MOVING IMMUNOTHERAPY TO FRONTLINE WITH CRT IN LOCALLY ADVANCED CERVICAL CANCER: NOT SO FAST!

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NCI Designated Comprehensive Cancer Center

FIGO CERVICAL CANCER STAGING 2014 VS 2018

FIGO 2018: radiographic LNs upstage to IIIC1/IIIC2

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Cervical Cancer

NCCN Guidelines Index
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Discussion

Table 1: International Federation of Gynecology and Obstetrics (FIGO) Surgical Staging of Cancer of the Cervix Uteri (2018)

Stage			Description
I			The carcinoma is strictly confined to the cervix (extension to the corpus should be disregarded).
	IA		Invasive carcinoma that can be diagnosed only by microscopy with maximum depth of invasion ≤5 mm[a]
		IA1	Measured stromal invasion ≤3 mm in depth
		IA2	Measured stromal invasion >3 mm and ≤5 mm in depth
	IB		Invasive carcinoma with measured deepest invasion >5 mm (greater than stage IA); lesion limited to the cervix uteri with size measured by maximum tumor diameter[b]
		IB1	Invasive carcinoma >5 mm depth of stromal invasion and ≤2 cm in greatest dimension
		IB2	Invasive carcinoma >2 cm and ≤4 cm in greatest dimension
		IB3	Invasive carcinoma >4 cm in greatest dimension
II			The cervical carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
	IIA		Involvement limited to the upper two-thirds of the vagina without parametrial invasion
		IIA1	IIA1 Invasive carcinoma ≤4 cm in greatest dimension
		IIA2	Invasive carcinoma >4 cm in greatest dimension
	IIB		With parametrial invasion but not up to the pelvic wall
III			The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or paraaortic lymph nodes
	IIIA		Carcinoma involves lower third of the vagina, with no extension to the pelvic wall
	IIIB		Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney (unless known to be due to another cause)
	IIIC		Involvement of pelvic and/or paraaortic lymph nodes (including micrometastases),[c] irrespective of tumor size and extent (with r and p notations).
		IIIC1	Pelvic lymph node metastasis only
		IIIC2	Paraaortic lymph node metastasis
IV			The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to stage IV
	IVA		Spread of the growth to adjacent organs
	IVB		Spread to distant organs

[a] Imaging and pathology can be used, when available, to supplement clinical findings with respect to tumor size and extent, in all stages. Pathological findings supersede imaging and clinical findings.
[b] The involvement of vascular/lymphatic spaces should not change the staging. The lateral extent of the lesion is no longer considered.
[c] Isolated tumor cells do not change the stage but their presence should be recorded.
[d] Adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate the case to Stage IIIC. Example: If imaging indicates pelvic lymph node metastasis,

CONCURRENT IO WITH DEFINITIVE CRT

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 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)[a]

R 1:1

- Cisplatin 40 mg/m^2 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/m^2 QW for 5 cycles[b] + EBRT followed by brachytherapy + Placebo Q3W for 5 cycles
- Placebo Q6W for 15 cycles

Primary endpoints:

- PFS per RECIST v1.1 by investigator review or histopathologic confirmation
- OS

Analysis populations:

- Efficacy: all randomized participants
- Safety: all randomized participants who received ≥1 dose of study drug

[a]Stratification for radiotherapy dose was due to the participation of Japan in which the radiotherapy standard of care recommended a lower dose. [b]A 6th cycle was allowed per investigator discretion. ENGOT-cx11/GOG-3047/KEYNOTE-A18 ClinicalTrials.gov identifier, NCT04221945.

KEYNOTE-A18

	Pembrolizumab-chemoradiotherapy (n=529)	Placebo-chemoradiotherapy (n=531)
Age		
Median age, years	49 (40–57)	50 (41–59)
Participants aged ≥ 65 years	56 (11%)	77 (15%)
Race		
White	254 (48%)	264 (50%)
Asian	155 (29%)	148 (28%)
Multiple	78 (15%)	86 (16%)
American Indian or Alaska Native	24 (5%)	22 (4%)
Black or African American	14 (3%)	8 (2%)
Native Hawaiian or Other Pacific Islander	2 (<1%)	1 (<1%)
Missing	2 (<1%)	2 (<1%)
ECOG-PS score*		
0	380 (72%)	397 (75%)
1	149 (28%)	134 (25%)
FIGO 2014 stage at screening		
IB2 to IIB	235 (44%)	227 (43%)
III to IVA	294 (56%)	304 (57%)
Lymph node involvement†		
Positive pelvic only	326 (62%)	324 (61%)
Positive para-aortic only	14 (3%)	10 (2%)
Positive pelvic and para-aortic	105 (20%)	104 (20%)
No positive pelvic or para-aortic	84 (16%)	93 (18%)
Histology		
Non-squamous‡	96 (18%)	80 (15%)
Squamous	433 (82%)	451 (85%)
Planned type of external beam radiotherapy		
IMRT or VMAT	469 (89%)	470 (89%)
Non-IMRT and non-VMAT	60 (11%)	61 (11%)
Planned total radiotherapy dose		
<70 Gy	47 (9%)	46 (9%)
≥70 Gy	482 (91%)	485 (91%)
PD-L1 combined positive score		
<1	22 (4%)	28 (5%)
≥1	502 (95%)	498 (94%)
Missing	5 (<1%)	5 (<1%)

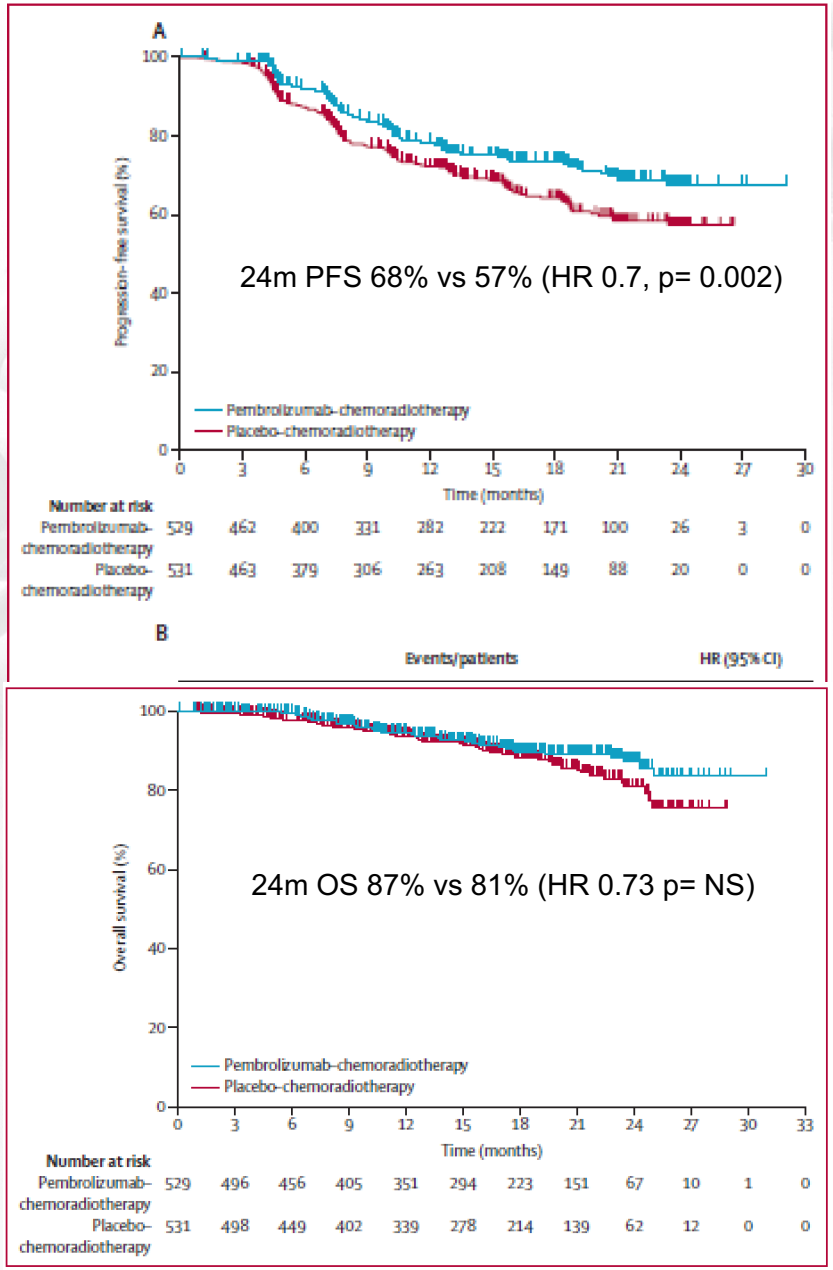

Figure 3: **Overall survival**
Kaplan–Meier estimates of overall survival in the intention-to-treat population. Tick marks indicate censoring of data.

Lorusso et al *Lancet* 2024

A18 TOXICITY ANALYSIS

	Pembrolizumab–chemoradiotherapy (n=528)		Placebo–chemoradiotherapy (n=530)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any adverse event*	525 (99%)	394 (75%)	526 (99%)	364 (69%)
Treatment-related adverse event†	507 (96%)	354 (67%)	509 (96%)	321 (61%)
Anaemia	313 (59%)	99 (19%)	292 (55%)	84 (16%)
Nausea	302 (57%)	7 (1%)	315 (59%)	9 (2%)
Diarrhoea	266 (50%)	22 (4%)	271 (51%)	23 (4%)
White blood cell count decreased	172 (33%)	102 (19%)	181 (34%)	111 (21%)
Neutrophil count decreased	153 (29%)	77 (15%)	148 (28%)	78 (15%)
Vomiting	132 (25%)	3 (<1%)	150 (28%)	7 (1%)
Leukopenia	125 (24%)	67 (13%)	92 (17%)	57 (11%)
Platelet count decreased	116 (22%)	25 (5%)	108 (20%)	13 (2%)
Neutropenia	113 (21%)	56 (11%)	92 (17%)	51 (10%)
Immune-mediated adverse event‡	167 (32%)	21 (4%)	54 (10%)	5 (<1%)
Hypothyroidism	102 (19%)	3 (<1%)	24 (5%)	0
Hyperthyroidism	60 (11%)	2 (<1%)	11 (2%)	0
Colitis	14 (3%)	4 (<1%)	9 (2%)	4 (<1%)
Thyroiditis	11 (2%)	1 (<1%)	1 (<1%)	0

- No overall difference in toxicities between groups:
  - G3 or higher AE (IO: 75% vs SOC: 69%)
- Immune-mediated AEs (all grade): 32% vs 10%
- No clinically meaningful difference in PRO (EORTC QLQ-C30) with 60% compliance in both groups

Lorusso et al *Lancet* 2024

FDA approves pembrolizumab with chemoradiotherapy for FIGO 2014 Stage III-IVA cervical cancer

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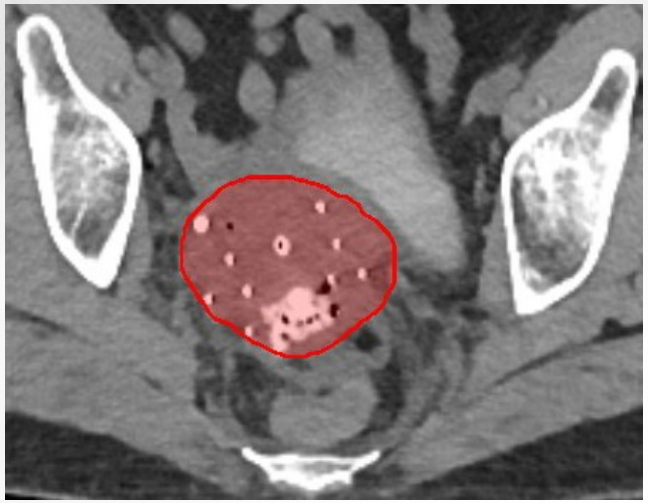
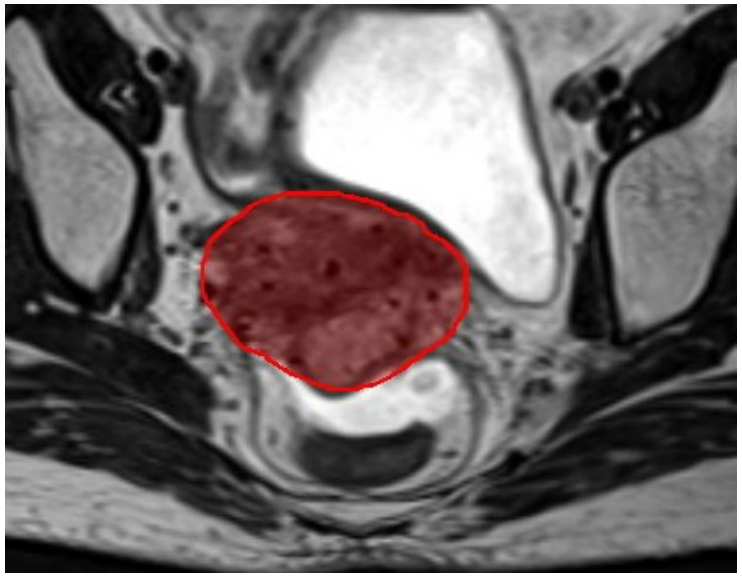
On January 12, 2024, the Food and Drug Admini
with chemoradiotherapy (CR
IVA cervical cancer.

RADIATION ADVANCEMENTS FOR LOCALLY ADVANCED CERVICAL CANCER

- Brachytherapy is critical of curative treatment
- EMBRACE I Prospective Trial (1,341 patients) - Established benchmark for treatment and clinical outcomes for LACC with CRT and high-quality image-guided brachytherapy:
  - **MRI-based Image-Guidance** to delineate high risk region
  - **Minimum EQD2 of 85Gy** to achieve > 85% local control
  - **Overall tx time < 50 days** optimizes local control (1-3% per week)



CT-based

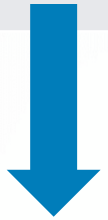


MRI-based

Potter et al *Lancet* 2021

COMPARISON OF CLINICAL OUTCOMES AND RT QUALITY

	EMBRACE-I (benchmark)	A18 (Pembro group)
PFS	5 yr: ~60%	2 yr: 68%
MRI-based IGABT	100%	Not defined
Median EQD2	90 (85-94)	87 Gy (83-92)
Overall treatment time: ≤ 50 days ≤ 56 days	 100% 0	 36% 75%



Missed opportunity to improve local control???

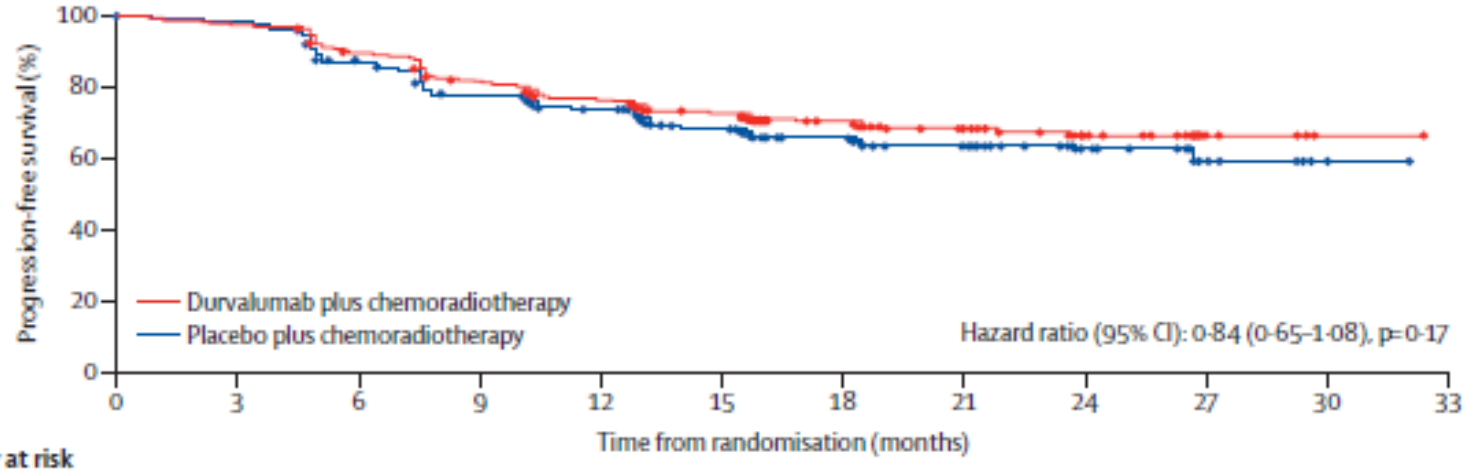
CALLA STUDY

Study population

- FIGO 2009 Stages I
  (N ≥1) OR IIIA to IV
- Nodal staging (pel
  para-aortic) may b
  or by imaging (REC
- No evidence of me
  (M0)

Stratification

- Stage: Stage <III ar
  Stage ≥III and N ne
  and N positive
- Region: United Sta
  European Union, South Korea, ar
  Japan versus rest of the world



Number at risk (number censored)												
Durvalumab plus chemoradiotherapy	385 (0)	363 (13)	330 (17)	294 (22)	270 (27)	215 (70)	163 (116)	110 (165)	43 (230)	11 (262)	1 (272)	0 (273)
Placebo plus chemoradiotherapy	385 (0)	368 (12)	318 (18)	282 (22)	257 (30)	203 (68)	146 (117)	109 (150)	49 (209)	14 (243)	2 (255)	0 (257)

	Durvalumab plus chemoradiotherapy (n=385)	Placebo plus chemoradiotherapy (n=385)
Age (years)	50·0 (41·0–57·0)	48·0 (40·0–57·0)
Race		
Asian	152 (40%)	148 (38%)
IIA	21 (6%)	13 (3%)
IIB	95 (25%)	97 (25%)
IIIA	54 (14%)	64 (17%)
IIIB	171 (44%)	172 (45%)
IVA	25 (7%)	19 (5%)
Nodal involvement		
N0	106 (28%)	94 (24%)
N1	279 (73%)	291 (76%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. FIGO=International Federation of Gynaecology and Obstetrics. N0=node negative. N1=node positive. *Patients with FIGO 2009 Stage IB2-IIB tumours if the tumours were node positive.

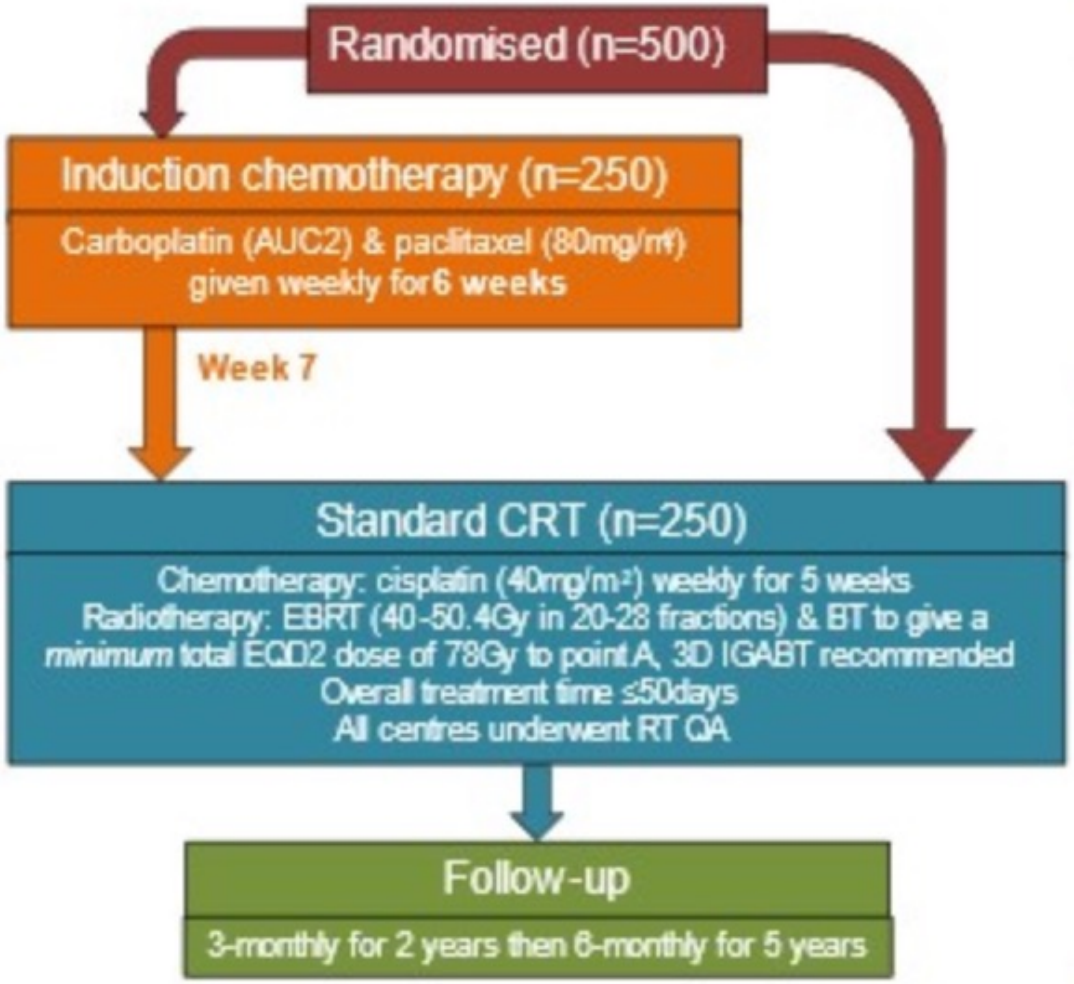
Table 1: Baseline characteristics

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

MADRID 2023 ESMO congress

Mary McCormack

INTERLACE TRIAL – PATIENT CHARACTERISTICS

FIGO 2008 Stage	
IB 1-2	9%
II	77%
IIIB	11%
IVA	3%
Nodal status	
N0	57%
Histology	
SCC	82%

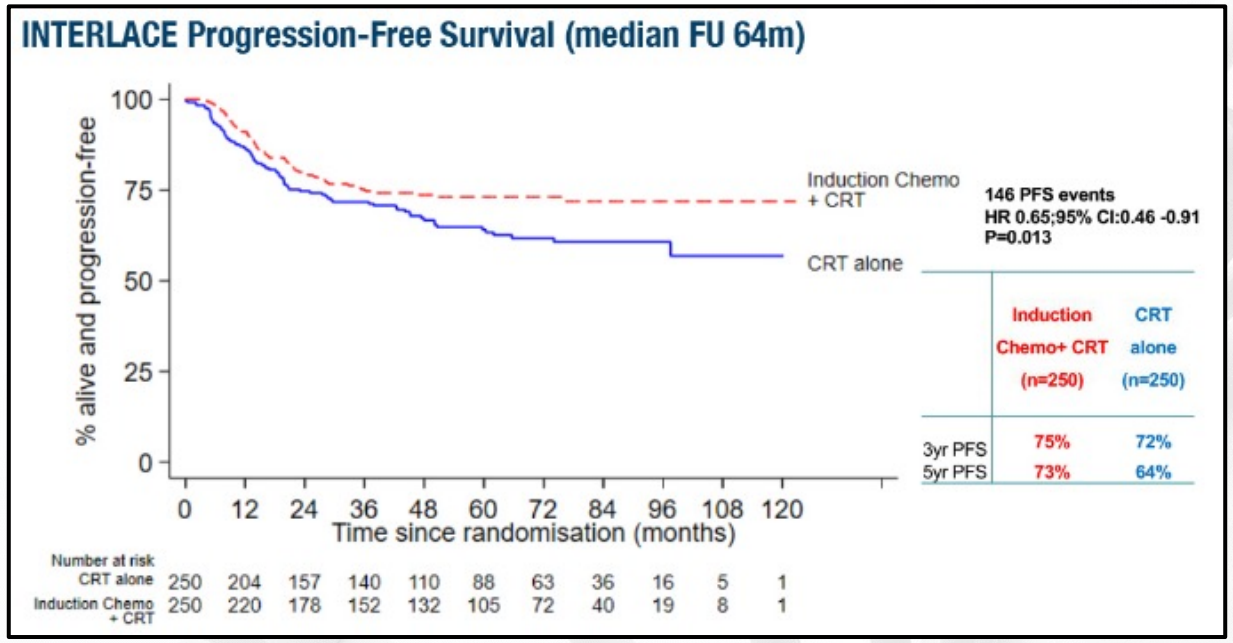
Adherence to Induction Chemotherapy

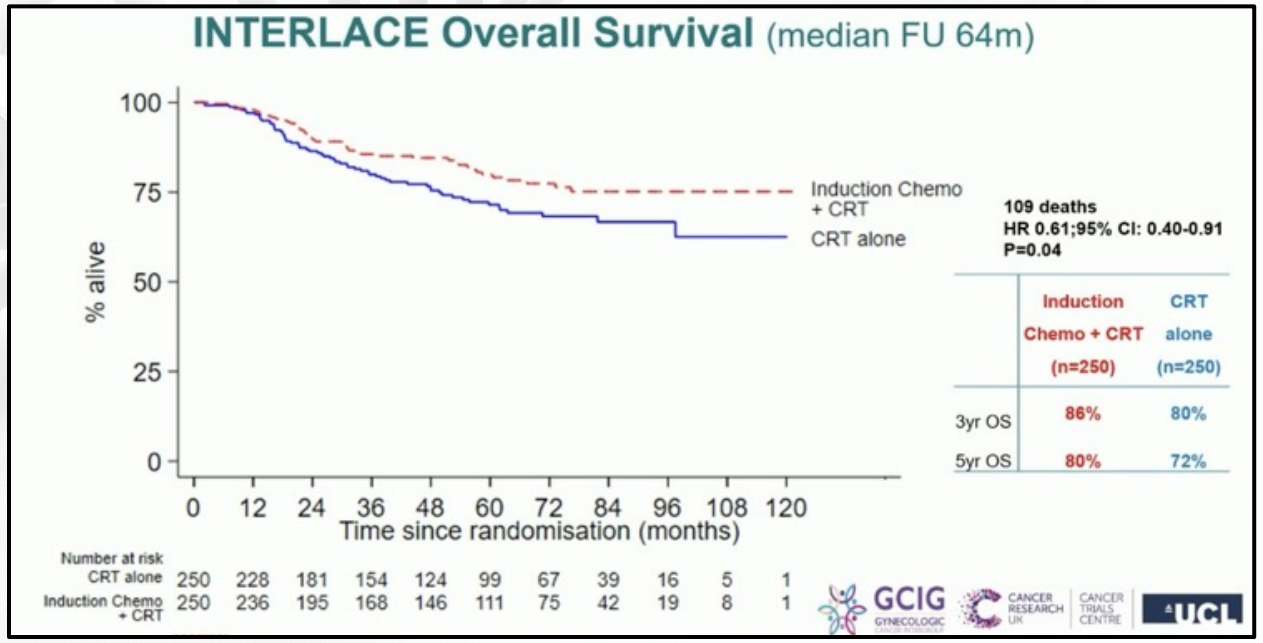
	Paclitaxel/Carboplatin (n=250) No. of patients (%)
Completed 6 weekly cycles	211 (84)
Completed at least 5 cycles	230 (92)
Main reasons for <6 cycles:	
Adverse events:	29 (11)
Haematological	9
Non-haematological	17
Both	3
Withdrawal/other	10 (4)
Median Interval from IC to RT days (range)	7 (5-53)

Adherence to Cisplatin

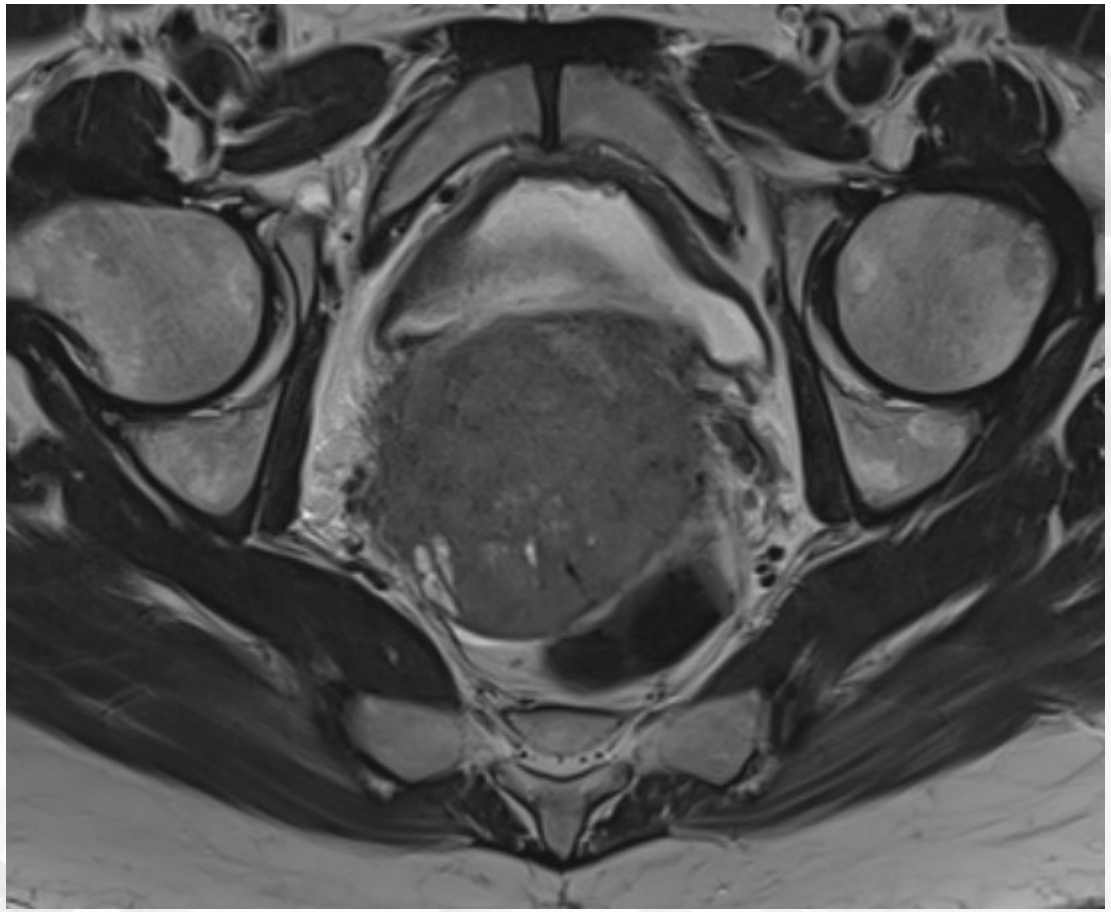
	CRT alone (n=250) No. of patients (%)	IC+ CRT (n=250)
Completed 5 weekly cycles	197 (79)	169 (68)
Completed at least 4 cycles	224 (90)	212 (85)
Main reasons for <5 cycles:		
Adverse events leading to discontinuation:	33 (13)	68 (27)
Haematological	4	34
Non-haematological	25	20
Both	4	14
Other	20 (8)	13 (5)

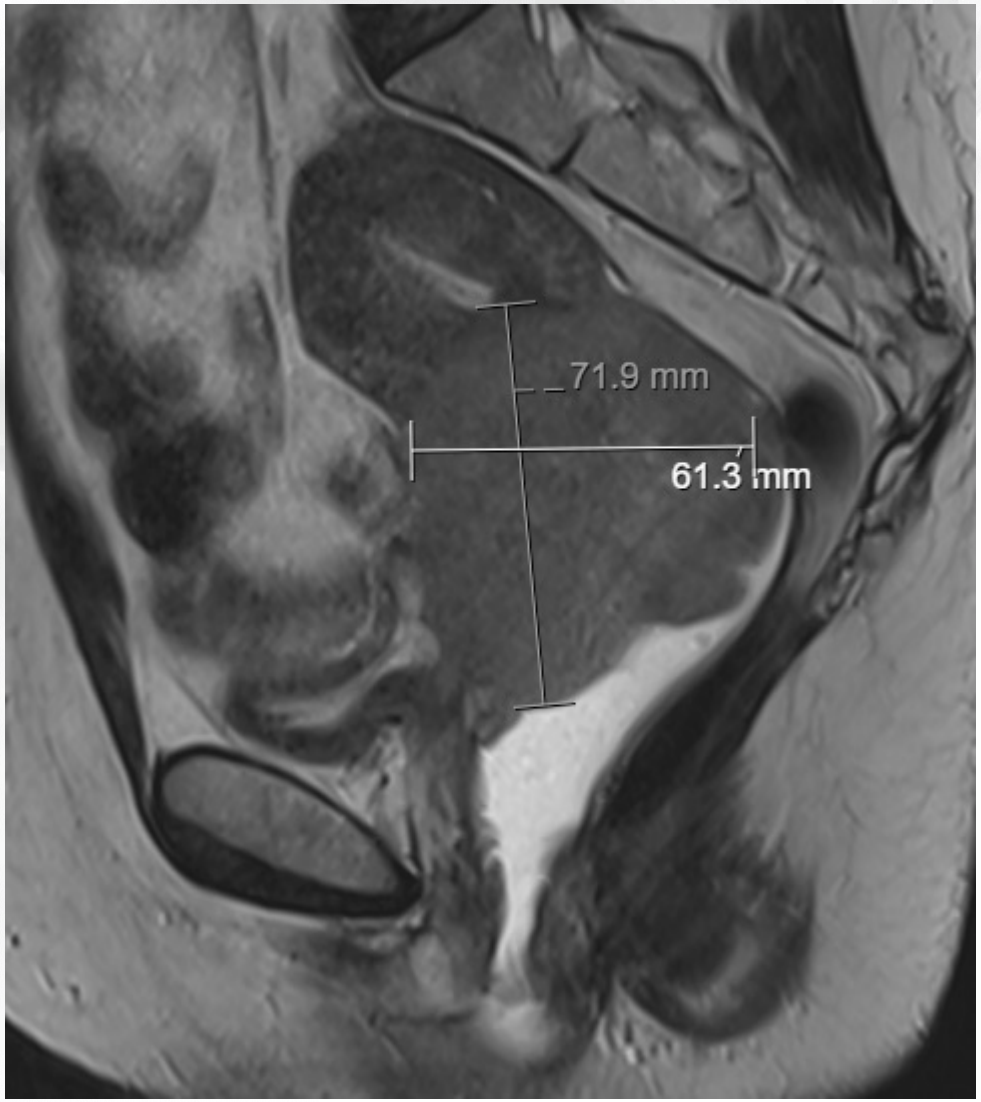
INTERLACE TRIAL – CLINICAL OUTCOMES



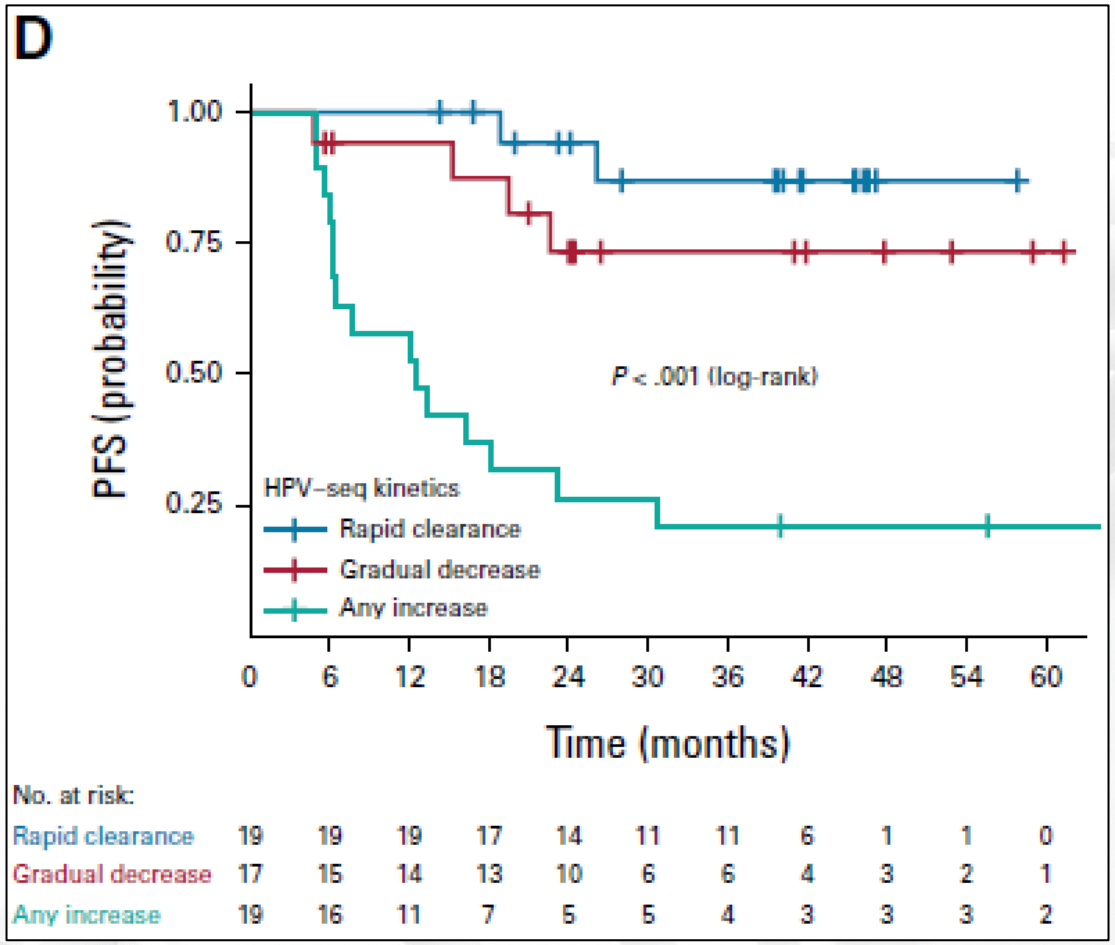


A18 OR INTERLACE?



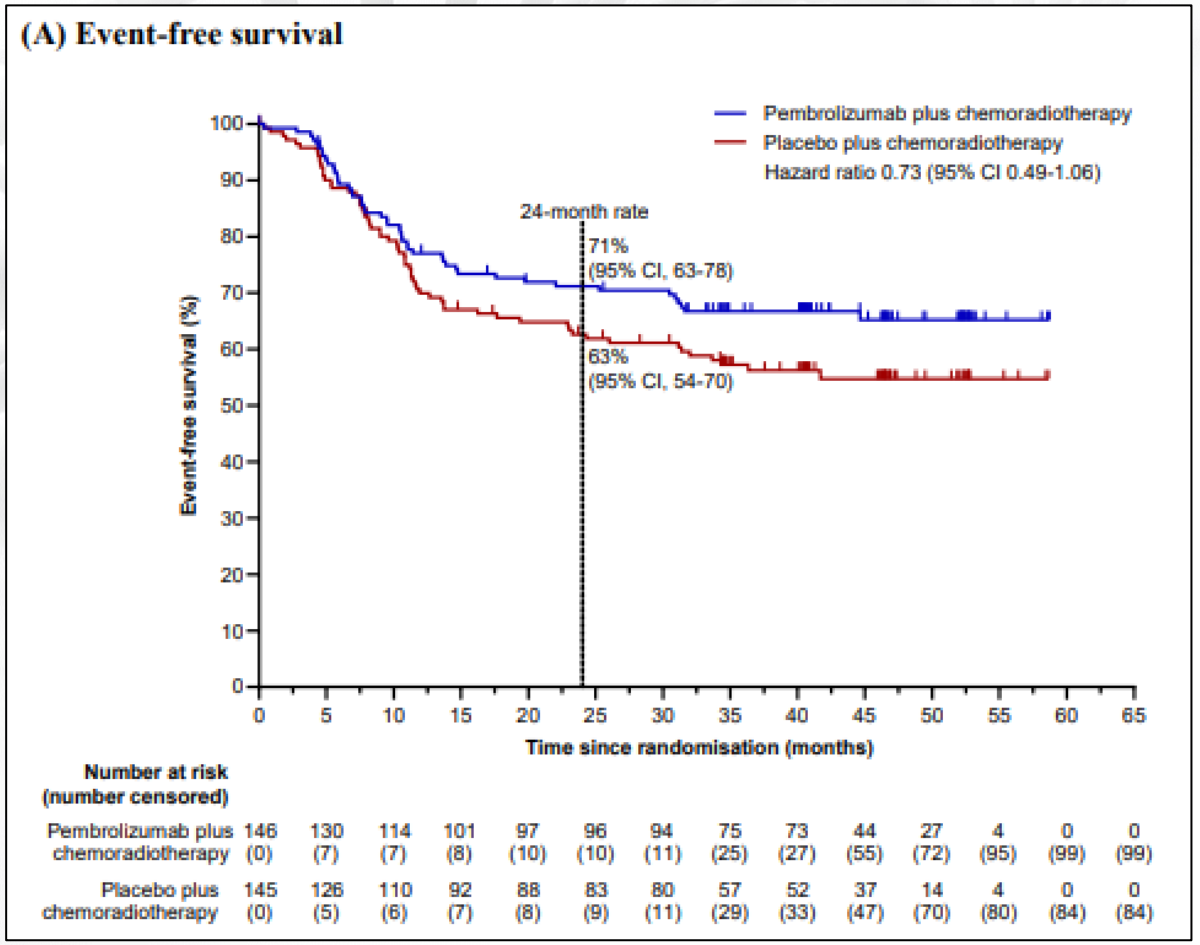


BIOMARKERS TO GUIDE TREATMENT INTENSIFICATION?



Rapid clearance of **ctHPV-DNA** associated with improved PFS

Han et al JCO 2023



Post-hoc analysis Keynote 412 showed improved EFS in patients with **PD-L1** CPS ≥ 20

Machiels et al Lancet Oncol 2024

IS YEAR-LONG MAINTENANCE IO FEASIBLE FOR THE US CERVICAL CANCER PATIENT POPULATION?

Table 1. Descriptive Characteristics of Patients With Cervical Cancer by Surveillance, Epidemiology, and End Results Program Summary Stage

Characteristic	Women, No. (%)			*P* value[a]
	All (N = 23 492)	Localized cancer (n = 11 998)	Regional and distant cancer (n = 11 494)	
Insurance status				
Uninsured	1882 (8.0)	751 (6.3)	1131 (9.8)	<.001
Any Medicaid	7646 (32.5)	3165 (26.4)	4481 (39.0)	
Insured	13 964 (59.4)	8082 (67.4)	5882 (51.2)	
Marital status				
Married	10 508 (44.7)	5870 (48.9)	4638 (40.4)	<.001
Not married	11 941 (50.8)	5530 (46.1)	6411 (55.8)	
Unknown	1043 (4.4)	598 (5.0)	445 (3.9)	
Yost SES quintile				
First (lowest SES)	5852 (24.9)	2652 (22.1)	3200 (27.8)	<.001
Second	5007 (21.3)	2414 (20.1)	2593 (22.6)	
Third	4328 (18.4)	2204 (18.4)	2124 (18.5)	
Fourth	3899 (16.6)	2192 (18.3)	1707 (14.9)	
Fifth (highest SES)	3159 (13.4)	1875 (15.6)	1284 (11.2)	

Patients with advanced disease are more likely to be:

1. **Uninsured or have Medicaid**
2. **Unmarried**
3. **In lowest SES quintile**

Hunter K et al JAMA Open 2023

CONCLUSION: CONCURRENT IO IS NOT FRONTLINE FOR ALL PATIENTS WITH ADVANCED STAGE CERVICAL CANCER

1. FDA approval for FIGO 2014 III-IVA (excludes node status in staging)
2. Quality of RT in A18 appears good but potentially missed opportunity for local control
3. No benefit to Concurrent PDL-1 (CALLA study)
4. Validated biomarkers are needed to guide treatment intensification
5. Financial and logistical feasibility of maintenance IO is uncertain

THANK YOU!

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