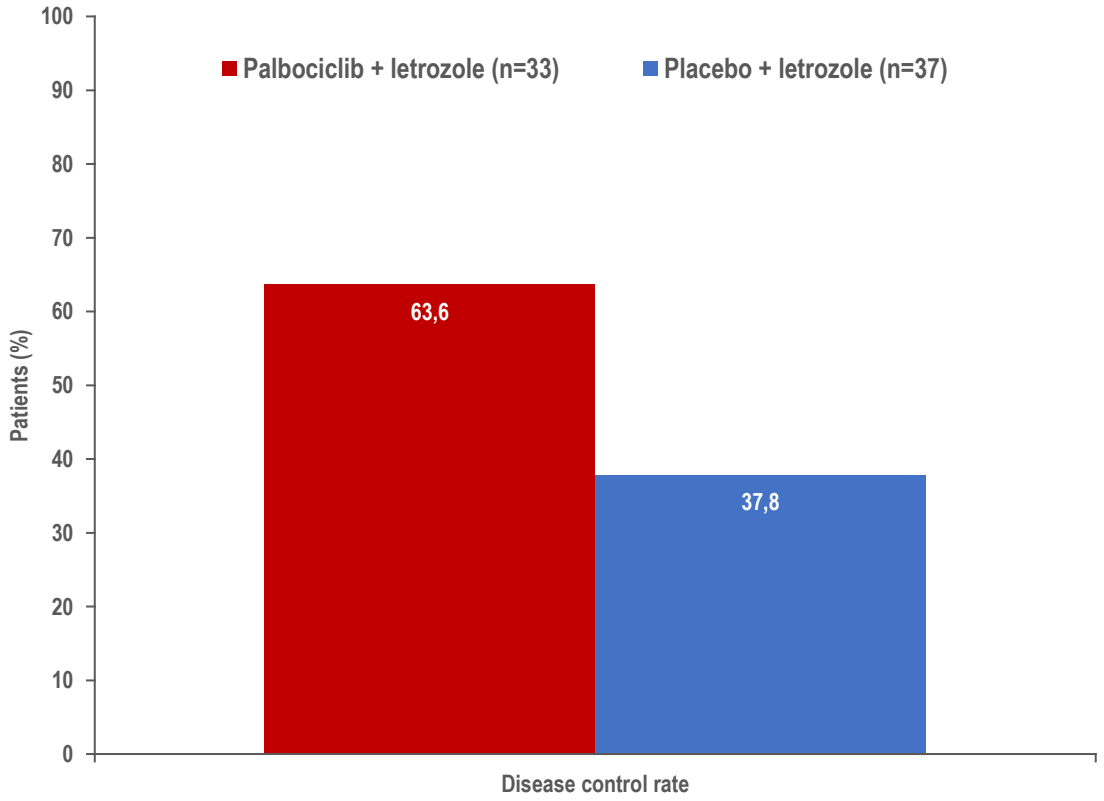
Primary endpoint: PFS



Number at risk

Palbociclib + letrozole	36	21	14
Placebo + letrozole	37	17	10

Secondary endpoint: Disease control rate*



CI = confidence interval; HR = hazard ratio

* = at 24 weeks

Mirza et al. ESMO 2020

ENGOT-en17/GINECO/EQ132-303/GOG-3075

- Grade 1 or Grade 2 Endometrioid
- No prior therapy for metastatic disease
- No prior endocrine therapy
- Stage IVB or Stage III/IV with measurable disease
- ECOG PS 0-1

n = 320

R

1:1

Double-Blinded

Letrozole 2.5 mg PO QD + Lerociclib 150 mg PO BID

Letrozole 2.5 mg PO QD + Placebo

Stratification variables:
- Tumor Stage (III vs. IV vs. recurrent)
- Tumor Grade (1 v. 2)
- Geographic Location

Primary endpoint: PFS by BICR
Secondary endpoints: PFS by IA, OS, ORR, DoR, QoL, AEs

- Hazard ratio for PFS: 0.63
- Significance level: 0.025 (1-sided)
- Randomization ratio: 1:1
- Median PFS in the control arm: 5 months
- Targeted PFS in the experimental arm: 7.94 months

Slomowitz et al.

Other New Kids in the Block

Antibody Drug Conjugates

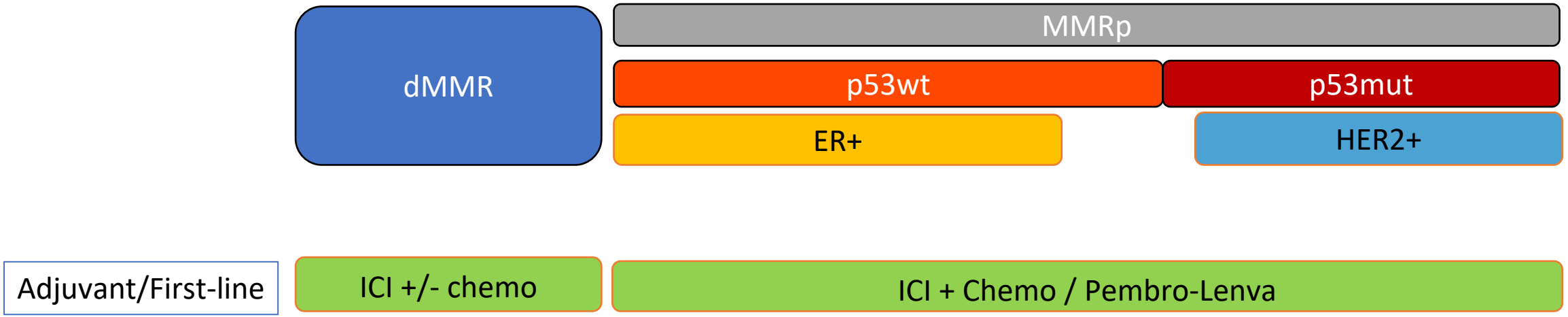
PARP inhibitors

mTOR inhibitors

PIK3CA

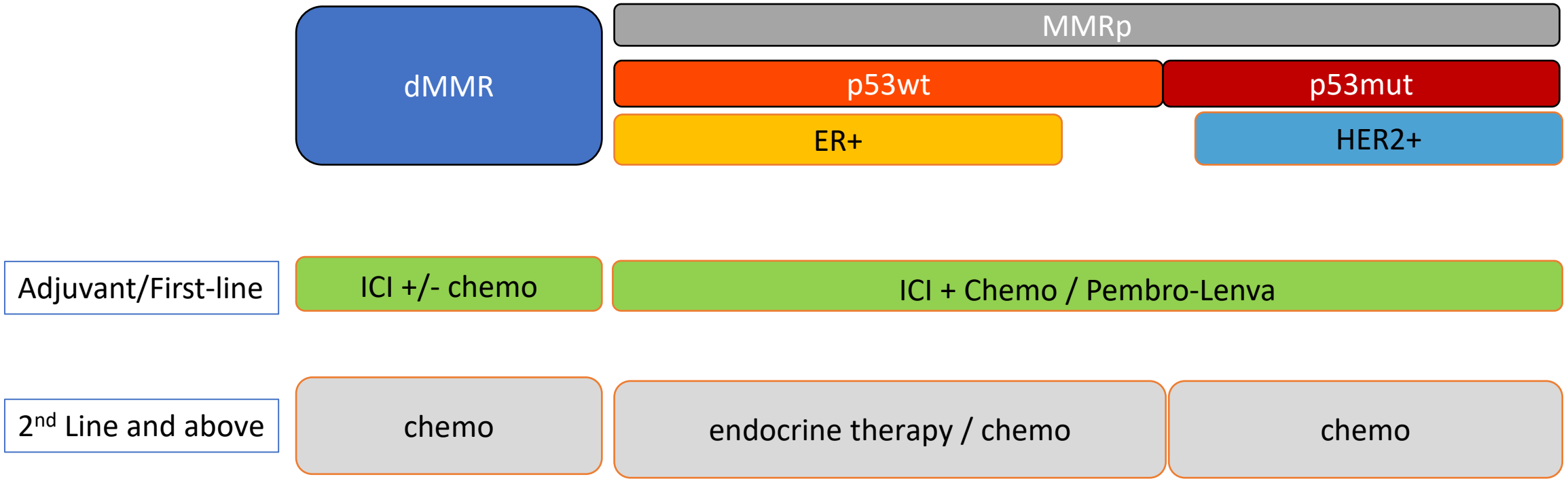
WEE1

Predicting the Future
Changing Landscape of Endometrial Cancer



Predicting the Future

Changing Landscape of Endometrial Cancer



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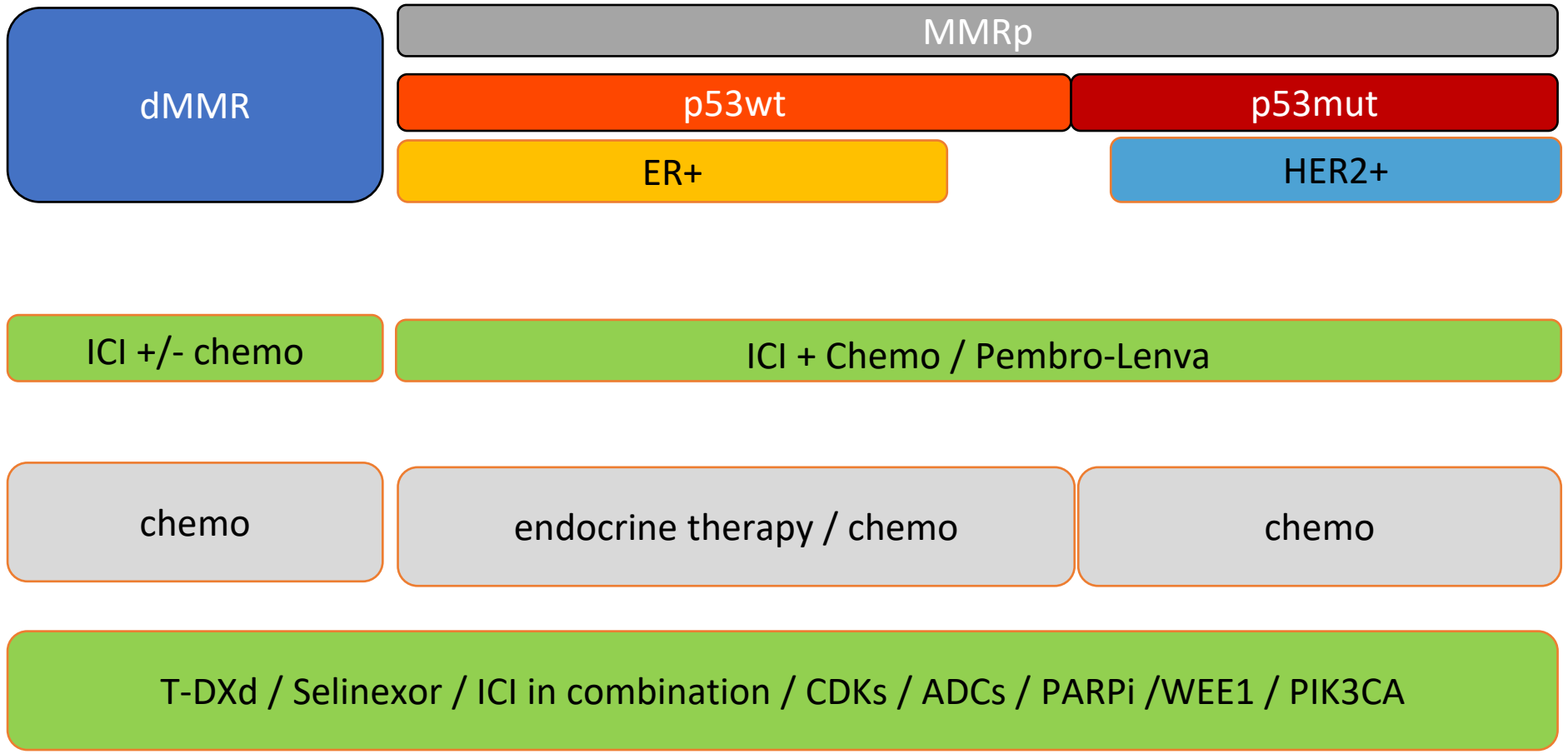

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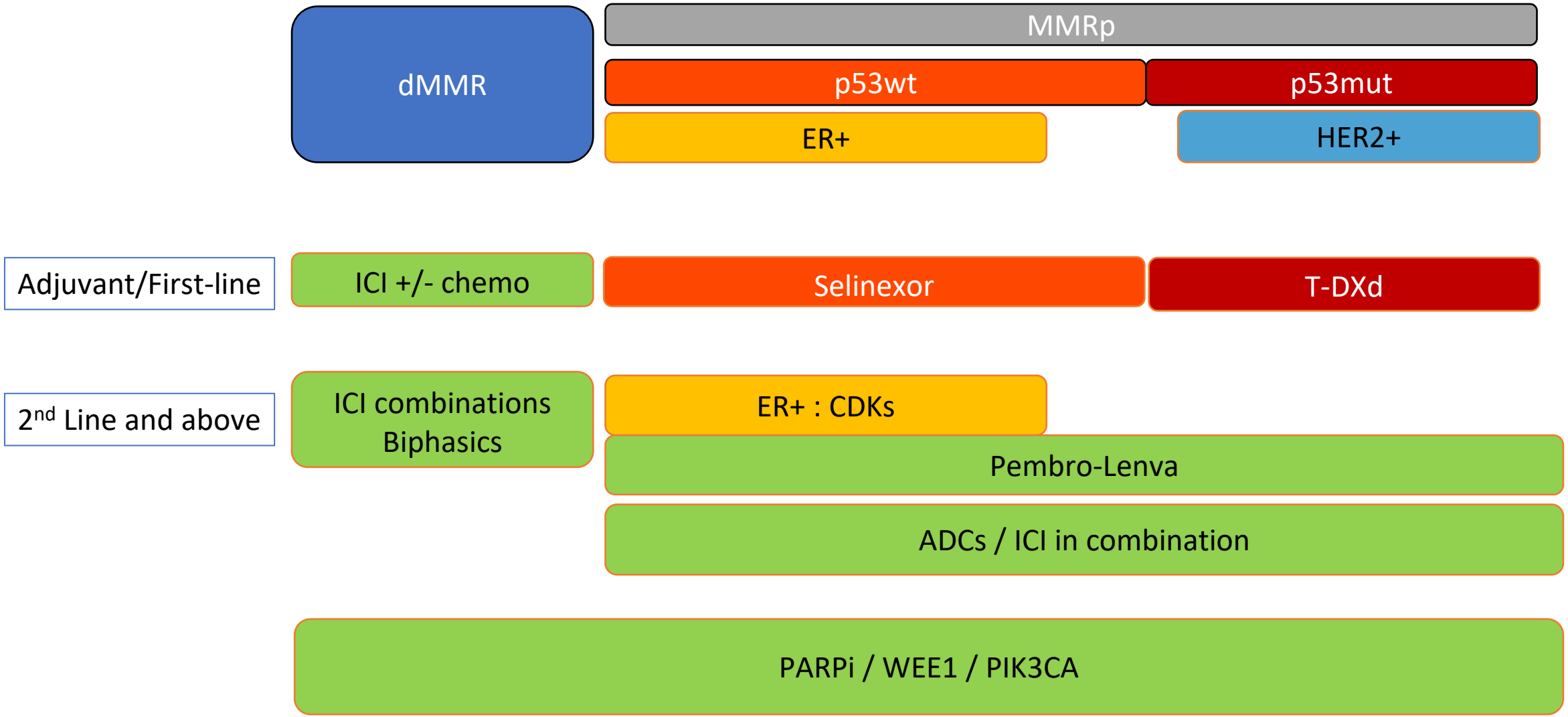

Key Takeaways

- Molecular profiling of this disease has completely transformed our therapeutic approach.
- RUBY & GY018 are not *baby steps but the Giant Leaps.*
- However, this is just the beginning of an unprecedented improvement in the outcome of our patients.
- We need more similar *Giant Leaps* to achieve our goal.
- This is a true Cinderella story.

Thank you

NSGO