Dendritic Cell Vaccine With Chemotherapy In Patients With Epithelial Ovarian Carcinoma After Primary Debulking Surgery

Interim Analysis Of A Phase 2, Open-label, Randomized, Multicenter Trial

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2 Frauenklinik (OB/GYN), University of Cologne, Cologne, Germany;
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8 University Hospital Motol, Prague, Czech Republic;
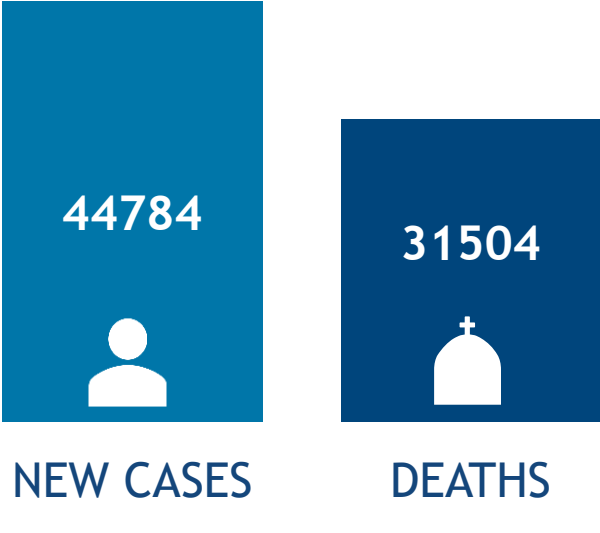9 SOTIO a.s., Prague, Czech Republic;
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Ovarian Cancer: Introduction

22 400

NEW CASES

14 070

DEATHS

UNITED STATES
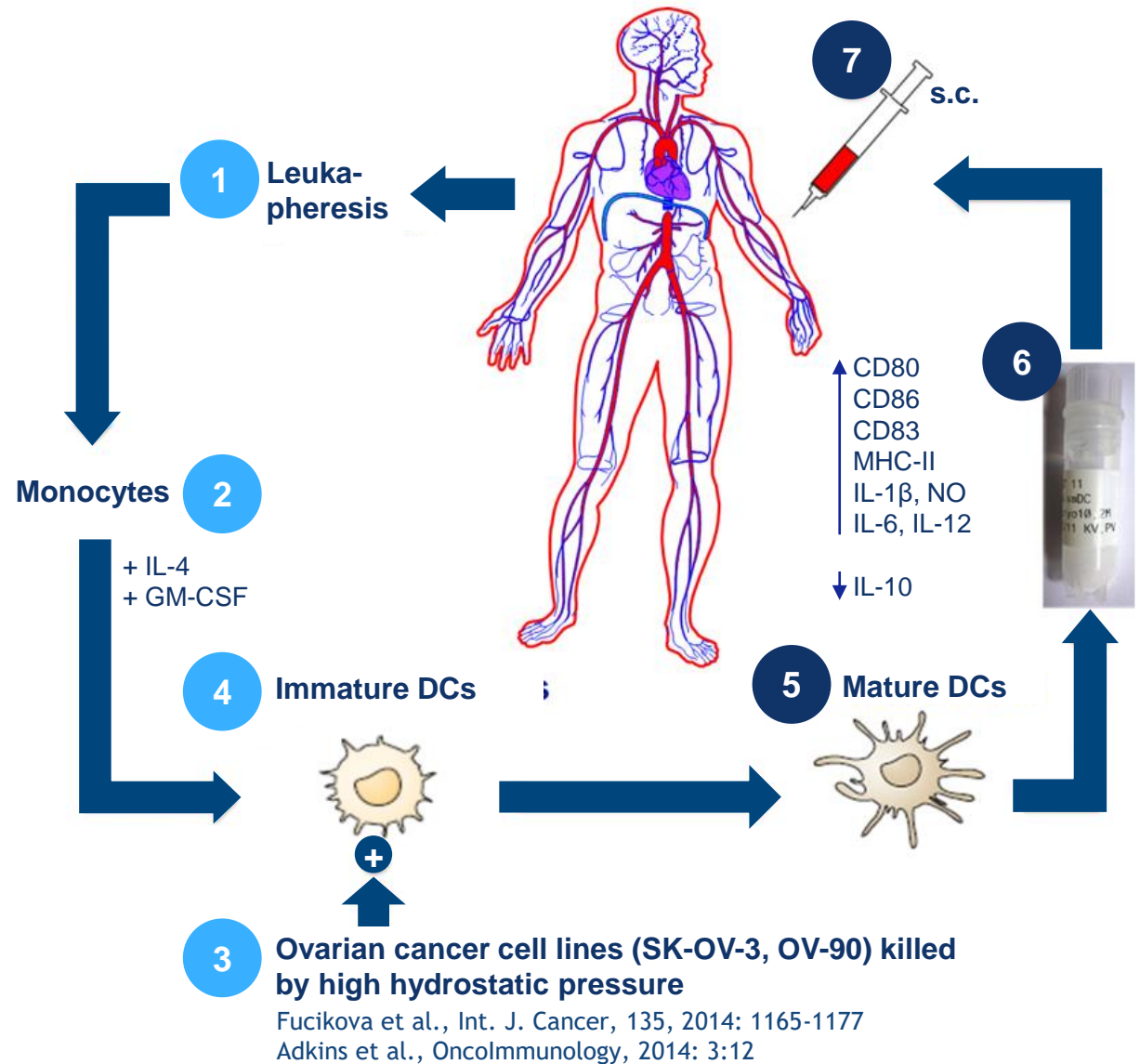2018[1]

44784

NEW CASES

31504

DEATHS
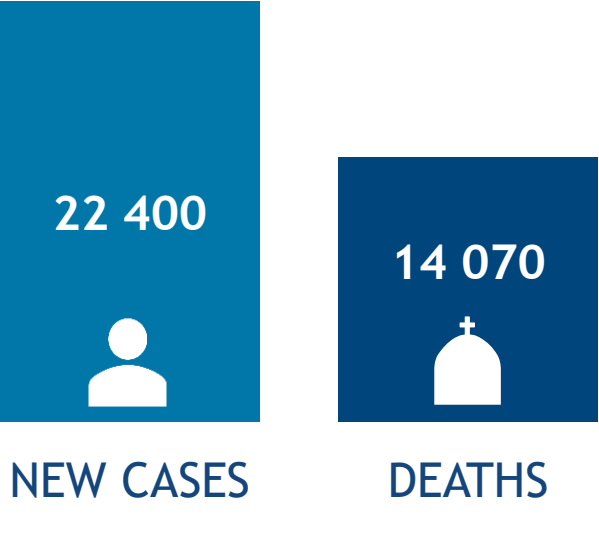
EUROPEAN UNION (EU28)
2018[2]

> **~70%**
> of Stage III/IV patients will relapse despite optimal surgery and CHT

1 American Cancer Society: Cancer Facts and Figures 2018. Atlanta, Ga: American Cancer Society, 2018

2 ECIS - European Cancer Information System; From https://ecis.jrc.ec.europa.eu, accessed on 24/05/2018 © European union, 2018
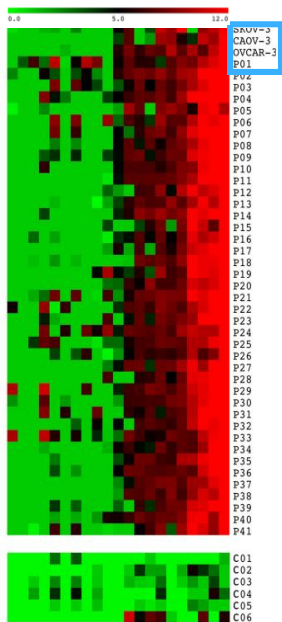
DCVAC/OvCa

1 Patient visits leukapheresis centre

2 Monocytes are separated

3 Ovarian carcinoma cell lines are killed by high hydrostatic pressure to induce immunogenic cell death

4 Immature DCs are mixed with killed tumor cells and maturation of DCs is induced

Kloudova et al., Oncotarget, 2016; 7(29):46120-46126
Fucikova et al., J Transl Med., 2011; 9:223

7 s.c.

1 Leuka-pheresis

↑ CD80
CD86
CD83
MHC-II
IL-1β, NO
IL-6, IL-12

↓ IL-10

6

Monocytes **2**

+ IL-4
+ GM-CSF

4 Immature DCs

5 Mature DCs

3 Ovarian cancer cell lines (SK-OV-3, OV-90) killed by high hydrostatic pressure

Fucikova et al., Int. J. Cancer, 135, 2014: 1165-1177
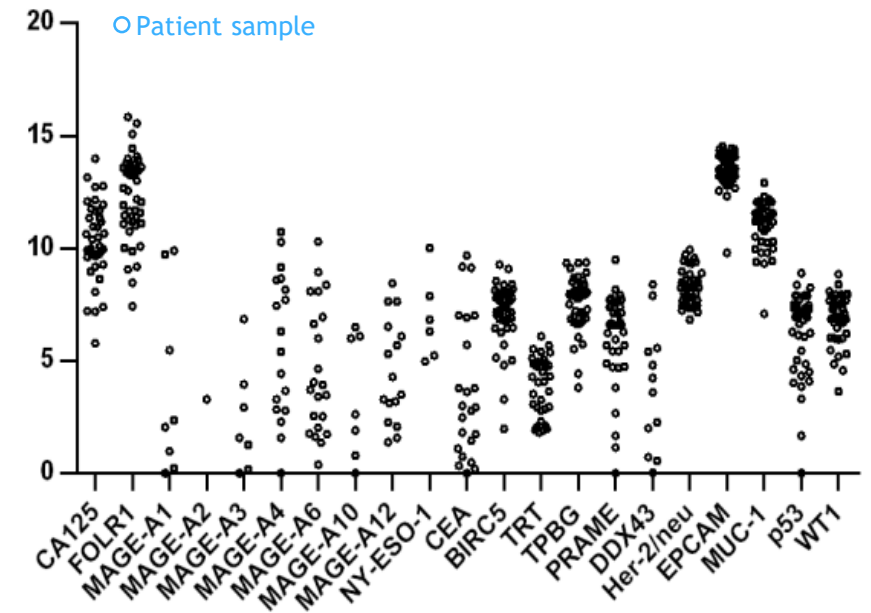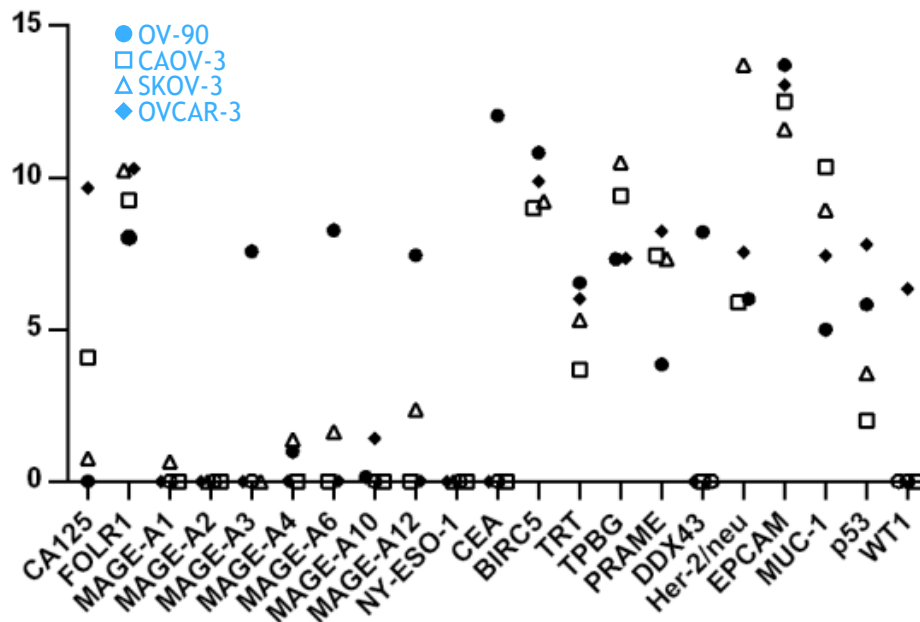Adkins et al., OncoImmunology, 2014: 3:12

Tumor Cell Lines Were Selected To Match The Antigen Profile in Primary Tumors

RELATIVE mRNA EXPRESSION OF 21 TAAS IN CANCER CELL LINES, PRIMARY TUMOR CELLS AND CONTROL OVCA TISSUE

qPCR results

Relative mRNA expression

Publication: Kloudova et al., Oncotarget, 2016

DCVAC/OvCa

5 Matured DCs are prepared

6 ~18 doses of DCVAC/OvCa are produced and frozen

7 Patient completes DCVAC treatment

Kloudova et al., Oncotarget, 2016; 7(29):46120-46126
Fucikova et al., J Transl Med., 2011; 9:223

7 s.c.

1 Leuka-pheresis

2 Monocytes

+ IL-4
+ GM-CSF

↑ CD80
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4 Immature DCs

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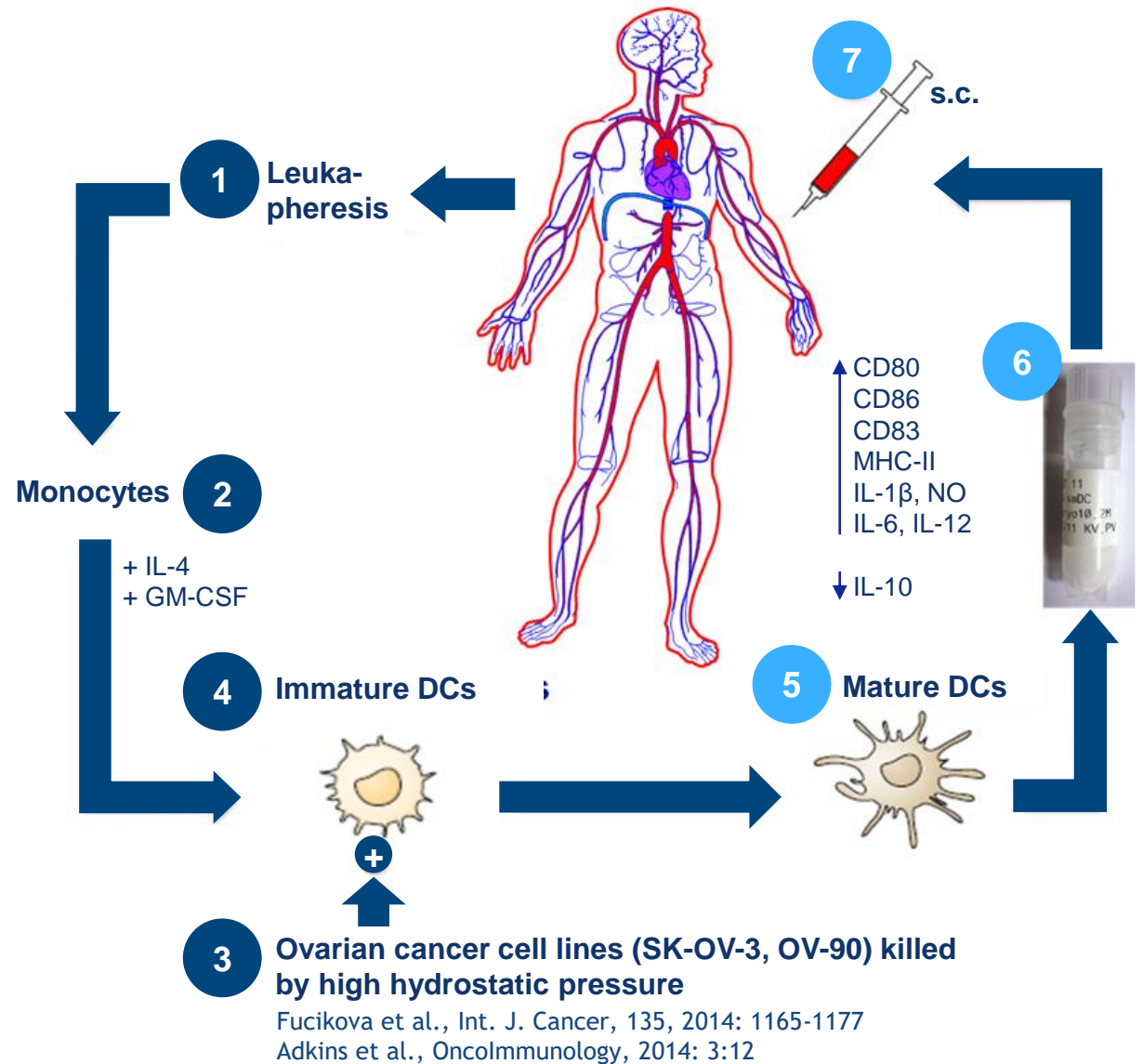
Study Design in First-Line Setting

Epithelial cancer of the ovary, fallopian tube and peritoneum

- FIGO stage III
- Serous, endometrioid, or mucinous
- PS 0 – 2
- <1 cm max. residuum
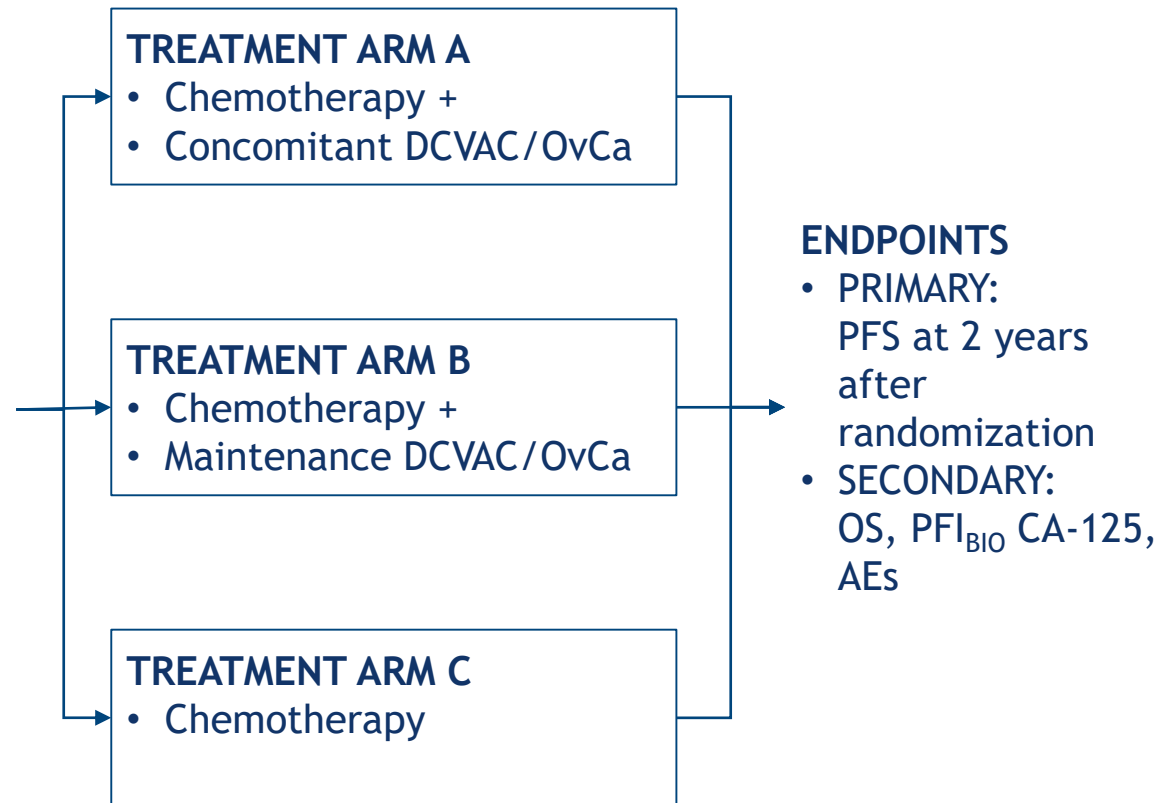- No prior systemic therapy

RANDOMIZATION
1:1:1

Stratification:
0 vs <1cm

TREATMENT ARM A
- Chemotherapy +
- Concomitant DCVAC/OvCa

TREATMENT ARM B
- Chemotherapy +
- Maintenance DCVAC/OvCa

TREATMENT ARM C
- Chemotherapy

ENDPOINTS
- PRIMARY: PFS at 2 years after randomization
- SECONDARY: OS, PFI$_{BIO}$ CA-125, AEs

STUDY TREATMENTS

- **6 CYCLES: Carboplatin** (AUC 5-7) + **Paclitaxel** (175mg/m^2)

- **10 DOSES: DCVAC/OvCa** (1 × 10^7 DCs/dose)

R=randomization; PFI=progression-free interval

Hypothesis For The Study Design

RATIONALE FOR
CONCOMITANT

———

Concomitant chemotherapy targets tumor-induced immune suppression.

Immune system **partially recovered** after each chemotherapy cycle

RATIONALE FOR
MAINTENANCE

———

Minimal tumor burden after chemotherapy sets the optimal conditions for immune stimulation.

Immune system **fully recovered** after completing cytotoxic therapy

Analysis Populations

ITT
—

All patients randomized

(n = 99)

mITT
—

Patients who received **≥1 dose** of therapy with post-baseline endpoint assessment

(n = 92)

PP
—

Patients who received **≥8 doses** of DCVAC/OvCa and/or **≥3 cycles** of chemotherapy

(n = 87)

Treatment Exposure
No Difference in Treatment Exposure in All Arms

INDICATOR	ARM A n = 31	ARM B n = 30	ARM C n = 31
N of 1st-line CHT cycles: mean ± SD, median (min - max)	5.90 ± 0.40, 6 (4-6)	5.80 ± 0.76, 6 (3-6)	5.68 ± 1.14, 6 (0-6)
N of 1st-line CHT non-responders: n (%)	1 (3.23%)	1 (3.33%)	0 (0.00%)
N of DCVAC/OvCa doses: mean ± SD, median (min - max)	9.61 ± 1.43, 10 (3-10)	9.47 ± 2.03, 10 (2-10)	Not applicable
N of pts with DCVAC/OvCa continued beyond progression and administered together with 2nd-line CHT: n (%)	3 (9.68%)	3 (10.00%)	Not applicable
Types of 2nd-line CHT started before completion of DCVAC/OvCa[1]	1 patient: doxorubicin & liposomal doxorubicin 1 patient: doxorubicin & gemcitabine 1 patient: topotecan	1 patient: doxorubicin & carboplatin 1 patient: cisplatin & doxorubicin & endoxan 1 patient: gemcitabine monotherapy	Not applicable

1 The number provided to each second-line therapy listed shows the number of patients with the particular treatment
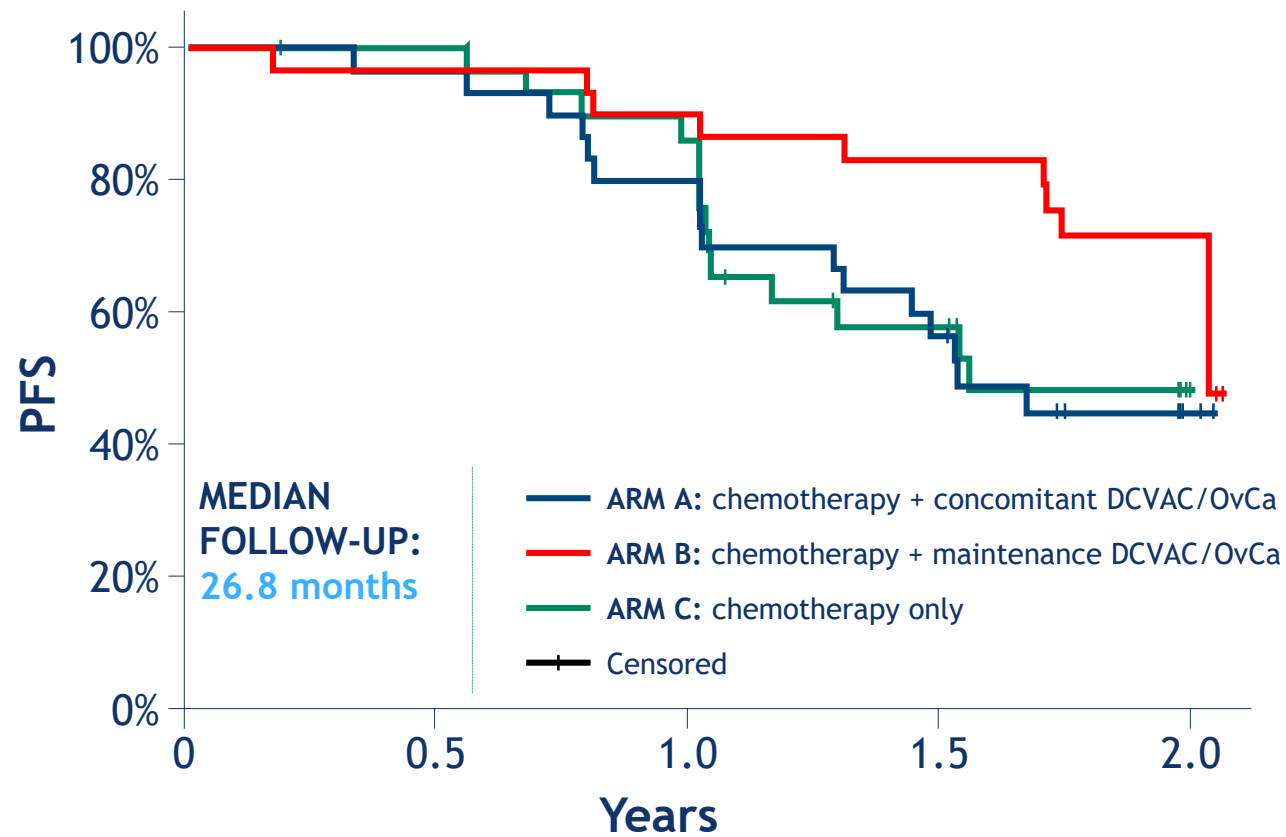
Baseline Characteristics in ITT
Known Prognostic Factors Are Balanced in All Arms (Also Comparable in mITT and PP)

INDICATOR GROUP	INDICATOR	ARM A n = 34	ARM B n = 34	ARM C n = 31	p-value
AGE	Median age (years)	61.5	57.5	62.0	0.49
RESIDUAL DISEASE	R0 (n, %)	29 (85%)	29 (85%)	26 (84%)	0.98
	R1 (n, %)	5 (15%)	5 (15%)	5 (16%)	
HISTOLOGY GRADE	High-grade tumors (n, %)	23 (74%)	22 (81%)	21 (87%)	0.46
	Lower-grade tumors (n, %)	8 (26%)	5 (19%)	3 (13%)	
	Collection in progress (n)	3	7	7	
HISTOLOGY TYPE	Endometrioid (n, %)	2 (6%)	6 (18%)	1 (3%)	0.09
	Serous (n, %)	31 (91%)	28 (82%)	30 (97%)	
	Mucinous (n, %)	1 (3%)	0	0	
CA 125	CA-125 baseline median (kU/L)	73.5	86.9	99.2	0.33
ECOG	0 (n, %)	17 (50%)	18 (53%)	20 (64%)	0.81
	1 (n, %)	12 (35%)	12 (35%)	8 (26%)	
	2 (n, %)	5 (15%)	4 (12%)	3 (10%)	

PFS
~ 6-month Benefit in mPFS and 57% Decrease in The Hazard of Progression in Arm B

MEDIAN FOLLOW-UP: 26.8 months

ARM A: chemotherapy + concomitant DCVAC/OvCa
ARM B: chemotherapy + maintenance DCVAC/OvCa
ARM C: chemotherapy only
Censored

PFS		ARM A	ARM B	ARM C
PATIENT COUNT	mITT	31	30	31
	PP	29	28	30
EVENTS	mITT	16	9	14
	PP	15	7	14
2-YEAR PFS RATE (%)	mITT	51.6	30	45.2
	PP	51.7	25	46.7
MEDIAN (MONTHS)	mITT	18.3	24.3	18.6
	PP	20	NE	18.6

ARMS COMPARISON		HR	95% CI	p-value
B vs. C	mITT	0.43	0.18-1.03	0.05
	PP	0.32	0.12-0.83	0.01
A vs. C	mITT	0.64	0.20-2.04	0.45
	PP	1.01	0.49-2.09	0.98

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PFI~BIO~ (Based on CA-125 Elevations)
PFI~BIO~ Supporting PFS Benefit

MEDIAN FOLLOW-UP: 26.8 months

ARM A: chemotherapy + concomitant DCVAC/OvCa
ARM B: chemotherapy + maintenance DCVAC/OvCa
ARM C: chemotherapy only
Censored
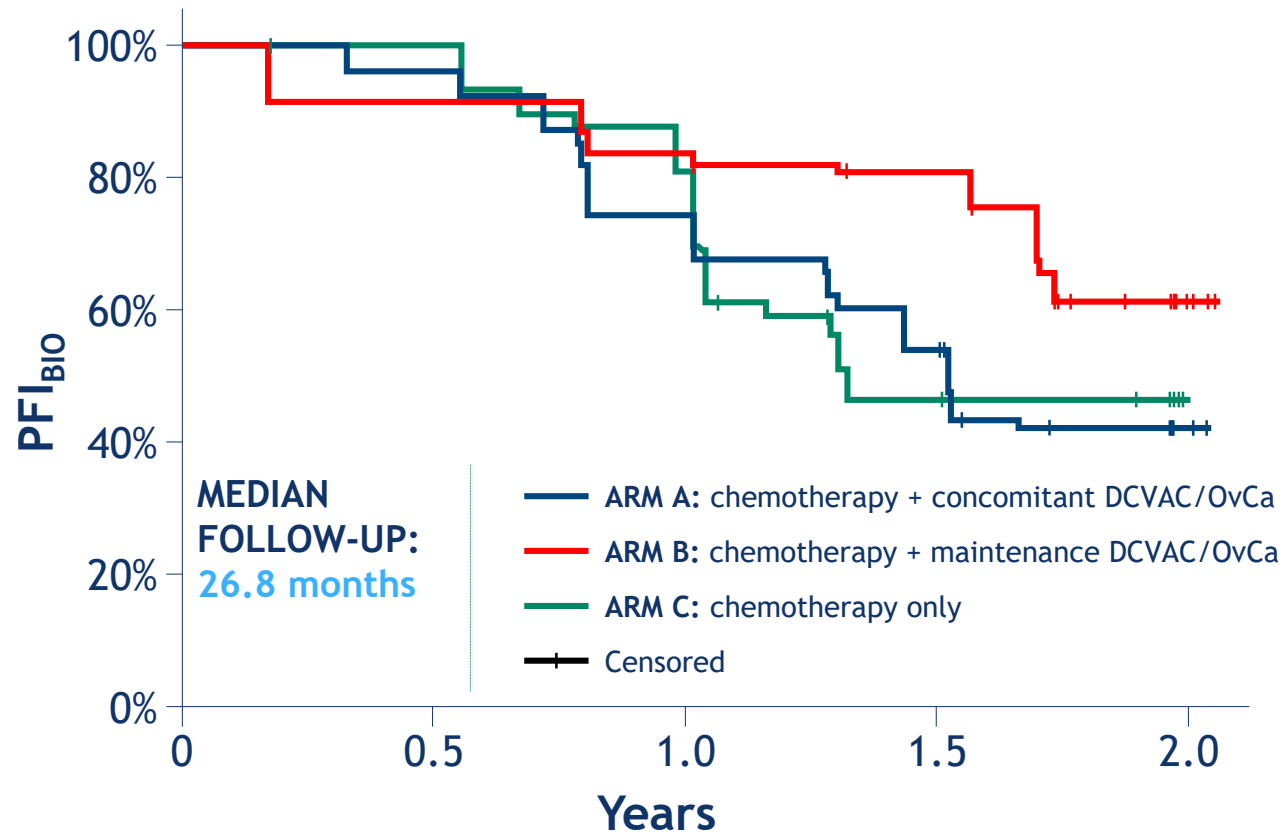
PFI~BIO~	ARM A	ARM B	ARM C
Patient count			
• mITT	31	30	31
• PP	29	28	30
Events			
• mITT	16	9	14
• PP	15	7	14
Median (months)			
• mITT	18.3	NE	NE
• PP	20	NE	NE

INDICATOR	HR	95% CI	p-value
B vs. C			
• mITT	0.48	0.21-1.12	0.08
• PP	0.37	0.15-0.93	0.03
A vs. C			
• mITT	1.06	0.52-2.17	0.88
• PP	0.99	0.48-2.06	0.98

OS
A Trend Towards Improved OS in Arm B

MEDIAN
FOLLOW-UP:
26.8 months
MATURITY:
14%

ARM A: chemotherapy + concomitant DCVAC/OvCa
ARM B: chemotherapy + maintenance DCVAC/OvCa
ARM C: chemotherapy only
Censored
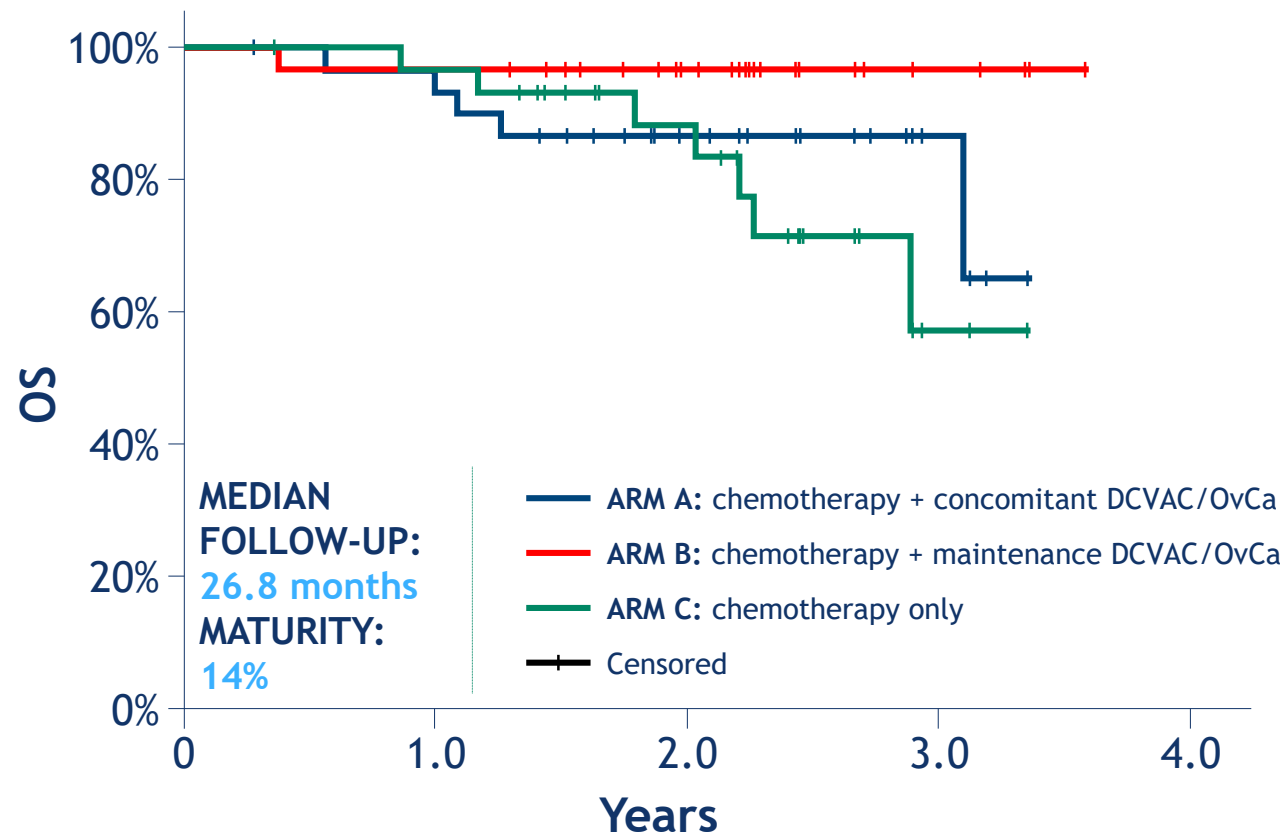
OS	ARM A	ARM B	ARM C
Patient count			
• mITT	31	30	31
• PP	29	28	30
Events			
• mITT	5	1	7
• PP	4	0	7
Median (months)			
• mITT	NE	NE	NE
• PP	NE	NE	NE

INDICATOR	HR	95% CI	p-value
B vs. C			
• mITT	0.13	0.02-1.08	0.03
• PP	0	0-NE	0.01
A vs. C			
• mITT	0.64	0.20-2.04	0.45
• PP	0.51	0.15-1.76	0.28

Adverse Events Causally-Related to DCVAC/OvCa (Per Investigator)
DCVAC/OvCa Has A Favorable Safety Profile

AE PREFERRED TERM	Severity (CTCAE grade v4.03)	ARM A Parallel DCVAC/OvCa (N=34)	ARM B Sequential DCVAC/OvCa (N=32)	ARM C Standard of Care (N=30)	Total (N=96)
Inflammation	Grade 1	1 (2.9%)	-	N/A	1 (1.0%)
Injection site erythema	Grade 1	-	1 (3.1%)	N/A	1 (1.0%)
Injection site pain	Grade 1	-	1 (3.1%)	N/A	1 (1.0%)
Drug hypersensitivity	Grade 2	-	1 (3.1%)	N/A	1 (1.0%)
Erythema	Grade 1	1 (2.9%)	-	N/A	1 (1.0%)

Summary

01 Maintenance DCVAC/OvCa showed a **gain of ~ 6 months in mPFS**

02 Maintenance DCVAC/OvCa showed **57% reduction in risk for progression or death**

03 Current **data for OS are trending in the same direction** as PFS

04 DCVAC/OvCa is **well tolerated**

05 Results warrant further assessment by e**xpanding Arms B and C** and a **Phase III trial being planned**