

Management of locally advanced disease

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Disclosures

- Trine Jakobi Nøttrup, Senior Consultant, Section lead
- Within the last 12 months I have received salary for presentations, transportation coverage and other expenses regarding similar presentations and meeting activity
- From GlaxoSmithKline Pharma A/S; Presentation, Podcast, Webinar
- From MSD Danmark ApS; Advisory Board
- From Astrazeneca A/S; Advisory Board, Presentation, Discussant
- From AMGEN; Presentation
- From BMS; Educational activity

Patient case

May 2022, 34 år, cervical cancer FIGO IIC2, iliac and paraoartal lymphnode spread

Concomittant treatment

eksternal beam radiotherapy 45/55/57 Gy in 25 fractions,
weekly cisplatin

brachytherapy, 2 fractions

After 30 months No sign of recurrence

Multiple pulmonar emboli during 2nd brachytherapy, prolonged anti coagulant treatment

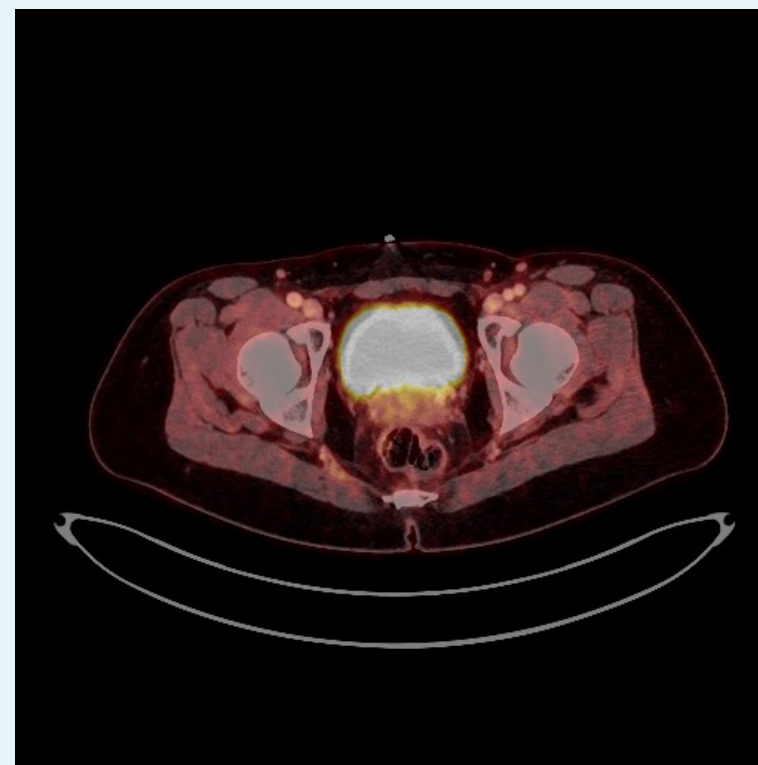
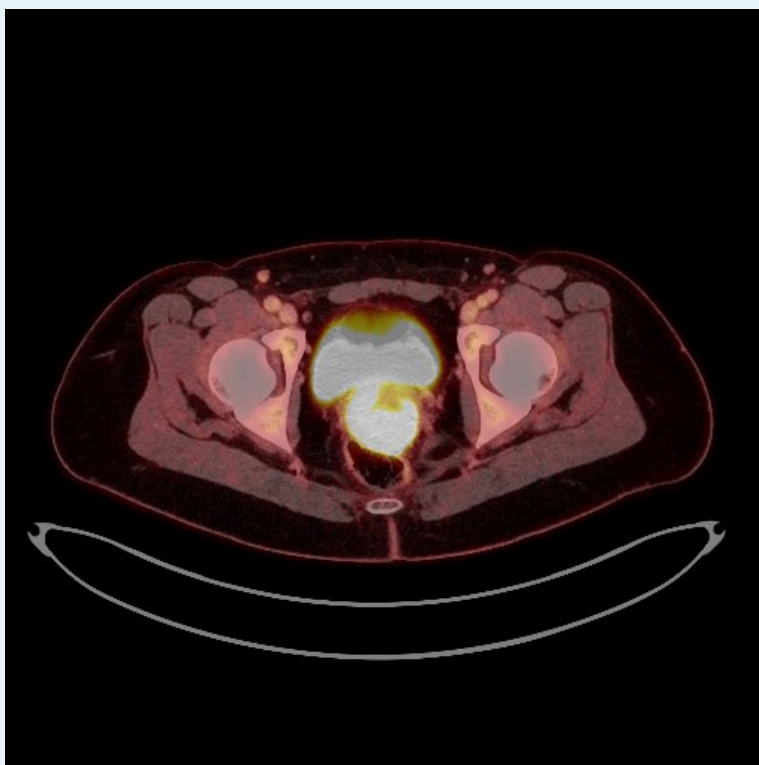
Hormon replacement therapy

January 2024 bacteriaemia with streptococcus

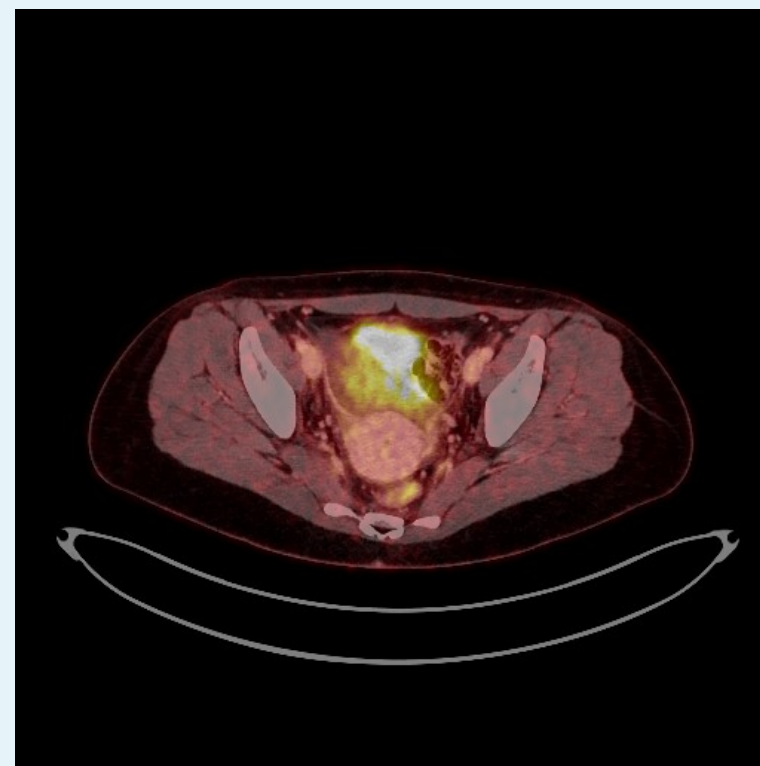
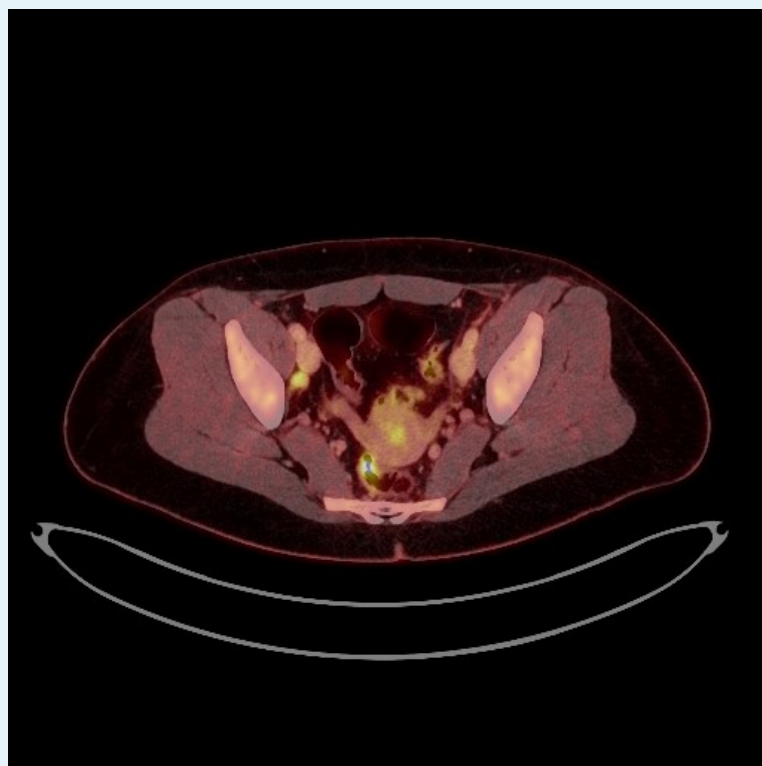
October 2024: living well, feels no late effects

Uses vaginal dilator and can have penetrative intercourse

PET/CT cervix, 2022 og 2024



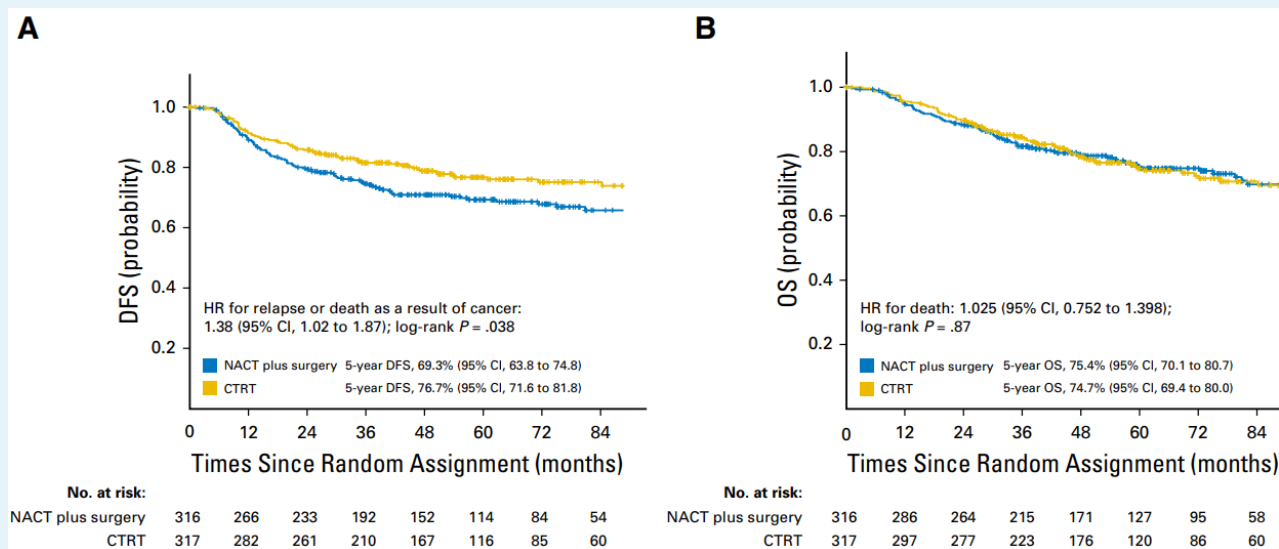
PET/CT iliac lymphnode, 2022 og 2024



Treatment related to FIGO stage and size

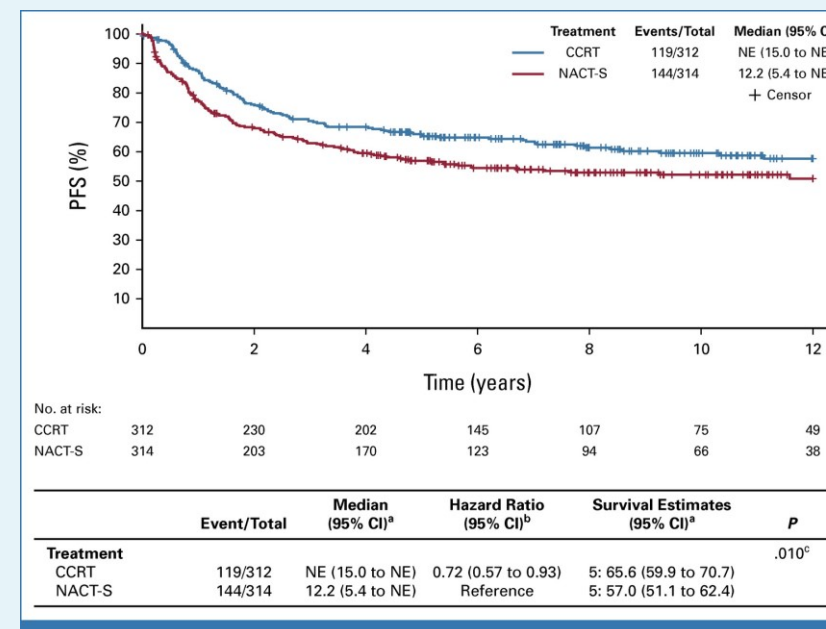
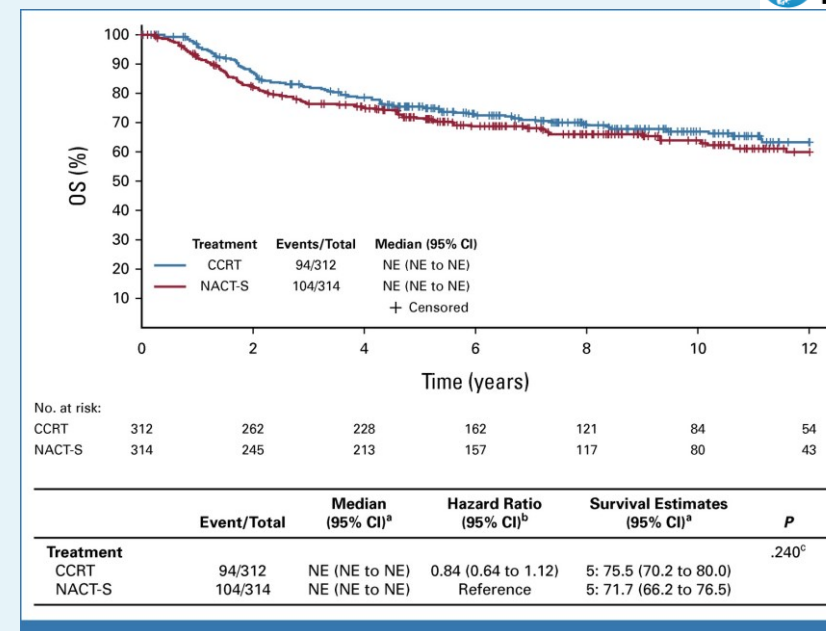
Stage	Size	Treatment	Special awareness
1A1+2	≤ 10 mm horisontalt	Konus/simpel hysterektomi	Hvis udbredt LVSI, da SN
1A1+2	horisontalt >10 - ≤17 mm	Konus/simpel hysterektomi + SN	Også uden LVSI
1A1+2	horisontalt >17- ≤ 20 mm	Radikal hysterektomi (B)/trakelektomi	Altid SN
IB1	≤ 20 mm	Radikal hysterektomi (B)/trakelektomi, SN + LK	Synlig tumor, konus uden frie rande Klinisk suspekte til frys og afbryd operation, hvis metastase
IB2	> 20 - ≤ 40 mm	Radikal hysterektomi (C1), SN + LK fjernelse	
IB3	> 40 mm	Radikal hysterektomi (C2), LK fjernelse eller stråle- kemoterapi	
IIA		Radikal hysterektomi (C2), LK fjernelse eller stråle- kemoterapi	
IIB		Radiotherapy and chemotherapy	Adjuvant therapy???????
IIIB			
IIIC1			
IIIC2			
IVA			
IVB		Systemic treatment	Immunotherapy

Neo Adjuvant therapy

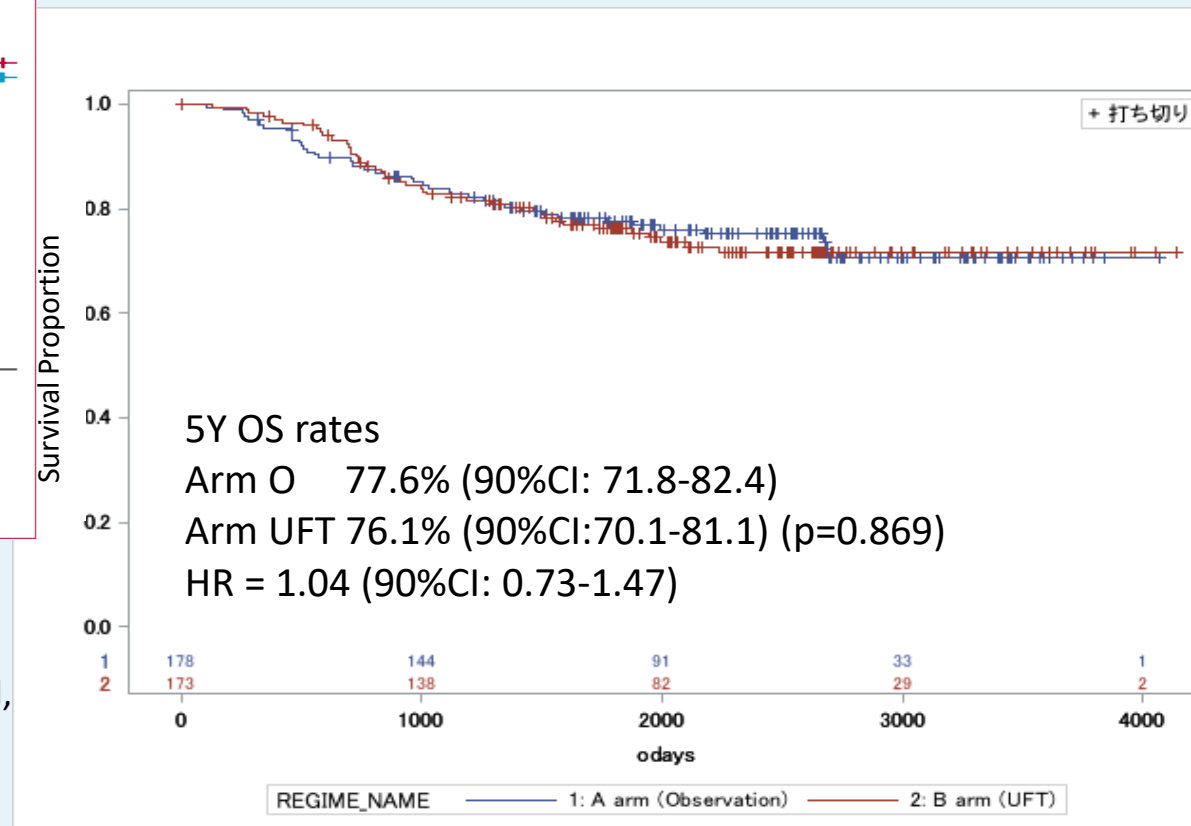
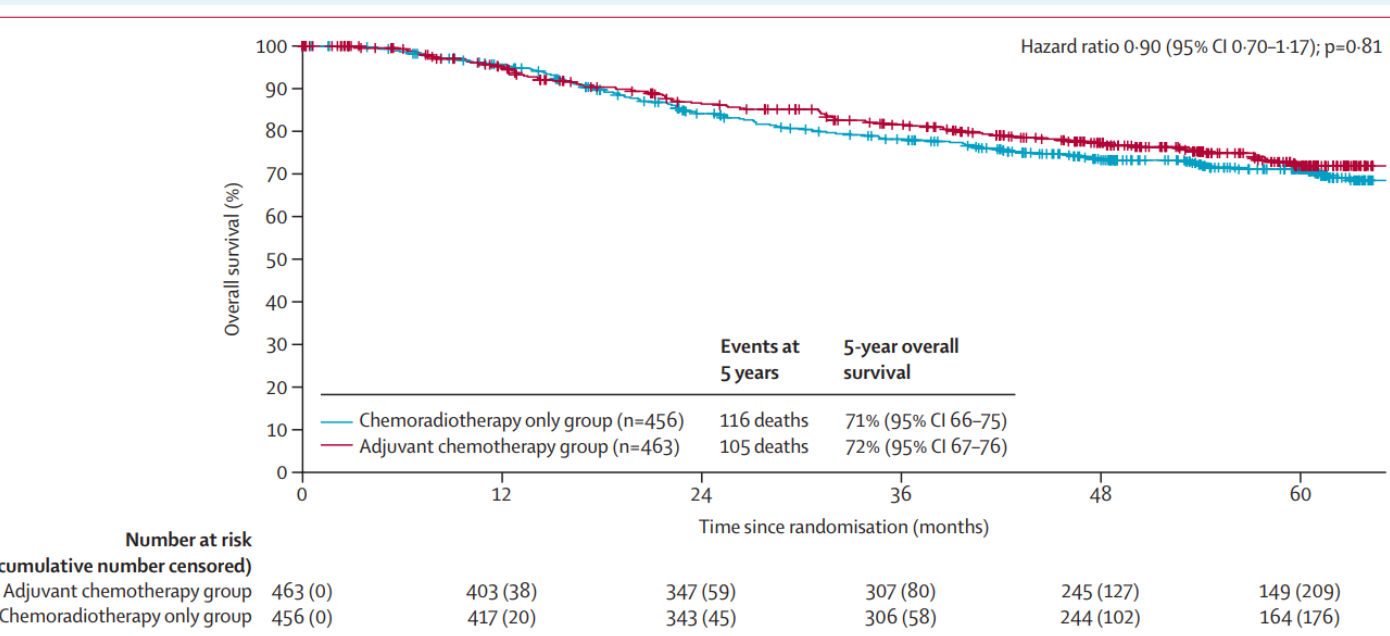


Gupta S, et al., Neoadjuvant Chemotherapy Followed by Radical Surgery Versus Concomitant Chemotherapy and Radiotherapy in Patients With Stage IB2, IIA, or IIB Squamous Cervical Cancer: A Randomized Controlled Trial. *J Clin Oncol* 36:1548-1555

Gemma G. Kenter et al., Randomized Phase III Study Comparing Neoadjuvant Chemotherapy Followed by Surgery Versus Chemoradiation in Stage IB2-IIB Cervical Cancer: EORTC-55994. *JCO* 41, 5035-5043(2023). DOI:10.1200/JCO.22.02852



Adjuvant therapy



Adjuvant chemotherapy following chemoradiotherapy as primary treatment for locally advanced cervical cancer versus chemoradiotherapy alone (OUTBACK): an international, open-label, randomised, phase 3 trial

Mileshkin, Linda R et al. The Lancet Oncology, Volume 24, Issue 5, 468 - 482

LBA31 Randomized phase III trial of maintenance chemotherapy with tegafur-uracil versus observation following concurrent chemoradiotherapy for locally advanced cervical cancer, GOTIC-002 LUFT trial Fujiwara, K. et al. Annals of Oncology, Volume 33, S1398

Treatment based om EMBRACE

Cervix/tumor 45 Gy, 1,8 Gy/fraction

- 5 days a week

Lymphnodes with no visible tumor 45 Gy, 1,8 Gy/fraction

- 5 days a week

Pelvic lymphodes with supected malignancy on imaging 55 Gy, 2,2 Gy/fraction

- 5 days a week

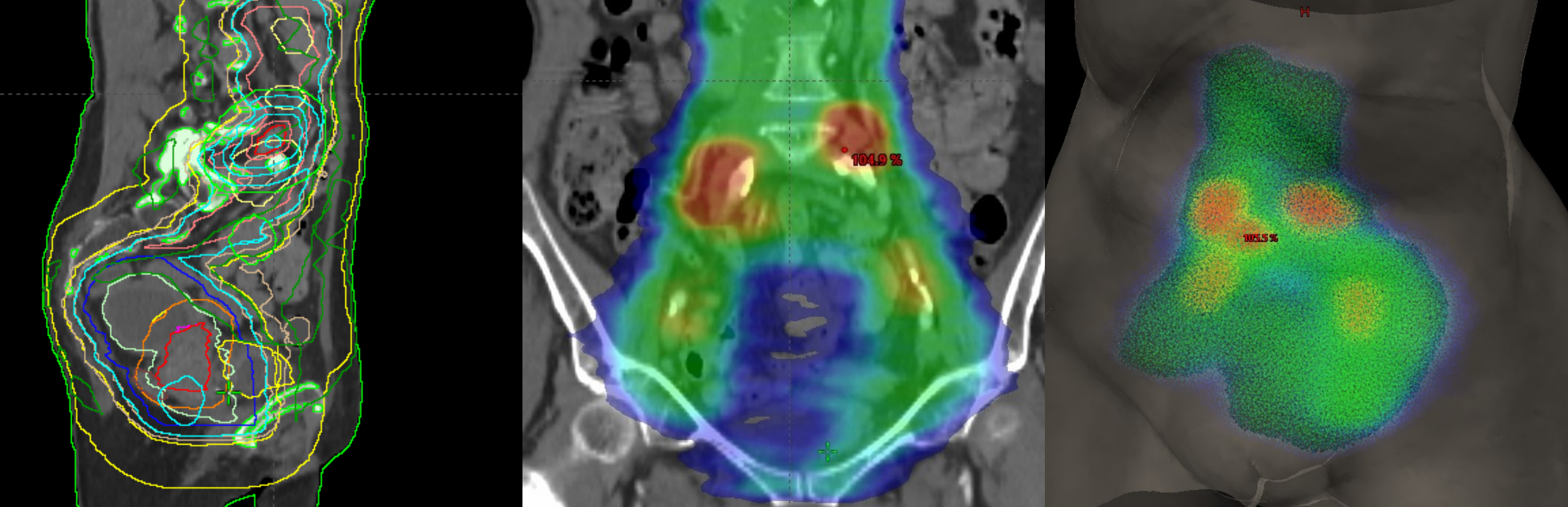
Paraaortal lymphodes with supected malignancy on imaging 57,5 Gy, 2,3 Gy/fraction

- 5 days a week

Every week iv cisplatin 40 mg/m², max 70 mg

Brachyterapi

- HDR or PDR



Contouring and doseplanning



Tumorshrinkage during extarnal beam therapy

EMBRACE I, 2008-15

N=1341, morbidity data N=1251

5 year

Pelvic control 87%

Lymphnode control 87%

Survival 74%

Disease free survival 68%

Grad 3-5 morbidity

gynecological/urologic 6,8 %

gastrointestinal 8,5 %

vaginal 5,7 %

fistula 3,2 %

98 Lokal Recurrences, Lokal control 92 %

Multivariate analysis

Histology

Minimum dose to 90 % CTV HR

Volume of CTV HR

Tumor above 45 cm³

Duration of treatment

Necrosis

Involvement in uterus or mesorectum

To simultaneous publicereade studier

Induction chemotherapy followed by standard chemoradiotherapy versus standard chemoradiotherapy alone in patients with locally advanced cervical cancer (GCIIG INTERLACE): an international, multicentre, randomised phase 3 trial

*Mary McCormack, Gemma Eminowicz, Dolores Gallardo, Patricia Diez, Laura Farrelly, Christopher Kent, Emma Hudson, Miguel Panades, Tony Mathew, Anjana Anand, Mojca Persic, Jennifer Forrest, Rajanee Bhana, Nicholas Reed, Anne Drake, Madhavi Adusumalli, Asima Mukhopadhyay, Margaret King, Karen Whitmarsh, John McGrane, Nicoletta Colombo, Choi Mak, Ranajit Mandal, Rahul Roy Chowdhury, Gabriela Alamilla-García, Adriana Chávez-Blanco, Hilary Stobart, Amanda Feeney, Simran Vaja, Anne-Marie Hacker, Allan Hackshaw, Jonathan Andrew Ledermann, on behalf of the INTERLACE investigators**

Pembrolizumab or placebo with chemoradiotherapy followed by pembrolizumab or placebo for newly diagnosed, high-risk, locally advanced cervical cancer (ENGOT-cx11/GOG-3047/KEYNOTE-A18): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 trial

Domenica Lorusso, Yang Xiang, Kosei Hasegawa, Giovanni Scambia, Manuel Leiva, Pier Ramos-Elias, Alejandro Acevedo, Jakub Cvek, Leslie Randall, Andrea Juliana Pereira de Santana Gomes, Fernando Contreras Mejía, Limor Helpman, Hüseyin Akilli, Jung-Yun Lee, Valeriya Saevets, Flora Zagouri, Lucy Gilbert, Jalid Sehouli, Ekkasit Tharavichitkul, Kristina Lindemann, Nicoletta Colombo, Chih-Long Chang, Marketa Bednarikova, Hong Zhu, Ana Oaknin, Melissa Christiaens, Edgar Petru, Tomoka Usami, Peng Liu, Karin Yamada, Sarper Toker, Stephen M Keefe, Sandro Pignata, Linda R Duska*, on behalf of the ENGOT-cx11/GOG-3047/KEYNOTE-A18 investigators†*

The Lancet, vol. 404, no. 10462, 2024, pp. 1525–35

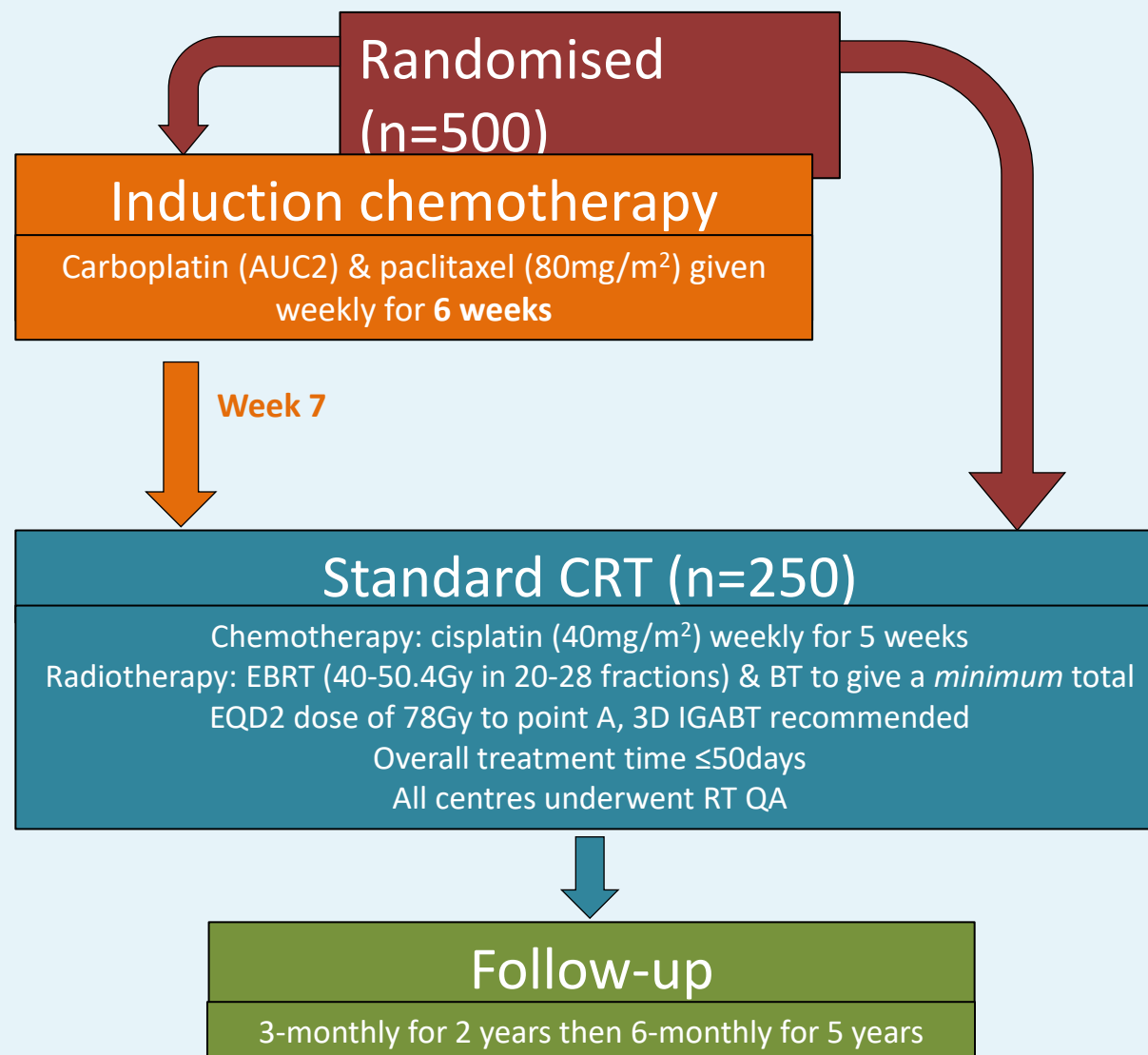
The Lancet, Volume 404, Issue 10460, 5–11
October 2024, Pages 1321-1332

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

ENGOT-cx11/GOG-3047/KEYNOTE-A18: 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 1.1 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 [EQ2D])

R
1:1
N = 1060

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

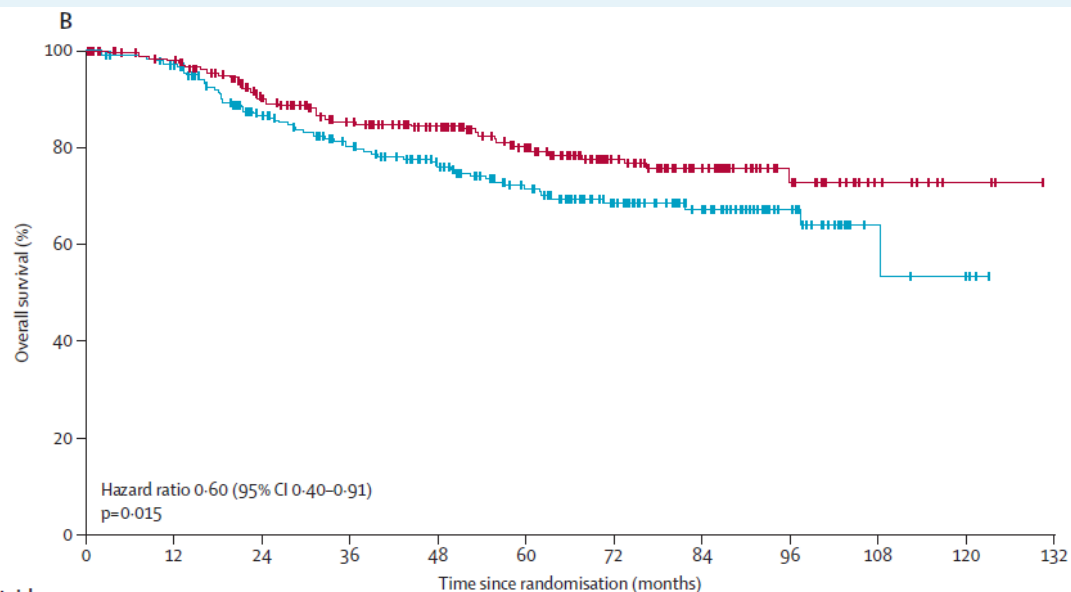
Pembrolizumab 400 mg Q6W for 15 cycles

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

Placebo Q6W for 15 cycles

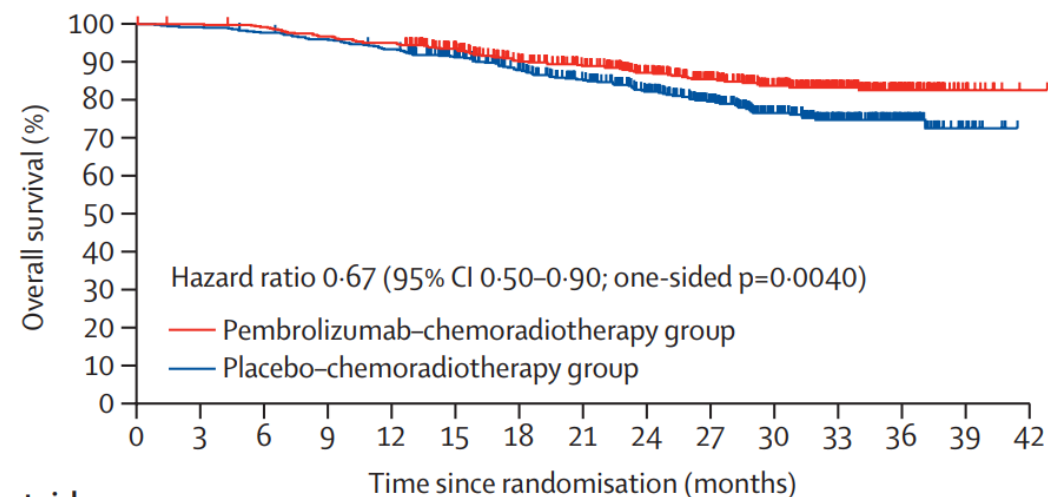
^aA 6th cycle was allowed per investigator discretion. EBRT, external beam radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; Gy, grays; IMRT, intensity-modulated radiotherapy; Q3W, every 3 weeks; Q6W, every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; VMAT, volumetric-modulated arc therapy. ENGOT-cx11/GOG-3047/KEYNOTE-A18 ClinicalTrials.gov identifier, NCT04221945.

OS gevinst



	0	12	24	36	48	60	72	84	96	108	120	132
Number at risk (number censored)												
Chemoradiotherapy alone	250 (0)	230 (13)	186 (33)	157 (49)	132 (66)	105 (86)	75 (112)	48 (138)	24 (163)	6 (179)	3 (181)	0 (184)
Induction chemotherapy with chemoradiotherapy	250 (0)	240 (5)	196 (31)	169 (48)	150 (65)	118 (90)	83 (122)	55 (148)	26 (176)	9 (193)	4 (199)	0 (202)

The Lancet, vol. 404, no. 10462, 2024, pp. 1525–35

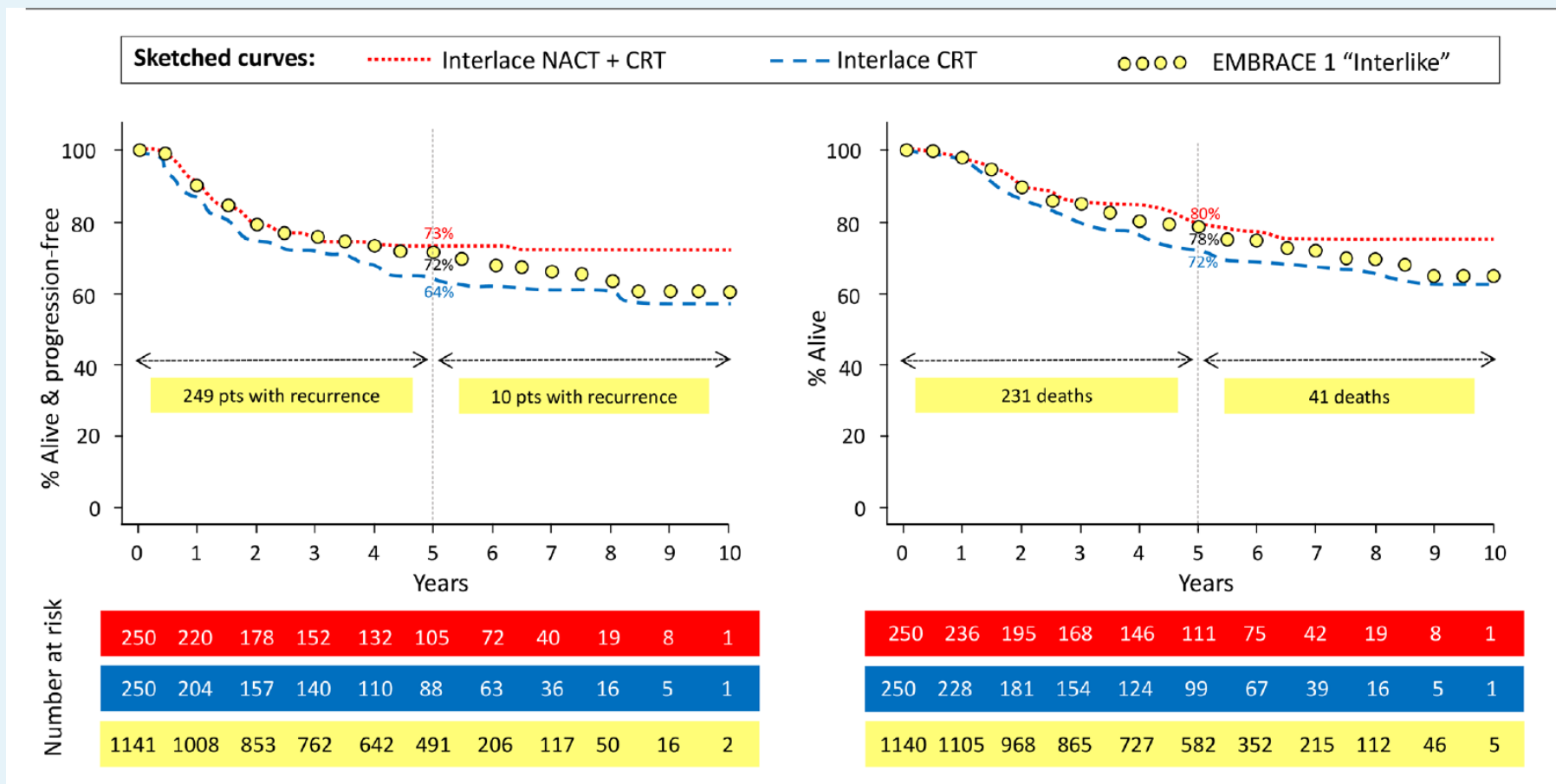


	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Number at risk (number censored)															
Pembrolizumab-chemoradiotherapy group	529 (0)	527 (2)	522 (3)	509 (3)	500 (3)	463 (32)	412 (68)	374 (100)	326 (141)	273 (188)	210 (246)	136 (319)	63 (391)	11 (443)	1 (453)
Placebo-chemoradiotherapy group	531 (0)	527 (0)	518 (1)	508 (2)	493 (3)	455 (30)	405 (64)	366 (92)	316 (129)	259 (177)	194 (233)	125 (298)	58 (365)	12 (410)	0 (422)

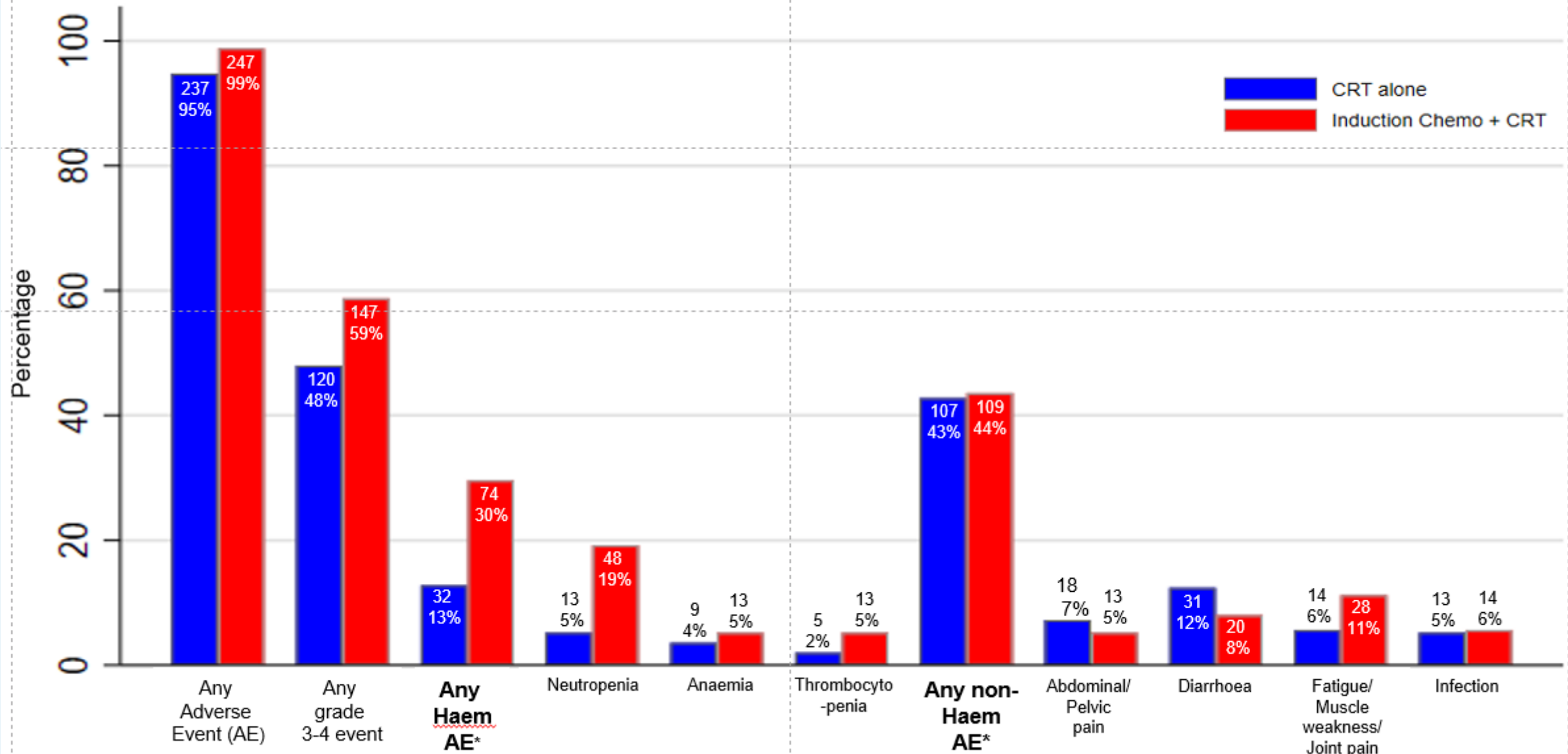
Did the look at the same population

	EMBRACE I	INTERLACE (chemo-arm)	KN A-18 (pembro-arm)
N	1341	250	528
Age	49 (41–60)	46 (26-78)	49 (22-87)
PS	?	PS=0 86%	PS=1 28,2%
N+	52,1%	42%	84,1%
IMRT/VMAT	41,0%	42%	88,7%
Duration of treatment	46 (42–50)	45 (36-70)	52 (12-139)
IG(A)BT	99,1%	30%	< 90%
Dose til cervix	90 Gy	86,6 Gy	87 Gy
In brief	No adj. therapy	6 weeks of chemotherapy before RT. Hairloss, muscle pain	2 years of pembrolizumab after radiotherapy, thyroid dysfunction, (colitis, pneumonitis, rash)

Are we making progress in curing advanced cervical cancer—again?



Adverse Events at any time



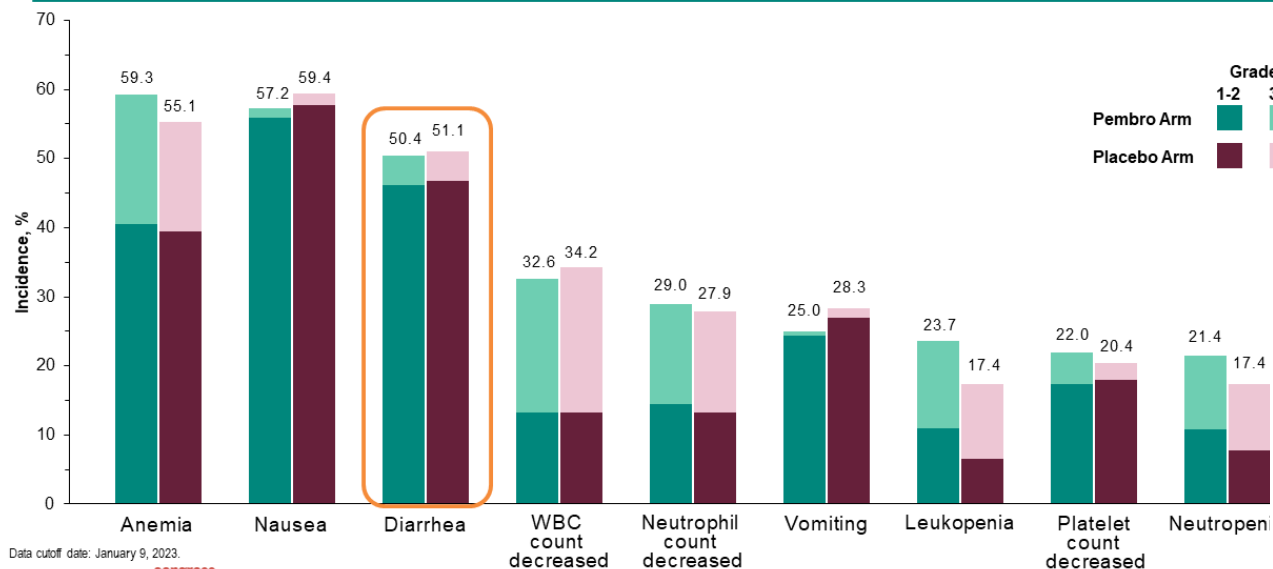
G5 AE in 3 patients- 2 CRT and 1 IC/CRT arm

*Grade 3-4 only 106 people (42%) reported grade 2 alopecia in the IC/CRT

Adverse events

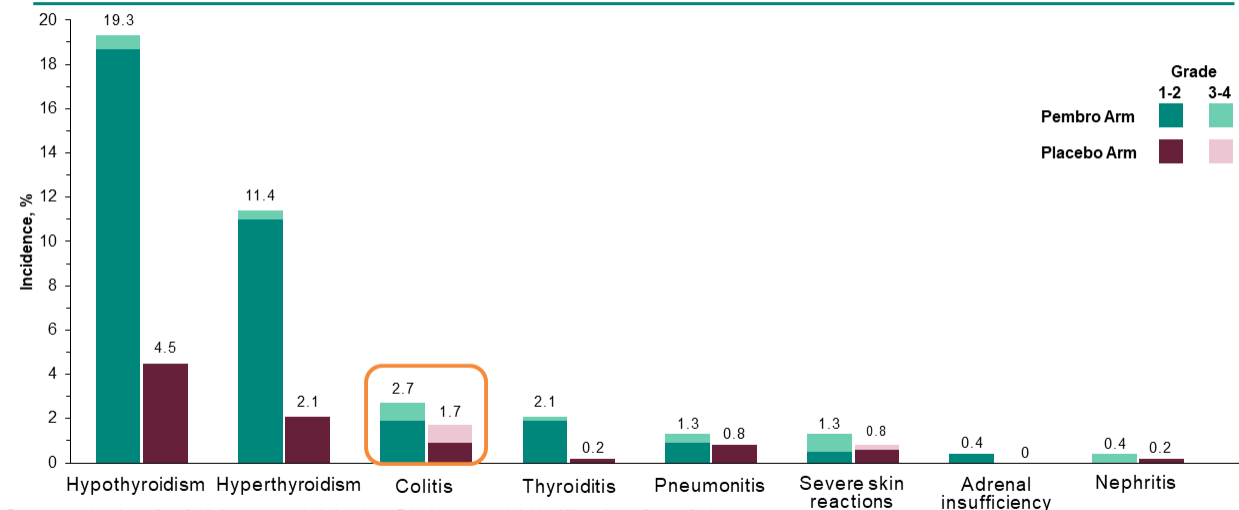
D Lorusso KNA18 ESMO 2023

Treatment-Related AEs, Incidence $\geq 20\%$ in Either Arm



D Lorusso KNA18 ESMO 2023

Immune-Mediated AEs, Incidence ≥ 2 Patients in Either Arm



Events were considered regardless of attribution to treatment by the investigator. Related terms were included in addition to the specific terms listed.
Data cutoff date: January 9, 2023.