With Immunotherapy first line - What are the future opportunities?

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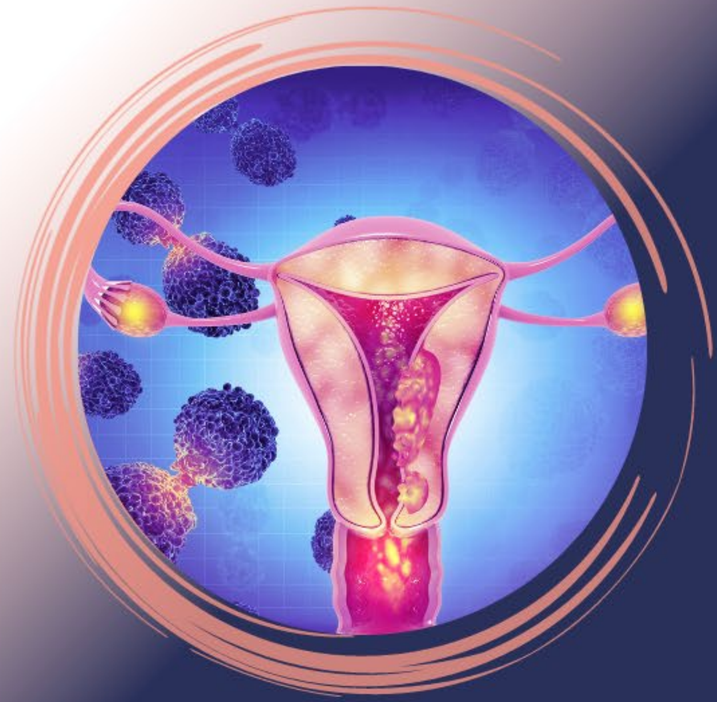


Immunotherapy Combination first line

Drug name	Dostarlimab	Pembrolizumab		Atezolizumab
	RUBY Part 1 | ENGOT-en6[1,2]	NRG-GY018[3,4]	KEYNOTE-B21 | ENGOT-en11[5,6]	AtTEnd | ENGOT-en7[7,8]
N	494	816	990	550
Study chair	Mirza	Eskander	Van Gorp	Colombo
Treatment arms	Dostarlimab + carboplatin/paclitaxel then dostarlimab **vs** Placebo + carboplatin/paclitaxel then placebo	Pembrolizumab + carboplatin/paclitaxel then pembrolizumab **vs** Placebo + carboplatin/paclitaxel then placebo	Pembrolizumab + carboplatin/paclitaxel **then** pembrolizumab ± RT ± cisplatin **vs** Placebo + carboplatin/paclitaxel **then** placebo ± RT ± cisplatin	Atezolizumab + carboplatin/paclitaxel then atezolizumab **vs** Placebo + carboplatin/paclitaxel then placebo
Stratification	MMR-MSI status, previous external pelvic radiotherapy, and disease status[2]	MMR status, ECOG PS, and previous chemotherapy[4]	MMR status, RT, histology, and FIGO surgical stage[6]	Histology, disease stage, MSI status, and country of experimental site[8]
Primary outcome(s)	PFS (IA), **OS**	PFS	DFS (IA), **OS**	PFS, **OS**

There are no completed direct head-to-head trials of these products in EC. There are inherent limitations in cross-study comparisons; caution should be exercised in comparing trials. This slide is for information purposes only and is not intended to imply or infer the noninferiority or superiority of any product, in terms of efficacy or safety.

DFS = disease-free survival; EC = endometrial cancer; ECOG = Eastern Cooperative Oncology Group performance status; ENGOT = European Network of Gynecological Oncological Trial Groups; FIGO = International Federation of Gynecology and Obstetrics; IA = investigator assessed; IO = immuno-oncology; MMR = mismatch repair; MSI = microsatellite instability; OS = overall survival; PFS = progression-free survival; RT = radiotherapy.

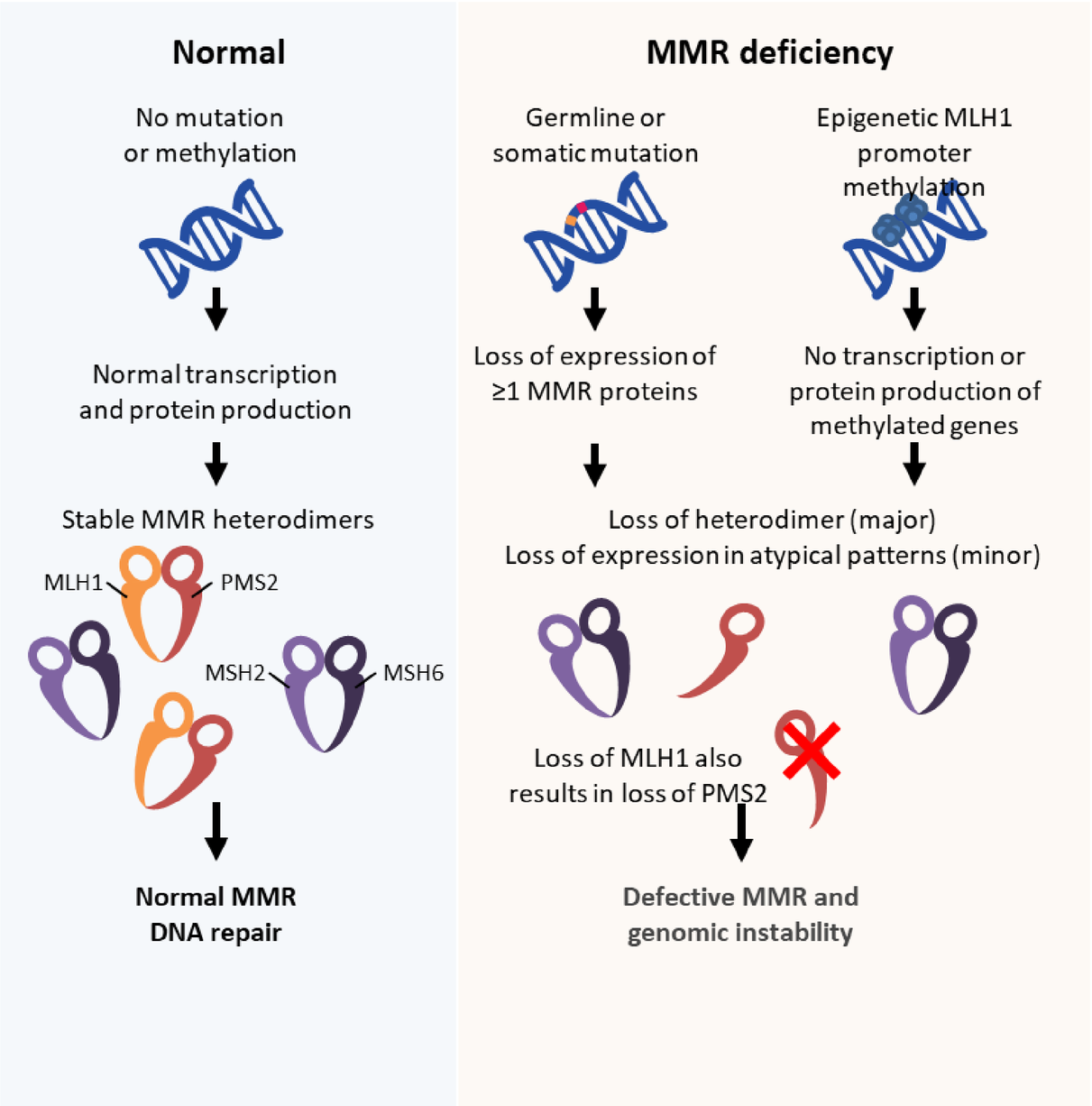
1. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT03981796. Accessed August 23, 2023. 2. Mirza MR, et al. *N Engl J Med.* 2023;388:2145-2158. 3. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT03914612. Accessed August 23, 2023. 4. Eskander RN, et al. *N Engl J Med.* 2023. 388:2159-2170. 5. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT04634877. Accessed August 23, 2023. 6. Van Gorp T, et al. *J Clin Oncol.* 2021;39(Suppl_15):TPS5608. 7. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT03603184. Accessed August 23, 2023. 8. Colombo N, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #LBA40.

Subgroup of MMRd

Mechanism of MMRd

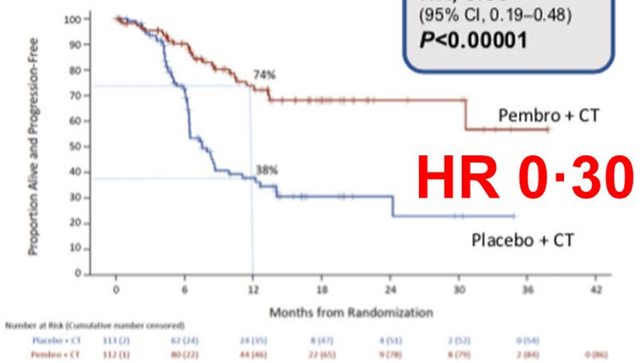
Somatic or germline mutation in an MMR gene is estimated to account for 10-20% of MMR deficiency in EC

MLH1 promoter methylation accounts for approximately 75%–80% of cases with MMR deficiency in EC



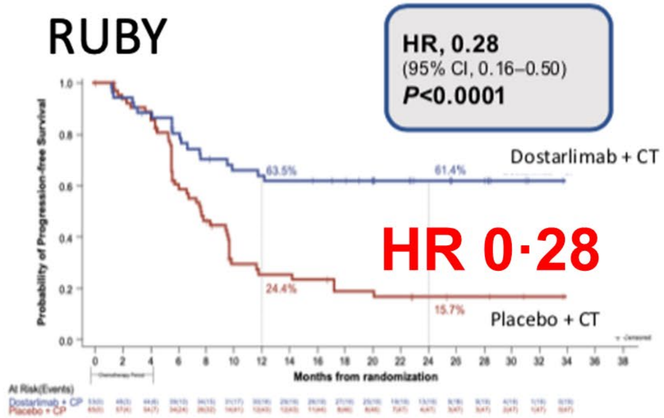
Benefit of IO combination

GY018



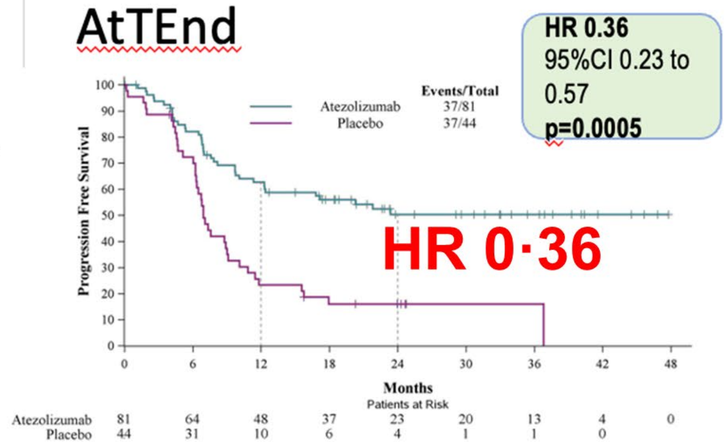
	No with events%	Median
Pembro + CT	23.2	NR (30.6-NR)
Placebo + CT	52.2	7.6 (6.4-9.9)

RUBY



	No with events%	Median
Dorsta + CT	35.8	NR (11.8-NR)
Placebo + CT	72.3	7.7 (5.6-9.7)

AtTEnd



	No with events%	Median
Atezo + CT	45.7	NR (12.3-NR)
Placebo + CT	84.1	6.9 (6.2-9.0)

NRG-GY018 – PFS and OS by mechanism of MMR loss

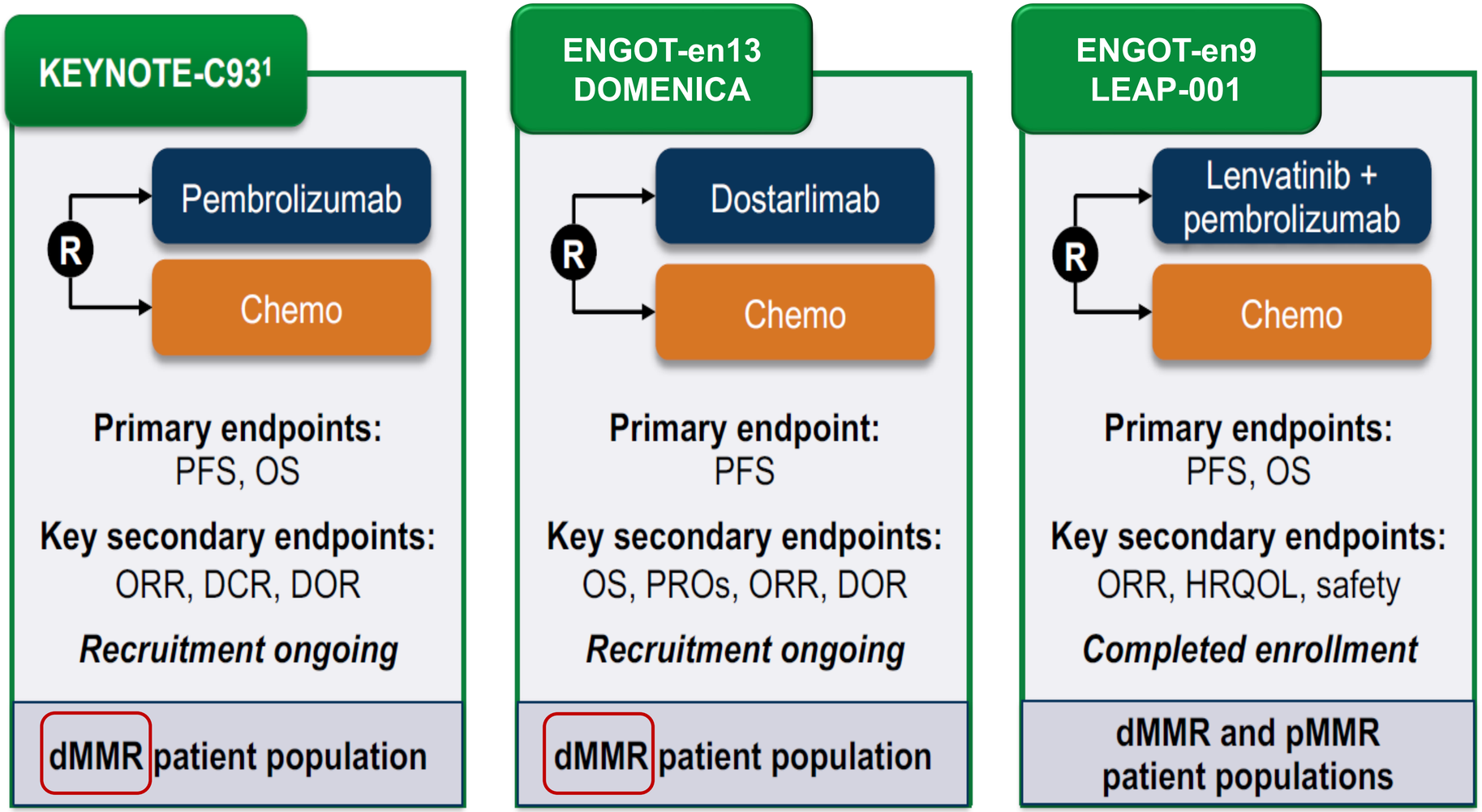
No difference in PFS was identified in dMMR EC patients based on mechanism of MMR loss

	dMMR population n=223
Mechanism of MMR loss, %	
MLH1 promoter hypermethylation	72
MMR protein loss secondary to gene mutation	13
Not evaluable	15
Median PFS by mechanism of MMMR loss	
MLH1 promoter hypermethylation	Not reached
MMR protein loss secondary to gene mutation	Not reached
12-month PFS by mechanism of MMR loss, %	
MLH1 promoter hypermethylation	75
MMR protein loss secondary to gene mutation	85
Median OS by mechanism of MMR loss	
MLH1 promoter hypermethylation	Not reached
MMR protein loss secondary to gene mutation	Not reached

dMMR = mismatch repair deficient; MLH1 = mutL homolog 1; MMR = mismatch repair; PFS = progression-free survival; OS = overall survival.

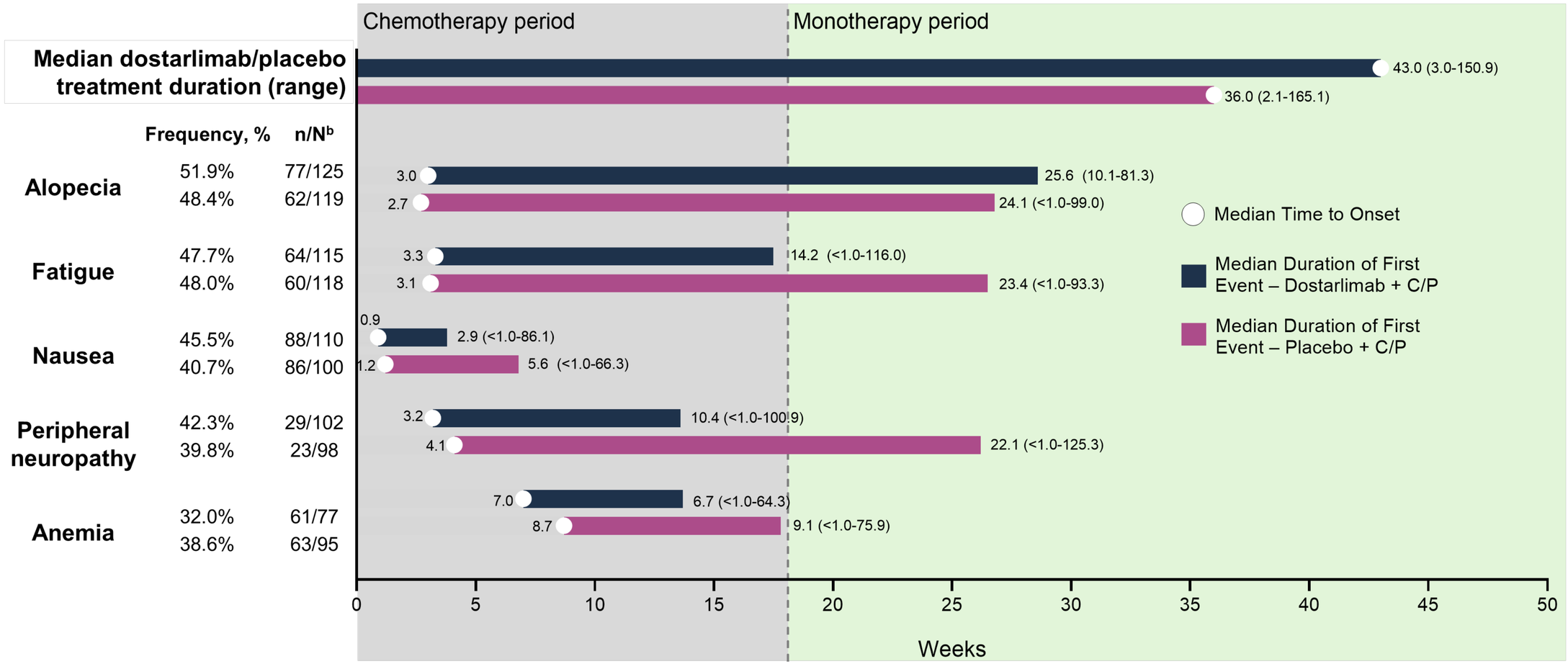
Eskander RN, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20–24, 2023; Madrid, Spain; Presentation #LBA43.

Do you need chemo in this group?



Why this is important?

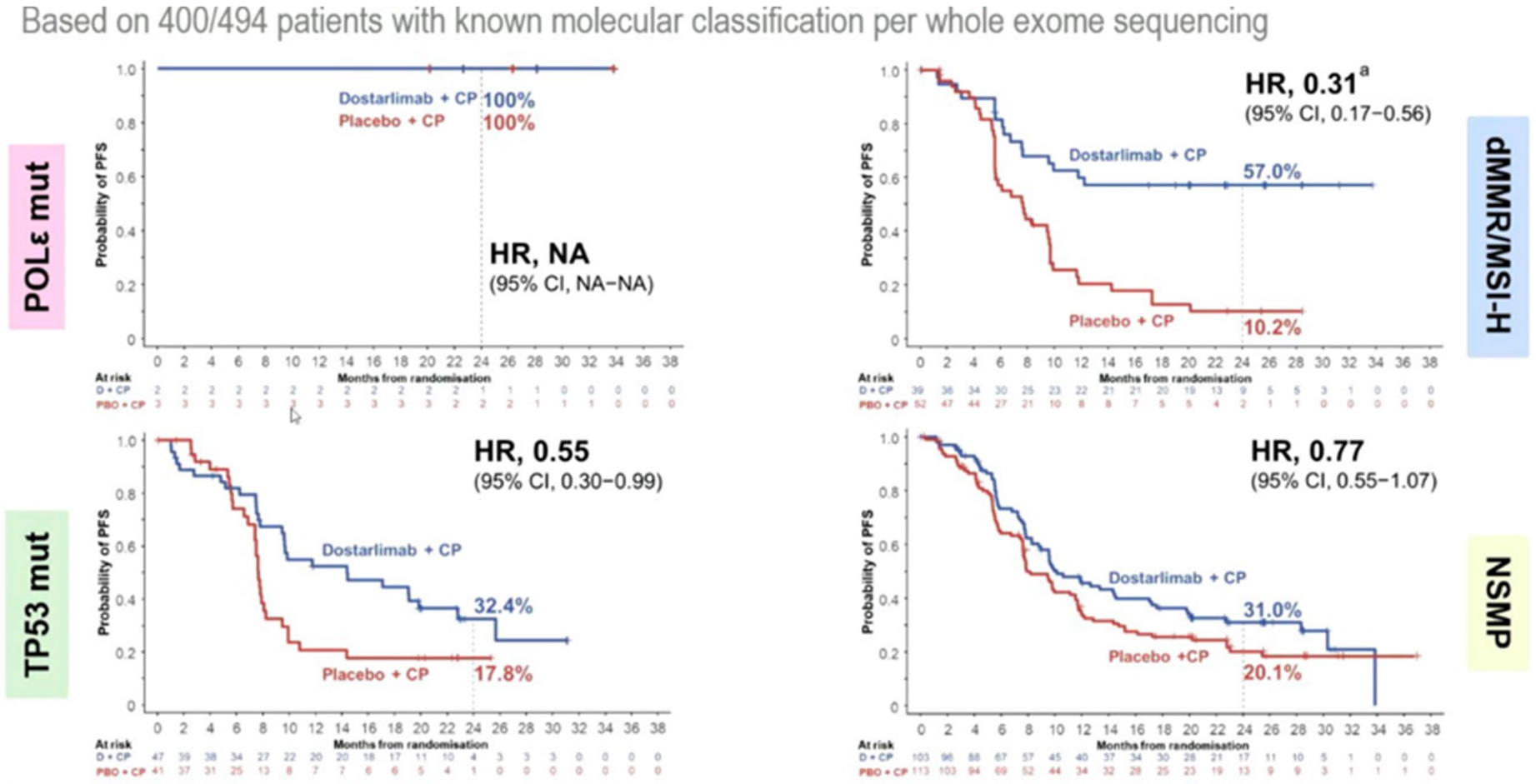
Sparing Chemo related toxicities



[a]TRAEs occurring in >30% in either arm. [b]n/N represents the number of patients with duration data over the number of patients with onset data.
The duration is defined as time from onset of any AE considered in this analysis to the first time the subject is free of any such event. It requires at least one day gap between the resolution of all events from first course to the onset of second course.
AE = adverse event; C/P = carboplatin-paclitaxel; TRAE = treatment-related adverse event.
Auranen A, et al. Presented at European Society of Gynecological Oncology (ESGO) Annual Meeting. September 28–October 1, 2023; Istanbul, Türkiye; Poster #540.

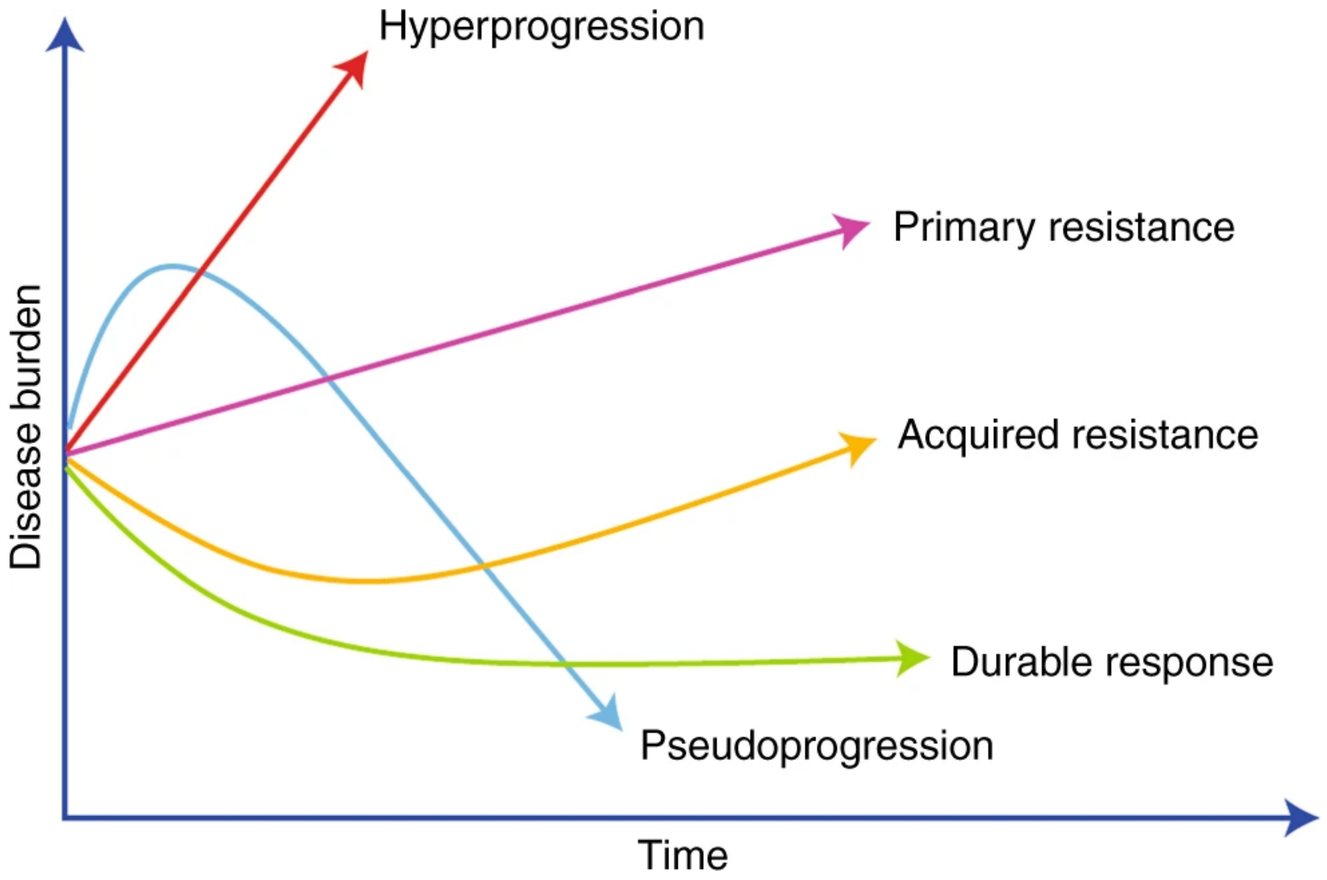
Beyond MMRd- Molecular Subgroup

PFS according biomarkers – RUBY trial



Mirza M et al. ESMO 2023

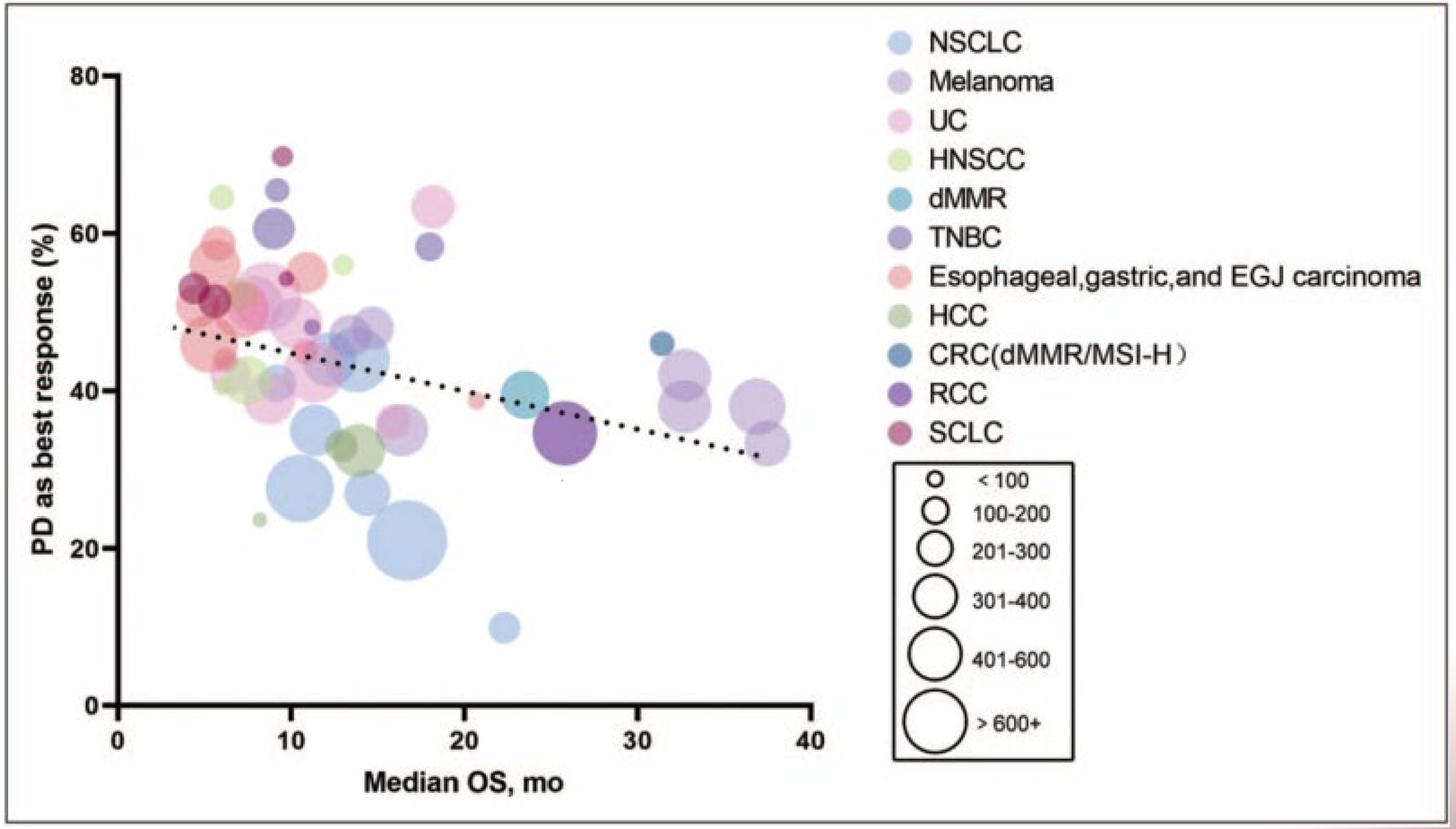
IO – Pattern of disease response



Baxter, M.A., Middleton, F., Cagney, H.P. *et al. Br J Cancer* 125, 1068–1079 (2021)

Primary Resistance

Primary resistance is common even in “hot” tumors

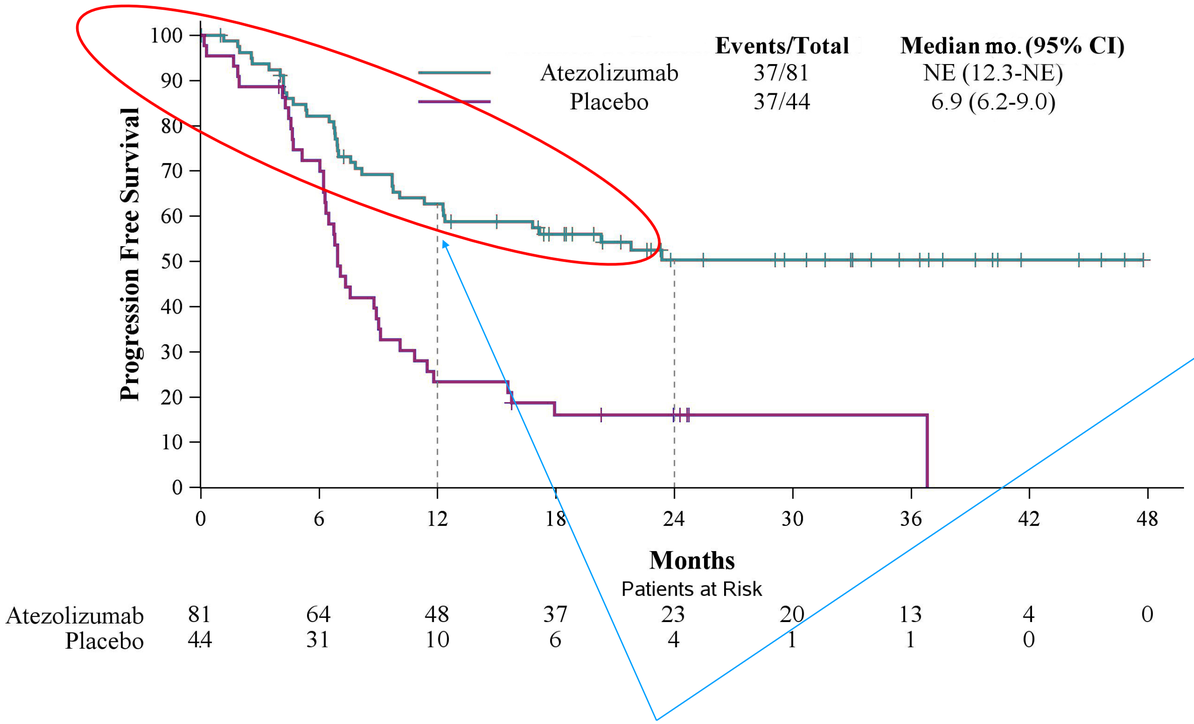


Gap in MMRd

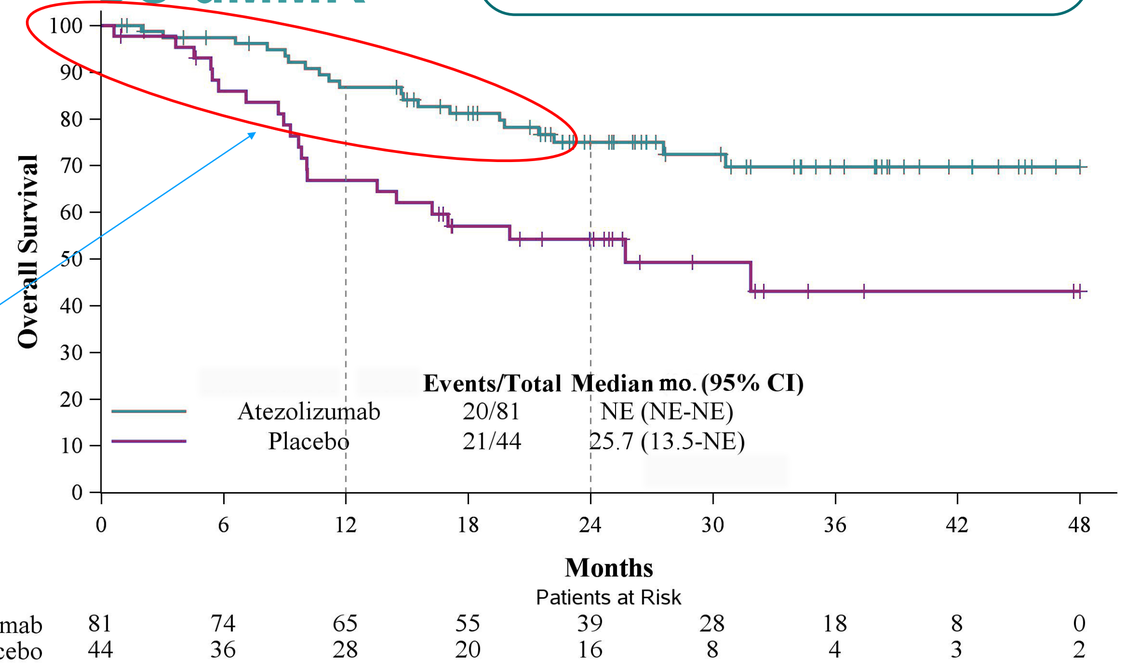
Subsequent immunotherapy

Atezolizumab arm	*6.2%*
Placebo arm	*40.9%*

PFS dMMR

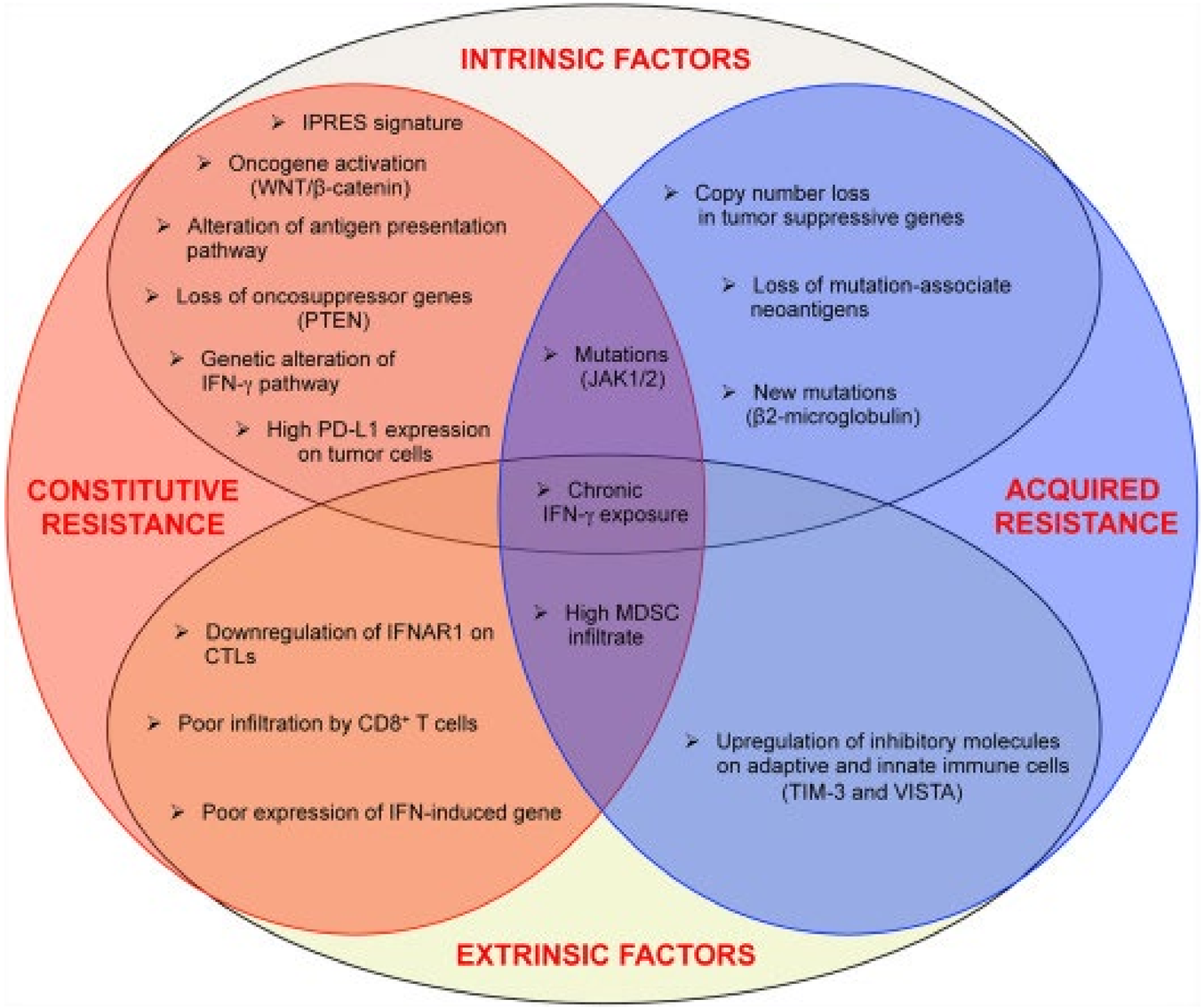


OS dMMR



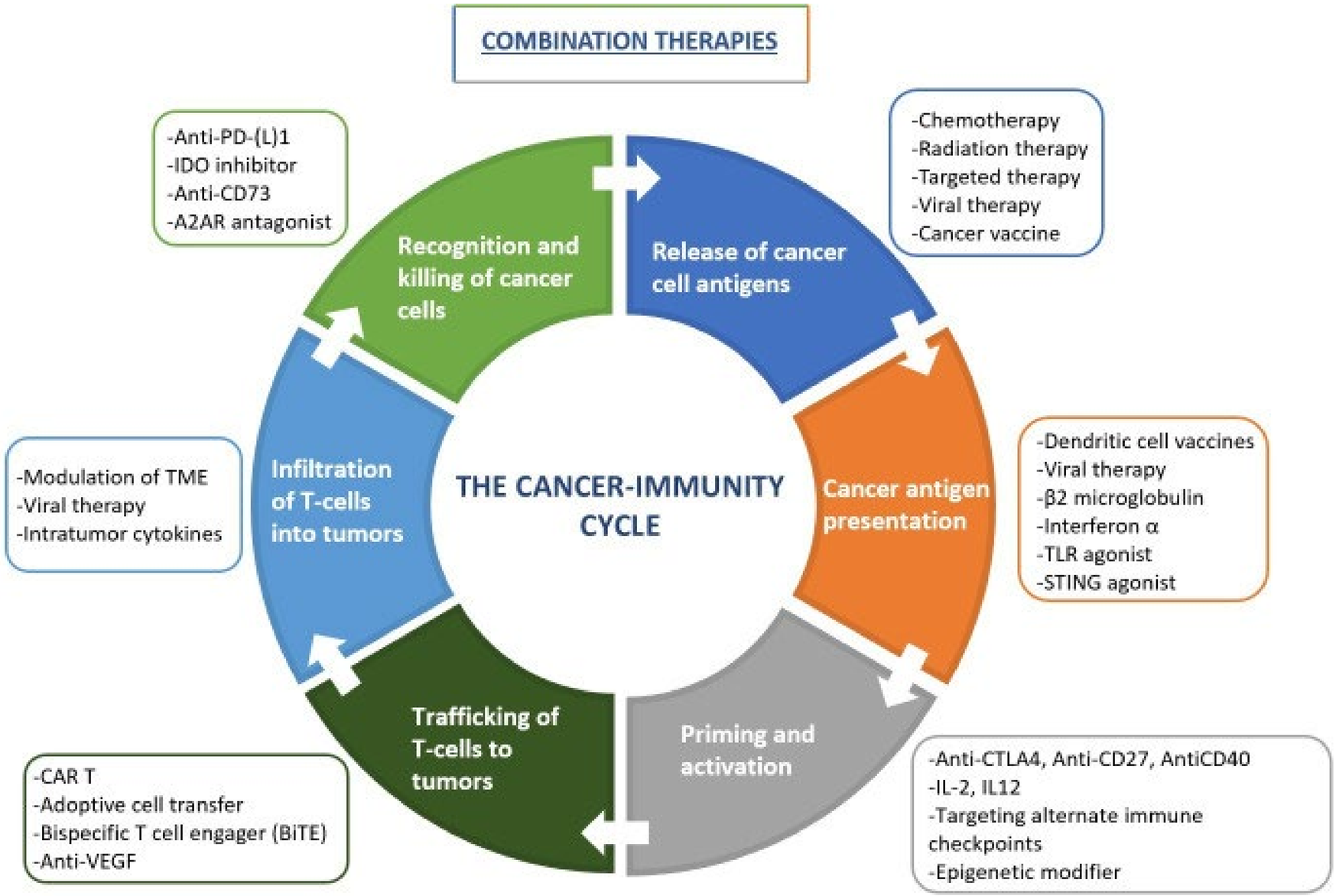
Redzone dMMR patients: IO + chemo
→ IO is not sufficient

Factors - Response and Resistance to IO



Bellone M, Elia AR. Constitutive and Factor Rev. 2017

Strategies to Prevent and Revert Resistance



Zhang T et al. J Immunother Cancer. 2023

Potential Strategies after IO

ALTERNATIVE PROANGIOGENIC PATHWAYS

IMMUNOTHERAPIES / ENHANCING IO

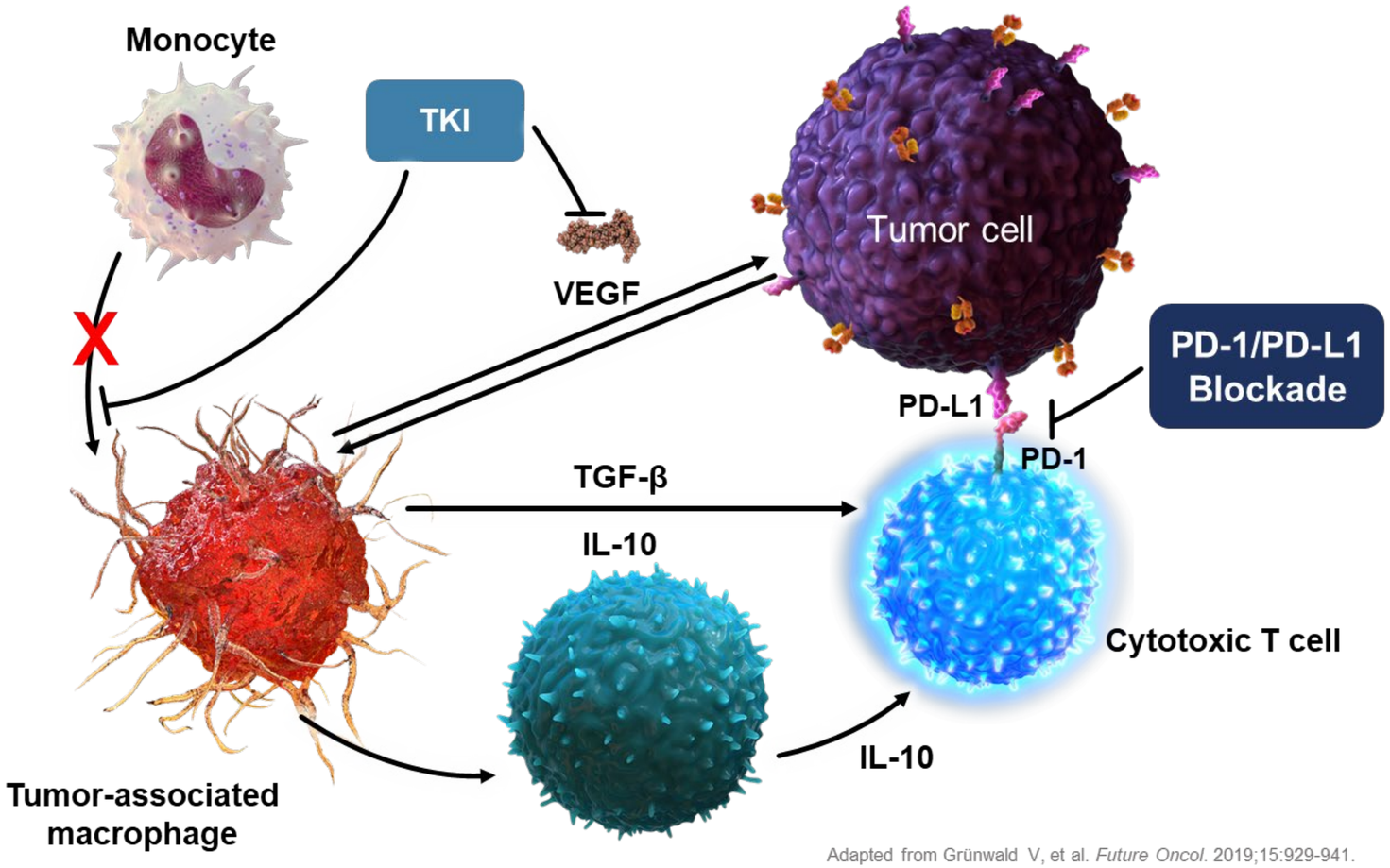
METABOLIC PATHWAYS

PARP INHIBITORS

Rationale for combining TKI and anti-PD-(L)1

The TKI lenvatinib[1]:

- Increases CD8+ T-cell function
- Increases cytotoxicity of NK cells
- Decreases expression of PD-1, CTLA-4, and TIM3 in T cells
- Inhibits T-cell exhaustion[1]



Adapted from Grünwald V, et al. *Future Oncol*. 2019;15:929-941.

CD8 = cluster of differentiation 8; CTLA-4 = cytotoxic T-lymphocyte associated protein 4; IL-10 = interleukin 10; NK = natural killer; PD-1 = programmed cell death-1; PD-L1 = programmed cell death ligand-1; TGF-β = transforming growth factor beta; TIM3 = T-cell immunoglobulin and mucin domain 3; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor.

1. Lu Y, et al. *Front Cell Dev Biol*. 2021;9:730240. 2. Grünwald V, et al. *Future Oncol*. 2019;15:929-941. 3. Marth C, et al. *Int J Gynecol Cancer*. 2022;32:93-100.

Approved Combination IO Approaches in Advanced/Recurrent EC: Phase 3 KEYNOTE-775

KEYNOTE-775

IO naive

Key Eligibility Criteria

- Advanced, metastatic, or recurrent EC
- Measurable disease by BICR
- 1 prior platinum-based chemotherapy regimen[a]
- ECOG PS 0-1
- Tissue available for MMR testing

1:1

Lenvatinib 20 mg po qd + Pembrolizumab[b] 200 mg IV q3w	Physician's Choice: Doxorubicin 60 mg/m^2 IV q3w[c] OR Paclitaxel 80 mg IV mg/m^2 IV q1w (3 weeks on/ 1 week off)

Treat until progression or unacceptable toxicity

Stratification Factors
- **MMR status (dMMR vs MMRp)**
- **MMRp by ECOG PS, geographic region, prior pelvic radiation**

Primary Endpoints
- **PFS by BICR and OS**

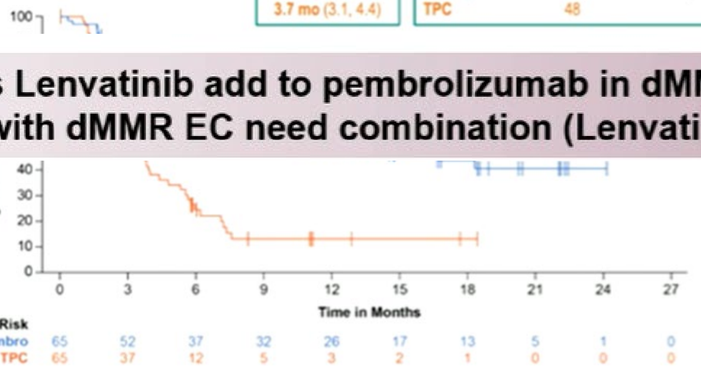
Secondary Endpoints
- **ORR, HRQoL, PK, safety**

Key Exploratory Endpoint
- **DOR**

PFS

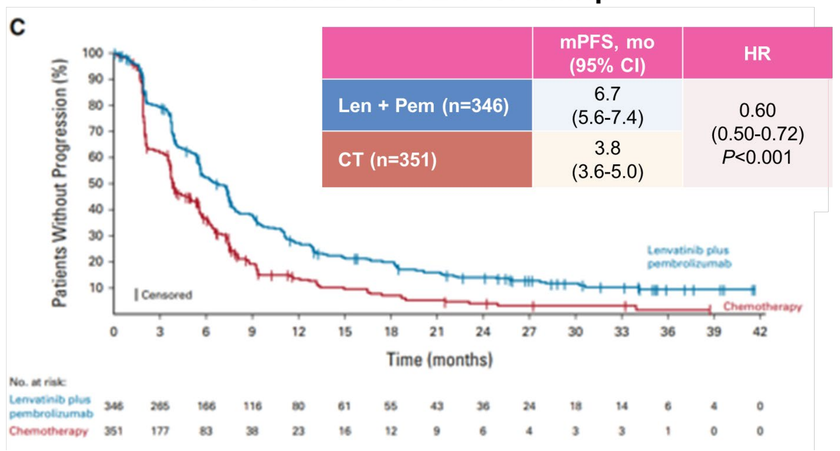
Median (95% CI)	
10.7 mo (5.6, NR)	LEN + pembro
3.7 mo (3.1, 4.4)	TPC

	Events	HR (95% CI)	*P*-value
LEN + pembro	34	**0.36** (0.23, 0.57)	< 0.0001
TPC	48		



How much does Lenvatinib add to pembrolizumab in dMMR EC?
Do all patients with dMMR EC need combination (Lenvatinib+pembrolizumab)?

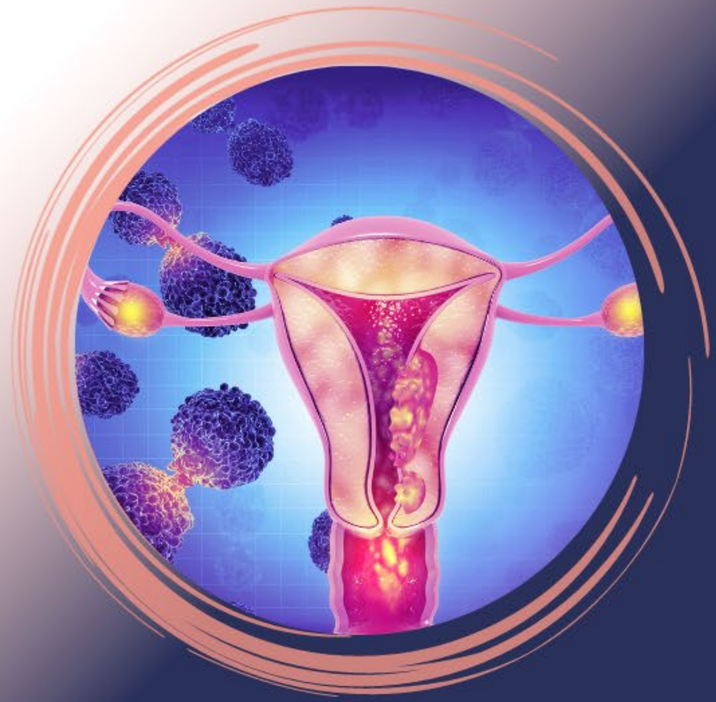
mPFS in KEYNOTE-775: MMRp[c]



	mPFS, mo (95% CI)	HR
Len + Pem (n=346)	6.7 (5.6-7.4)	0.60 (0.50-0.72) *P*<0.001
CT (n=351)	3.8 (3.6-5.0)	

[a] Patients may have received up to 2 prior platinum-based CT regimens if 1 was given in the neoadjuvant or adjuvant treatment setting. [b] Maximum of 35 doses. [c] Maximum cumulative dose of 500 mg/m^2. [c]These data were full FDA approval based on mPFS of 6.6 vs 3.8 (HR 0.60) and mOS of 17.4 vs 12.0 (HR 0.68). Makker V, et al. *J Clin Oncol.* 2023;JCO2202152. doi:10.1200/JCO.22.02152.

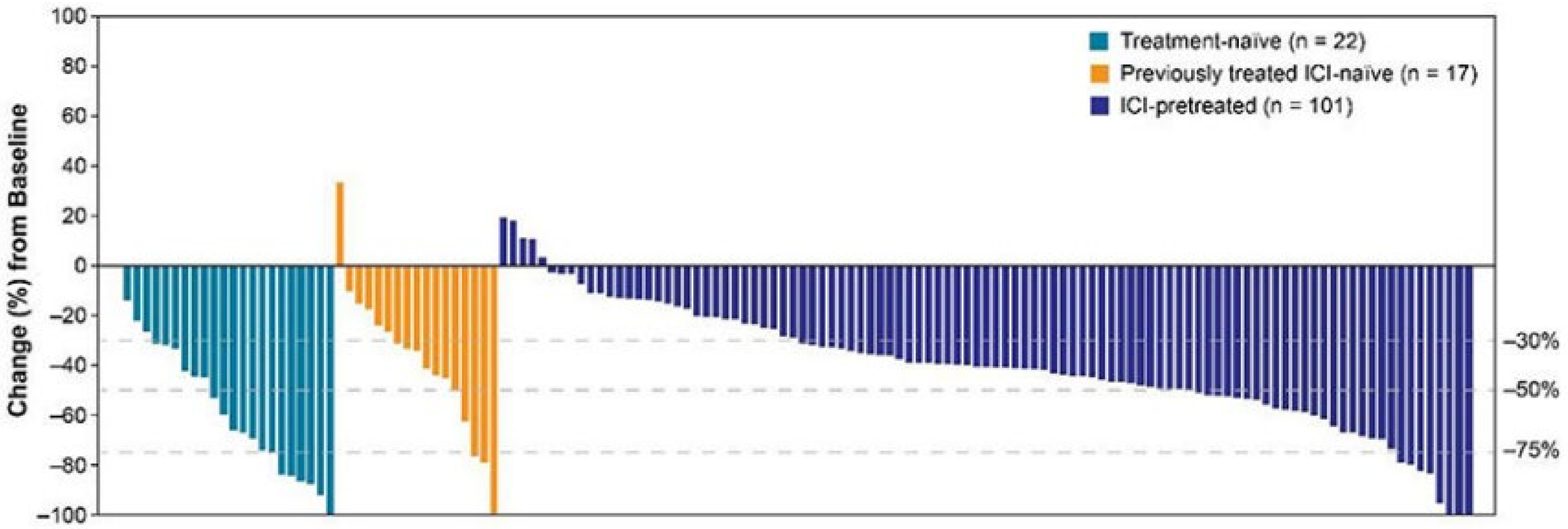
IO after IO in Endometrial Cancer
➔ Need for Clinical Trial



Combination in Renal Cell Carcinoma

Pembrolizumab-lenvatinib

Pts with either treatment-naive or previously treated (Study 111/KEYNOTE-146): a phase 1b/2 study



Chung-Han Lee et al, Lancet Oncology 2011

IO after IO in Renal Cell Carcinoma

Atezolizumab plus cabozantinib versus cabozantinib monotherapy for patients with renal cell carcinoma after progression with previous immune checkpoint inhibitor treatment (CONTACT-03): a multicentre, randomised, open-label, phase 3 trial

Sumanta Kumar Pal, Laurence Albiges, Piotr Tomczak, Cristina Suárez, Martin H Voss, Guillermo de Velasco, Jad Chahoud, Anastasia Mochalova, Giuseppe Procopio, Hakim Mahammedi, Friedemann Zengerling, Chan Kim, Takahiro Osawa, Martín Angel, Suyasha Gupta, Omara Khan, Guillaume Bergthold, Bo Liu, Melania Kalaitzidou, Mahrukh Huseni, Christian Scheffold, Thomas Powles, Toni K Choueiri

CONTACT-03 trial

Key eligibility criteria

- Advanced/metastatic clear cell or non–clear cell[a] RCC with or without a sarcomatoid component
- Radiographic progression on or after prior ICI treatment
  - ICI as adjuvant, 1L or 2L (single agent or in combination with another permitted agent)
  - ICI in the immediately preceding line of therapy

R 1:1

N=522

Atezolizumab 1200 mg IV q3w + Cabozantinib 60 mg daily PO

Cabozantinib 60 mg daily PO

Stratification factors

- **IMDC risk group**
  0 vs 1-2 vs ≥3
- **Histology**
  Dominant clear cell without sarcomatoid vs dominant non-clear cell without sarcomatoid vs any sarcomatoid[b]
- **Most recent line of ICI**
  Adjuvant vs 1L vs 2L

Primary endpoints

- Independent centrally-assessed PFS[c]
- OS

Key secondary endpoints

- Investigator-assessed PFS[c]
- ORR (per central review and per investigator)[c]
- Duration of response (per central review and per investigator)[c]
- Safety

IO after IO in Renal Cell Carcinoma

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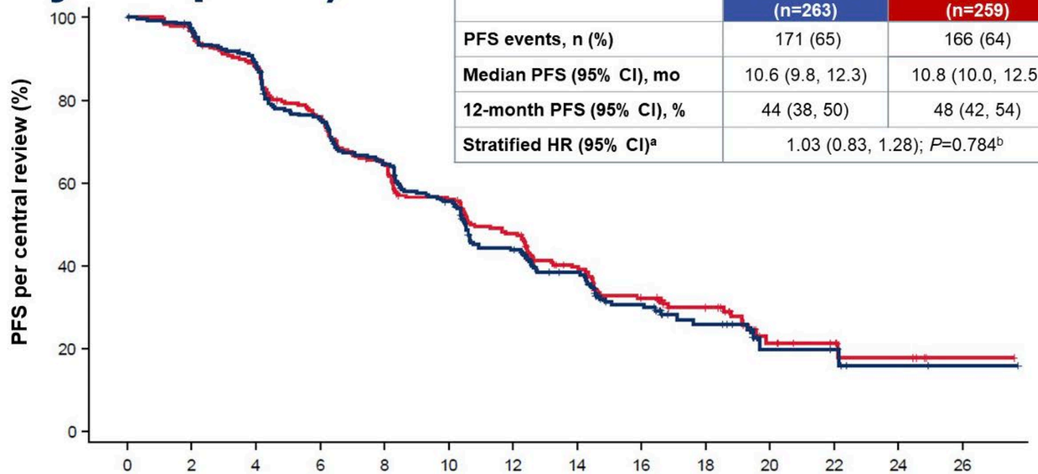
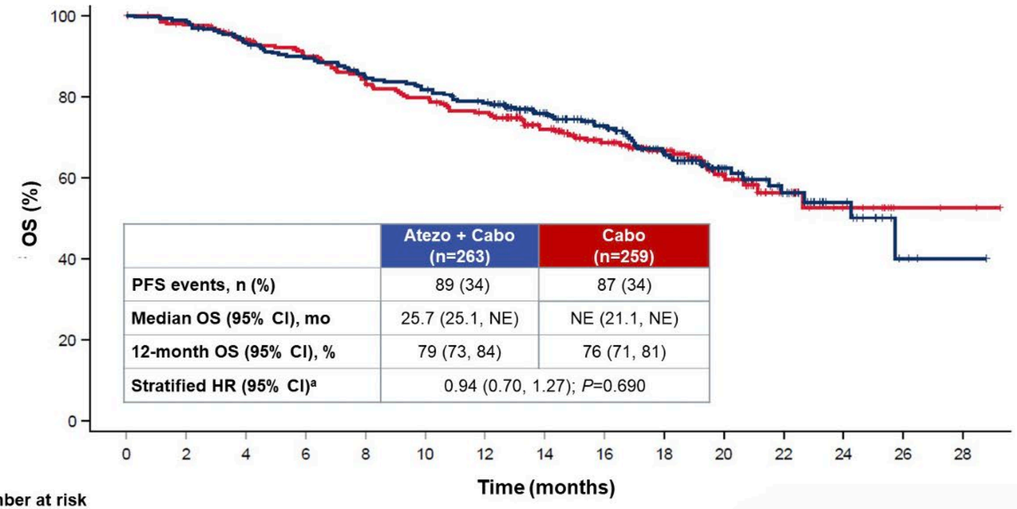
CONTACT-03 trial

Primary analysis of centrally reviewed PFS (primary endpoint)

	Atezo + Cabo (n=263)	Cabo (n=259)
PFS events, n (%)	171 (65)	166 (64)
Median PFS (95% CI), mo	10.6 (9.8, 12.3)	10.8 (10.0, 12.5)
12-month PFS (95% CI), %	44 (38, 50)	48 (42, 54)
Stratified HR (95% CI)[a]	1.03 (0.83, 1.28); *P*=0.784[b]	

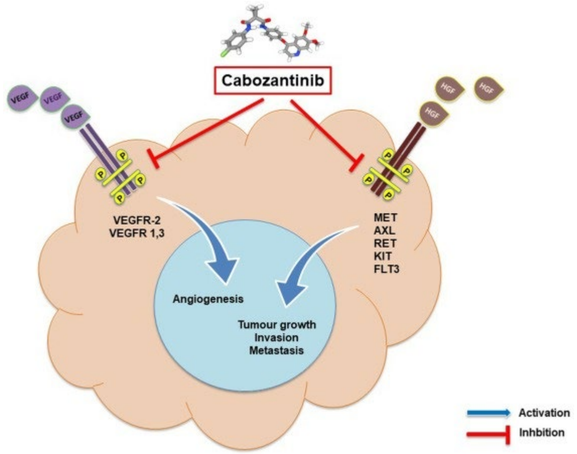


Interim analysis of OS (primary endpoint)



	Atezo + Cabo (n=263)	Cabo (n=259)
PFS events, n (%)	89 (34)	87 (34)
Median OS (95% CI), mo	25.7 (25.1, NE)	NE (21.1, NE)
12-month OS (95% CI), %	79 (73, 84)	76 (71, 81)
Stratified HR (95% CI)[a]	0.94 (0.70, 1.27); *P*=0.690	

IO after IO in Endometrial Cancer



PFS Endpoint

MSS/MSI Stratification

Advanced Recurrent Endometrial Cancer
At least one line of previous platinum
ECOG 0-2

2:1

Biopsy

ARM A
Cabozantinib 40mg PO daily
Nivolumab 240mg IV q2w
From cycle 5: 480mg IVq4w

ARM B
Nivolumab 240mg IV q2w
From cycle 5: 480mg IVq4w

Cross Over

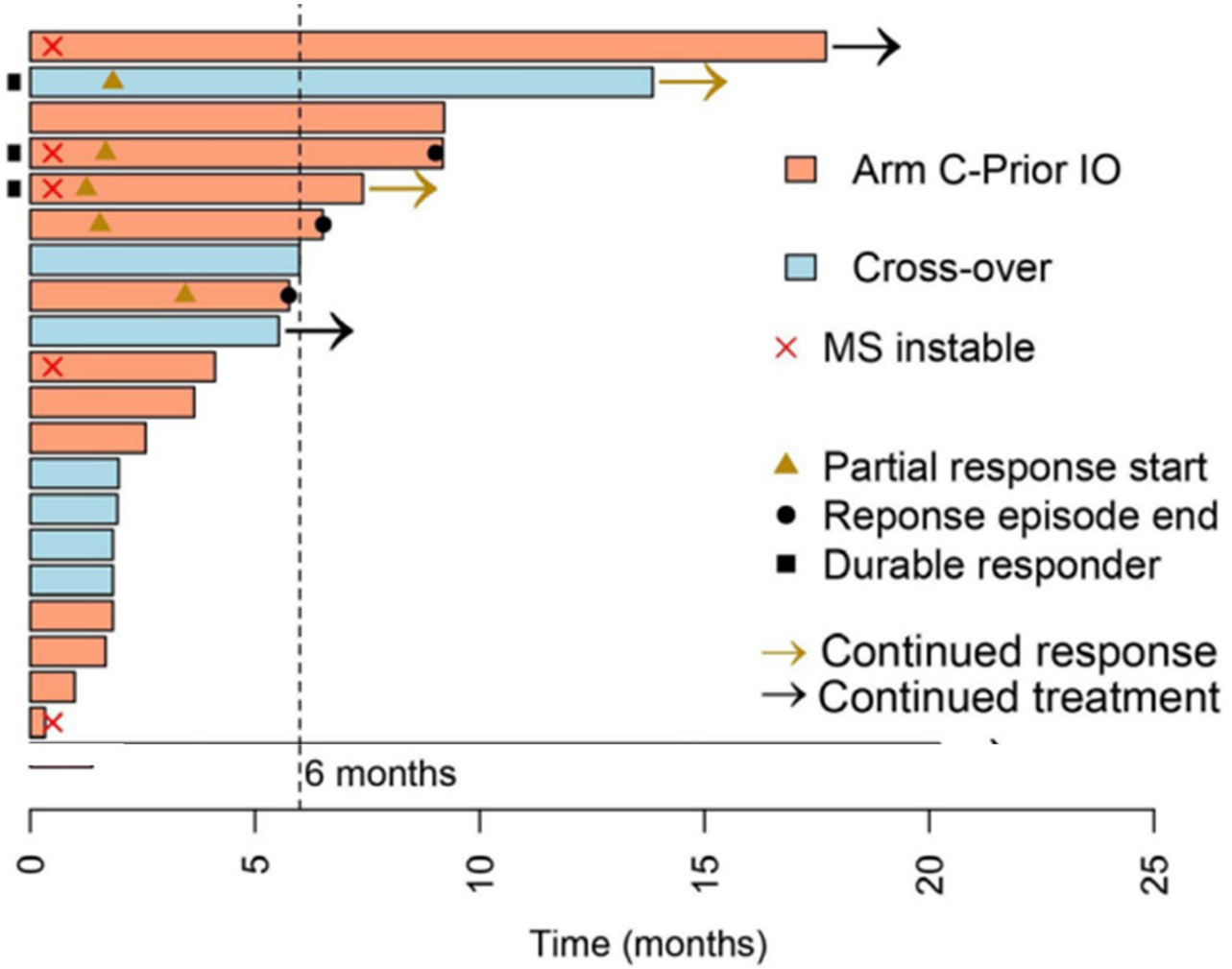
Cross Over from Arm B -
Post progression on immune therapy
OR
Recurrent Carcinosarcoma

ARM C
Cabozantinib 40mg PO daily
Nivolumab 240mg IV q2w
From cycle 5: 480mg IVq4w

Lheureux S et al, JITC 2022

SEOUL IGCS 2023

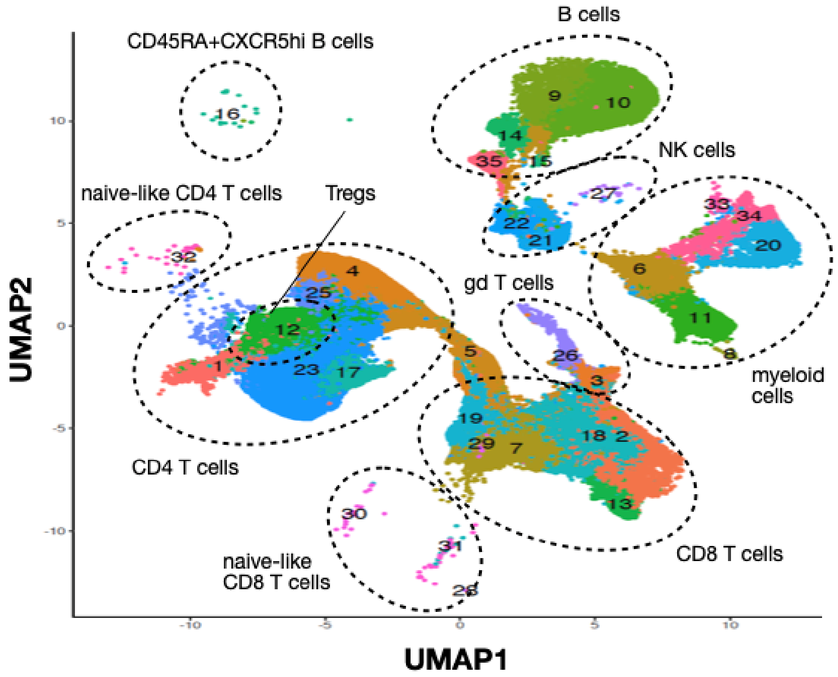
Exploratory Cohort: Post IO



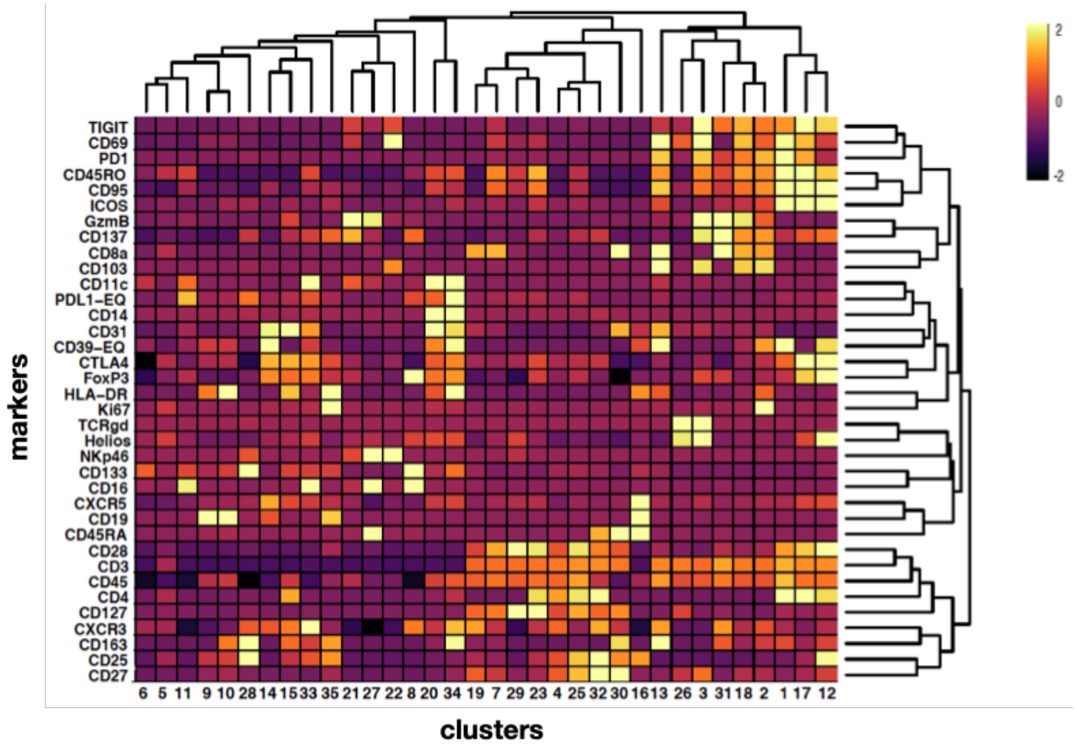
Lheureux S et al, JITC 2022

Baseline Biopsy - CyTOF

- Mass cytometry (CyTOF): High dimensional examination of the immune system to identify potential predictive markers of response
- Baseline biopsies analyzed by CyTOF using a 37-marker immune profiling panel.
- UMAP clustering of pooled CD45+ cells resulted in 35 unique immune populations defined by their lineage and phenotypic markers.



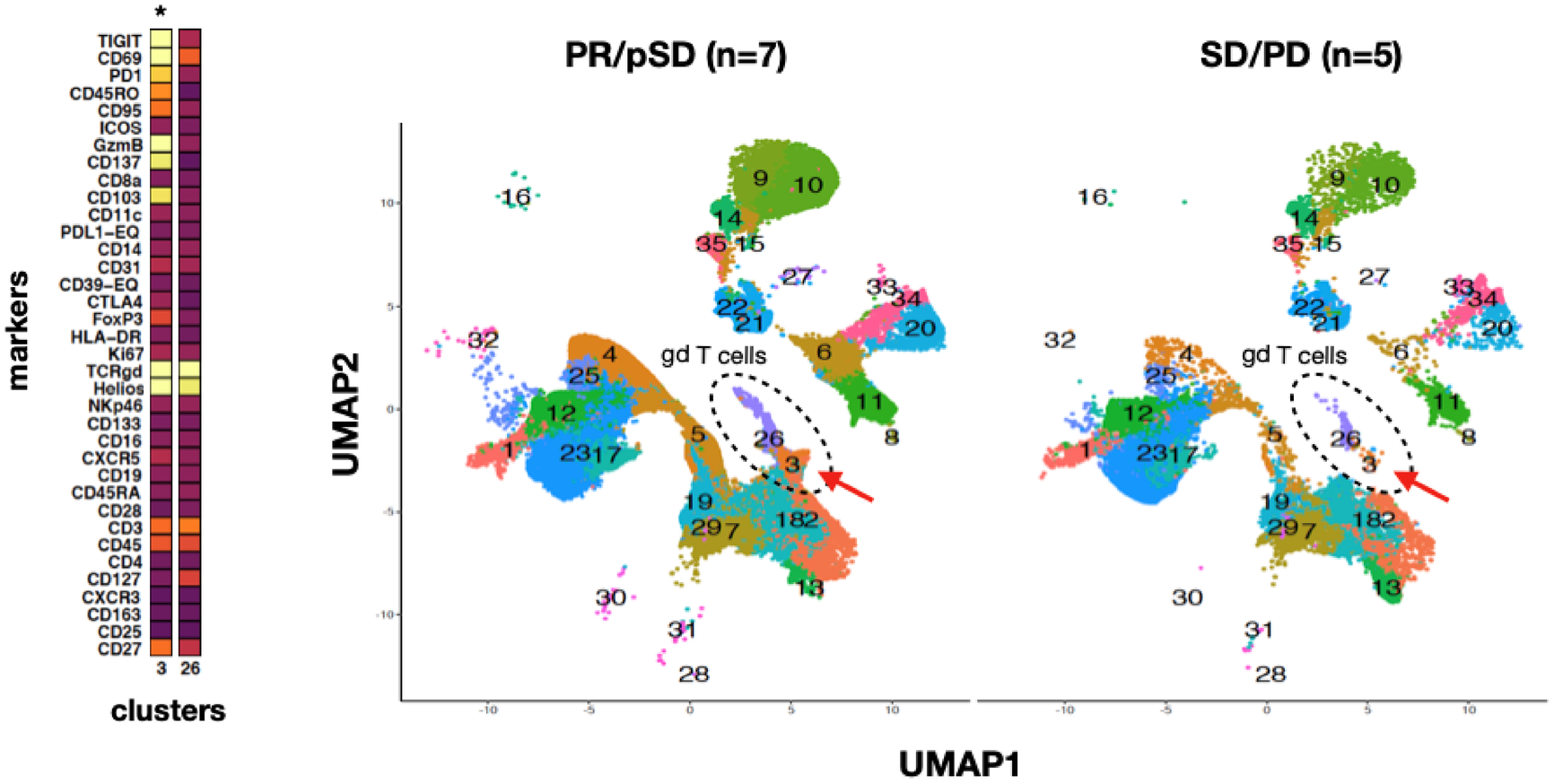
Cohort C (n=12)



Potential Biomarkers

Cohort C – Prior IO

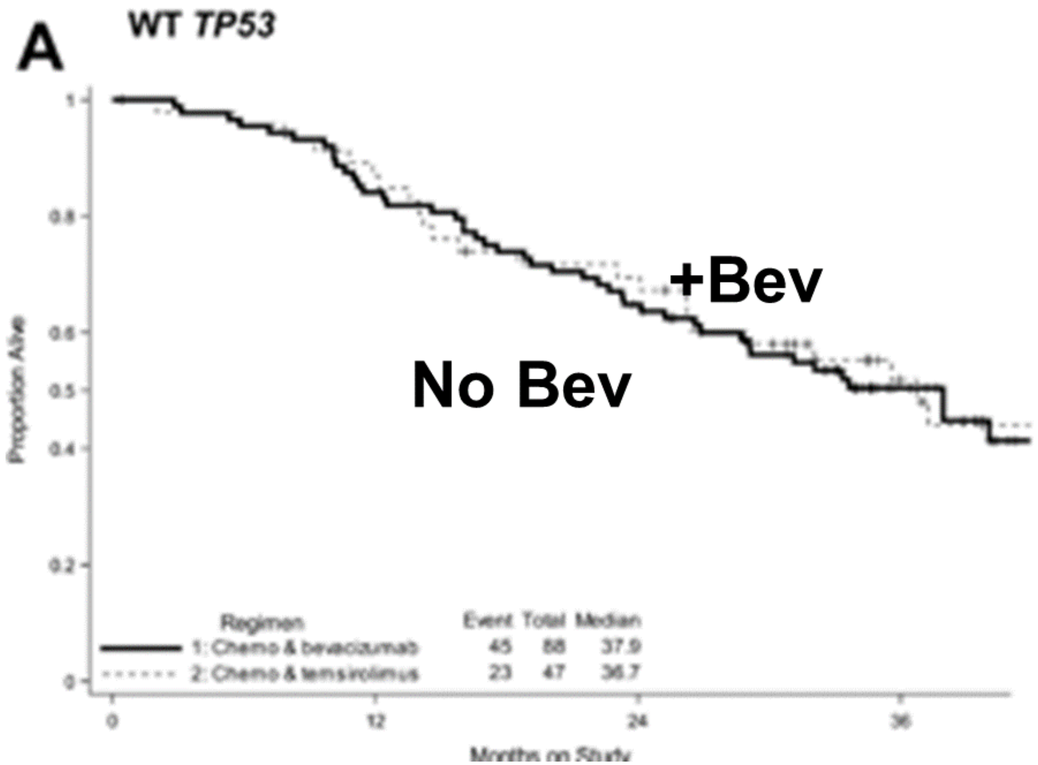
Non-progressors had higher proportions of
activated tissue-resident (CD103+CD69+) γδ T cells than progressors (adjusted p=0.009)

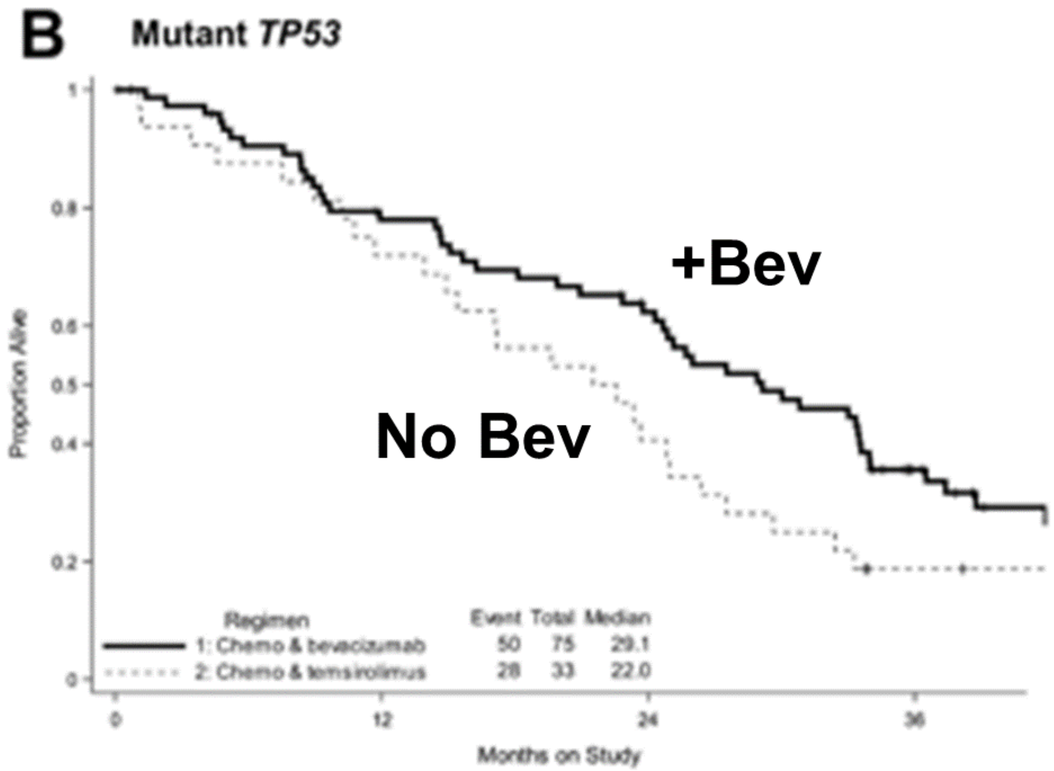


Approach based on Molecular Subgroup

p53 as predictive biomarker: GOG 86P

Patients based on TP53 status and Bev





Gynecol Oncol. 2021 April ; 161(1): 113–121. doi:10.1016/j.ygyno.2021.01.025.

Potential Strategies post IO

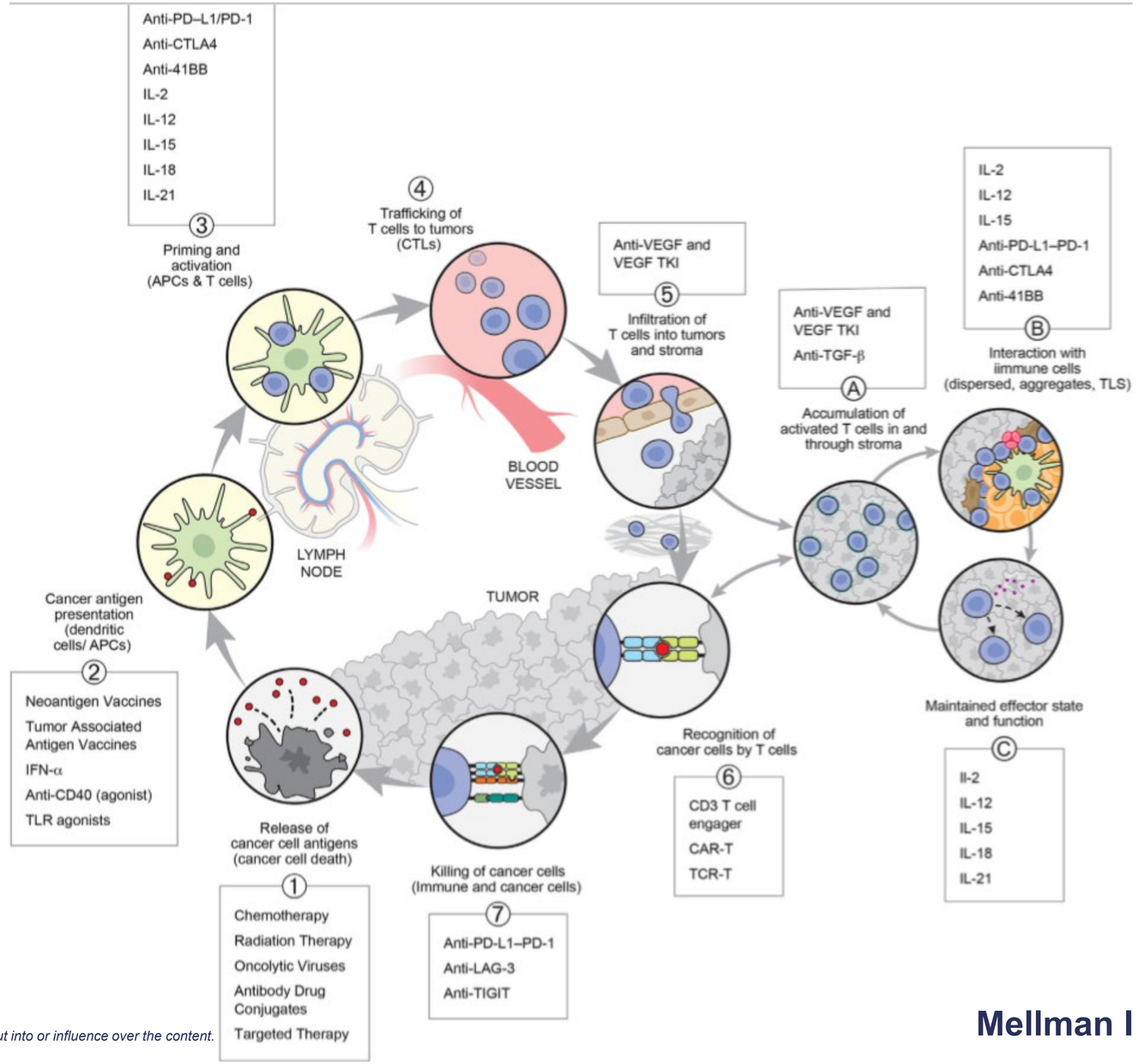
ALTERNATIVE PROANGIOGENIC PATHWAYS

IMMUNOTHERAPIES / ENHANCING IO

METABOLIC PATHWAYS

PARP INHIBITORS

Therapies to Target the Cancer – Immunity Cycle



Mellman I et al, Cell 2023

Combination Therapy

- Role of CTLA4 and T-regs in dMMR and POLE EC and dMMR CRC

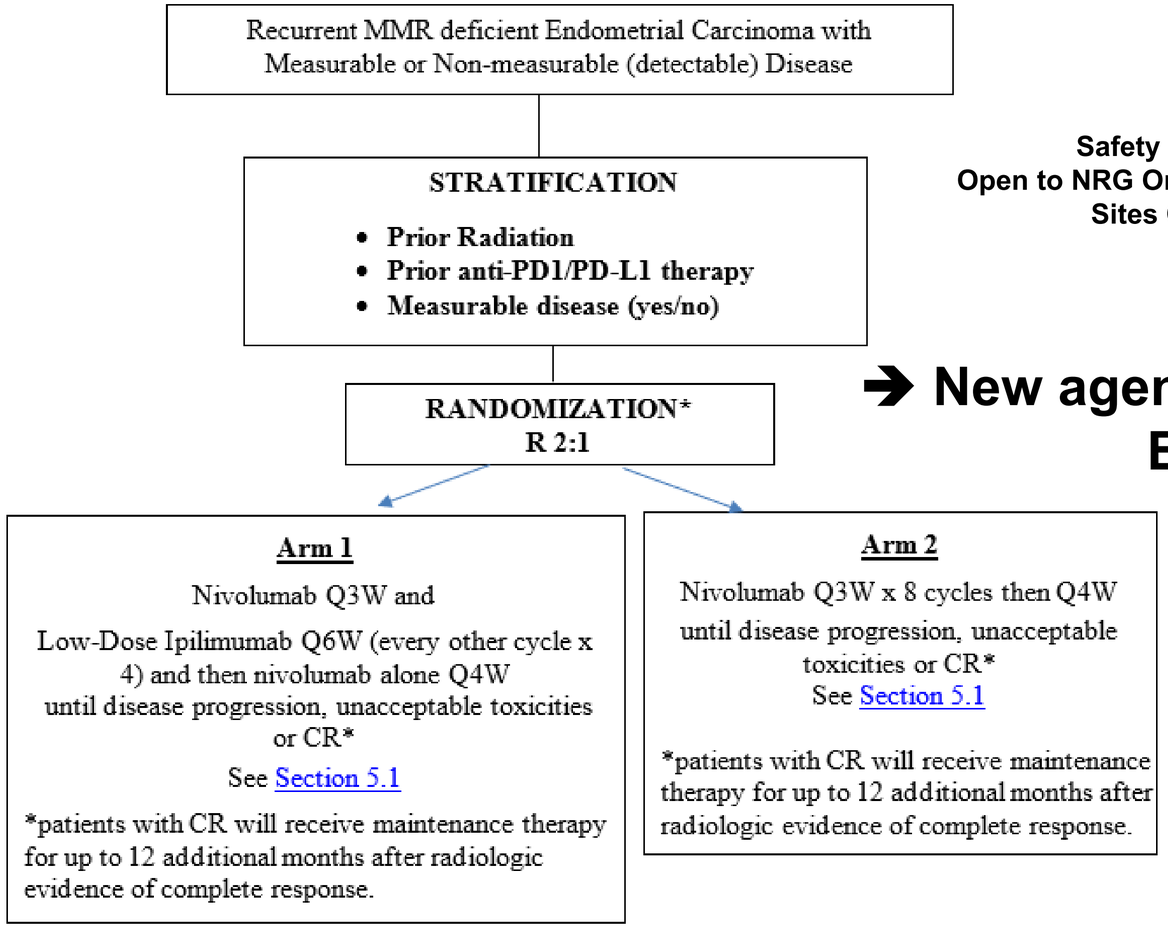
- **Rationale**
  - Dual immune checkpoint

  - Immune evasion mechanism of dMMR tumors
    - Up-regulation of PD1, CTLA4 and other exhaustion markers like LAG3
    - CTLA4 up-regulated in dMMR and POLE EC

  - Targeting T-regs
    - Immunosuppressive cells
    - In EC, high T-regs counts, T-regs/CD8 ration→ worse outcome and prognosis

Yamagami et al, Int J Gynecol Cancer. 2011;
De Jong et al, Gynecol Oncol 2009;
Van Gool et al Clin Cancer Res, 2015
Liosa et al Cancer Discov. 2015

Recurrent MMRd – NRG GY025



Safety lead-in
Open to NRG Oncology Phase I Sites ONLY

➔ **New agent combining dual checkpoint inhibitor**
Ex: PD1/CTLA4 – PD1/TIGIT

*Randomization is 2:1 (Arm 1 vs Arm 2). Twice as many patients will be randomized to Arm 1.

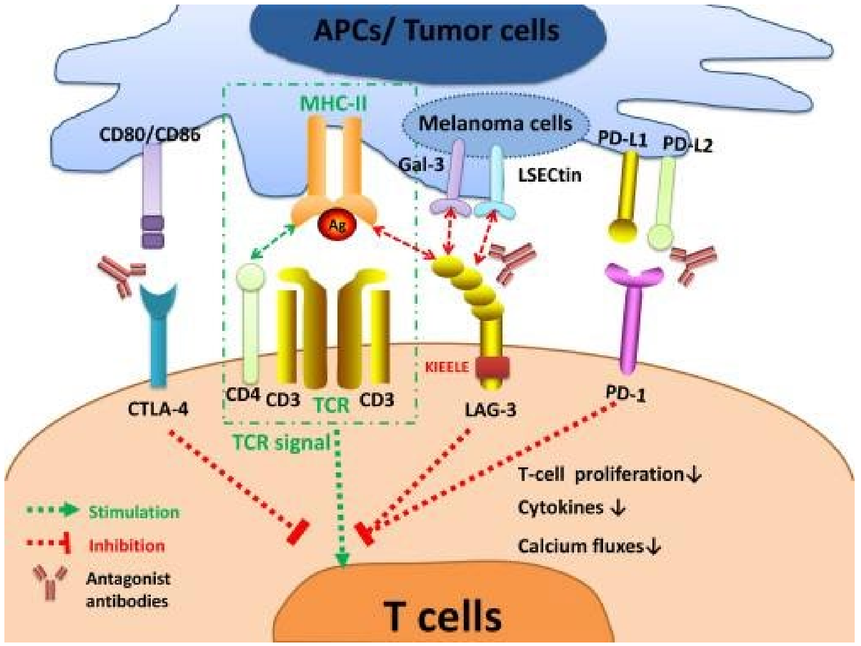
Study Chairs: Haider Mahdi, MD, MPH; K. Moore, MD; Matthew Powell, MD; Stephanie Gaillard, MD, PhD.

NCT05112601. Updated April 28, 2022. Accessed May 10, 2022. https://clinicaltrials.gov/ct2/show/NCT05112601

Combination ICI (PD1-LAG3)

- LAG-3 and PD-1 are distinct inhibitory immune checkpoints that contribute to T-cell exhaustion

- Simultaneous blockade of LAG-3 and PD-1 may synergistically restore T-cell activation and enhance antitumor immunity.



Melanoma pre-treated

Table: LBA18 Response by LAG-3[a] and PD-L1[b] expression

	All Patients		LAG-3 ≥ 1%		LAG-3 < 1%	
	n	ORR (%)	n	ORR (%)	n	ORR (%)
All	61	7 (11)	33	6 (18)	20	1 (5.0)
PD-L1 expression						
≥ 1%	20	1 (5.0)	16	1 (6.3)	4	0
< 1%	24	4 (17)	11	3 (27)	13	1 (7.7)

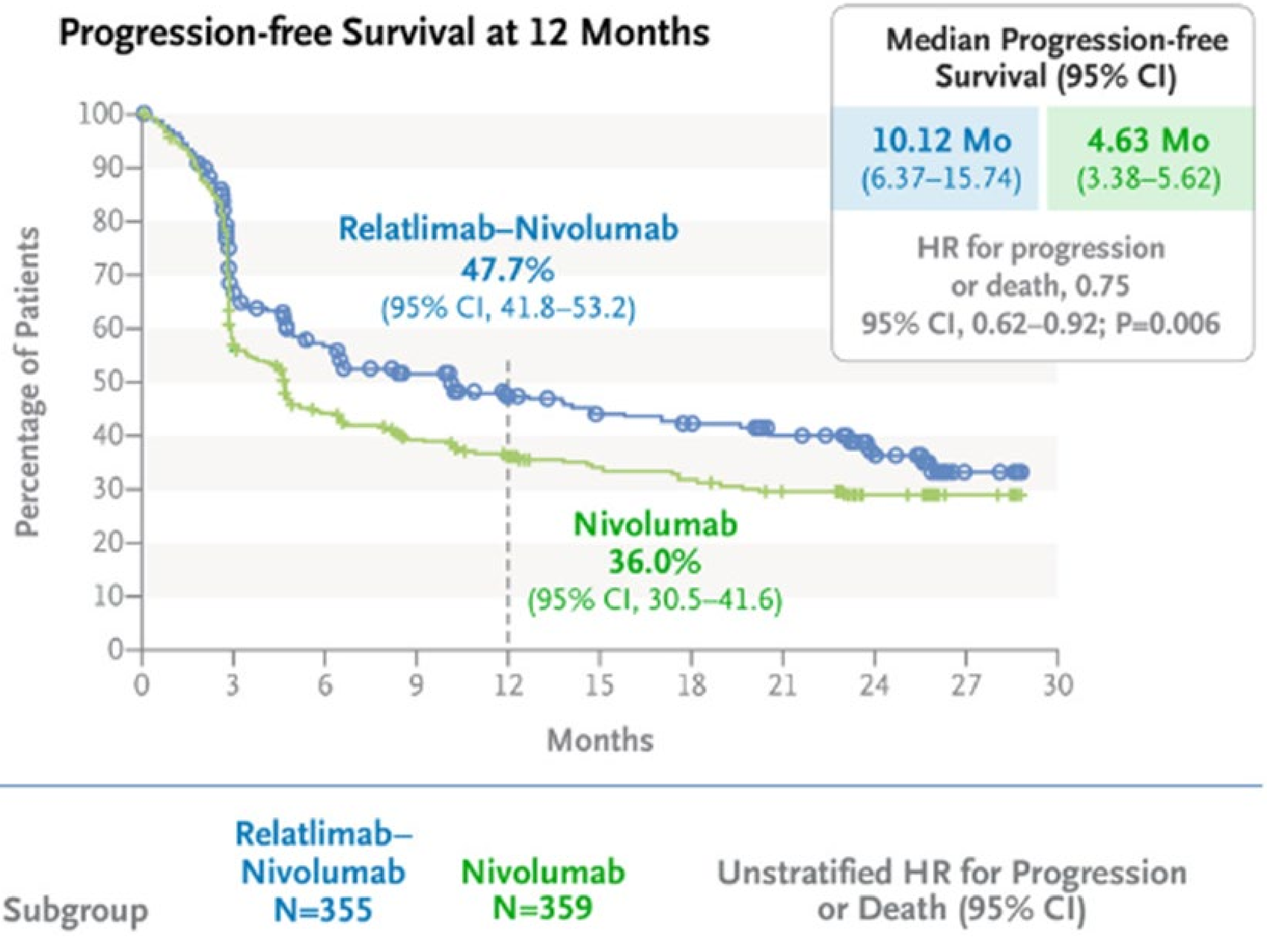
[a]Immunohistochemistry (IHC) with percentage of positive cells among all nucleated cells within the tumor and invasive margin using mouse antibody clone 17B4. Expression ≥ 1% was identified in 33/53 (62%) of evaluable samples.

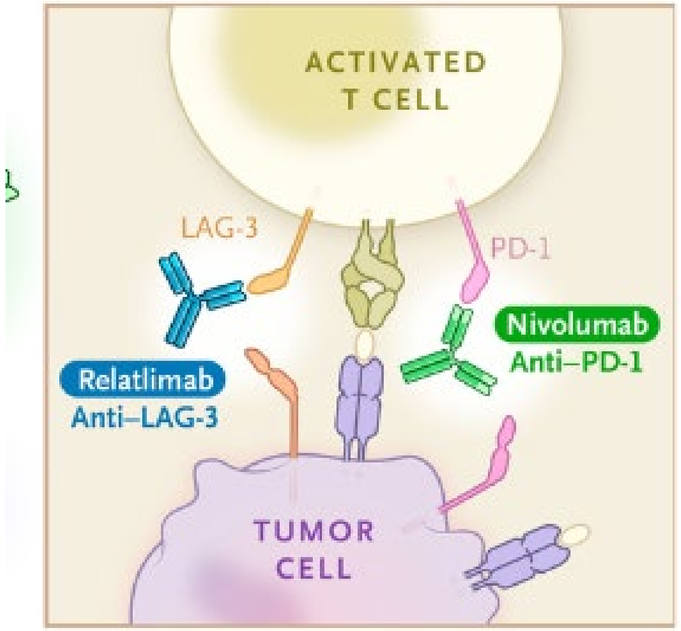
[b]Tumor cell expression determined using Dako PD-L1 IHC 28-8 kit. Expression ≥ 1% was identified in 20/44 (45%) of evaluable samples.

Ascierto PA et al, ESMO 2017

Combination ICI (PD1-LAG3)

Untreated Melanoma





Tawbi HA et al, NEJM 2023

Potential Strategies post IO

ALTERNATIVE PROANGIOGENIC PATHWAYS

IMMUNOTHERAPIES / ENHANCING IO

METABOLIC PATHWAYS

PARP INHIBITORS - ADC

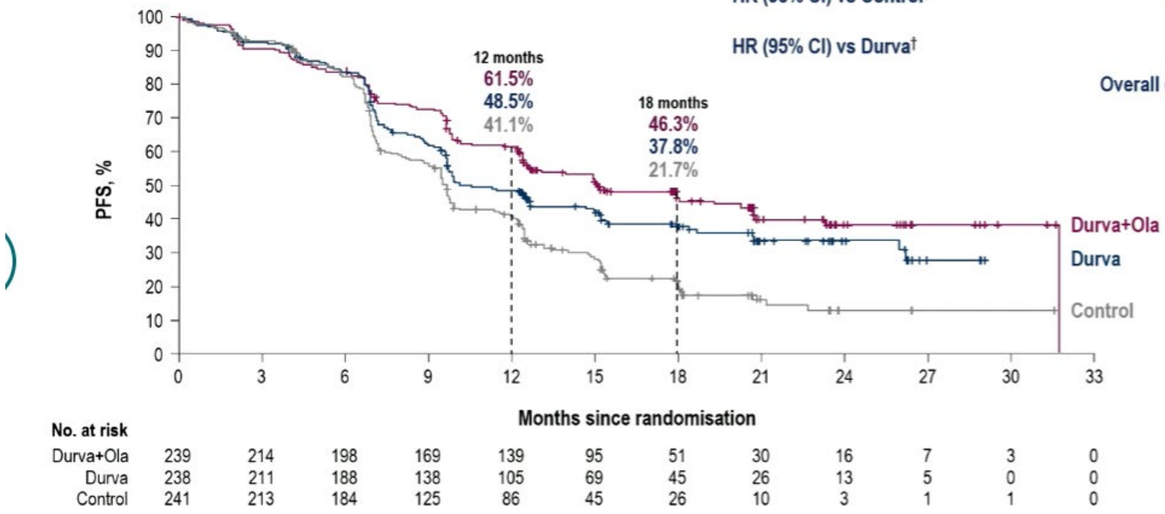
Importance of the molecular profiling

Benefit of IO combo and DDR agents

DUO-E: PFS by Subgroup

PFS: ITT population

Primary endpoint



No. at risk

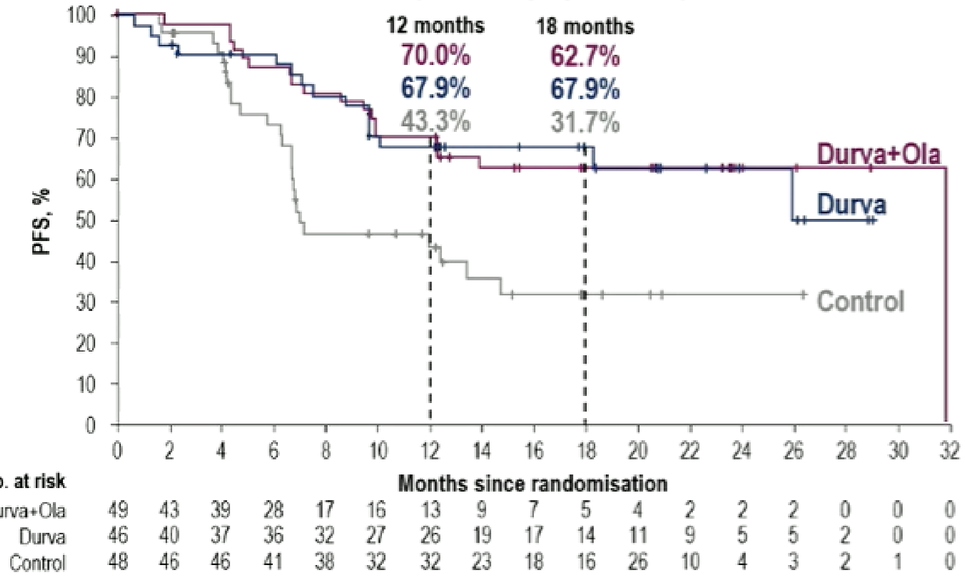
Durva+Ola	239	214	198	169	139	95	51	30	16	7	3	0
Durva	238	211	188	138	105	69	45	26	13	5	0	0
Control	241	213	184	125	86	45	26	10	3	1	1	0

	Control (N=241)	Durva (N=238)	Durva+Ola (N=239)
Events, n (%)	173 (71.8)	139 (58.4)	126 (52.7)
Median PFS (95% CI),* months	9.6 (9.0–9.9)	10.2 (9.7–14.7)	15.1 (12.6–20.7)
HR (95% CI) vs Control†		**0.71** (0.57–0.89); *P*=0.003	**0.55** (0.43–0.69); *P*<0.0001
HR (95% CI) vs Durva†			0.78 (0.61–0.99)

Overall data maturity 61.0%

Prespecified exploratory analysis

dMMR (20% of population)



No. at risk

Durva+Ola	49	43	39	28	17	16	13	9	7	5	4	2	2	2	0	0	0
Durva	46	40	37	36	32	27	26	19	17	14	11	9	5	5	2	0	0
Control	48	46	46	41	38	32	32	23	18	16	26	10	4	3	2	1	0

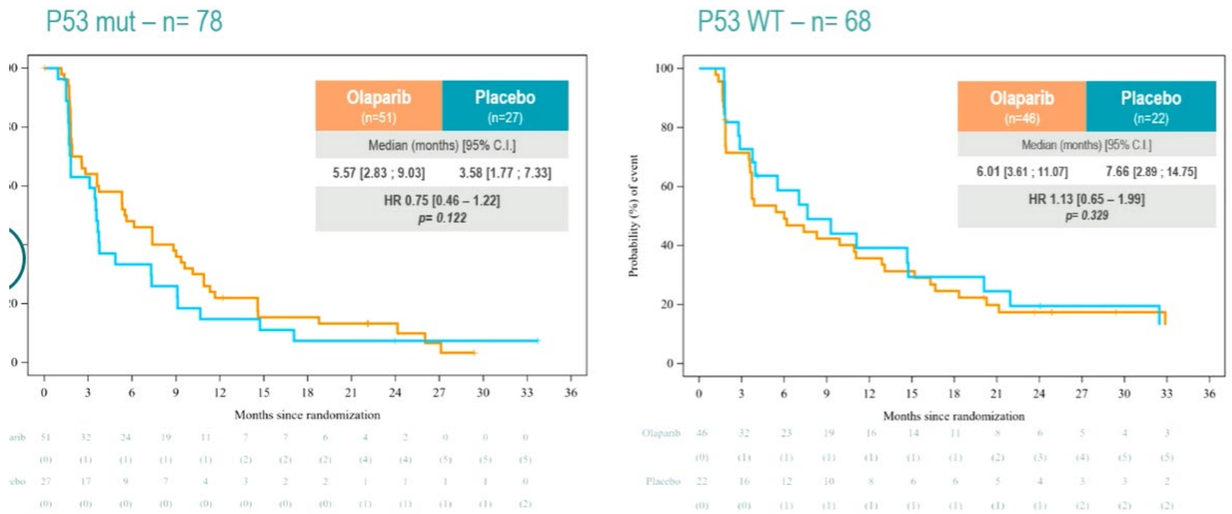
	Control (N=49)	Durva (N=46)	Durva+Ola (N=48)
Events, n (%)	25 (51.0)	15 (32.6)	18 (37.5)
Median PFS (95% CI),* months	7.0 (6.7–14.8)	NR (NR–NR)	31.8 (12.4–NR)
HR (95% CI) vs Control†		**0.42 (0.22–0.80)**	**0.41 (0.21–0.75)**
HR (95% CI) vs Durva†			**0.97 (0.49–1.98)**

Westin et al ESMO 2023

Importance of the molecular profiling

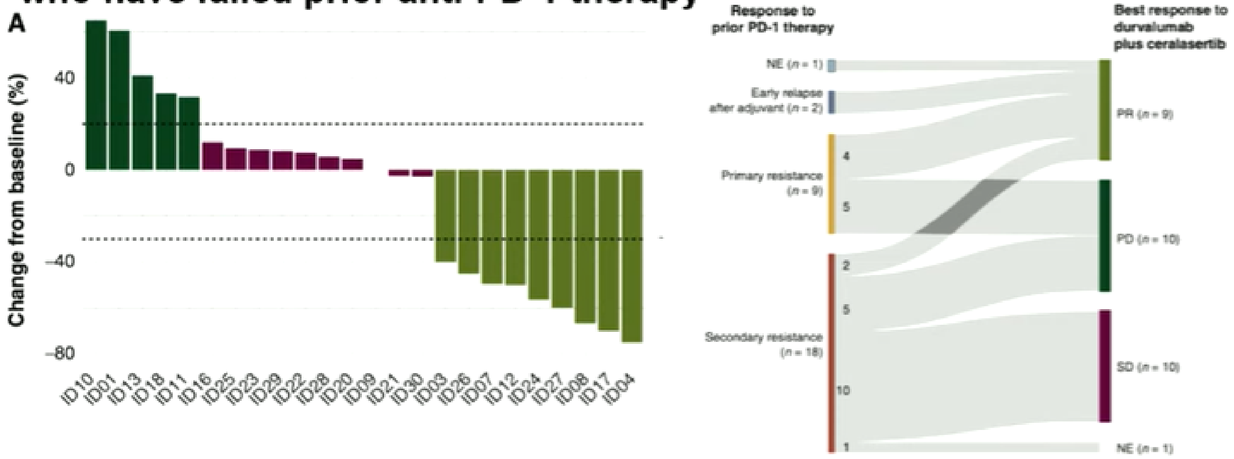
Benefit of AO combo and DDR agents

UTOLA: PFS by TP53 Status



Joly F et al, ESMO 2023

Phase II study of ceralasertib (AZD6738) in combination with durvalumab in patients with advanced/metastatic melanoma who have failed prior anti-PD-1 therapy



Response rate 31%

Kim et al Ann Oncol. 2022 Feb;33(2):193-203.

Median duration of response 8.8 months

Tumours with an immune-enriched microenvironment or alterations in the DDR pathway were more likely to respond

Conclusion / Discussion

Considerations In the post IO setting

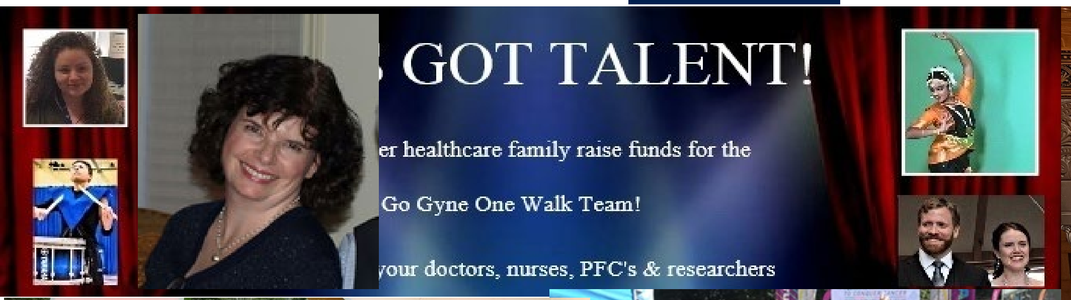
- Time of Progression: PD during IO versus post IO likely different
- Combination Strategies
- Type of Molecular Subgroup - Biomarkers
- New drug design: Improving drug delivery (ADC)
  Improve inhibition by dual targeting (bifunctional Mabpair)
- Need for Clinical trials & Biomarkers assessment

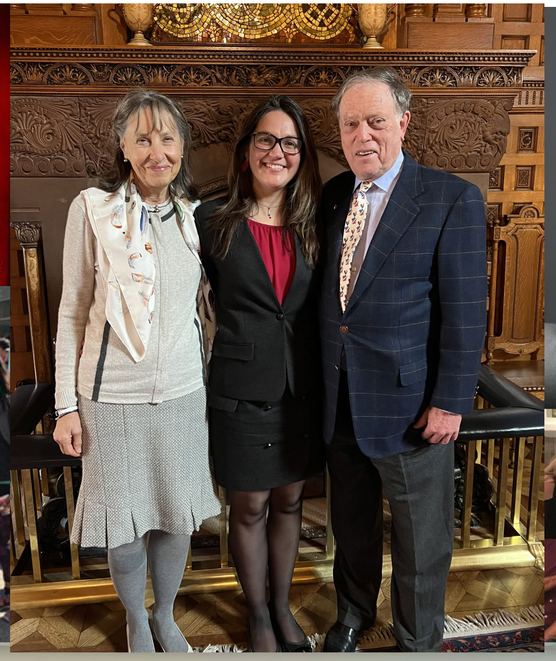
HOPE

BRAS DRUG DEVELOPMENT PROGRAM

UNIVERSITY OF TORONTO

Thank you to patients, clinical & research teams & research funds





Canadian Cancer Society

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OICR Ontario Institute for Cancer Research

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The Princess Margaret Cancer Foundation