2021 ASCO ANNUAL MEETING

ASCO Direct Highlights
Annual Conference of South Carolina Oncology Society

Gynecologic Oncology

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8/7/2021

Disclosure of Conflict(s) of Interest

- Brian Orr, MD, MS reported **no** relevant financial relationships or relationships with ineligible companies of any amount during the past 24 months.

Gynecologic Cancer Highlights

Ovarian Cancer

- Bevacizumab Maintenance – 15 vs 30 months
- PARP Inhibitors
  - PAOLA-1 – PFS2 update
  - EFFORT Trial – PARP Resistant Population
  - CAPRI Study – PARP Resistant Population
- VITAL – Tumor Plasmid vaccine
- SOVO1 – Dendritic vaccine trial
- Mirvetuximab + Bevacizumab - Final Analysis
- Pembrolizumab + Liposomal Doxorubicin + Bevacizumab

Uterine Cancer

- TOTEM – Surveillance Study
- TAPUR – HER2 targeted therapy

Cervical Cancer

- OUTBACK
- GX-188E – DNA vaccine + Pembrolizumab
- ANLOTINIB+SINTILIMAB

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Optimal treatment duration of bevacizumab combined with carboplatin and paclitaxel in patients with primary epithelial ovarian, fallopian tube or peritoneal cancer

A prospective randomized Phase III ENGOT/GCIG Study of the AGO Study Group, GINECO, NSGO AGO-OVAR 17 BOOST / GINECO OV118 / ENGOT Ov-15 / NCT01462890

Performed according to ENGOT Model A. Financial support and drug supply provided by F. Hoffmann-La Roche Ltd.

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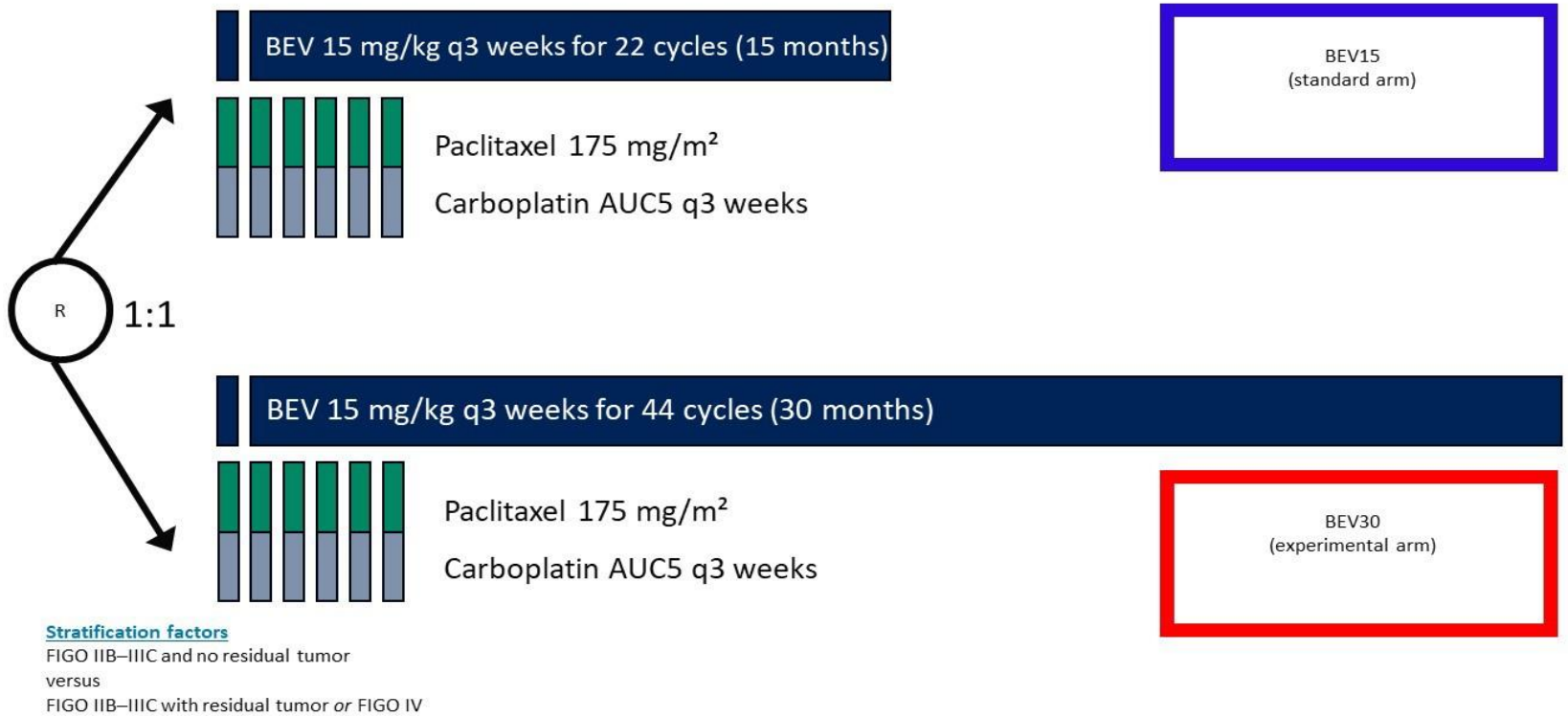
Trial design
AGO-OVAR 17 BOOST / GINECO OV118 / ENGOT Ov-15

- Histologically confirmed epithelial ovarian, fallopian tube, or peritoneal cancer (excluding non-epithelial and borderline tumors)
- FIGO stage IIB–IV (any grade/ histologic subtype)
- Primary debulking surgery ≤8 weeks before treatment start, >4 weeks before first BEV dose
- Adequate coagulation parameters, bone marrow, liver, and renal function
- ECOG PS 0–2
- Standard BEV exclusion criteria

n= 927 Nov 2011 – Aug 2013



Stratification factors
FIGO IIB–IIIC and no residual tumor
versus
FIGO IIB–IIIC with residual tumor *or* FIGO IV

Jacobus Pfisterer, AGO Study Group & Gynecologic Oncology Center, Kiel, Germany on behalf of AGO Study Group, GINECO and NSGO

Patient characteristics I

	BEV15 n=464	BEV30 n=463	Total n=927
Age, years			
Median (range)	61 (25–86)	60 (21–89)	61 (21–89)
ECOG performance status, n (%)			
0	236 (51)	266 (57)	502 (54)
1	205 (44)	181 (39)	386 (41)
2	23 (5)	16 (3)	39 (4)
Residual tumor, n (%)			
No	277 (60)	259 (56)	536 (58)
Yes	187 (40)	204 (44)	391 (42)
Histo-type/grading, n (%)			
High-grade serous	362 (78)	368 (79)	730 (79)
Other	102 (22)	95 (21)	197 (21)

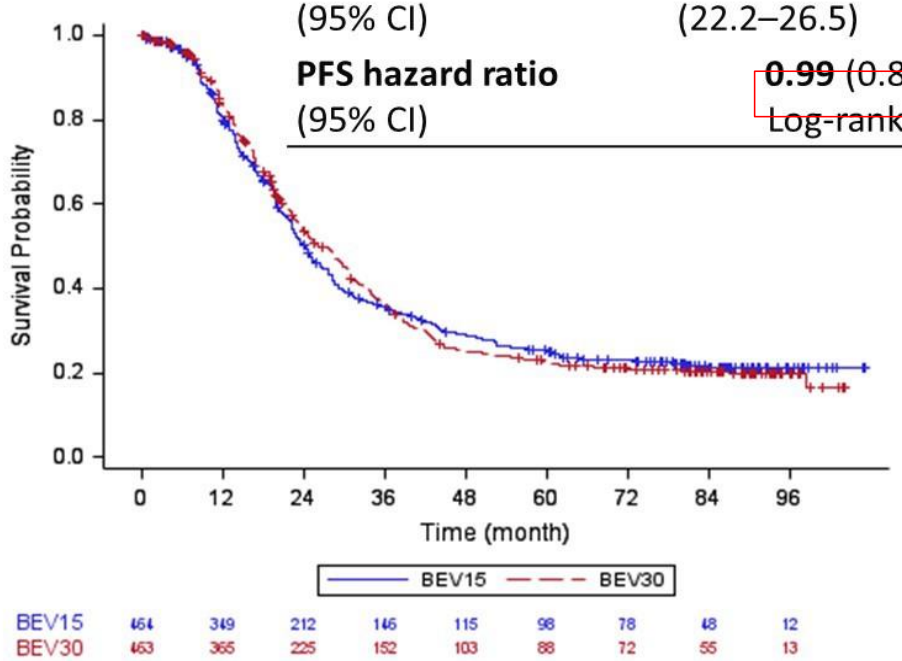
***BRCA* mutation status** not available

Jacobus Pfisterer, AGO Study Group & Gynecologic Oncology Center, Kiel, Germany on behalf of AGO Study Group, GINECO and NSGO

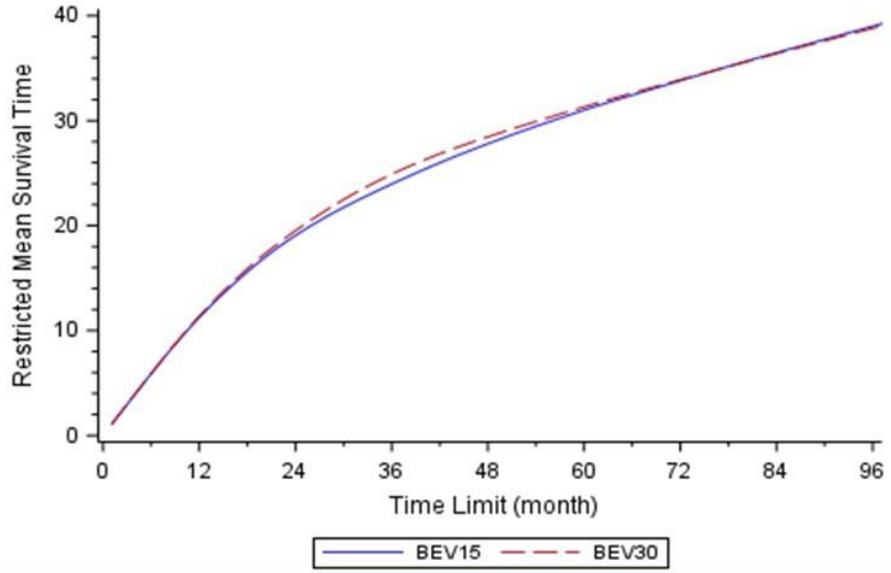
Clinical characteristics were well balanced across all the arms with respect to performance status, residual tumor after primary surgery, and histologic subtype.

Primary endpoint: PFS

	BEV15 n=464	BEV30 n=463
PFS events, n (%)	333 (72)	340 (73)
Median PFS, months (95% CI)	**24.2** (22.2–26.5)	**26.0** (23.7–29.7)
PFS hazard ratio (95% CI)	**0.99** (0.85–1.15) Log-rank p=0.90	



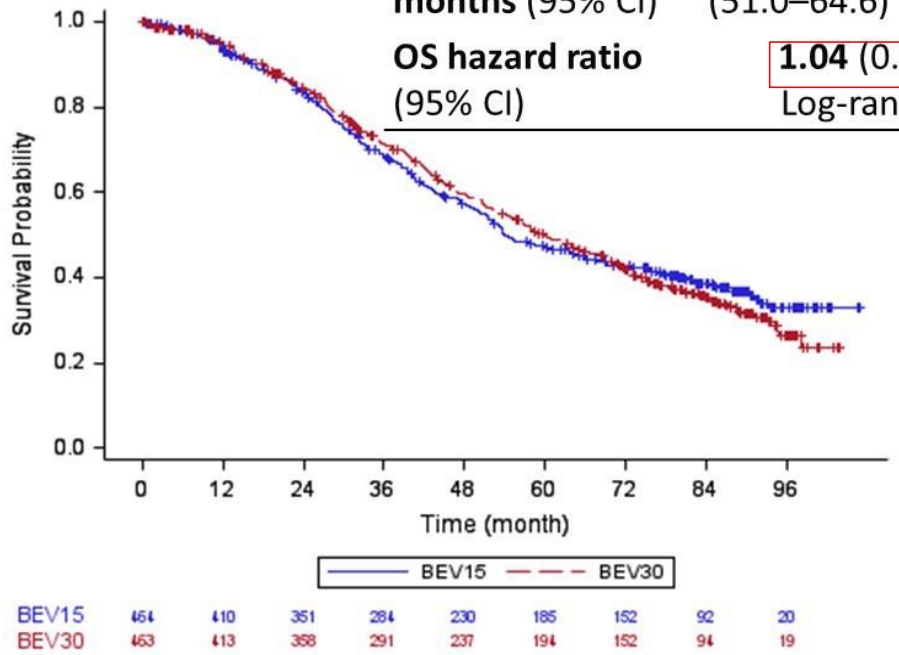
	BEV15 n=464	BEV30 n=463
Restricted mean PFS, months (95% CI)*	**39.5** (36.3–42.7)	**39.3** (36.2–42.4)
* Restricted at last event time	p=0.92	



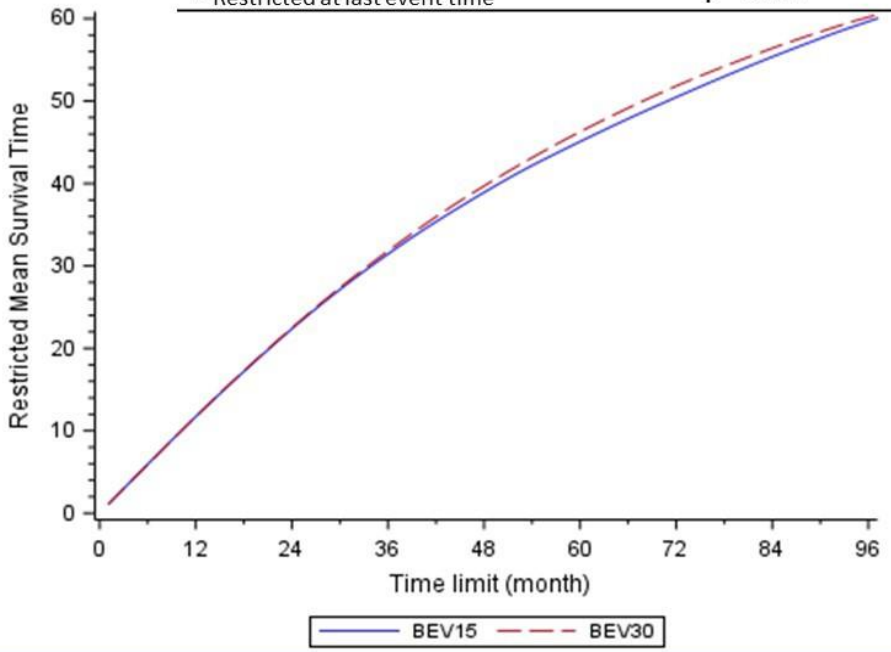
Presented By: **Jacobus Pfisterer,** AGO Study Group & Gynecologic Oncology Center, Kiel, Germany on behalf of AGO Study Group, GINECO and NSGO

Overall survival

	BEV15 n=464	BEV30 n=463
OS events, n (%)	257 (55)	275 (59)
Median OS, months (95% CI)	**54.3** (51.0–64.6)	**60.0** (54.0–68.6)
OS hazard ratio (95% CI)	**1.04** (0.87–1.23) Log-rank p=0.68	



	BEV15 n=464	BEV30 n=463
Restricted mean OS, months (95% CI)*	**60.4** (57.2–63.6)	**60.8** (57.8–63.8)
* Restricted at last event time	p=0.87	



Presented By: **Jacobus Pfisterer,** AGO Study Group & Gynecologic Oncology Center, Kiel, Germany on behalf of AGO Study Group, GINECO and NSGO

Conclusions

- Longer treatment with bevacizumab for up to 30 months was feasible.
- Safety data were consistent with the known bevacizumab profile. There were no new safety signals.
- Although the median PFS of about 2 years was longer than in the original trials (e.g. ICON7/AGO-OVAR 11), longer treatment with bevacizumab for up to 30 months improved neither PFS nor OS in patients with primary epithelial ovarian, fallopian tube, or peritoneal cancer.
- Further analyses (eg. QoL) are ongoing.
- The duration of treatment for bevacizumab with 15 months as part of the first-line treatment in advanced ovarian cancer remains standard of care.

Jacobus Pfisterer, AGO Study Group & Gynecologic Oncology Center, Kiel, Germany on behalf of AGO Study Group, GINECO and NSGO

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Progression-free survival and second progression-free survival by disease stage in patients with homologous recombination deficiency-positive newly diagnosed advanced ovarian cancer receiving bevacizumab with maintenance olaparib or placebo in the Phase III PAOLA-1/ENGOT-ov25 trial

Patricia Pautier, MD

Institut Gustave-Roussy, Villejuif and GINECO, France

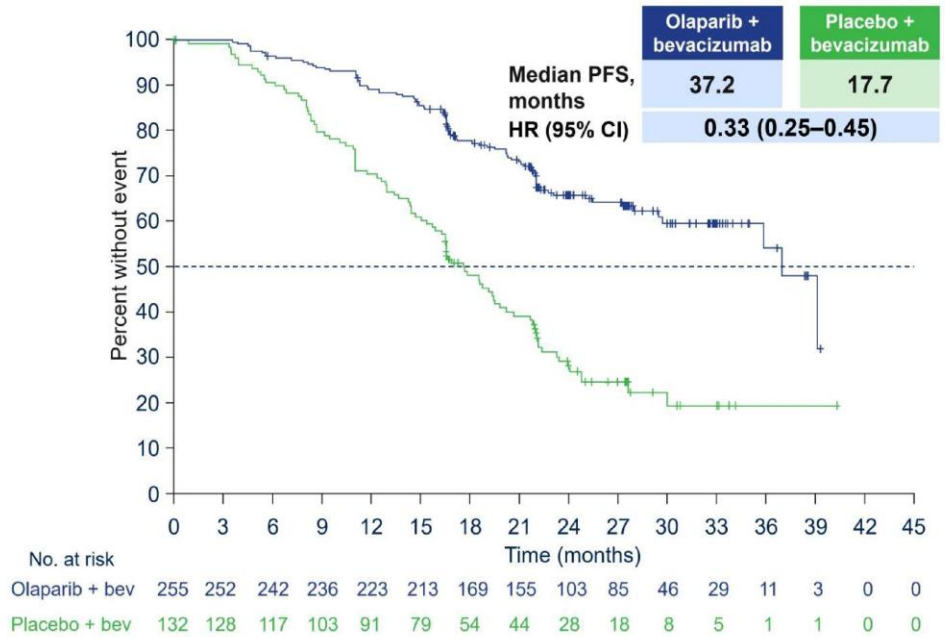
June 4–8, 2021

ClinicalTrials.gov identifier: NCT02477644.
This study was funded ARCAGY Research; AstraZeneca; Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA; and F. Hoffmann-La Roche Ltd.

Background and objective

- In the Phase III PAOLA-1/ENGOT-ov25 trial, the addition of first-line maintenance olaparib to bevacizumab for patients with HRD-positive tumors with advanced HGOC resulted in a substantial PFS benefit,[1] leading to approval of this regimen in countries including the USA, EU, and Japan.[2–4]
- We aimed to explore the efficacy of maintenance olaparib plus bevacizumab in patients with HRD-positive tumors by FIGO disease stage and surgical outcome.

PFS among HRD-positive patients (including BRCAm)

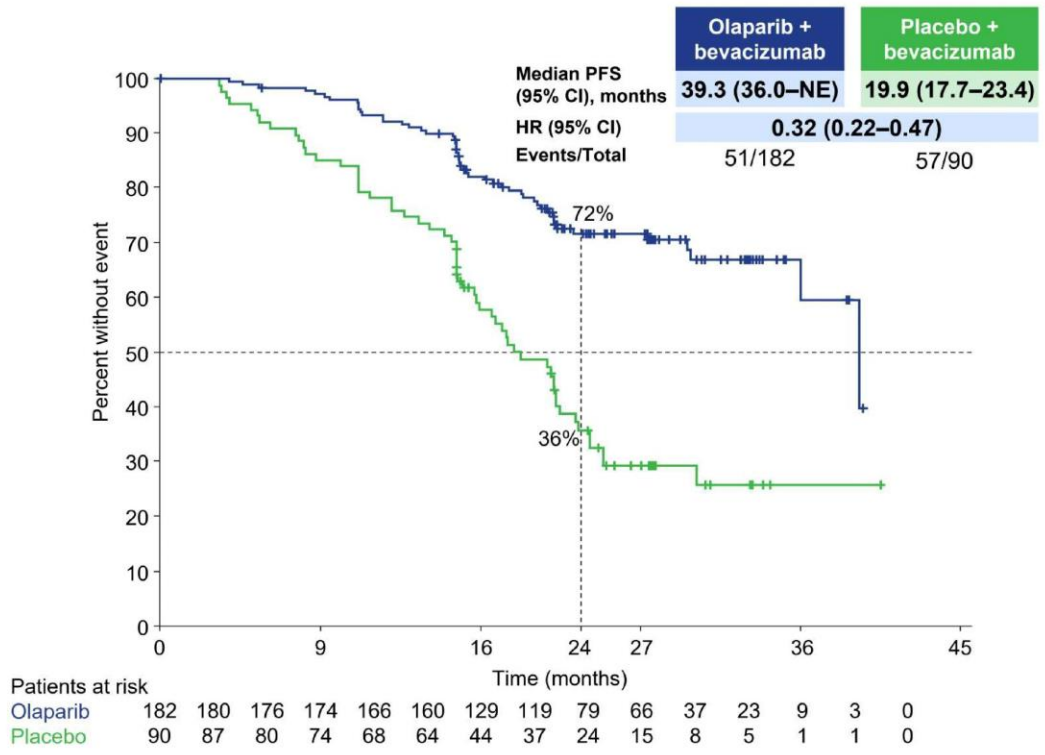


BRCAm, *BRCA1* and/or *BRCA2* mutation; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HGOC, high-grade ovarian cancer; HR, hazard ratio; HRD, homologous recombination deficiency (genomic instability and/or BRCAm); PFS, progression-free survival.

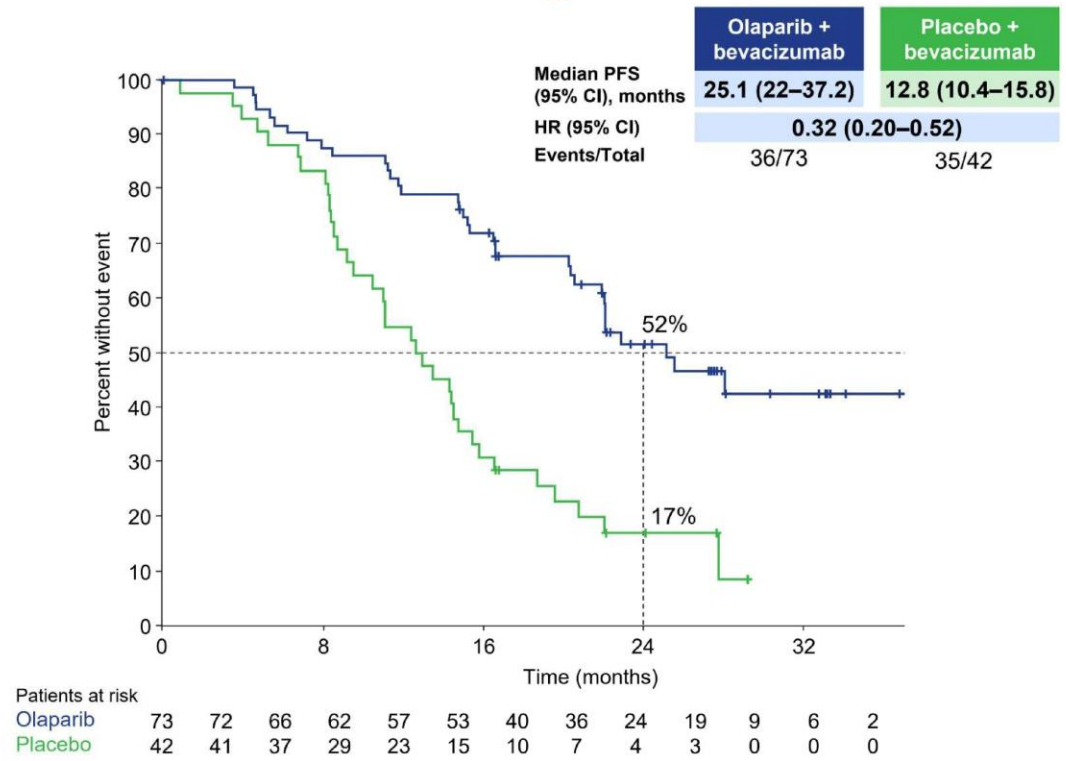
1. Ray-Coquard I *et al. N Engl J Med* 2019;381:2416–28; 2. AstraZeneca. Lynparza (olaparib) [package insert]. US FDA website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208558s014lbl.pdf (accessed April 2021); 3. Lynparza (olaparib) [SmPC]. EMA website. https://www.ema.europa.eu/en/documents/product-information/lynparza-epar-product-information_en.pdf (accessed April 2021); 4. Lynparza (olaparib) [list of approved products]. PMDA website. https://www.pmda.go.jp/files/000239841.pdf (accessed April 2021).

PFS by FIGO stage in patients with HRD-positive tumors

Stage III*



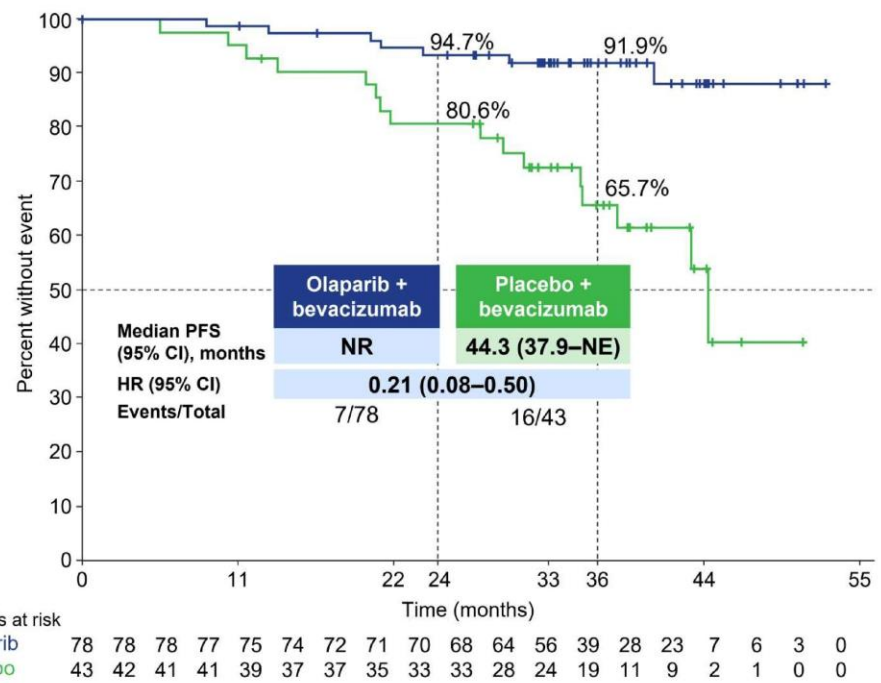
Stage IV†



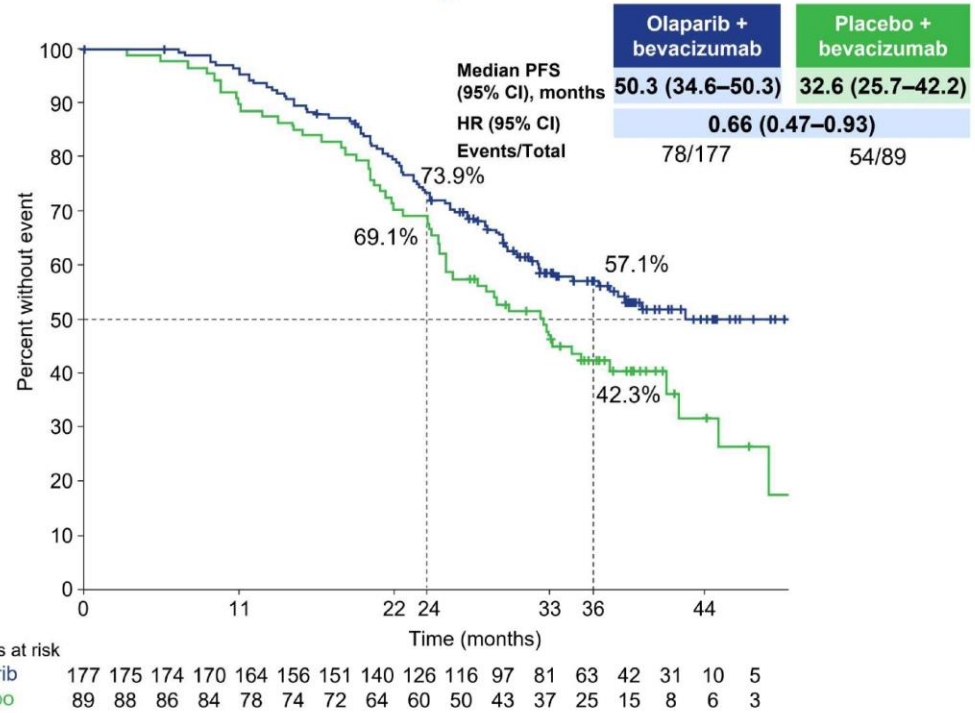
The median time from the first cycle of chemotherapy to randomization was 7 months. *Median follow-up: 24.8 months; †Median follow-up: 24.0 months.
NE, not estimable.

PFS2 by FIGO stage and surgical outcome in patients with HRD-positive tumors

Lower risk*



Higher risk†



The median time from the first cycle of chemotherapy to randomization was 7 months. *Patients with HRD-positive tumors who had stage III disease and complete resection following upfront surgery (median follow-up overall: 37.0 months); †Stage III patients with residual disease after upfront surgery or who received neoadjuvant chemotherapy, or HRD-positive stage IV patients (median follow-up overall: 37.5 months).
NR, not reached; PFS2, second progression-free survival.

Conclusions

- In patients with HRD-positive tumors, the addition of maintenance olaparib to bevacizumab provided a substantial PFS and PFS2 benefit irrespective of FIGO disease stage.
- Remarkably, the 2-year and 3-year PFS2 rates were >90% with maintenance olaparib plus bevacizumab in lower-risk patients with HRD-positive tumors who benefitted from complete resection during upfront surgery.

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EFFORT: EFFICACY OF ADAVOSERTIB IN PARP RESISTANCE: A RANDOMIZED 2-ARM NON-COMPARATIVE PHASE II STUDY OF ADAVOSERTIB WITH OR WITHOUT OLAPARIB IN WOMEN WITH PARP-RESISTANT OVARIAN CANCER

Shannon N. Westin, MD, MPH[1]

Robert L. Coleman[2], Bryan Fellman[1], Ying Yuan[1], Anil Sood[1], Pamela Soliman[1], Alexi Wright[3], Neil Horowitz[3], Susana Campos[3], Panagiotis Konstantinopoulos[3], Charles Levenback[1], David Gershenson[1], Karen Lu[1], Virginia Bayer[1], Sobiya Tukdi[1], Alexis Rabbit[3], Lone Ottesen[4], Robert Godin[4], Gordon Mills[5], Joyce F. Liu[3]

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[4]AstraZeneca, Cambridge, UK
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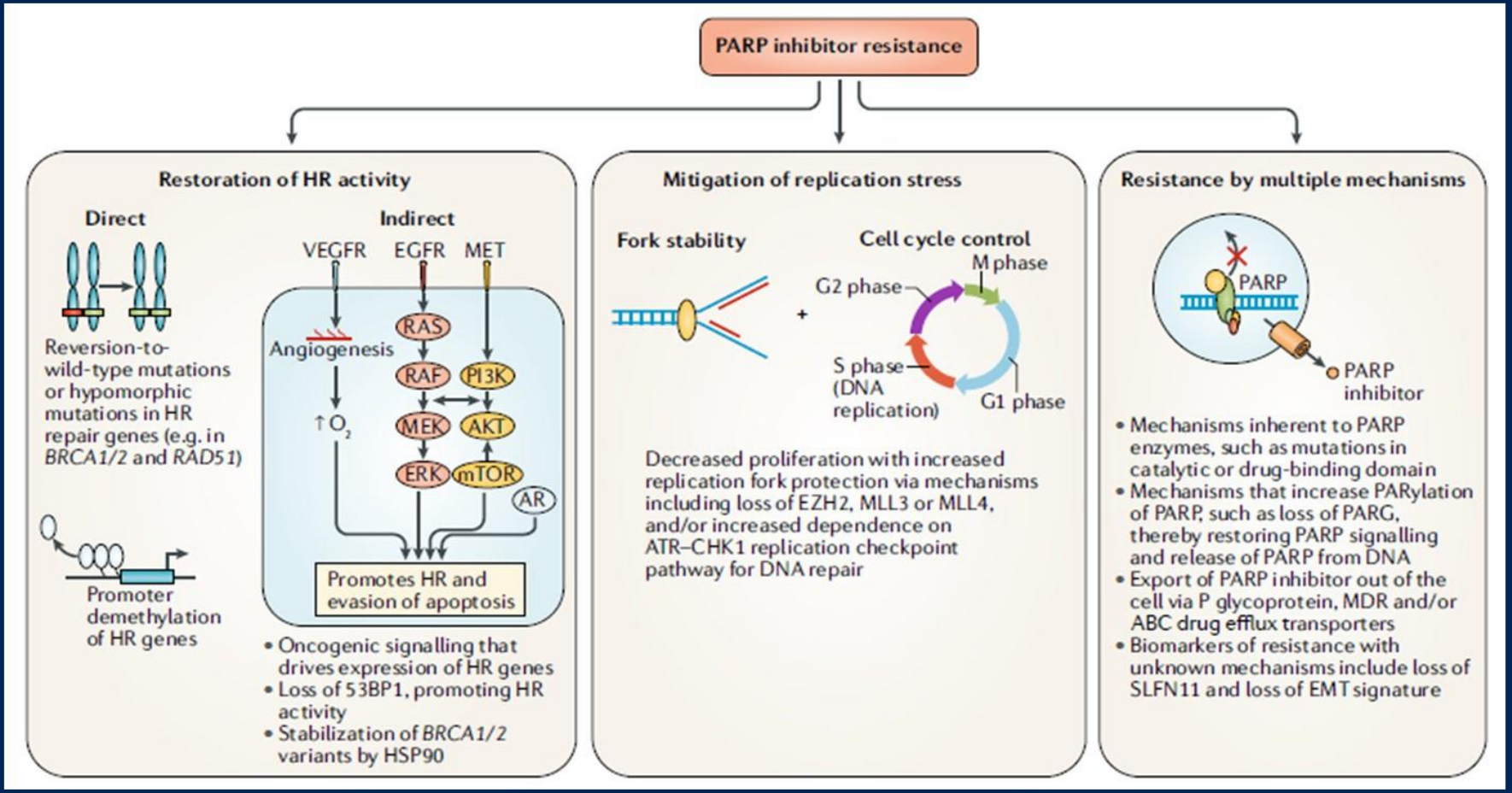
June 7, 2021

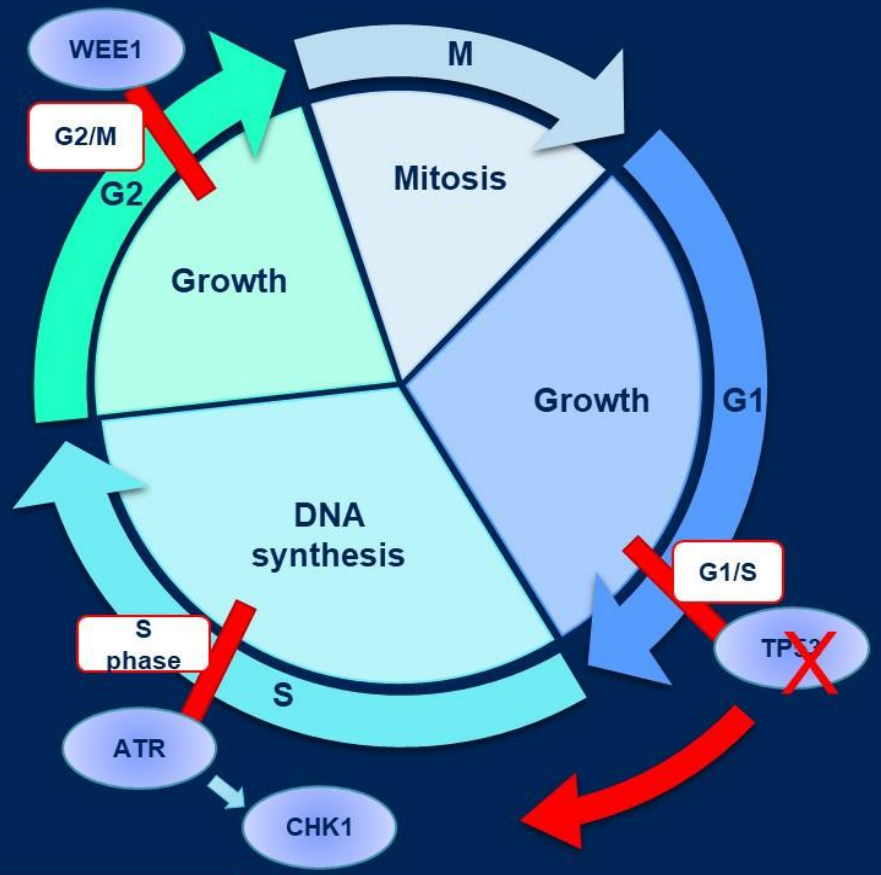
PARP Inhibitor Resistance Mechanisms



Pilie PG, et al. *Nat Rev Clin Oncol*. 2019.

Synthetic Lethality: p53 mutation and WEE1 inhibition

- **WEE1 regulates the G2/M checkpoint**
- **Cells with p53 mutation/loss lose G1/S checkpoint**
- Increases replication stress
- Increases dependence on G2/M checkpoint



Slide courtesy of Joyce Liu, MD

Study Objectives

Primary

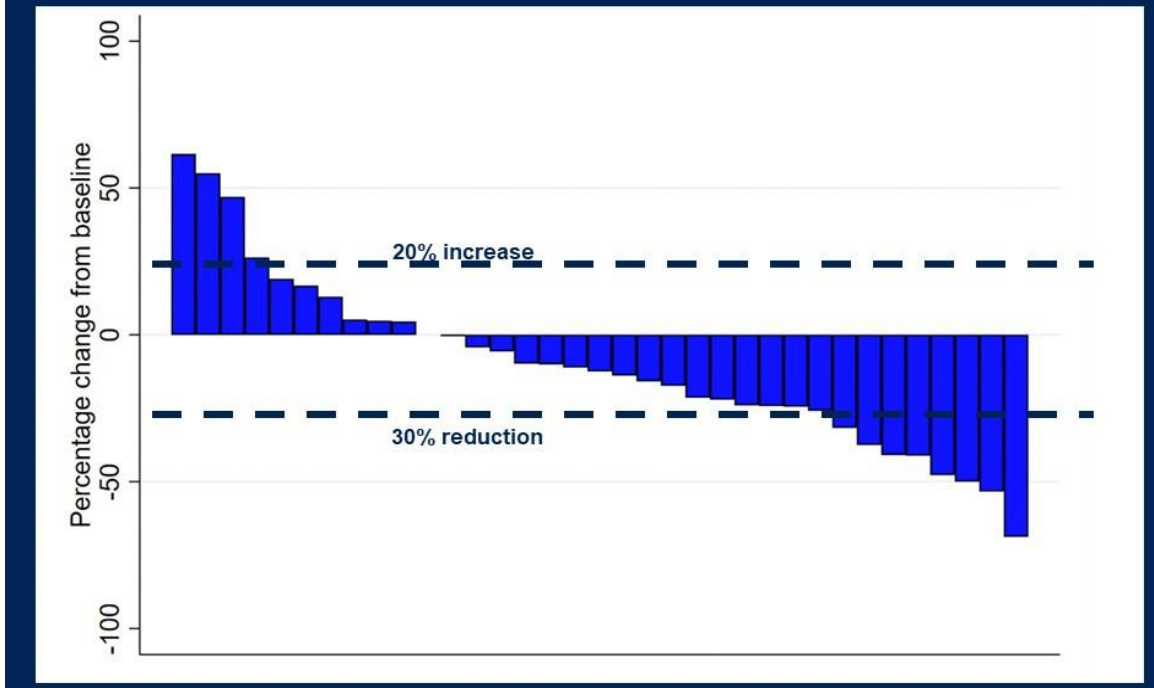
1.To determine the objective response of adavosertib alone and in combination with olaparib in patients with recurrent ovarian cancer in whom progression has been documented following PARP inhibitor therapy

Secondary

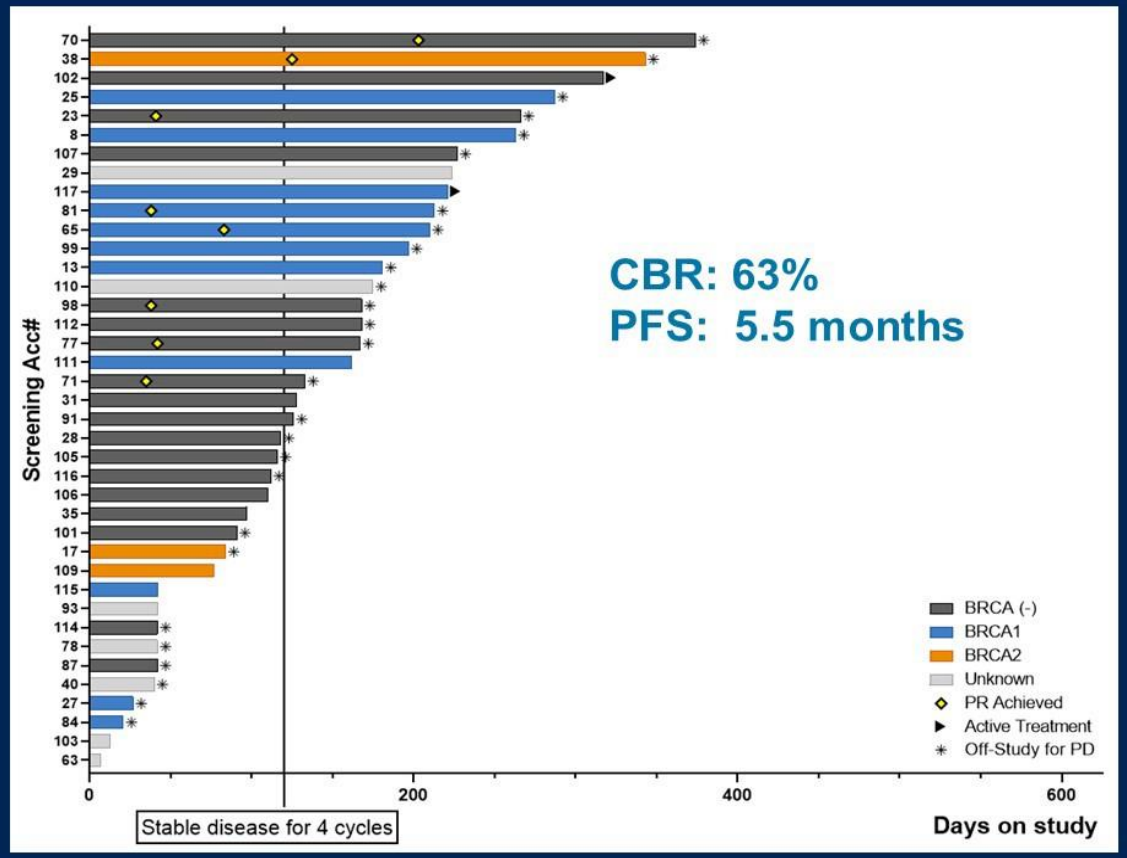
1. To evaluate overall safety and tolerability
2. To determine response duration of these combinations
3. To evaluate disease control rate (defined as objective response + stable disease >16 wks)
4. To evaluate progression free survival and overall survival of this population
5. To evaluate efficacy of each arm based on BRCA status

Response to Therapy

Adavosertib Alone



ORR: 23%
DOR 5.5 months

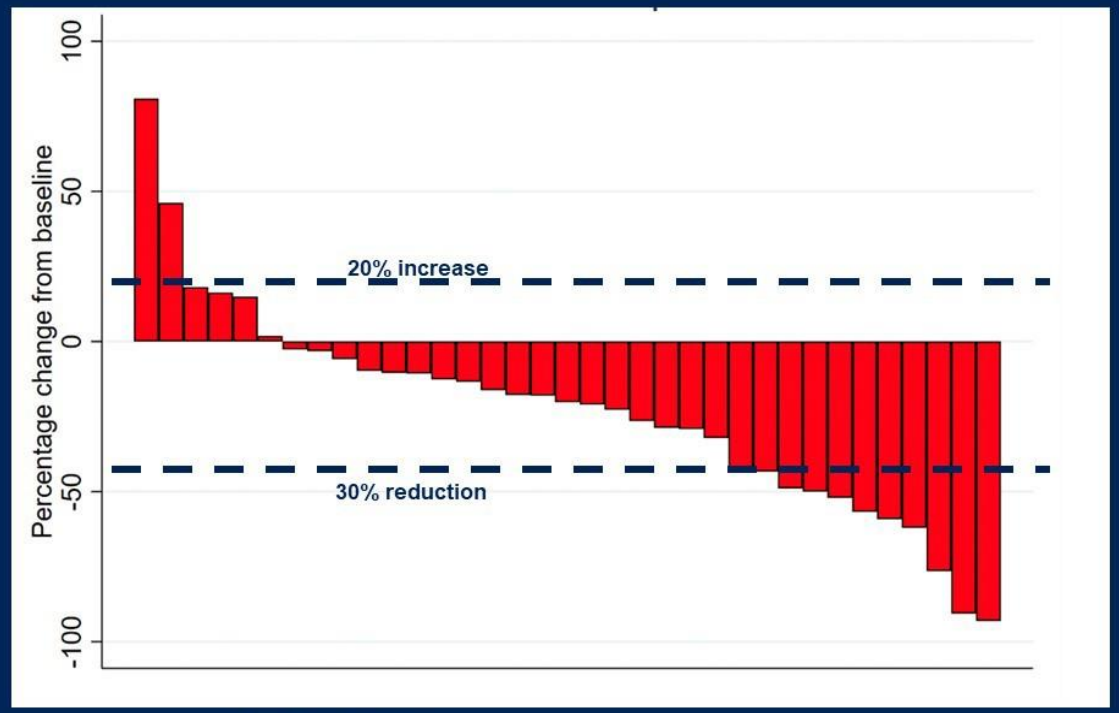


CBR: 63%
PFS: 5.5 months

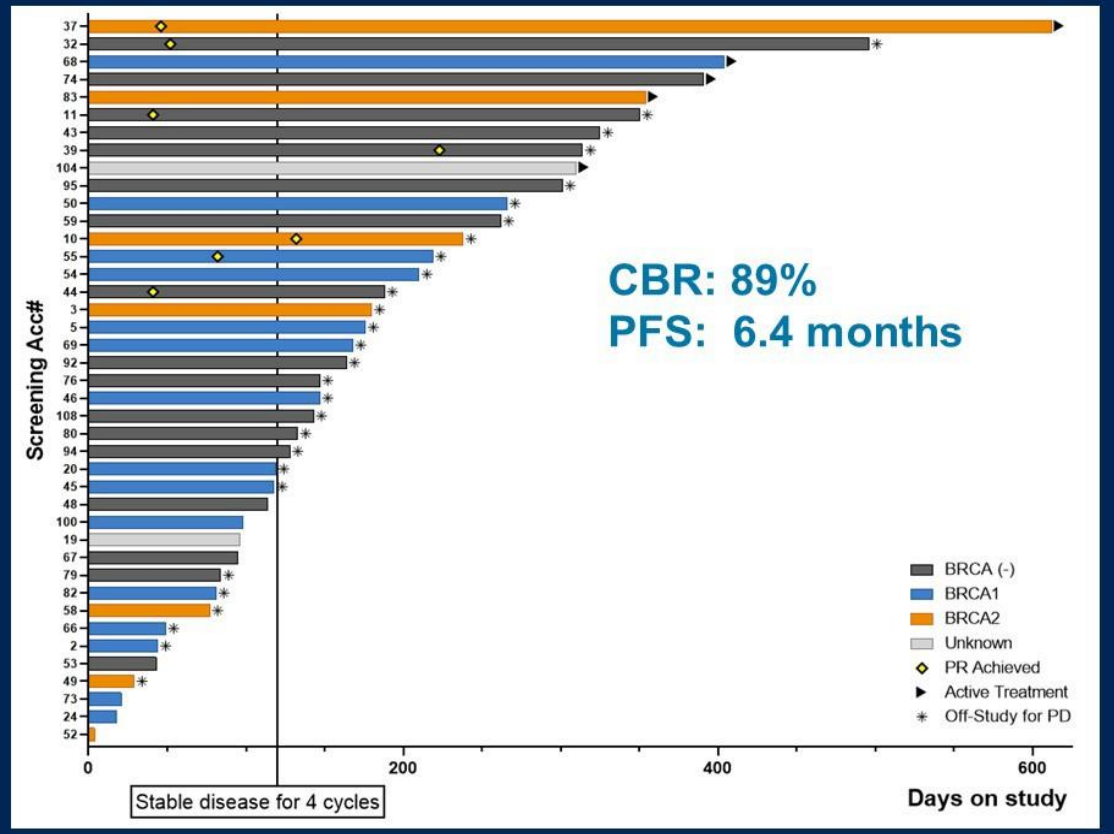
Presented By: Shannon N. Westin, MD, MPH

Response to Therapy

Adavosertib and Olaparib



ORR: 29%
DOR 5.5 months



CBR: 89%
PFS: 6.4 months

Presented By: Shannon N. Westin, MD, MPH

Conclusions

- Adavosertib alone and in combination with olaparib demonstrated efficacy in patients with PARPi-resistant ovarian cancer
  - Irrespective of *BRCA* status
- Toxicities were generally manageable with supportive care, although dose interruptions and dose reductions may be necessary
- Ongoing translational work to assess role of HRD and other aberrations is ongoing

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COMBINATION OF PARP & ATR INHIBITION (OLAPARIB & CERALASERTIB) SHOWS CLINICAL ACTIVITY IN ACQUIRED PARP INHIBITOR RESISTANT RECURRENT OVARIAN CANCER

Presented by: Stephanie L. Wethington

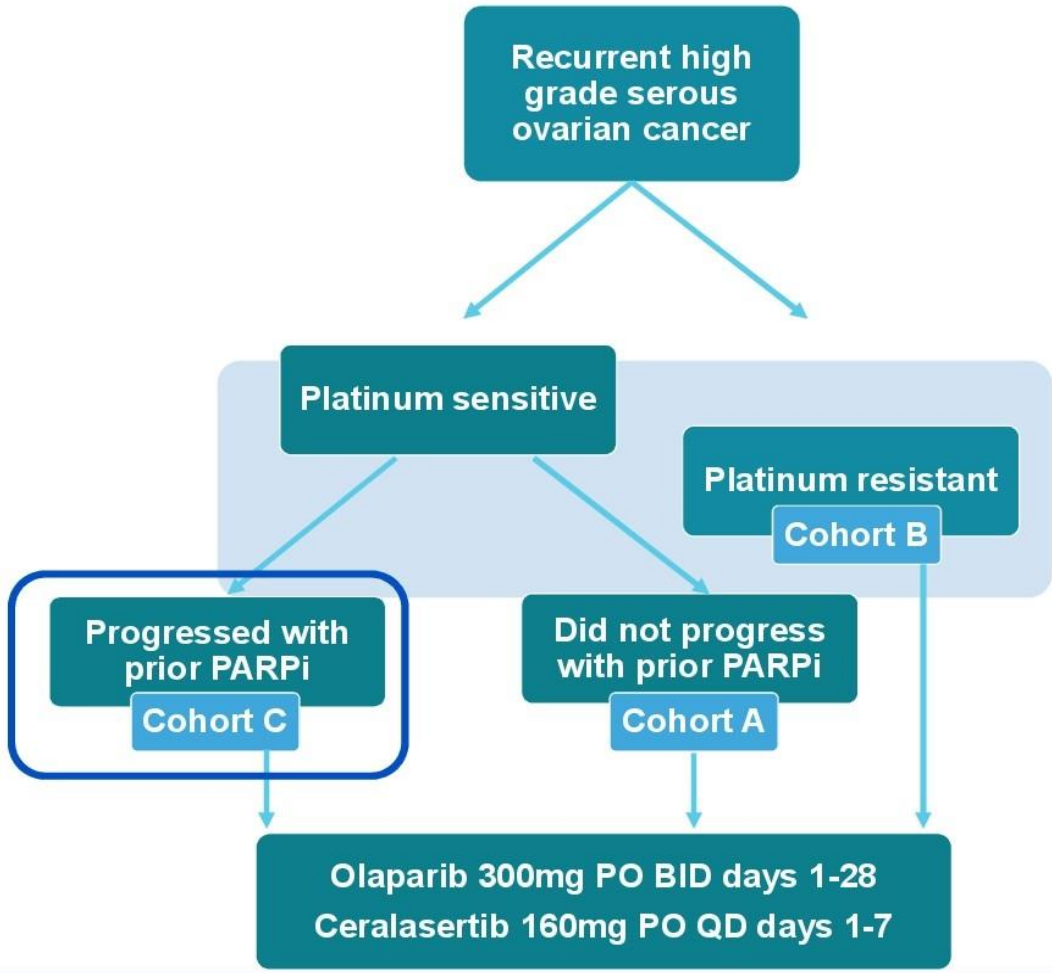
On behalf of: Payal Shah, Lainie Martin, Janos L. Tanyi, Nawar Latif, Mark Morgan, Drew Torigian, Cheyenne Pagan, Diego Rodriguez, Susan Domchek, Ronny Drapkin, Ie-Ming Shih, Simon Smith, Emma Dean, Deborah K. Armstrong, Stephanie Gaillard, and Fiona Simpkins

June 2021

Combination ATR and PARP Inhibition (CAPRI) Study Design

Aim

- Determine the efficacy and tolerability of the combination of olaparib (PARPi) and ceralasertib (ATRi) in patients who have progressed with prior PARPi (Cohort C)



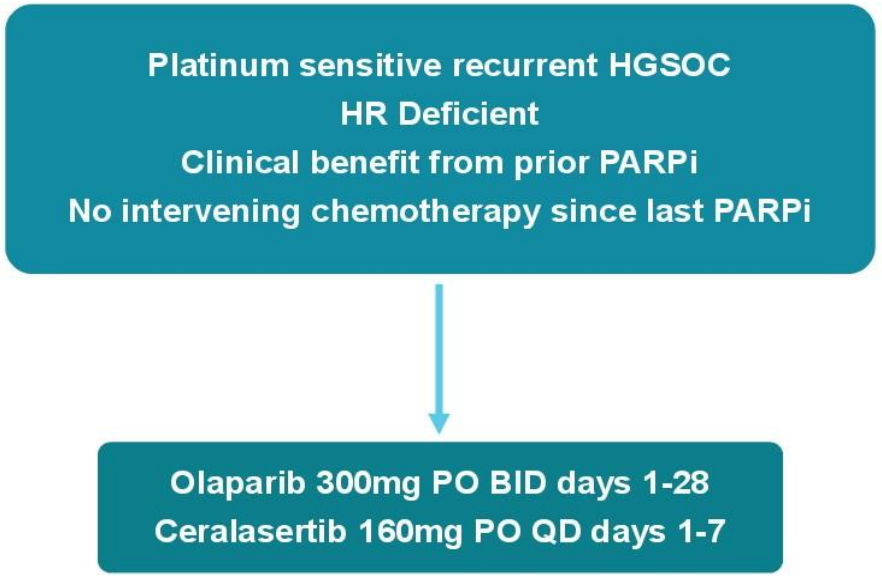
Eligibility criteria for PARPi-resistant Cohort C (CAPRI)

Core inclusion criteria

- Platinum sensitive recurrent HGSOC
- Homologous recombination deficiency
  - Germline/somatic $BRCA^{MUT}$
  - Other HRD mutation
  - HRD positive (≥42 on Myriad My Choice)
- Derived clinical benefit from prior PARPi therapy and then progressed with measurable disease on imaging
- No intervening chemotherapy since PARPi
- Clinical benefit from prior PARPi
  - Maintenance ≥12 months in the front line setting
  - Maintenance ≥6 months in platinum sensitive recurrence
  - Treatment with a decline in CA125 or response on imaging

Treatment regimen, 28 day cycle until progression

- Olaparib 300mg PO BID days 1-28
- Ceralasertib 160mg PO QD days 1-7



Ceralasertib + olaparib demonstrate clinical activity in patients with PARPi resistance

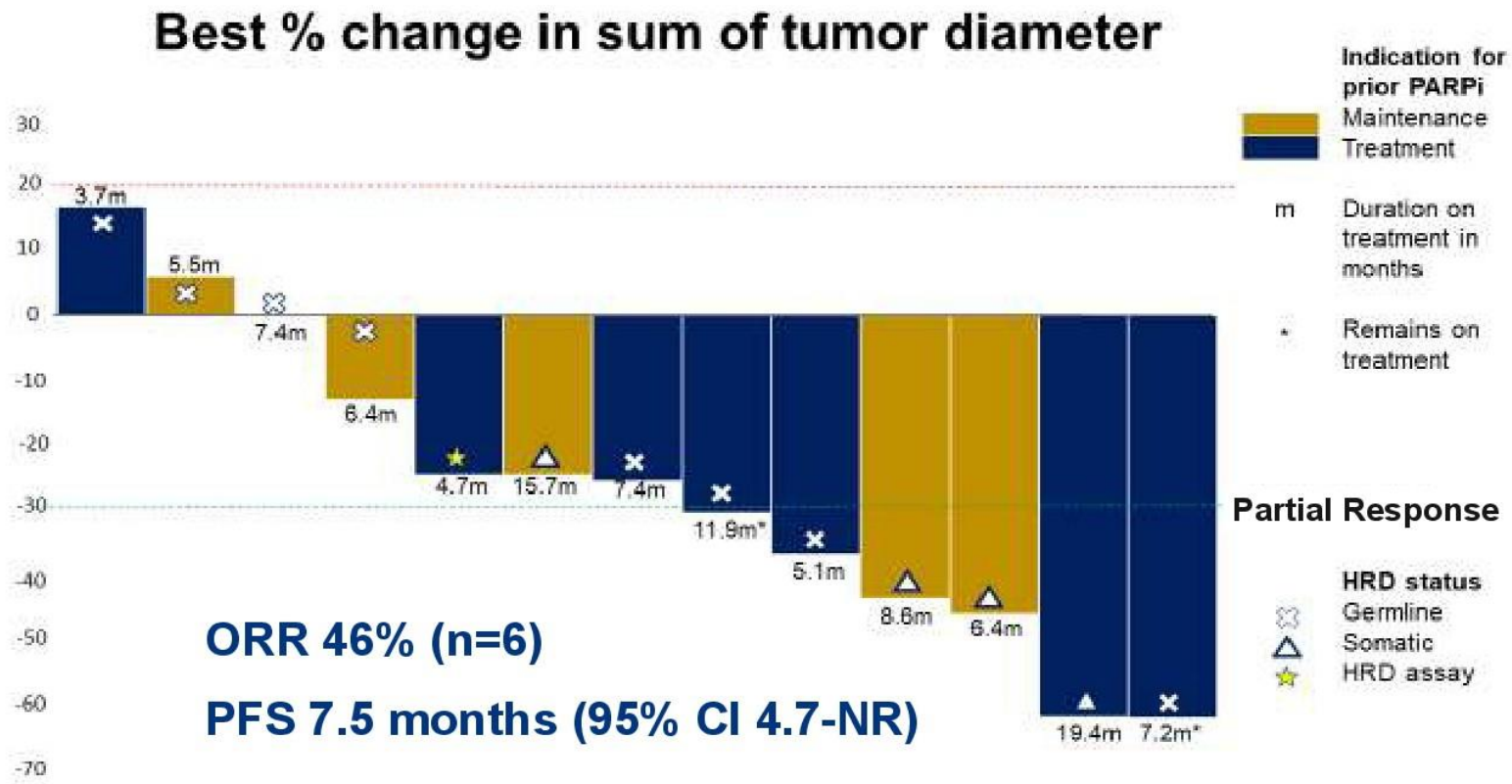
13 subjects

BRCA/HRD

- Germline BRCA^{MUT} 69% (n=9)
- Somatic BRCA^{MUT} 23% (n=3)
- Positive HRD score 8% (n=1)

Prior PARPi

- 1st line maintenance 8% (n=1)
- 2nd line maintenance 38% (n=5
- Treatment 54% (n=7)



Safety: combination is well tolerated

2 treatment interruptions
- 1 thrombocytopenia
- 1 COVID-19 infection

4 dose reductions
- 3 olaparib
- 1 ceralasertib

No patient discontinued treatment due to toxicity

Adverse Event Summary

	Any Grade n (%)	Grade 3 or 4 n (%)
Hematologic		
Anemia	6 (46.2)	1 (7.7)
Thrombocytopenia	7 (53.8)	3 (23.1)
Leukopenia	1 (7.7)	1 (7.7)
Neutropenia	2 (15.4)	1 (7.7)
Non-hematologic		
Fatigue	10 (76.9)	0 (0.0)
Dizziness	3 (23.1)	0 (0.0)
Generalized Muscle Weakness	1 (7.7)	0 (0.0)
Flu-like symptoms	1 (7.7)	0 (0.0)
Headache	2 (15.4)	0 (0.0)
Anorexia	3 (23.1)	0 (0.0)
Dyspnea	1 (7.7)	0 (0.0)
Abdominal pain	2 (15.4)	0 (0.0)
Mucositis	3 (23.1)	0 (0.0)
Nausea	9 (69.2)	0 (0.0)
Vomitting	4 (30.8)	0 (0.0)
Diarrhea	5 (38.5)	0 (0.0)
Constipation	1 (7.7)	0 (0.0)
Dyspepsia	3 (23.1)	0 (0.0)
Dysgeusia	5 (38.5)	0 (0.0)
Dehydration	1 (7.7)	0 (0.0)
Elevated Creatinine	3 (23.1)	0 (0.0)
Hypomagnesemia	1 (7.7)	0 (0.0)
Hematuria	1 (7.7)	0 (0.0)

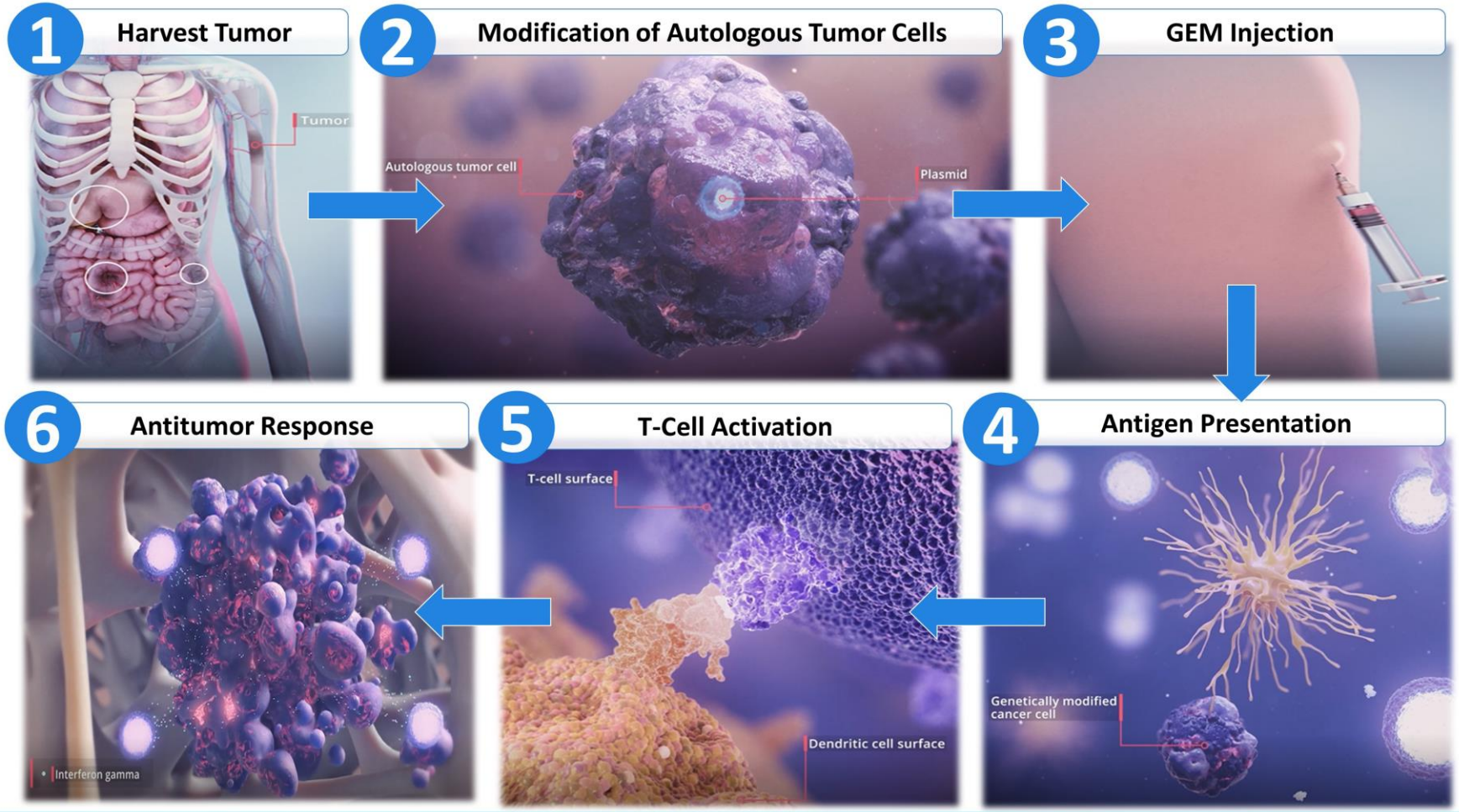
Conclusions

- Combination olaparib and ceralasertib is well tolerated
- Combination shows a signal of clinical activity in patients who have progressed on a PARPi as the most recent therapy
- Future clinical trials investigating this combination are warranted
- Tumor molecular profiling to refine biomarkers of response (e.g *BRCA*^{REV}) to this combination is critical and are ongoing

MAINTENANCE GEMOGENOVATUCEL-T (GEM) IN NEWLY DIAGNOSED ADVANCED OVARIAN CANCER: EFFICACY ASSESSMENT OF HOMOLOGOUS RECOMBINATION PROFICIENT (HRP) PATIENTS IN THE PHASE IIB VITAL TRIAL

Rodney P. Rocconi, MD
University of South Alabama Mitchell Cancer Institute
Mobile, Alabama

The Role of GEM in the Cancer Immunity Cycle

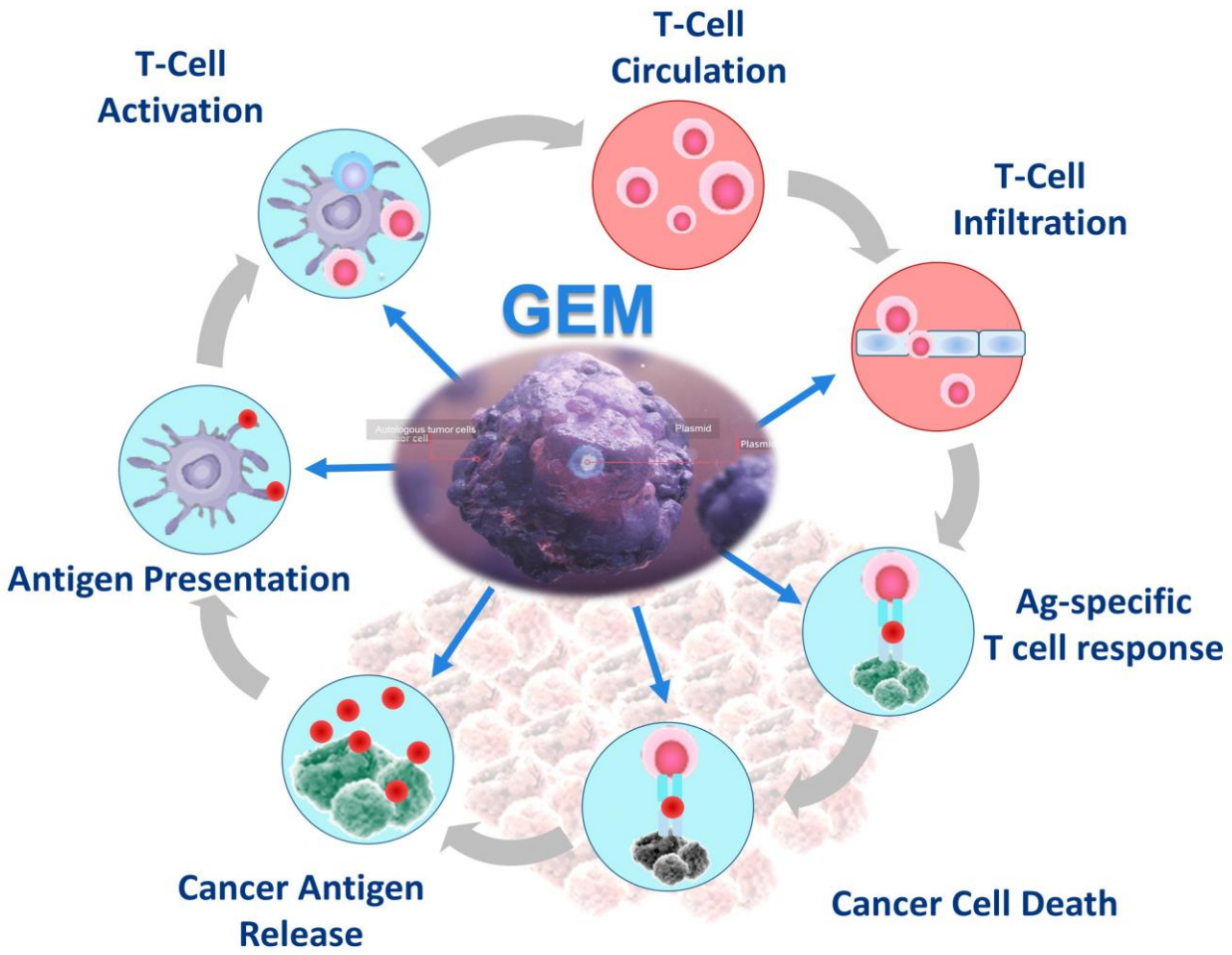


The Role of GEM in the Cancer Immunity Cycle

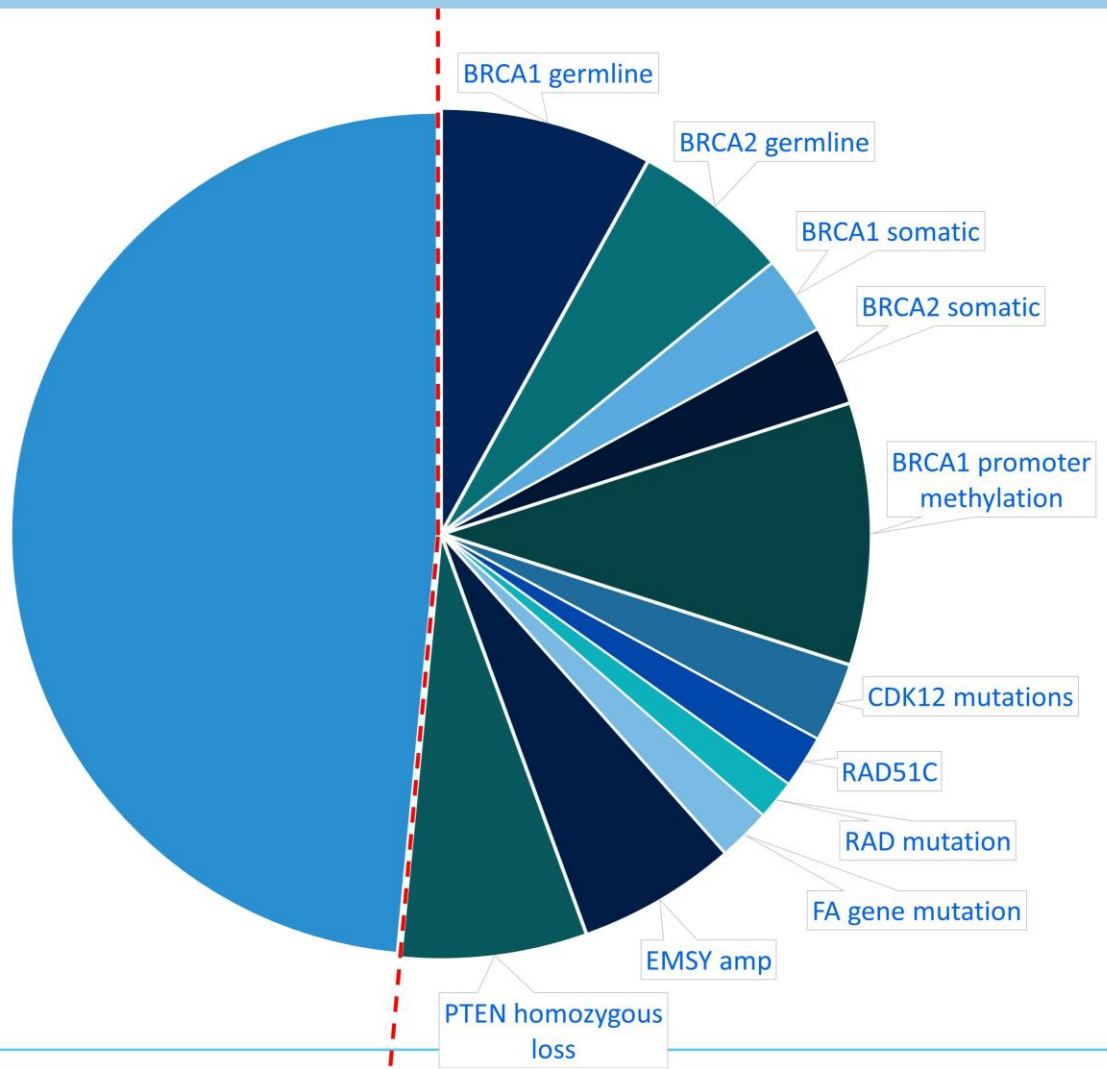
Produce Cancer Neoantigen Specific Responses

Increase Neoantigen-MHC I Presentation & CD8+ T cells (GM-CSF)

Block Immunosuppressive Cytokines (shRNA-furin)



Limitations of Frontline Maintenance in HRP Ovarian Cancer



HR PROFICIENT

HR DEFICIENT

* Myriad also reports 50% of tumors are HRP

1: Konstantinopoulos et al Can Disc 2015 | 2: Chart adapted from Konstantinopoulos et al.

Bevacizumab in Frontline Maintenance HRP Ovarian Cancer

Toxicity

- 66% ≥ Grade 3 toxic effect
- HTN, wound healing, GI perforation, hemorrhagic events, VTE, non-GI fistula, leukoencephalopathy, nephrotic syndrome[1]

Marginal survival benefit

- PFS benefit, HR = 0.717
- OS benefit, HR = 0.96
- Particularly in the BRCA-wt, HRP group OS 20 months less than HRD[2-4]

1: Rocconi et al. Lancet Oncol 2020 |
2: McClung, Wenham Int. J. Womens Health 2016 |
3: Tewari et al. J Clin Oncol 2019 | 4: Burger et al. N Engl J Med 2011 |
5. Gonzalez Martin et al. N Engl J Med 2019 | 6. Todisco et al. Int J Cancer 2021

Niraparib in Frontline Maintenance HRP Ovarian Cancer

Toxicity

- 60-70% ≥ Grade 3 toxicity: thrombocytopenia, anemia, neutropenia
- 69-80% Dose modification[5]

MDS / AML

- Recent data all PARP-inh risk[6]
  - 3yr = 1-2%
  - 5yr = 6.9%

Marginal survival benefit

- PFS benefit 2.7 months over placebo
- HR = 0.68
- No OS benefit in BRCA-wt, HRP population (HR = 0.96)[5]

1: Rocconi et al. Lancet Oncol 2020 |
2: McClung, Wenham Int. J. Womens Health 2016 |
3: Tewari et al. J Clin Oncol 2019 | 4: Burger et al. N Engl J Med 2011 |
5. Gonzalez Martin et al. N Engl J Med 2019 | 6. Todisco et al. Int J Cancer 2021

Methods: Study Endpoints

- ***Primary Endpoint***
  - Recurrence Free Survival (RFS) of per-protocol population (PP) from randomization based on RECIST 1.1

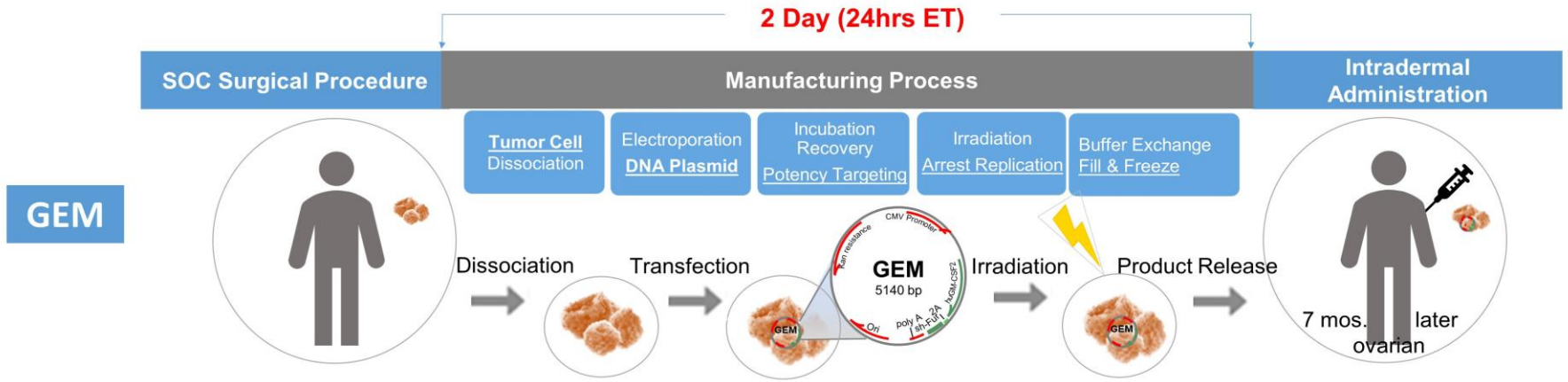
- ***Secondary Endpoints***
  - Overall Survival (OS)
  - Safety / Toxicity
  - RFS and OS of BRCA & HR status

Methods: Translational Endpoints

- ***Subgroup Analysis***
  - HR Mutation including BRCA
  - HR proficient (as determined by MyChoice by Myriad)

- ***Post-Hoc STRING Analysis***
  - DNA polymorphism data across 981 genes was utilized to calculate the protein interaction probability in HRP, TP53-m subpopulation
  - HRP/TP53 mutated population analyzed for RFS and OS

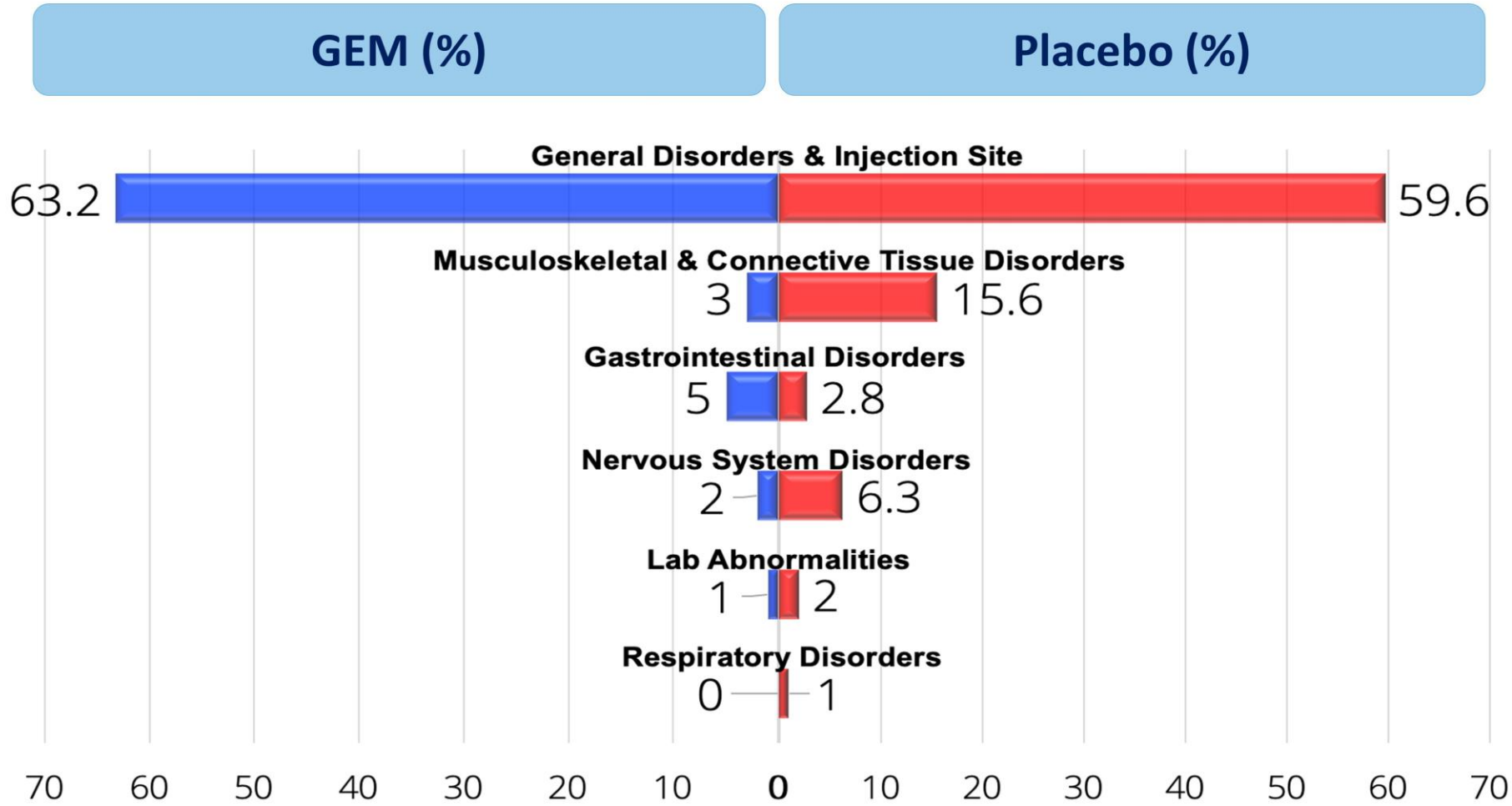
Methods: Manufacturing Process & Product Release



GEM: Autologous Tumor, GMCSF-bi-shRNA^{furin} DNA plasmid

Release Criteria	GEM
Purity / Safety	Bacterial endotoxin Sterility Mycoplasma
Potency, Identity / Specificity	Number of viable tumor cells Cell Viability (≥70%)
Efficacy	GMCSF (Increase of ≥30 pg/million cells) TGF-B1 (Knockdown ≥30% or Undetectable)
Quantity	Total Cell Count

Adverse Events (Grades 1-3)

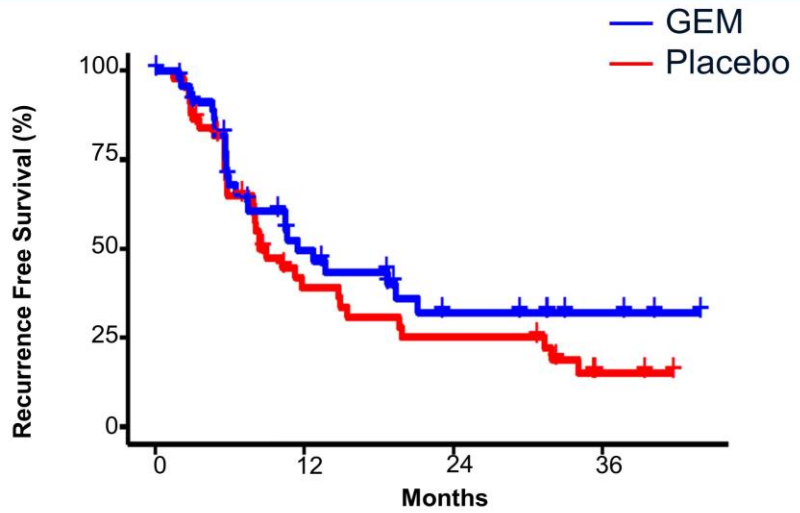


Demographics

Treatment Arm	ALL Patients (PP) GEM N=47	ALL Patients (PP) Placebo N=44	HRP GEM N=25	HRP Placebo N=20
Age-Years				
Median	63	62.5	64	64
Range	42-84	38-79	51-84	46-79
Staging				
III	80.9%	88.6%	72.0%	85.0%
IV	19.1%	11.4%	28.0%	15.0%
ECOG				
0	55.3%	79.5%	48.0%	75.0%
1	44.7%	20.5%	52.0%	25.0%
Frontline chemotherapy				
Adjuvant	83.0%	84.1%	17.0%	15.9%
Neoadjuvant	17.0%	15.9%	83.0%	84.1%
Frontline surgery residual disease status				
Macroscopic	34.0%	25.0%	32.0%	30.0%
Microscopic/NED	66.0%	75.0%	68.0%	70.0%

VITAL Study (All Patients)

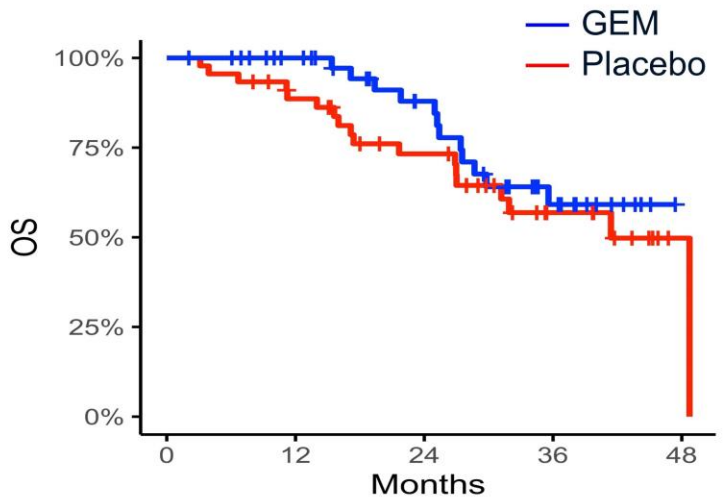
RFS (from randomization)



No. at Risk				
GEM	47	17	7	3
Placebo	44	14	9	2

Group	N	N (%)	Median RFS (mo)	HR	p-value* (log-rank)
GEM	47	26 (55)	11.5	0.688	0.078
Placebo	44	33 (75)	8.4		

OS (from randomization)

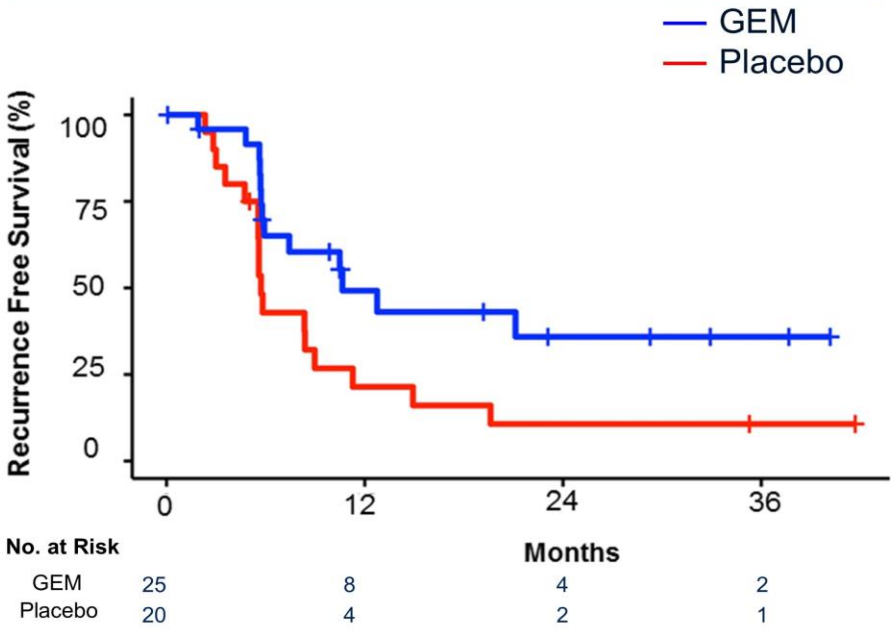


No. at Risk					
GEM	47	34	14	7	1
Placebo	44	30	11	9	0

Group	N	N (%)	Median RFS (mo)	HR	p-value* (log-rank)
GEM	47	26 (55)	NA	0.630	0.110
Placebo	44	33 (75)	16.0		

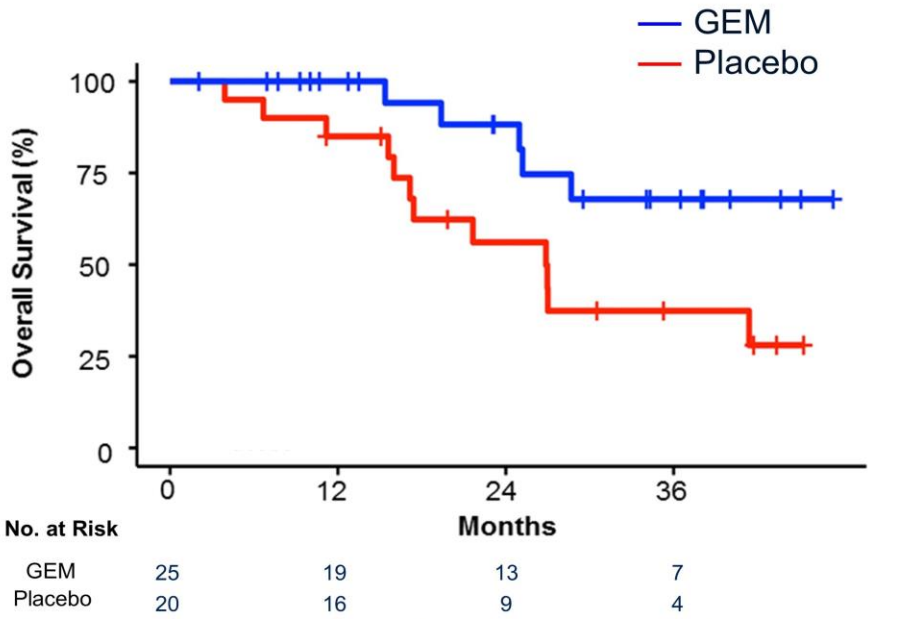
VITAL Study (HRP Patients)

RFS (from randomization)



Group	N	N (%)	Median RFS (mo)	HR	p-value* (log-rank)
GEM	25	13 (52)	10.6	0.386	0.007
Placebo	20	17 (85)	5.7		

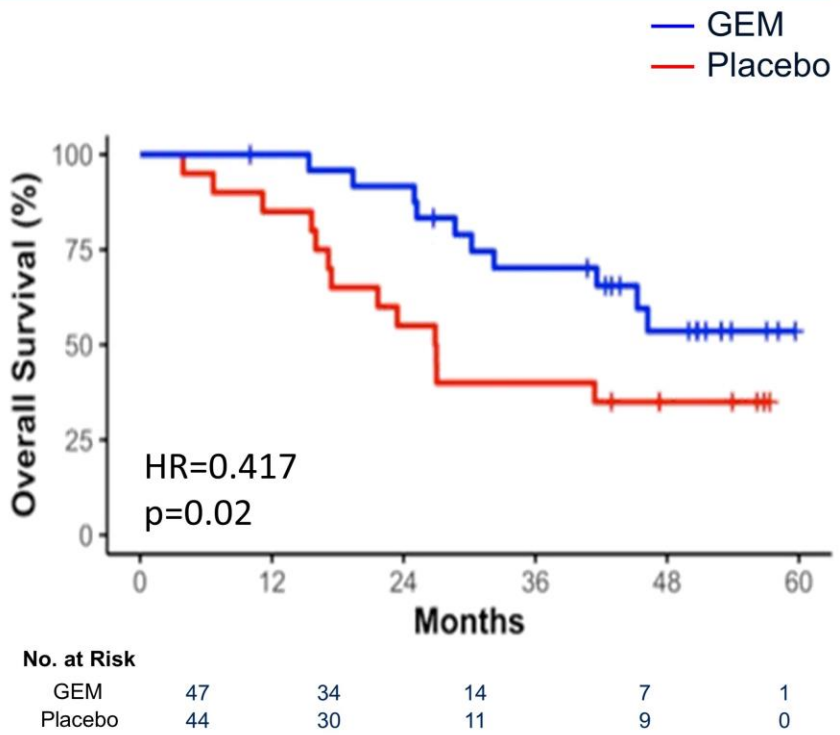
OS (from randomization)

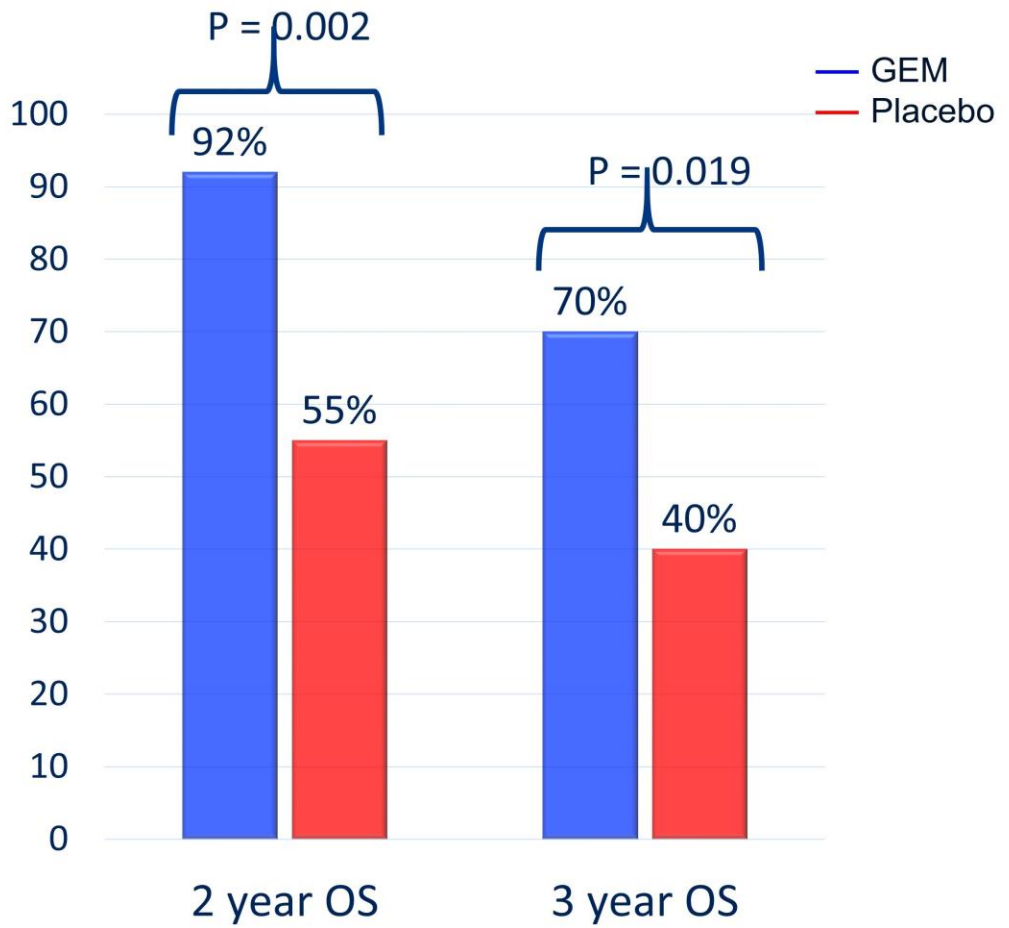


Group	N	N (%)	Median OS (mo)	HR	p-value* (log-rank)
GEM	25	5 (20)	NR	0.342	0.019
Placebo	20	12 (60)	26.9		

Updated Survival in HRP (April 2021)

OS (from randomization)





Conclusions VITAL Study in HRP

GEM in Upfront Maintenance Therapy for Ovarian Cancer

- Novel autologous vaccine specific to each patient
- Excellent tolerability that is ideal for maintenance therapy
- Failed to meet primary endpoint of RFS in all patients

GEM in HRP cohort

- Statistically significant benefit in both *Recurrent Free & Overall Survival*
- Updated survival data encouraging GEM over placebo
  - 2-year OS ***92 vs. 55%***
  - 3-year OS ***70 vs. 40%***

Translational Studies

- STRING analysis of HRP/P53-mutated subcohort demonstrated improvements in survival
- Potential predictive biomarkers for efficacy and survival

Conclusions VITAL Study in HRP

HR Proficient Landscape

- Despite efficacy of current options of maintenance therapies for ovarian cancer
- Majority of benefit is seen in HR Deficient ovarian cancers
- Significant adverse events

GEM in Upfront Maintenance Therapy for Ovarian Cancer

- Tolerability and efficacy of GEM in HRP ovarian cancer is particularly encouraging
- Potentially fulfills an unmet need in HRP ovarian cancer

2021 ASCO ANNUAL MEETING

DENDRITIC CELL VACCINE (DCVAC) COMBINED WITH CHEMOTHERAPY (CMT) IN PATIENTS WITH NEWLY DIAGNOSED EPITHELIAL OVARIAN CARCINOMA (EOC) AFTER PRIMARY DEBULKING SURGERY (PDS): BIOMARKER EXPLORATORY ANALYSIS OF A PHASE 2, OPEN-LABEL, RANDOMIZED, MULTICENTER TRIAL (SOV01, NCT02107937)

L. Rob[1], D. Cibula[2], P. Knapp[3], P. Mallmann[4], J. Klat[5], L. Minar[6], P. Bartos[7], J. Chovanec[8], P. Valha[9], M. Pluta[10], Z. Novotny[11], J. Spacek[12], B. Melichar[13], D. Kieszko[14], J. Fucikova[15], T. Hrnciarova[2,15], R. P. Korolkiewicz[15], M. Hraska[15], J. Bartunkova[15], R.Spisek[15]

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Presented by:

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June 4, 2021

Patients

N=99
1:1:1 randomization
Women with ovarian carcinoma[1] eligible to receive first-line standard of care chemotherapy after optimal primary debulking surgery
(<1 cm max. residuum)

Regimen

- **Parallel**[2] **DCVAC/OvCa** with platinum-based chemo[3]
- **Sequential**[4] **DCVAC/OvCa** after platinum-based chemo[3]
- **Standard-of-care** platinum-based chemo[3]

End points

Primary: PFS at 2 yrs after randomization

Secondary/exploratory:
OS, proportion of patients in remission after 6 and 12 months, biological PFI, immune response, proportion of patients requiring 2nd-line chemo, TFST, AEs, changes in QoL, **predictive and prognostic biomarkers**

1) Epithelial cancer of the ovary, fallopian tube and peritoneum, FIGO stage III, serous, endometrioid, or mucinous PS 0 – 2, <1 cm max. residuum, no prior systemic therapy
2) 5 doses of DCVAC/OvCa concomitantly with platinum-based chemo, continued 5 doses of DCVAC/OvCa as maintenance; 1 × 10^7 DCs/dose
3) Carboplatin (AUC 5-7) + paclitaxel (175 mg/m^2), 6 cycles
4) 10 doses of DCVAC/OvCa as maintenance subsequent to platinum-based chemo; 1 × 10^7 DCs/dose

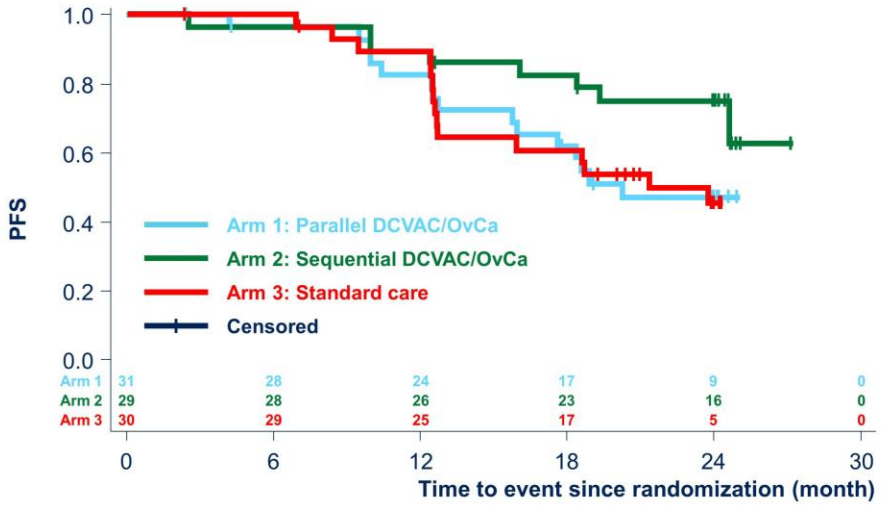
Characteristics, mITT population (all randomized patients except those DCVAC/OvCa who failed to receive at least 1 dose of DCVAC/OvCa; primary population)	**Statistic**	**Parallel DCVAC (N=31)**	**Sequential DCVAC (N=29)**	**SoC (N=30)**
Age at randomization (derived) [years]	n	31	29	30
	Mean (StD)	58.7 (12)	55.8 (11.4)	61.3 (7.5)
	Median	61.7	55.9	62.3
Type of epithelial ovarian cancer	n	31	29	30
Endometrioid	n (%)	2 (6.5%)	6 (20.7%)	1 (3.3%)
Mucinous	n (%)	1 (3.2%)	0	0
Serous	n (%)	28 (90.3%)	23 (79.3%)	29 (96.7%)
Post-surgery residual lesion	n	31	29	30
Maximal residuum <1 cm	n (%)	4 (12.9%)	5 (17.2%)	5 (16.7%)
Zero residuum	n (%)	27 (87.1%)	24 (82.8%)	25 (83.3%)
$CD8^+$ T cells count/mm^2 in tumor tissue (collected as exploratory characteristic)	n	29	23	26
	Mean (StD)	91 (147.9)	198.6 (252.4)	117.4 (116)
	Median	40.4	110.5	85.5

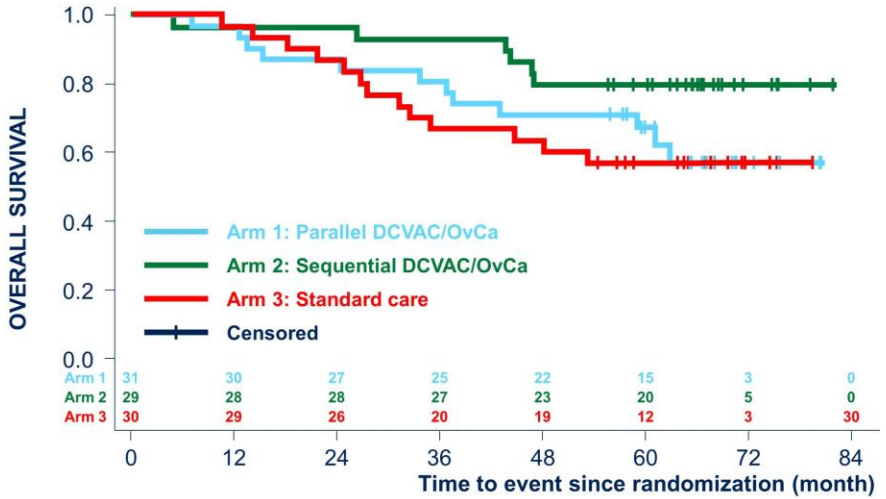
No clinically relevant difference affecting the efficacy comparison except CD8+ counts (lowest in parallel DCVAC/OvCa)

Final analysis: PFS and OS on primary analysis population

PFS	Parallel DCVAC	Sequential DCVAC	SoC
Patient count	31	29	30
Median time (months)	20.3	NA	21.4
Comparison vs. SoC arm			
HR estimate	0.98	0.39	
HR 95% CI	(0.48; 2.00)	(0.16; 0.96)	
Log-rank p-value	0.9483	0.0336	

OS	Parallel DCVAC	Sequential DCVAC	SoC
Patient count	31	29	30
Median time (months)	NA	NA	NA
Comparison vs. SoC arm			
HR estimate	0.84	0.40	
HR 95% CI	(0.38; 1.84)	(0.15; 1.06)	
Log-rank p-value	0.6631	0.0557	



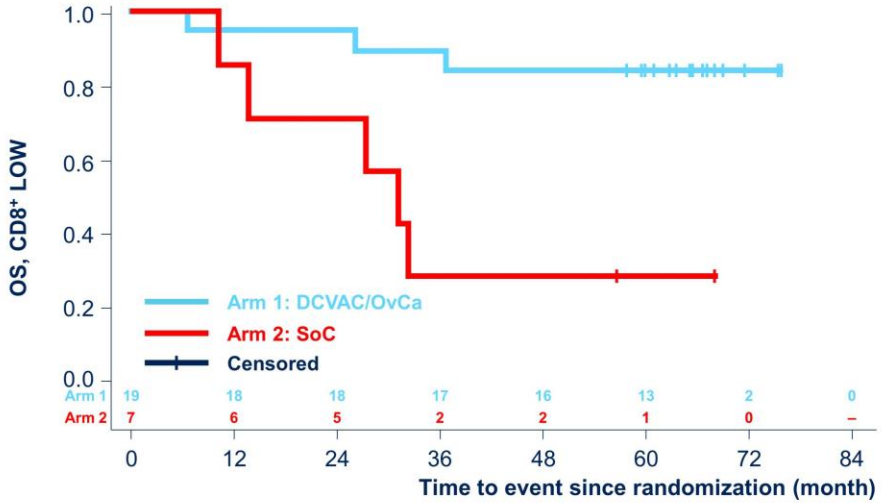


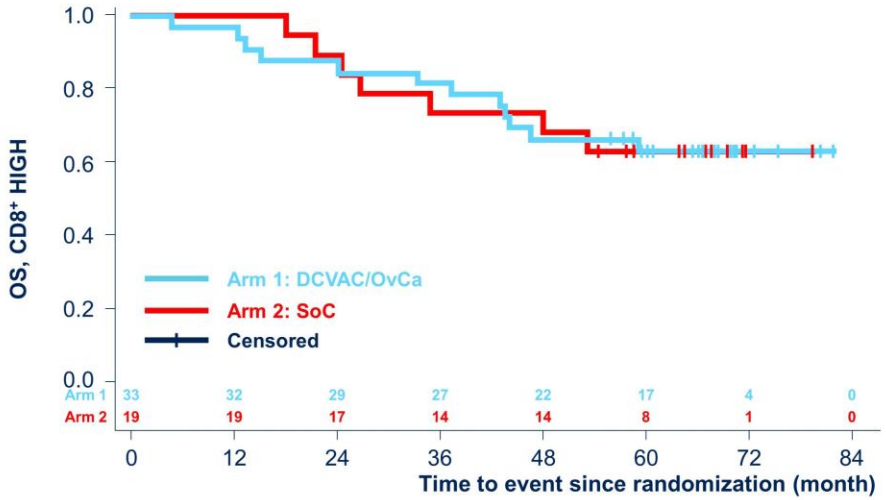
Significant PFS benefit of sequential DCVAC/OvCa as compared to SoC only

Final analysis: OS on primary analysis population per CD8⁺ T cells levels (threshold 30 CD8⁺ T cells/mm²)

OS low CD8⁺ T cells levels	DCVAC	SoC
Patient count	19	7
Median time (months)	NA	31.2
Comparison vs. SoC arm		
HR estimate	0.15	
HR 95% CI	(0.04; 0.65)	
Log-rank p-value	0.0038	

OS high CD8⁺ T cells levels	DCVAC	SoC
Patient count	33	19
Median time (months)	NA	NA
Comparison vs. SoC arm		
HR estimate	0.99	
HR 95% CI	(0.39; 2.52)	
Log-rank p-value	0.9830	





Significant OS improvement by DCVAC/OvCa in patients with low CD8⁺ T cells levels in tumor

Consistent trend observed also on ITT population

Final analysis: Patients with treatment-emergent AEs in the safety population Suspected relationship to DCVAC/OvCa (per investigator)

MedDRA primary system organ class Preferred term	Parallel DCVAC (N=34)	Sequential DCVAC (N=32)
Any TEAE	2 (5.9%)	2 (6.3%)
General disorders and administration site conditions	1 (2.9%)	1 (3.1%)
Inflammation	1 (2.9%)	0
Injection site erythema	0	1 (3.1%)
Injection site pain	0	1 (3.1%)
Skin and subcutaneous tissue disorders	1 (2.9%)	0
Erythema	1 (2.9%)	0
Immune system disorders	0	1 (3.1%)
Drug hypersensitivity	0	1 (3.1%)

DCVAC/OvCa is well tolerated regardless of DCVAC/OvCa administration schedule

Summary

01 **Combination of Pt-based chemo with DCVAC may potentially be beneficial in optimally debulked patients, markedly prolonging PFS and OS**

02 **Exploratory analyses shown $CD8^+$ T cells potential as a predictive marker of DCVAC/OvCa clin. efficacy**

- Reduction of number of deaths in patients with low $CD8^+$ T cells count. Death occurrence over 4-year follow-up: **17%** in parallel DCVAC vs. **14%** in sequential DCVAC vs. **71%** in SoC

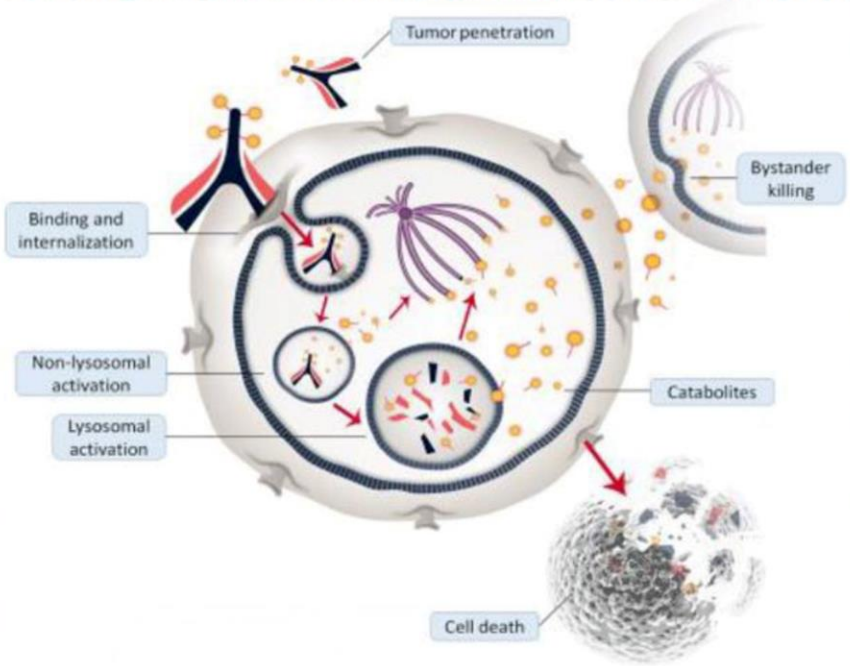
03 **$CD8^+$ T cells count allows a selection of patients who benefit the most from DCVAC application**

- Optimal PDS reduce the initial tumor burden, improving patient prognosis
- Pt- based chemo regimens improves immune effector cells function, (including DCs and $CD8^+$ T cells), and induce the immunogenic cell death

04 **Addition of DCVAC to first-line chemotherapy is safe and well tolerated**

2021 ASCO ANNUAL MEETING

Mirvetuximab Soravtansine, a folate receptor alpha-targeting antibody drug conjugate, in combination with bevacizumab in patients with platinum-agnostic ovarian cancer: final analysis



David M. O'Malley[1], Ana Oaknin[2], Ursula A. Matulonis[3], Gina M. Mantia-Smaldone[4], Peter Lim[5], Cesar Castro[6], Diane Provencher[7], Sanaz Memarzadeh[8], Patrick Zweidler-McKay[9], Jiuzhou Wang[9], Brooke Esteves[9], Kathleen N. Moore[10] Lucy Gilbert[11]

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Background

- The incorporation of PARPi into the treatment paradigm has resulted in an increasing population of women with recurrent ovarian cancer for whom a non-platinum based regimen would be appropriate
- Mirvetuximab soravtansine (MIRV) is a folate receptor-α (FRα) targeting ADC that delivers the potent tubulin-targeting maytansinoid DM4 directly to the tumor
- MIRV has encouraging activity in platinum-resistant ovarian cancer (PROC):
  - Monotherapy in high FRα patients: 24% to 47% confirmed objective response rate (ORR)[1,2]
  - With bevacizumab (BEV) in medium and high FRα patients: 39% to 56% confirmed ORR[3]
- The AURELIA trial[4] showed that in patients with platinum-resistant ovarian cancer, the addition of BEV to chemotherapy:
  - Significantly improved progression-free survival (PFS) in comparison to chemotherapy alone (median PFS: 6.7 months vs. 3.4 months); and
  - Demonstrated a higher ORR over chemotherapy alone (27% vs. 12%)
- In this trial, MIRV was combined with BEV as a novel, targeted, non-platinum based regimen designed to address the unmet need in a broader population of recurrent ovarian cancer patients

[1]Moore ASCO 2017; [2]Moore ESMO 2019; [3]O'Malley *Gyn Onc* 2020; [4]Pujade-Lauraine *J Clin Oncol* 2014

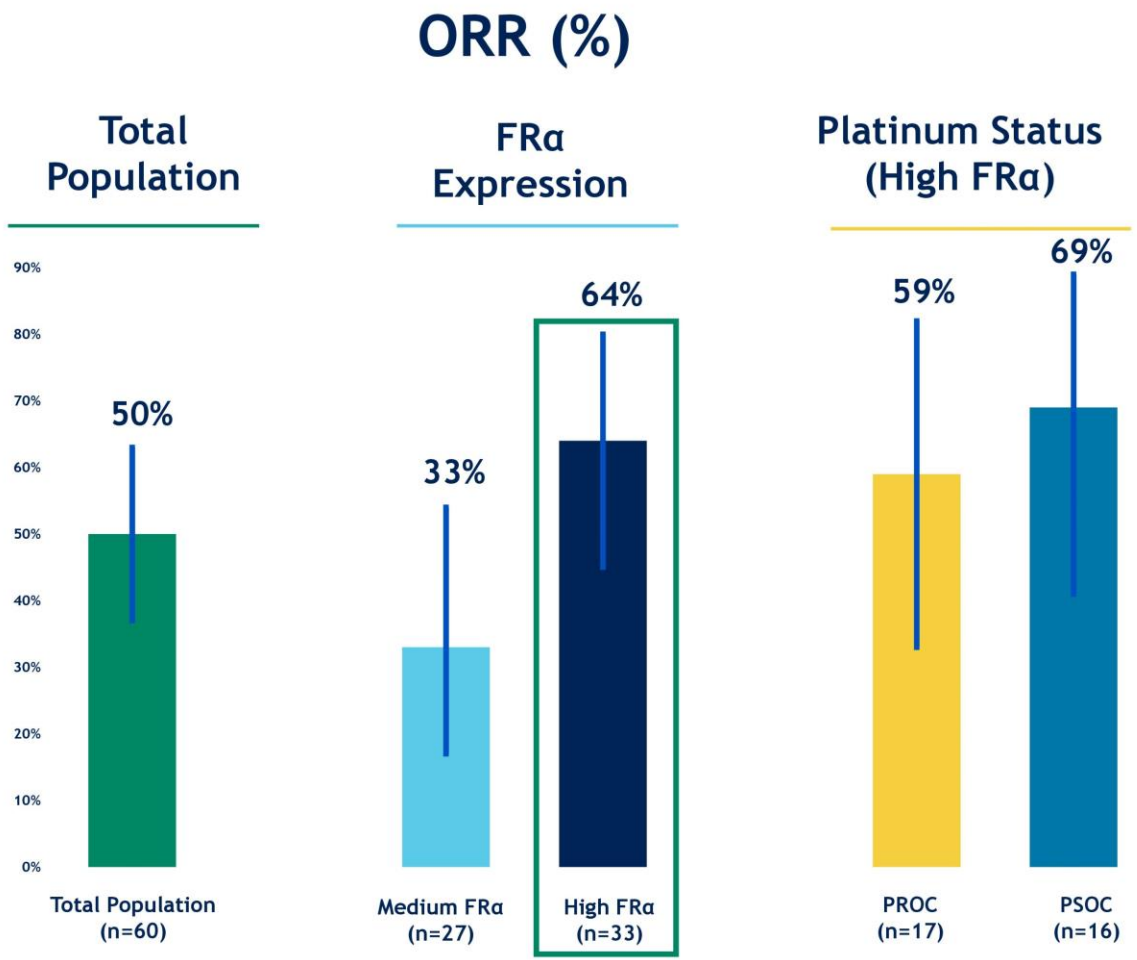
Patient Demographics

Characteristic		All Patients (N = 60)
Age median (range)		60 (44-83 years)
Primary cancer diagnosis n (%) (Recurrent, High Grade)	Epithelial ovarian cancer	41 (68)
	Fallopian tube cancer	15 (25)
	Primary peritoneal	4 (7)
ECOG PS, n (%)	0	44 (73)
	1	16 (27)
No. of prior systemic therapies, n (%)	1	20 (33)
	2	21 (35)
	≥3*	19 (32)
	Median (range)	2 (1-4)
FRα expression n (%)	High (≥75% PS2+) **	33 (55)
	Medium (≥50% PS2+) **	27 (45)
Prior exposure, n (%)	Platinum compounds	60 (100)
	Taxanes	60 (100)
	Bevacizumab	24 (40)
	PARP inhibitor	21 (35)
Platinum free interval	≤ 6 months	32 (53)
	> 6 - ≤ 12 months	20 (33)
	> 12 months	8 (13)

*1 patient had 4 priors

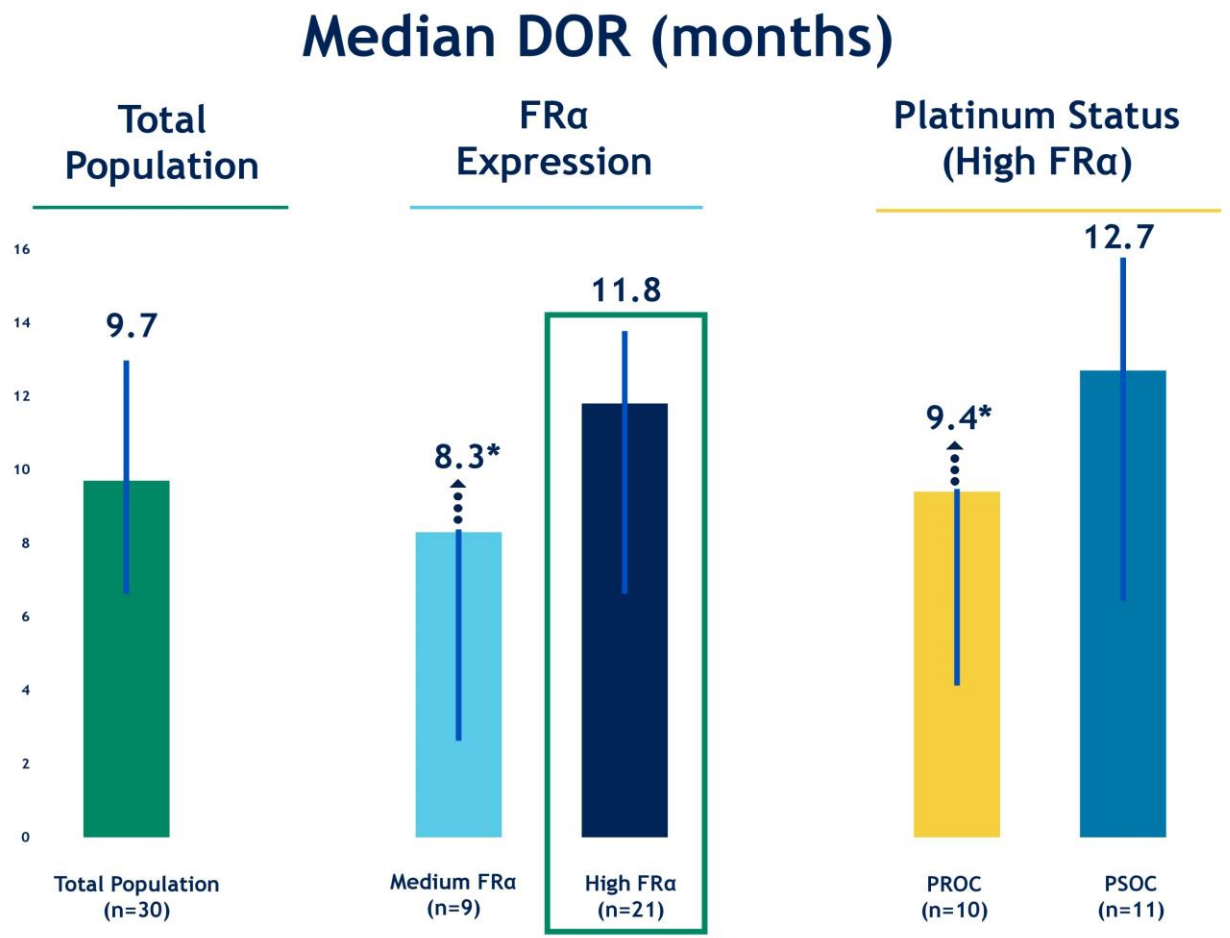
PS2+ Scoring: ≥50 or ≥75% of tumor cells with FRα membrane staining with ≥ 2+ intensity

Confirmed ORR by FRα Expression and Platinum Status



- **50% ORR** (30/60) for overall cohort
- **64% ORR** (21/33) in high FRα tumors
  - **59% ORR** (10/17) in PROC subset
  - **69% ORR** (11/16) in PSOC subset

Median Duration of Response (mDOR) by FRα Expression and Platinum Status

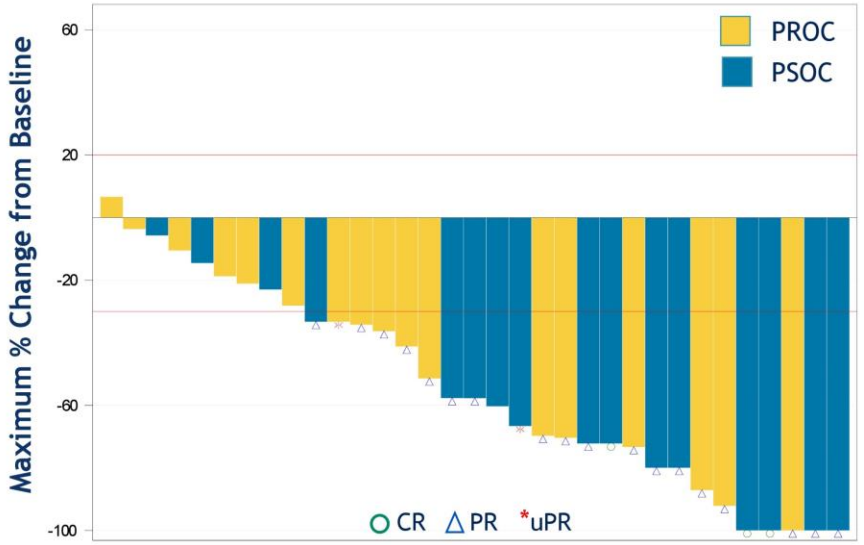


- **9.7 mo mDOR** for overall cohort
- **11.8 mo mDOR** in high FRα tumors
  - **9.4 mo mDOR** in PROC subset
  - **12.7 mo mDOR** in PSOC subset

*Upper limit of 95% confidence interval not reached

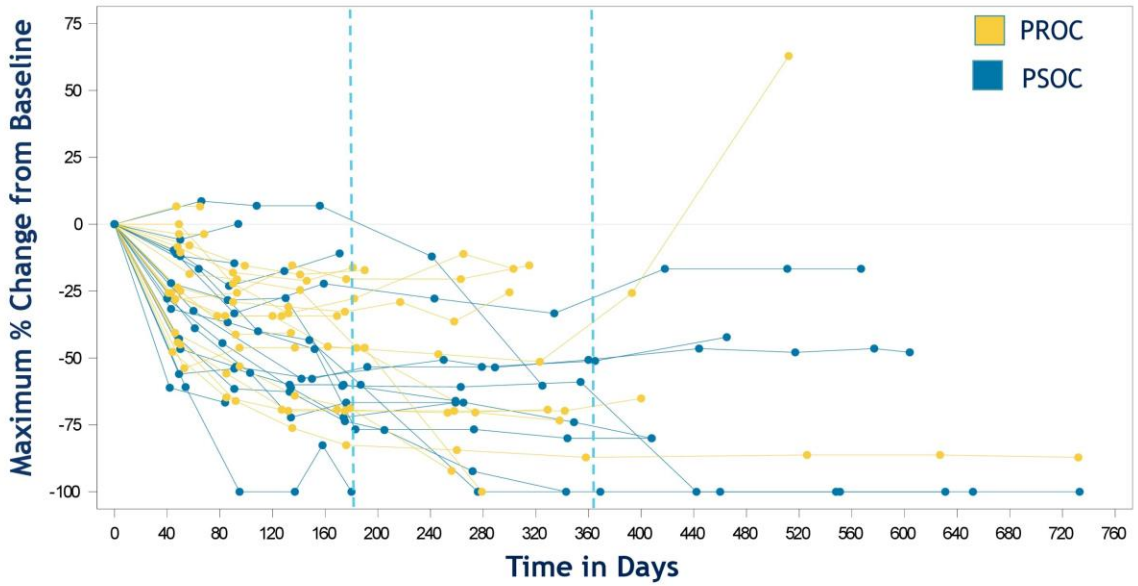
High FRα Tumors Showed a Deep Response and Durable Benefit

Maximum % Change from Baseline



- **97% (32/33)** of patients demonstrated tumor burden reduction

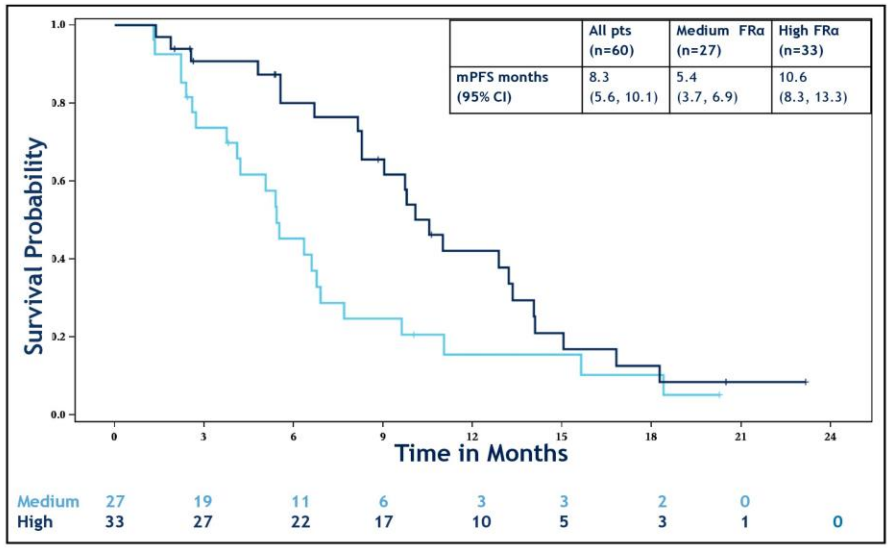
Percent Change and Duration from Baseline



- Rapid tumor shrinkage, with early responses
- Durable benefit in both PSOC and PROC

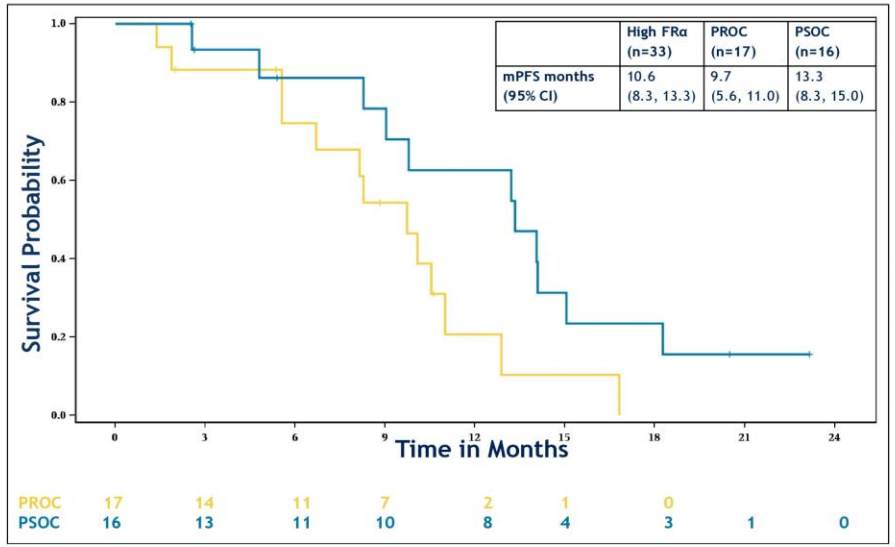
Longer PFS in High FRα Tumors Regardless of Platinum Status

Medium and High FRα Tumors



- mPFS 10.6 months in high FRα tumors
- mPFS 5.4 months in medium FRα tumors
- High FRα 6-month and 12-month PFS rate of 80% and 42%, respectively

High FRα Tumors (PROC and PSOC)



- mPFS 9.7 months in high FRα PROC tumors
- mPFS 13.3 months in high FRα PSOC tumors

mPFS = median progression free survival

Treatment-Related Emergent Adverse Events >20%

N=60	All Grades	Grade 3/4
Adverse Event	N (%)	N (%)
Diarrhea^	37 (62)	1 (2)
Blurred vision	36 (60)	0 (0)
Fatigue^	36 (60)	2 (3)
Nausea	34 (57)	0 (0)
Keratopathy†	26 (43)	0 (0)
Peripheral neuropathy*	24 (40)	1 (2)
Dry eye	20 (33)	3 (5)
Decreased appetite	20 (33)	0 (0)
Hypertension^	19 (32)	10 (17)
Headache	17 (28)	0 (0)
AST increased	17 (28)	2 (3)
Vomiting	17 (28)	0 (0)
Abdominal pain	16 (27)	0 (0)
Visual acuity reduced	14 (23)	0 (0)
Thrombocytopenia	14 (23)	2 (3)
Neutropenia	13 (22)	8 (13)
ALT increased	13 (22)	3 (5)
Dysphonia^	13 (22)	0 (0)
Asthenia	13 (22)	0 (0)
Weight decrease^	13 (22)	1 (2)

AST, aspartate aminotransferase; ALT, alanine aminotransferase;
*Includes neuropathy peripheral, peripheral sensory neuropathy, paresthesia, and hypoesthesia
† Includes keratopathy, keratitis, corneal deposits, and corneal epithelial microcysts

- **Most AEs were low grade**
  - GI and Ocular were most frequent
  - Ocular AE class effect of ADC manageable with eye drops
- **Grade 3+ events were infrequent**
  - 17% hypertension
  - 13% neutropenia
- **Eighteen patients (30%) discontinued BEV and/or MIRV** due to treatment-related AEs
  - Discontinuations occurred after a median of 13 cycles of treatment
  - Discontinuations by agent
    - MIRV: 23%
    - BEV: 18%

AE rates are similar for MIRV/BEV compared with MIRV alone (n=243 from FORWARD I), when adjusted for exposure
^Exceptions (p <0.05, not adjusted for multiplicity testing) include Diarrhea, Fatigue, Hypertension, Dysphonia, and Weight Decrease

Conclusions

- MIRV was combined with BEV in a broad population of recurrent ovarian cancer patients in need of more effective non-platinum based treatments

- With a 64% ORR, 11.8 month mDOR, and 10.6 month mPFS, the combination of MIRV with BEV has promising activity in high FRα recurrent ovarian cancer with up to 3 priors, irrespective of platinum status, and is compelling in light of available therapies reported in less heavily pre-treated populations[4,5,6]
    - In high FRα PSOC patients, which represents a growing patient population, the combination of MIRV with BEV achieved a 69% ORR, 12.7 month mDOR and a 13.3 month mPFS
    - In high FRα PROC patients the combination of MIRV with BEV achieved a 59% ORR, 9.4 month mDOR and a 9.7 month mPFS

- Adverse events were manageable and consistent with the side effect profiles of each agent

- The strength of these mature data in a broader population of recurrent ovarian cancer, warrants further development of this novel, targeted combination and supports MIRV as the combination partner of choice for BEV

[4]Pujade-Lauraine *J Clin Oncol* 2014; [5]Aghajanian *J Clin Oncol* 2012; [6]Coleman *Lancet Oncol* 2017

2021 ASCO ANNUAL MEETING

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

PEMBROLIZUMAB IN COMBINATION WITH BEVACIZUMAB AND PEGYLATED LIPOSOMAL DOXORUBICIN IN PATIENTS WITH PLATINUM RESISTANT EPITHELIAL OVARIAN CANCER.

Michels J.[1], Ghiringhelli F.[2], Frenel J.-S.[3], Brard C.[4,5], You B.[6], Floquet A.[7], Eberst L.[8], Rastislav B.[9], Genestie C.[10], Balleyguier C.[11], Broutin S.[12], Pautier P.[1], Colomba E.[1], Pommeret F.[1], Massard C.[9], Marabelle A.[9*] and Leary A.[1*]

[1]Medical oncology department, Gustave Roussy Cancer Campus, Villejuif, France; [2]Medical oncology department, Centre Georges François Leclerc, Dijon, France; [3]Medical oncology department, Institut de Cancérologie de l'Ouest, Saint-Herblain, France; [4]Service de Biostatistique et d'Epidémiologie, Gustave Roussy, Université Paris-Saclay, Villejuif, France; [5]Oncostat U1018, Inserm, Université Paris-Saclay, Equipe Labellisée Ligue Contre le Cancer, Villejuif, France; [6]Medical Oncology, Institut de Cancérologie des Hospices Civils de Lyon (IC-HCL), CITOHL, Université Lyon, EA 3738 CICLY, Lyon, France; [7]Medical oncology department, Institut Bergonié, Bordeaux, France; [8]Institut de Cancérologie de Strasbourg Europe, Département d'oncologie, Strasbourg, France; [9]Early drug development department, Gustave Roussy Cancer Campus, Villejuif, France; [10]Pathology department, Gustave Roussy Cancer Campus, Villejuif, France; [11]Radiology department, Gustave Roussy Cancer Campus, Villejuif, France; [12]Pharmacy, Gustave Roussy Cancer Campus, Villejuif, France

Presented on June, 4th 2021 by Judith Michels ASCO21 Abstract 5522

Platinum resistant epithelial ovarian cancer
Immunotherapy

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

- The AURELIA trial has shown that adding bevacizumab to chemotherapy improved PFS[1].
- Larger phase 1b and 2 studies found a modest effect of anti-PD-1/anti-PD-L1 therapies[2-4] +/- chemotherapy[5,6] or PARP inhibitors[7].
- Promising combination trials to enable the efficacy of anti-PD-1 blockade with anti-CTLA-4 blockade[8] or antiangiogenic agents[9].

[1]Pujade-Lauraine E et al, 2014; [2]Hamanishi J. et al, 2015; [3]Disis et al, 2019; [4]Matulonis UA et al, 2019; [5]Pujade-Lauraine E et al, SGO 2019; [6]Lee E.K. et al, 2020; [7]Lampert EJ et al, 2020; [8]Zamarin D. et al, 2020; [9]Zsiros E.et al, 2020.

CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival; PD-1, programmed death 1; PD-L1, programmed death ligand 1; ORR, overall response rate;

Study design

NCT03596281 open-label, phase Ib trial, conducted in two phases, with a modified toxicity probability interval design, in heavily pretreated patients with platinum resistant OC

Drug escalation phase

- Pembrolizumab + PLD
- Pembrolizumab + bevacizumab
- Pembrolizumab + bevacizumab + PLD at MTD-1

PLD 20mg/m2

Primary objective

- Safety/Tolerability, RP2D

Key secondary objectives

- BOR per RECIST v1.1

Expansion phase

- Pembrolizumab + Bevacizumab + PLD at MTD

PLD 30mg/m2

Primary objective

- BOR per RECIST v1.1
- Duration of response

Key secondary objectives

- Safety/Tolerability

Key exploratory objectives

- PD-L1 status
- pharmacokinetic of bevacizumab

Pembrolizumab 200mg Q3W until a discontinuation criteria
PLD Q3W until a discontinuation criteria
Bevacizumab 400mg Q3W for a total of six doses.

BOR, best overall response; MTD, maximum tolerated dose; PD-L1, programmed death-ligand 1; PLD, pegylated liposomal doxorubicine; RP2D, recommended phase 2 dose;

Baseline characteristics

Characteristics	N=22
Median age (range), years	70 (47-77)
ECOG performance status, n (%)	
0	17 (77)
1	5 (23)
Primary tumor type: ovary, n (%)	22 (100)
Histology at diagnosis	
Serous high grade, n (%)	20 (91)
Clear cell, n (%)	2 (9)
BRCA mutations	
BRCA1[1], n (%)	3 (14)
BRCA2[2], n (%)	1 (5)
no, n (%)	15 (68)
Prior antiangiogenic therapy, n (%)	18 (82)
Prior treatment with PARP inhibitors, n (%)	9 (41)
Prior chemotherapy regimens	
1, n (%)	9 (41)
≥2, n (%)	12 (54)

- Prior treatment regimens, median 3, range 1-13
- Most patients (82%) were previously challenged with antiangiogenic agents

[1]Two germline and one somatic,
[2]One somatic

Safety: Treatment-related adverse events

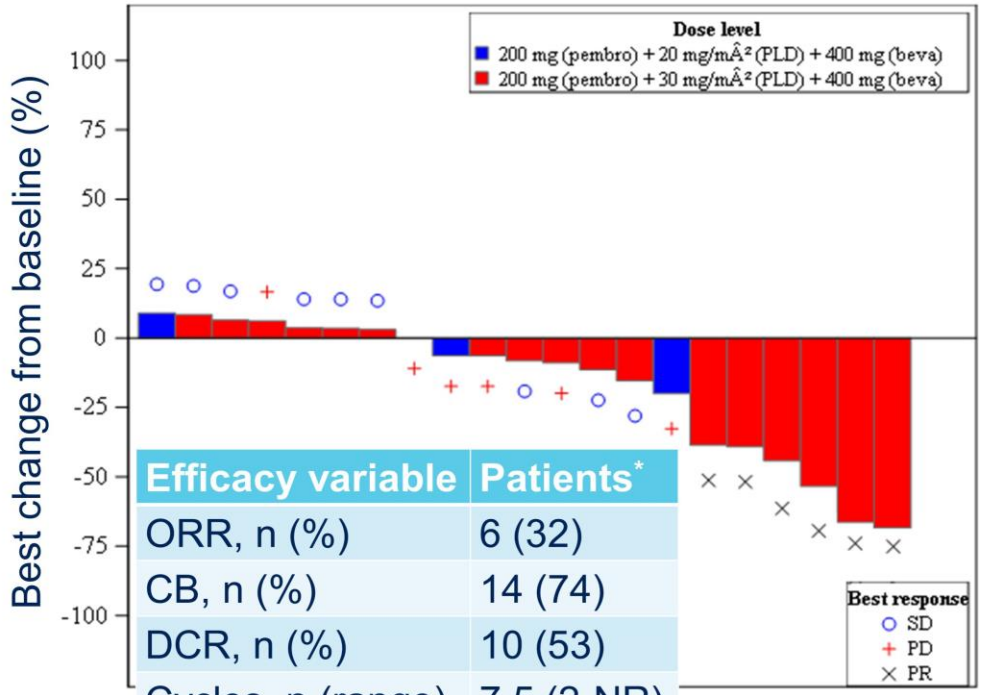
TRAE, n (%)	Grade 3
Any	11 (50)
Palmar-plantar erythrodysesthesia syndrome	3 (14)
Hypertension	2 (9)
Thromboembolic event	1 (5)
Cerebellar disorder	1 (5)
Hyperthyroidism	1 (5)
Hyponatremia	1 (5)
Thrombopenia	1 (5)
Neutropenia	1 (5)

- Toxicity profile similar to bevacizumab[1], PLD[2], and pembrolizumab[3]
- No Dose limiting toxicity
- No grade 4 toxicity

[1]Perren T.J. et al, NEJM 2011; [2]Pujade-Lauraine E et al JCO 2010; [3]Matulonis U.A. et al, Annals 2019

Tumor response according to investigator assessment

Waterfall plot - Change from baseline to the BOR

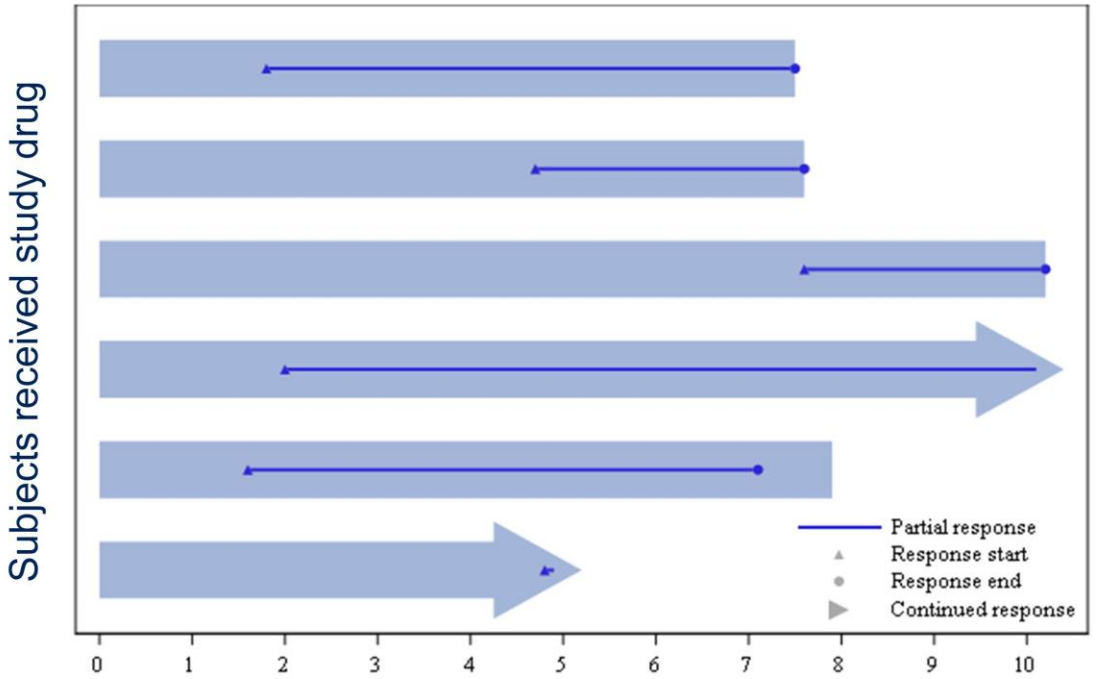


Efficacy variable	Patients*
ORR, n (%)	6 (32)
CB, n (%)	14 (74)
DCR, n (%)	10 (53)
Cycles, n (range)	7.5 (2-NR)

*treated at MTD (n=19)

Patient

Swimmer plot - Duration of response



Months

BOR, best overall response; CB, clinical benefit (PR+SD≥6 months); DCR, disease control rate (PR+SD); MTD, maximum tolerated dose; NR, not reached; ORR, overall response rate (PR) per RECIST v1.1; PR, partial response; SD, stable disease;

Conclusions

- RP2D of PLD 30mg/m2 in combo with pembrolizumab and bevacizumab q3w
- No DLT and no new safety signals were observed

- Pembrolizumab+bevacizumab+PLD showed clinical activity in heavily pretreated platinum resistant ovarian cancer patients, including those priorly treated with antiangiogenic therapy, with 32% of ORR, 74% of CB and 53% of DCR

- Further exploratory analysis are evaluated
- An expansion cohort with pembrolizumab+bevacizumab is ongoing

Gynecologic Cancers Highlights

Ovarian Cancer

- Bevacizumab Maintenance – 15 vs 30 months
- PARP Inhibitors
  - PAOLA-1 – PFS2 update
  - EFFORT Trial – PARP Resistant Population
  - CAPRI Study – PARP Resistant Population
- VITAL – Tumor Plasmid vaccine
- SOVO1 – Dendritic vaccine trial
- Mirvetuximab + Bevacizumab - Final Analysis
- Pembrolizumab + Liposomal Doxorubicin + Bevacizumab

Uterine Cancer

- TOTEM – Surveillance Study
- TAPUR – HER2 targeted therapy

Cervical Cancer

- OUTBACK
- GX-188E – DNA vaccine + Pembrolizumab
- ANLOTINIB+sintilimab

2021 ASCO ANNUAL MEETING

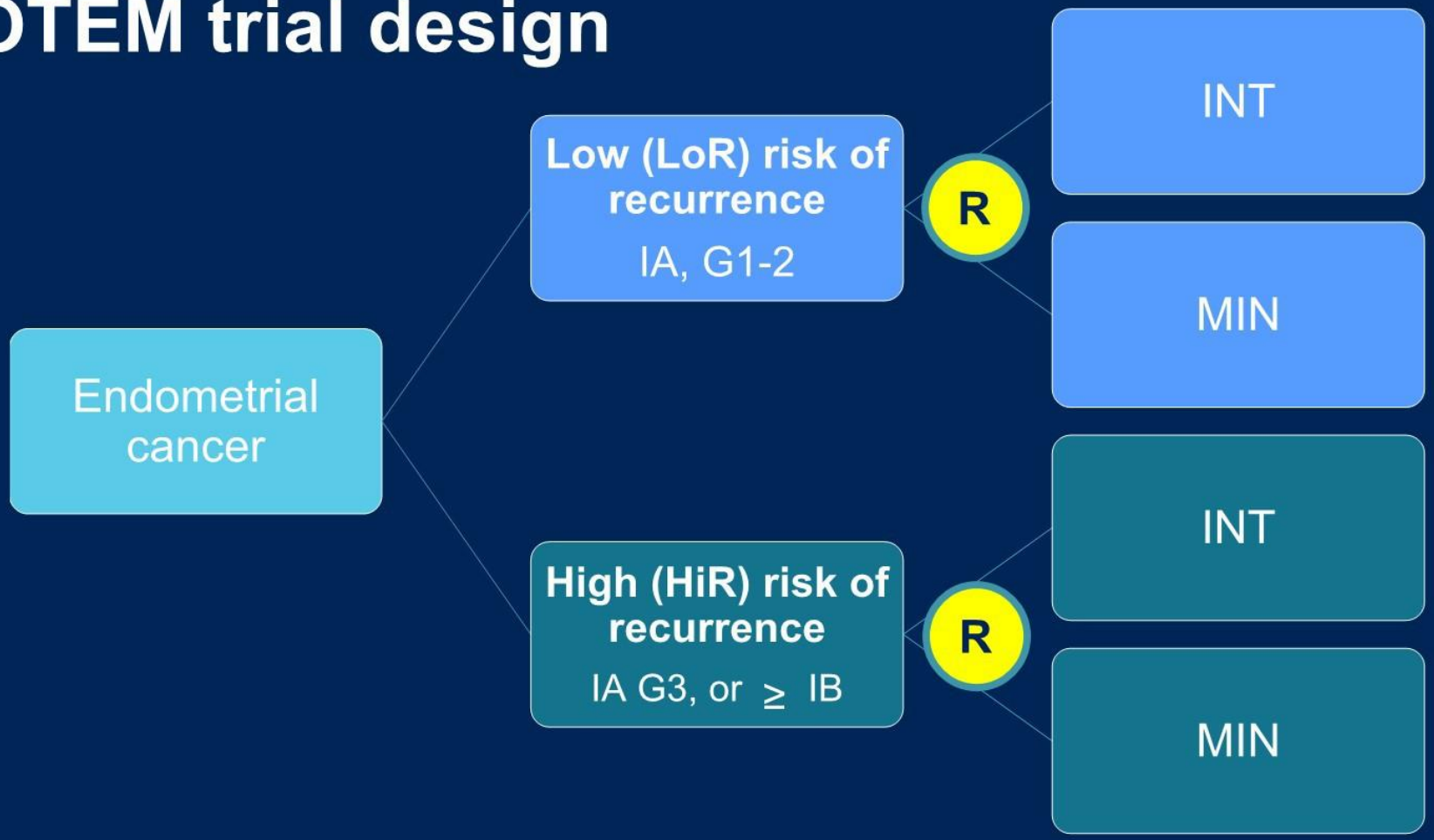
INTENSIVE VERSUS MINIMALIST FOLLOW-UP IN PATIENTS TREATED FOR ENDOMETRIAL CANCER: A MULTICENTRIC RANDOMIZED CONTROLLED TRIAL *THE TOTEM STUDY - NCT00916708*

Paolo Zola,

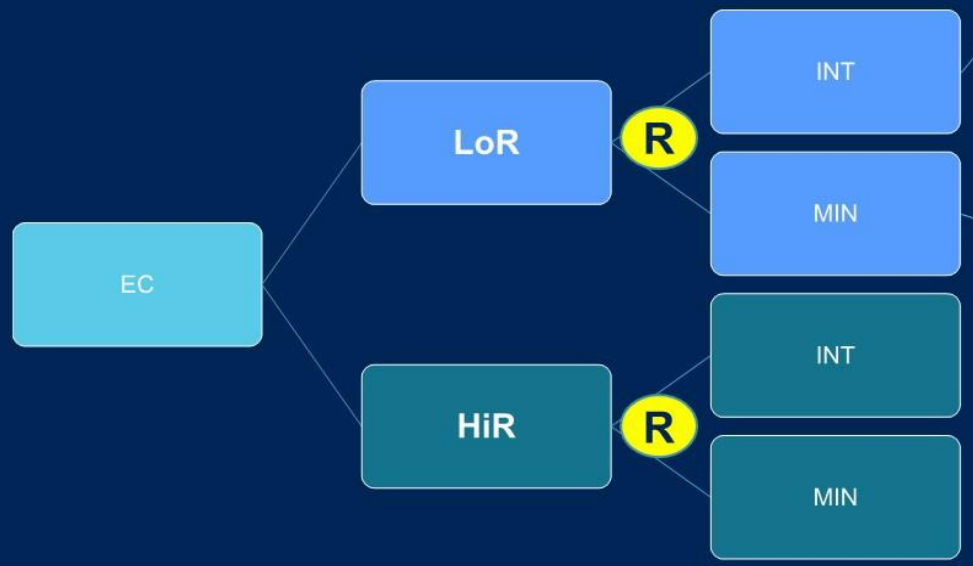
Gynecologic Oncology Unit, Dep. Surgical Sciences, University Of Turin, Italy

07th June, 2021

TOTEM trial design



follow-up program

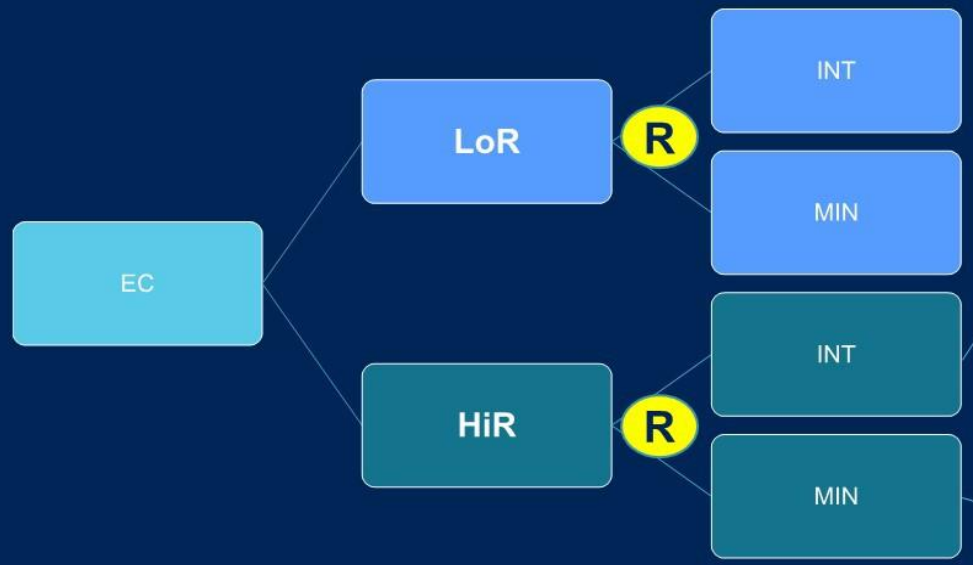


	Months since randomization														
PROCEDURES	0	4	6	8	12	16	18	20	24	30	36	42	48	54	60
Clinical Examination	X	X		X	X	X		X	X	X	X	X	X	X	X
Pap Smear					X				X		X		X		X
CT chest, abdomen, pelvis					X				X						

	Months since randomization														
PROCEDURES	0	4	6	8	12	16	18	20	24	30	36	42	48	54	60
Clinical Examination	X		X		X		X		X	X	X	X	X	X	X

In case of clinical suspicion or abnormal test results further unscheduled exams were allowed

follow-up program



	Months since randomization																
PROCEDURES	0	4	6	8	12	16	18	20	24	28	30	32	36	42	48	54	60
Clinical Examination	X	X		X	X	X		X	X	X		X	X	X	X	X	X
Ca125		X		X	X	X		X	X	X		X	X	X	X	X	X
Abdomen & TV US		X		X		X		X		X		X		X		X	
Pap Smear					X				X				X		X		X
CT chest, abdomen, pelvis					X				X				X		X		X

	Months since randomization																
PROCEDURES	0	4	6	8	12	16	18	20	24	28	30	32	36	42	48	54	60
Clinical Examination	X	X		X	X	X		X	X		X		X	X	X	X	X
CT chest, abdomen, pelvis					X				X								

In case of clinical suspicion or abnormal test results further unscheduled exams were allowed

Endpoints

Primary endpoint:

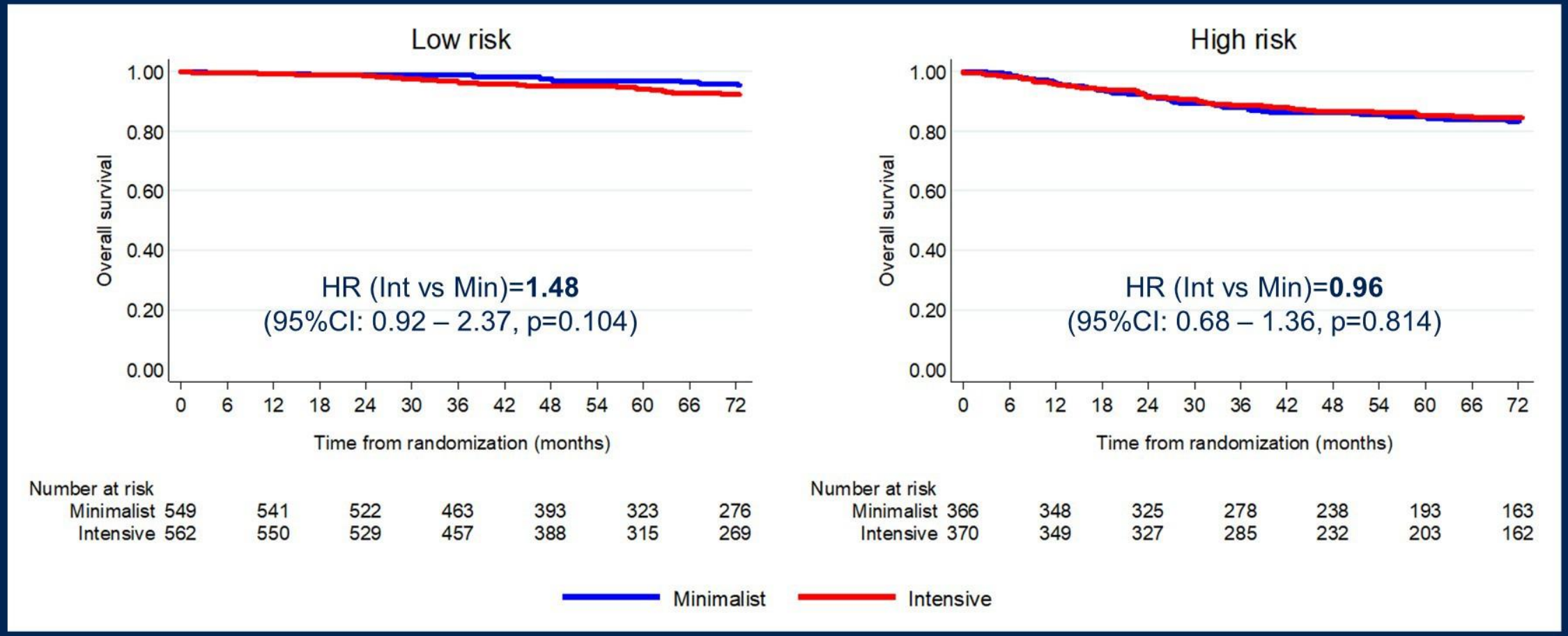
- ✓ Overall survival (OS): time from randomization to death or last verification of vital status

The vital status was checked at the local registries for all Italian patients

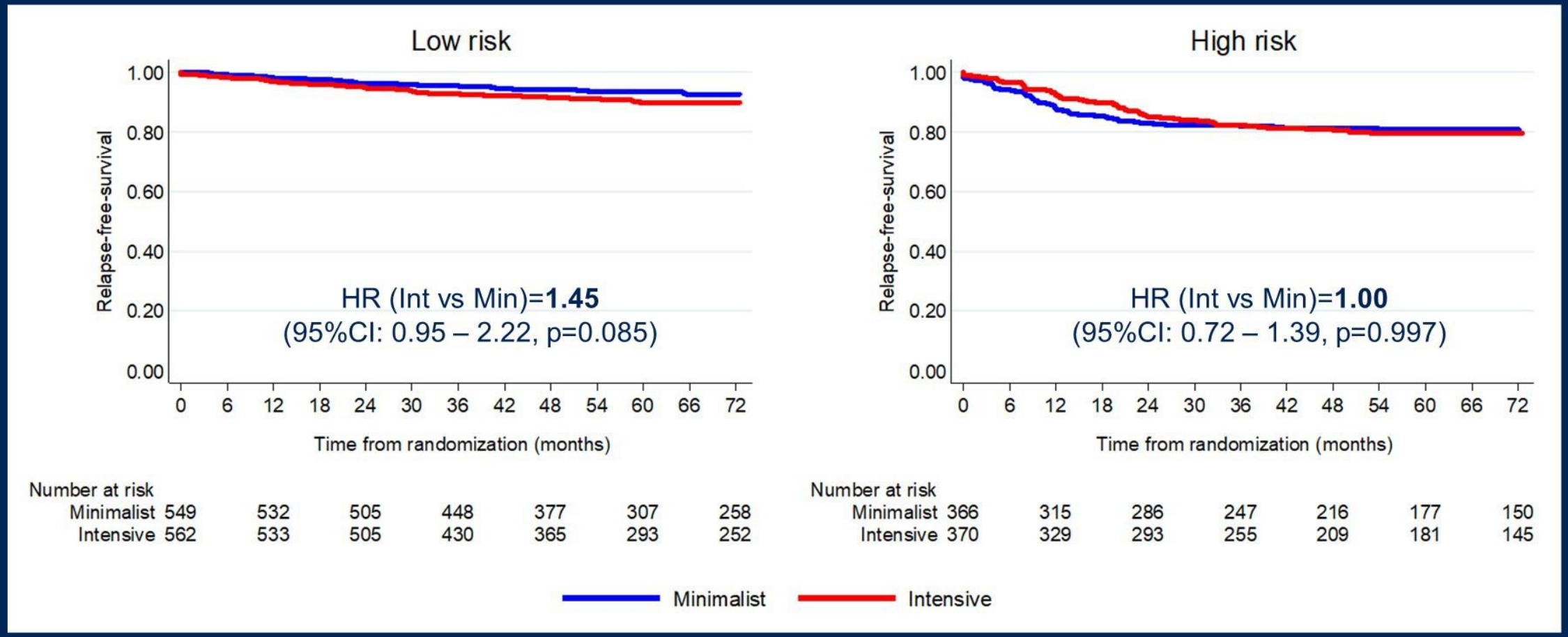
Secondary endpoints:

- ✓ Relapse free survival (RFS): time from randomization to endometrial cancer relapse or death from any cause
- ✓ Health-related quality of life (HRQL): SF-12, PGWBI
- ✓ Compliance to the follow-up program
- ✓ Costs

Overall survival, by risk



Relapse Free Survival, by risk



Conclusions

- ✓Intensive follow-up in endometrial cancer treated patients does not improve OS, even in HiR patients
- ✓The HRQL, in our study, is not influenced by different regimens of follow-up
- ✓According to our data there is no need to routinely add vaginal citology, laboratory or imaging investigations to the minimalist regimens used in this trial

2021 ASCO ANNUAL MEETING

PERTUZUMAB PLUS TRASTUZUMAB IN PATIENTS WITH UTERINE CANCER WITH *ERBB2* OR *ERBB3* AMPLIFICATION, OVEREXPRESSION OR MUTATION: RESULTS FROM THE TARGETED AGENT PROFILING AND UTILIZATION REGISTRY (TAPUR™) STUDY

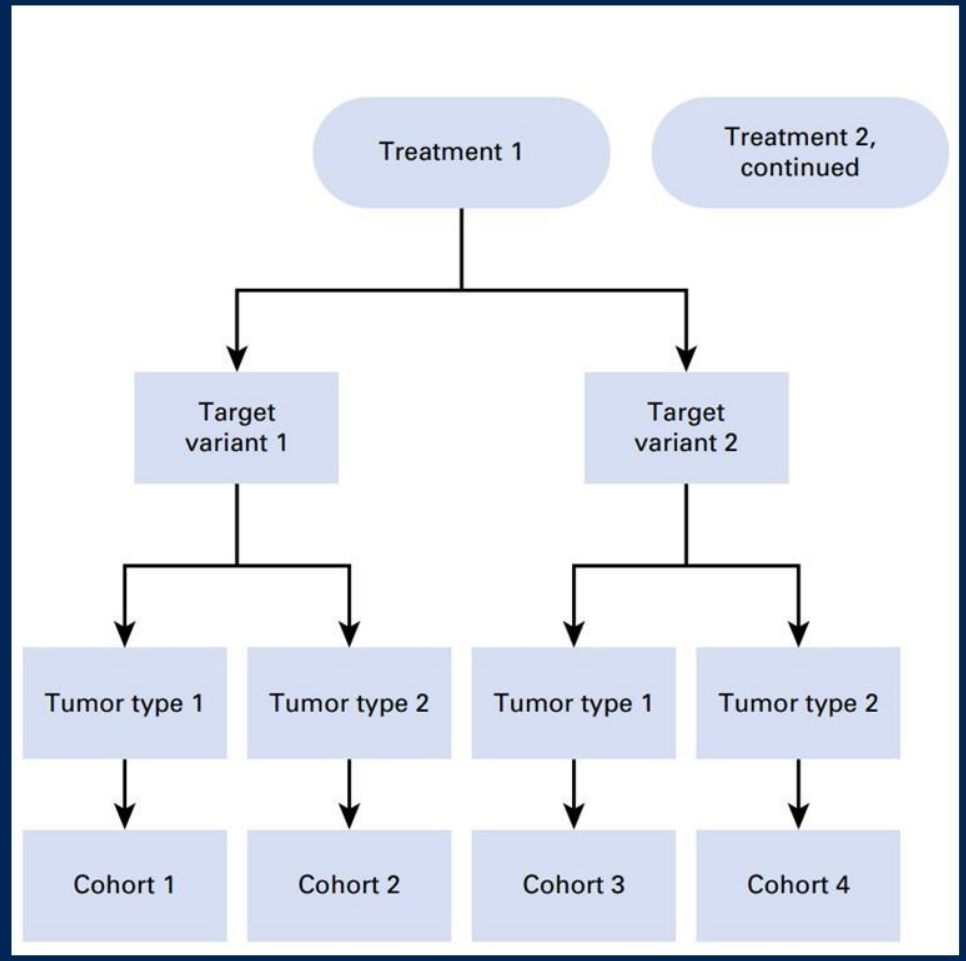
ASCO TAPUR™
Targeted Agent and Profiling Utilization Registry Study

Hussein Moustapha Ali-Ahmad, MD, Michael Rothe, MS, Pam K. Mangat, MS, Elizabeth Garrett-Mayer, PhD, Eugene R. Ahn, MD, John Chan, MD, Michael L. Maitland, MD, PhD, Ani S. Balmanoukian, MD, Sapna R. Patel, MD, Zachary Reese, MD, Charles W. Drescher, MD, Charles A. Leath III, MD, Rui Li, MD, Apostolia Maria Tsimberidou, MD, PhD, Richard L. Schilsky, MD, FACP, FSCT, FASCO

June 7, 2021

TAPUR Study

- Non-randomized, phase II, basket trial
- 18 treatments
- 85+ genomic targets
- All solid tumors
- Pre-specified genomic matching rules and eligibility criteria
- Virtual Molecular Tumor Board



Primary Objective and Study Endpoints

- **Objective: Evaluate the anti-tumor activity of commercially available targeted agents in patients with advanced cancers with specific genomic alterations**
- **Primary Endpoint: Disease control (DC) defined as objective response (OR) or stable disease (SD) at 16+ weeks per RECIST v1.1**
- **Other Endpoints:**
  - Progression free survival (PFS)
  - Overall survival (OS)
  - Grade 3-5 adverse events (AEs) or serious adverse events (SAEs) at least possibly related to Pertuzumab + Trastuzumab are reported

Key Eligibility Criteria and Treatment Administration

- Advanced uterine cancer
- ECOG Performance Status 0-2
- Adequate organ function
- Measurable disease
- Genomic test performed in CLIA-certified, CAP-accredited laboratory
- *ERBB2* or *ERBB3* amplification or overexpression or any of 13 pre-specified *ERBB2* mutations
- Dose administration per package insert (until disease progression)
    - Pertuzumab initial dose of 840 mg IV over 60 min, followed by 420 mg IV over 30-60 min every 3 weeks and Trastuzumab initial dose of 8mg/kg IV over 90 min, then 6mg/kg over 30-60 min every 3 weeks

Demographics and Clinical Characteristics (N=28)

Characteristic[1]		
Age, years	Median (range)	69 (44, 90+)
Sex, N (%)	Male	0 (0)
	Female	28 (100)
Race, N (%)	White	21 (75)
	Black	2 (7)
	Asian	1 (4)
	More than one race	1 (4)
	Other	2 (7)
	Prefer not to answer	1 (4)
Ethnicity, N (%)	Hispanic or Latino	2 (7)
	Not Hispanic or Latino	25 (89)
	Prefer not to answer	1 (4)
ECOG, PS, N (%)	0	9 (32)
	1	16 (57)
	2	3 (11)
Number of prior systemic treatments, N(%)	1-2	12 (43)
	≥3	16 (57)

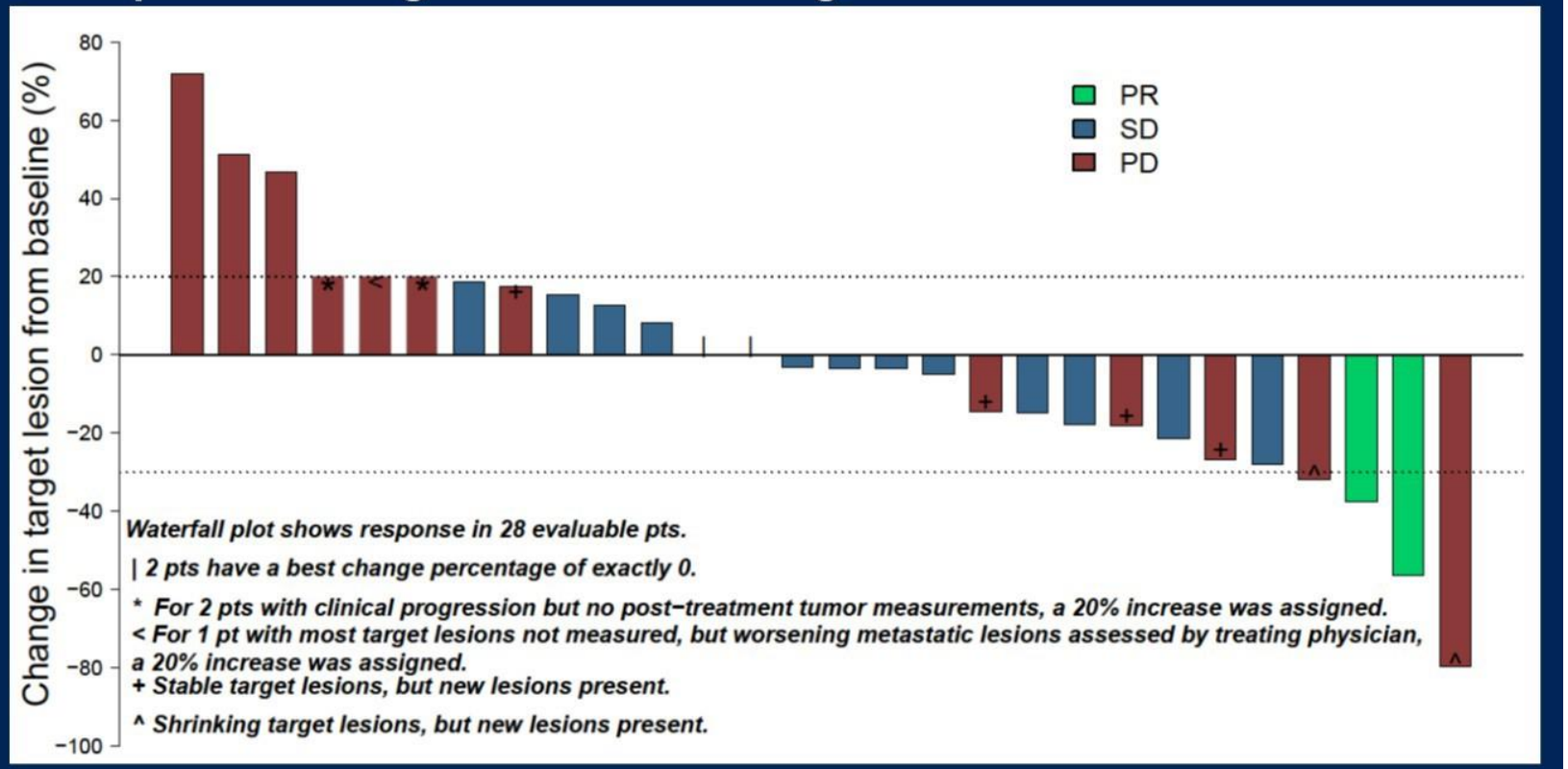
Characteristic[1,2]	
Genomic alteration, N (%)	
ERBB2 amplification	21 (75)
ERBB2 overexpression	1 (4)
ERBB2 mutations	4 (14)
ERBB3 amplification	1 (4)
ERBB2 amplification and mutation	1 (4)

[1]Percentages may not add up to 100% due to rounding.
[2]Of 5 patients with tumors with *ERBB2* mutations, there were 2 tumors with V842I, 2 tumors with S310F, and 1 tumor with R678Q

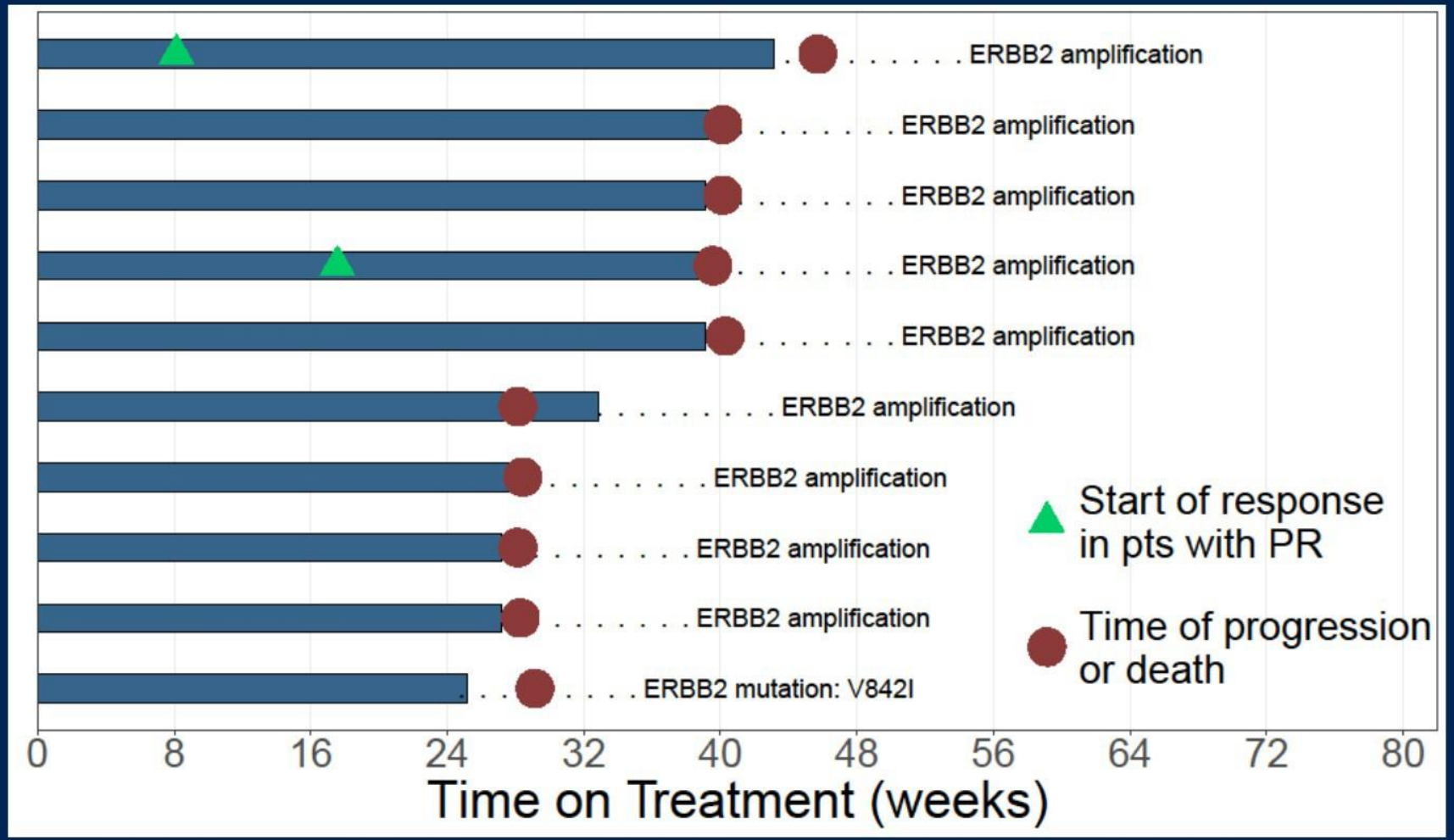
Efficacy Outcomes

Efficacy Outcomes (N=28)	
DC rate, % (95% CI)	37 (21, 50)
OR rate, % (95% CI)	7 (1, 24)

Best percent change from baseline target lesion size N=28



Time on Treatment in Pts with SD16+ or OR (n=10)



Conclusions

- Pertuzumab + Trastuzumab demonstrated anti-tumor activity in heavily pre-treated patients with uterine cancer with *ERBB2* amplification and/or certain mutations
- Additional study warranted to confirm the efficacy of Pertuzumab + Trastuzumab in this patient population

Gynecologic Cancer Highlights

Ovarian Cancer

- Bevacizumab Maintenance – 15 vs 30 months
- PARP Inhibitors
  - PAOLA-1 – PFS2 update
  - EFFORT Trial – PARP Resistant Population
  - CAPRI Study – PARP Resistant Population
- VITAL – Tumor Plasmid vaccine
- SOVO1 – Dendritic vaccine trial
- Mirvetuximab + Bevacizumab - Final Analysis
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Uterine Cancer

- TOTEM – Surveillance Study
- TAPUR – HER2 targeted therapy

Cervical Cancer

- OUTBACK
- GX-188E – DNA vaccine + Pembrolizumab
- ANLOTINIB+sintilimab

2021 ASCO ANNUAL MEETING

Adjuvant chemotherapy following chemo-radiation as primary treatment for locally advanced cervical cancer compared to chemo-radiation alone: The randomised phase 3 OUTBACK Trial (ANZGOG 0902, RTOG 1174, NRG 0274)

Linda Mileshkin*, Kathleen N Moore*, Elizabeth H Barnes, Val Gebski, Kailash Narayan, Nathan Bradshaw Yeh Chen Lee, Katrina Diamante, Anthony Fyles, William Small Jr, David K Gaffney, Pearly Khaw, Susan Brooks, Spencer Thompson, Warner Huh, Matthew J Carlson, Cara Matthews, Danny Rischin, Martin Stockler, Bradley J Monk

6th June, 2021

* Equal; first authors

ANZ GOG

NRG ONCOLOGY
Advancing Research. Improving Lives.™

GCIG GYNECOLOGIC CANCER INTERGROUP

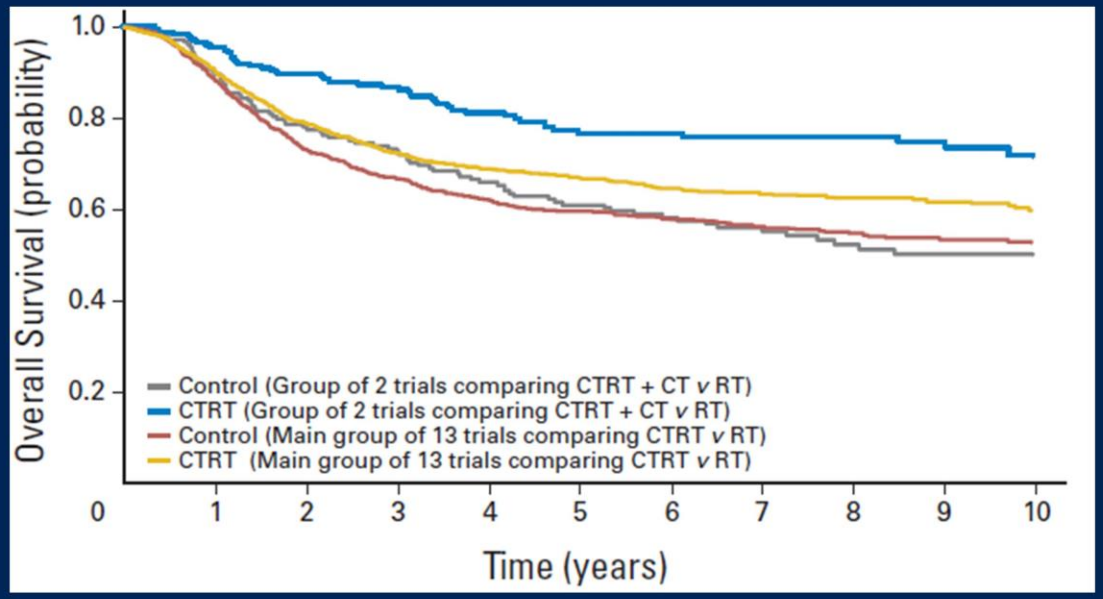
NHMRC Clinical Trials Centre

How can we reduce distant failures?

2008 meta-analysis also suggested more benefit in the 2 trials that gave cycles of additional adjuvant chemo ('OUTBACK')[1] absolute 5-year OS benefit of 19%

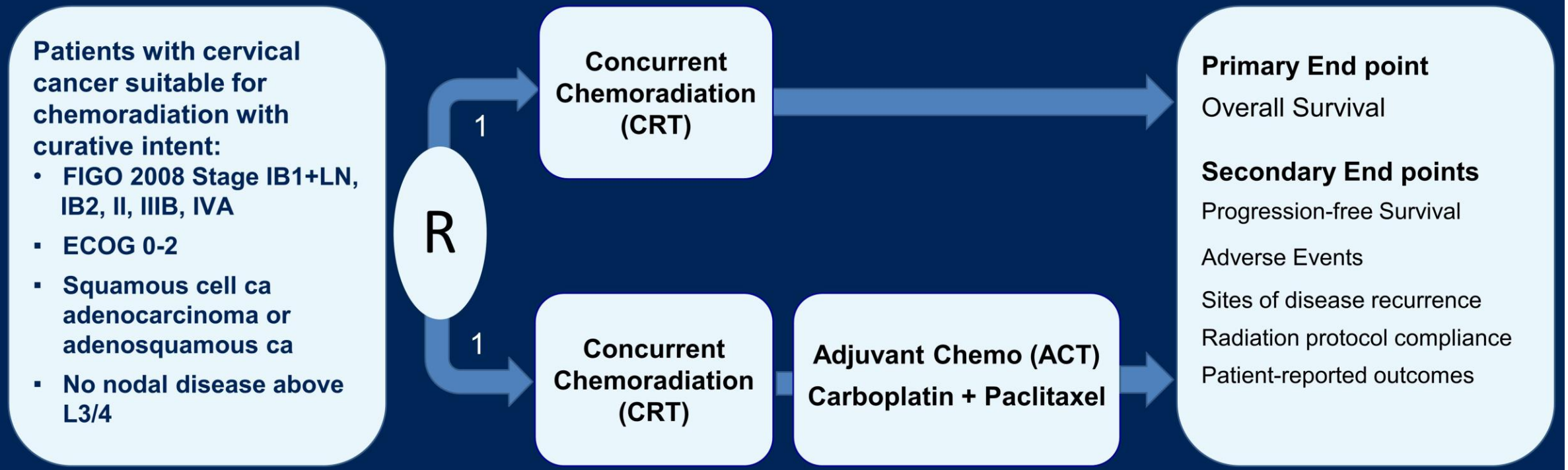
A subsequent randomized trial suggested additional benefit from the use of concurrent cisplatin-gemcitabine followed by 2 cycles of cisplatin-gemcitabine[2]

9% improvement in PFS and OS at 3 yrs



1. Chemoradiotherapy for cervical cancer meta-analysis collaboration, JCO 2008
2. Duenas-Gonzalez et al, JCO 2011

OUTBACK Schema



Stratification Factors

- Pelvic or common iliac nodal involvement
- Requirement for extended-field radiotherapy
- FIGO 2008 stage: IB/IIA or IIB or IIIB/IVA
- Age <60 or ≥60 years
- Hospital/site

Trial Objectives

To determine the effects of adjuvant chemotherapy after chemoradiation on

1. Overall survival (primary objective)
2. Progression-free survival
3. Acute and long-term toxicities
4. Patterns of disease recurrence
5. Global health status and quality of life
6. Other patient-reported outcomes, including psycho-sexual health*

To determine associations between outcomes and

7. RT compliance*
8. Post treatment FDG-PET response*
9. Biomarkers from tissue and blood*

* To be reported later

Study Treatments

Standard chemoradiation (CRT) in both treatment groups

- 40-45 Gy of external beam XRT in 20 to 25 fractions including a nodal boost plus brachytherapy
- Cisplatin 40mg/m^2 weekly during XRT

Adjuvant chemotherapy (ACT) after CRT in the experimental group

- Carboplatin AUC 5 and paclitaxel 155 mg/m^2, 3-weekly x 4 cycles

Statistical analysis and sample size

Original Protocol

780 participants (390 per group) for 80% power, 2-sided alpha of 5% for an absolute improvement of 10% in overall survival at 5 years from 63% to 73% with 3 years accrual and median time to recurrence of 12 months

Protocol amended to increase sample size after discussion with the IDSMC (2016)

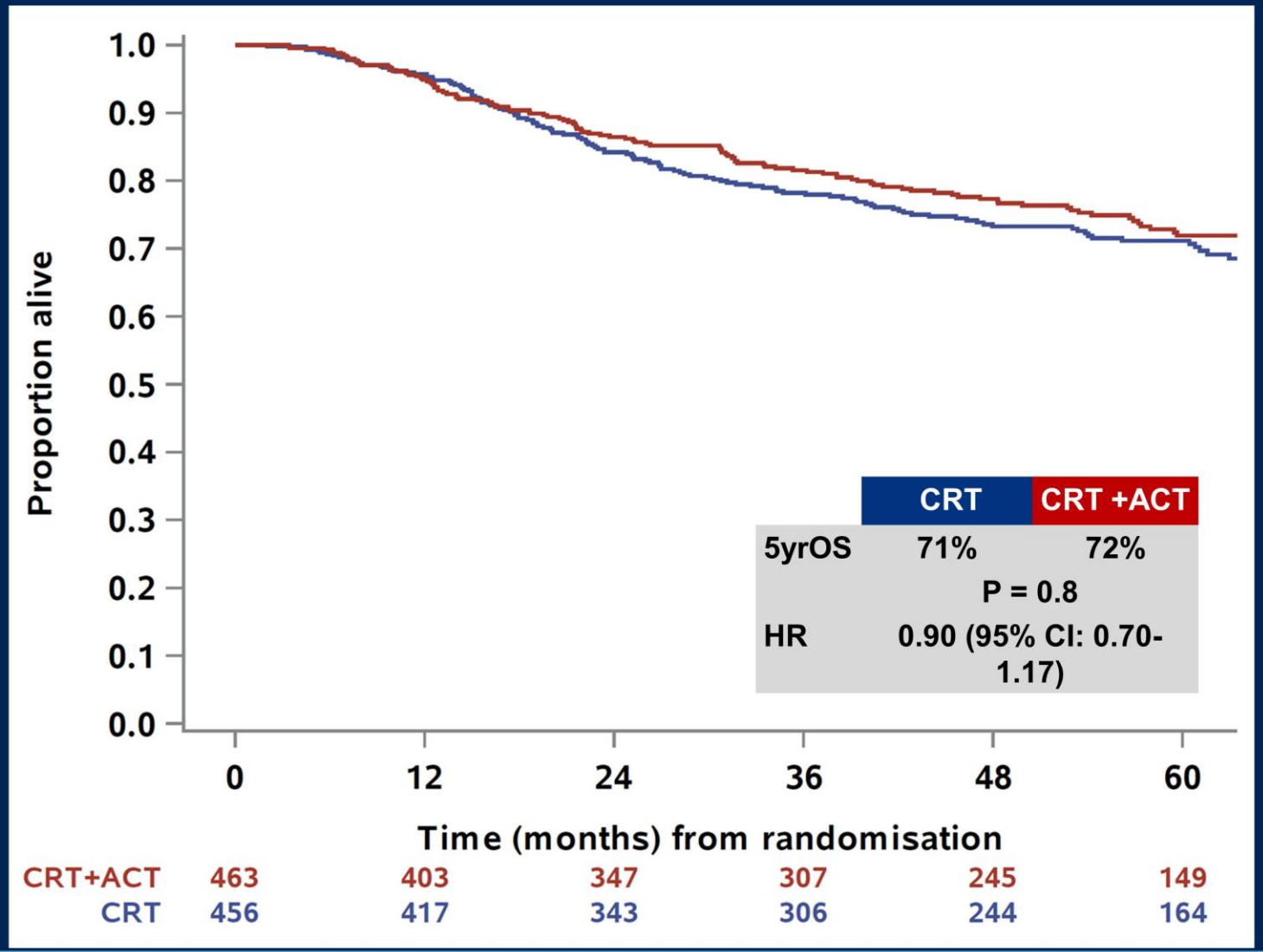
900 participants (450 per group) for 80% power, 2-sided alpha of 5% for an absolute improvement of 8% in overall survival at 5 years from 72% to 80% to account for

a) non-adherence with adjuvant chemotherapy (16% had not started it)

b) lower than expected event rate

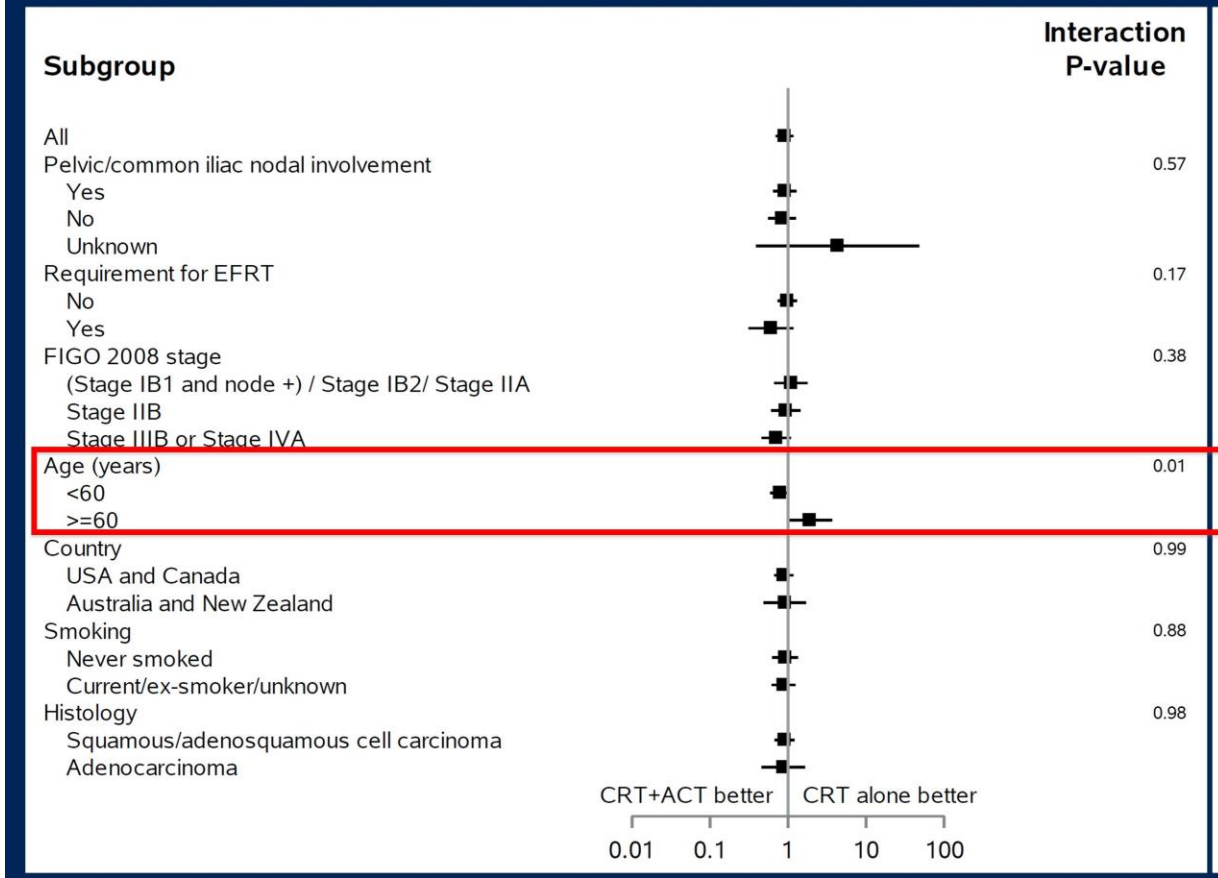
Primary analysis	direct comparison of survival rates at 5 years (Kaplan-Meier method)
Secondary analyses	log-rank test, proportional hazards regression, hazard ratios

Overall Survival

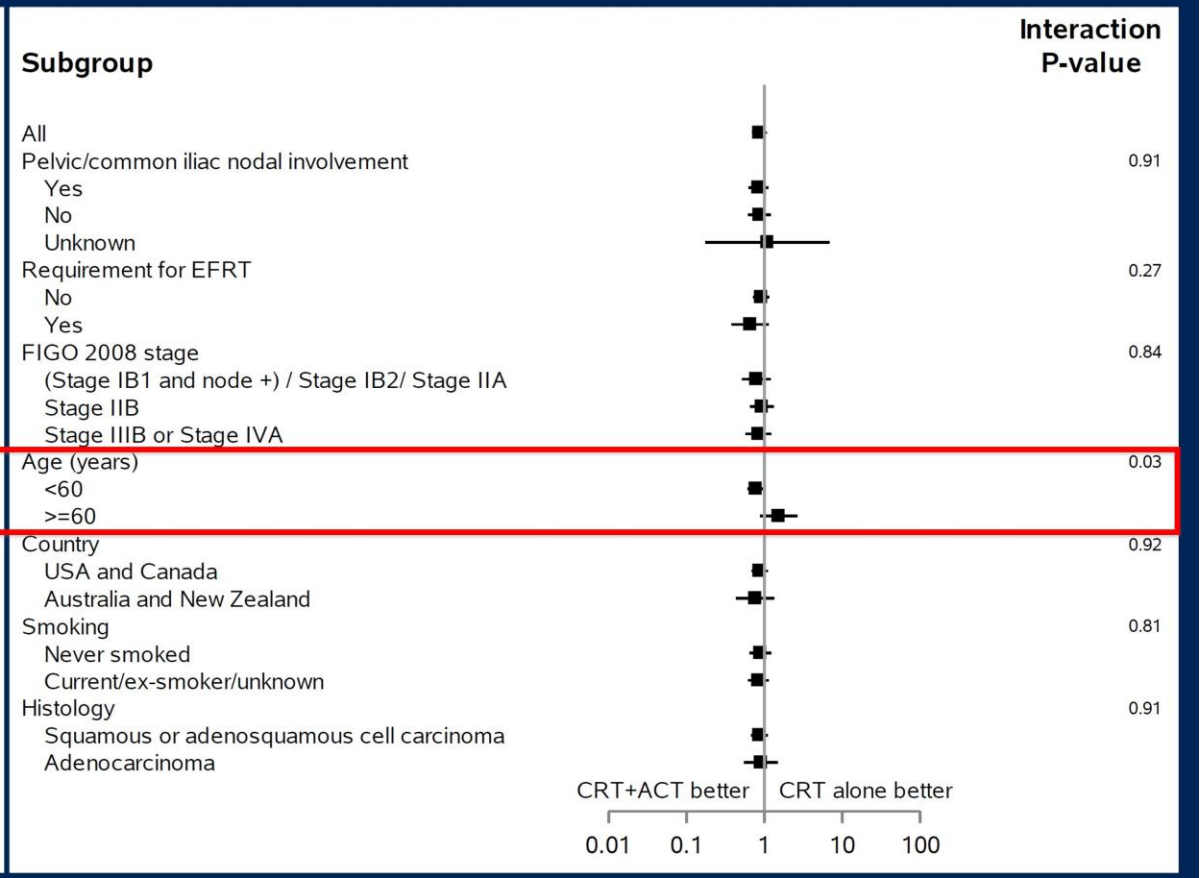


Treatment effect in subgroups

Overall survival



Progression-free survival

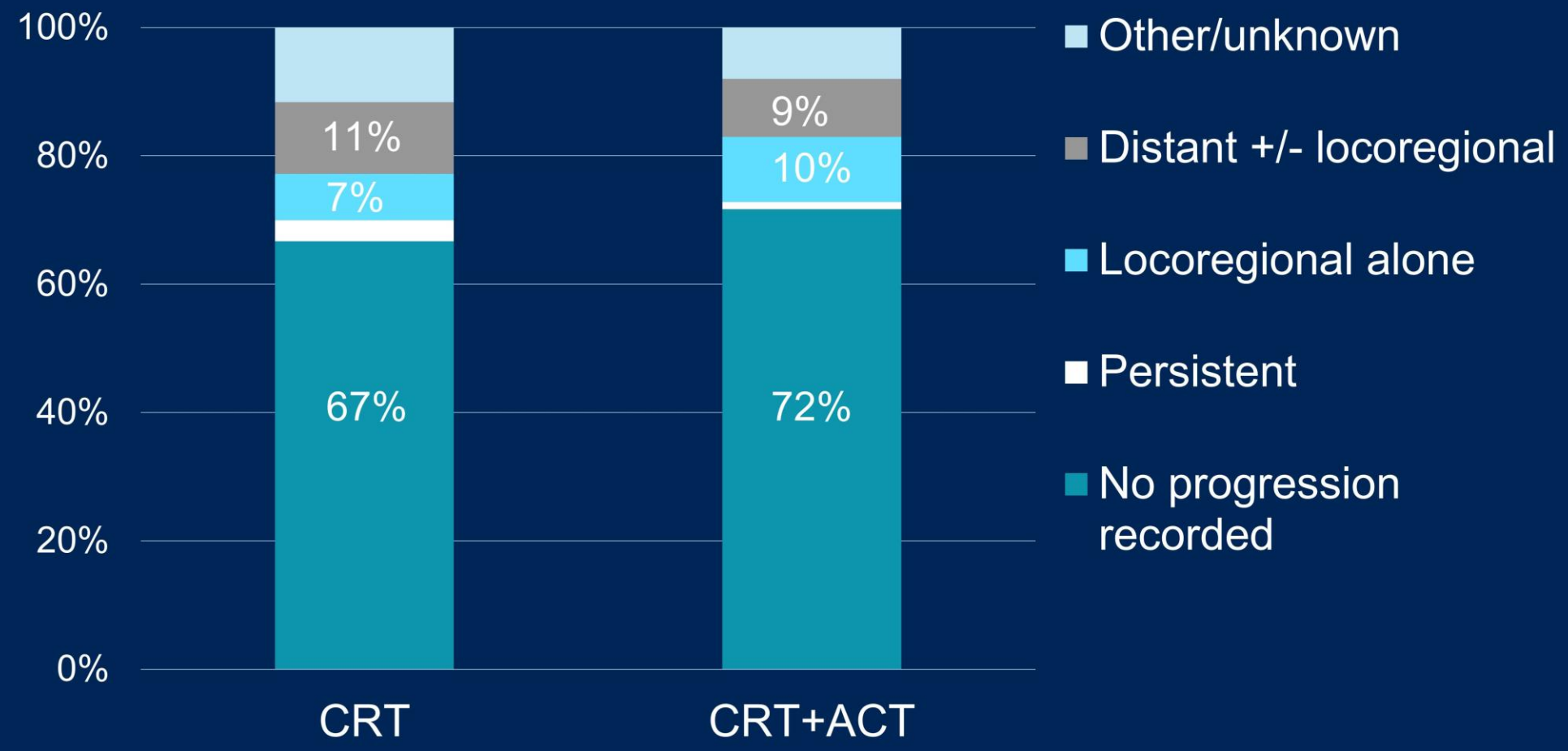


Sensitivity analysis

Effect of ACT in those who did and did not complete CRT

	Survival Rates at 5 years (%)					Hazard ratios from Cox regressions		Interaction P
	CRT	CRT +ACT	Difference	(95% CI)	P	(95% CI)	P	
Overall survival								
Completed CRT	**71%**	**74%**	**+3.3**	**(-4 to 11)**	**0.37**	**0.81 (0.60-1.08)**	**0.15**	0.11
Did not complete CRT	73%	64%	-9.2	(-24 to 5)	0.21	1.32 (0.77-2.25)	0.32	
Progression-Free Survival								
Completed CRT	**62%**	**66%**	**+4.8**	**(-3 to 12)**	**0.22**	**0.78 (0.60-1.00)**	**0.05**	0.12
Did not complete CRT	60%	51%	-8.6	(-23 to 6)	0.26	1.16 (0.75-1.80)	0.49	

Patterns of disease recurrence



Adverse Events in ≥15%

	CRT		CRT+ACT		P-value
Adverse event	**Grade 1-2 n(%)**	**Grade 3-5 n(%)**	**Grade 1-2 n(%)**	**Grade 3-5 n(%)**	
Hematological					
Anemia	**259 (57)**	**35 (8)**	**238 (66)**	**66 (18)**	**<0.0001**
Neutrophil count decreased	**84 (19)**	**34 (8)**	**117 (32)**	**71 (20)**	**<0.0001**
Platelet count decreased	**140 (31)**	**5 (1)**	**192 (53)**	**16 (4)**	**<0.0001**
General					
Alopecia	**40 (9)**		**284 (79)**		**<0.0001**
Fatigue	**361 (80)**	**8 (2)**	**327 (91)**	**9 (2)**	**<0.0001**
Myalgia	**52 (11)**		**141 (39)**	**3 (1)**	**<0.0001**
Dehydration	40 (9)	14 (3)	50 (14)	9 (2)	0.071
Creatinine increased	57 (13)	5 (1)	59 (16)	3 (1)	0.30
Neurological					
Peripheral sensory neuropathy	**130 (29)**	**1 (0)**	**271 (75)**	**16 (4)**	**<0.0001**
Hearing impaired	**47 (10)**		**51 (14)**	**4 (1)**	**0.019**

Febrile neutropenia rate = 2% in both arms

Adverse event	CRT Grade 1-2 n(%)	CRT Grade 3-5 n(%)	CRT+ACT Grade 1-2 n(%)	CRT+ACT Grade 3-5 n(%)	P-value
Gastrointestinal					
Abdominal pain	**179 (40)**	**16 (4)**	**175 (48)**	**19(5)**	**0.0086**
Nausea	**335 (74)**	**14 (3)**	**296 (82)**	**11 (3)**	**0.016**
Vomiting	**165 (36)**	**11 (2)**	**166 (46)**	**15 (4)**	**0.0042**
Diarrhea	323 (71)	21 (5)	277 (77)	21 (6)	0.064
ALT increased	**77 (17)**	**4 (1)**	**98 (27)**	**2 (1)**	**0.002**
Pelvic-related					
Pelvic pain					0.20
Urinary tract pain					**0.039**
Vaginal pain					0.84
Dermatitis radiation	64 (14)	1 (0)	64 (18)	1 (0)	0.37
Cystitis noninfective	102 (23)	6 (1)	95 (26)	6 (2)	0.40
Hemorrhage bladder	76 (17)	7 (2)	54 (15)	5 (1)	0.76
Hemorrhage rectum	62 (14)	2 (0)	65 (18)	1 (0)	0.23
Vaginal discharge	167 (37)		147 (41)		0.26
Vaginal dryness	56 (12)		53 (15)	1 (0)	0.33
Vaginal stricture	57 (13)	10 (2)	39 (11)	5 (1)	0.49

Beyond 1 year, only difference between arms was increased peripheral neuropathy (7% versus 2% grade 2 sensory)
No sign of increased late radiation toxicity

Conclusions and Implications for Practice

Adjuvant chemotherapy given after standard cisplatin-based chemoradiation for women with locally advanced cervical cancer did not improve OS or PFS

Pelvic chemoradiation with concurrent weekly cisplatin continues to be the standard of care for the treatment of locally advanced cervical cancer

These findings do not support the use of adjuvant chemotherapy with carboplatin and paclitaxel after chemoradiation with weekly cisplatin

Further research should focus on adjuvant therapies that may be more tolerable and effective when given after standard therapy

Abstract ID: 5511

Efficacy and safety results of GX-188E, a therapeutic DNA vaccine, combined with pembrolizumab administration in patients with HPV 16- and/or 18- positive advanced cervical cancer: Phase II interim analysis results (KEYNOTE-567)

Jong Sup Park[1], Sooyoung Hur[2], Myong Cheol Lim[3], Yong-Man Kim[4], Jae Hong No[5], Byoung-Gie Kim[6], Chi Heum Cho[7], Sung Hoon Kim[8], Dae Hoon Jeong [9], Jae-Kwan Lee[10], Kyungun Kim [11], Yoon-Jeong Choi[1], You Suk Suh[1], Jung Won Woo[1], and Young Chul Sung[1].

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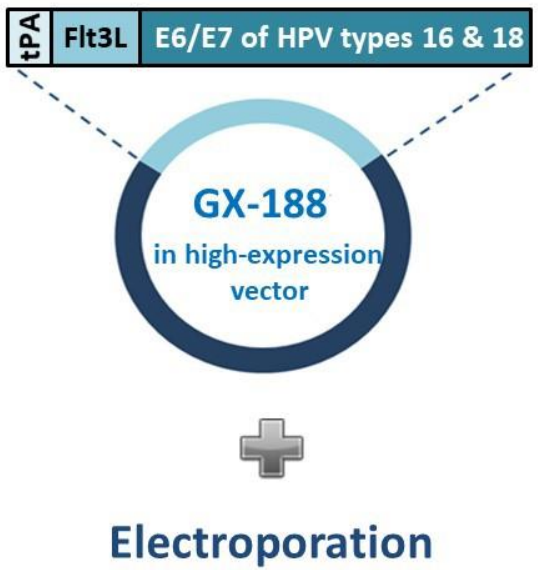
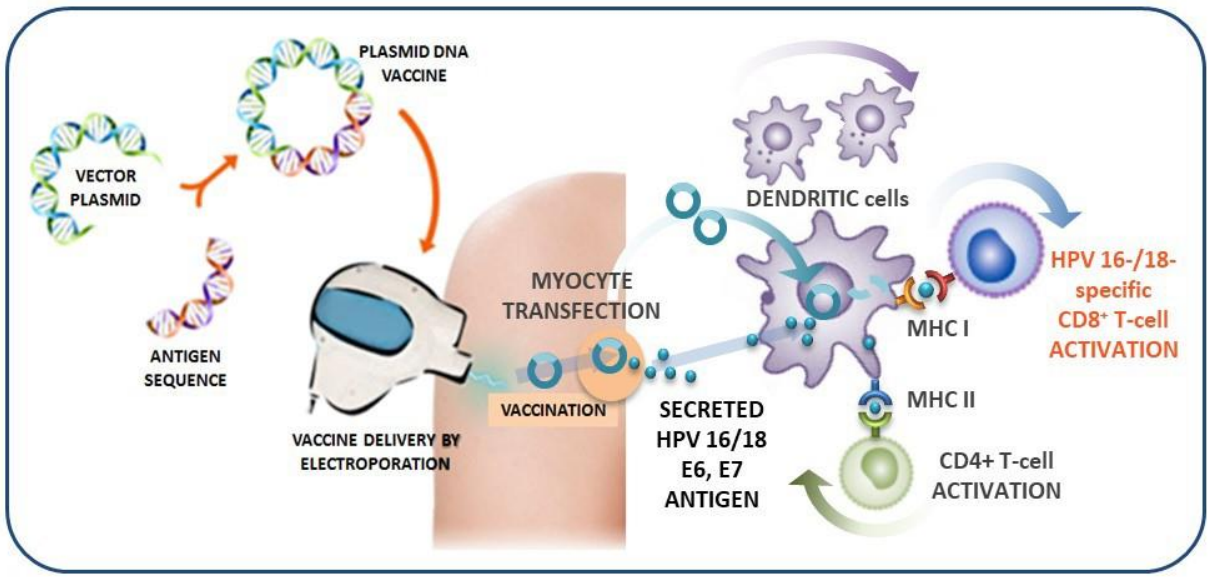
GX-188E
Therapeutic DNA Vaccine for HPV types 16 and 18 caused Diseases

- GX188: Rationally designed DNA vaccine to enhance HPV 16/18, E6- and E7-specific $CD8^+$ T cell responses[1]
- HPV(human papillomavirus) 16 and 18 account for 70% of cervical cancer: also cause oropharyngeal, vaginal, vulvar cancers, etc.[2]
- Anti-PD-1 monotherapy (pembrolizumab) in advanced cervical cancer showed ORR of 12.2% regardless of PD-L1 expression and 14.6% in PD-L1-positive (CPS $\geq$ 1), receiving accelerated approval as 2L (Keynote-158)[3]
- Phase I and II trials of GX-188E demonstrated safety and therapeutic effects in patients with high grade CIN caused by HPV 16/18[1,4]

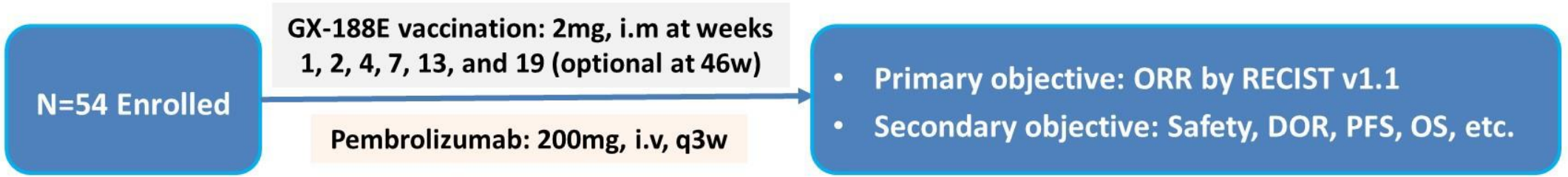




1.Kim TJ et al. (2014) Nat Commun 30:5317 2.Human Papillomavirus and Related Diseases Report, WHO 2019 3.Chung HC et al. (2019) J Clin Oncol 37:1470 4.Choi YJ et al. (2019) Clin Cancer Res 26:1616

Overview of Clinical Study Design (GX-188E + Pembrolizumab)

- Ongoing, phase II, open-label trial of GX-188E + Pembrolizumab treatment (NCT03444376) in previously treated patients with HPV-16-/18-caused advanced cervical cancer. (N=60)



Key Eligibility

- advanced, inoperable or metastatic cervical cancer with failed SOC (≥2L)
- HPV 16 or 18 positive
- ECOG 0 - 1
- ≥ 6 month life expectancy
- measurable by RECIST v1.1

Tumor Assessment

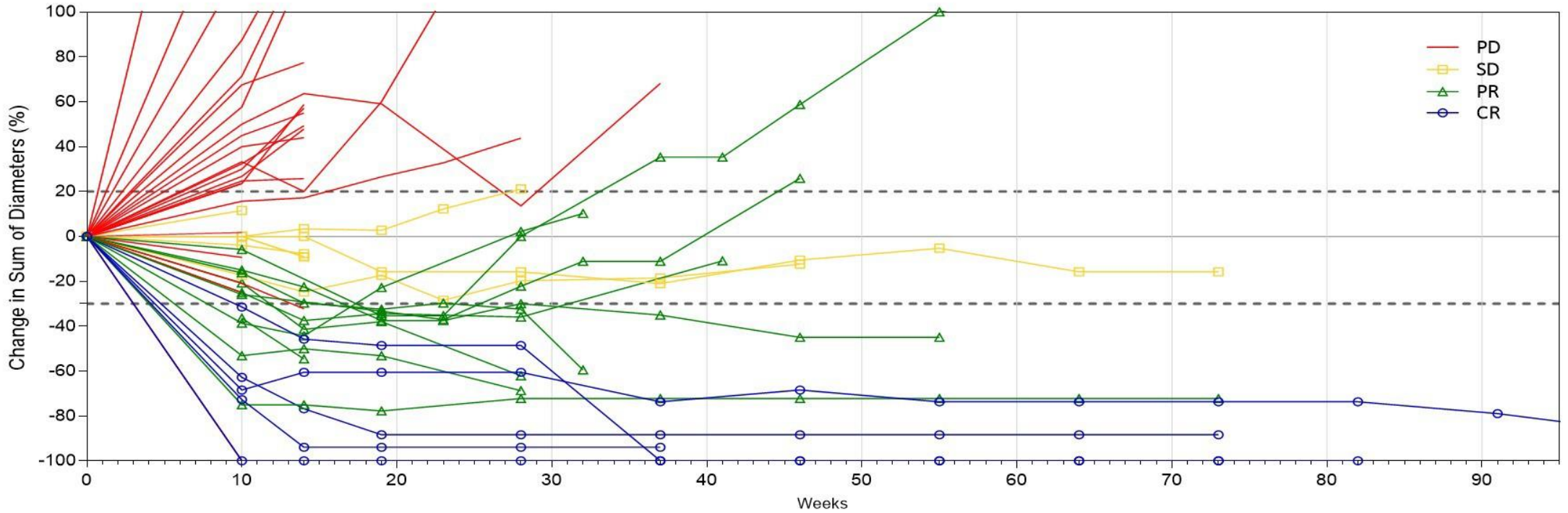
- at 10w and at every 9 weeks afterwards (N=26)
- confirmatory assessment at 4w post progression

Exploratory/Biomarker Objectives

- T cell response
- PD-L1, CEA, TA4, etc.

Change in Tumor Burden

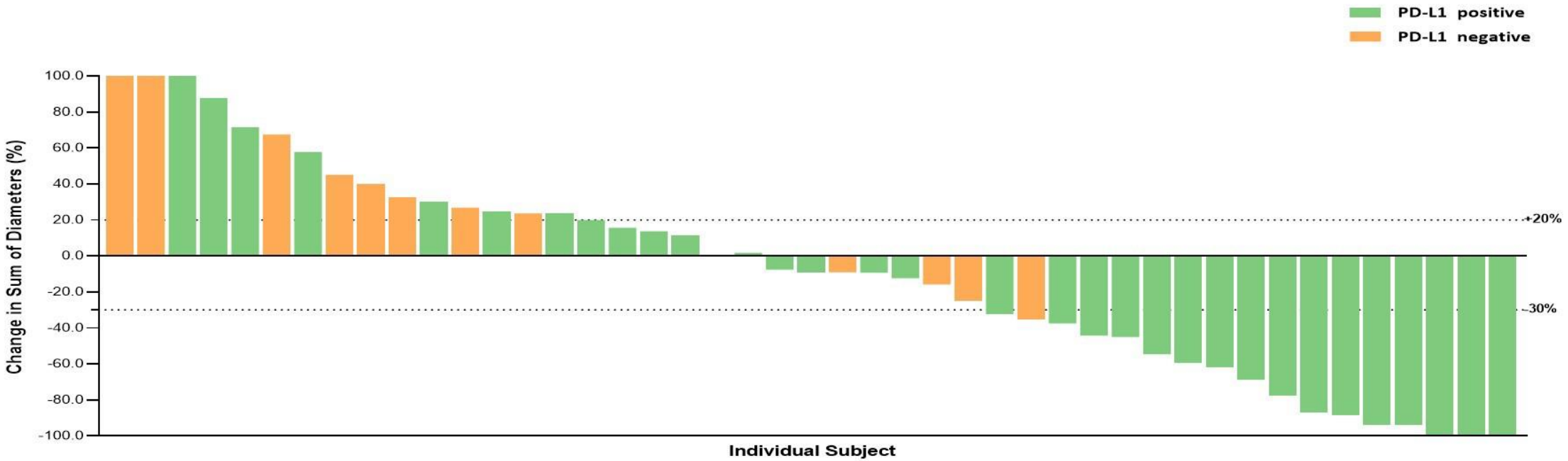
Percent change in target lesions from baseline assessed by RECIST v 1.1 in patients with one or more evaluable post-baseline imaging assessments (N=48)



- Currently, median follow-up is 6.1 months (range; 1.7 – 24.2 months) as of March 2021.

Tumor Regression from Baseline for PD-L1 +/-

Maximum changes from baseline in target lesion size assessed by RECIST v 1.1 in patients with one or more evaluable post-baseline imaging assessments (N=45*)



- PD-L1-positive patients responded better to GX-188E + Pembrolizumab (41.7%) than PD-L1-negative (8.3%)
- Target lesion reduction is also observed in 1 out of 12 PD-L1-negative tumors.

** Among 48 patients, 3 patients (1607, 1608, 1802) were not included in this graph because target lesion were assessed as not evaluable by BICR.*

Summary

GX-188E + Pembrolizumab combination treatment in patients with heavily pretreated, recurrent cervical cancer

- safe and tolerable with similar safety profile to that of pembrolizumab monotherapy
- markedly improved response rate of 33.3% (16/48)
- showed higher response rates in PD-L1-positive, HPV 16, and squamous cell carcinoma

PD-L1+	HPV 16	SCC
41.7 %	35.3 %	33.3 %

- demonstrated clinical responses also in PD-L1-negative, HPV 18, and adenocarcinoma.

GX-188E combined with pembrolizumab is safe and efficacious treatment for patients with HPV 16-/18-caused recurrent or metastatic cervical cancer who failed from SoC.

2021 ASCO ANNUAL MEETING

ANLOTINIB PLUS SINTILIMAB IN PATIENTS WITH RECURRENT ADVANCED CERVICAL CANCER: A PROSPECTIVE, MULTICENTER, SINGLE-ARM, PHASE II CLINICAL TRIAL

Qin Xu

Fujian Cancer Hospital

April 28, 2021

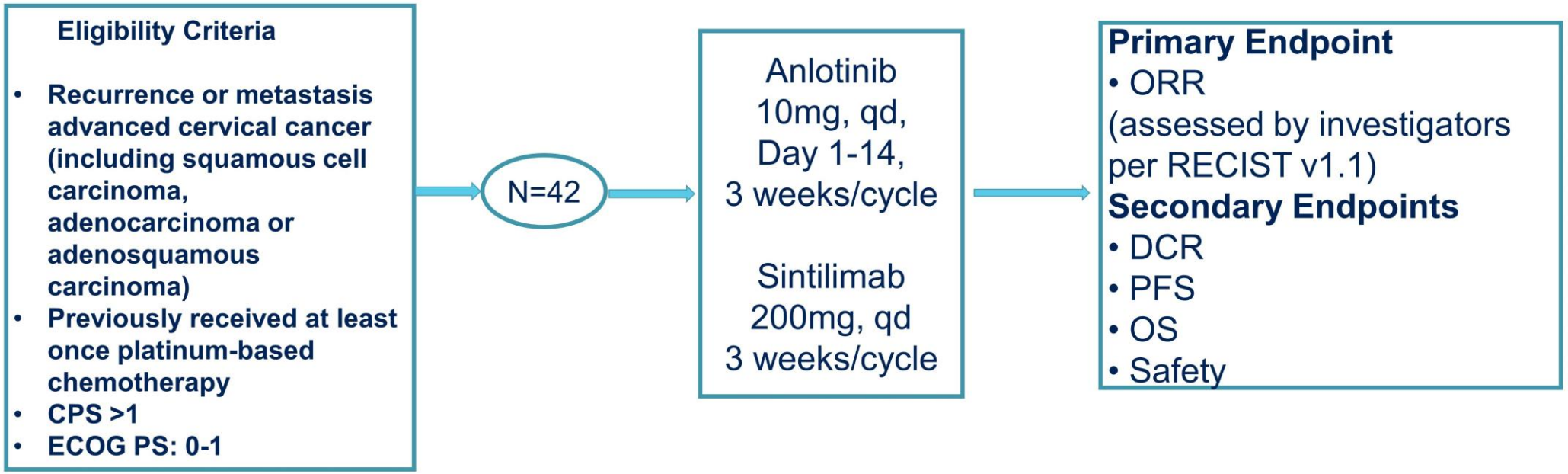
Background

- Anlotinib is a novel multi-target tyrosine kinase inhibitor, inhibiting tumour angiogenesis and proliferative signalling[1]. Sintilimab is a fully humanized, high-affinity monoclonal antibody against programmed cell death-1 (PD-1)[2].
- It is difficult for patients with recurrent advanced cervical cancer to obtain clinical benefits after the failure of standard chemotherapy. However, antiangiogenic therapy combined with immune checkpoint inhibitors have become a promising strategy for advanced cervical cancer[3].
- This phase II, single-arm study (ChiCTR1900023015) aims to evaluate the efficacy and safety of anlotinib plus sintilimab in patients with recurrent advanced cervical cancer.

1.Shen GS, Zheng FC, Ren DF, et al. Anlotinib: a novel multi-targeting tyrosine kinase inhibitor in clinical development. J Hematol Oncol. 2018;11 (1):120.
2.Yuankai Shi, Hang Su, Yongping Song, et al. （2019）Safety and activity of sintilimab in patients with relapsed or refractory classical Hodgkin lymphoma (ORIENT-1): a multicentre, single-arm, phase 2 trial. The Lancet Haematology，doi:10.1016/S2352-3026(18)30192-3
3.Dai F, Kloepper J, Amoozgar Z, et al. Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges[J]. Nature Reviews Clinical Oncology, 2018.

Study Design

An multicentre, open-label, single-arm, phase 2 study



Baseline Characteristics

Characteristics	Patiants n(%)
Age, years, median (IQR)	52(47-58)
Histology	
Squamous cell carcinoma	35(83.3)
Adenocarcinoma	5(11.9)
Adenosquamous carcinoma	2(4.8)
FIGO stage at initial diagnosis	
IA	1(2.4)
IB	4(9.5)
IIA	6(14.3)
IIB	6(14.3)
IIIB	8(19.0)
IIIC	6(14.3)
IVB	4(9.5)
unknown	7(16.7)
Metastasis	
YES	38(90.5)
NO	4(9.5)
ECOG	
0	6(14.3)
1	36(85.7)

- Between September 2019 and April 2021, 42 patients with a median age of 52 years (IQR:47-58), FIGO histopathological stage I (11.9%), II (28.6%), III (33.3%), IV (9.5%) and undiagnosed (16.7%) were enrolled.

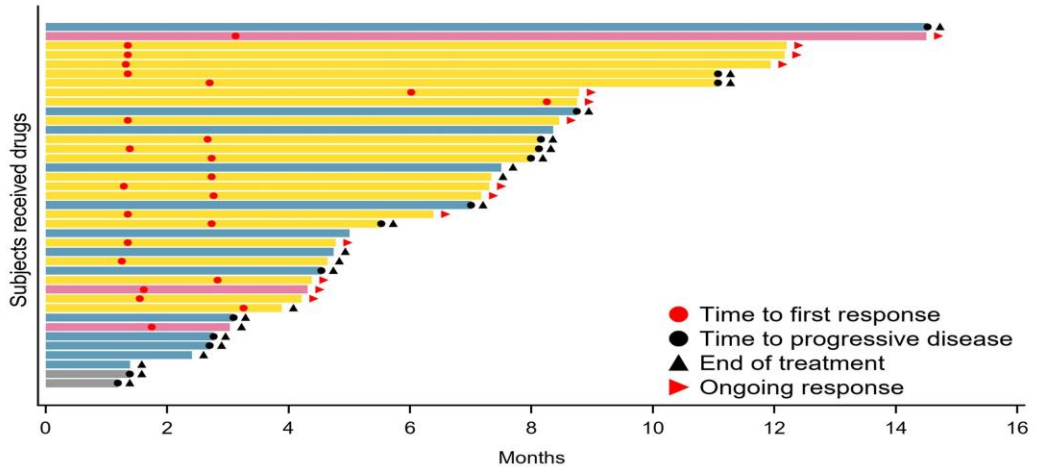
Efficacy

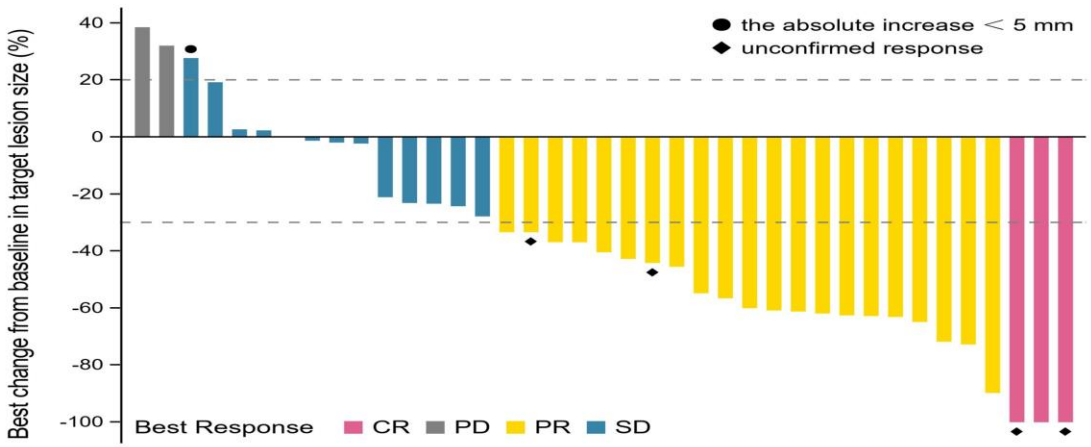
Best Response	n(%)
Complete Response(CR+)	3(7.7)
Partial Response(PR*)	21(53.8)
Stable Disease(SD)	13(33.3)
Progression Disease(PD)	2(5.1)
ORR(CR+PR), %(n,95%CI)	61.5(24, 44.9-75.9)
DCR(CR+PR+SD), %(n,95%CI)	94.9(37, 80.7-98.8)

+Two patients were not confirmed

*Two patients were not confirmed

Antitumor activity was assessed in the response-evaluable population (n=39) – 3 patients in the safety population did not have a postbaseline scan and were excluded from the response evaluable population





Safty

- The most common adverse events (AEs) were grade 1 or 2.
- The grade 3 AEs were hypertension (4.8%), hyponatremia (4.8%),immune pneumonia(2.4%) ,immune myocarditis (2.4%),diarrhea (2.4%) and hypertrigly -ceridemia (2.4%).
- No higher AEs and treatment-related death were observed.

Adverse Events	Total n(%)	Grade of AEs		
		Grade 1 n(%)	Grade 2 n(%)	Grade 3 n(%)
Hypothyroidism	14(33.3)	0(0)	14(33.3)	0(0)
hypertension	10(23.8)	5(11.9)	3(7.1)	2(4.8)
AST	9(21.4)	7(16.7)	2(4.8)	0(0)
diarrhea	8(19.0)	5(11.9)	2(4.8)	1(2.4)
ALT	7(16.7)	5(11.9)	2(4.8)	0(0)
hand-foot syndrome	7(16.7)	3(7.1)	4(9.5)	0(0)
hypertriglyceridemia	7(16.7)	6(14.3)	0(0)	1(2.4)
anemia	5(11.9)	1(2.4)	4(9.5)	0(0)
hypercholesterolemia	5(11.9)	5(11.9)	0(0)	0(0)
Rash	3(7.1)	2(4.8)	1(2.4)	0(0)
Swelling and aching of gum	2(4.8)	2(4.8)	0(0)	0(0)
dental ulcer	2(4.8)	2(4.8)	0(0)	0(0)
hyponatremia	2(4.8)	0(0)	0(0)	2(4.8)
Fatigue	2(4.8)	2(4.8)	0(0)	0(0)
Immune pneumonia	2(4.8)	0(0)	1(2.4)	1(2.4)
Immune myocarditis	1(2.4)	0(0)	0(0)	1(2.4)

Conclusions

- Anlotinib plus sintilimab showed a promising efficacy
—ORR of 61.5%, DCR of 94.9% in advanced cervical cancer

- Anlotinib plus sintilimab was generally well tolerated
—The most common adverse events (AEs) were grade 1 or 2

- We will report more data in the future

Gynecologic Cancer Highlights

Ovarian Cancer

- Bevacizumab Maintenance – 15 vs 30 months: **More bevacizumab is not better**
- PARP Inhibitors
  - PAOLA-1 – PFS2 update: **Continued impressive results for HRD patients**
  - EFFORT Trial – PARP Resistant Population:
  - CAPRI Study – PARP Resistant Population:

  ▶ **Potential combinations for PARP resistance**
- VITAL – Tumor Plasmid vaccine:
- SOVO1 – Dendritic vaccine trial:

  ▶ **Novel approach to extending frontline response**
- Mirvetuximab + Bevacizumab - Final Analysis: **Demonstrated efficacy for ADC+bev**
- Pembrolizumab + Liposomal Doxorubicin + Bevacizumab: **Benefit of adding pembro**

Uterine Cancer

- TOTEM – Surveillance Study: **Confirmatory de-escalation of intense monitoring**
- TAPUR – HER2 targeted therapy: **Activity signal for ERBB mutation tumors**

Cervical Cancer

- OUTBACK: **No benefit of adding chemotherapy to radiation**
- GX-188E – DNA vaccine + Pembrolizumab: **Promising activity signal for combination**
- ANLOTINIB+sintilimab: **Another disease site showing notable CPI+TKI activity**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