Endometrial carcinoma Progression on immunotherapy

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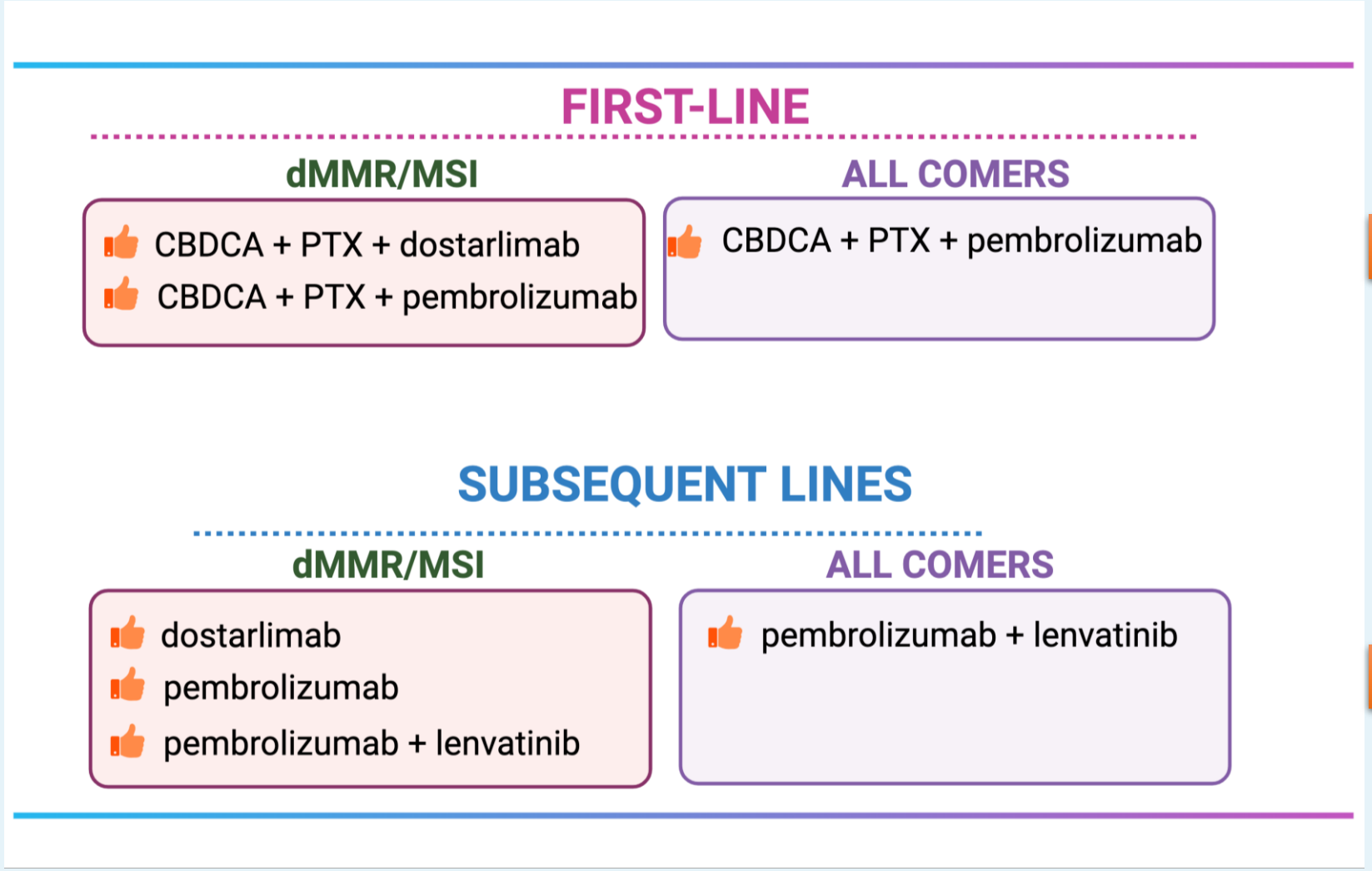
ICIs in recurrent/metastatic EC

Positive results both in 1st and 2nd line, next step adjuvant



Chemotherapy + ICIs

ICIs +/- TKI

Post ICIs: emerging issues

Patient selection

- Definition of resistance
- What is the current options post ICIs

Factors to integrate

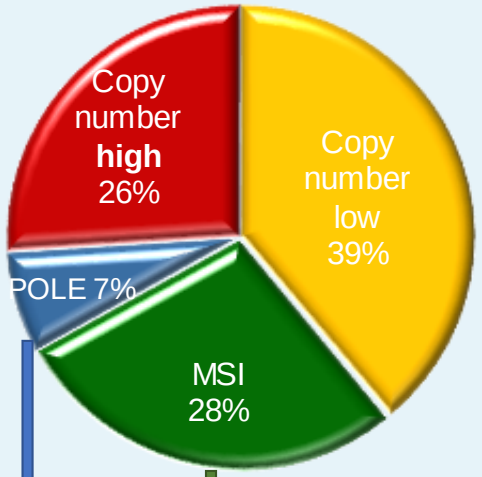
- Time to progression, definition of resistance to ICI, MSS status, other biomarkers,

Bypassing resistance

- ICIs combinational approaches
- alternative strategies after ICIs failure

Immunotherapy paradigm shift: who benefits?

The TGCA molecular classification

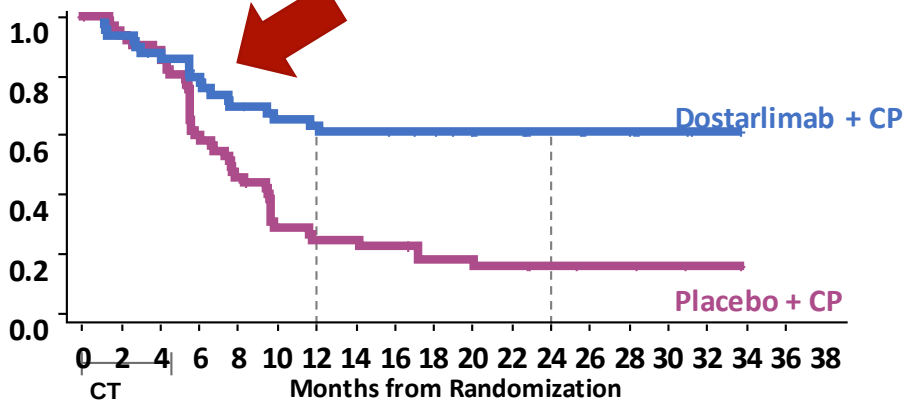


	POLE	MSI	Copy Number Low	Copy Number High
MSI/MLH methylation	Mixed MSI high, low, stable	MSI high	MSI stable	MSI stable
Molecular profile	POLE (100%) PTEN (94%) PIK3CA (71%) FBXW7 (82%) ARID1A (76%) KRAS (53%) PD1/PD-L1 overexpression	PTEN (88%) RPL22 (37%) KRAS (35%) PIK3CA (54%) ARID1A (37%) PD-1/PD-L1 overexpression	PTEN (77%) CTNNB1 (52%) PIK3CA (53%) ARID1A (42%) FGFR2 (10.9%)	TP53 (92%) PPP2R1A (22%) FBXW7 (22%) PIK3CA (47%) PTEN (11%) FGFR (7%) HER2 (25%)
Potential drugs	PI3K/PTEN/AKT/ mTOR pathway • Anti-PD-1/PD-L1 • Hormones	PI3K/PTEN/AKT/mTOR pathway • Anti-PD-1/PD-L1 • Hormones	• PI3K/PTEN/AKT/mTOR pathway • Hormones • FGFR-I	• **HER2- I** • PI3K- I • PARP-I • Wee-1 I • FGFR-I

Stelloo E, et al. *Clin Cancer Res.* 2016;22;4215-4224.

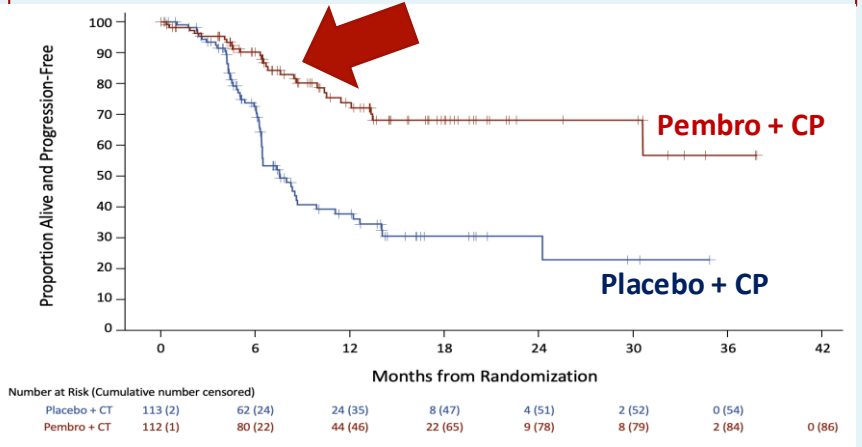
dMMR/MSI-H population: non responders
ICIs in combination

PFS in RUBY study (NCT03981796)

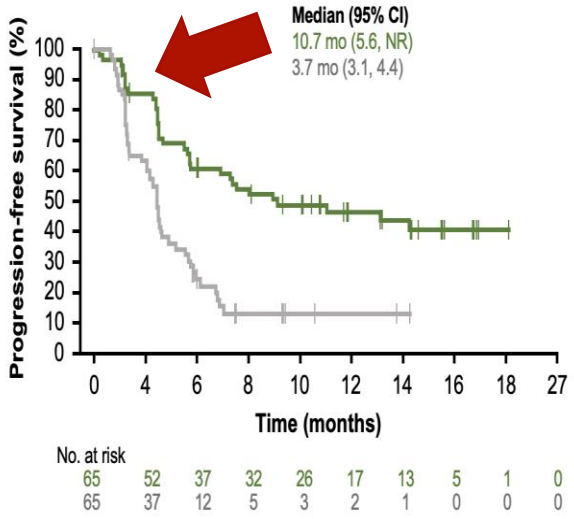


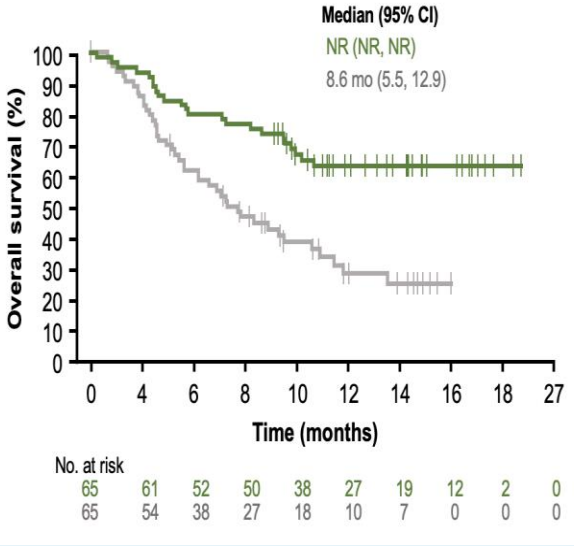
About 30% of MSI-H patients do not benefit

PFS in NRG-GY018 study (NCT03914612)



PFS/OS in MK-775





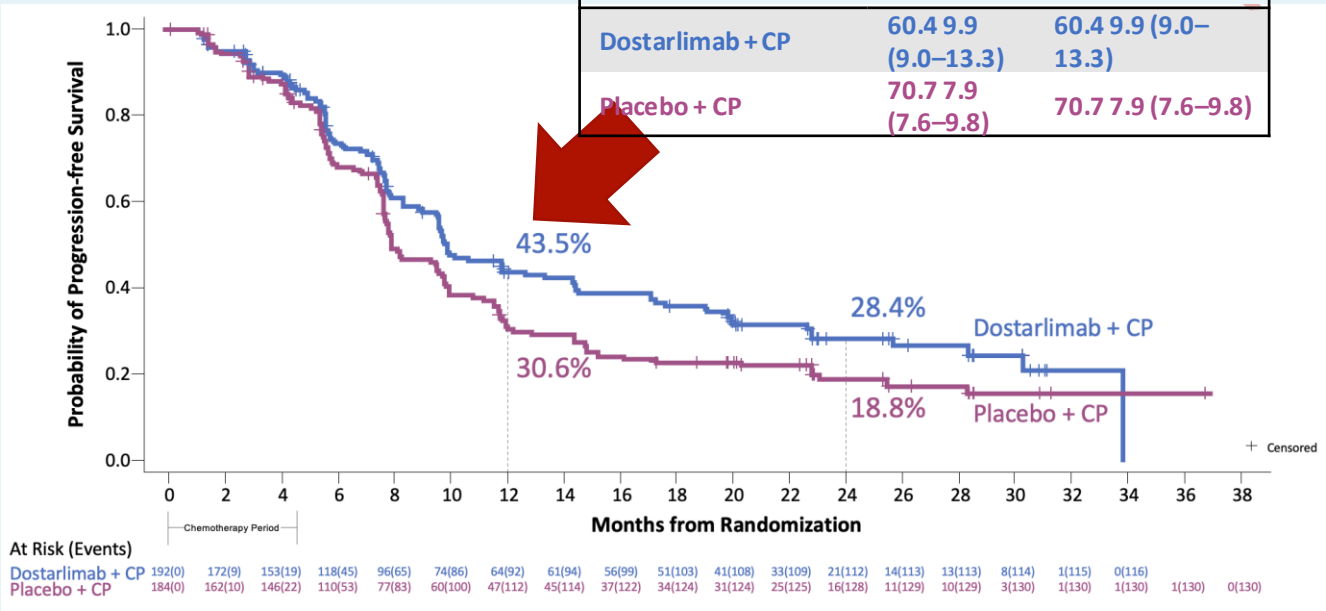
About 20% of MSI-H patients do not benefit

pMMR/MSS population: responders
ICI + chemotherapy

About 15 to 20% of MSS patients do benefit to combination

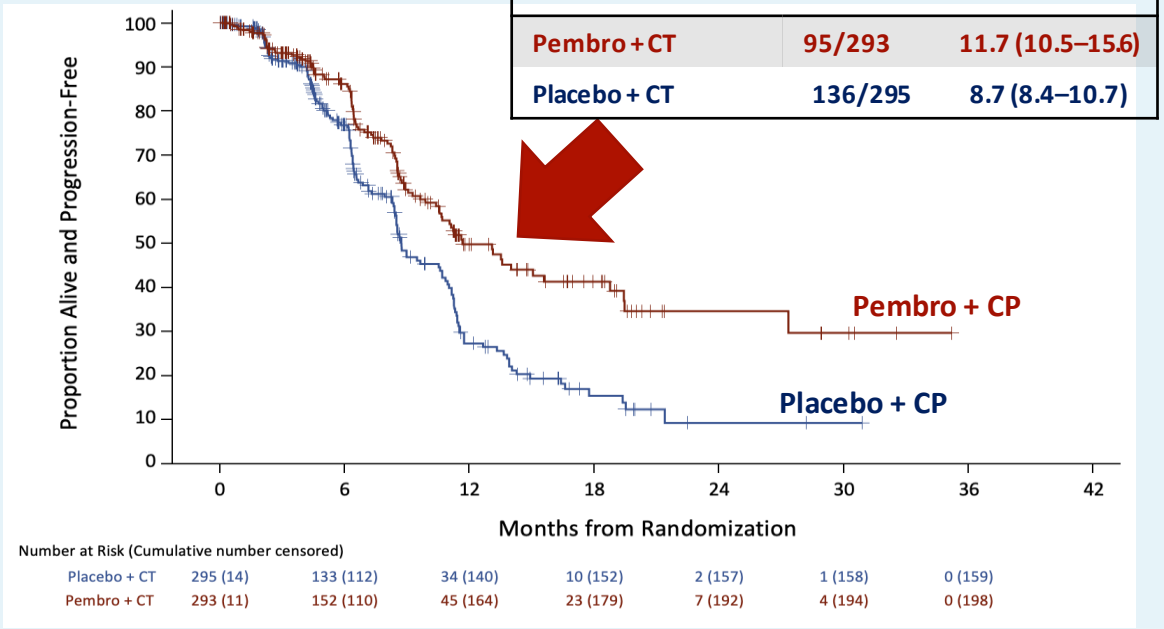
PFS in RUBY study (NCT03981796)

	Events (%)	mPFS (95%CI)
Dostarlimab + CP	60.4 9.9 (9.0–13.3)	60.4 9.9 (9.0–13.3)
Placebo + CP	70.7 7.9 (7.6–9.8)	70.7 7.9 (7.6–9.8)



PFS in NRG-GY018 study (NCT03914612)

	Events (n)	mPFS (95%CI)
Pembro + CT	95/293	11.7 (10.5–15.6)
Placebo + CT	136/295	8.7 (8.4–10.7)



STIC consensus to define resistance to ICIs in addition to CT or TKI

Combination with chemotherapy

Table 3 Minimum exposure and best response definition for primary resistance to immune checkpoint inhibitor–chemotherapy combinations in advanced tumor settings

Resistance phenotype	Exposure requirement	Timing of RECIST progression*	Confirmatory scan
Primary resistance†	6–8 weeks‡	≤6 months	Not required
Secondary or late resistance†	>6 months	>6 months	Not required

*Regardless of best response.
†For patients that experience recurrent disease after stopping therapy for reasons other than toxicity, no uniform clinical definitions of resistance applicable across disease states could be described.
‡For rapidly progressing disease, any exposure is adequate.
RECIST, Response Evaluation Criteria In Solid Tumors.

ICI- targeted therapy combination

Table 1 Clinical definition for primary resistance to immunotherapy–targeted therapy combinations

Resistance phenotype	Drug exposure requirement	Best response
Primary resistance	8–12 weeks* (2 cycles)	PD SD <6 months

*In the absence of toxicity or progression while on treatment.
PD, progressive disease; SD, stable disease.

Table 2 Clinical definition for secondary resistance to immunotherapy–targeted therapy combinations

Resistance phenotype	Drug exposure requirement	Best response
Secondary resistance	>6 months	CR, PR SD ≥6 months

CR, complete response; PR, partial response; SD, stable disease.

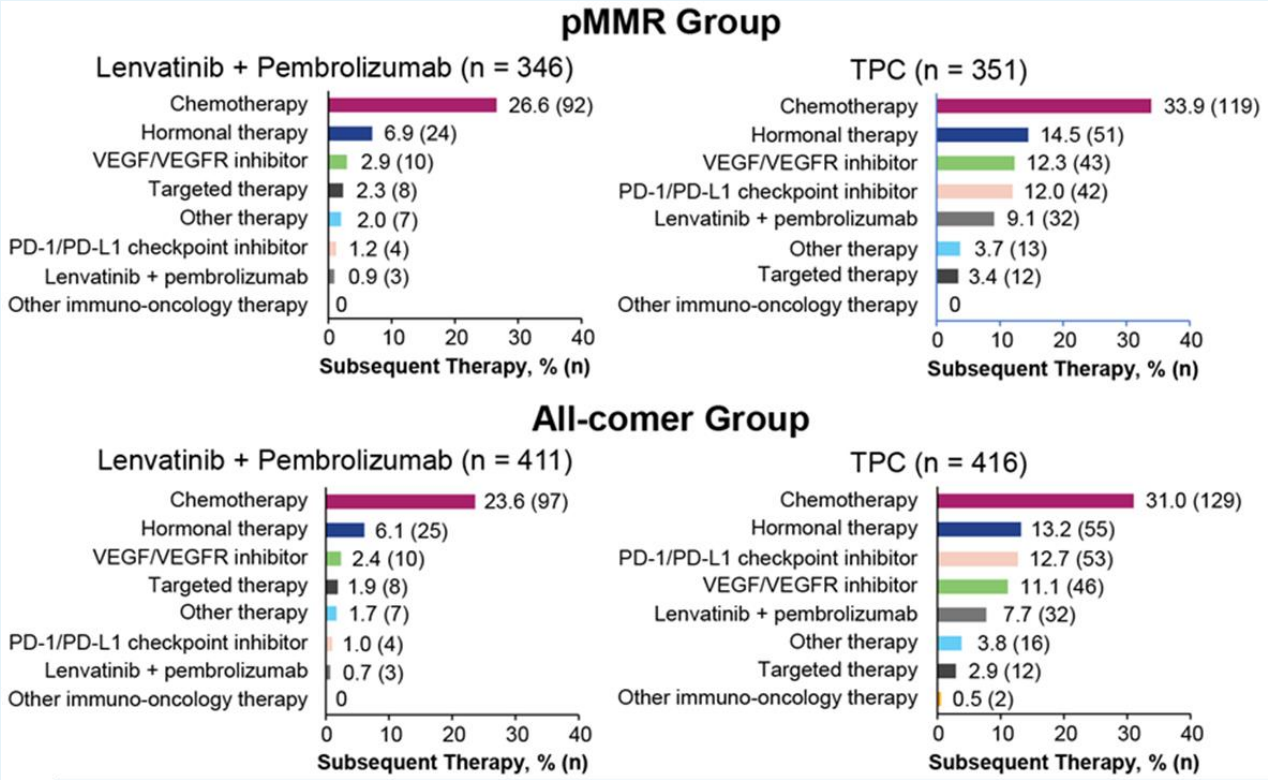
Journal of immunotherapy of cancer 2023
http://dx.doi.org/10.1136/jitc-2022-005923

Efficacy of subsequent therapies post ICIs

Keynote 755: Subsequent Systemic Anticancer Therapies Received

- most commonly doxorubicin (n = 58) in the lenvatinib + pembrolizumab arm and paclitaxel (n = 57) in the TPC arm.
- 78/200 (39%) patients in the TPC arm received lenvatinib + pembrolizumab as a subsequent therapy.

Subsequent Therapies Received by Treatment Type



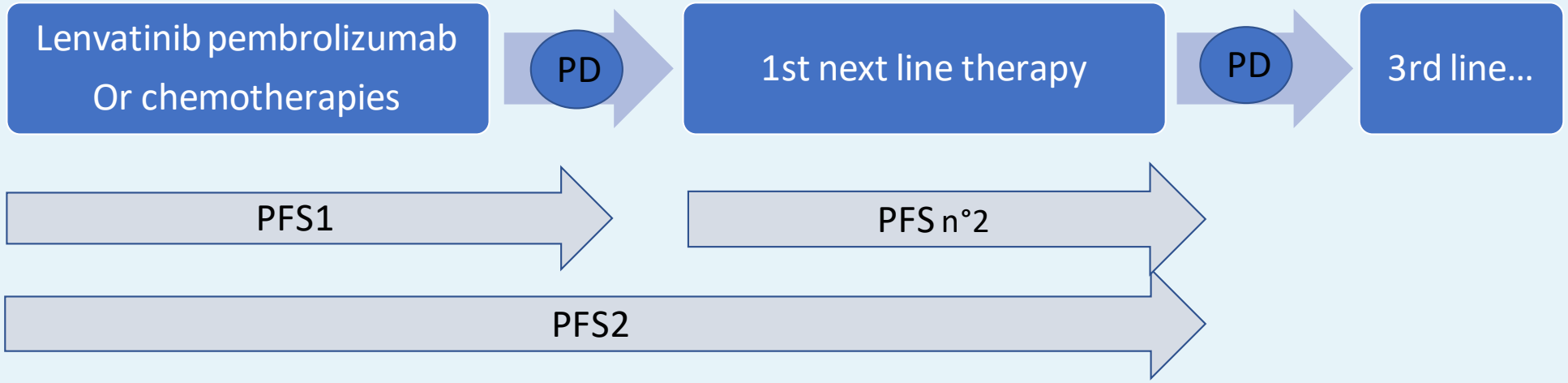
Subsequent Therapies Received by Treatment and by Number of Subsequent Therapy Lines

Subsequent Anticancer Therapies, n (%)	pMMR Group		All-comer Group		Total
	LEN + Pembro (n = 346)	TPC (n = 351)	LEN + Pembro (n = 411)	TPC (n = 416)	(N = 827)
Any subsequent anticancer therapy	109 (31.5)	176 (50.1)	115 (28.0)	200 (48.1)	315 (38.1)
Subsequent anticancer therapies received in ≥ 5% of all patients					
Paclitaxel	33 (9.5)	50 (14.2)	35 (8.5)	57 (13.7)	92 (11.1)
Carboplatin	30 (8.7)	47 (13.4)	30 (7.3)	52 (12.5)	82 (9.9)
Doxorubicin	55 (15.9)	16 (4.6)	58 (14.1)	18 (4.3)	76 (9.2)
Gemcitabine	14 (4.0)	34 (9.7)	15 (3.6)	35 (8.4)	50 (6.0)
Pembrolizumab	4 (1.2)	38 (10.8)	4 (1.0)	46 (11.1)	50 (6.0)
Subsequent LEN + pembro	3 (0.9)	32 (9.1)	3 (0.7)	32 (7.7)	35 (4.2)
Number of lines of subsequent anticancer therapy received					
1	6 (1.7)	11 (3.1)	6 (1.5)	13 (3.1)	19 (2.3)
2	81 (23.4)	134 (38.2)	85 (20.7)	152 (36.5)	237 (28.7)
≥ 3	55 (15.9)	78 (22.2)	58 (14.1)	85 (20.4)	143 (17.3)

Percentages are out of all patients, regardless of whether subsequent therapy was received; patients may have received > 1 subsequent therapy regimen.

Impact of ICI on next PFS ?

PFS2 data Outcomes post-progression Keynote 755



Lenva Pembro	7,3 months	8,7 months	ITT
Chemotherapy	3,8 months	5,7 months	
Lenva Pembro	6,7 months	7,7 months	pMMR
Chemotherapy	3,8 months	6,0 months	

No significant difference in PFS n°2

<u>Progressing on Lenva Pembro has no impact on efficacy for subsequent lines</u>

Post ICI treatment summary

- In 1st line (RUBY & NRG GY018)
  - dMMR 10% progressed during CT, 20% at 6 months and 40% at 2 years
  - pMMR 10% progressed during CT, 30% at 6 months and 70% at 2 years
- In relapse post platinum based CT (Keynote 755)
  - dMMR 35% progressed at 6 months and 40% at 2 years
  - pMMR 50% progressed at 6 months and 80% at 2 years
- Standard therapy remains chemotherapy (monotherapy or combo)
- No data to suggest detrimental impact (perhaps better to receive IO in 1st line for efficacy in the next line)

Post ICIs: emerging issues

Patient selection

- Definition of resistance
- What is the current options

Factors to integrate

- Time to progression, definition of resistance to ICI,
- MSS status, other biomarkers

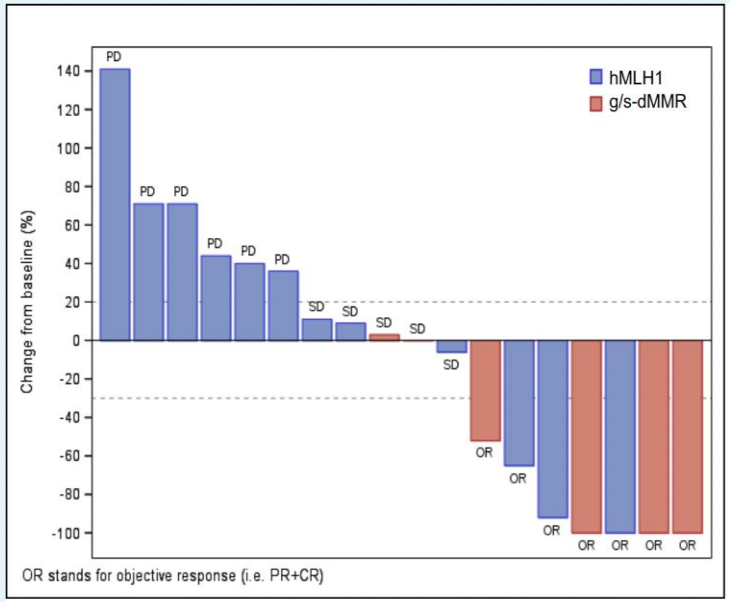
Bypassing resistance

- ICI combinational approaches
- alternative strategies after ICIs failure

Could mechanisms underlying dMMR/MSI-H ECs alter responses to ICI?

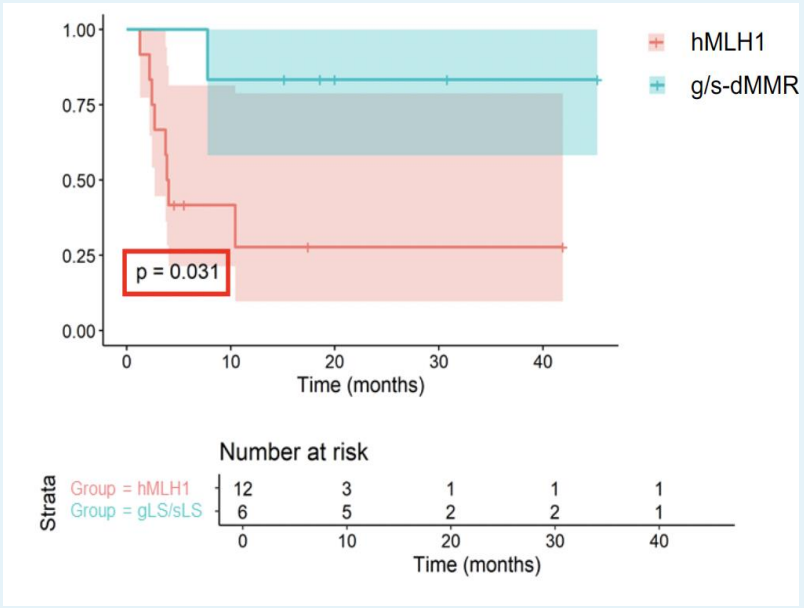
Data from Pembrolizumab studies

Objective Response Rates



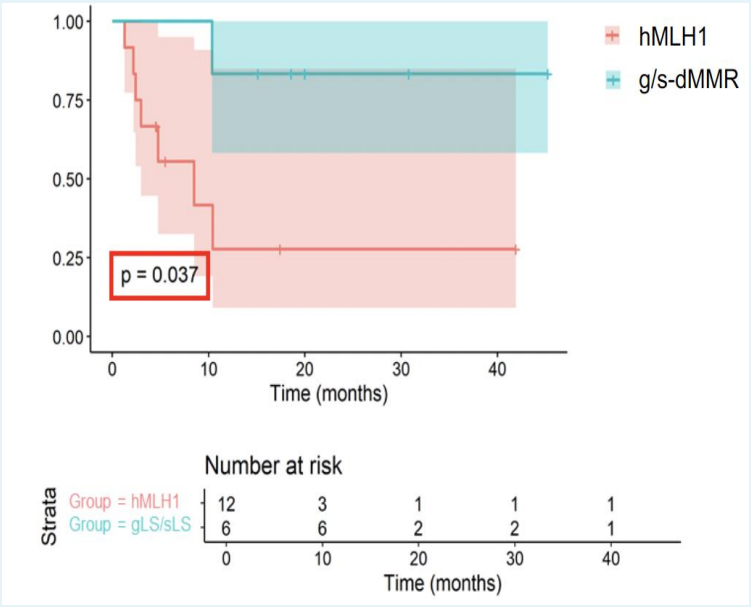
ORR: 38.8%(7/18 pts)
g/s-dMMR:66.7%(4/6 pts)
hMLH1:25.0%(3/12pts)
P = 0.141

Recurrence-Free Survival



Median RFS
hMLH1: 4.0 mos
g/s-dMMR: NR

Overall Survival



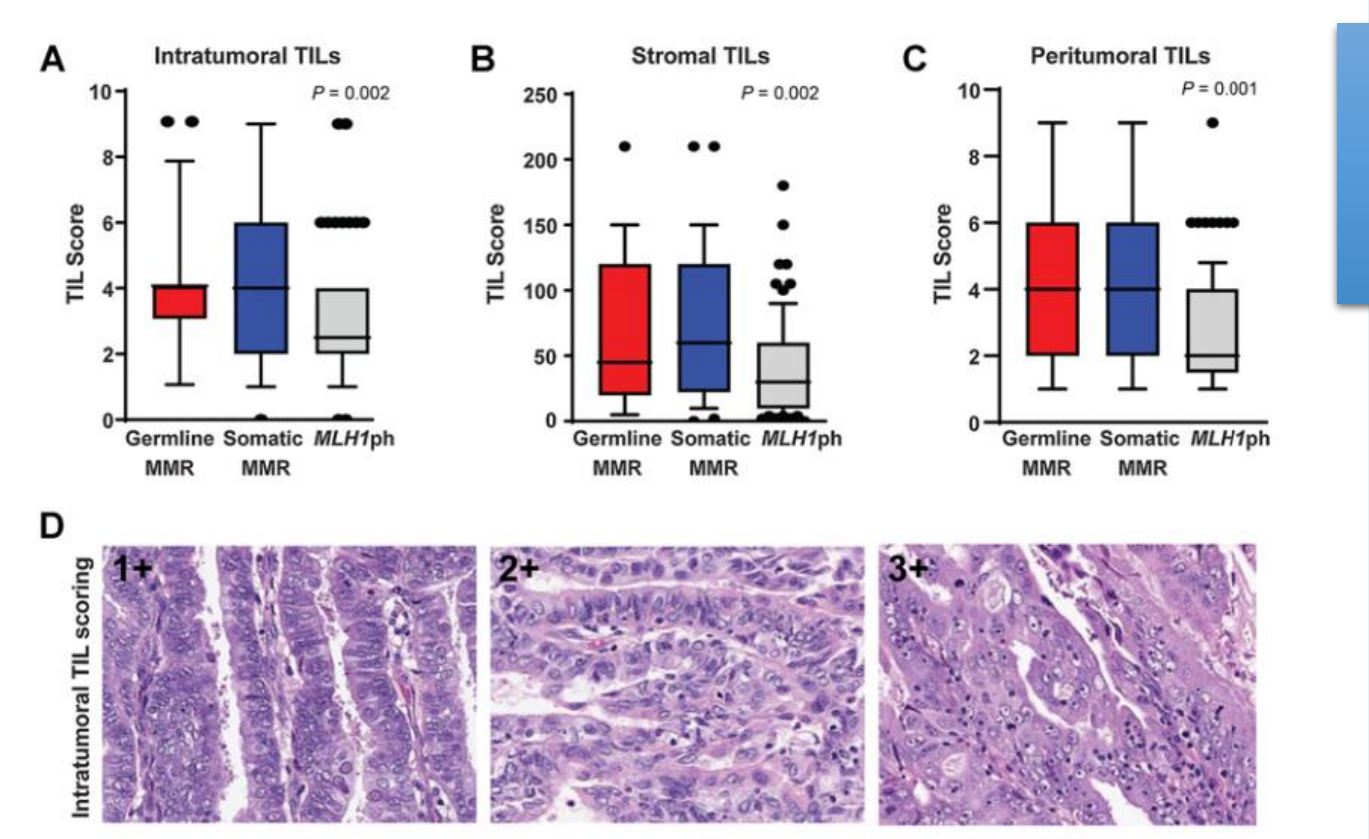
Median OS
hMLH1: 8.5mos
g/s-dMMR: NR

Lindsay Borden et al. Presented at SGO Meeting, March 2022

Median follow-up: 9.5 months

Courtesy Ana Oaknin, MD PhD

Molecular background behind ICIs response
distinct **dMMR/MSI-H populations**



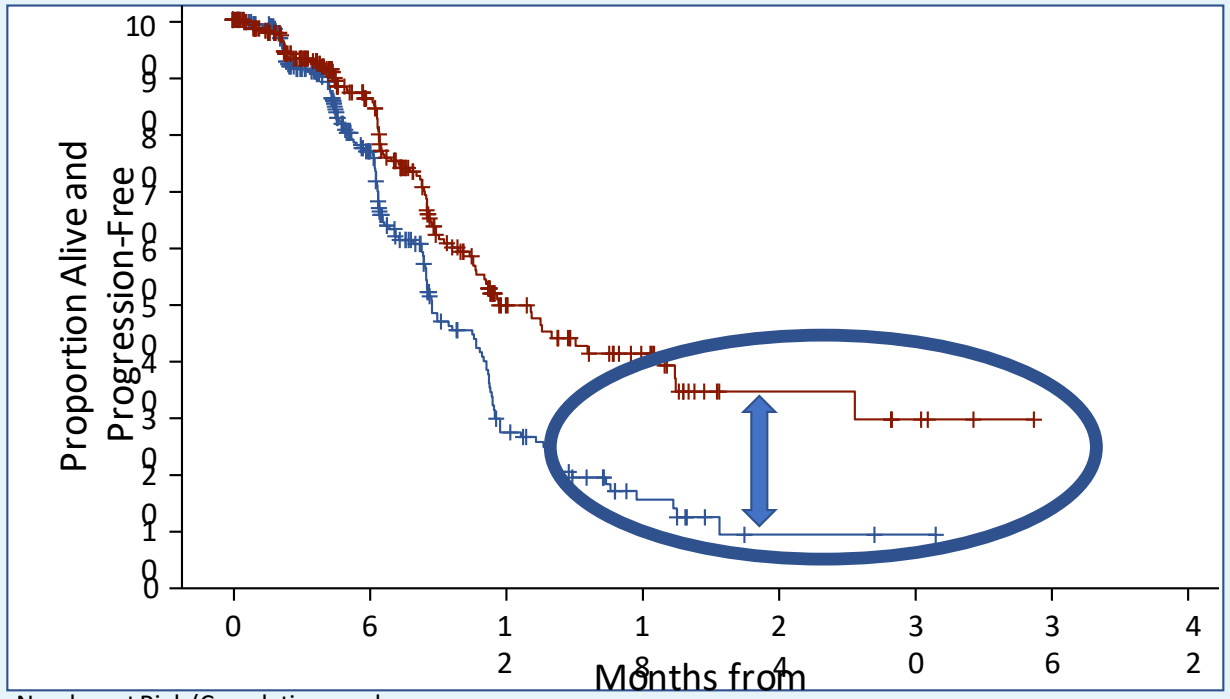
distinct molecular and immune profiles
MLH1ph
vs.
somatic or germline MMR mutations

Should be considered for the next line of treatment ?

Manning-Geist et al., Clinical Cancer Research, 2022

Molecular background behind ICIs response distinct pMMR/MSS populations

GY018 **About 10 - 15% of MSS patients do benefit: who are these patients?** RUBY



	Events, n/N	Median (95% CI), mo
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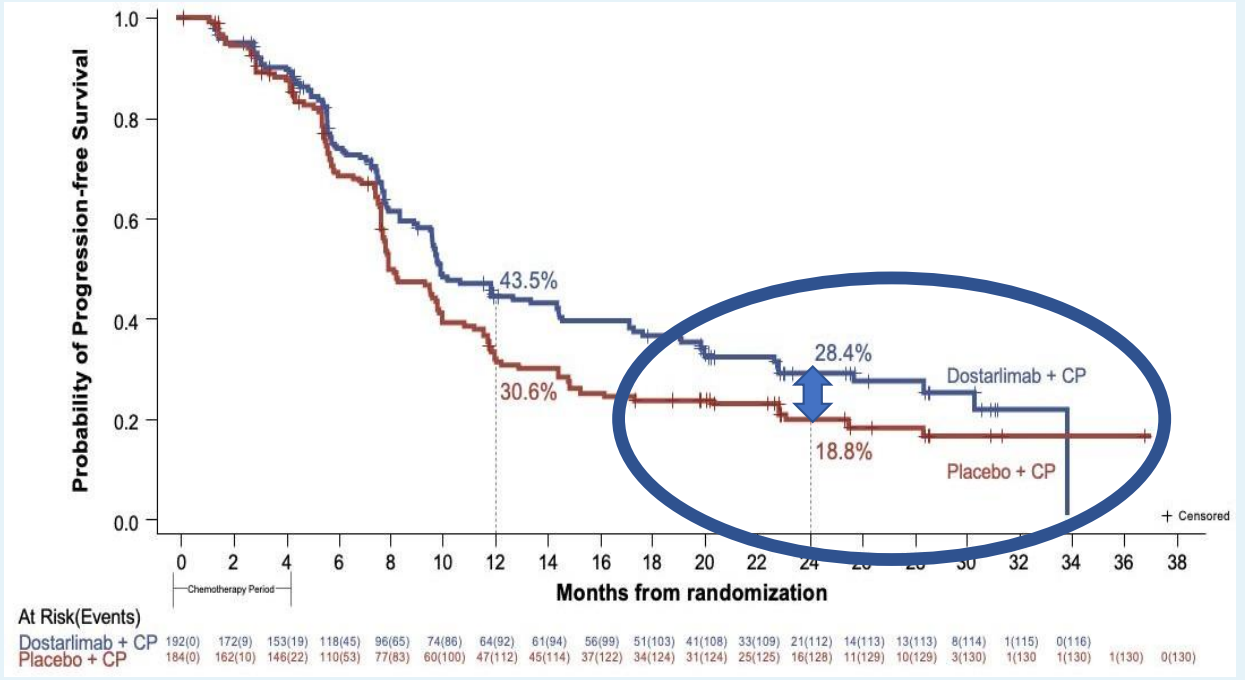
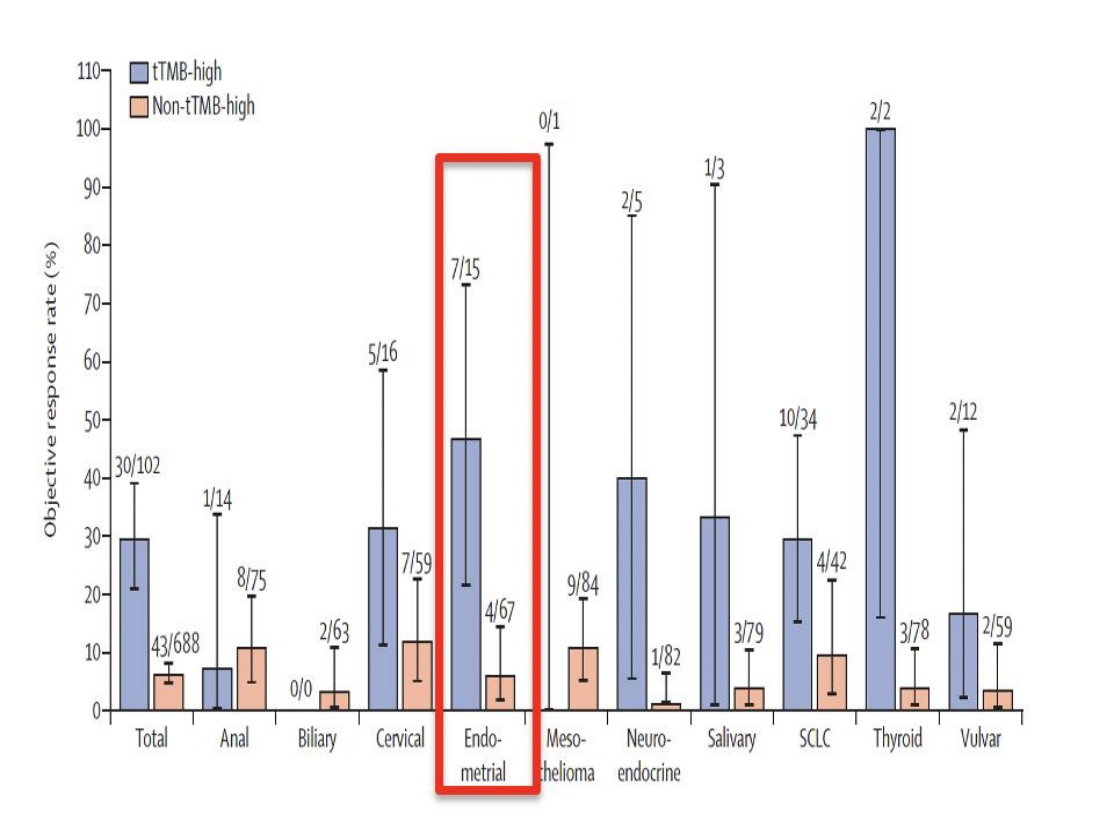


	No. with event, %	Median (95%CI), mo
Dostarlimab + CP	60.4	9.9 (9.0–13.3)
Placebo + CP	70.7	7.9 (7.6–9.8)
PFS maturity	65.4	

Beyond dMMR/MSI-H:

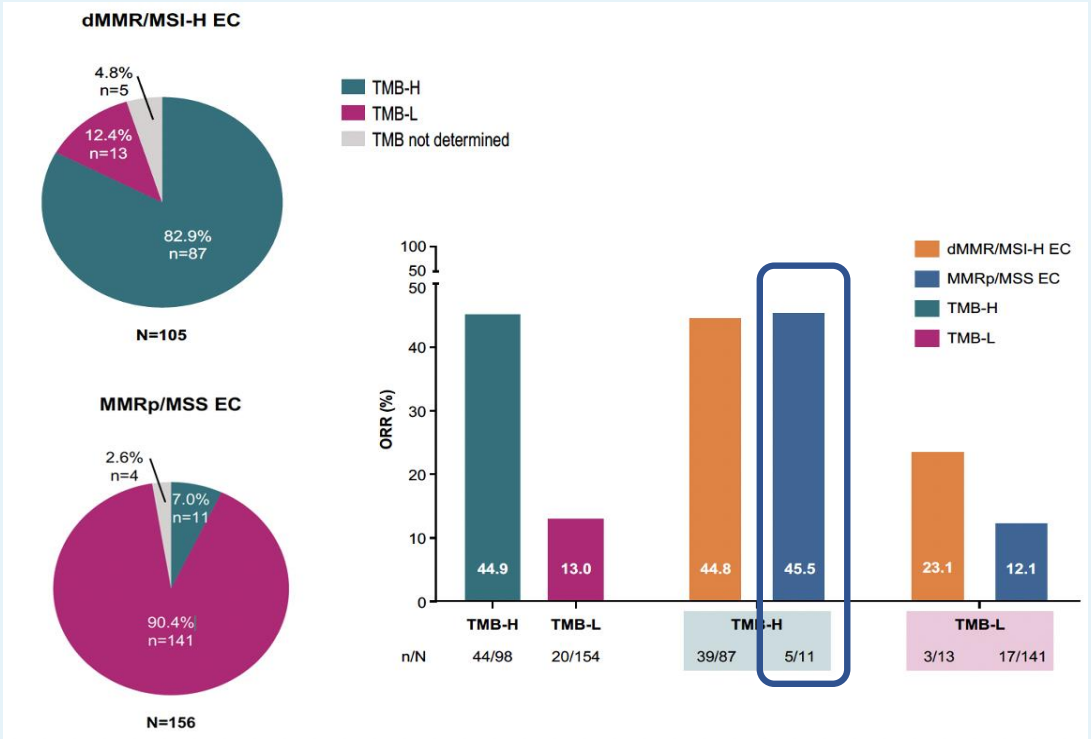
Tumour Mutational Burden(TMB)as biomarker

KEYNOTE-158



Marabelle A et al;Lancet Oncol. 2020 Oct;21(10):1353-1365; Oaknin A. et al. Presented at ESMO 2021

GARNET



TMB-high (TMB-H):≥10 mutations/Mb

Need to be considered for the next line of treatment ?

Courtesy Ana Oaknin, MD PhD

Post ICIs: emerging issues

Patient selection

- Definition of resistance
- What is the current options

Factors to integrate

- Time to progression, definition of resistance to ICI,
- MSS status, other biomarkers

Bypassing resistance

- ICI combinational approaches
- alternative strategies after ICIs failure

ICIs after ICIs as monotherapy ORR of 4.6%

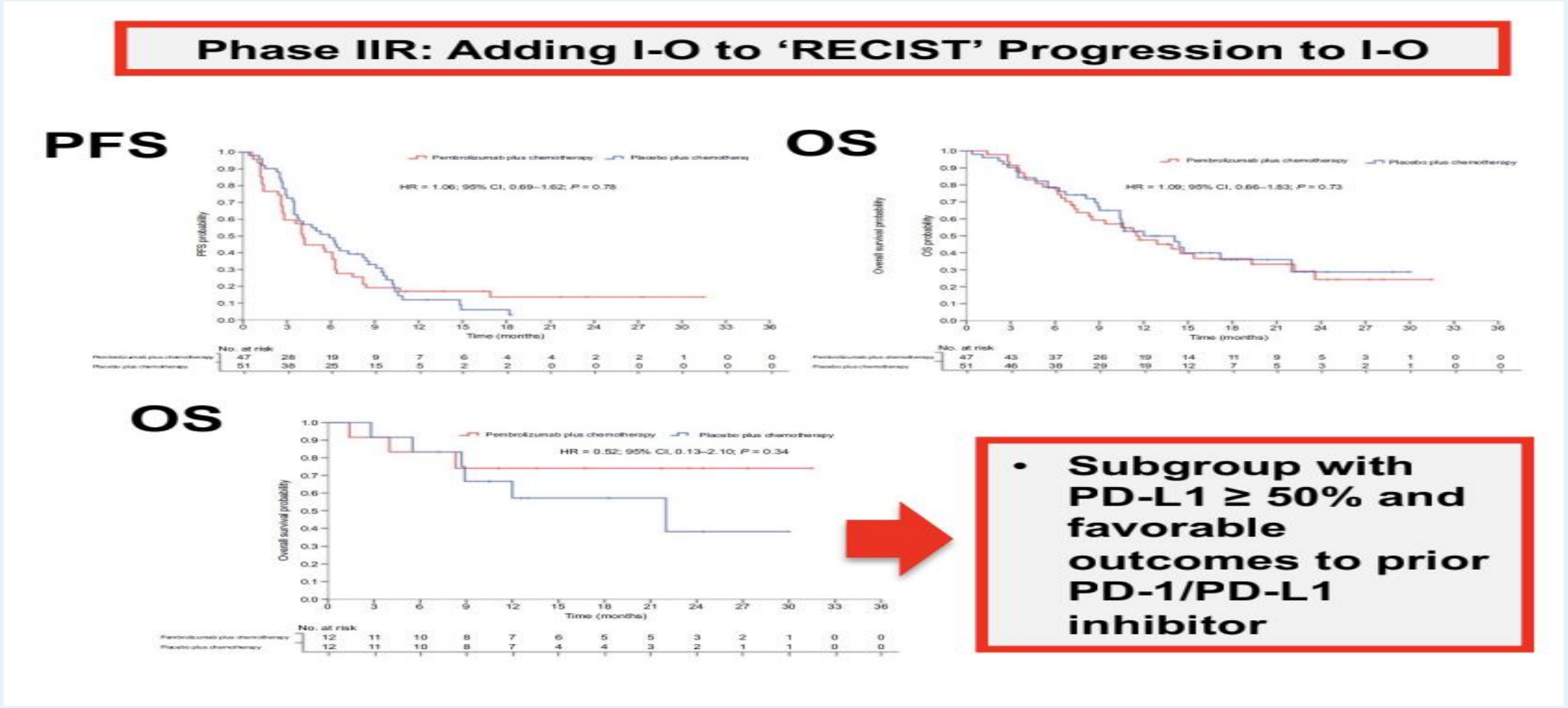
Table 1 Summary of results of clinical trials with anti-PD-1/PD-L1 as single agents (only data for anti-PD-1/PD-L1 arms are reported)

Study name/ code (NCT)	Study phase	Type of Cancer	Treatment	Patients evaluated for response	Time to first tumor assessment (weeks)	ORR by RECIST criteria	ORR by immune-related response criteria	Rate of patients treated beyond progression	ORR after initial PD	First author and date of publication
15–286 (NCT02673333)	2	Adrenocortical carcinoma	Pembrolizumab	39	9	9 (23.1%)	Not reported	Not reported	2 (5.1%)	Raj 2020 [12]
16–032 (NCT02730130)	2	Breast cancer	Pembrolizumab plus RT	17	13	3 (17.6%)	3 (17.6%)	Not reported	Not reported	Ho 2019 [13]
2014–1315 (NCT02364076)	2	Thymic carcinoma	Pembrolizumab	40	6	9 (22.5%)	Not reported	Not reported	0 (0%)	Giaccone 2018 [14]
20,151,049 (NCT02658019)	2	Hepatocellular carcinoma	Pembrolizumab	28	9	9 (32.1%)	Not reported	15 (53.6%)	1 (3.6%)	Feun 2019 [15]
Alliance A091401 (NCT02500797)	2	Sarcoma	Nivolumab	38	6	2 (5.3%)	Not reported	18 (47.4%)	0 (0%)	D'Angelo 2018 [16]
Attraction-2 (NCT02267343)	3	Gastric cancer	Nivolumab	268	6	30 (11.2%)	Not reported	95 (35.5%)	Not reported	Kang 2017 [17]
CD-ON-MEDI4736–1108 (NCT01693562)	1/2	UC	Durvalumab	42	6	13 (31.0%)	Not reported	2 (4.8%)	2 (4.8%)	Massard 2016 [18]
		NSCLC		256		39 (15.2%)		99 (38.7%)	Not reported	Antonia 2019 [19]
CA-210-001 (NCT00729664)	1	Advanced solid tumors	Nivolumab	160	6	17 (10.6%)	Not reported	Not reported	4 (2.5%)	Brahmer 2012 [20]
CheckMate-003 (NCT00730639)	1	RCC	Nivolumab	34	8	10 (29.4%)	Not reported	Not reported	3 (8.8%)	MCDermott 2015 [21]
		Melanoma		107		33 (30.8%)	Not reported	Not reported	4 (3.7%)	Topalian 2014 [22]
		NSCLC		129		22 (17.1%)	Not reported	Not reported	6 (4.7%)	Gettinger 2015 [23]
CheckMate-004 (NCT01024231)	1	Melanoma	Nivolumab	30	8	6 (20.0%)	Not reported	Not reported	3 (10.0%)	Wolchock 2013 [24]
CheckMate-010 (NCT01354431)	2	RCC	Nivolumab	168	6	35 (20.8%)	38 (22.8%)	36 (21.4%)	2 (1.2%)[a]	Motzer 2015 [25], George 2016 [8], Pignon 2019 [6]
CheckMate-012 (NCT01454102)	1	NSCLC	Nivolumab	52	11	12 (23.1%)	Not reported	Not reported	3 (5.8%)	Gettinger 2016 [26]
CheckMate-017 (NCT01642004)	3	Squamous NSCLC	Nivolumab	135	9	27 (20.0%)	Not reported	27 (20.0%)	9 (6.7%)	Brahmer 2015 [27]
CheckMate-025 (NCT01668784)	3	RCC	Nivolumab	406	8	Not reported	Not reported	153 (37.7%)	20 (4.9%)	Escudier 2017 [28]
CheckMate-026	3	NSCLC	Nivolumab	211	6	55 (26.1%)	Not reported	77 (36.5%)	Not reported	Carbone 2017 [29]

- 44 clinical trials included
- 30% of patients received ICIs beyond PD
- 232/5053 pts achieved a response

Spagnolo et al., BMC Cancer (2021) 21:425

Continuation of Pembrolizumab with Additional Chemotherapy after Progression with PD-1/PD-L1 Inhibitor Monotherapy in Patients with Advanced NSCLC: A Randomized, Placebo-Controlled Phase II Study : 98 pts

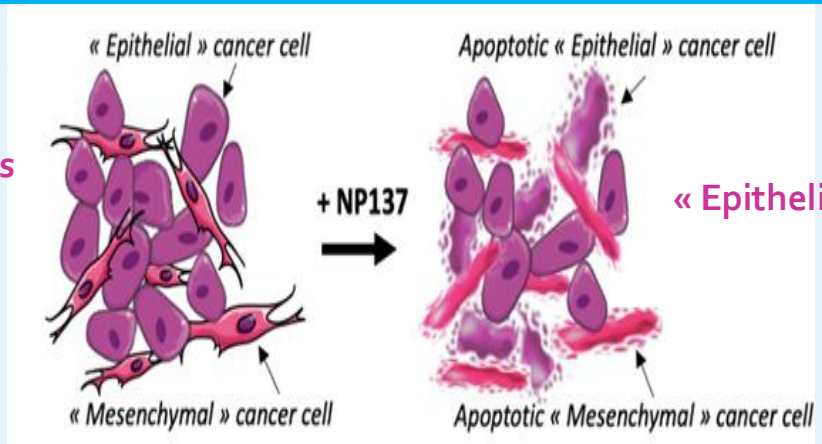


Jung HA et al, Clin Cancer Res 2022

ICIs after ICIs: combination approaches

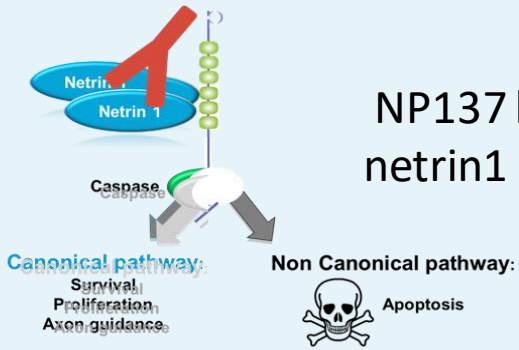
Chemotherapy + NP137 +/- Pembrolizumab

PRE-CLINICAL DATA



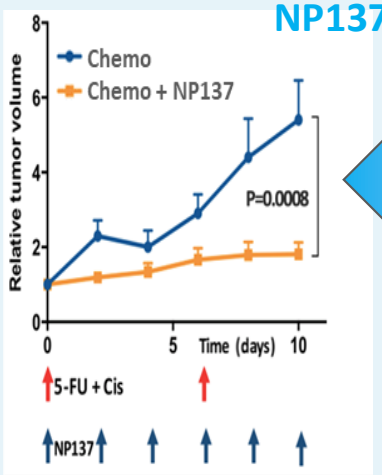
Heterogenous phenotype

« Epithelialization »



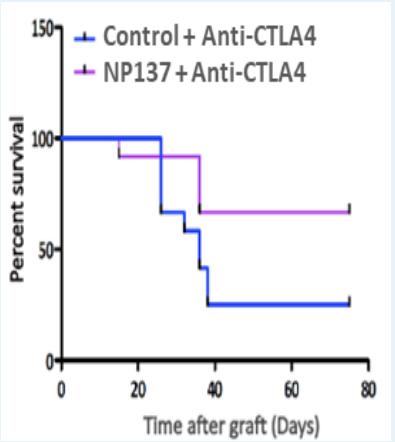
NP137 blocking netrin1 receptor

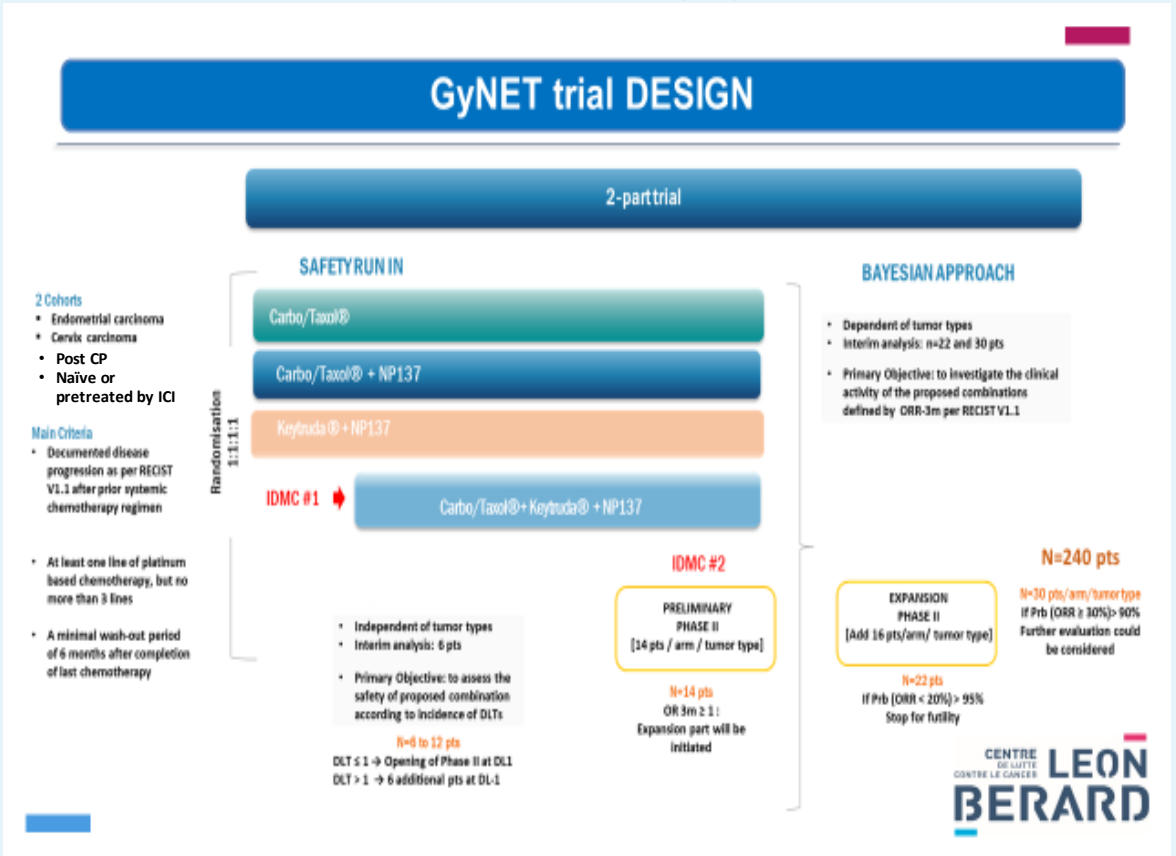
NP137 PROMOTES SENSITIVITY TO:



CHEMOTHERAPY

IMMUNOTHERAPY

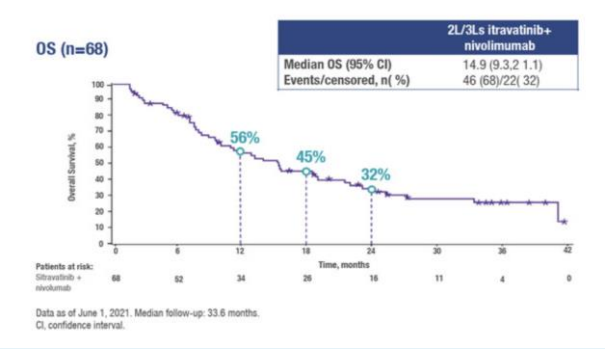




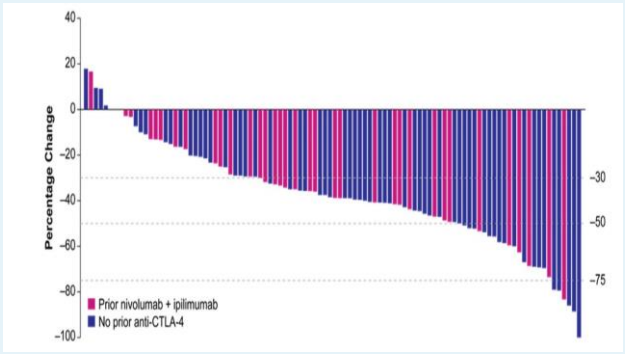
ICIs after ICIs: combination approaches

ICIs+TKIs combo in ICIs pretreated patients

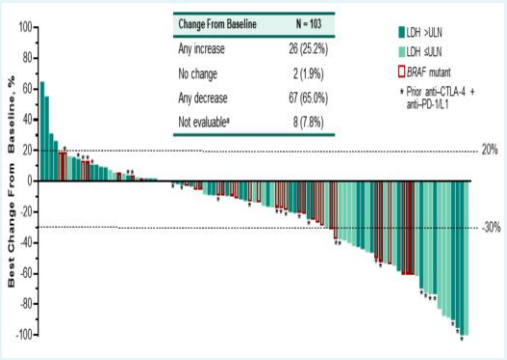
Author	Tumor	No patients	Drugs	ORR (%)	PFS (months)	OS (months)
Kai He et al , 2023 (MRTX-500)	NSCLC	89	Nivolumab Sitravatinib	17%	5.6	15
Lee et al, 2021 (Keynote 146)	RCC	104	Pembrolizumab Lenvatinib	55%	12.2	30.3
Arance et al, 2023 (LEAP 004)	Melanoma	103	Pembrolizumab Lenvatinib	33.3%	4.2	14.0
Lheureux et al, 2022	Endometrial	20 post ICI	Nivolumab Cabozantinib	25%	5.5	ND



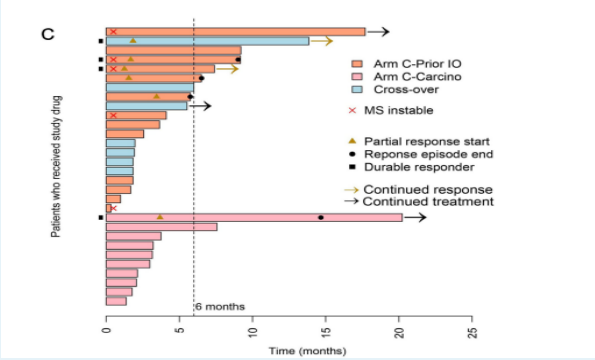
Kai He et al., J Thoracic Surgery 2023



Lee et al., Lancet Oncol 2021.



Arance et al., JCO 2023



J Immunother Cancer. 2022

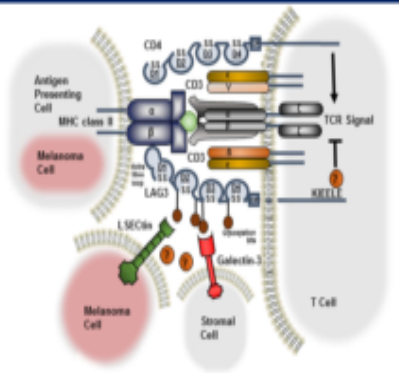
ICIs after ICIs: combination approaches

ICI + Lag3 inh (relatlimab): ANGY trial proposal

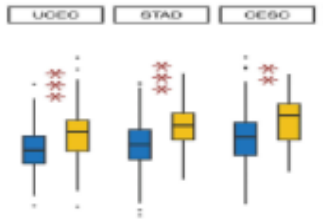
Rationale LAG3 and Gyn cancer

- Lag3 is expressed by activated CD4 and CD8 T cells, NK cells and pDC
- LAG3 plays a protective role in autoimmune diseases by dampening CD4+ T cell responses by promoting Treg suppression.
- overexpressed along with other ICP (PD-1 for example)

- Rational :
  - Considerable LAG3 expression observed in cervical cancer & endometrial carcinoma (MSS)
  - MSS EC harboring PD-L1, LAG-3 may be a potential immunotherapeutic target
  - MSI EC Positive LAG-3 expression in TCs may be a predictor of improved RFS



(Andrews et al., 2017, Immunol Rev.)



Supplementary Table 2. Univariate and multivariate analyses of clinicopathological parameters and immune-related markers for PD-1 positivity in MSS EC

Immune-related markers	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
PD-L1	9.281 (2.56–33.653)	<0.001		
CD3	4.018 (1.65–9.783)	0.002		
CD8	7.226 (2.269–23.009)	<0.001		
LAG-3	5.922 (2.37–14.801)	<0.001	3.117 (1.132–8.583)	0.027

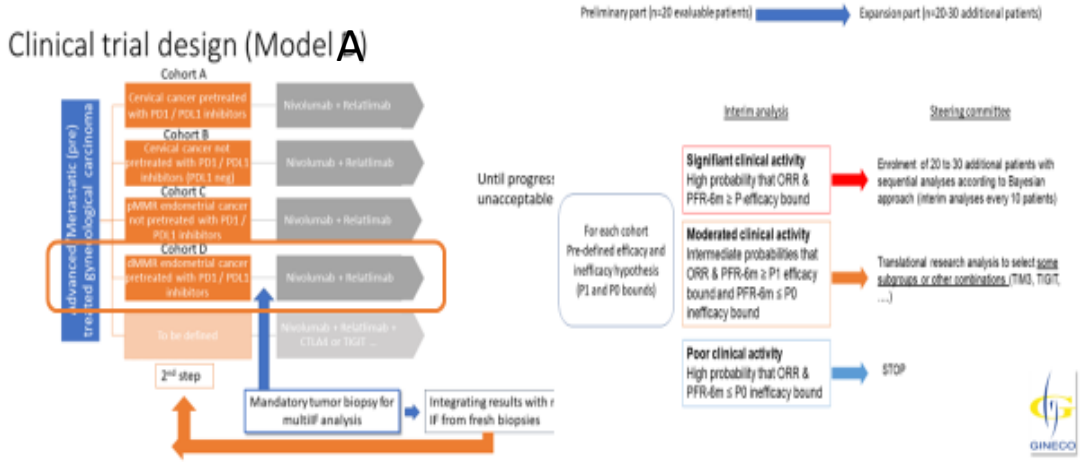
CD, cluster of differentiation; CI, confidence interval; EC, endometrial cancer; LAG, lymphocyte activation gene; MSS, microsatellite stable; OR, odds ratio; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

(Hong et al., 2023, J Gyn Oncol

ANGY Clinical trial design

ENGOT GINECO group, multicentric, open-label, phase I/II trial

→ **Phase II trial:** adaptive Bayesian approach allowing to quickly stop treatment cohorts without evidence of efficacy and/or select promising treatment cohorts
Preliminary step = assess clinical activity of the proposed therapeutic combination in 2-3 tumor types (4 independent cohorts)
For each cohort: clinical activity will be assessed by sequential statistical analysis at specific time points
Translational studies from the objective 2 will be analyzed in parallel of activation of the extension cohorts to define treatment arms and patient selection according to individual tumor biomarkers



Alternative immunotherapy after ICIs:

ADCs: new frontiers

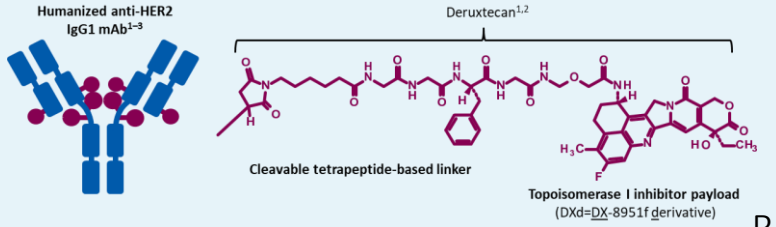
- HER2
- Folate receptor alpha
- Trop2
- Tissue factor
- Napi2B
- FGRF2

Target antigen	Function	Expression	ADC
Folate receptor alpha	Transmembrane protein involved in transport of folate into cells necessary for metabolism, DNA synthesis, repair, and proliferation	Ovarian: 80–96% Endometrial: 41%	Mirvetuximab soravtansine STRO-002 MORAb-202
Tissue Factor	Thromboplastin or factor III, involved in extrinsic coagulation pathway leading to generation of thrombin/clot formation.	Ovarian: 96% Endometrial: 15% Cervical: 34%	Tisotumab vedotin
NaPi2b	Sodium-dependent phosphate transport protein expressed in epithelial cells.	Ovarian: 80–100%	Lifastuzumab vedotin XMT-1536
Mesothelin	Hypothesized to be involved in cell adhesion. Expressed on mesothelial cells.	Ovarian: 60–88%	Anetumab ravtansine DMOT4039A BMS-986148
MUC16	Transmembrane protein with role in adhesion/peritoneal metastases. CA-125 represents the extracellular, cleaved portion.	Ovarian: 80%	DMUC4064A

Alternative immunotherapy after ICIs:

ADCs: anti-HER2

Trastuzumab Deruxtecan (T-DXd)



An open-label, multicenter study (NCT04482309)

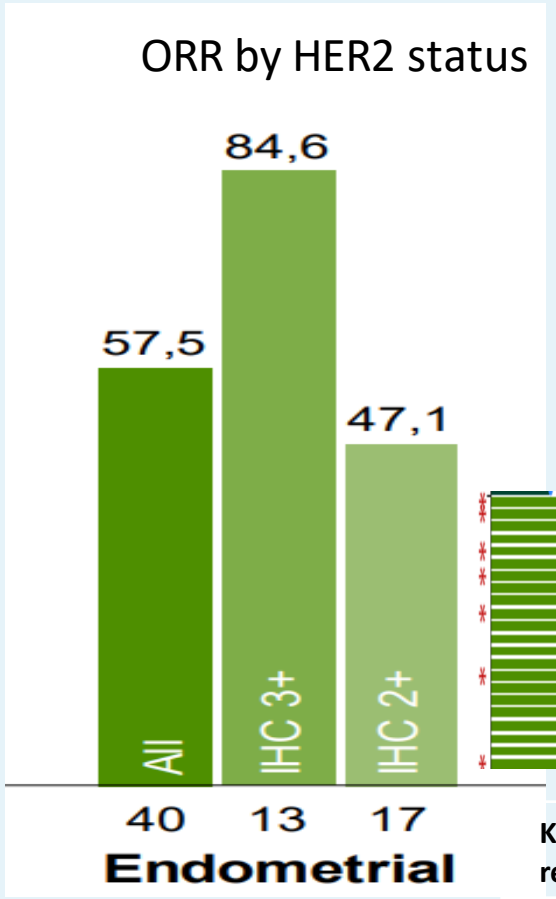
- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer guidelines[1])[a]
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1

T-DXd 5.4 mg/kg q3w

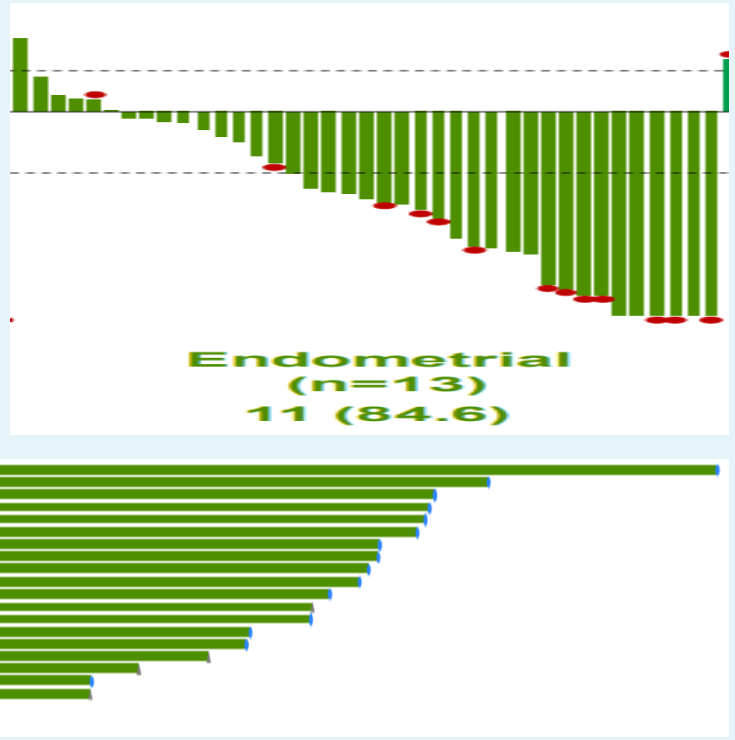
n≈40 per cohort planned

(Cohorts with no objective responses in the first 15 patients were to be closed)

- Cervical cancer
- Endometrial cancer
- Ovarian cancer
- Biliary tract cancer
- Pancreatic cancer
- Bladder cancer
- Other tumors[b]



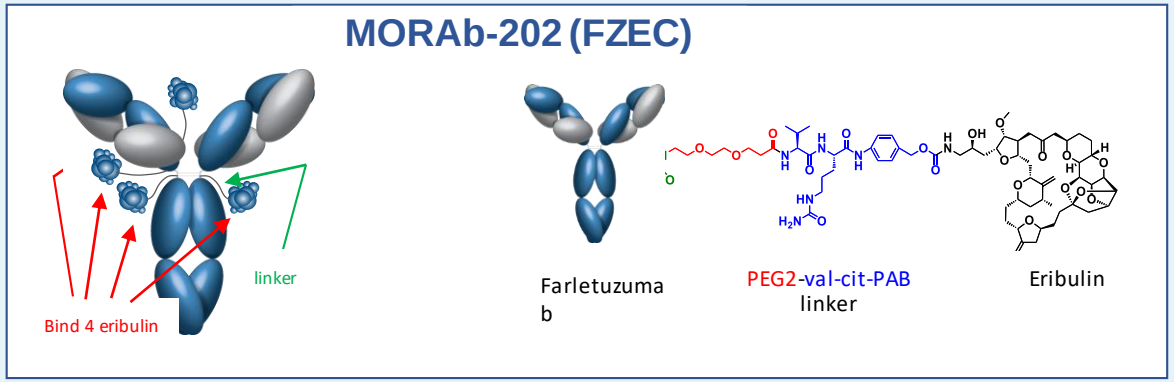
Best Percentage Change in Target Lesion From Baseline



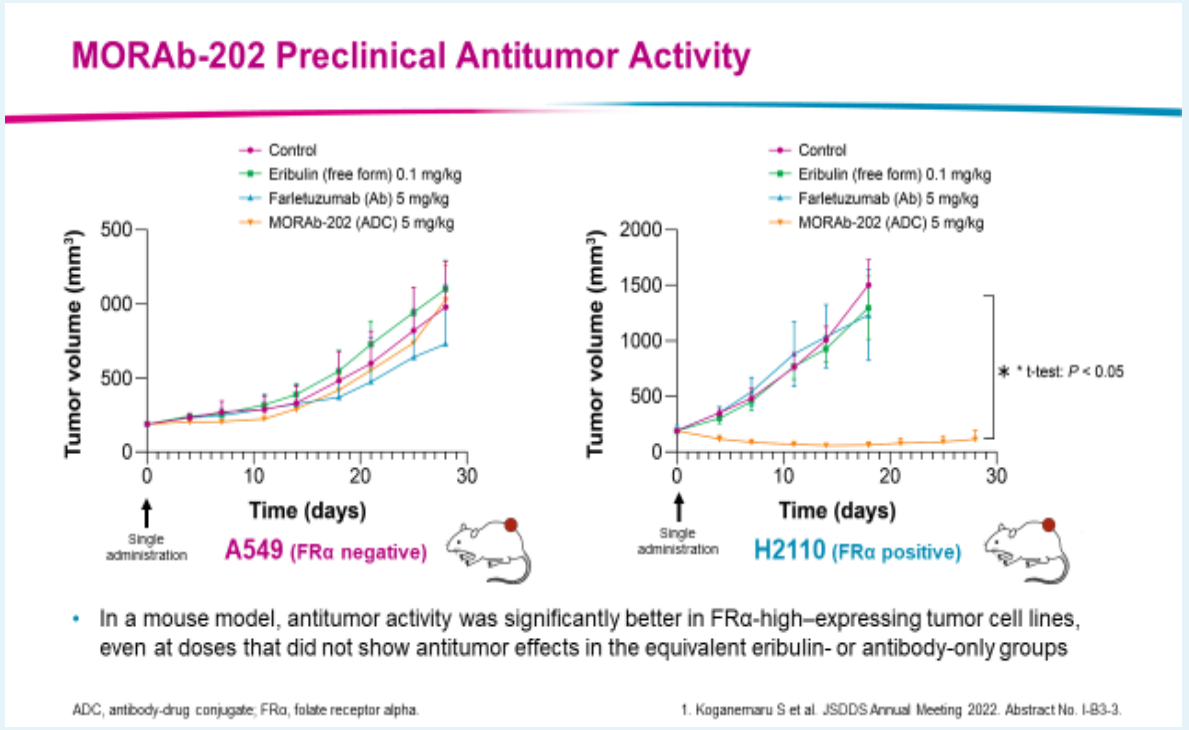
Kaplan-Meier estimate of response at 12 months (%)	Endometrial 72.3

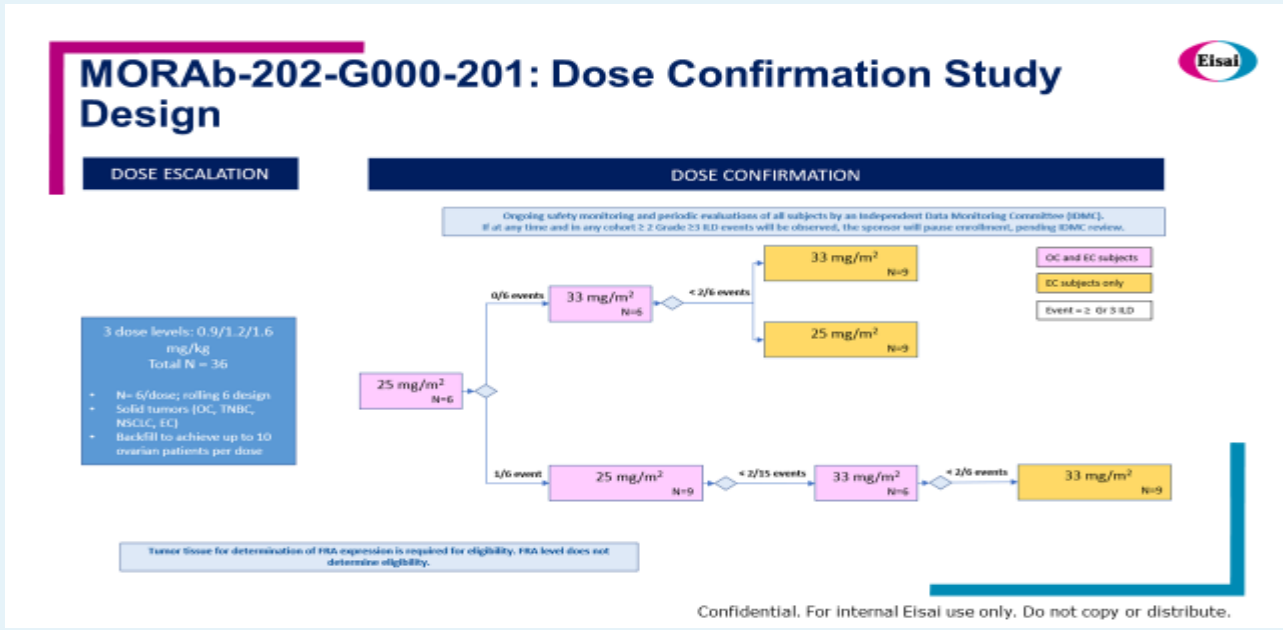
Bardia, et al, Annals of Oncology, 2021

Alternative immunotherapy after ICIs:
ADCs: anti-Folates



MORAb-202 (farletuzumab ecteribulin) is an antibody–drug conjugate comprised of the humanized anti-folate receptor-alpha (FRα) monoclonal antibody, farletuzumab, conjugated to the potent cytotoxic microtubule inhibitor, eribulin, by a cathepsin B-cleavable linker



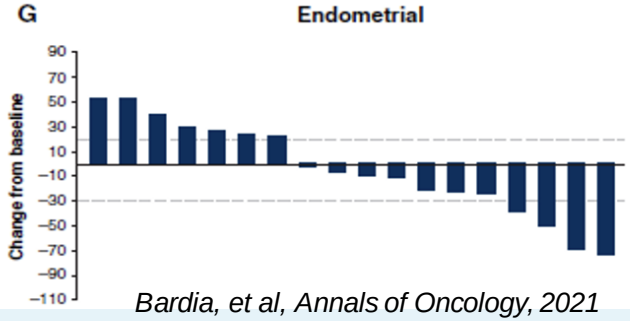


Alternative immunotherapy after ICIs:
ADCs: anti-trop2

Sacituzumab-govitecan (anti-Trop-2 + SN-38)

IMMU-132-01: Single ARM, PI/II, open label, basket trial evaluating Sacituzumab govitecan

	Endometrial Ca
Total, n	18
Dose (mg/kg)	10
ORR, % (95% CI)	**22.2 (6.4-47.6)**
CR, n (%)	0
PR, n (%)	4 (22.2)
SD, n (%)	6 (33.3)
Median DOR, months (95% CI)	**NR (9.1-NR)**
Median OS, months (95% CI)	11.9 (4.7-NR)
Median PFS, months (95% CI)	3.2 (1.9-9.4)
CBR, n (%) [95% CI]	8 (44.4) [21.5-69.2]



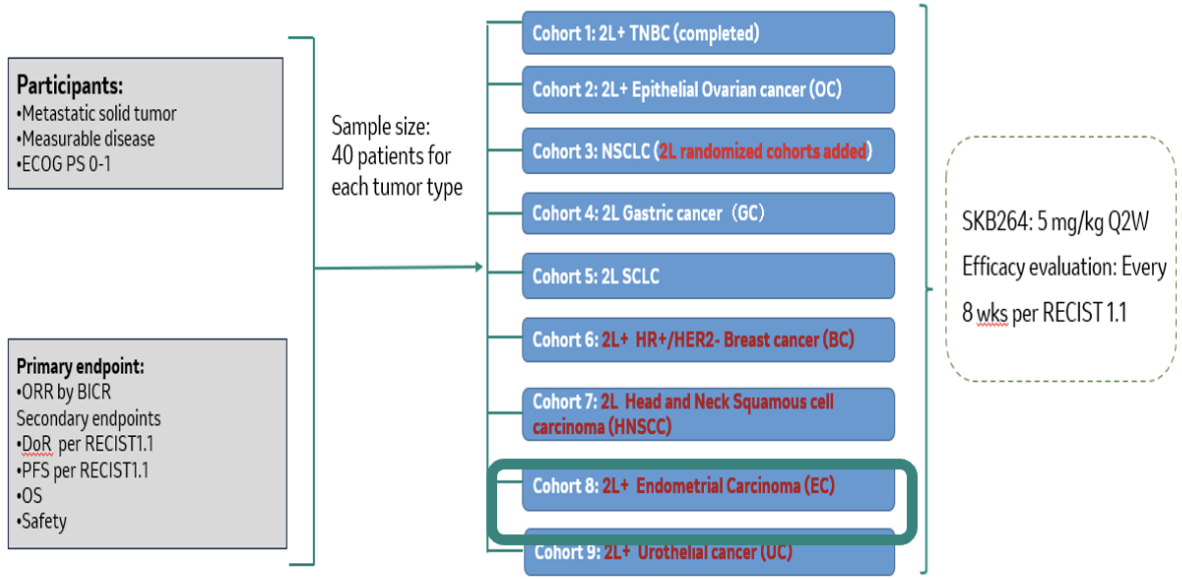
Bardia, et al, Annals of Oncology, 2021

*P2 Inv Initiated Study in 2L EC (n = 50) that is 2+ IHC for TROP2 is still recruiting (FPE Feb 2020)

- NCT04251416

MK-2870/SKB264 (anti-Trop-2 + anti-DNA topoisomerase I)

MK-2870-001: PI/II, Multicohort, open label, evaluating MK-2870/SKB264



Red: Denotes cohorts added to original Kelun FIH study

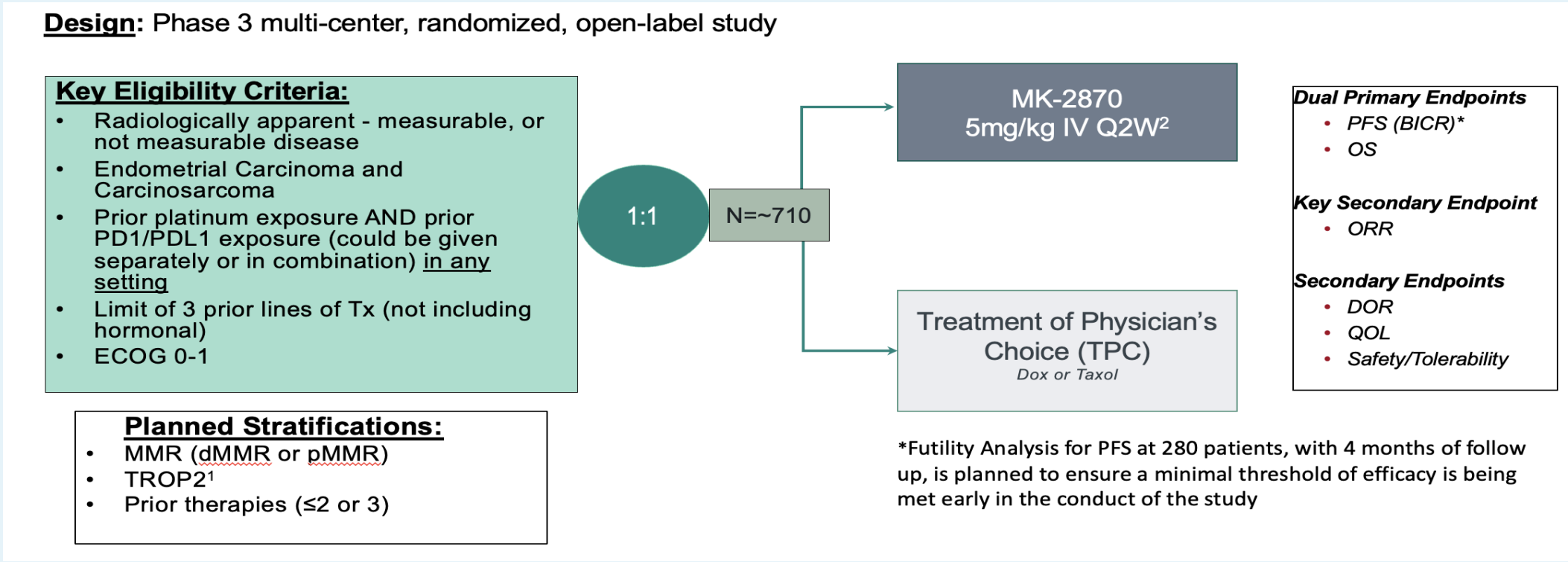
MERCK

- Endometrial cohort added with amendment Q4 of 2022. FPE T: 12/30/2022, LPI for CN:12/30/2023 (30pts) and 10pts US (LPI: March 2024).
- Enrolled patient population expected to be mostly IO naïve as IO in EC not currently approved/widely accessible in China
- Data from EC cohort, can be used to check the assumptions used for the Ph3 component of the study and adjust SAP if warranted (though small sample size, different tx setting to be taken into consideration)

Courtesy Ketta Lorusso

Alternative immunotherapy after ICIs: ADCs: MK-2870-005

Randomized Phase 3 study in post platinum/post ICIs in Endometrial cancer, evaluating MK-2870 versus TPC



Courtesy Ketta Lorusso

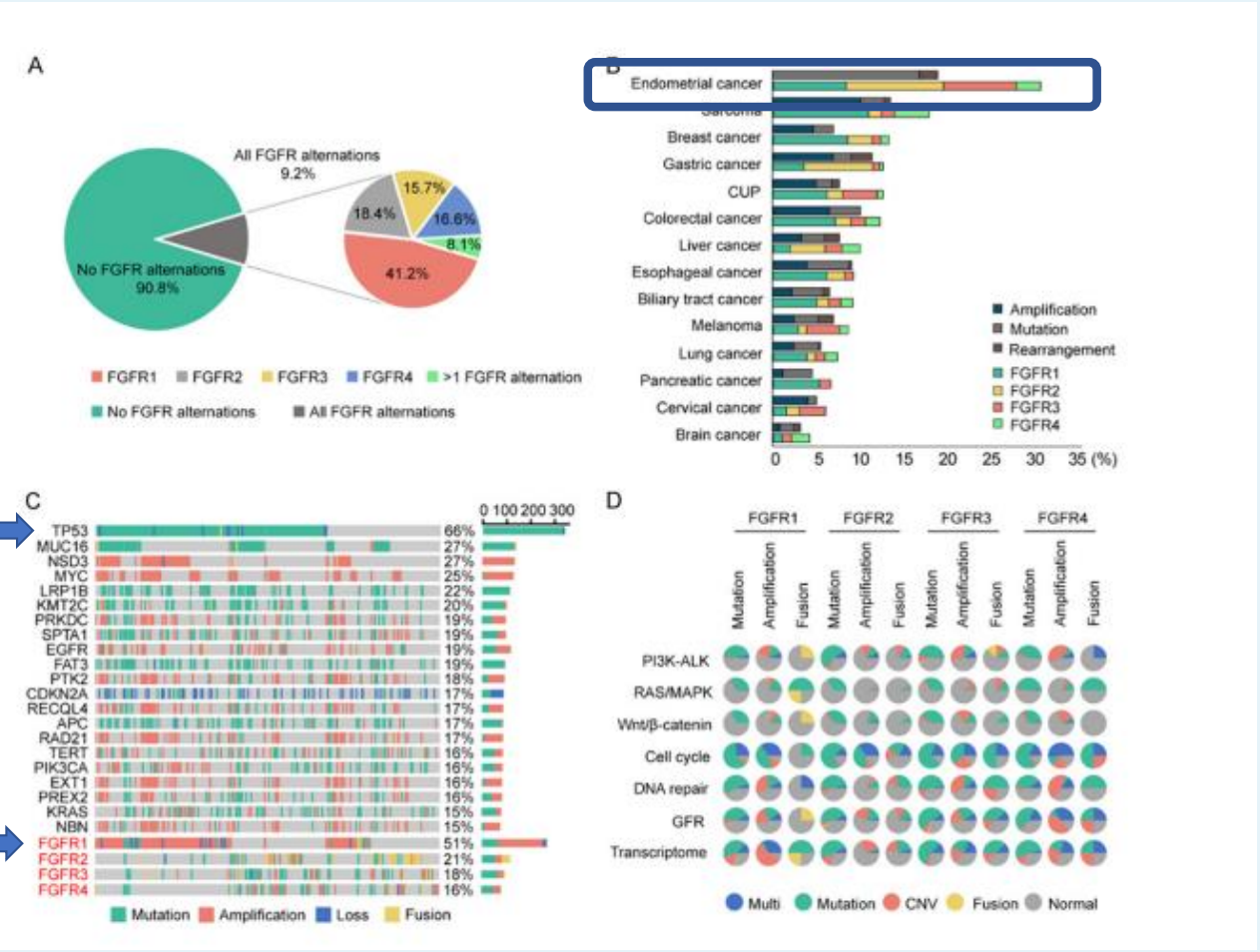
Molecular Profile of Endometrial Cancers
potential targets via molecular alterations

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**
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+(50-60%) PIK3R1 M+(40-50%)		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%	20-30%		3%	17%	0%
Erbb alterations	0	low	low	ErbB2 A+ 25-30% (serous)	ErbB2 A+ (13-20%) ErbB3 A+/M+ (13%)	ErbB2 M+ (12%) ErbB2 A+ (16%)
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%)	ARID1A M+(35-40%)		PPP2R1A M+(20%) FBXW7 M+(20% of UC)	ARID1A (25%) PPP2R1A (28%) FBXW7 M+(35-40%) CCNE1 A+ (42%) Sox17 A+ (25%)	ARID1A (25%) TERT promoter mutations

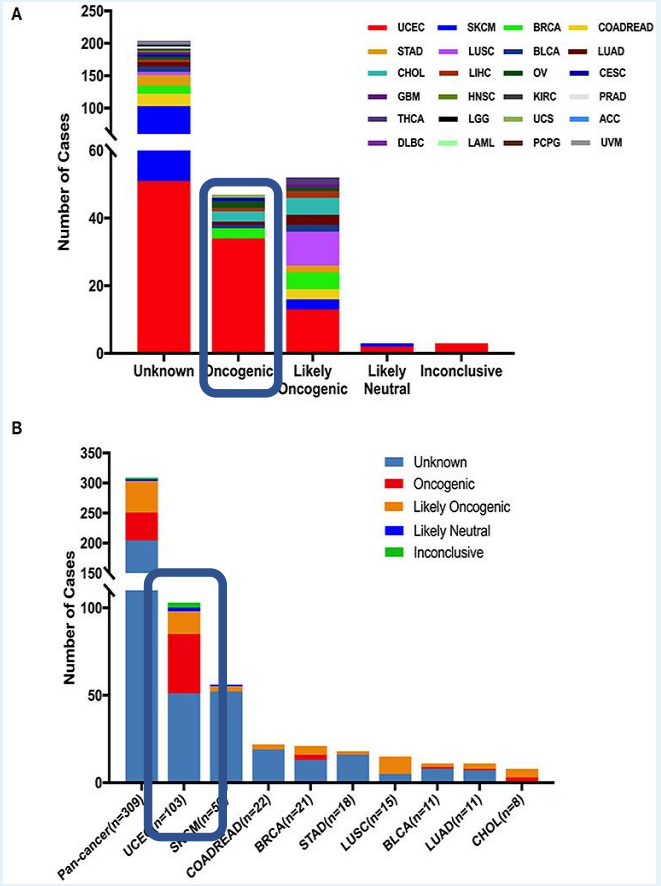
Morice. Lancet. 2016;387:1094; Levine, Nature ***volume 497****, pages 67–73 (02 May 2013)*

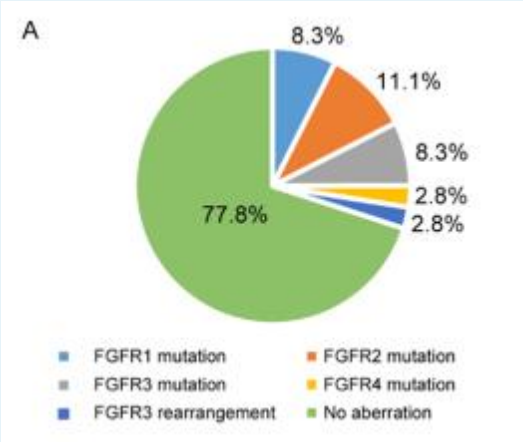
Molecular targetable alterations

FGFR 1-4 alterations in cancer



Endometrial carcinoma





Am J Cancer Res 2021;11(8):3893-3906
Front. Oncol., 21 April 2021

Phase I Dose-Escalation Study of JNJ-42756493, an Oral Pan–Fibroblast Growth Factor Receptor Inhibitor, in Patients With Advanced Solid Tumors

Josep Tabernero, Rastislav Bahleda, Rodrigo Dienstmann, Jeffrey R. Infante, Alain Mita, Antoine Italiano, Emiliano Calvo, Victor Moreno, Barbara Adamo, Anas Gazzah, Bob Zhong, Suso J. Platero, Johan W. Smit, Kim Stuyckens, Moitreyee Chatterjee-Kishore, Jordi Rodon, Vijay Peddareddigari, Feng R. Luo, and Jean-Charles Soria

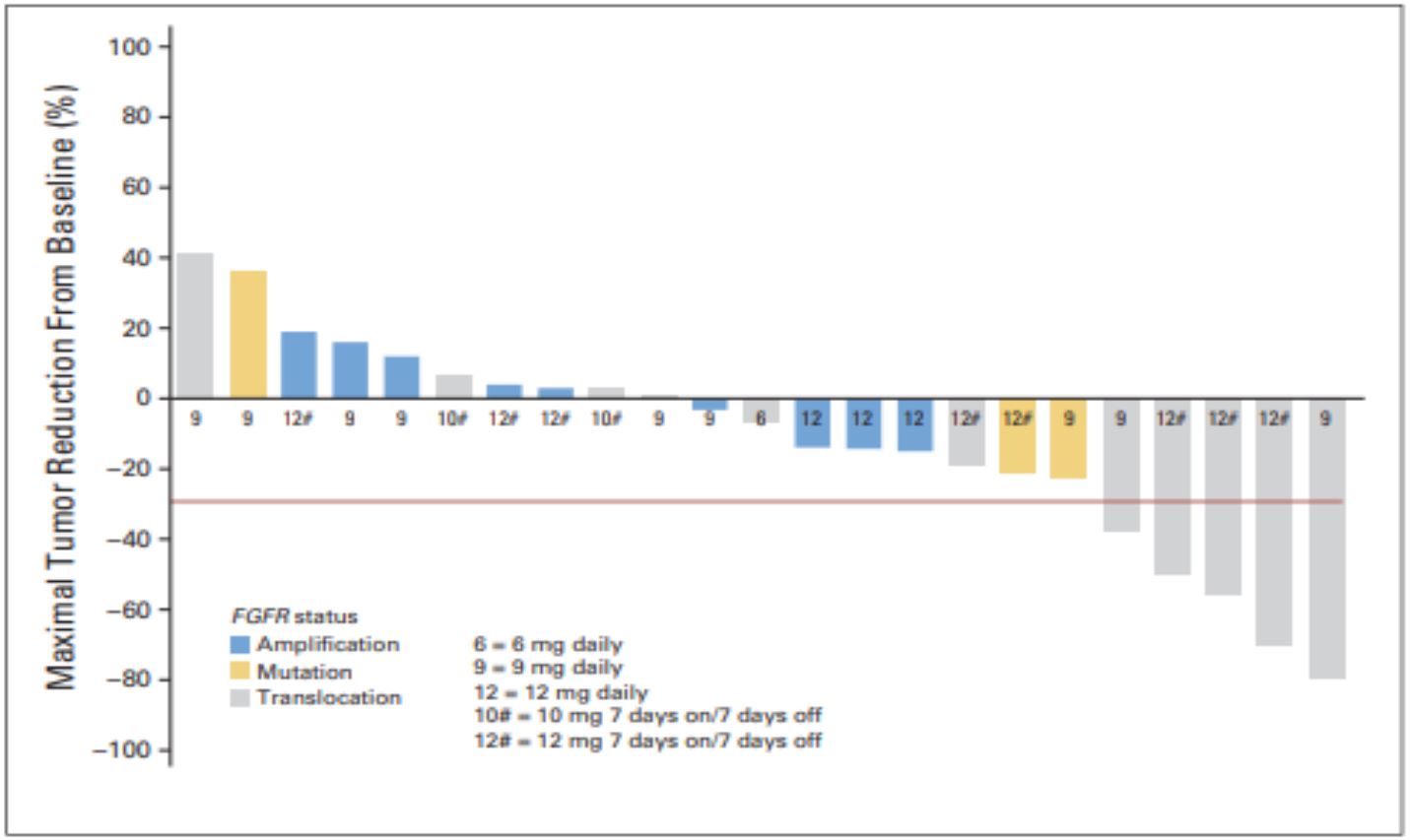


Fig 2. Relative change from baseline in target lesion size (at best tumor response). Figure shows the percent change of the lowest sum of the longest diameters from baseline for patients with fibroblast growth factor receptor (FGFR) alterations in tumor receiving JNJ-42756493 at doses greater than 6 mg (n = 23).

Journal of Clinical Oncology 32(15_suppl):2501-2501

Molecular targetable alterations

Rational for Parpi in Endometrial carcinoma

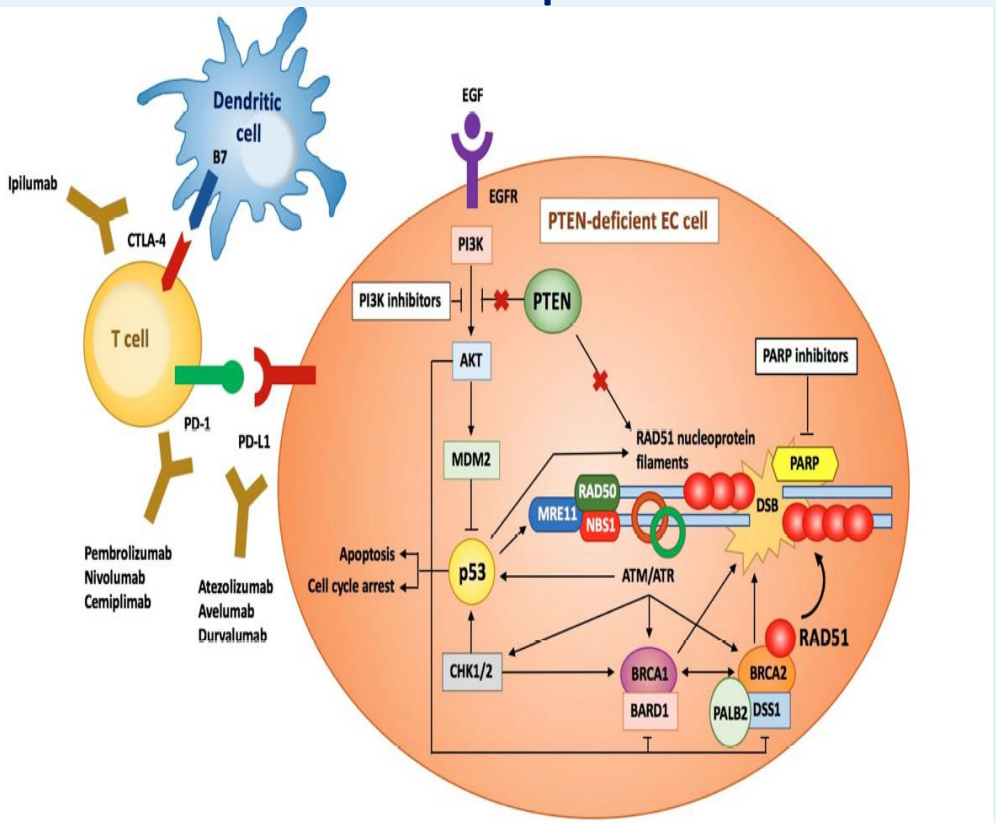
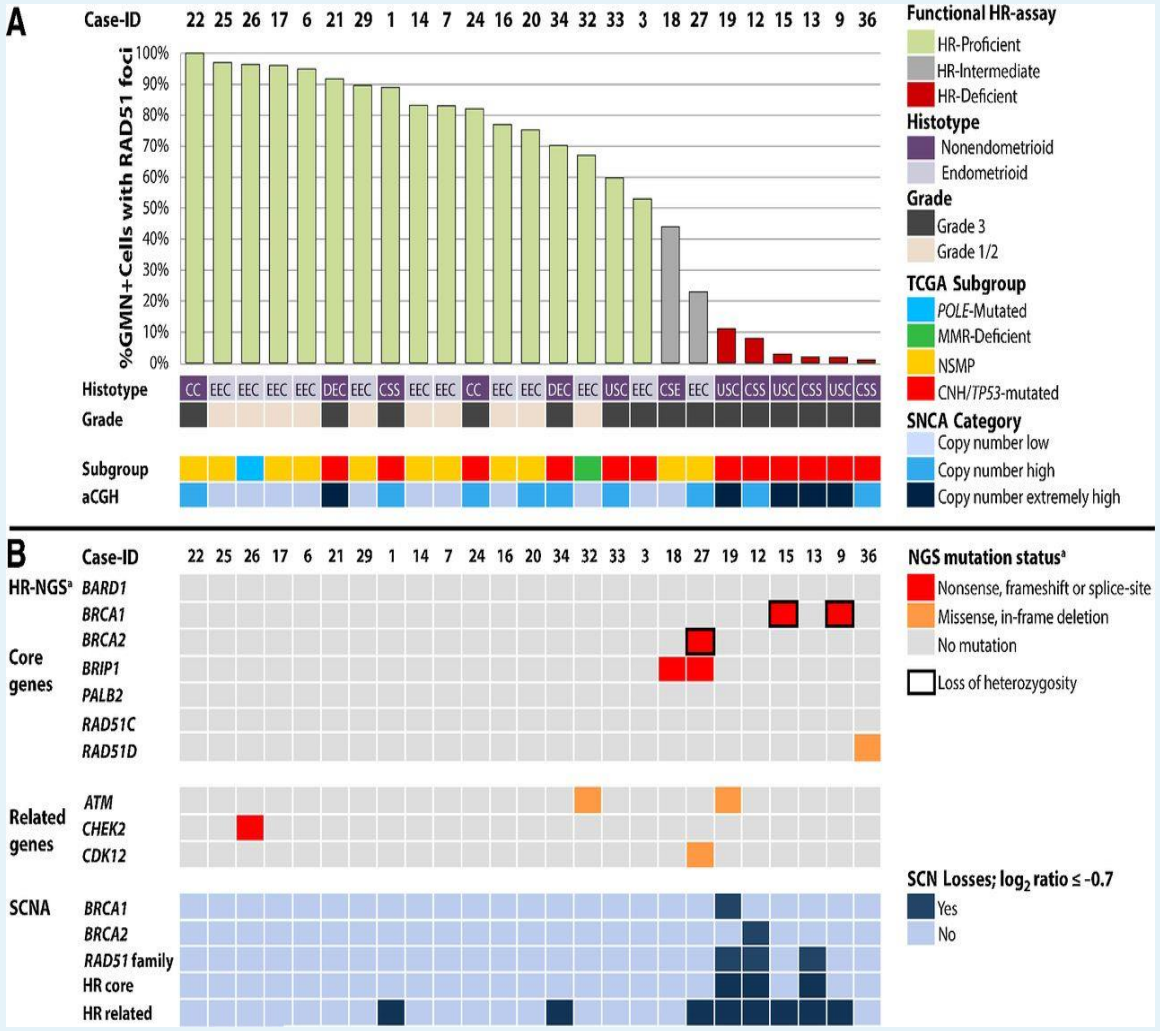


Figure 1 Overview of the HR pathway in PTEN-deficient EC cells. When DSBs occur, ATM, ATR and CHK1/2 kinases phosphorylate BRCA1, that is stabilized by BARD1. BRCA2, whose correct conformation is maintained by DSS1 and PALB2, carries RAD51 to the site of DNA damage, where it forms nucleoprotein filaments and stabilizes DNA double strands. The EGFR activates PI3K/AKT pathway, that in turn inhibits p53. Conversely, PTEN inhibits the PI3K pathway and thus activates p53, that induces cell apoptosis and cycle arrest and increases the expression of the RAD51 and the MRN complex (RAD50, MRE11, NBS1), involved in the DSBs repair. Moreover, PTEN upregulates RAD51. Therefore, mutant PTEN inhibits p53 and RAD51 expression, thus impairing the HR system. Similarly, mutant p53 downregulates the MRN complex and RAD51 levels.

Musacchio et al, Cancer mangement & Research 2020

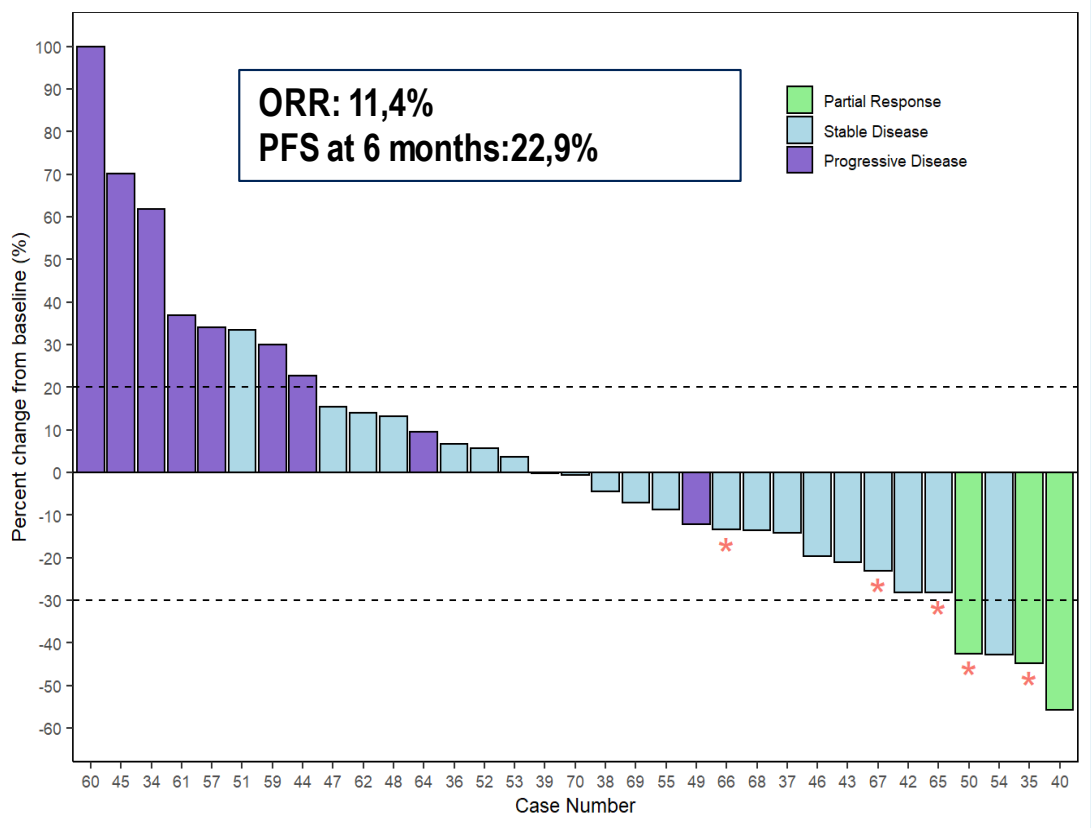


De Jonge et al, Cancer Research 2019

Molecular targetable alterations

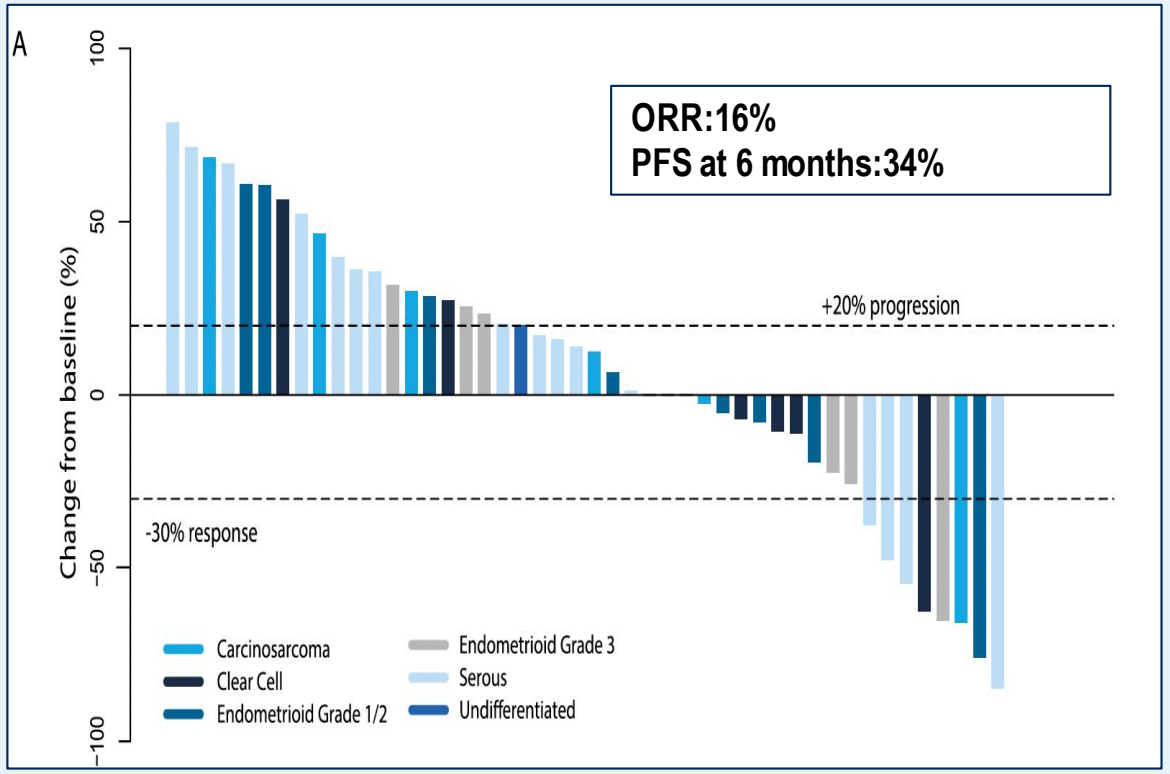
ICI's Activity and PARP inhibitors: Combination Approaches

- **Phase 2:Talazoparib** 1mg PO daily and **Avelumab** 10 mg/kg IV every 2 weeks **in N= 35 previously pretreated recurrent MSS EC patients.**



Panagiotis Konstantinopoulos MD, PhD et al. Jama 2022

- **Phase 2 DOMEC trial: Durvalumab** 1500 mg i.v. every 4weeks **and Olaparib** 300mg/12h **in N=50 previously pretreated recurrent (20%dMMR) EC patients.**



C.C.B. Post et al; Gynecol Oncol. 2022 May;165(2):223-229

Molecular targetable alterations

Parpi alone or in combination in 1st line ?
in which population?

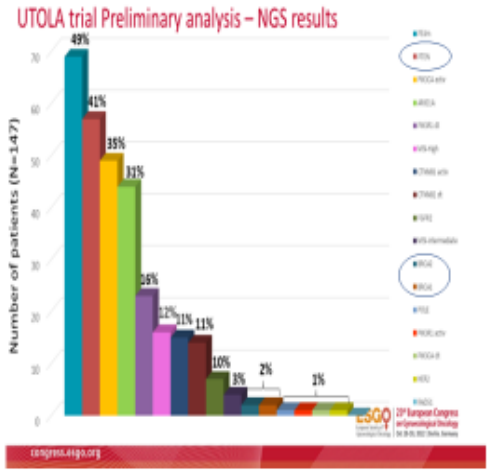
The UTOLA trial

Randomization: 2:1
N= 147
Primary endpoint: Progression free survival
End of recruitment 2021

STRATIFICATION FACTORS:
- * IHC P53 Y/N and MMR Y/N *
- Response to Chemotherapy : objective response VS stable
- Center

* HRD status will be explored via FOCI –RAD51 and AI

LBA ESMO Madrid 2023 F Joly 1st author



NCT03745950

Combination Approaches:Leveraging ICI's Activity
Adding an ICI to standard 1st Line Chemotherapy(PC*)

Newly diagnosed Stage III/Stage IV or recurrent EC. N=699 MSI status: Stratification factor	GOG-3041/ENGOT-EN11/DUO-E/ NCT04269200	A Randomised, Multicentre, Double-blind, Placebo-controlled, Phase III Study of First-line Carboplatin and Paclitaxel in Combination With Durvalumab, Followed by Maintenance Durvalumab With or Without Olaparib in Patients With Newly Diagnosed Advanced or Recurrent Endometrial Cancer
Recurrent or primary advanced (Stage III or IV) endometrial cancer Part 1 N = 470 Part 2 N = 270	GOG-3031/ENGOT-EN6/RUBY NCT03981796	A Phase 3, Randomized, Double-blind, Multicenter Study of Dostarlimab With or Without Niraparib Plus Carboplatin-paclitaxel Versus Placebo Plus Carboplatin-paclitaxel in Patients With Recurrent or Primary Advanced Endometrial Cancer

Press release from Astra Zeneca Announcing positive results
ESMO 2023 Madrid

*PC: Paclitaxel/Carboplatin

2022 ASCO ANNUAL MEETING #ASCO22 PRESENTED BY: Ana Oaknin, MD PhD

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

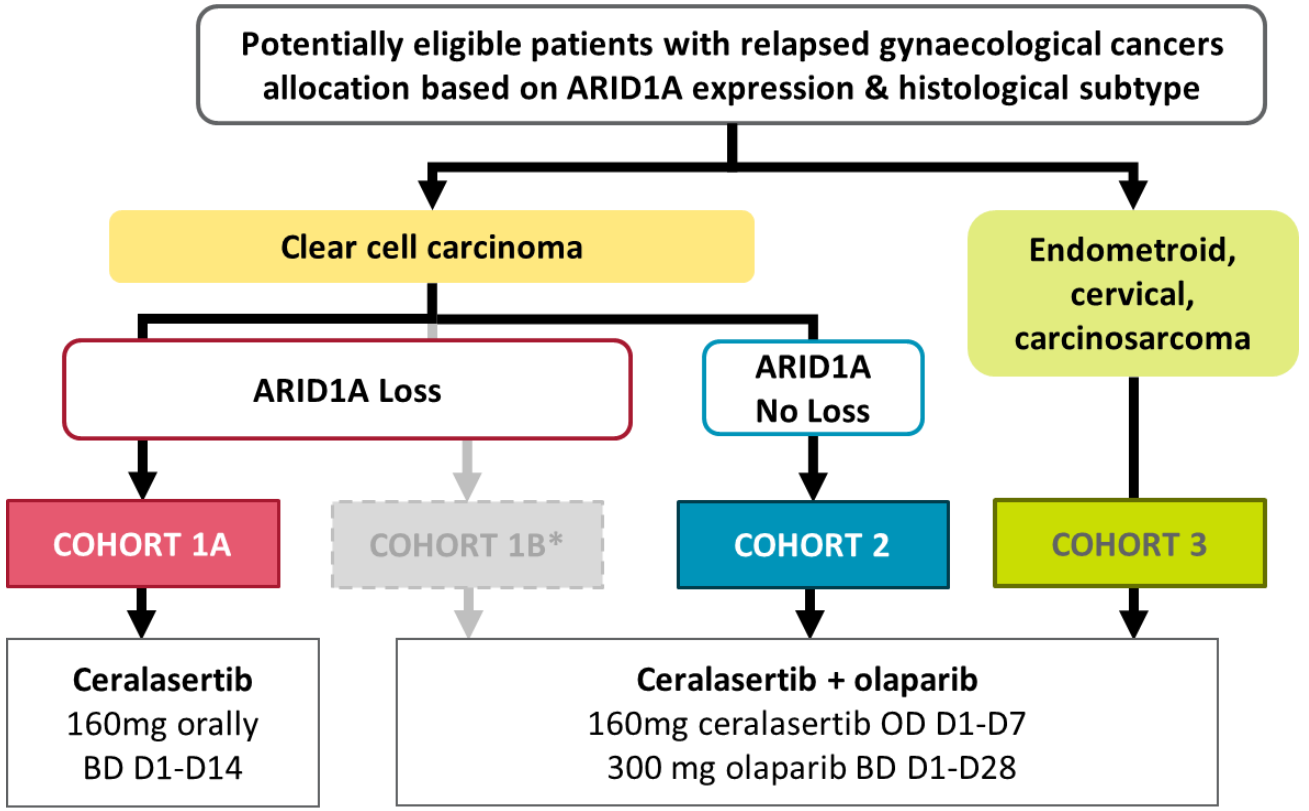
MOLECULAR TARGETABLE ALTERATIONS
PARPI + ATRI

ATARI trial (Olaparib + ceralasertib)

Design: Multi-centre, international, open-label, multiple two-stage parallel cohorts platform phase II clinical trial

Primary endpoint: Objective response rate (ORR) by RECIST 1.1

Secondary endpoints: Disease Control Rate (DCR; OR or SD for 16 weeks or more), duration OR (DOR), PFS, OS, safety & tolerability



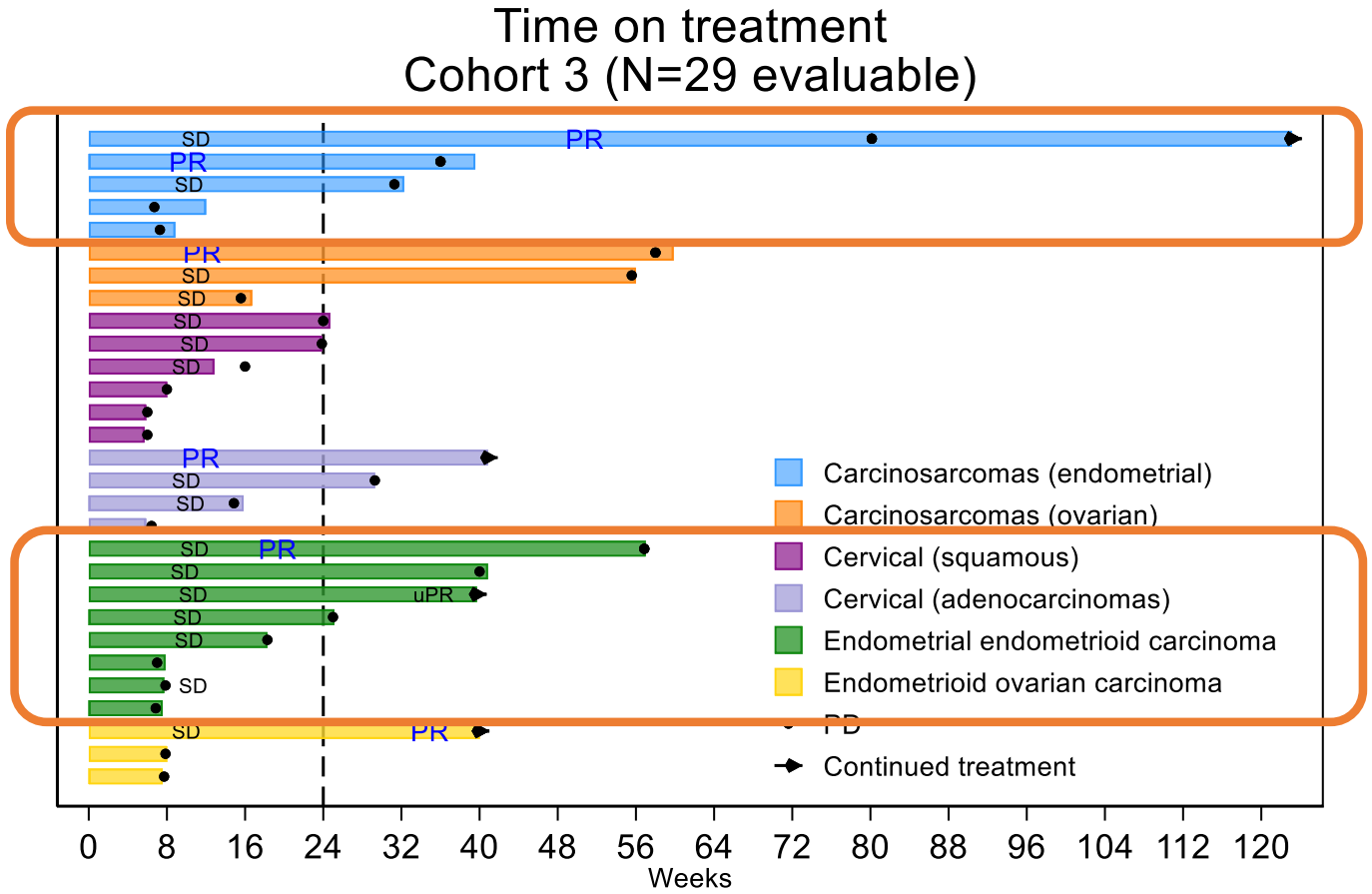
Each cohort → Two-stage optimal Simon design with p0=10%, p1=30%, α=0.05 and 80% power

- Stage 1: 2+ responses/10 evaluable patients
- Stage 2: 6+ responses/**29 evaluable patients**

Susana Banerjee

PARPi + ATRi

ATARI TRIAL COHORT 3: NON-CLEAR CELL SUBTYPES



Each bar represents duration on treatment for one subject in the study.
uPR = unconfirmed response, PR by local review but SD via central review

Endpoint	N=29
Objective Response Rate*	**6 (21%)**
Unconfirmed OR	1 (3%)
Median DOR (weeks), IQR	41.0 (32.9 – 49.9)
DCR (ORR or SD≥16 weeks)	15 (52%)
Treated ≥24 weeks	13 (45%)
PFS at 16 weeks (95%CI)	54% (35, 70)
Median PFS, months (95%CI)	5.5 (1.8, 8.3)

*Responses confirmed or ascertained by central review
**Not estimable

Median OS, months (95%CI)	21.5 (6.0, NE**)

Susana Banerjee

Conclusion

- ICIs have radically reshaped the EC treatment paradigm & are currently approved in the 2L+ setting, but moving upfront
- New issues have to be addressed:
  - ➢ A better understanding beyond dMMR/MSI and MMRp/MSS dichotomic classification is required to better select patients for ICIs therapy AND subsequent therapies
  - ➢ Clinical trials are needed to investigate the rechallenge with ICIs after ICIs failure, probably more in combination than alone
  - ➢ Alternative immunotherapeutic approaches and alternative non immunotherapy based treatments deserve further investigation after failure of ICIs even in EC
- Lessons from the past:
  - Phase II ≠ access to the drugs but give signals
  - Anticipated biomarkers and subgroups are the future
  - International collaborations will help (ENGOT, GOG, GCIG, and other friends)