SOV01 – Randomizovaná, multicentrická studie fáze II zkoumající imunoterapii na bázi dendritických buněk (DCVAC/OvCa) u pacientek s epiteliálním ovariálním karcinomem (EOC) po primární chirurgické léčbě.

LUKÁŠ ROB[1], Peter Mallmann[2], Pawel Knapp[3], Bohuslav Melichar[4], Jaroslav Klát[5], Luboš Minář[6], Zdeněk Novotný[7], Jiřina Bartůňkova[8], Radek Špíšek[9], Ladislav Pecen[9], Hariz Iskandar Bin Hassan[9], Josef Chovanec[10], David Cibula[11], **SOV01 zkoušející lékaři;**

[1] Gynekologicko-porodnická klinika, 3. LF UK a FN Královské Vinohrady, Praha;

[2] Gynekologicko-porodnická kliniky, Kolínská univerzita, Kolín nad Rýnem, Německo;

[3] Gynekologicko-porodnická klinika, Lékařská akademie Bialystok, Bialystok, Polsko;

[4] Onkologická klinika, Univerzita Palackého v Olomouci;

[5] Gynekologicko-porodnická klinika, FN Ostrava;

[6] Gynekologicko-porodnická klinika, FN Brno;

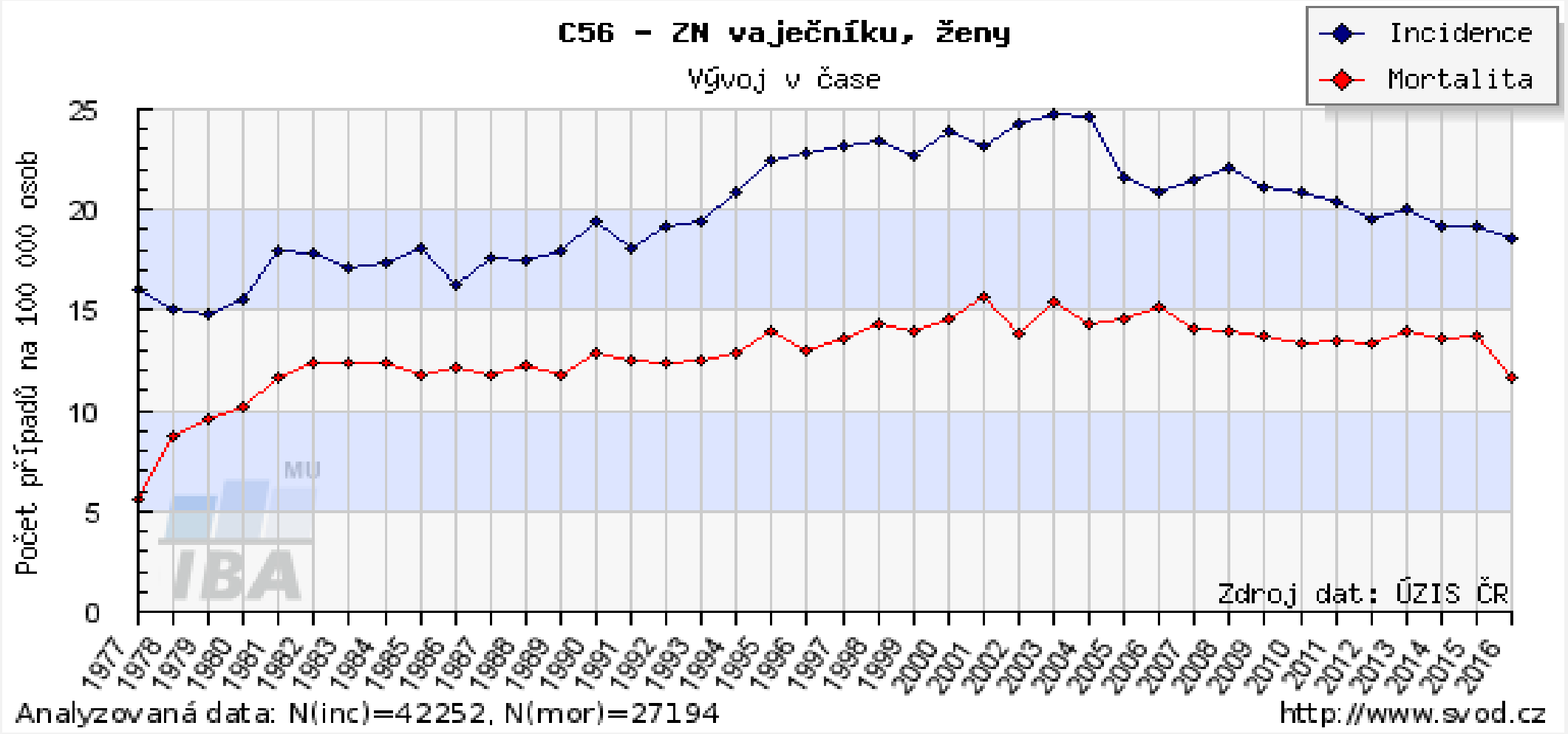
[7] Gynekologicko-porodnická klinika, UK Plzeň a FN Plzeň;

[8] **Ústav Imunologie, 2. LF UK a FN Motol, Praha;**

[9] SOTIO a.s., Praha;

[10] Masarykův Onkologický Ústav, Brno;

[11] Gynekologicko-porodnická klinika, 1. LF UK a VFN Praha.


C56 - ZN vaječníku, ženy
Vývoj v čase
Incidence
Mortalita
Počet případů na 100 000 osob
0
5
10
15
20
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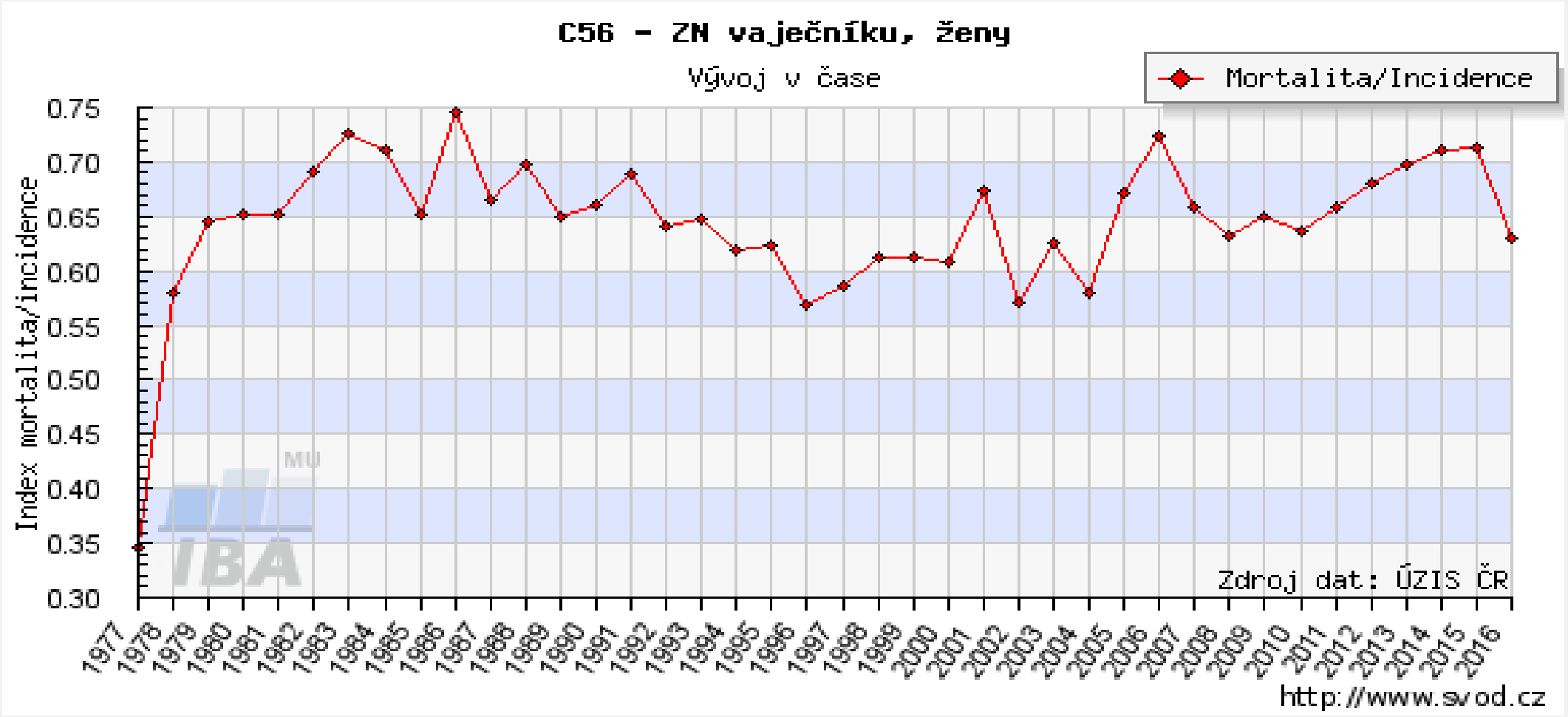
Zdroj dat: ÚZIS ČR
Analyzovaná data: N(inc)=42252, N(mor)=27194
http://www.svod.cz


C56 - ZN vaječníku, ženy
Vývoj v čase
Mortalita/Incidence
Index mortalita/incidence
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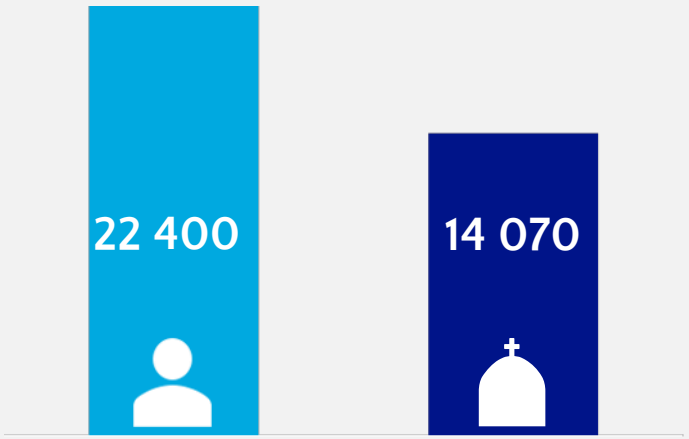
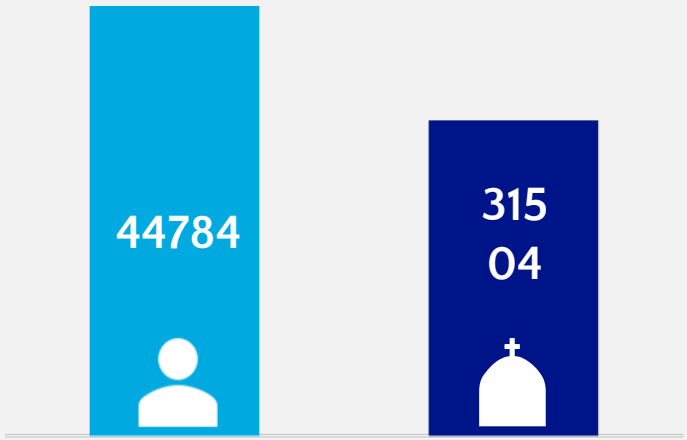
2016
Zdroj dat: ÚZIS ČR
http://www.svod.cz

Ovariální karcinomy: USA / Europe



UNITED STATES 2018[1]



EUROPEAN UNION (EU28) 2018[2]

~70%

Stádií III/IV relabuje i po optimální chirurgické léčbě a chemoterapie

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

Jak zlepšit léčebné výsledky – OS

A. primární léčby – cíl zlepšit celkové přežití OS x PFI?

1. zlepšení výsledků chirurgické léčby … „can we do more?“ centralizace
2. optimalizace adjuvantní pooperační chemoterapie

   inovativní postupy (sekvenční x maitenance)

   + maintenance … PARP inhibitory

   + maintenance imunoterapie …

B. sekundární léčby recidiv

cíl prodloužení života (PFI) 2,3,4 linie…

léčba paliativní

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Prof. Jiřina Bartůňková

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SOTIO as part of PPF Group

PPF

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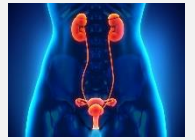
Clean Laboratory in Beijing

GMP

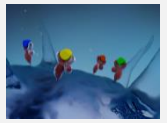
Phase I/II clinical trial for patients with Lung cancer

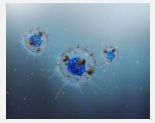
Based on positive signals new Phase II ovarian clinical trials launched

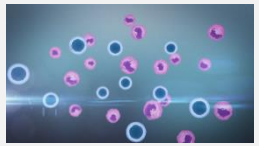


Prof. Radek Špíšek

2000 2010 2011 2012 2013 2014 2015 2017 2018 2019







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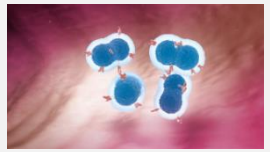

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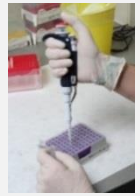

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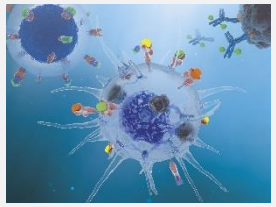


Start of global DCVAC/OvCa Phase III clinical trial

Feasibility and methodological study

Clinical Immunology (2007) 122, 18–27

available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/yclim

In vitro assessment of dendritic cells pulsed with apoptotic tumor cells as a vaccine for ovarian cancer patients

Zuzana Tobiásová [a], Dagmar Pospíšilová [a], Ashley M. Miller [d], Ivo Minárik [a,c], Klára Sochorová [a], Radek Špíšek [a], Lukáš Rob [b], Jiřina Bartůňková [a,*]

[a] Department of Immunology, Charles University, 2nd Medical School and Faculty Hospital Motol, V Úvalu 84, 150 06 Praha 5, Prague, Czech Republic
[b] Department of Obstetrics and Gynecology, 2nd Medical School and Faculty Hospital Motol, Prague, Czech Republic
[c] Department of Urology, 2nd Medical School and Faculty Hospital Motol, Prague, Czech Republic
[d] Immune and Gene Therapy Laboratory, Cancer Centre Karolinska, Karolinska Institute, Stockholm, Sweden

Feasibility and methodological study

Oncotarget. 2016 Jul 19; 7(29): 46120–46126.
Published online 2016 Jun 14. doi: [10.18632/oncotarget.10028]
PMCID: PMC5216785
PMID: 27323861

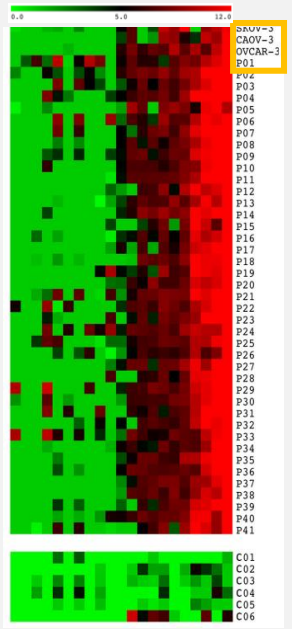
Expression of tumor antigens on primary ovarian cancer cells compared to established ovarian cancer cell lines

Kamila Kloudová,[1,3] Hana Hromádková,[1] Simona Partlová,[1,3] Tomáš Brtnický,[2] Lukáš Rob,[2] Jiřina Bartůňková,[1] Michal Hensler,[3] Michael J. Halaška,[2] Radek Špíšek,[1,3] and Anna Fialová[1,3]

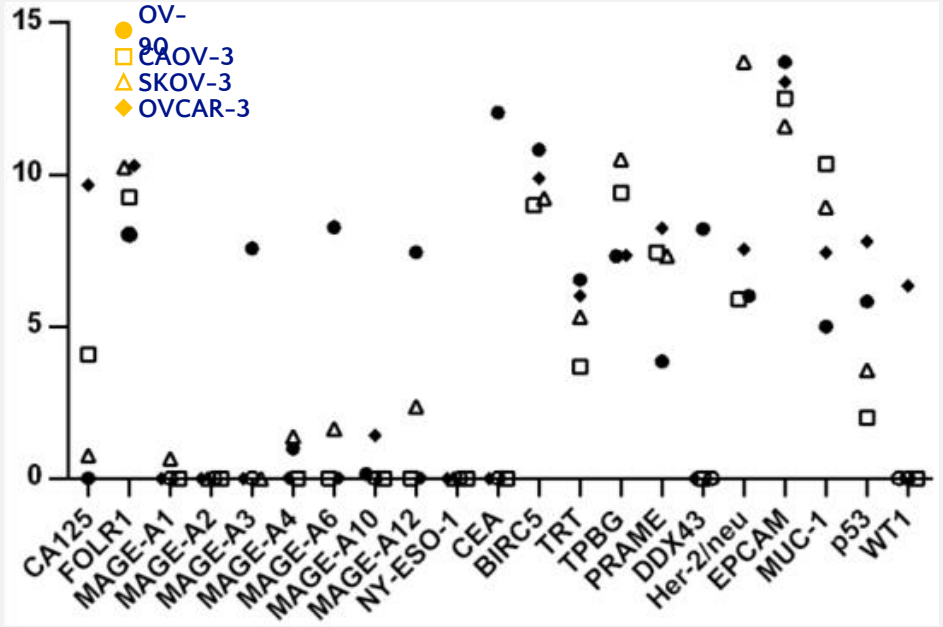
Tumor Cell Lines Were Selected To Match The Antigen Profile in Primary Tumors

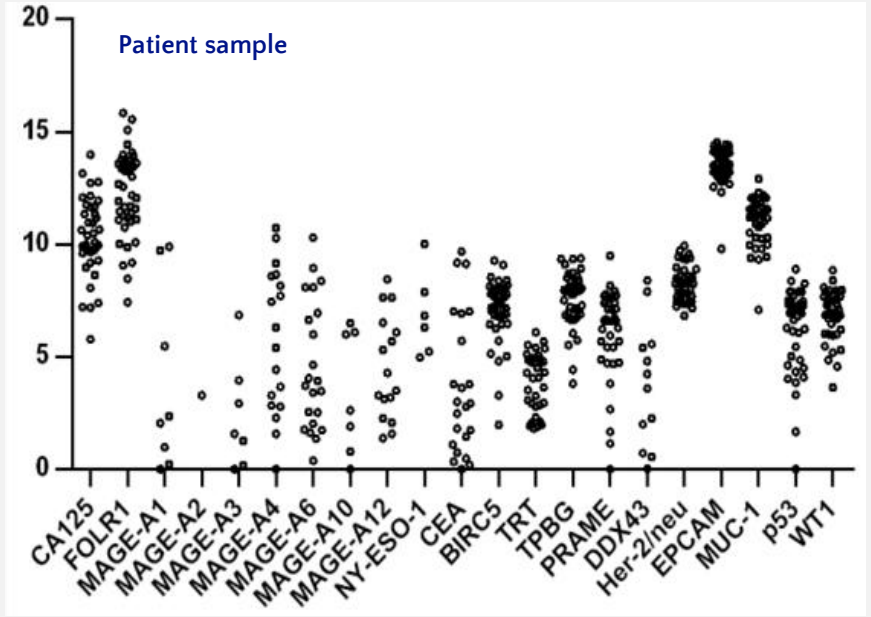
RELATIVE mRNA EXPRESSION OF 21 TAAS IN CANCER CELL LINES, PRIMARY TUMOR CELLS AND CONTROL OVCA TISSUE

qPCR results



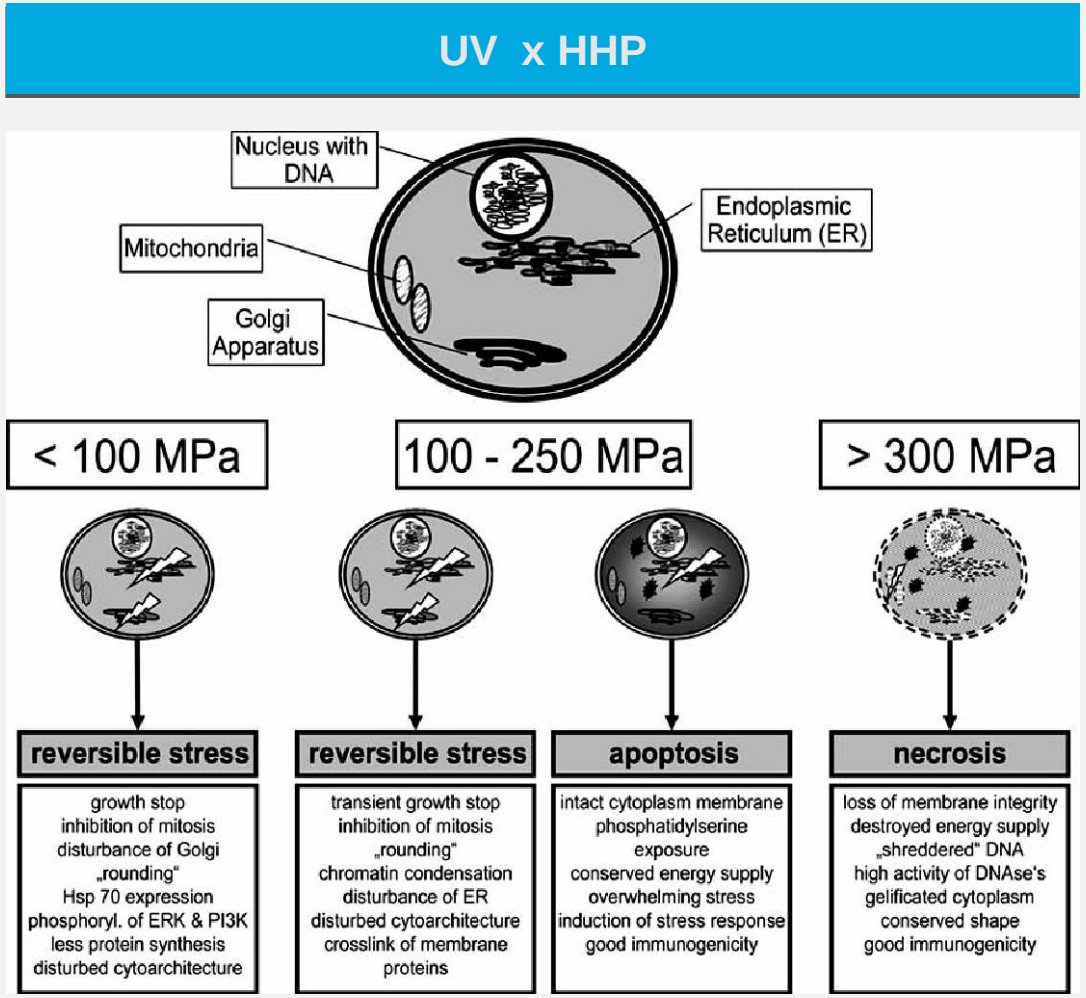
Relative mRNA expression

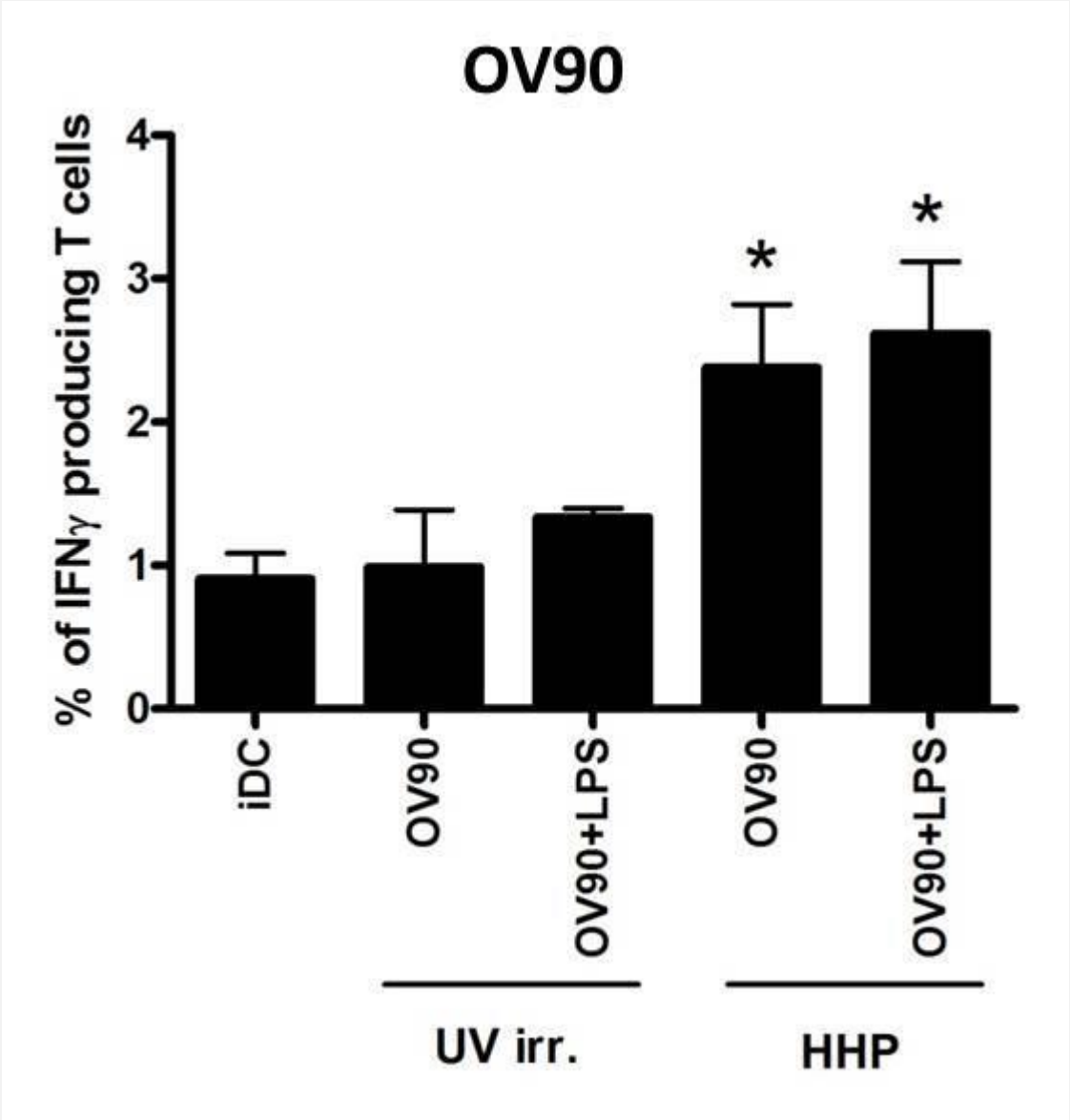




Publication: Kloudova et al., Oncotarget, 2016

High hydrostatic pressure within 100–250 MPa induces immunogenic cell death





The induction of tumor-specific T cells by high hydrostatic pressure and UV irradiation killed OV-90 cells.

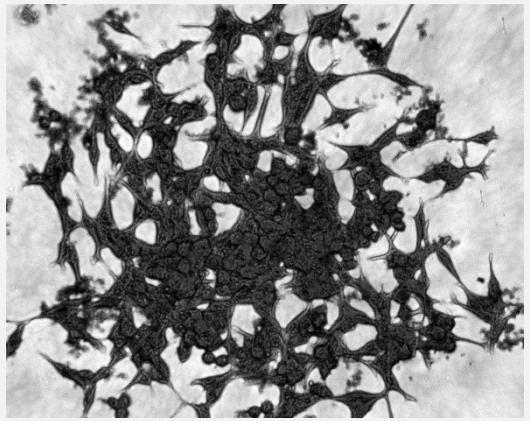
The data show a summary of five independent experiments.

* P value for comparison with irradiated tumor cells, P <0.05.

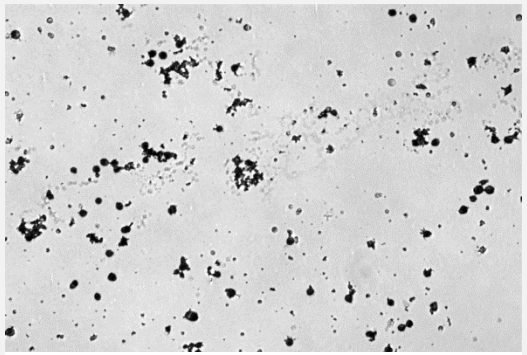
Tumor cells treated by HHP are not able to proliferate – safety!

Cell morphology comparison on day 14 of cultivation (Scale bar = 100 µm)

Positive control LNCaP

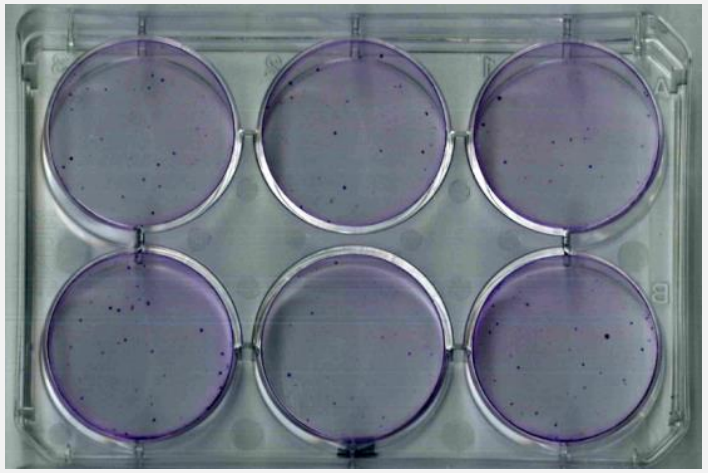


HPP treated LNCaP

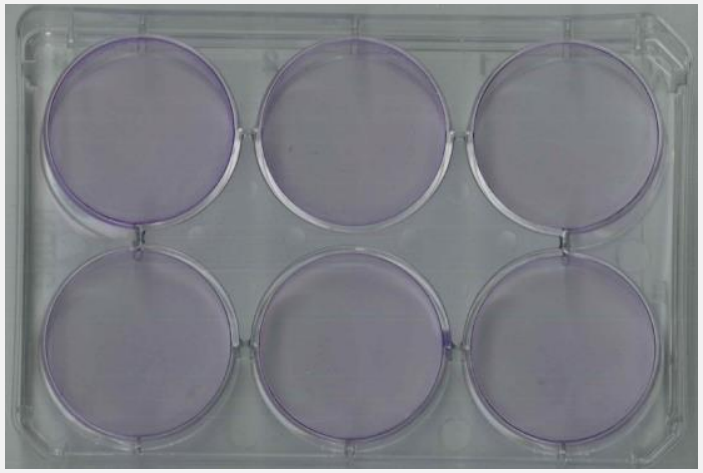


Colony forming efficiency

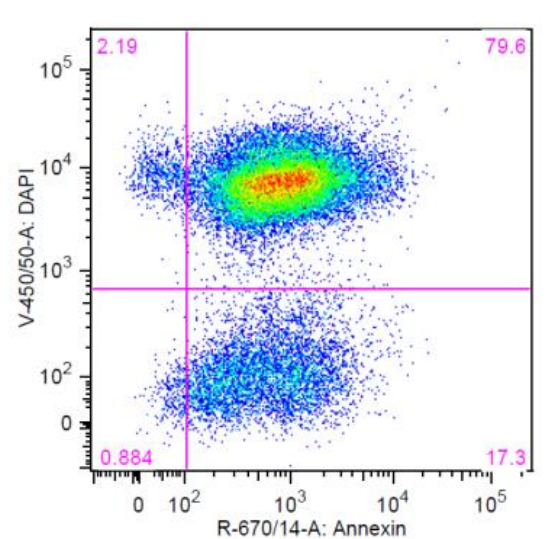
Positive control



HHP treated LNCaP



Detection of double negative cells for Annexin V/DAPI by flow cytometry



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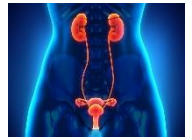
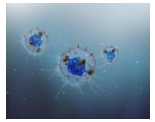
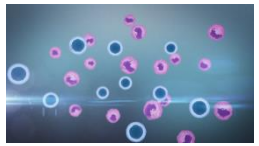


Prof. Radek Špíšek

2000 | **2010** | **2011** | **2012** | **2013** | **2014** | **2015** | **2017** | **2018** | **2019**





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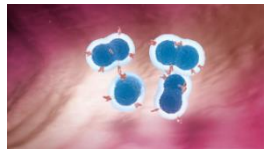

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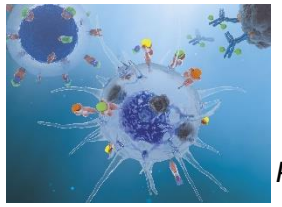
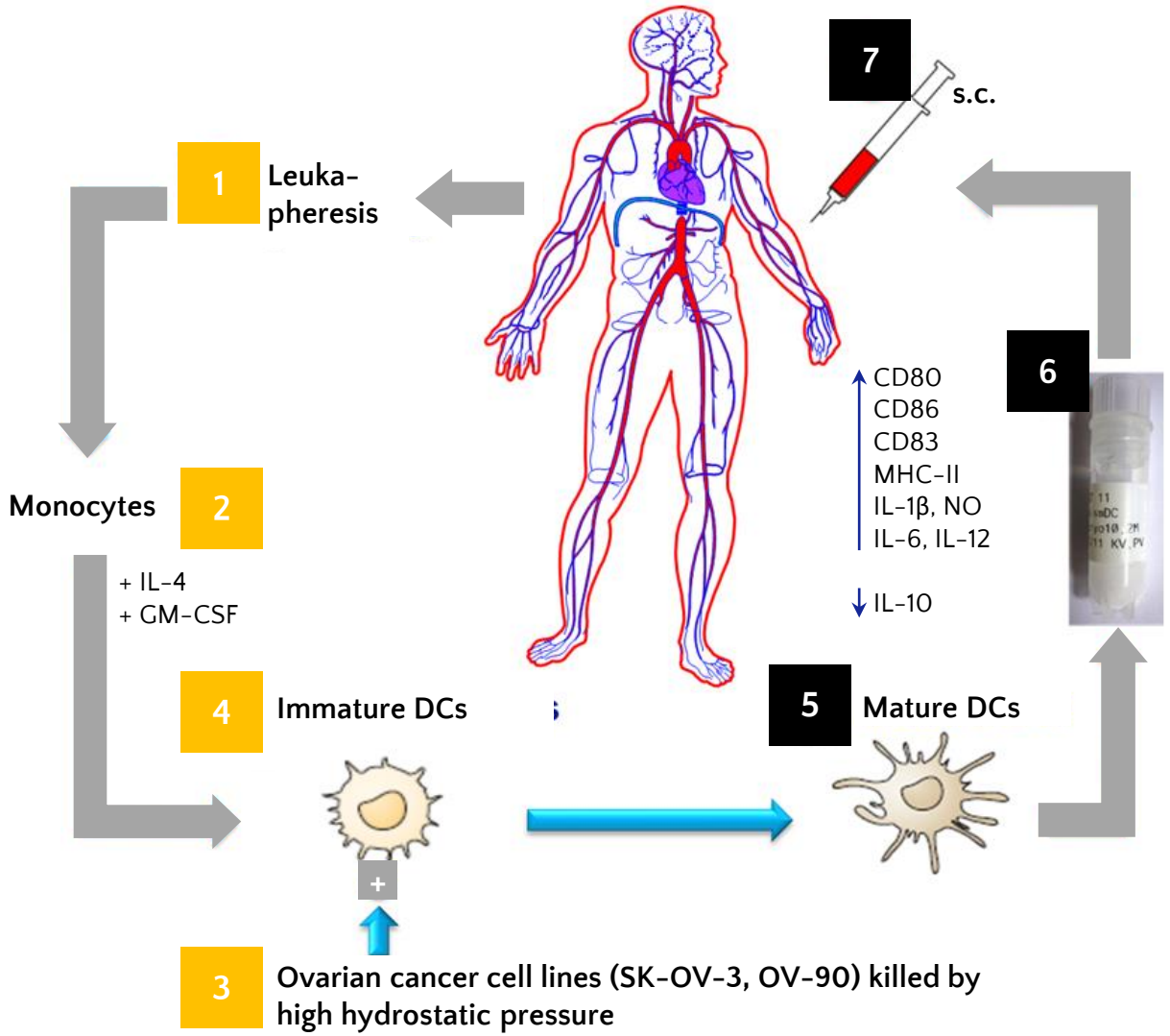


Start of global DCVAC/OvCa Phase III clinical trial

SOV01/ 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

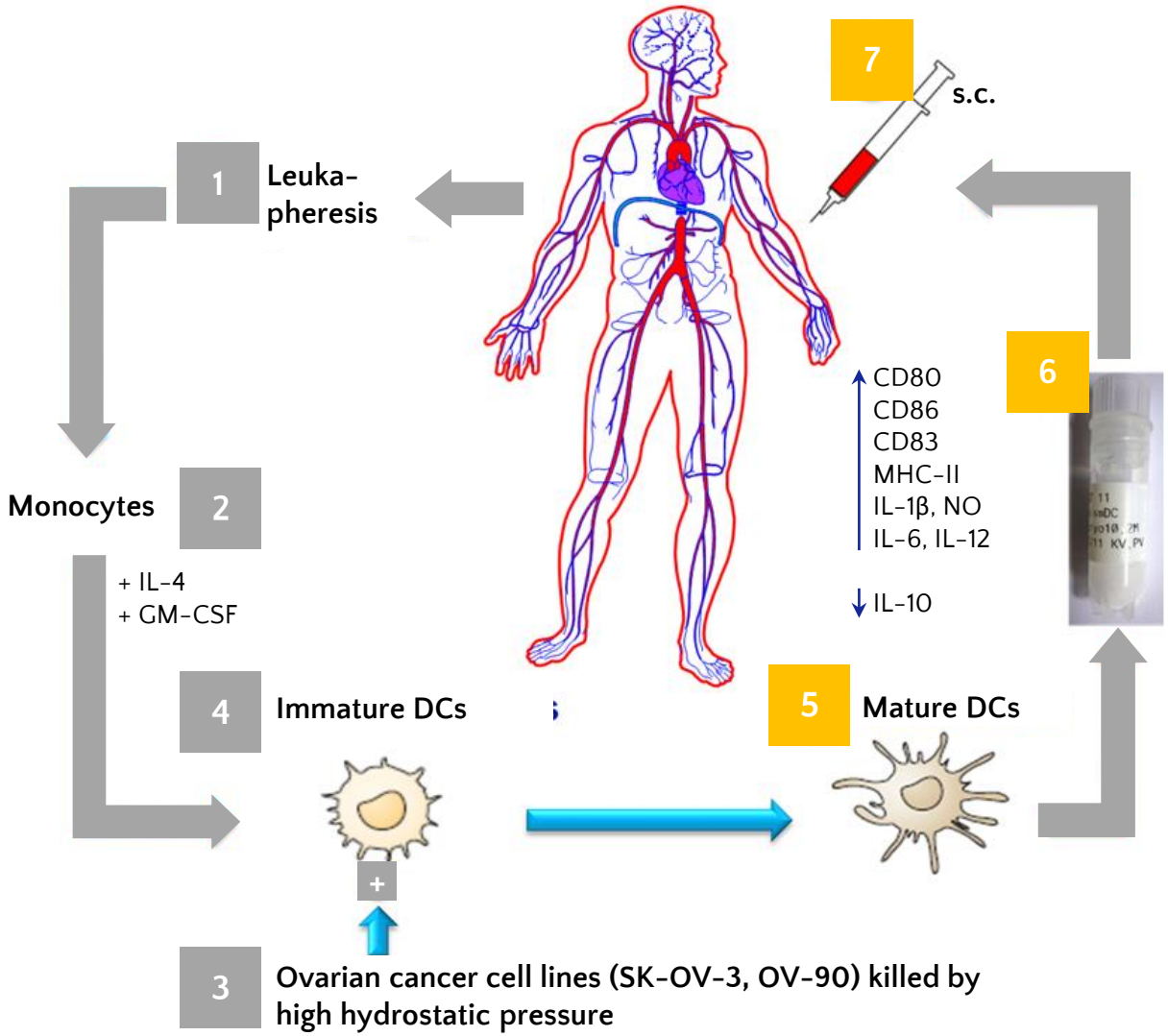
Fucikova et al., Int. J. Cancer, 135, 2014: 1165-1177; Adkins et al., OncoImmunology, 2014: 3:12

DCVAC/OvCa

5 Matured DCs are prepared

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

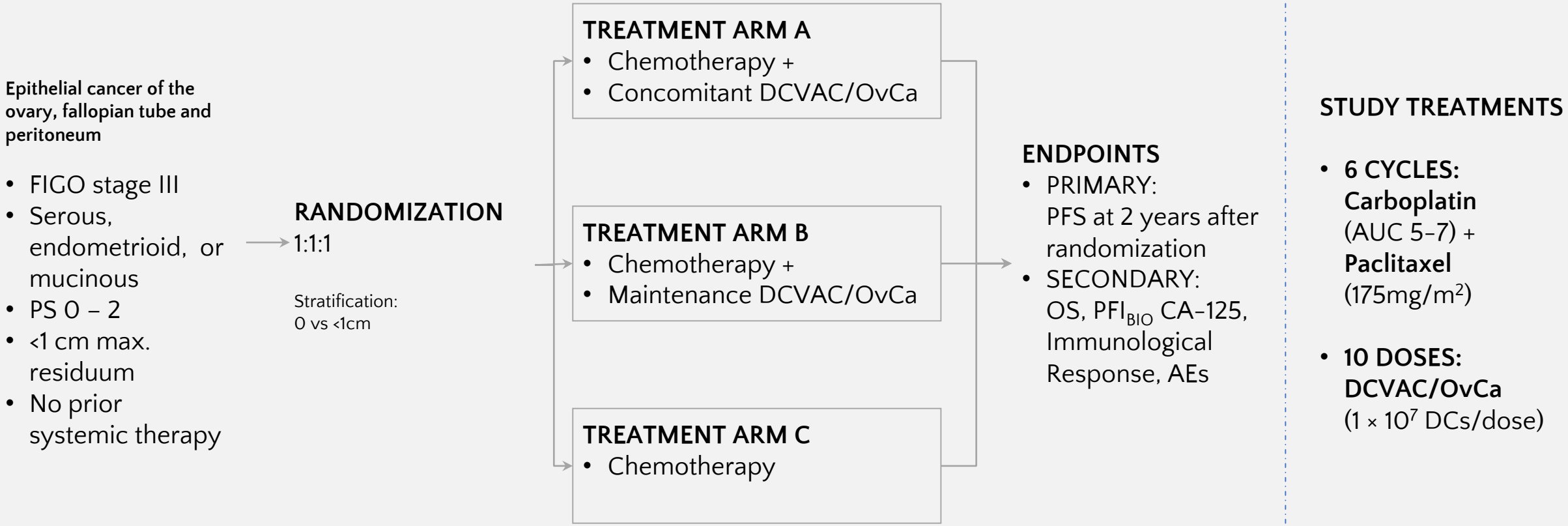
7 Patient completes DCVAC treatment



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

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

SOV01 – studie (2013–2016) – prezentováno ASCO 2018



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

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%)	

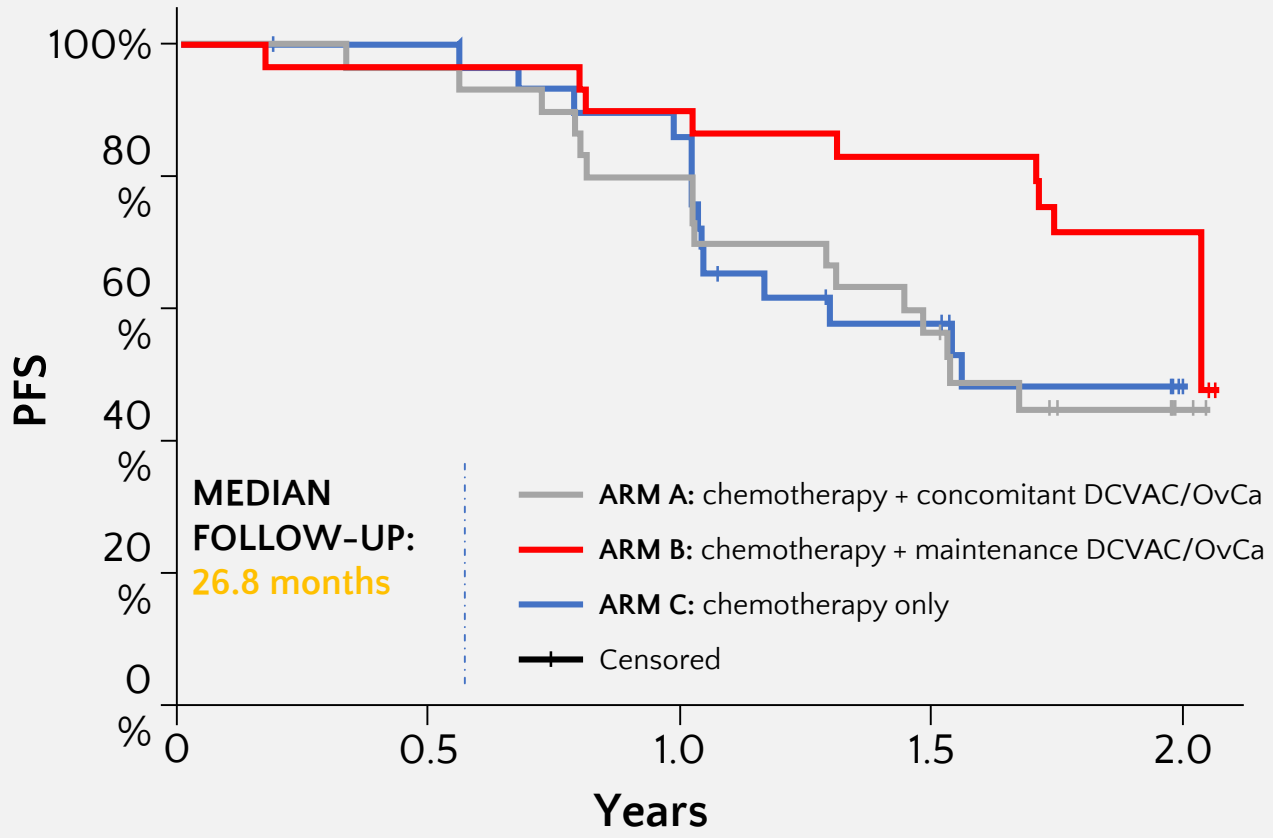
Adverse Events Assessed by the Investigator as Causally-Related to DCVAC/OvCa

DCVAC/OvCa Appears To Be Safe Without Potentiating the Side Effects of ChT

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%)

PFS

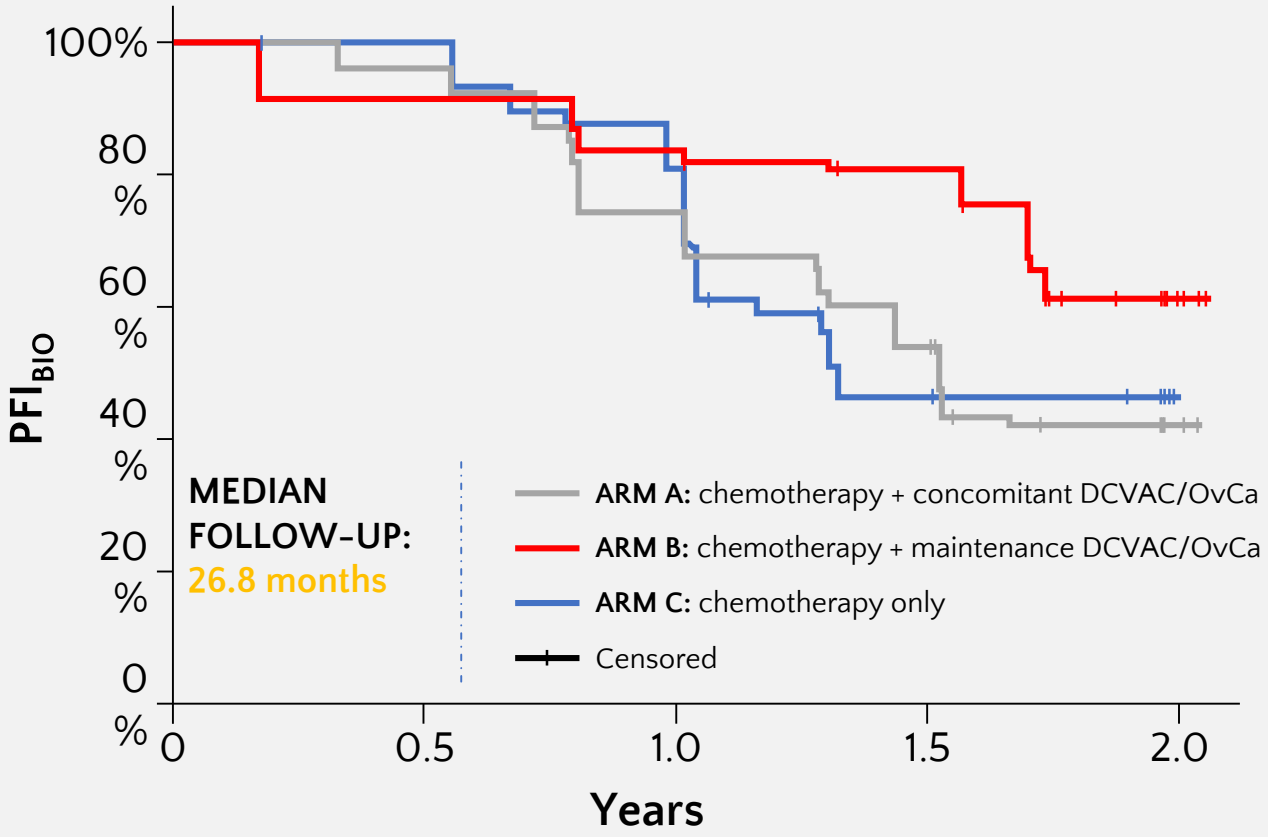
6-month Benefit in mPFS and 57% Decrease in The Hazard of Progression in Arm B



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

PFI$_{BIO}$ (Based on CA-125 Elevations)

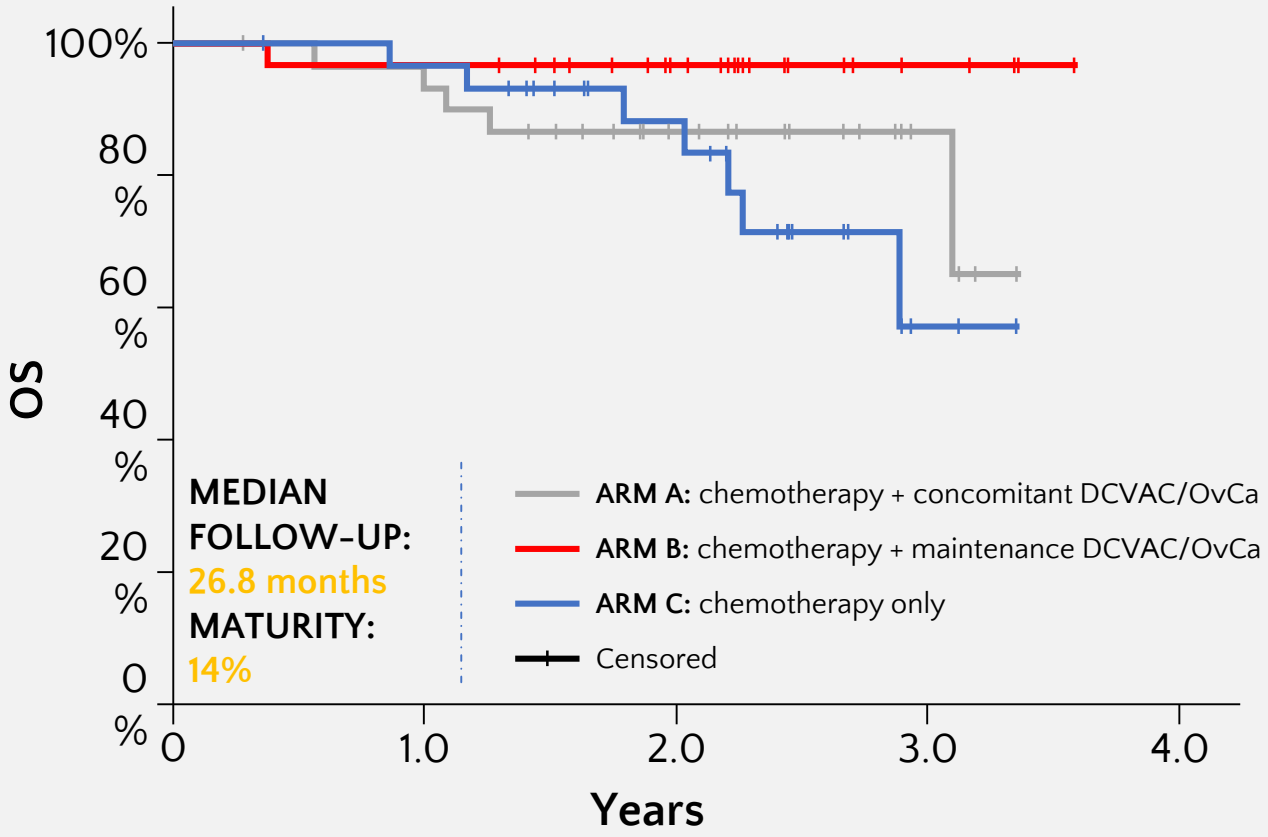
PFI$_{BIO}$ Supporting PFS Benefit



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



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

Souhrn

01 Maintenance DCVAC/OvCa zvýšil o 6 měsíců **PFS**

02 Maintenance DCVAC/OvCa prokazuje téměř **60% redukci rizika progrese nebo smrti**

03 Současná **data OS mají stejný trend jako PFS**

04 DCVAC/OvCa je **velice dobře snášená**

05 Optimistické výsledky fáze II. s využitím maintenance **DCVAC/OvCa musí být ověřeny ve fázi III. studie**

Budoucnost I. linie léčby ovariálních karcinomů

- Základem léčebného úspěchu u pokročilých EOC je radikální chirurgická léčba s následnou adjuvantní chemoterapií. „Být ve správný čas na správném místě“
- Jedním z inovativních postupů je maintanance využití aktivní buněčné imunoterapie.
- SOV01/ DCVAC/OvCa – velice optimistické výsledky, které ale musí potvrdit fáze 3
- DCVAC/OvCa – aktivní buněčná imunoterapie má extrémně příznivý profil toxicity
  – budoucnost maintanance ev. kombinace s PARP.

Děkuji za pozornost