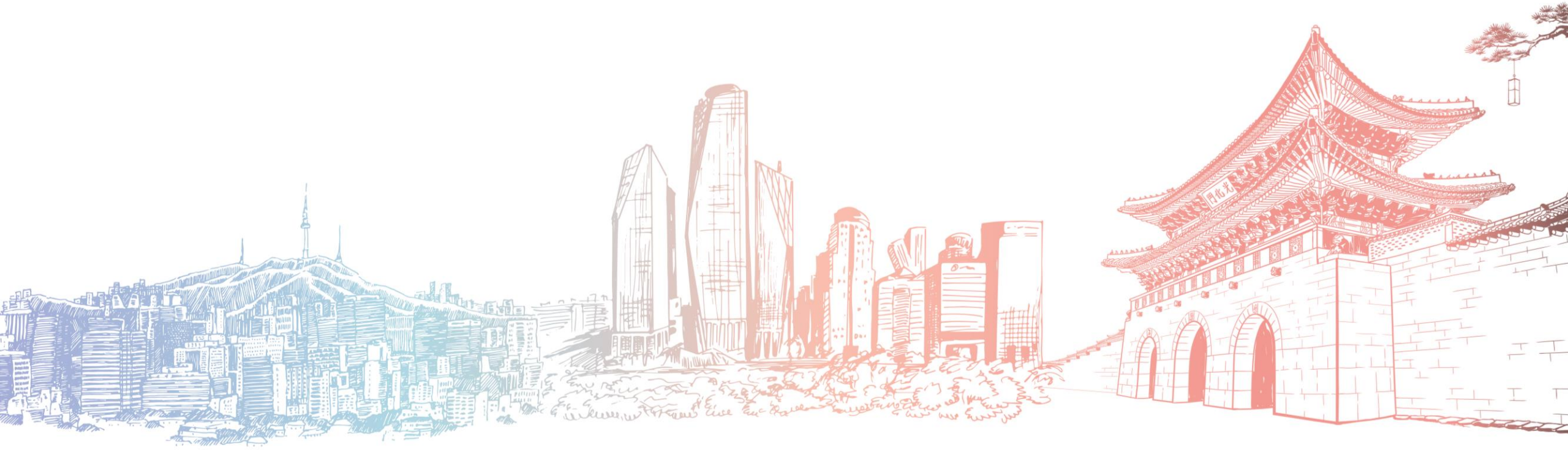
Expansion of ICI: investigating combination with PARPi or TKI and beyond for treatment of primary advanced/recurrent EC

Dr. David SP Tan



Disclosures

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- He has participated on advisory boards for AstraZeneca, MSD, Roche, Bayer, Genmab, GSK, Esai, PMV, BioNTech, Ellipses Pharma, and Boehringer Ingelheim
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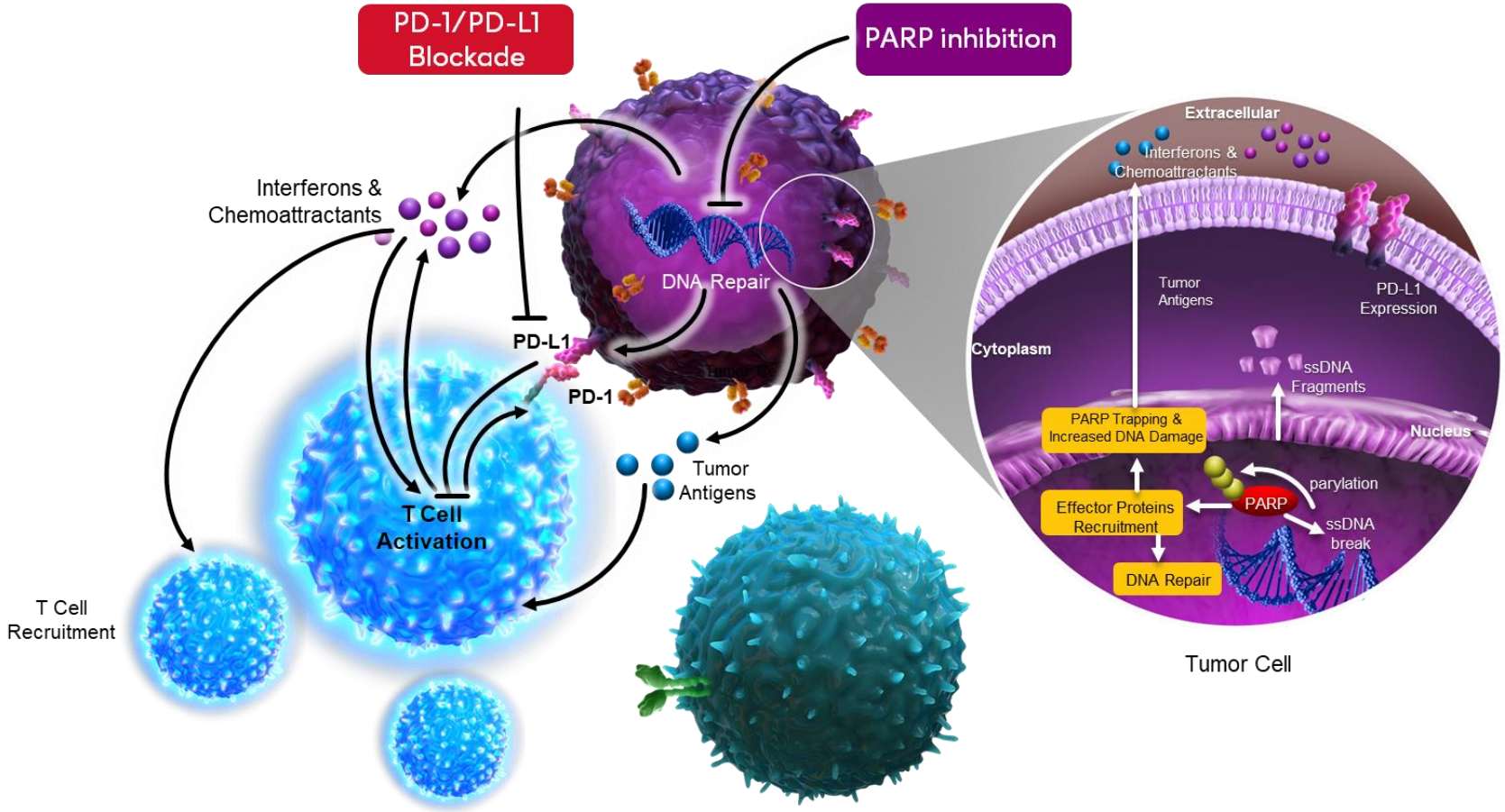
Rationale for combining PARPi and anti–PD-(L)1[1-3]

Some ECs have HRD and high **PARP-1** expression, suggesting therapeutic potential of PARP inhibitors[2]

RUBY Part 2 is currently investigating the combination of dostarlimab + niraparib[4]

DUO-E is currently investigating the combination of durvalumab + olaparib[5]



DNA = deoxyribonucleic acid; EC = endometrial cancer; HRD = homologous recombination deficiency; p53abn = p53 abnormal; PARP = poly adenosine diphosphate-ribose polymerase; PARPi = poly adenosine diphosphate-ribose polymerase inhibitor; PD-1 = programmed cell death-1; PD-L1 = programmed cell death ligand-1; ssDNA = single-stranded DNA.

1. Jiao S, et al. *Clin Cancer Res*. 2017;23:3711-3720. 2. Arciuolo DT, et al. *Int J Mol Sci*. 2022;23:11684. 3. Vikas P, et al. *Front Oncol*. 2020;10:570. 4. Mirza MR, et al. *Ann Oncol*. 2021;32:S770-S771. 5. Westin SN, et al. *J Clin Oncol*. 2023; DOI: 10.1200/JCO.23.02132.

DUO-E | ENGOT-en10 | GOG-3041 | NCT04269200[1,2]

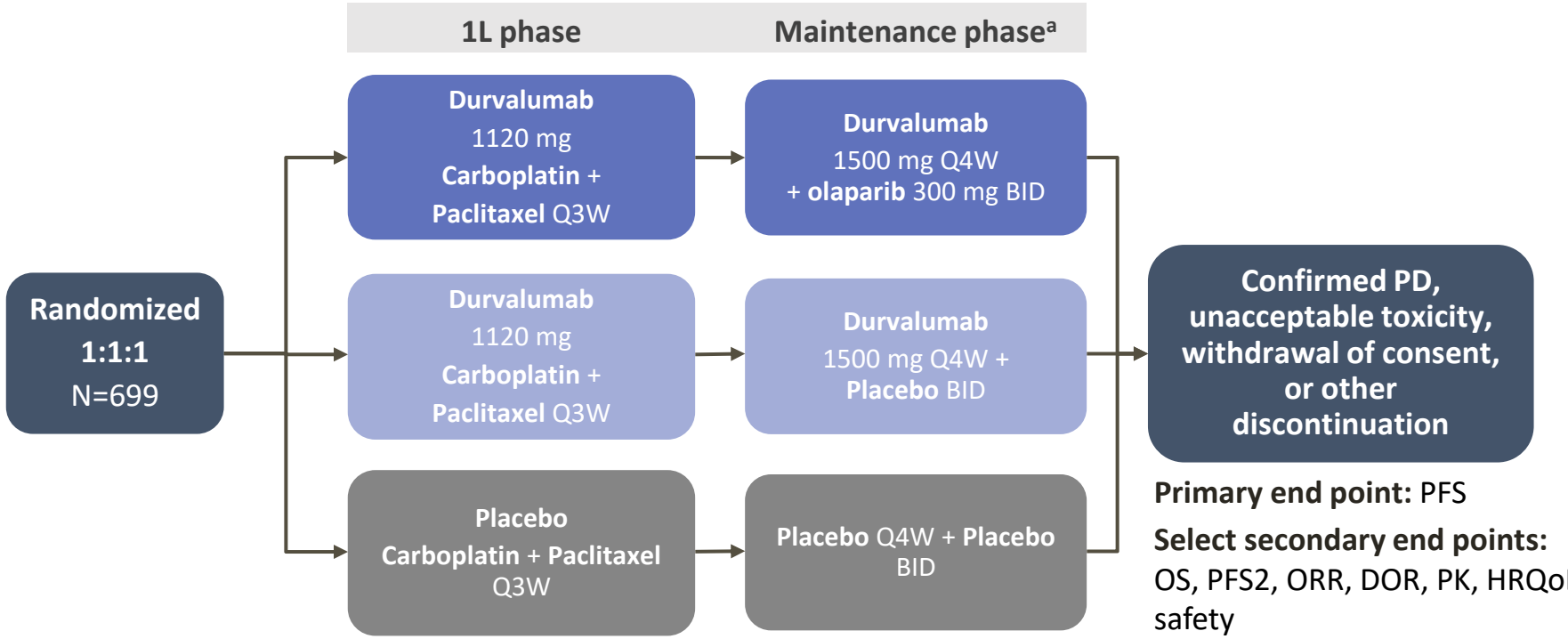
Durvalumab + carboplatin/paclitaxel followed by durvalumab + olaparib

Eligible patients:

- Recurrent or primary advanced (stage III or IV) endometrial cancer
- ECOG PS 0-1
- Age ≥18 years
- Naïve to first line systemic anticancer treatment
- Naïve to PARPi and IO
- Adjuvant chemotherapy allowed if ≥12 months from last treatment to relapse

Stratification:

- MMR status
- Disease status
- Geographic region



Dual PFS primary end point in ITT; gatekeeping strategy applied to PFS (primary end point) and OS (secondary end point)

Primary end point: PFS

Select secondary end points: OS, PFS2, ORR, DOR, PK, HRQoL, safety

Start date: May 5, 2020
Status: Recruiting

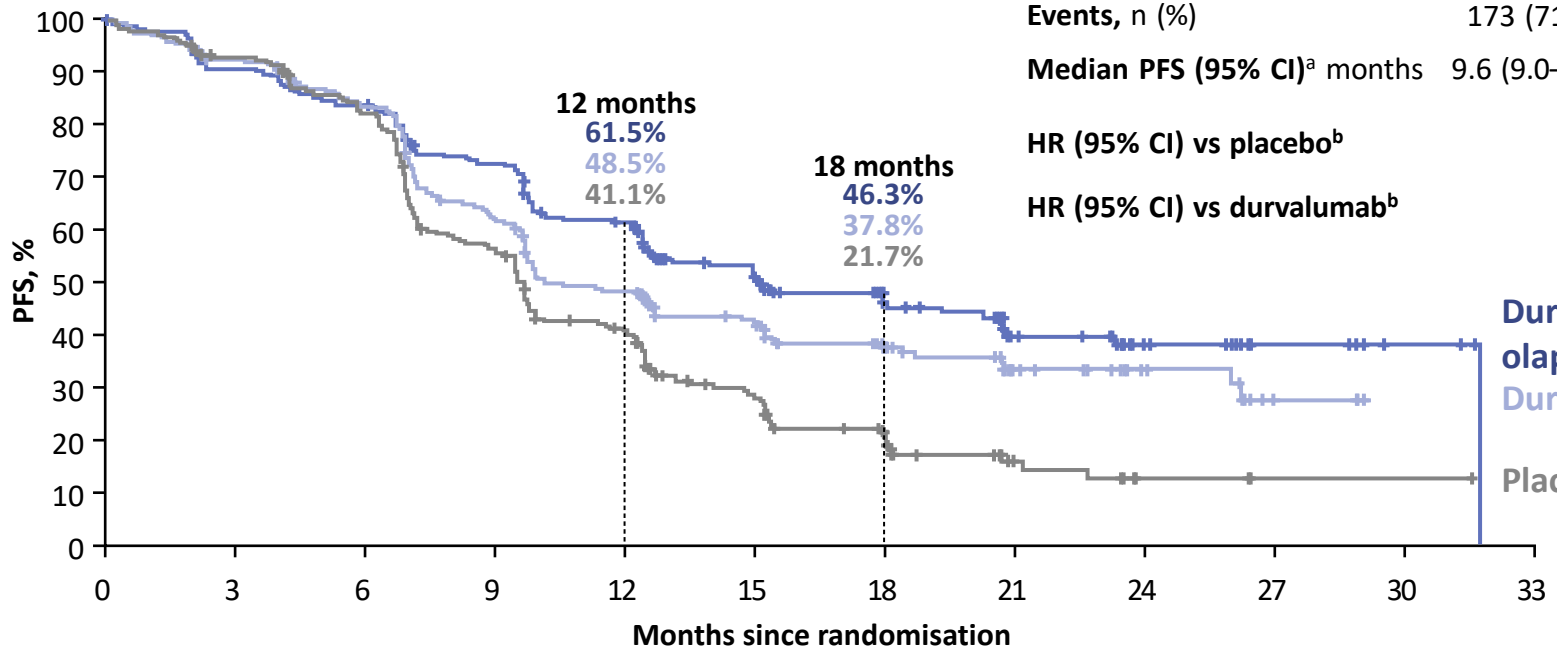
[a]Patients who achieve and maintain disease control (complete response, partial response, or stable disease) during the chemotherapy phase (minimum of 6 cycles) will receive maintenance therapy.
1L = first line; BID = twice daily; DOR = duration of response; EC = endometrial cancer; ECOG PS = Eastern Cooperative Oncology Group performance status; ENGOT = European Network of Gynecological Oncological Trial Groups; HRQoL = health-related quality of life; MMR = mismatch repair; ORR = objective response rate, OS = overall survival; PD = progressive disease; PFS = progression-free survival; PFS2 = time to second disease progression or death; PK = pharmacokinetics; QxW = every x weeks.

1. National Library of Medicine. Available at https://clinicaltrials.gov/ct2/show/NCT04269200. Accessed August 14, 2023. 2. Westin SN et al. *J Clin Oncol* 2023; DOI: 10.1200/JCO.23.02132.

DUO-E: primary end point PFS in ITT population

Durvalumab + carboplatin/paclitaxel followed by durvalumab + olaparib

	Placebo + C/P N=241	Durvalumab + C/P N=238	Durvalumab + olaparib + C/P N=239
Events, n (%)	173 (71.8)	**139 (58.4)**	**126 (52.7)**
Median PFS (95% CI)[a] months	9.6 (9.0–9.9)	**10.2 (9.7–14.7)**	**15.1 (12.6–20.7)**
HR (95% CI) vs placebo[b]		**0.71** (0.57–0.89); *P*=0.003	**0.55** (0.43–0.69); *P*<0.0001
HR (95% CI) vs durvalumab[b]			0.78 (0.61–0.99)



No. at risk

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

Adapted from Westin SN, et al. *J Clin Oncol*. 2023; DOI: 10.1200/JCO.23.02132 published by the American Society of Clinical Oncology.

The median (range) duration of follow up for PFS was 12.6 (0.0-31.6), 15.4 (0.0-29.1), and 15.4 (0.0-31.7) months in censored patients for the placebo, durvalumab, and durvalumab + olaparib arms, respectively. PFS rates were estimated by the KM method.
[a]CI for median PFS is derived based on the Brookmeyer Crowley method. [b]The primary PFS analysis for each comparison was performed separately. The HR and CI were estimated from a Cox proportional hazards model stratified by MMR and disease status. The CI was calculated using a profile likelihood approach. The P value was calculated using a log rank test stratified by MMR and disease status.
CI = confidence interval; CP = carboplatin/paclitaxel; HR = hazard ratio; ITT = intention to treat; KM = Kaplan Meier; MMR = mismatch repair; PFS = progression-free survival.
Westin SN, et al. *J Clin Oncol*. 2023; DOI: 10.1200/JCO.23.02132.

DUO-E | Summary of safety end points

	Chemotherapy + maintenance phase			Maintenance phase		
Safety, n (%)	Placebo + C/P → Placebo + Placebo N=236	Durvalumab + C/P → Durvalumab + Placebo N=235	Durvalumab + C/P→ Durvalumab + Olaparib N=238	Placebo + C/P → Placebo + Placebo N=169	Durvalumab + C/P → Durvalumab + Placebo N=183	Durvalumab + C/P→ Durvalumab + Olaparib N=192
Any AE	236 (100)	232 (98.7)	237 (99.6)	143 (84.6)	158 (86.3)	184 (95.8)
Grade ≥3 AEs	133 (56.4)	129 (54.9)	160 (67.2)	28 (16.6)	30 (16.4)	79 (41.1)
AEs with outcome of death	8 (3.4)	4 (1.7)	5 (2.1)	2 (1.2)	0	3 (1.6)
Any irAE[a]	16 (6.8)	66 (28.1)	56 (23.5)	6 (3.6)	27 (14.8)	27 (14.1)
AEs of special interest for olaparib						
MDS/AML[b]	0	0	0	0	0	0
New primary malignancies[b]	3 (1.3)	1 (0.4)	2 (0.8)	2 (1.2)	1 (0.5)[e]	1 (0.5)
Pneumonitis[c]	1 (0.4)	4 (1.7)	12 (5.0)	0	3 (1.6)	8 (4.2)
AEs leading to dose reduction of olaparib/placebo[d]	5 (2.1)	14 (6.0)	65 (27.3)	4 (2.4)	13 (7.1)	63 (32.8)

[a]As assessed by the investigator, and programmatically derived from individual causality assessments for combination studies. Missing responses are counted as related;[b]MDS/AML and new primary malignancies include AEs from first dose of investigational product (durvalumab/olaparib/placebo) until the end of the study (includes cases reported beyond the safety follow up period); [c]Grouped term: includes pneumonitis, bronchiolitis, and interstitial lung disease; As assessed by the investigator, and programmatically derived from individual causality assessments for combination studies. Missing responses are counted as related; [d]For durvalumab/placebo, this includes dose interruption during infusion as well as doses that were skipped or delayed.
[e]Excludes one event of basal cell carcinoma.
AE = adverse event; AML = acute myeloid leukemia; C/P = carboplatin/paclitaxel; EC = endometrial cancer; irAE = immune-related adverse event; MDS = myelodysplastic syndrome.
Westin SN, et al. *J Clin Oncol*. 2023; DOI: 10.1200/JCO.23.02132.

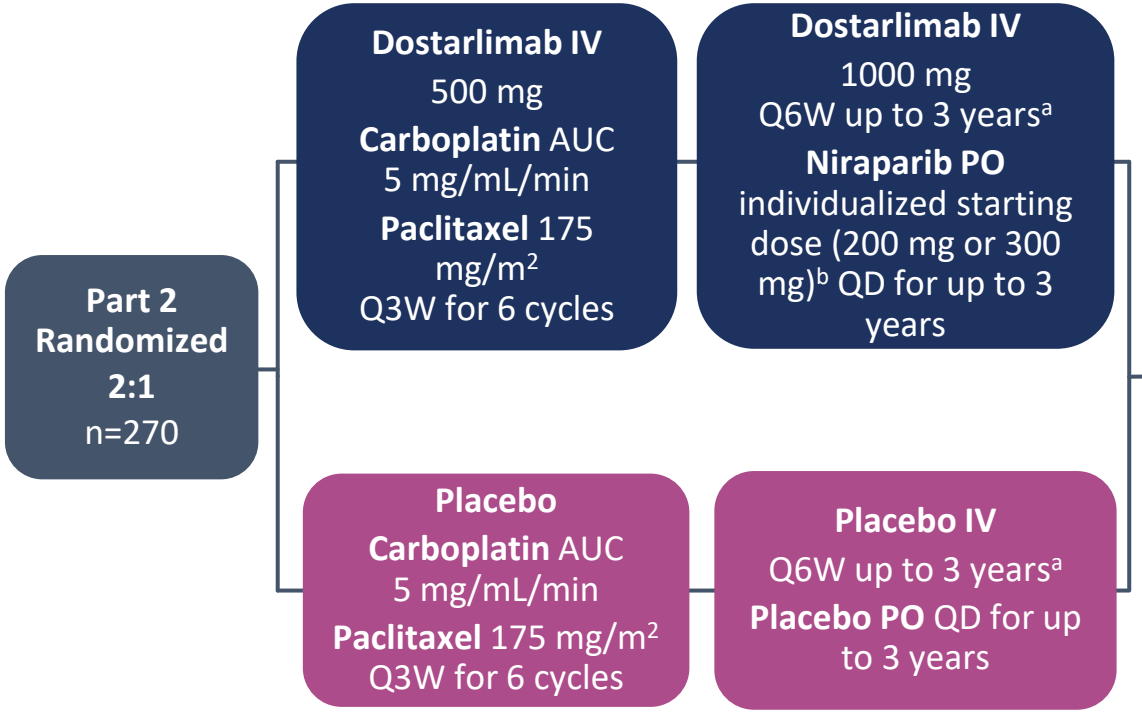
RUBY Part 2 | ENGOT-EN6 | GOG-3031 | NCT03981796

Eligible patients:

- Histologically or cytologically proven EC with recurrent or advanced disease
- Stage III or IV disease or first recurrent EC with low potential for cure by radiation therapy or surgery alone or in combination
- Naive to systemic anticancer therapy or had a recurrence or PD ≥6 months after completing systemic anticancer therapy
- ECOG PS 0-1
- Adequate organ function

Stratification:

- MMR/MSI status
- Prior radiotherapy
- Disease status



Primary end point: PFS[c]

Secondary end points: OS, PFS[d], PFS2, ORR[e], DOR[f], DCR[g], QOL, pharmacokinetics and immunogenicity, safety[h]

Start date: July 18, 2019

Status: Active, not recruiting

[a]Treatment ends after 3 years, PD, toxicity, withdrawal of consent, investigator's decision, or death, whichever occurs first. Continued treatment with dostarlimab or placebo beyond 3 years may be considered following discussion between the Sponsor and the Investigator. [b]Niraparib starting dose: 300 mg in patients with an actual body weight ≥77 kg and platelet count ≥150,000/µL; 200 mg in patients with an actual body weight <77 kg or platelet count <150,000/µL or both. [c]PFS by IA – all patients with recurrent or primary advanced EC (ITT population). [d]PFS by BICR per RECIST v1.1 (not IA) – ITT and dMMR/MSI-H populations. [e]ORR by BICR and IA. [f]DOR by BICR and IA, [g]DCR by BICR and IA. [h]All AEs assessed for intensity according to CTCAE v4.03.

AUC = area under the plasma or serum concentration-time curve; BICR = blinded independent central review; CTCAE = Common Terminology Criteria for Adverse Events; DCR = disease control rate; dMMR = mismatch repair deficient; DOR = duration of response; EC = endometrial cancer; ECOG PS = Eastern Cooperative Oncology Group performance status; IA = investigator assessed; ITT = intention to treat; IV = intravenous; MMR = mismatch repair; MSI = microsatellite instability; MSI-H = microsatellite instability-high; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PFS2 = time to second disease progression or death; PO = administered orally; PRO = patient-reported outcome; PS = performance status; Q = quarter; QD = once-daily; QoL = quality of life; QxW = every x weeks; RECIST = Response Evaluation Criteria in Solid Tumors.

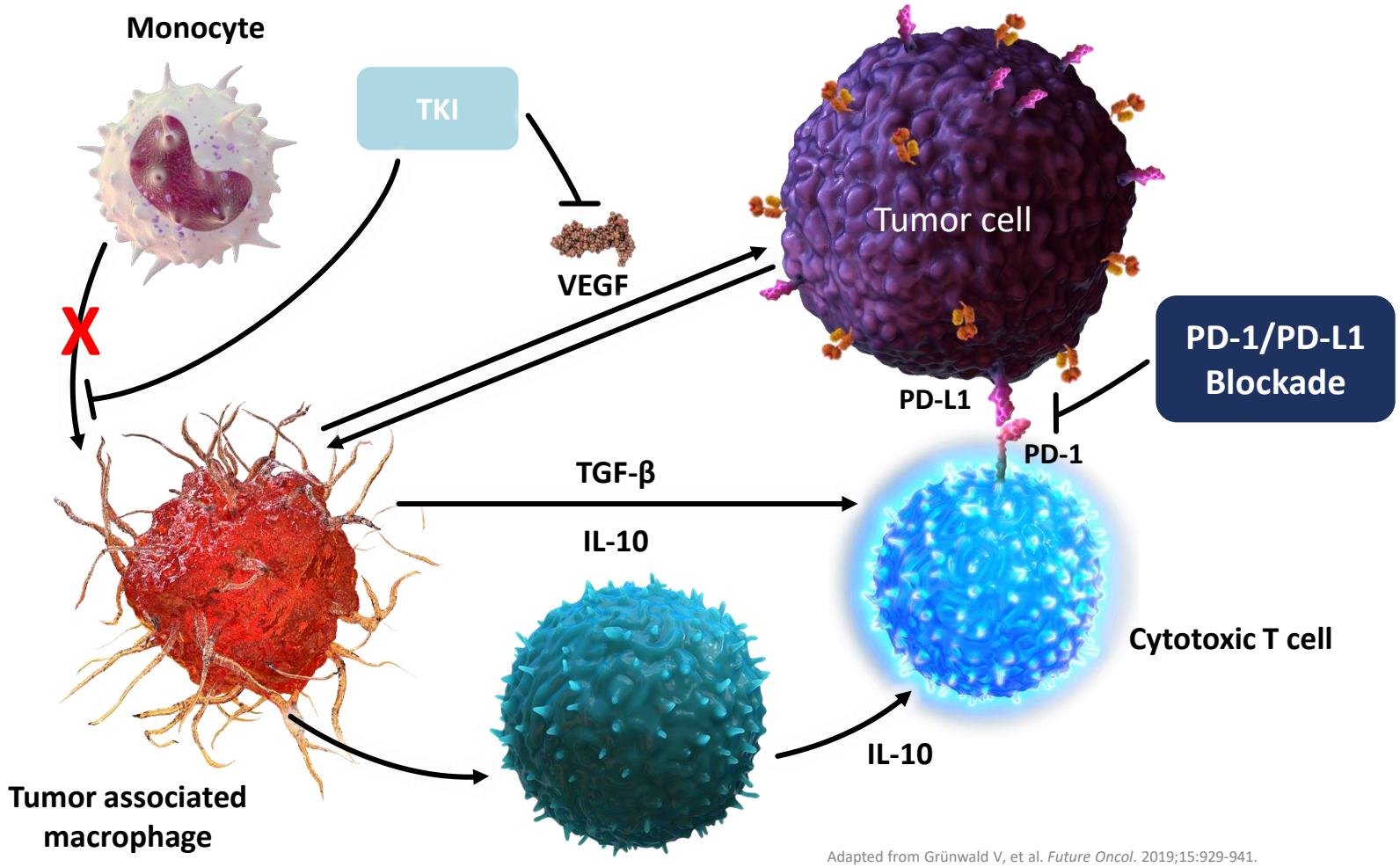
National Library of Medicine. Available at https://clinicaltrials.gov/ct2/show/NCT03981796. Accessed August 14, 2023.

Rationale for combining TKI and anti–PD-(L)1[1,2]

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]

LEAP-001 is currently investigating the combination of pembrolizumab plus lenvatinib[3]



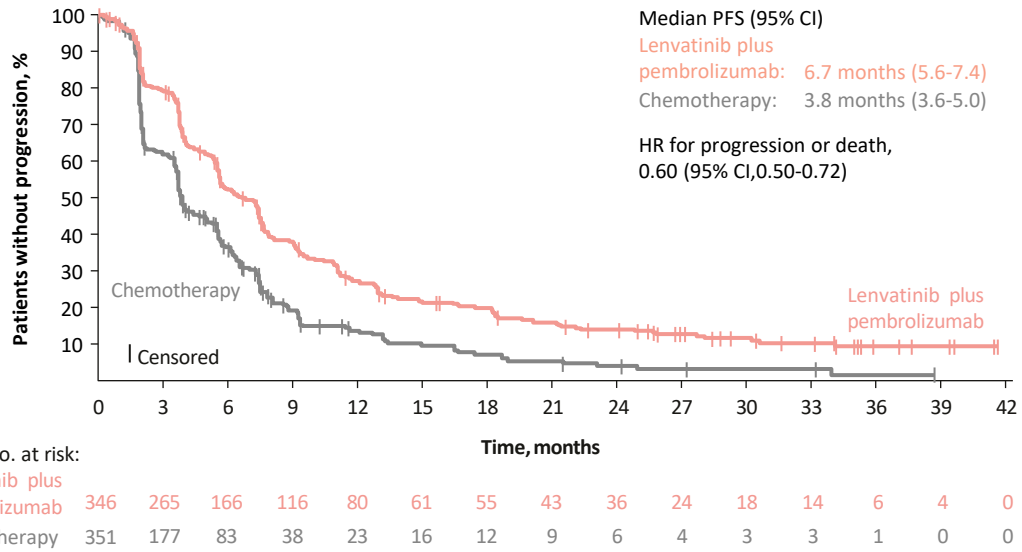
Adapted from Grünwald V, et al. *Future Oncol*. 2019;15:929-941.

CD8 = cluster of differentiation 8; CTLA-4 = cytotoxic T-lymphocyte associated protein 4; IL-10 = interleukin 10; IO = immuno-oncology; 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.

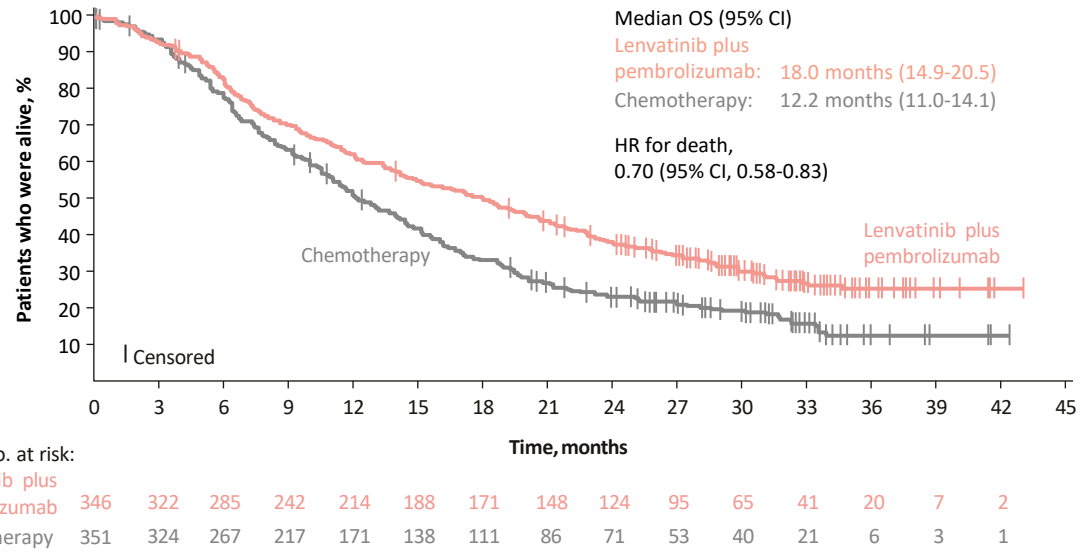
The combination of PD-1 and TKI has been evaluated in previously treated EC[1]

KEYNOTE-775[1]



No. at risk:

Lenvatinib plus pembrolizumab	346	265	166	116	80	61	55	43	36	24	18	14	6	4	0
Chemotherapy	351	177	83	38	23	16	12	9	6	4	3	3	1	0	0



No. at risk:

Lenvatinib plus pembrolizumab	346	322	285	242	214	188	171	148	124	95	65	41	20	7	2
Chemotherapy	351	324	267	217	171	138	111	86	71	53	40	21	6	3	1

Adapted from Makker V, et al. *J Clin Oncol.* 2023;41(16):2904-2910.

Pembrolizumab + lenvatinib is approved for advanced/recurrent EC (EU)[2] with progression following platinum-based therapy and for advanced MMRp EC (US)[3] with progression

CI = confidence interval; EC = endometrial cancer; EU = European Union; HR = hazard ratio; mo = months; MMRp = mismatch repair proficient; mPFS = median progression-free survival; PD-1 = programmed cell death protein 1; PFS = progression-free survival; TEAE = treatment-emergent adverse event; TKI = tyrosine kinase inhibitor; US = United States.

1. Makker V et al. *J Clin Oncol* 2023;41:2904-2910. 2. Keytruda (pembrolizumab) [summary of product characteristics]. Merck Sharp & Dohme B.V., Haarlem, The Netherlands; 2023. 3. Keytruda (pembrolizumab) [prescribing information]. Merck & Co., Inc., Whitehouse Station, NJ, USA; 2023.

KEYNOTE-775: Safety in the MMRp population

	Pembrolizumab + lenvatinib	Doxorubicin or paclitaxel
Safety population, N	406	388
Grade ≥3 TRAE, n (%)	320 (78.8)	233 (60.1)
Any TRAE leading to discontinuation of pembrolizumab, n (%)	49 (12.1)	NA
TRAE leading to death, n (%)	6 (1.5)	9 (2.3)

The most common TEAEs (>20% of patients) in the pembrolizumab + lenvatinib arm were hypertension (61.8%), hypothyrodism (55.7%), diarrhea (43.1%), nausea (39.9%) and decreased appetite (37.9%), fatigue (28.6%), proteinuria (26.6%), vomiting (24.4%), weight decreased (22.7%), arthralgia (22.2%), and palmar-plantar erythrodysesthesia syndrome (20.7%)

MMRp = mismatch repair-proficient; NA = not applicable; TRAE = treatment-related adverse event.
Makker V, et al. *J Clin Oncol.* 2023;41:2904-2910.

LEAP-001 | ENGOT-en9 | MK-7902-001 | NCT03884101

Enrollment & eligibility
- Newly diagnosed Stage III-IV or recurrent EC
- ECOG PS 0 or 1

Stratification:[2]
- MMRp and dMMR
- MMRp further stratified by ECOG PS, measurable disease, and prior chemoradiation

Randomized 1:1
N = 875

Pembrolizumab 200 mg IV Q3W + **lenvatinib** 20 mg PO QD[a]
MMRp, n≈306
dMMR, n≈132[b]

Paclitaxel 175 mg/m^2 IV Q3W + **Carboplatin** AUC 6 IV Q3W[c,d]
MMRp, n≈306
dMMR, n≈132[b]

Primary end points: PFS (BICR) and OS
Secondary end points: ORR, HRQoL, safety, and tolerability

Start date: April 11, 2019
Status: Active, not recruiting

[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.

AUC = area under the curve; BICR = blinded independent central review; DCR = disease control rate; dMMR = deficient mismatch repair; DOR = duration of response; EC = endometrial cancer; ECOG PS = Eastern Cooperative Oncology Group performance status; ENGOT = European Network of Gynaecological Oncological Trial Groups; 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.

1. National Library of Medicine. https://www.clinicaltrials.gov/ct2/show/NCT03884101. Accessed August 14, 2023. 2. Marth C et al. *Int J Gynecol Cancer*. 2022;32:92-100.

As ICIs move to earlier in the treatment algorithm, how do we treat patients who relapse? What comes after ICI?

ICI = immune checkjpoint inhibitor..

Is there a role for ICI rechallenge following prior ICI therapy in EC?

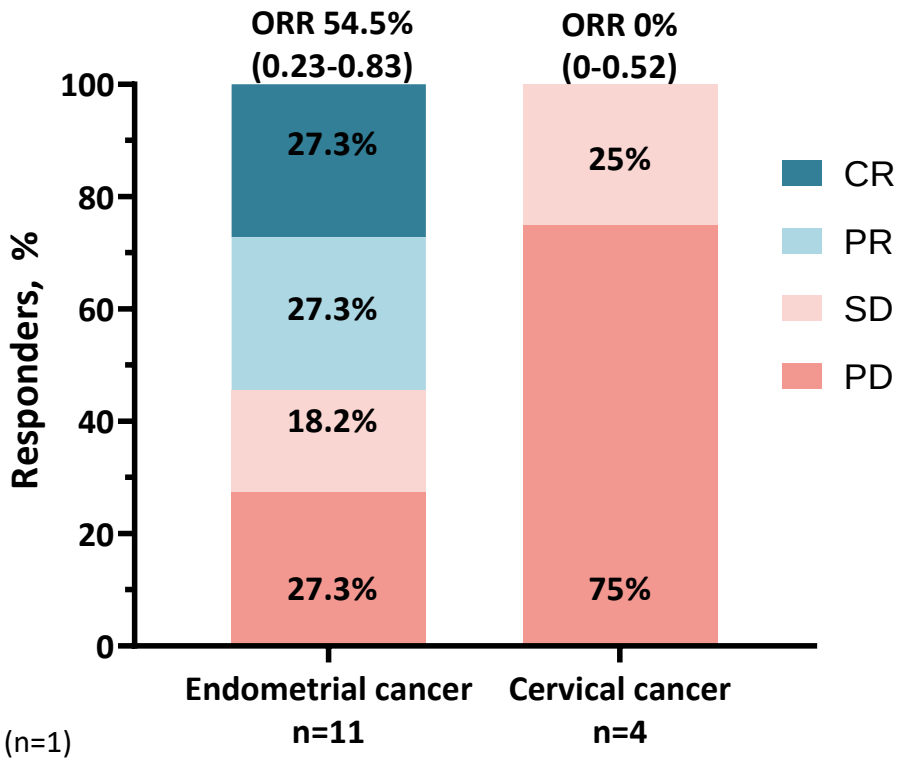
- Patient selection—three scenarios
  - Long PFS post-ICI therapy followed by PD
  - PD during/immediately post-ICI therapy
  - Prior premature withdrawal from ICI therapy due to toxicity
- Choice of rechallenge therapy
  - Rechallenge with PD-1 inhibitor alone or with pembrolizumab/lenvatinib

EC = endometrial cancer; ICI = immune checkpoint inhibitor; PD = progressive disease; PD-1 = programmed cell death-1; PFS = progression-free survival.

ICI rechallenge?

Single center, retrospective study evaluated 11 patients with EC who received subsequent immunotherapy

Patient characteristics	EC n=11	Cervical cancer n=4
MMR status, n (%)		
dMMR	8 (72.7)	0
MMRp	3 (27.3)	1 (25.0)
Unknown	0	3 (75.0)
TMB status, n (%)		
Low	1 (9.1)	0
Medium	0	0
High	3 (27.3)	0
Unknown	7 (63.6)	4 (100)



EC Grade 3 and 4 AE
- 1L ICI
  - GI or colitis, n=1
- 2L ICI
  - Endocrine, n=1
  - GI or colitis, n=1

Cervical cancer did not report any Grade 3 and 4 AEs

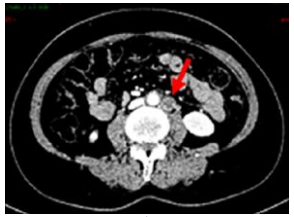
ICI agents received
- 1L ICI
  - EC: pembrolizumab (n=9), dostarlimab (n=1), atezolizumab (n=1)
  - CC (n=1 each): pembrolizumab, nivolumab, atezolizumab, balstilimab
- 2L ICI
  - EC: pembrolizumab (n=4), pembrolizumab/ lenvatinib (n=4), nivolumab (n=2), ipilimumab/ nivolumab (n=1)
  - CC: pembrolizumab (n=-3). other (n=1)

1L = first line; 2L = second line; AE = adverse event; CR = complete response; dMMR = mismatch repair deficient; GI = gastrointestinal; ICI = immune-checkpoint inhibitor; MMR = mismatch repair; MMRp = mismatch repair proficient; ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease; TMB = tumor mutational burden.

Morton M, et al. *Obstet Gynecol.* 2023;142:360–363.

ICI rechallenge?

Case report: Patient with dMMR EC, PR after anti-VEGFR-1/2/3 + anti-PD-1 and unacceptable toxicities re-established PR when restarted on anti-PD-1



- Grade 2 interstitial pneumonia
- Grade 3 immunotherapy-associated myocarditis
- Secondary *Pneumocystis jirovecii* (+)
- Symptomatic treatment

Treatment start

Total hysterectomy + lymph node dissection

Adjuvant therapy start

- Liposomal paclitaxel + carboplatin: × 3 cycles
- RT to pelvis and para-aortic area: 50.4 GY/ 28 fractions

1L treatment
- Fruqintinib + sintilimab Q3W: × 2 cycles

Rechallenge start

ICI rechallenge
- Zimberelimab monotherapy: × 6 cycles

Evaluation after 2 cycles: PR

2020 Nov 23 | 2021 Jan 12 | 2021 May 12 | 2021 June 30 | 2022 Jan 25 | Disease in remission | 2022 May 10

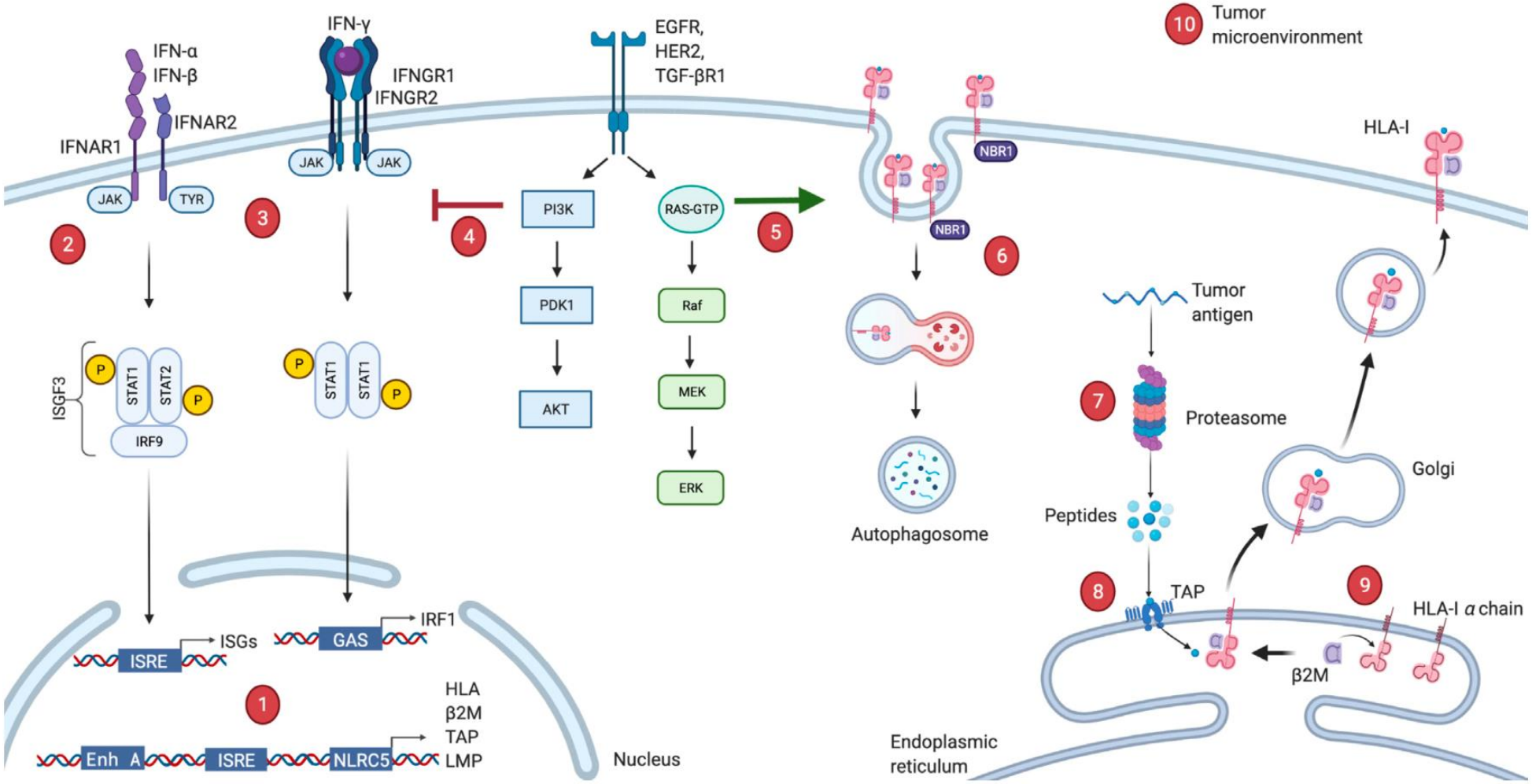
PR | PD | PR

Adapted from Chen Y, et al. *Front Immunol.*2022; 13:987345.

dMMR = mismatch repair deficient; EC = endometrial cancer; ICI = immune checkpoint inhibitor; PD = progressive disease; PR = partial response; PD-1 = programmed cell death-1; Q3W = every 3 weeks; RT = radiotherapy; VEGFR = vascular endothelial growth factor receptor.

Chen Y, et al. *Front Immunol.*2022; 13:987345.

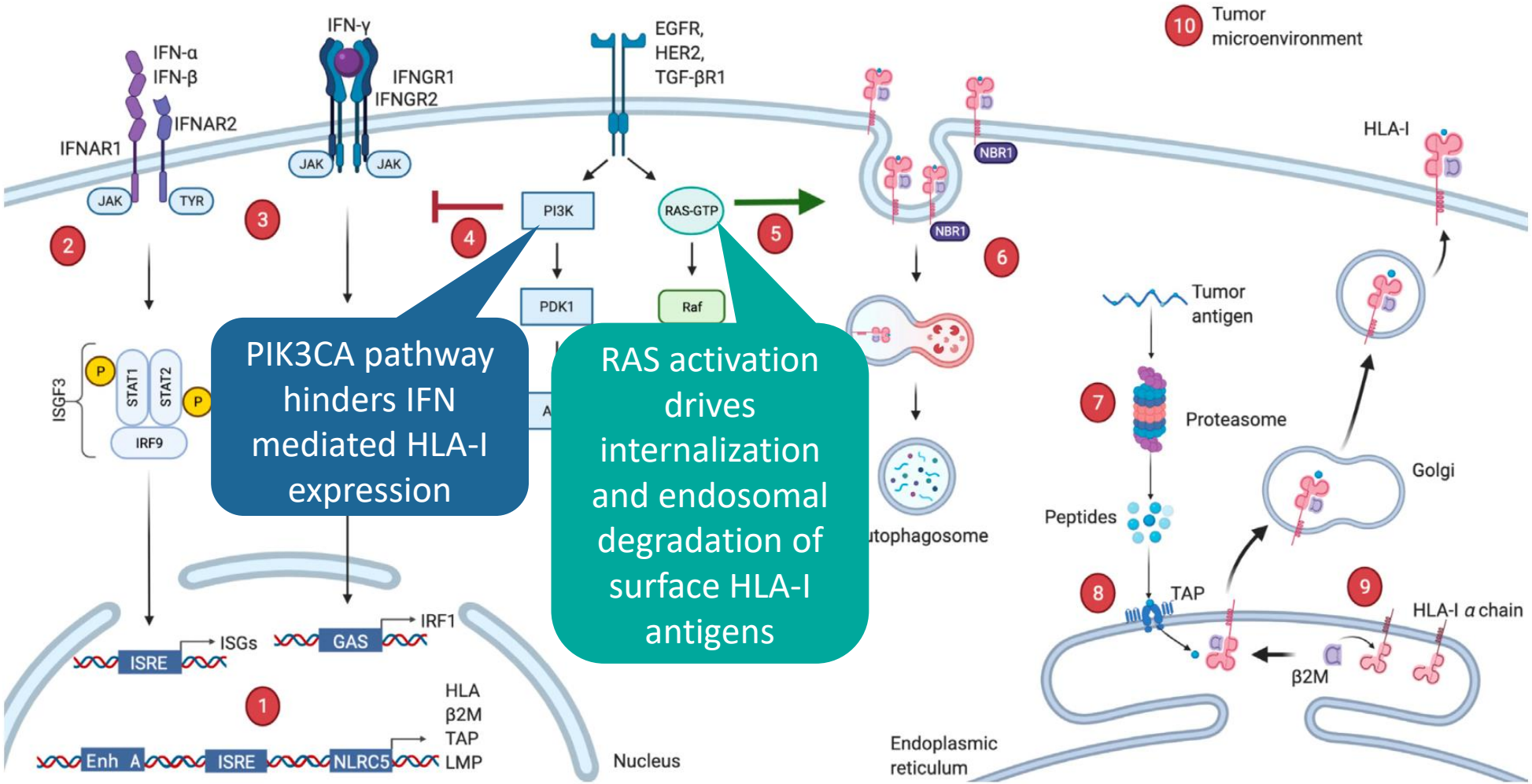
HLA-I dysregulation and immune resistance



Adapted from Hazini A, et al. *J ImmunoTher Cancer.* 2021;9:e002899.

β2M = β−2-microglobulin; ER = endoplasmic reticulum; HLA = human leucocyte antigen; IFNAR1 = interferon alpha and beta receptor 1; IL-10 = interleukin 10; ISRE = interferon stimulated response element; RAS = reticular activating system; TAP1 = transporter associated with antigen processing 1; TGF-β = transforming growth factor-β.
Hazini A, et al. *J ImmunoTher Cancer.* 2021;9:e002899.

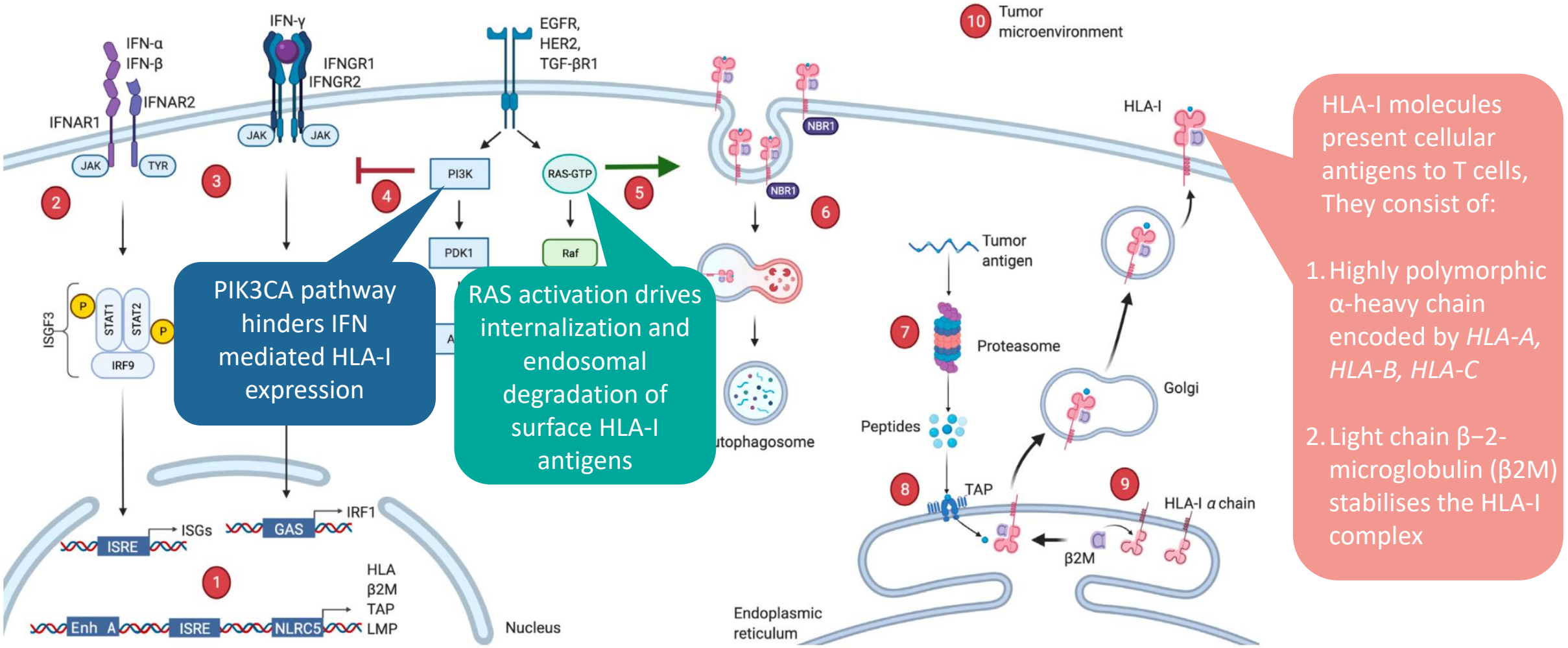
HLA-I dysregulation and immune resistance



Adapted from Hazini A, et al. *J ImmunoTher Cancer.* 2021;9:e002899.

β2M = β−2-microglobulin; ER = endoplasmic reticulum; HLA = human leucocyte antigen; IFN = interferon; IFNAR1 = interferon alpha and beta receptor 1; IL-10 = interleukin 10; ISRE = interferon stimulated response element; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RAS = reticular activating system; TAP1 = transporter associated with antigen processing 1; TGF-β = transforming growth factor-β.
Hazini A, et al. *J ImmunoTher Cancer.* 2021;9:e002899.

HLA-I dysregulation and immune resistance



HLA-I molecules present cellular antigens to T cells, They consist of:

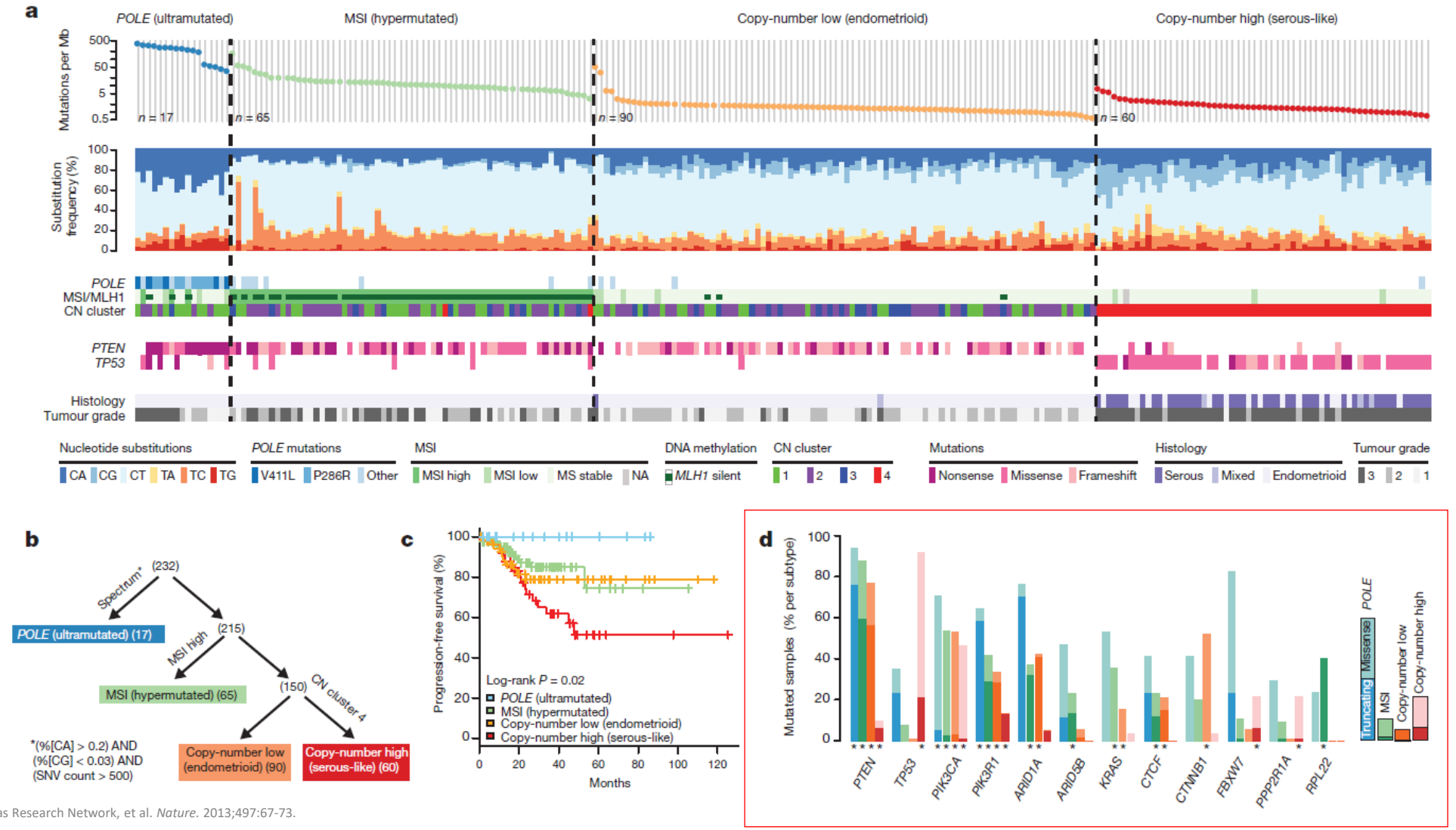
1. Highly polymorphic α-heavy chain encoded by *HLA-A, HLA-B, HLA-C*
2. Light chain β−2-microglobulin (β2M) stabilises the HLA-I complex

Adapted from Hazini A, et al. *J ImmunoTher Cancer.* 2021;9:e002899.

β2M = β−2-microglobulin; ER = endoplasmic reticulum; HLA = human leucocyte antigen; IFNAR1 = interferon alpha and beta receptor 1; IL-10 = interleukin 10; ISRE = interferon stimulated response element; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RAS = reticular activating system; TAP1 = transporter associated with antigen processing 1; TGF-β = transforming growth factor-β.

Hazini A, et al. *J ImmunoTher Cancer.* 2021;9:e002899.

Histomolecular classification: TCGA

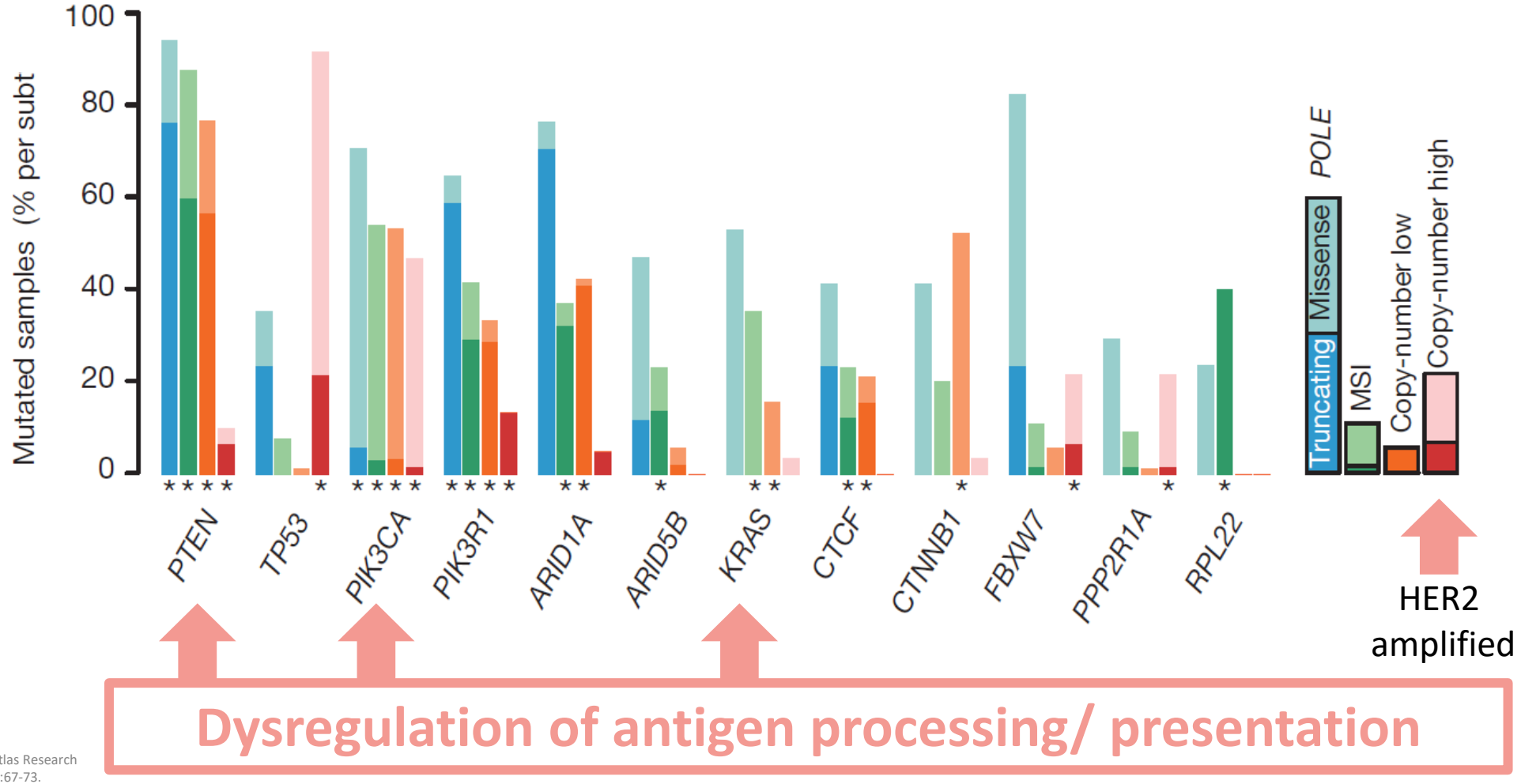


Adapted from Cancer Genome Atlas Research Network, et al. *Nature.* 2013;497:67-73.

CNH = copy-number high; CNL = copy-number low; MLH = mutL homolog; MSI, microsatellite instability; POLE = polymerase ε; TCGA = The Cancer Genome Atlas.

1. Cancer Genome Atlas Research Network, et al. *Nature.* 2013;497:67-73.

Differential mutational frequencies further differentiate the TCGA molecular classifications



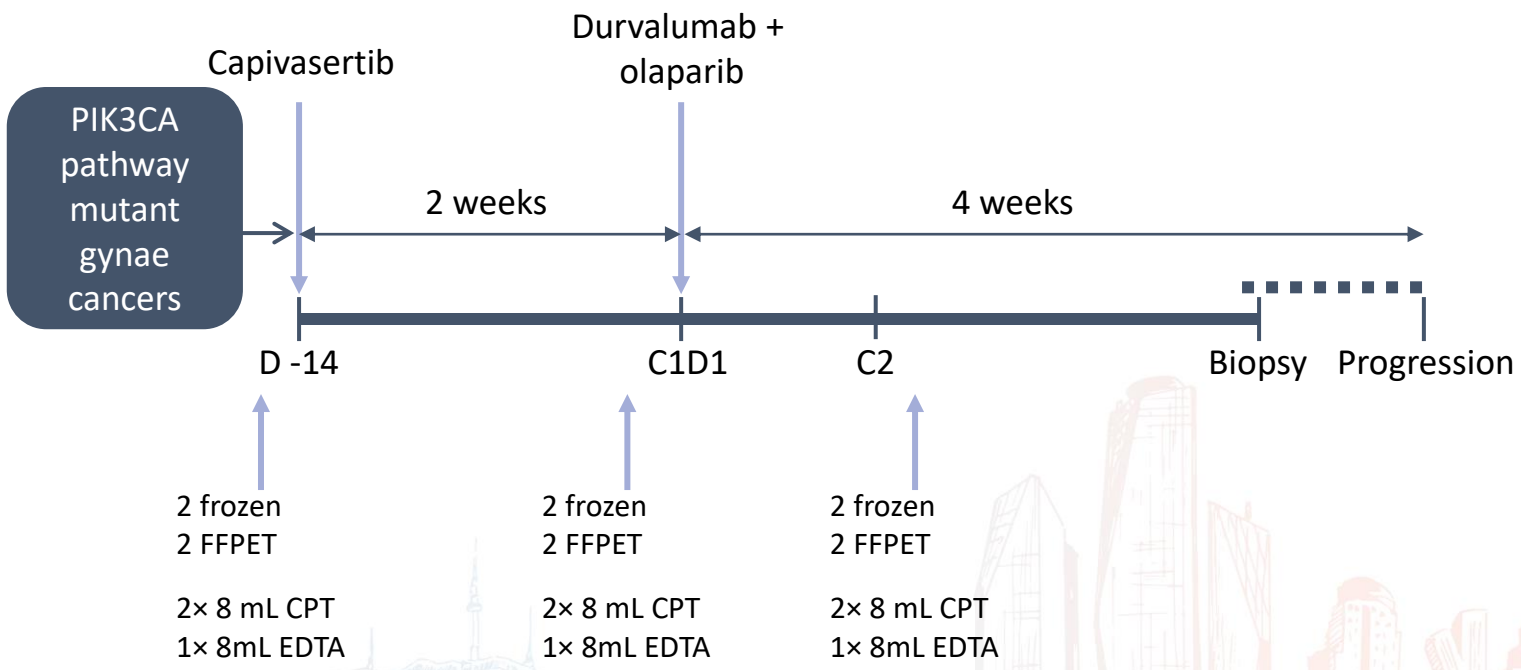
Adapted from Cancer Genome Atlas Research Network, et al. *Nature.* 2013;497:67-73.

HER2 = human epidermal growth factor receptor 2; KRAS = Kirsten rat sarcoma virus; MSI, microsatellite instability; POLE = polymerase ε; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN = phosphatase and tensin homolog
TCGA = The Cancer Genome Atlas.

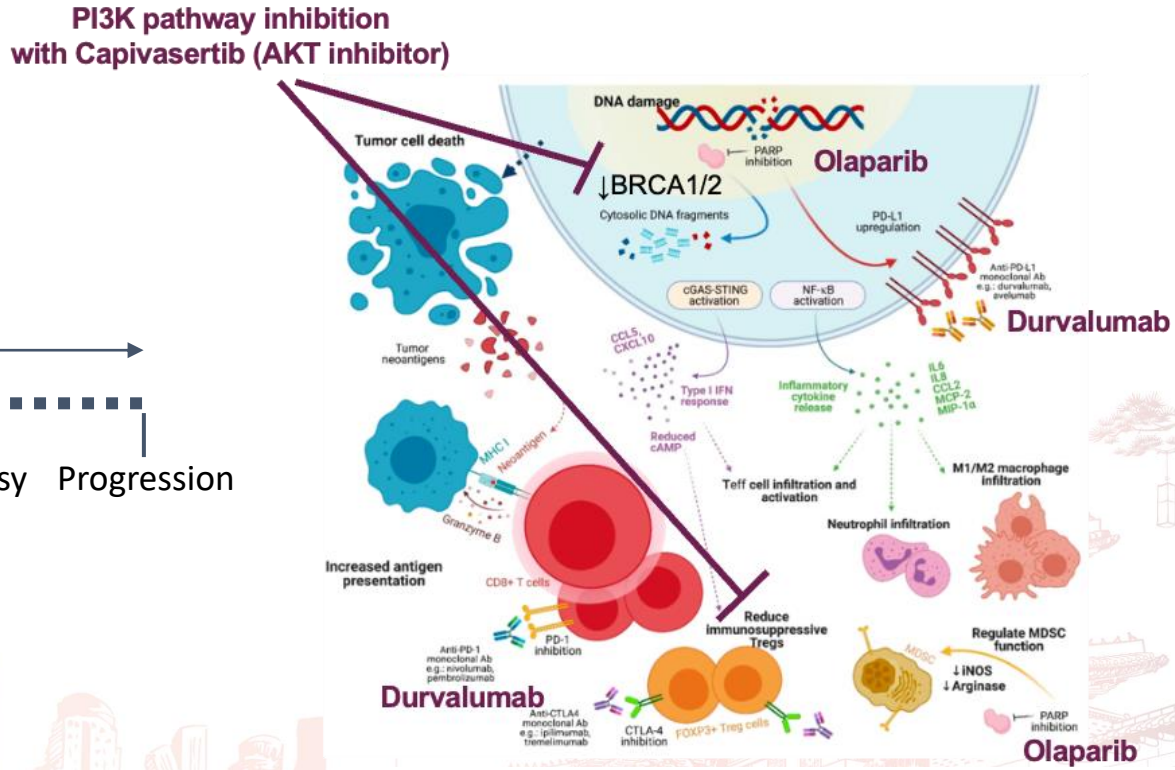
1. Cancer Genome Atlas Research Network, et al. *Nature.* 2013;497:67-73.

MEDIPAC | NCT03772561 | PI: David Tan

Phase I/II study of combined durvalumab, olaparib, and the AKT inhibitor capivasertib (AZD5363) in solid tumors



Provided by Dr. Tan.



Adapted from Pham MM, et al. *Trends Cancer* 2021;7(10): 958-970.[7]

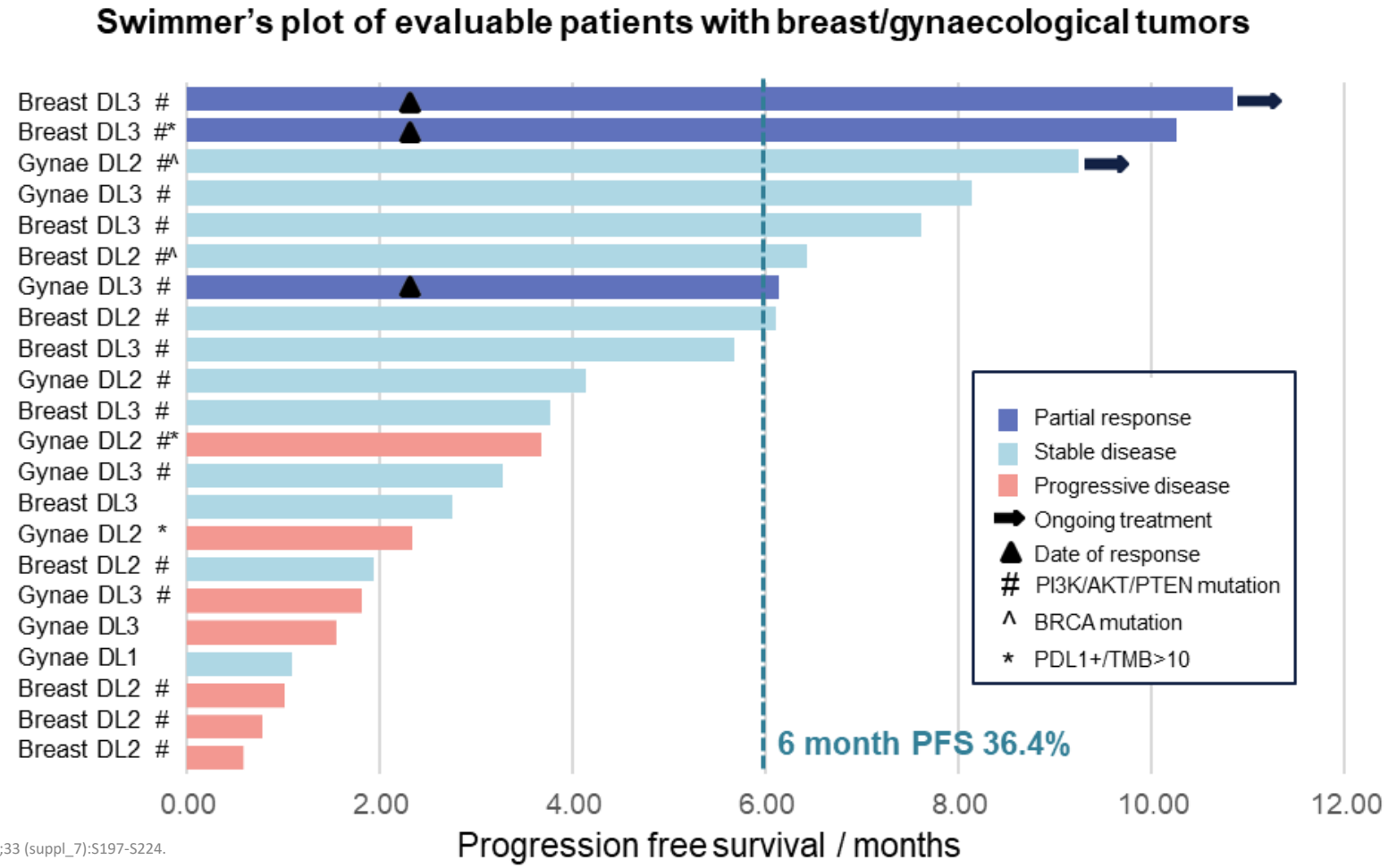
- The PI3K/AKT pathway → tumorigenesis, interacting with DNA damage response and immune regulatory networks[1,2]
- PI3K pathway inhibition → downregulation of BRCA1/2 → sensitisation to PARP inhibition[3]
- PI3K pathway inhibition promotes HLA processing machinery and selectively inhibits Treg cells[4]
- Combination of capivasertib and olaparib tolerable with efficacy signal[5,6]

AKT = protein kinase B; BRCA1/2 = BReast CAncer gene 1/2; C = cycle; D = day; FFPET = formalin-fixed paraffin-embedded tissue; PARP = poly (ADP-ribose) polymerases; PI3K = phosphoinositide 3-kinases; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; Treg = regulatory T cell.

1. Yap TA, et al, *CA Cancer J Clin*. 2011;61(1):31-49. 2. Courtney KD et al, *J Clin Onc* 2010;28(6):1075–1083. 3. Juvekar A et al, *Cancer Discov* 2012;2(11):1048-63. 4. Abu-Eid R et al, *Cancer Immunol Res* 2014; 2(11):1080–1089. 5. Yap TA, et al, *Cancer Discov* 2020;10(10):1528-1543. 6. Westin et al, Ann Onc 2017;28 (suppl_5):391P. 7. Pham MM, et al. *Trends Cancer* 2021;7(10): 958-970.

Efficacy of durvalumab in combination with olaparib and capivasertib in patients with advanced or metastatic cancers

MEDIPAC | dose expansion



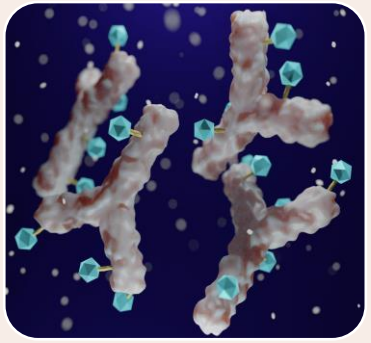
Dose expansion in PIK3CA/mTOR pathway activated gynae cancers ongoing – recruiting at National University Cancer Institute Singapore, NUH.

Adapted from Lim J, et al. *Ann Oncol* 2022;33 (suppl_7):S197-S224.

Gynae = gynaecological; PFS = progression-free survival.
Lim J, et al. *Ann Oncol* 2022;33 (suppl_7):S197-S224.

What other targets are being evaluated?

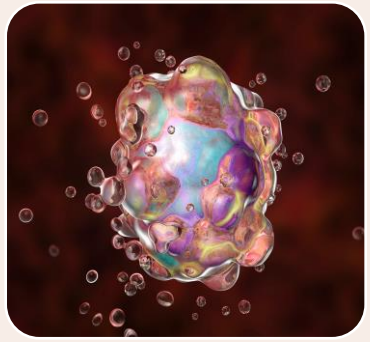
Targeting HER2



Trastuzumab deruxtecan:
DESTINY-PanTumor02 (phase 2)[1]
ORR: 57.5%

Trastuzumab ± C/P:
NCT01367002 (phase 2)[2]
PFS: 12.9 vs 8.0 mo

Kickstarting apoptosis

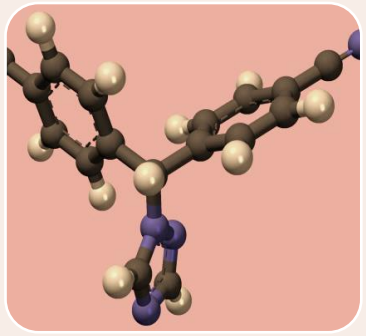


Selinexor:
SIENDO (phase 3)[3]
PFS: 5.7 vs 3.8 mo

XPORT-EC-042 (phase 3)[4]
TIP

Navtemadlin:
EURUS (phase 2/3)[5]
TIP

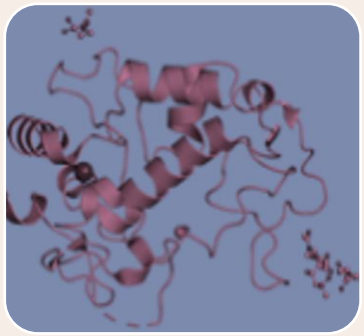
Revisiting endocrine therapy



Letrozole + abemaciclib:
NCT03675893 (phase 2)[6]
ORR: 30%

Letrozole + palbociclib:
PALEO (phase 2)[7]
PFS: 8.3 vs 3.0 mo

FR-α inhibition



Mirvetuximab soravtansine + gemcitabine:
NCT02996825 (phase 1)[8]
TIP

Farletuzumab ecteribulin:
NCT03386942 (phase 1)[9,10]
BOR: 1 PR, 2 SD

Inhibiting TROP-2

Sacituzumab govitecan:
NCT04251416 (phase 2)[11]
PFS: 5.7 mo

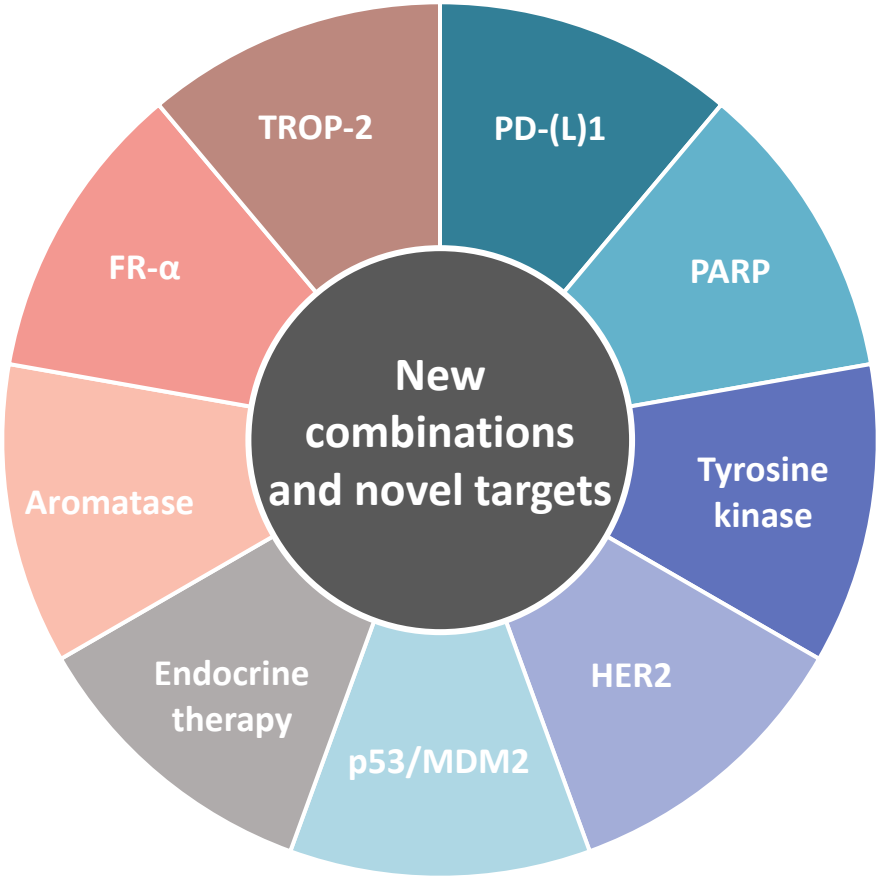
MK-2870:
MK-2870-005-ENGOT-en23 (phase 3)[12]
TIP

BOR = best overall response; FR-α = folate receptor alpha; HER2 = human epidermal growth factor 2; mo = month; ORR = objective response rate; PFS = progression-free survival; PR = partial response; SD = stable disease; TIP = trial in progress; TROP-2 = Trophoblast cell surface antigen 2.

1. Meric-Bernstam F, et al. *J Clin Oncol.* 2023;41(suppl_17):LBA3000. 2. Fader AN, et al. *Clin Cancer Res*. 2020;26:3928-3935. 3. Makker V, et al. *J Clin Oncol.* 2022;40:5511-5511. 4. Vergote IB, et al. *J Clin Oncol*. 2023;41(16_suppl):TPS5627-TPS5627. 5. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT05797831. Accessed August 23, 2023. 6. Konstantinopoulos PA, et al. *J Clin Oncol*. 2022;41:599-608. 7. Mirza MR, et al. *Ann Oncol*. 2020;31(s4):S1160. 8. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT02996825. Accessed August 23, 2023. 9. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT03386942. Accessed August 23, 2023. 10. Shimizu T, et al. *Clin Cancer Res*. 2021;27:3906-3915. 11. Santin A, et al. *J Clin Oncol.* 2023;41(suppl_16):abst 5599. 12. Gynecologic Cancer Intergroup. https://gcigtrials.org/content/mk-2870-005-engot-en23. Accessed September 28, 2023.

Conclusions

- DUO-E is the first Phase 3 trial looking at the efficacy of a PARPi (**olaparib**) in combination with an anti–PD-L1 (**durvalumab**) + chemotherapy in advanced/recurrent EC
- DUO-E showed statistically significant PFS improvement of anti–PD-L1 + chemo followed by maintenance anti–PDL-1 ± PARPi vs chemo alone in the ITT population for patients with newly diagnosed advanced or recurrent endometrial cancer
  - Benefit in dMMR is predominantly driven by anti-PD-L1
  - Benefit of PARPi + anti–PD-L1 appears to be mostly limited to the MMRp population
- RUBY Part 2 is also assessing the efficacy and safety of the PARPi **niraparib** in combination with **dostarlimab** + chemotherapy in advanced/recurrent EC
- Clinical trials exploring anti-PD-1 monotherapy in dMMR/MSI-H and combination approaches with TKIs in a broad patient population continue to try to improve treatment options for patients



ADC = antibody drug conjugate; EC = endometrial cancer; FR-α = folate receptor alpha; HER2 = human epidermal growth factor 2; ICI = immune checkpoint inhibitor; PARP = poly (ADP-ribose) polymerase; PD-1 = programmed cell death protein-1; PD-L1 = programmed death-ligand 1; TKI = tyrosine kinase inhibitor; TROP-2 = trophoblast cell surface antigen 2.

Panel discussion

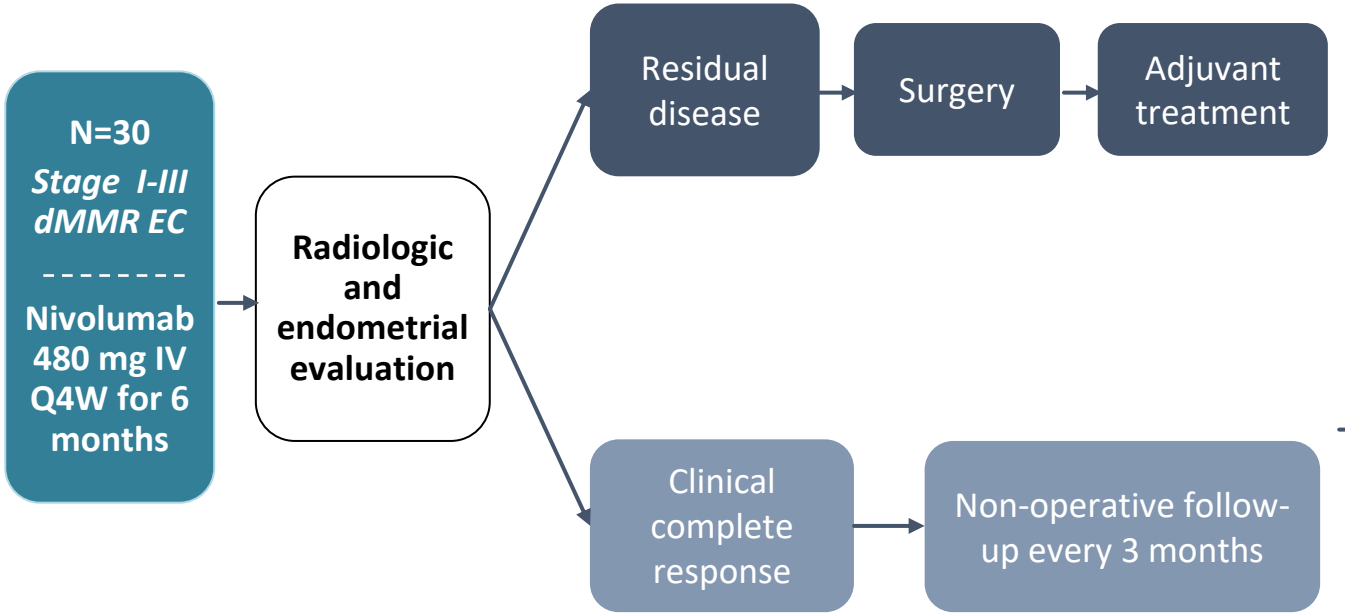
NIVEC | NCT05795244

Phase 2, non-randomized, open-label, study of nivolumab induction in patients with surgically completely resectable dMMR EC

Eligibility criteria

- Histologically- or cytologically-confirmed EC or carcinosarcoma (mixed mullerian tumor)
- Clinical stage: Stage I - IIIC2 and surgically completely resectable
- No evidence of distant metastases
- dMMR or MSI-H subtype
- ECOG PS 0 or 1
- Patients with a life expectancy of at least 3 months

Study design: Simon's two stage minimax design



Primary end point: Complete response rate

Secondary end points: ORR, PFS, OS, toxicity

Exploratory end points: Genomic and immune biomarkers

Start date (estimated): April 2023

Status: Recruiting

Estimated primary completion date: March 2025

dMMR = mismatch repair deficient; EC = endometrial cancer; ECOG = Eastern Cooperative Oncology Group; IV = intravenous; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PS = performance status; Q4W = every 4 weeks.
National Library of Medicine. https://classic.clinicaltrials.gov/ct2/show/NCT05795244. Accessed August 29, 2023.

DOVE | APGOT-ov7 | ENGOT-ov80

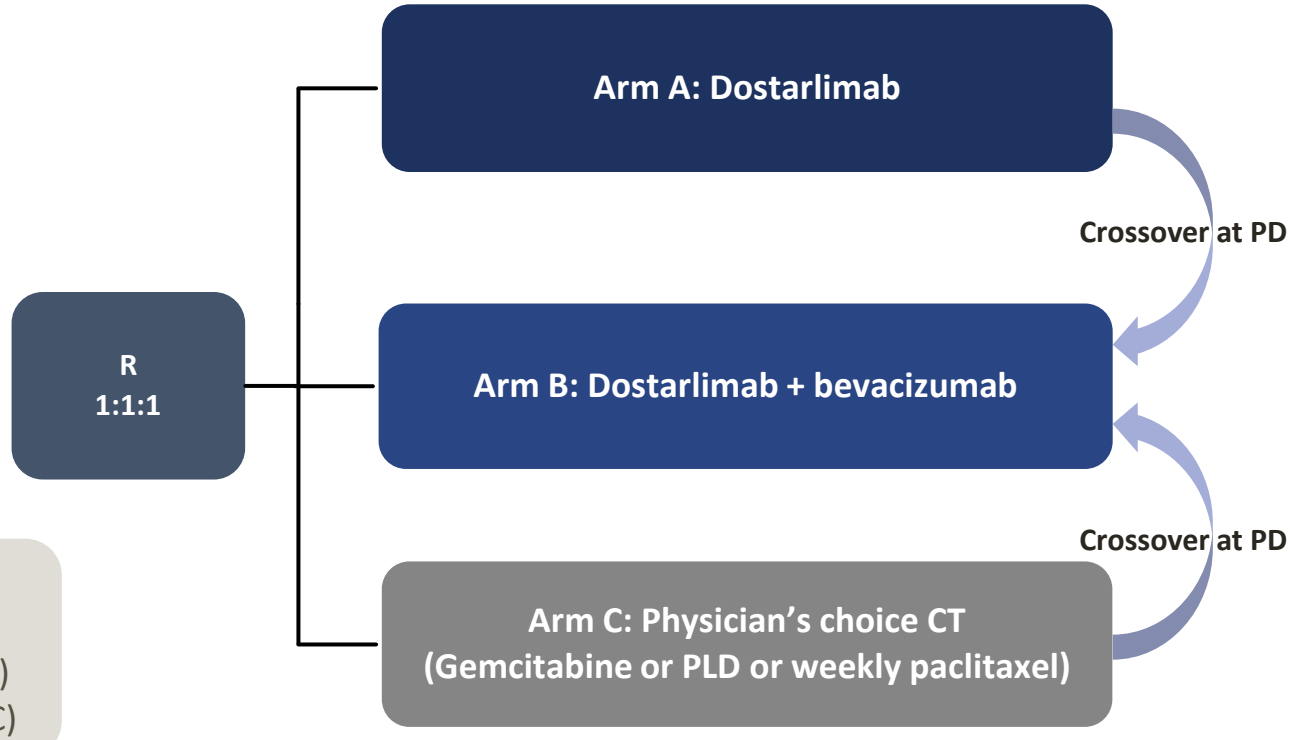
Asia-Pacific Gynecologic Oncology Trials Group clinical trial in recurrent gynecological clear cell carcinoma

Eligible patients:

- Histologically confirmed clear cell carcinoma
- PFI < 12 months
- At least one prior line of platinum-based chemotherapy
- ≤ 5 prior lines of therapy
- No prior ICI use
- Measurable disease
- Mandatory biopsy and/or archival tissues

Stratification:

- Prior bevacizumab use
- Prior lines of therapy (1 or >1)
- Primary origin (OC vs. non-OC)



Primary end point:

Investigator-assessed PFS (RECIST 1.1)

Secondary end points:

ORR, DCR, CBR PFS2, OS, DOR, safety and tolerability

Exploratory end points:

Immune biomarker c matched samples

CBR = clinical benefit rate; DCR = disease control rate; CT, chemotherapy; ICI = immune checkpoint inhibitor; OC = ovarian cancer; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFI = platinum-free interval; PFS2 = time to second disease progression or death; PLD = pegylated liposomal doxorubicin; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

Lee J-Y et al. Presented at the Gynecologic Cancer Intergroup Spring Meeting (Oral presentation). May 31- June 1, 2023, Chicago, US.