

Nastal nový štandard liečby inoperabilného karcinómu krčka maternice?

Zuzana Dolinská, Pavol Bíreš, Andrej Jurík a kol.

- ☒ Nemám potenciálny konflikt záujmov
- ☐ Deklarujem nasledujúci konflikt záujmov

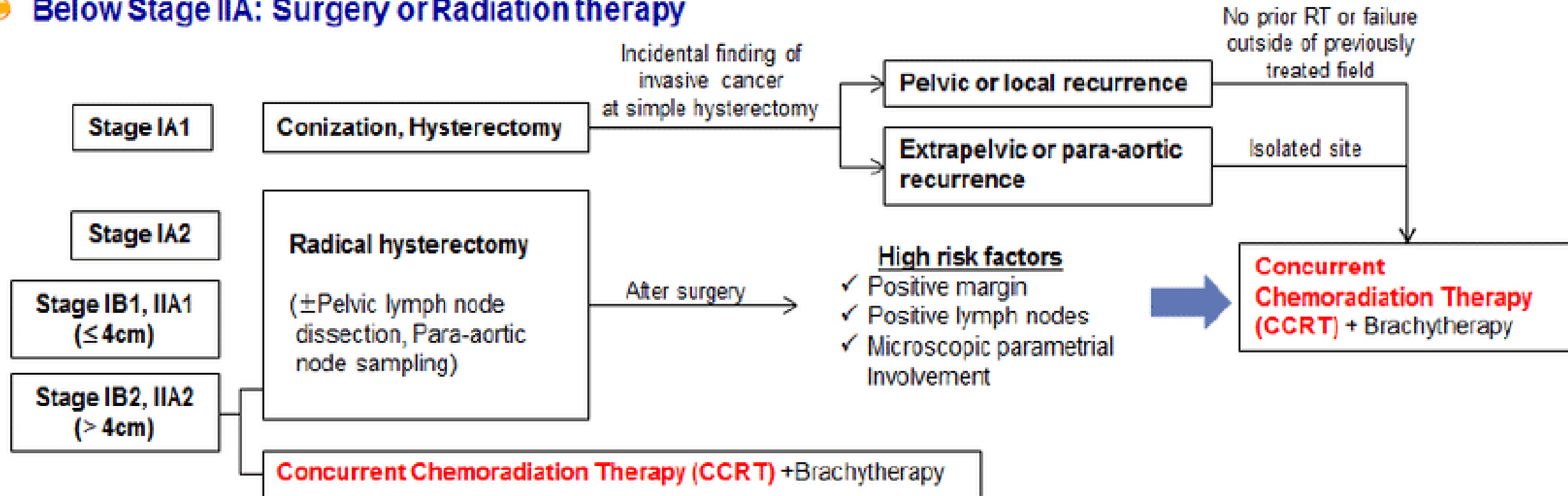
Forma finančného prepojenia	Spoločnosť
Participácia na klinických štúdiách/firemnom grante	
Nepeňažné plnenie (v zmysle zákona)	
Prednášajúci	
Akcionár	
Konzultant/odborný poradca	
Ostatné príjmy (špecifikovať)	

Fakty o lokálne pokročilom ochorení C53

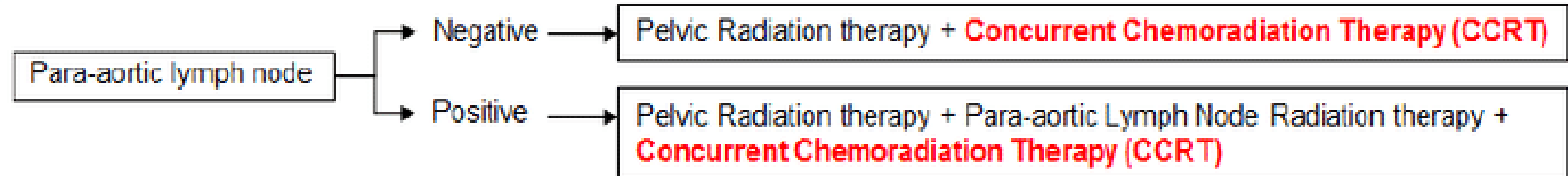


- Viac ako 50% pac. zrelabuje do 2 r. od stanovenia dg
- Viac ako dve dekády je štandardom rádiochemoterapia
(od 1990- metaanalýza CRT pre FIGO IB3- IVA)
- Konkomitantná cDDP prináša 6% zlepšenie v OS (metaanalýza)
- Adjuvantná CHT po RT-CHT nepriniesla benefit v OS
- Median OS od rekurencie je 12 mesiacov
- zlepšenie EXRT - IMRT, VMAT
- inovácie v BT- používanie 3D- IGBT
- HBT Hybrid brachytherapy (intrakavitálna a intersticiálna BT)

Below Stage IIA: Surgery or Radiation therapy



Beyond Stage IIB:





Schémy liečby Chemo + EXRT + Brachy

— CHEMO - cDDP
— EXRT
— BRACHY

Schéma A

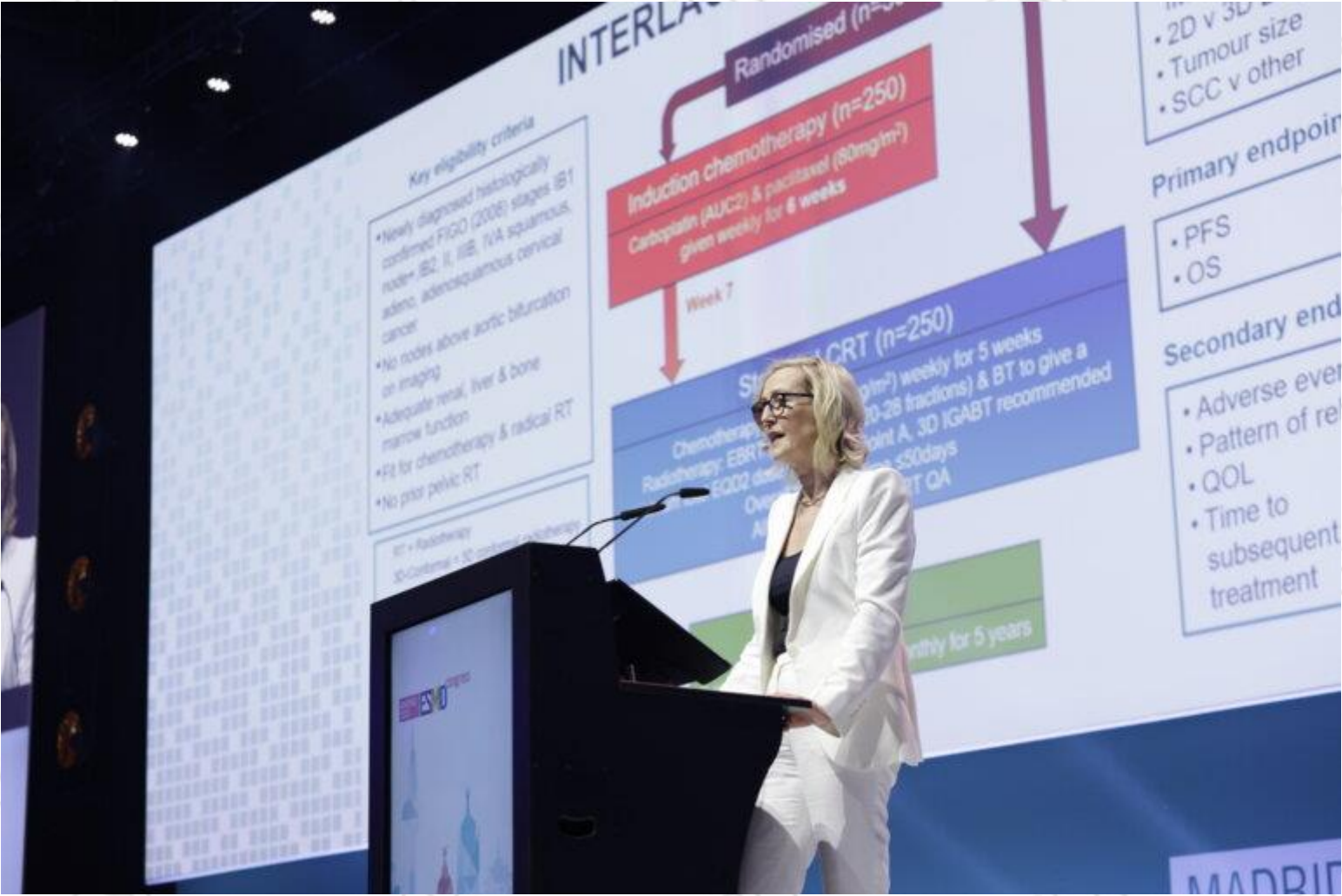


Schéma B





Mary McCormack, London, UK,
during the Presidential Symposium 2 at the ESMO Congress 2023 (Madrid, Spain, 20-24 October)





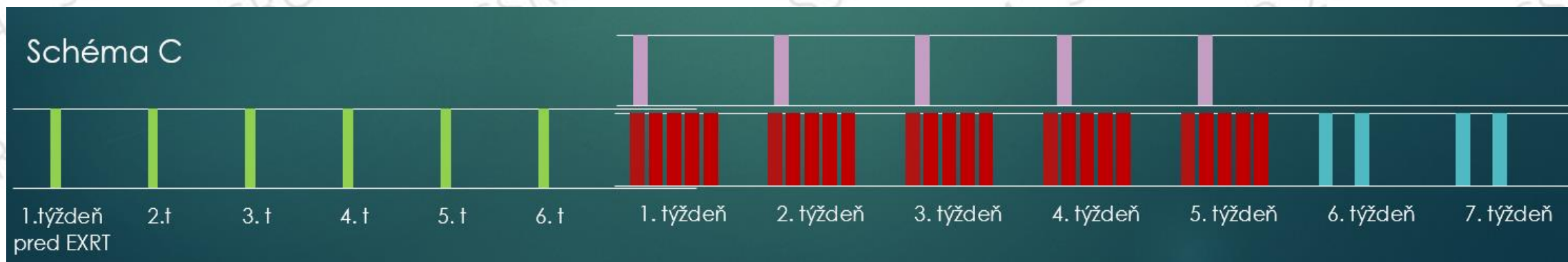
INTERLACE trial

— CHEMO - CBDCA + PACLITAXEL

— CHEMO - cDDP

— EXRT

— BRACHY



INTERLACE Trial Design

Key eligibility criteria

- Newly diagnosed histologically confirmed FIGO (2008) stages IB1 node+, IB2, II, IIIB, IVA squamous, adeno, adenosquamous cervical cancer
- No nodes above aortic bifurcation on imaging
- Adequate renal, liver & bone marrow function
- Fit for chemotherapy & radical RT
- No prior pelvic RT

RT = Radiotherapy

3D-Conformal = 3D conformal radiotherapy

IMRT = Intensity modulated radiotherapy

EBRT = External beam radiotherapy

BT = Brachytherapy

IGABT = Image-guided adaptive brachytherapy

RT QA = Radiotherapy quality assurance

Stratified by

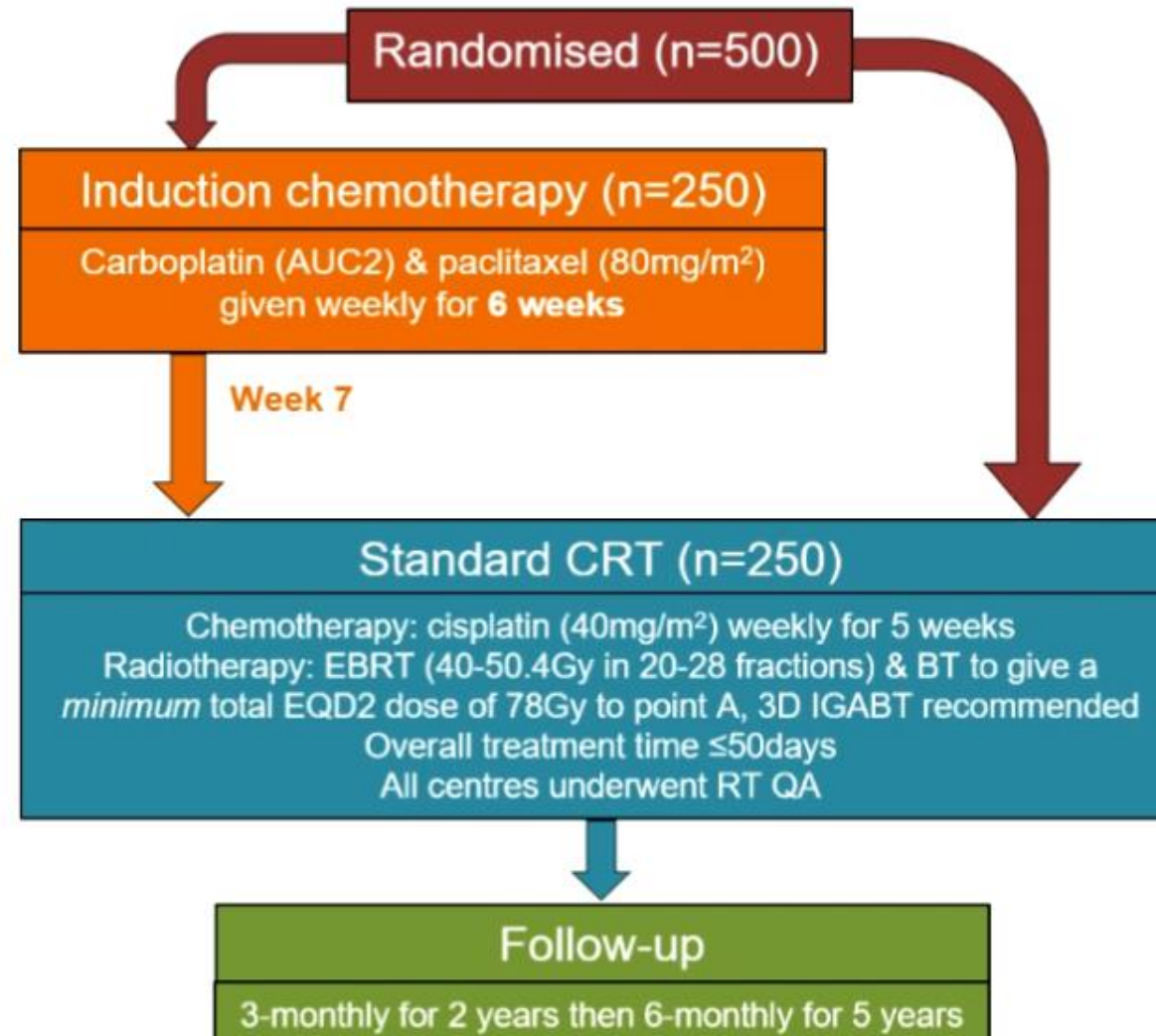
- Site
- Stage
- Nodal status
- 3D-Conformal v IMRT EBRT
- 2D v 3D BT
- Tumour size
- SCC v other

Primary endpoints

- PFS
- OS

Secondary endpoints

- Adverse events
- Pattern of relapse
- QOL
- Time to subsequent treatment



Prevzáté z: McCormack: A random phase III trial of induction chemotherapy followed by chemoradiation compared with chemoradiation alone in locally advanced cervical cancer. ESMO 2023

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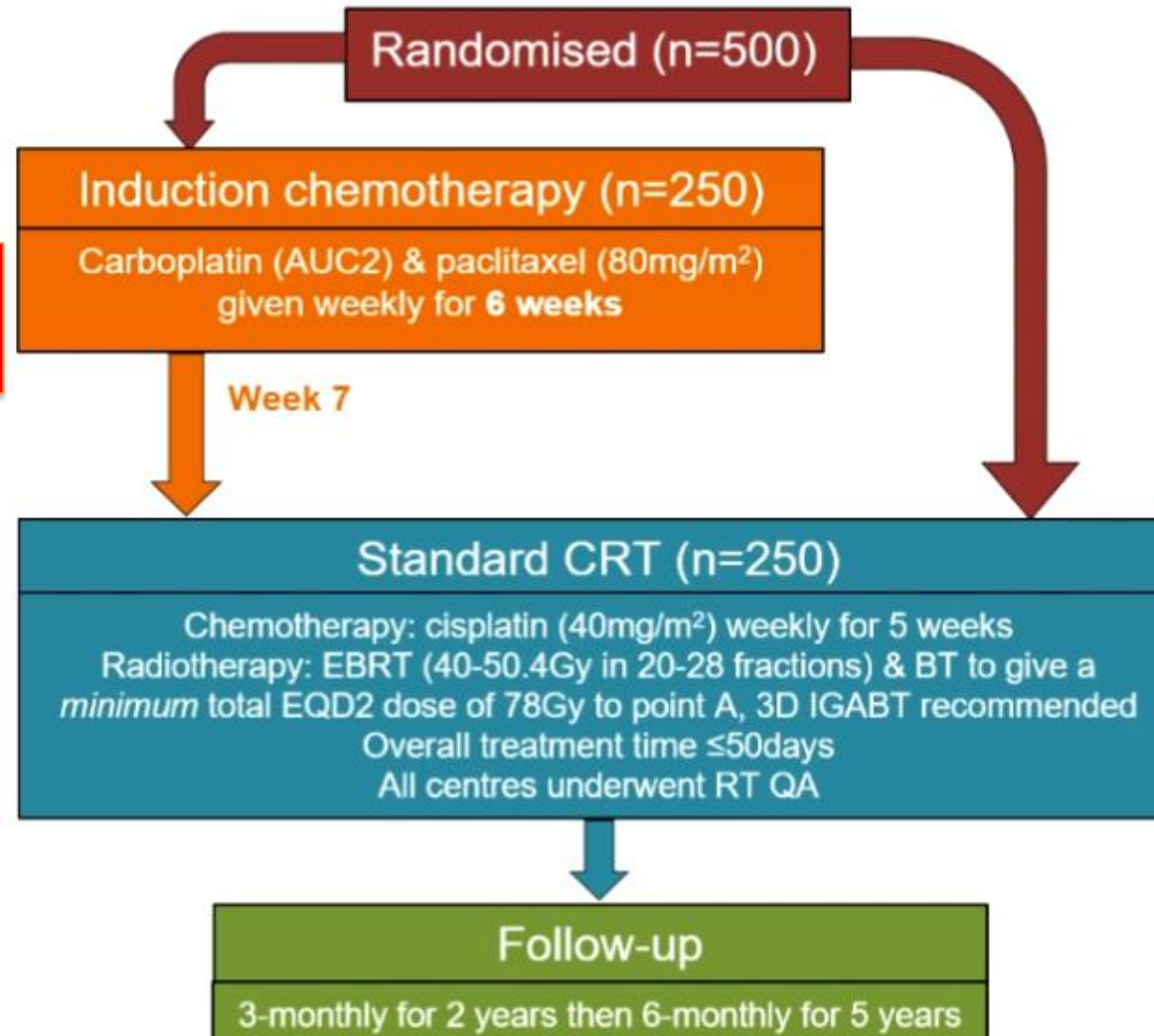
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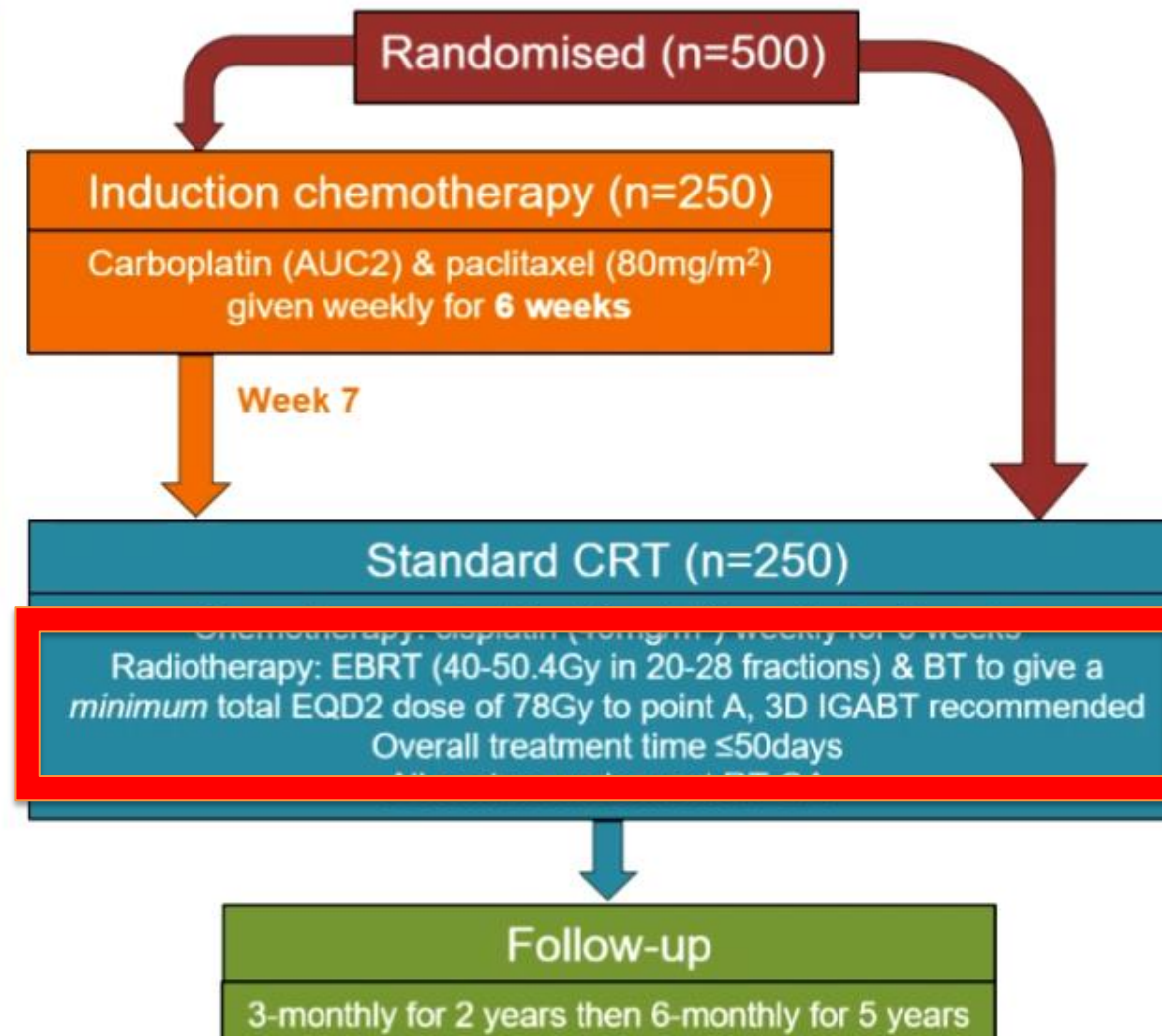
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INTERLACE trial

- 11/2012- 11/2022, 32 centier, 5 krajín, FU 64 mes.
- Median veku 46r. (24- 78r.)
- SCC, adenoCa, adenoskvamózny Ca
- FIGO 1B1 N+, IB2,II,IIIB,IVA OTT 45 dní
- 500 pac. → CRT 5x cDDP
- → IC (6xCBDCA, Paklitaxel) – CRT
- Čas od IC po CRT 7 dní

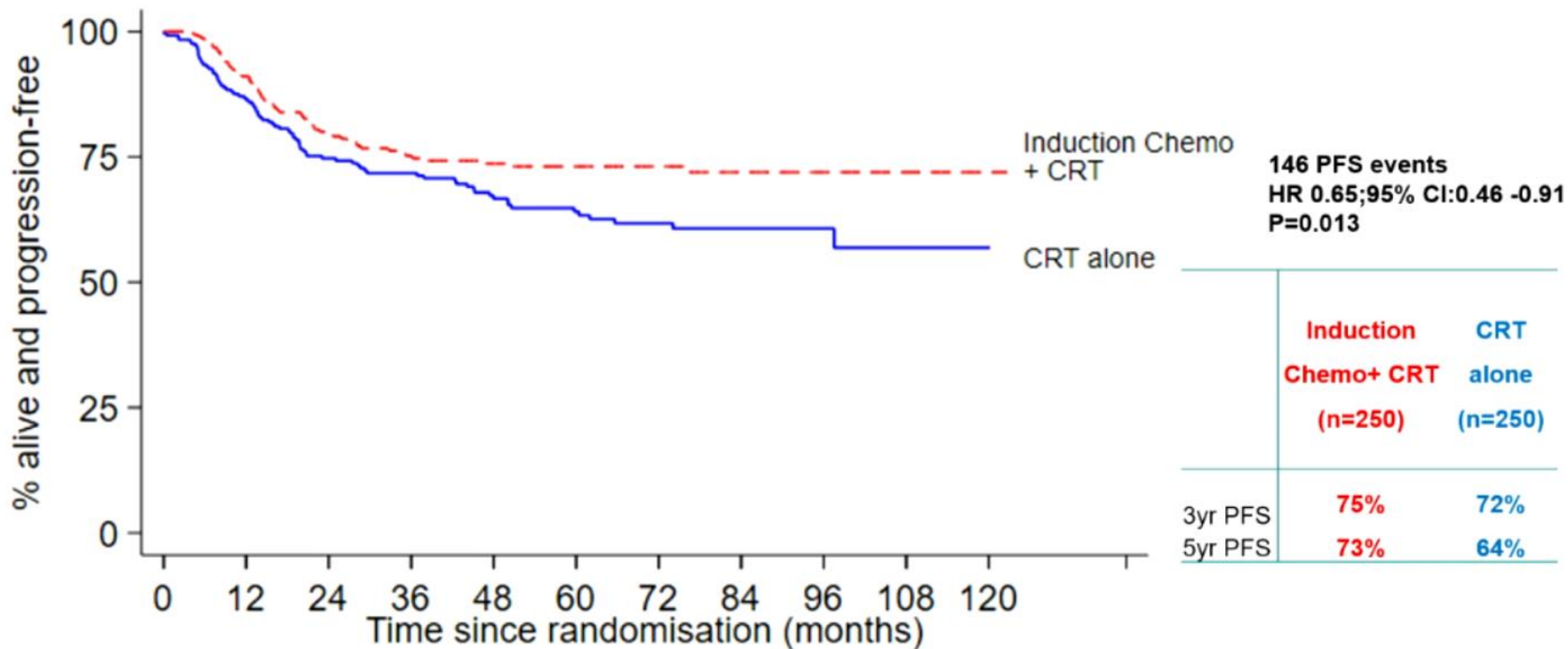
	CRT alone (N=250)	Induction Chemo + CRT (N=250)
FIGO stage (2008)	No. of patients (%)	
IB1	2 (<1)	2 (<1)
IB2	23 (9)	19 (8)
IIA	14 (6)	17 (7)
IIB	176 (70)	178 (71)
IIIB	30 (12)	26 (10)
IVA	5 (2)	8 (3)
Cell type		
Non-squamous	45 (18)	44 (18)
Squamous	205 (82)	206 (82)
Nodal status		
Negative	142 (57)	146 (58)
Positive	108 (43)	104 (42)
Longest tumour diameter, cm median (range)	4.9 (1.8-12.8)	4.8 (1.3-13.5)



INTERLACE trial

- 84% (IC/CRT) vs. 89% (CRT) malo 4/5 cyklov cisplatiny
 - V CRT ramene 92% and 89% ukončilo EXRT a BT
 - V IC/CRT ramene 97% and 95%
- | | | |
|---------------------|--------------|------------|
| • Toxicita ≥ 3 | 59% (IC/CRT) | 48 % (CRT) |
| • PFS 5y. | 73% | 64% |
| • OS 5y. | 80% | 72% |

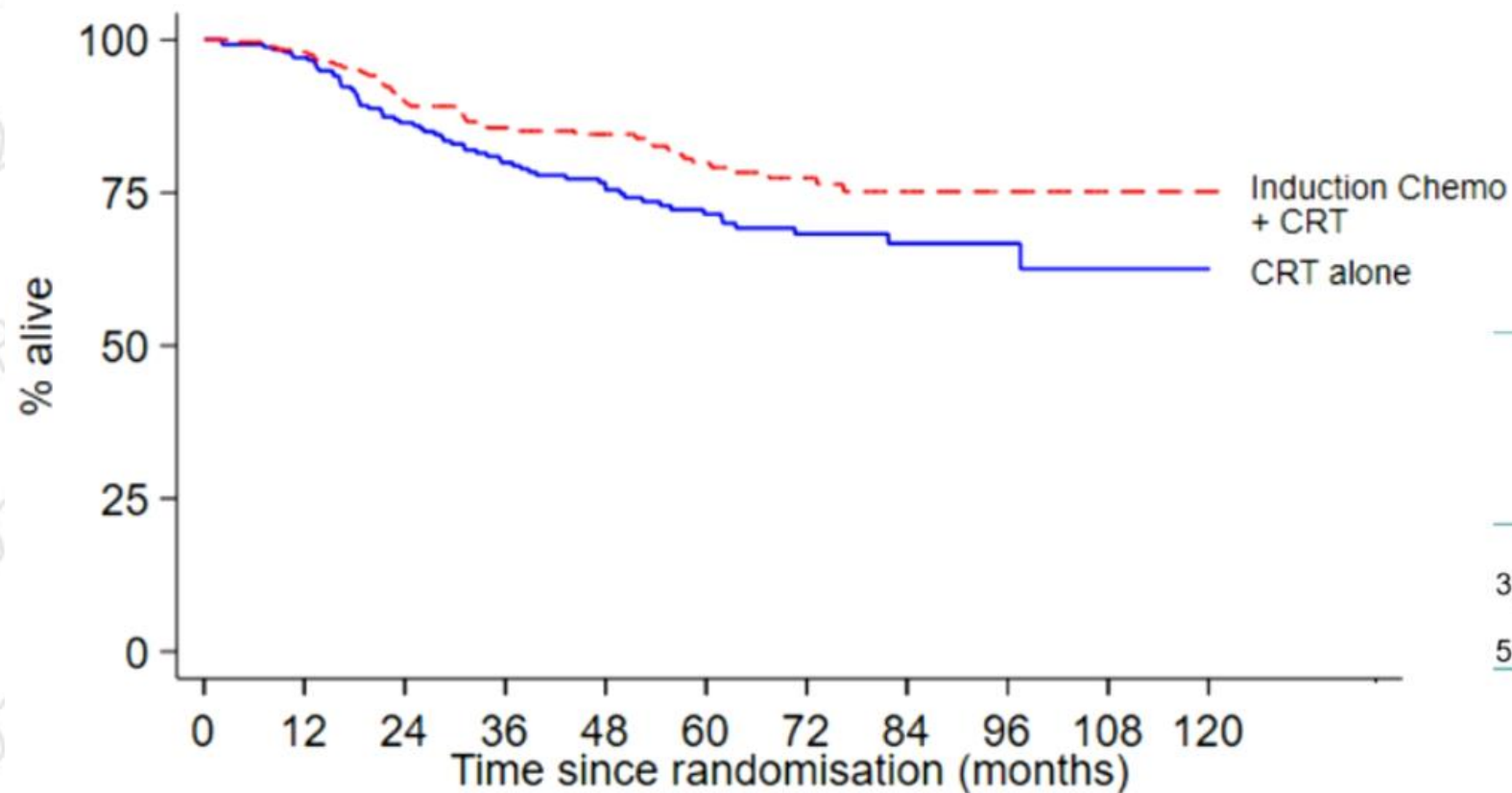
PFS



Number at risk	250	204	157	140	110	88	63	36	16	5	1
CRT alone	250	220	178	152	132	105	72	40	19	8	1
Induction Chemo + CRT											



OS



109 deaths
HR 0.61; 95% CI: 0.40-0.91
P=0.04

	Induction Chemo + CRT (n=250)	CRT alone (n=250)
3yr OS	86%	80%
5yr OS	80%	72%

Number at risk	250	228	181	154	124	99	67	39	16	5	1
CRT alone	250	236	195	168	146	111	75	42	19	8	1
Induction Chemo + CRT	250	236	195	168	146	111	75	42	19	8	1



GCIG
GYNECOLOGIC
CANCER INTERGROUP



CANCER
RESEARCH
UK

CANCER
TRIALS
CENTRE



Toxicita liečby v NOÚ- 7 pacientok



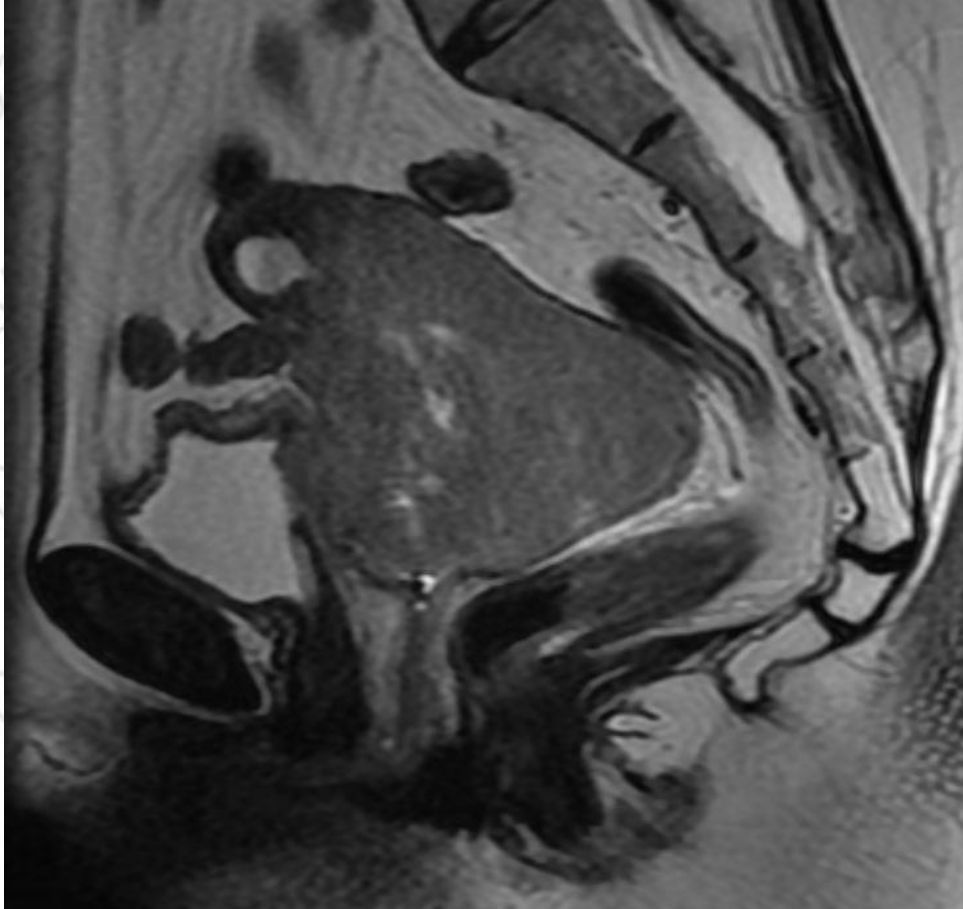
- Trombóza VIC, VII 1x
- Embólia a.pulmonalis 1x
- Ototoxicita 1x
- Leukopénia G 2 7x
- Trombocytopénia G3 1x
- 2 pacientky EXRT boost
- čas liečby BT skupina 49/90, 41/97, 41/81, 43/86, 44/84,
čas liečby v EXRT boost sk. 49/92, 62/128



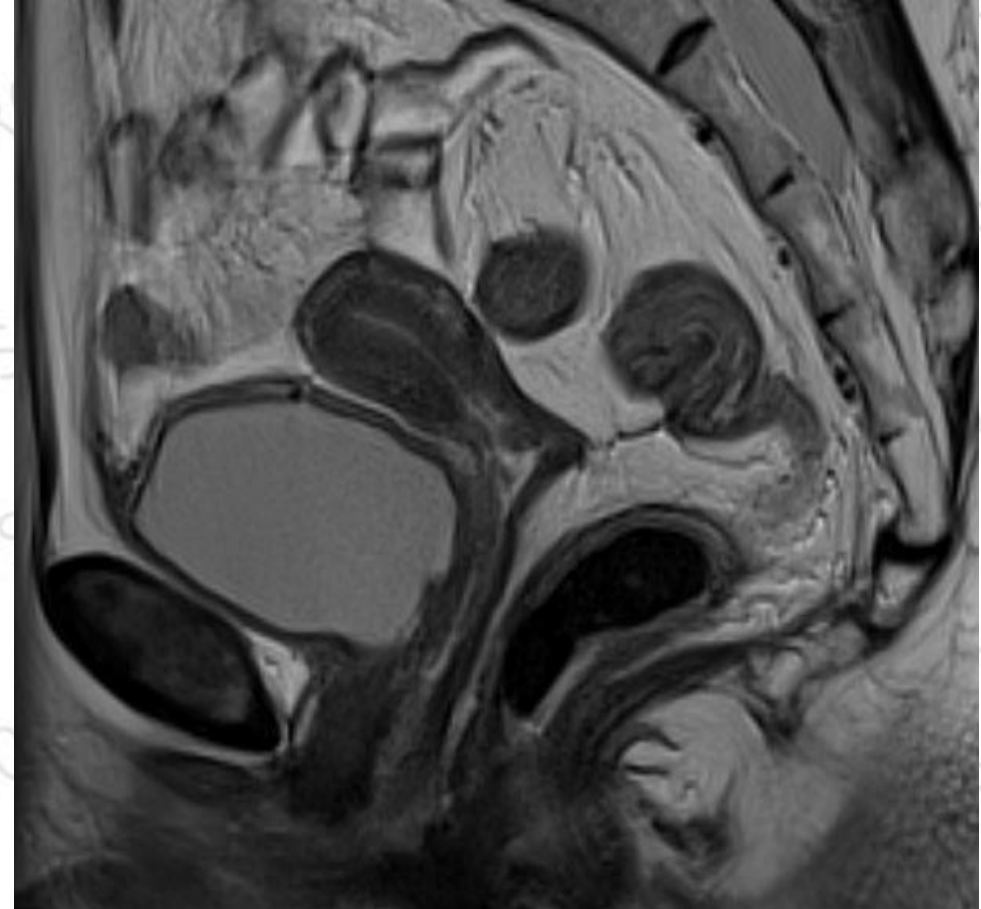
Kazuistika

- 59 ročná pacientka s Dg Ca krčka maternice inop., histológia dlaždicovobunkový nekeratinizujúci karcinóm, G3, FIGO IVA
- Tumor iniciálne viac ako 9 cm
- Po 3-4 cykloch II.B
- Trombóza v.iliaca interna, v.iliaca comunis

IV.A štádium



II.B štádium





Konečne zmena po desaťročiach

Lepšie PFS, OS

Lepšie naplánovanie celej liečby

Akceptovateľná toxicita

Regresia ochorenia v čase brachyterapie

Dostupná liečba



NÁRODNÝ
ONKOLOGICKÝ ÚSTAV
umenie liečiť





ENGOT-cx11/GOG-3047/KEYNOTE-A18 (NCT04221945): Randomized, Double-Blind, Phase 3 Study

Key Eligibility Criteria

- FIGO 2014 stage IB2-IIB (node-positive disease) or FIGO 2014 stage III-IVA (either node-positive or node-negative disease)
- RECIST v1.1 measurable or non-measurable disease
- Treatment naïve

Stratification Factors

- Planned EBRT type (IMRT or VMAT vs non-IMRT or non-VMAT)
- Stage at screening (stage IB2-IIB vs III-IVA)
- Planned total radiotherapy dose (<70 Gy vs ≥70 Gy [EQD2])^a

R
1:1
N=1060

Cisplatin 40 mg/m² QW for 5 cycles^b + EBRT followed by brachytherapy
+
Pembrolizumab 200 mg Q3W for 5 cycles

Pembrolizumab 400 mg Q6W for 15 cycles

Cisplatin 40 mg/m² QW for 5 cycles^b + EBRT followed by brachytherapy
+
Placebo Q3W for 5 cycles

Placebo Q6W for 15 cycles

End Points^c

- Primary: PFS (per RECIST v1.1) by investigator or histopathologic confirmation and OS
- Key secondary: 24-month PFS, ORR, patient-reported outcomes, and safety

Median (range) follow-up time from randomization to data cutoff date (Jan 9, 2023) was 17.9 (0.9-31.0) mo



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^aStratification for radiotherapy dose was due to the participation of Japan in which the radiotherapy standard of care recommended a lower dose. ^bA 6th cycle was allowed per investigator discretion. ^cThe protocol-specified first interim analysis (IA1) was planned to occur at completion of enrollment and when ~237 events (PD or death) had occurred. For PFS, initial 1-sided alpha was $\alpha = 0.025$; for OS, initial 1-sided alpha was 0. The prespecified analysis plan allows alpha from successful hypothesis to be passed to the other hypothesis.





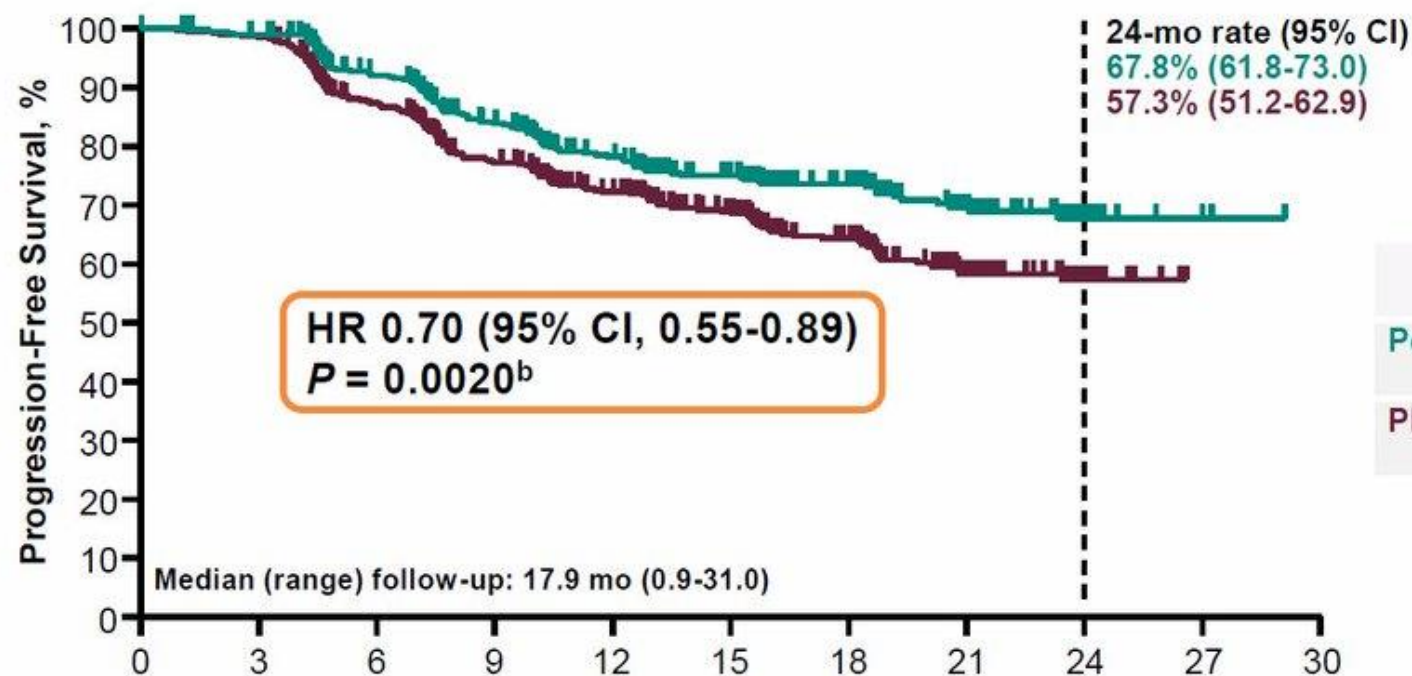
KEYNOTE- A18

Checkpoint inhibition improves outcomes in high-risk, locally advanced cervical cancer

In the KEYNOTE-A18 study, the combination of pembrolizumab and concurrent chemoradiotherapy significantly improved progression-free survival



Primary Endpoint: Progression-Free Survival^a



	Pts w/ Event	Median, mo (95% CI)
Pembro Arm	21.7%	NR (NR-NR)
Placebo Arm	29.0%	NR (NR-NR)

No. at risk

529	462	400	331	282	222	171	100	26	3	0
531	463	379	306	263	208	149	88	20	0	0



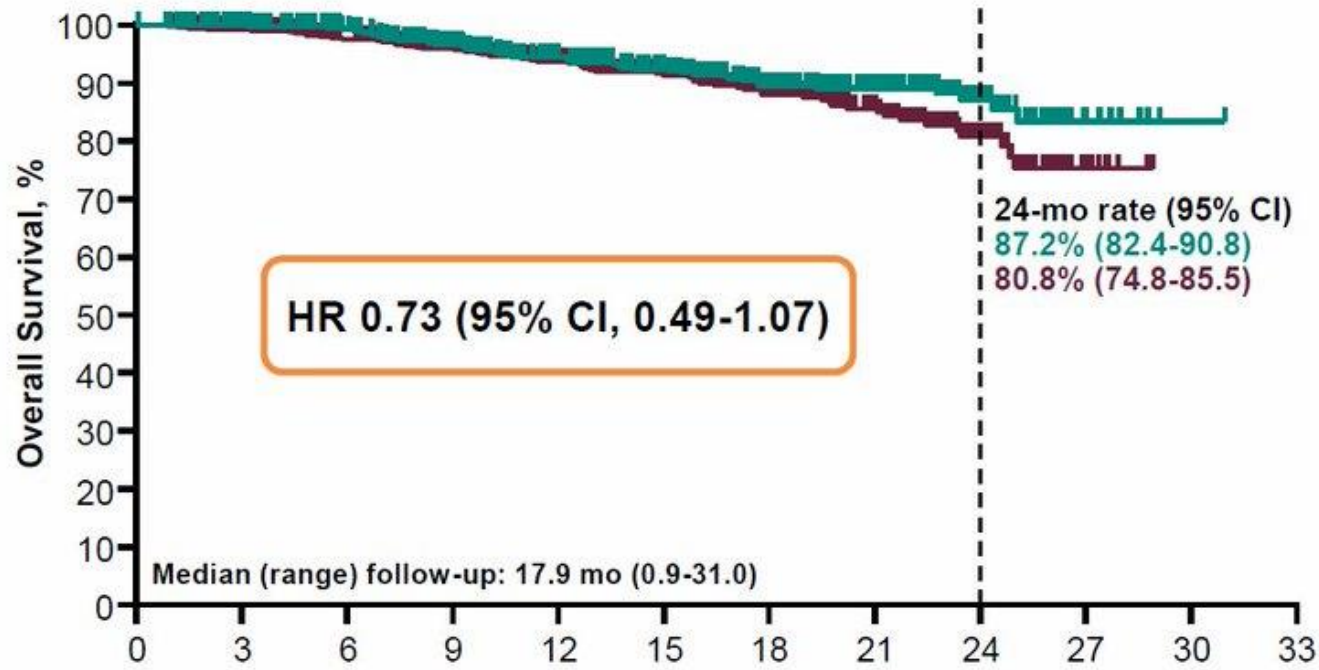
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Response assessed per RECIST v1.1 by investigator review or histopathologic confirmation. ^aEvaluated in all randomized participants. ^bWith 269 events (88.5% information fraction), the observed $P = 0.0020$ (1-sided) crossed the prespecified nominal boundary of 0.0172 (1-sided) at this planned first interim analysis. The success criterion of the PFS hypothesis was met, and thus no formal testing of PFS will be performed at a later analysis. Data cutoff date: January 9, 2023.





Primary Endpoint: Overall Survival^a



No. at risk											
529	496	456	405	351	294	223	151	67	10	1	0
531	498	449	402	339	278	214	139	62	12	0	0

	Pts w/ Event*	Median, mo (95% CI)
Pembro Arm	8.3%	NR (NR-NR)
Placebo Arm	11.1%	NR (NR-NR)

*42.9% information fraction^b



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^aEvaluated in all randomized participants. ^bAt this analysis, 103 of the 240 deaths expected at the final analysis had occurred.
Data cutoff date: January 9, 2023.



Summary and Conclusions

- Pembrolizumab combined with chemoradiotherapy and then continued after chemoradiotherapy provided statistically significant and clinically meaningful improvements in progression-free survival versus chemoradiotherapy alone in patients with newly diagnosed, previously untreated, high-risk, locally advanced cervical cancer
 - Benefit generally consistent across all prespecified subgroups
 - High-quality radiotherapy delivery was ensured
- At this first interim analysis, the estimate of effect on overall survival supports the progression-free survival results
- Safety profile for pembrolizumab plus chemoradiotherapy was manageable and as expected
- **These data support pembrolizumab plus chemoradiotherapy as a new standard of care for patients with newly diagnosed, previously untreated, high-risk, locally advanced cervical cancer**



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Ďakujem za pozornosť

