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G-ART
Advanced Radiation Therapy



Radioimmunotherapy in cervical cancer: Who does really benefit?

Alina Emiliana Sturdza

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Medical University of Vienna, October 19th, 2026

Declaration of interest

Alina Emiliana Sturdza

- The Department of Radiation Oncology at the Medical University of Vienna receives financial and/or equipment support for research and educational purposes from Elekta AB and Varian Medical Systems Inc

- The author receives teaching honorary from Elekta AB, MSD, GMX and Stiftung Philanthropie Österreich

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Outline

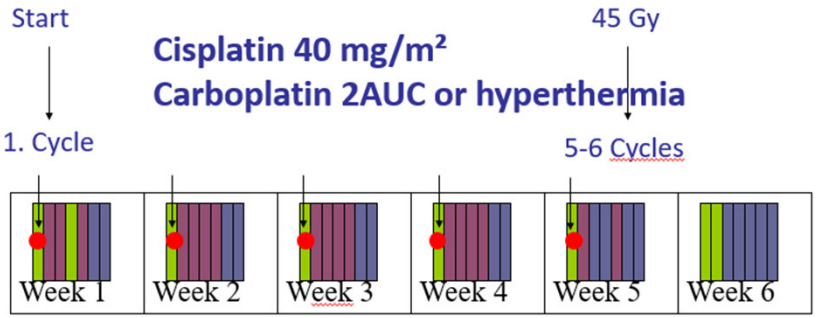
- Summary of the current evidence on the treatment of LACC
- The use ICI in the treatment of LACC
- New Horizons

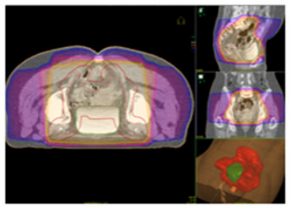
Standard radiochemotherapy treatment

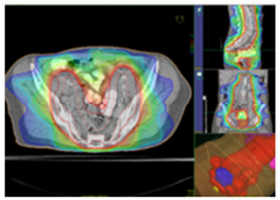
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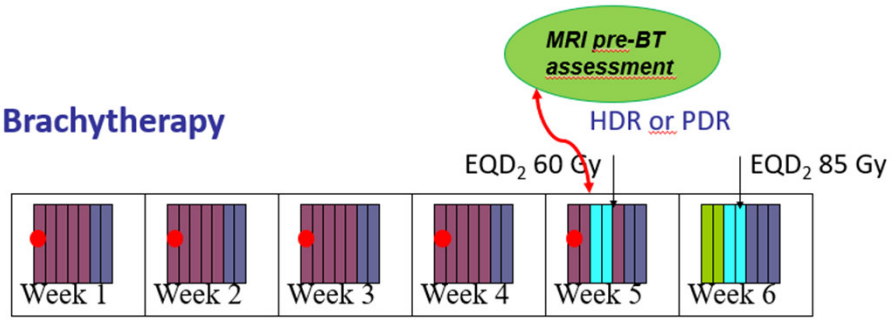
Primary radiochemotherapy in cervical cancer

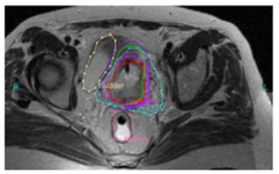
External beam radiotherapy and concurrent chemotherapy



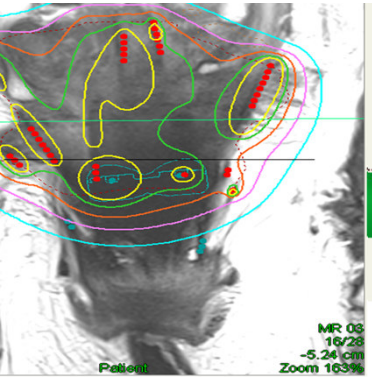


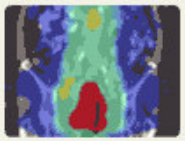






Cibula et al, ESGO/ESTRO/ESP Guidelines for LACC, 2023





EMBRACE

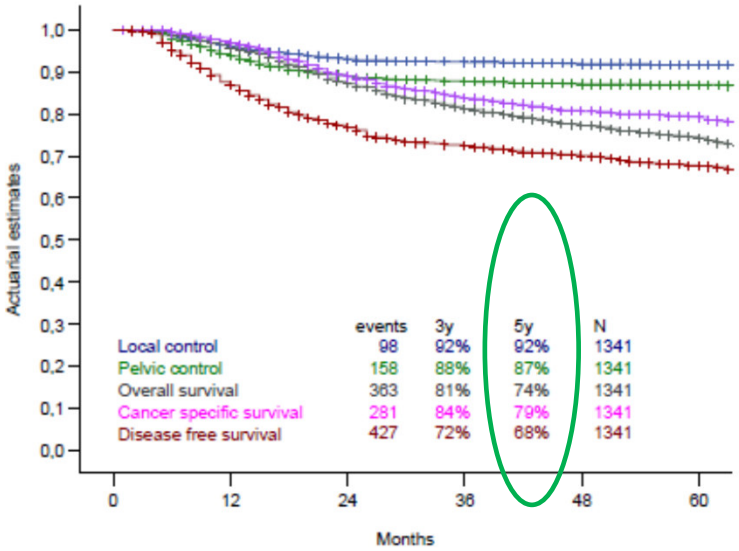
{ Image guided intensity modulated External beam radiochemotherapy and MRI based adaptive BRAchytherapy in locally advanced CErvical cancer }



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State of the art MRI guided adaptive Brachytherapy

Overall local and pelvic control, overall survival, cancer specific survival and disease free survival
EMBRACE I



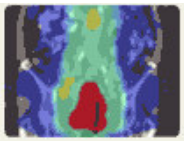
1341 Patients accrued in 7 years

	Gastrointestinal	Genitourinary	Vaginal	Fistula*	Overall (gastrointestinal, genitourinary, vaginal, and fistula)
	8,5%	6,8%	5,7%	3.2%	
Grade 3 adverse events					
Number of events	83	93	54	18	248
Number of patients	54 (4·3%)	59 (4·7%)	50 (4·0%)	13 (1·0%)	128 (10·2%)
Actuarial 5-year cumulative incidence of grade 3 or higher morbidity (95% CI)	8·5% (6·9–10·6)	6·8% (5·4–8·6)	5·7% (4·3–7·6)	3·2% (2·2–4·5)	18·4% (16·0–21·2)
Grade 4 adverse events					
Number of events	34	19	5	24	82
Number of patients	27 (2·2%)	16 (1·3%)	5 (0·4%)	21 (1·7%)	55 (4·4%)
Actuarial 5-year cumulative incidence of grade 4 or higher morbidity (95% CI)	3·0% (2·0–4·3)	1·0% (0·6–1·9)	0·5% (0·2–1·2)	2·1% (1·5–3·2)	5·2% (4·0–6·9)

Data are n, n (%), or actuarial cumulative incidence (95% CI). Adverse events were classified according to the Common Terminology Criteria for Adverse Events, version 3.0. Data were available for 1251 patients. Grade 5 events are not listed because they were not always allocated to a single organ system.
Eight gastrointestinal events, four genitourinary events, four fistulas, and five septic infections contributed to treatment-related death in 12 patients.
*15 vesico-vaginal, 10 recto-vaginal, 4 sigmoid-vagina, 13 other fistulas.

Table 4: Grade 3–4 morbidity

Pötter et al, Lancet Oncology, 2021



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{ Image guided intensity modulated External beam radiochemotherapy and MRI based adaptive BRAchytherapy in locally advanced CErvical cancer }



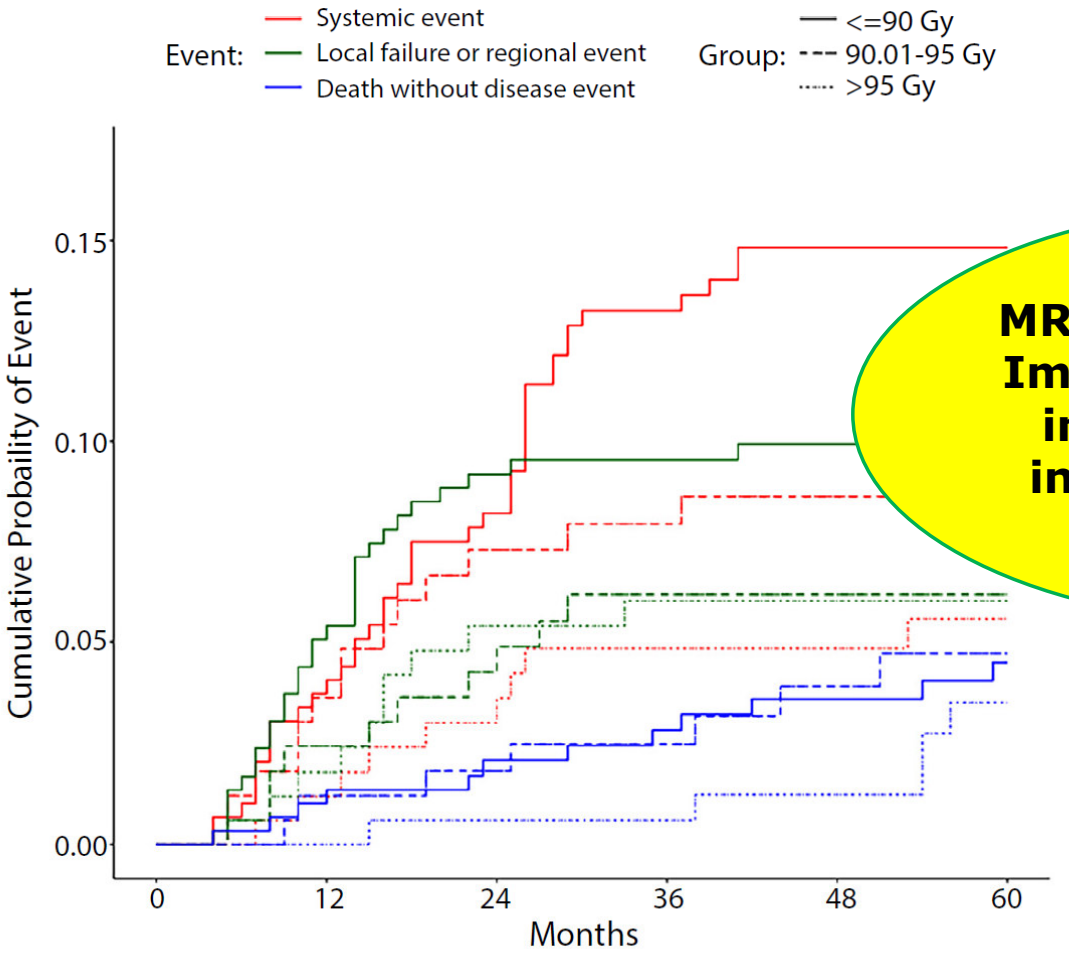
	Number of patients	CTV_{HR} volume, cm^{3*}	CTV_{HR} $D_{90\%}$ $EQD2_{10}$, Gy	Local failure (n)	Pelvic failure (n)	Any failure (n)	Patients dead (n)	5-year local control (95% CI)	5-year pelvic control (95% CI)	5-year disease-free survival (95% CI)	5-year overall survival (95% CI)
IB1	124	22 (17–27)	91 (87–95)	2	6	20	24	98% (94–100)	95% (87–98)	76% (67–83)	83% (75–89)
IB2	119	26 (20–38)	89 (84–93)	9	18	36	35	92% (84–96)	84% (75–90)	65% (56–73)	73% (64–81)
IIA1	38	23 (14–31)	91 (85–96)	3	4	6	7	91% (73–97)	88% (71–95)	75% (58–86)	80% (63–90)
IIA2	31	34 (24–42)	87 (80–91)	3	6	10	8	89% (68–96)	77% (55–89)	65% (44–79)	74% (53–87)
IIB	693	27 (19–36)	90 (86–95)	55	78	146	152	91% (88–93)	88% (85–90)	73% (69–76)	78% (75–82)
IIIA	13	30 (24–35)	84 (82–88)	0	0	2	3	100%	100%	76% (43–92)	76% (42–91)
IIIB	190	40 (30–56)	88 (83–91)	15	24	61	78	92% (86–95)	86% (79–90)	59% (52–66)	64% (57–71)
IVA	34	57 (39–89)	86 (78–89)	3	6	10	17	91% (75–97)	81% (62–91)	47% (28–63)	52% (33–68)
IVB	98	34 (22–47)	89 (85–92)	8	16	40	38	89% (79–95)	81% (70–88)	48% (37–58)	61% (49–70)
Total	1341†	28 (20–40)	90 (85–94)	98	158	331	363†	92% (90–93)	87% (85–89)	68% (65–70)	74% (72–77)

Data are n, median (IQR), or Kaplan-Meier estimates (95% CI). *Mean dose delivered over all fractions. †One patient with unknown FIGO stage. FIGO=The International Federation of Gynaecology and Obstetrics. CTV_{HR}= high-risk clinical target volume. $D_{90\%}$=minimal dose to 90% of the clinical target volume. $EQD2_{10}$=equi-effective dose in 2 Gy per fraction of 10 Gy.

Table 3: CTV_{HR} volume, and dose and clinical outcomes according to $FIGO_{2009}$ stage

Pötter et al, Lancet Oncology, 2021

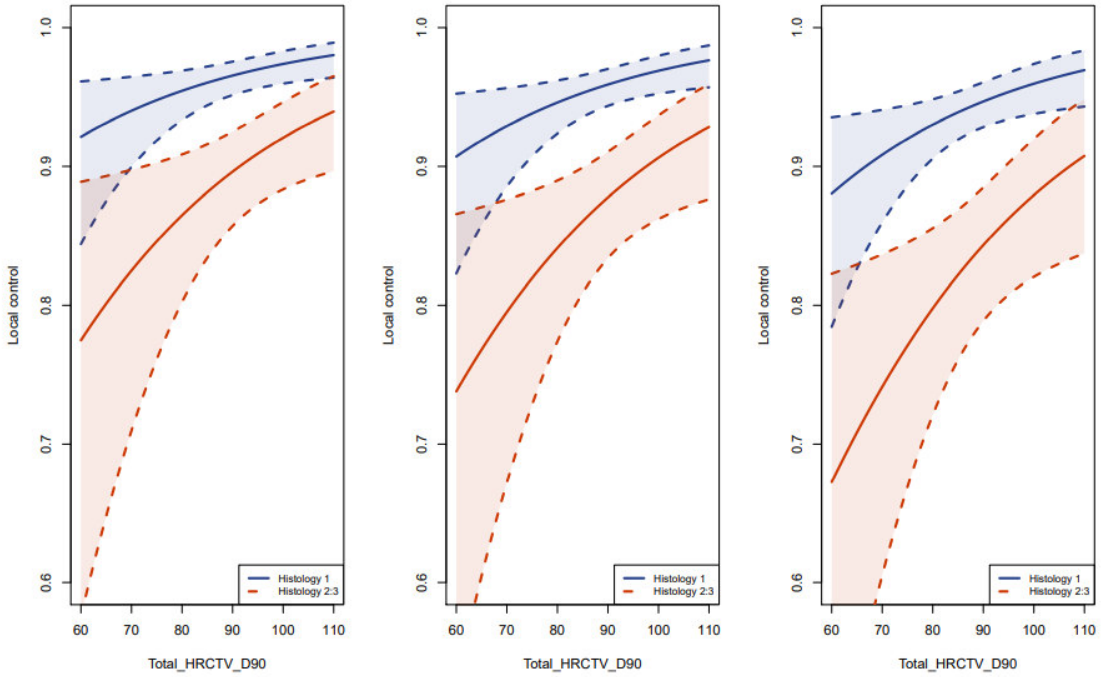
The dose to the tumour has an impact on the Overall Survival



MRI guided Interstitial Implants are essential in large tumours to increase the dose to >90Gy

Knoth J. et al., Int Jour of Rad Onc Biol Phys, 2025

Dose-effect relationships in cervical cancer



HRCTV vol: <20cm3 HRCTV vol: 20-40cm3 HRCTV vol: >40cm3

Blue lines: Squamous cell carcinoma

Red lines: Adeno- and adenosquamous carcinoma

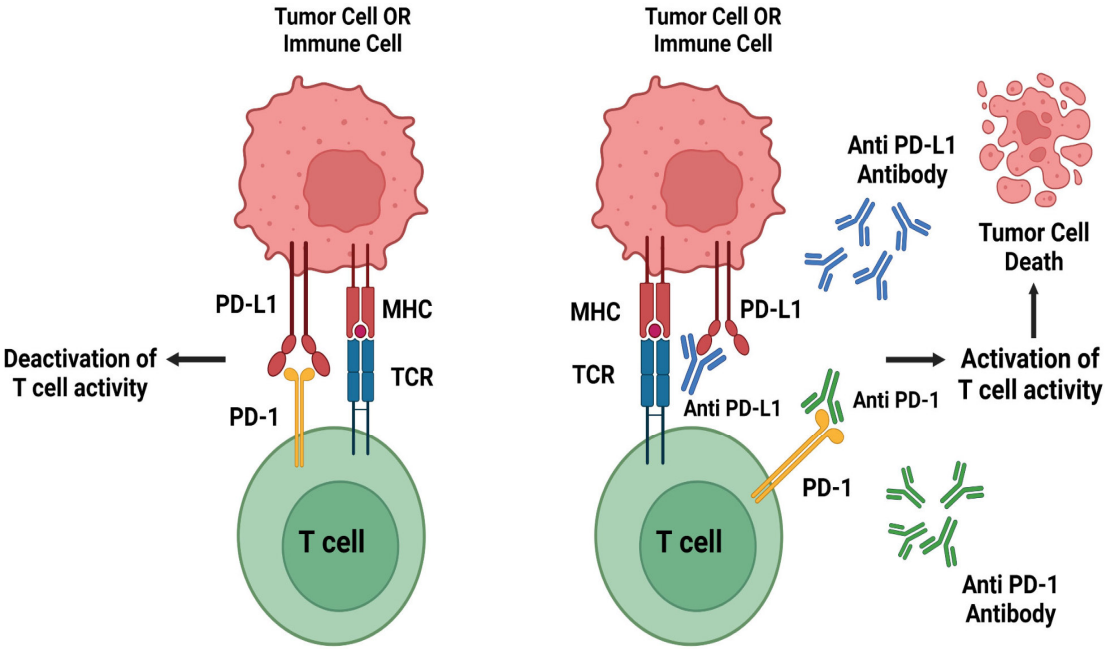
Dotted lines: 95% CI

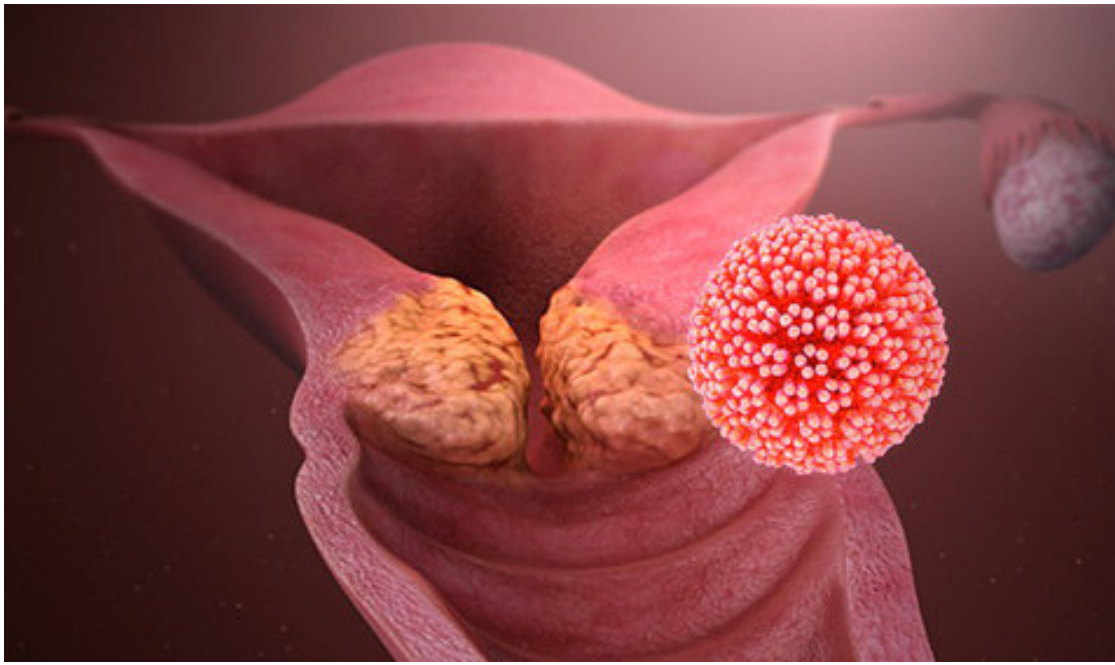
Prospe
Multic
Analys
Embra
N=1318

AdenoCa and Adeno-SCC need more tailored systemic and radiation treatment

Schmid M et al. JCO, 2022

Molecular risk factors in cervical cancer





BioEMBRACE: PDL 1

No influence on OS

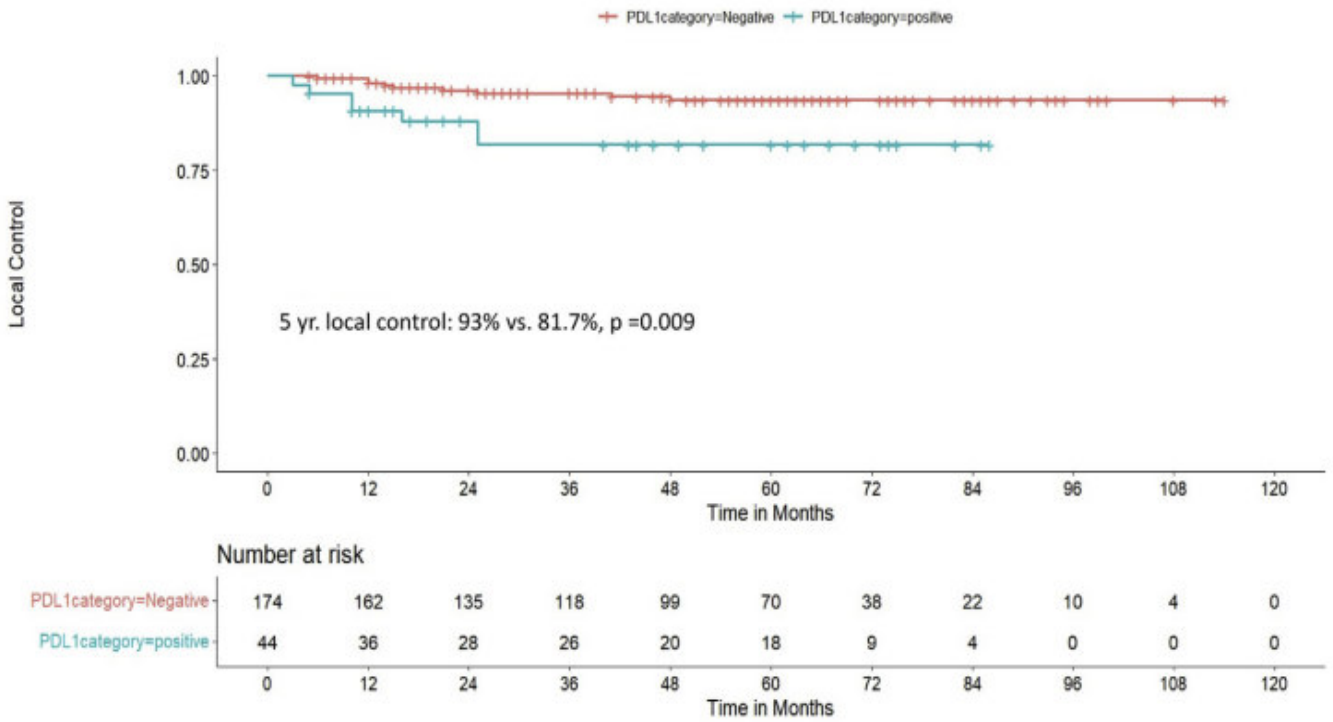


Fig. 1. Figure depicts the difference in local control based on PD-L1 expression in the baseline biopsy. The 5-year local control was 93% versus 81.7% ($P = .009$).

Chopra S. et al, 2024. IJRBP

BioEMBRACE: PDL 1 and p16 combinations

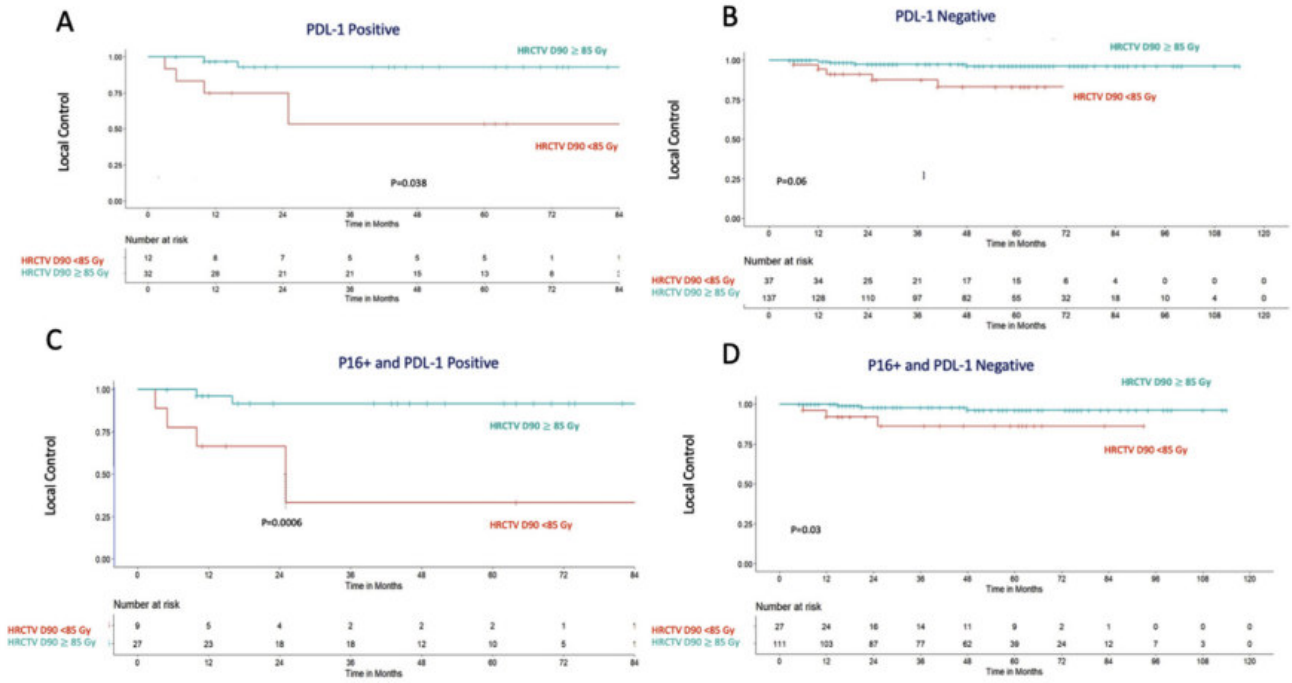
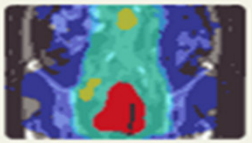


Fig. 3. Figure depicting the difference in local control based on 90% of high-risk clinical target volume dose (HR-CTV D90) received from a combination of external radiation and brachytherapy. In the PD-L1−positive cohort (PD-L1 > 1%), a detriment in local control was observed with equivalent doses in 2 Gy < 85 Gy (A), whereas the difference in local control was not significant in patients who were PD-L1−negative (PDL ≤ 1%) (B). In the P16-positive cohort, the local control was compromised in patients who had coexpression of PD-L1 > 1% (C) and received equivalent doses in 2 Gy < 85 Gy (C). In p16-positive patients and PD-L1−negative patients, the extent of detriment was less, though the difference was statistically significant (D).

HR-CTV D90 should be more than 85Gy (EBRT + IGABT)

Chopra S. et al, 2024. IJRBP



EMBRACE-II

{ Image guided intensity modulated External beam radiochemotherapy and MRI based adaptive BRAchytherapy in locally advanced CErvical cancer }

M&M: Multi-parametric treatment prescription

EBRT: 25x 1.8 Gy (45 Gy) +/- LN-Boost (55/57.5 Gy LP/PA)

BT: ≥45 Gy (total ≥ 90 Gy EQD2)

Chemotherapy: weekly cisplatin 40mg/m2

Table 4
Planning aims (soft constraints) and limits for prescribed dose (hard constraints) for treatment planning in EMBRACE II. The EQD2 is calculated using $\alpha/\beta = 10$ for targets, $\alpha/\beta = 3$ for OAR and a repair halftime of 1.5 h. The total EQD2 include 45 Gy/25 fractions delivered by EBRT.

Target	D90 CTV_{HR} $EQD2_{10}$	D98 CTV_{HR} $EQD2_{10}$	D98 GTV_{res} $EQD2_{10}$	D98 CTV_{IR} $EQD2_{10}$	Point A $EQD2_{10}$
Planning Aims	>90 Gy <95 Gy	>75 Gy	>95 Gy	>60 Gy	>65 Gy
Limits for Prescribed Dose	>85 Gy	–	>90 Gy	–	–
OAR	Bladder D_{2cm3} $EQD2_3$	Rectum D_{2cm3} $EQD2_3$	Recto-vaginal point $EQD2_3$	Sigmoid D_{2cm3} $EQD2_3$	Bowel D_{2cm3} $EQD2_3$
Planning Aims	<80 Gy	<65 Gy	<65 Gy	<70 Gy*	<70 Gy*
Limits for Prescribed Dose	<90 Gy	<75 Gy	<75 Gy	<75 Gy*	<75 Gy*

* For the sigmoid/bowel structures these dose constraints are valid in case of non-mobile bowel loops resulting in the situation that the most exposed volume is located at a similar part of the organ

EMBRACE II Protocol
www.embracestudy.dk

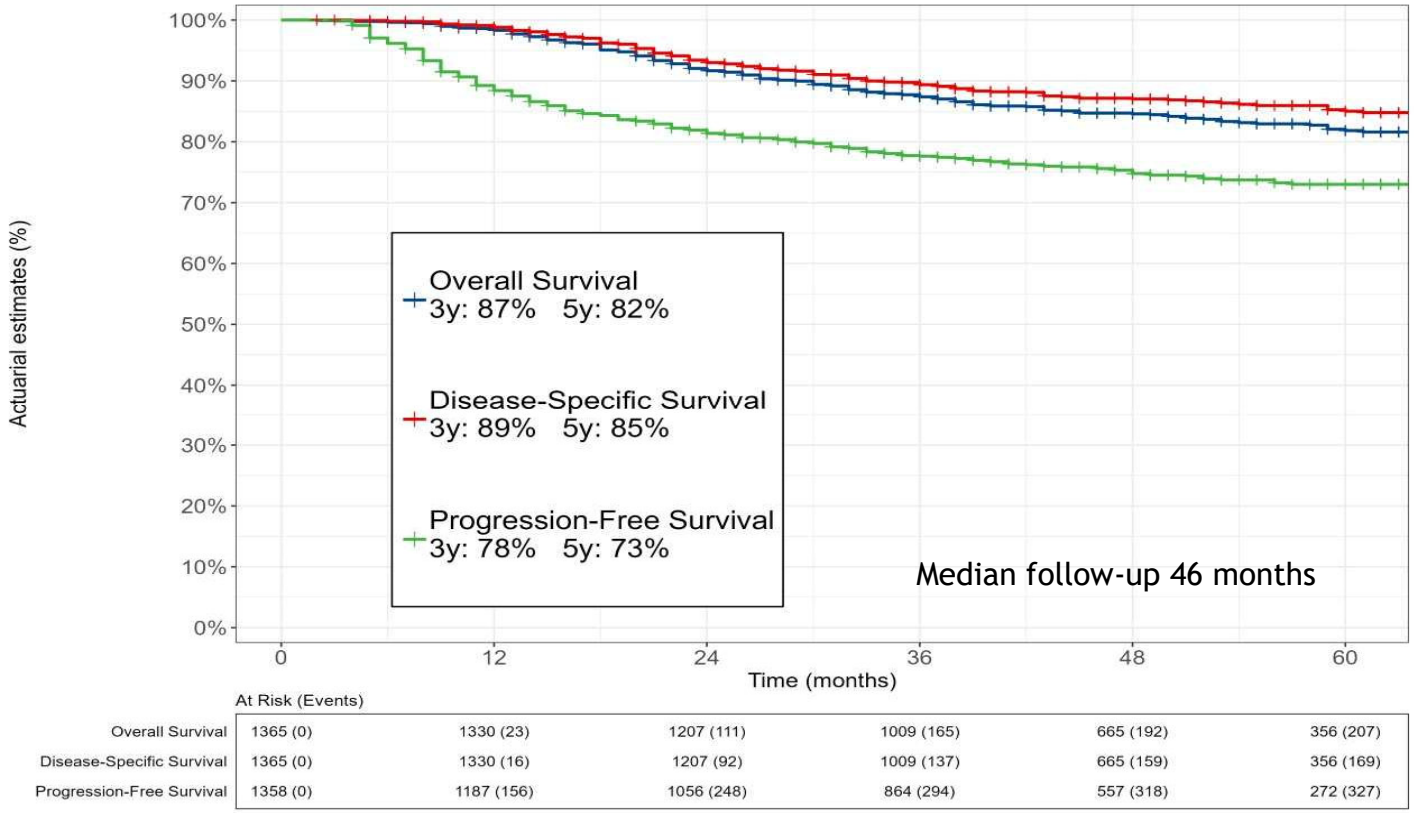
Pötter et al, ESTRO Congress, Vienna, May 2025

EMBRACE-II

{ Image guided intensity modulated External beam radiochemotherapy and MRI based adaptive BRAchytherapy in locally advanced CErvical cancer }

Results: Survival – overall cohort

(based on data from 11/2024)



At Risk (Events)

Overall Survival	1365 (0)	1330 (23)	1207 (111)	1009 (165)	665 (192)	356 (207)
Disease-Specific Survival	1365 (0)	1330 (16)	1207 (92)	1009 (137)	665 (159)	356 (169)
Progression-Free Survival	1358 (0)	1187 (156)	1056 (248)	864 (294)	557 (318)	272 (327)

Results: G3-5 late morbidity

(urinary, GI, vagina, n=1309)

	events	patients	% (crude)
≥ total G3	170	116	8.9%
G3	159	106	8.1
G4	9	8	<1%
G5	-	2	< 0.2%
≥ G3 urinary	51	37	2.8%
≥ G3 gastrointestinal	65	49	3.7%
≥ G3 vagina	43	42	3.2%
Fistula		11 (9 G3, 2 G4)	0.8%

Pötter et al, ESTRO Congress, Vienna May 2025

2018

CTLA-4 and PD-1



Ipilimumab

Dr. James P. Allison and **Dr. Tasuku Honjo**

Selected Trials in LACC

Author (year)	Trial name/ID	*P*	Treatment arms (Dose)	Endpoints	Number of evaluable cases	Disease status	PD-L1 positive (CPS ≥ 1%) (%)	ORR (%)	PFS (M)	OS (M)
Immunotherapy after CCRT										
Da Silva et al. (2021) [45]	GOG-9929/ NCT01711515	I	Adjuvant Ipilimumab IV Q3W following CCRT	Safety, Secondary PFS/ OS	21	FIGO stages IB2/ IIA with positive PALN or FIGO stages IIB/IIIB/ IVA with positive pelvic- and/or PALN	–	–	12-Month PFS 81%	12-Month OS 90%
Combination with CCRT										
Mayadev et al. (2025) [50]	NRG-GY017/ NCT03738228	I	Atezolizumab	Toxicity	30	Locally advanced, node-positive cervical cancer	30–83%	–	2-Year DFS 59–79%	–
Monk et al. (2023) [51]	CALLA/ NCT03830866	III	Durvalumab Q4W + CCRT vs placebo + CCRT	PFS	770	FIGO 2009 stage IB2–IIB lymph node positive, stage ≥ III any lymph node status	96 vs 97 (TAP score)	83 vs 81	12-Month PFS 76·0% vs 73.3%	–
Lorusso et al.[a] (2023) [52]	ENGOT-cx11/ GOG-3047/ KEYNOTE-A1[illegible]/ NCT04221945	III	Pembrolizumab or placebo Q3W + CCRT- > 15 cycles Pembrolizumab or placebo Q6W	PFS/OS	1060	FIGO 2014 stage IB2-IIB with node-positive disease or stage III-IVA	–	–	24-Months PFS of 67.8% vs 57.3%	–
Nakamura et al.[b] (2023) [55]	GOTIC-018/JMA IIA00425	I	Nivolumab + CCRT	Safety	30	FIGO 2009 stage IB–IVA	46.7% (TPS)	93.3–100	12-Month PFS 100%	–
Rodrigues et al. (2023) [53]	NiCOL/ NCT03298893	I	Nivolumab (240 mg) Q2W + CCRT- > Maintenance Nivolumab (6 months)	DLT	21	Immunotherapy-naïve adult patients, FIGO 2018 stages IB3-IVA	–	93.8%	–	–
Neoadjuvant chemotherapy with immunotherapy										
Li et al. (2024) [56]	NACI/ NCT04516616	II	Camrelizumab (anti-PD-1) + chemotherapy- > surgery or CCRT	ORR	85	FIGO 2018 stage IB3,IIA2, IIB/ IIIC1r	42 (CPS ≥ 10)	98	–	–

P phase, *M* months, *ORR* overall response rate, *PFS* progression free survival, *OS* overall survival, *CCRT* concurrent chemoradiotherapy, *Q* quaque, *PALN* para aortic lymph nodes, *SCC* squamous-cell carcinoma *TAP* tumour area positivity, *DLT* dose-limiting toxicities

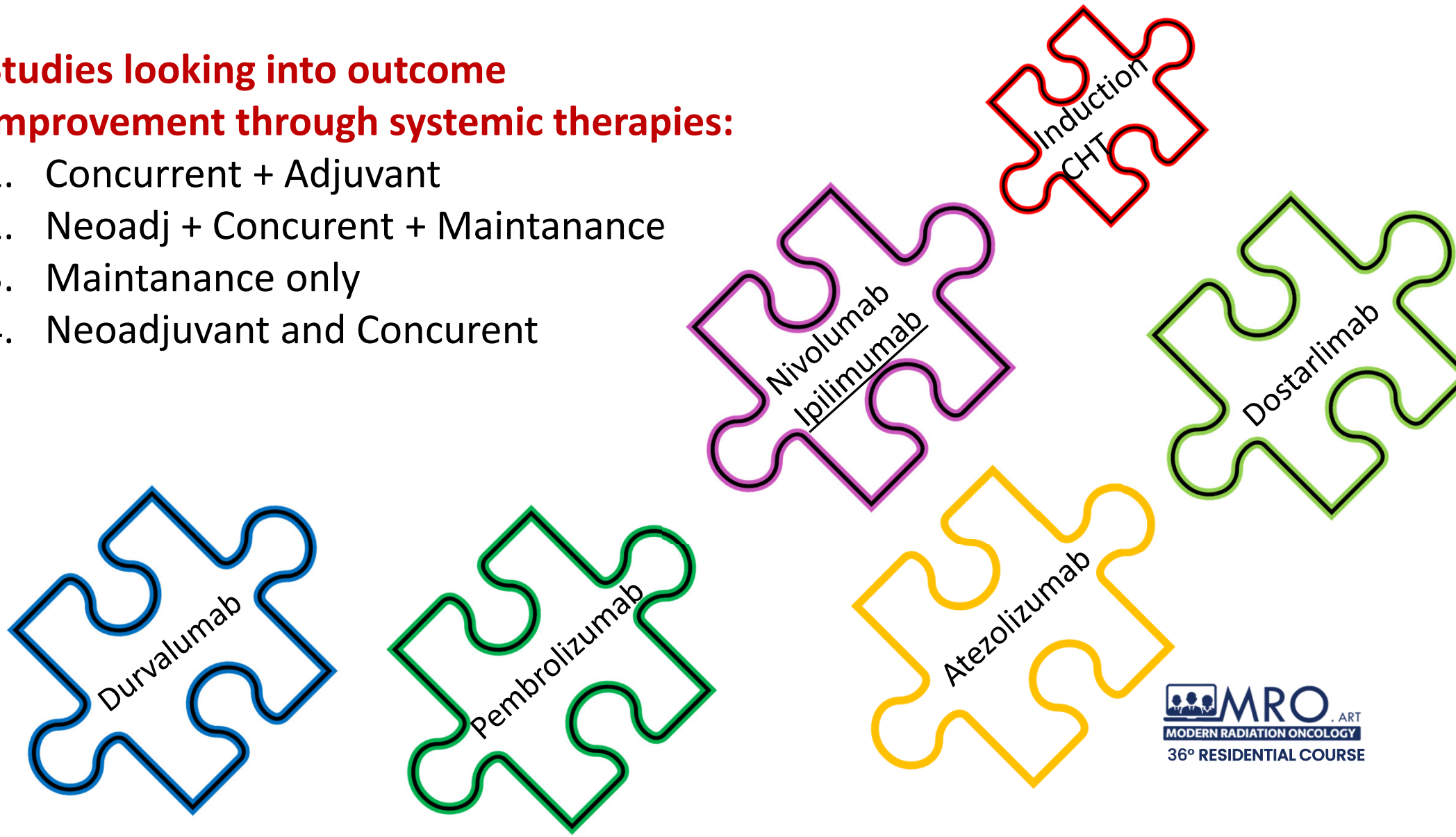
[a]ESMO (European Society for Medical Oncology) congress 2023

[b]ASCO congress 2023

Ogasawara A, Hasegawa K, IJCL, 2025

Studies looking into outcome improvement through systemic therapies:

1. Concurrent + Adjuvant
2. Neoadj + Concurent + Maintanance
3. Maintanance only
4. Neoadjuvant and Concurent



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INTERLACE TRIAL

N=500

McCormack M, et al. Lancet, 2024

Accrual: 2012-2022

500 PATIENTS

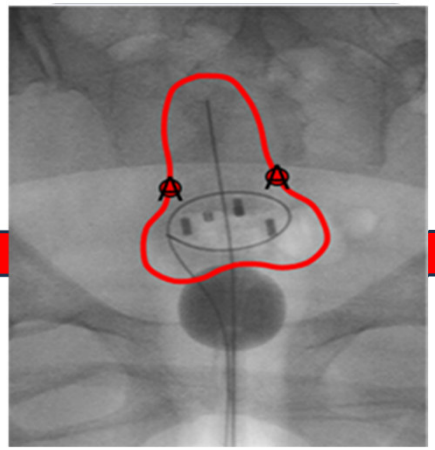


250

STANDARD

250

2D BT to point A



$FIGO_{2009}$: IB1 N+, IB2, II, IIIB, IVA

Squamous, Adeno, Adeno-sq.

No N > Aortic bifurcation on imaging

Adequate renal, liver & bone marrow function

Fit for CHT & RT

CHEMORADIATION



EBRT

45-50.4 Gy

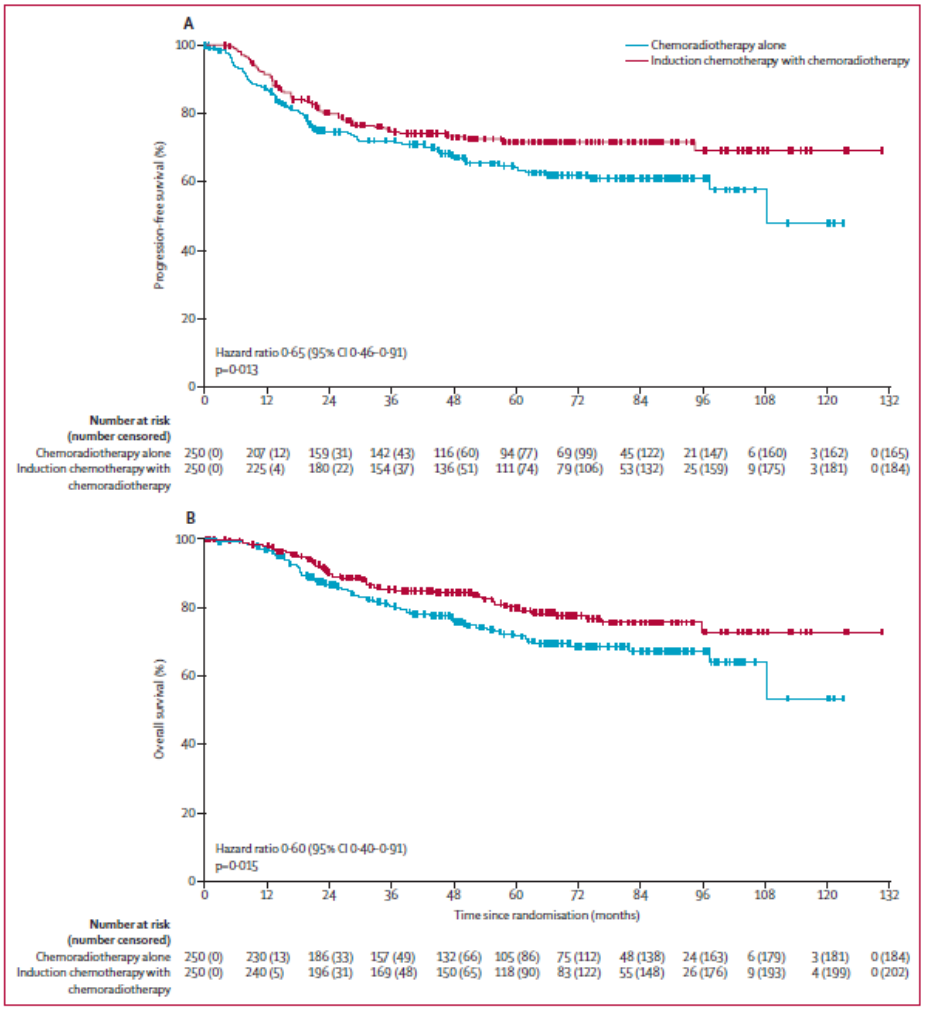
Cispl. 40 mg/m^2/w



BT

Point A or 3D

≥78 Gy to p. A



INTERLACE TRIAL

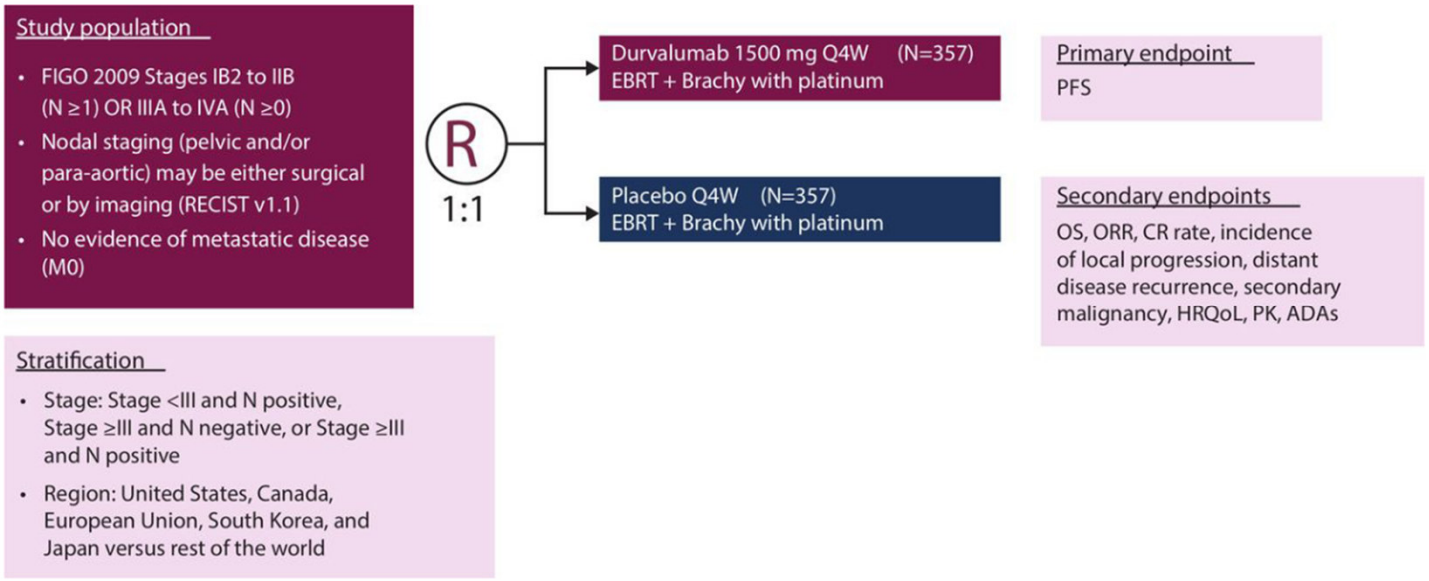
40% N+, no PAN

Median FU: 67 Mo
OS@5 years: 80% experimental vs 72% standard arm

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The CALLA Study



770 Patients randomized 1:1

Patients with high risk of recurrence:

66% with stage IIIA–IVA
74% LN-positive
11% with para-aortic LN involvement

Centralised QA of the radiotherapy plans

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Durvalumab versus placebo with chemoradiotherapy for locally advanced cervical cancer (CALLA): a randomised, double-blind, phase 3 trial

Bradley J Monk, Takafumi Toita, Xiaohua Wu, Juan C Vázquez Limón, Rafal Tarnawski, Masaki Mandai, Ronnie Shapira-Frommer, Umesh Mahantshetty, Maria del Pilar Estevez-Diz, Qi Zhou, Sewanti Limaye, Francisco J Ramirez Godinez, Christina Oppermann Kussler, Szilvia Varga, Natalia Valdiviezo, Daisuke Aoki, Manuel Leiva, Jung-Yun Lee, Raymond Sulay, Yulia Kreynina, Wen-Fang Cheng, Felipe Rey, Yi Rong, Guihao Ke, Sophie Wildsmith, Andrew Lloyd, Hannah Dry, Ana Tablante Nunes, Jyoti Mayadev

The CALLA Study

Median FU: 18.5 Mo

PFS: not statisticaly significant
In post-hoc analyses:
PFS Benefit in patients with PD-L1 expression TAP≥20%

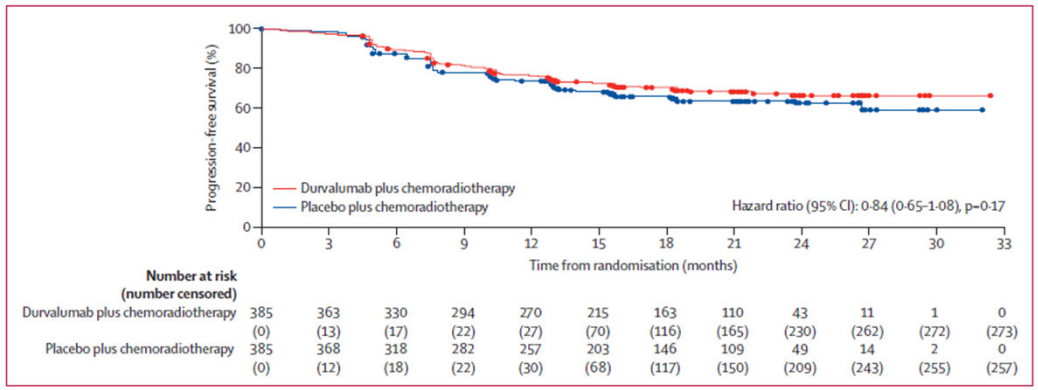
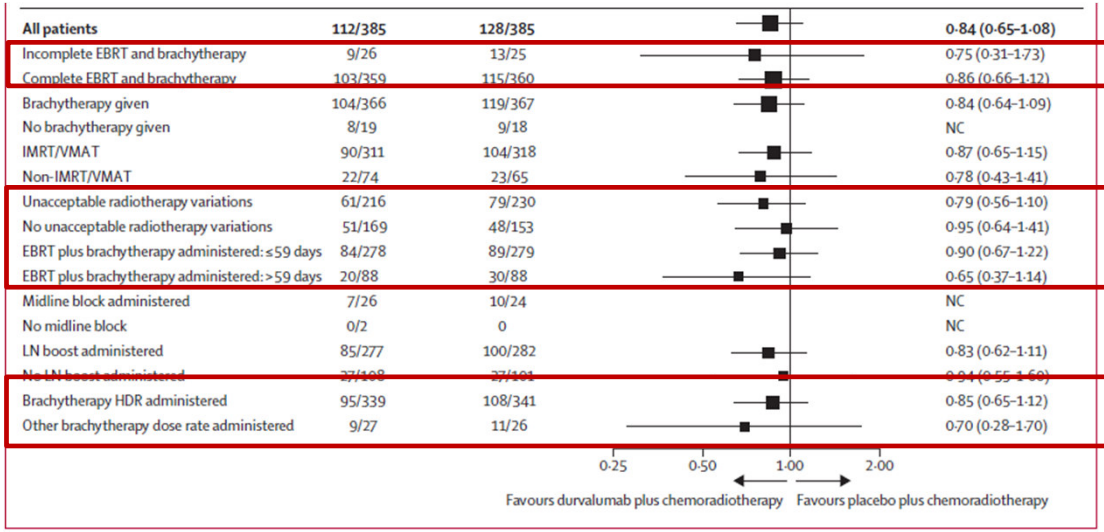


Figure 2: **Kaplan-Meier plot of progression-free survival**
Progression-free survival, as per Response Evaluation Criteria in Solid Tumors version 1.1 as assessed by investigator or histopathological confirmation of local tumour progression. Data maturity was 31%.



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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY DRIVING INNOV. IN ONCOLOGY

ORIGINAL ARTICLE

Ultrasensitive detection and tracking of circulating tumor DNA to predict relapse and survival in patients with locally advanced cervical cancer: phase III CALLA trial analyses

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ctDNA and cHPV DNA

Department of Radiation Oncology

Mayadev et al, Annals of Oncology, 2025

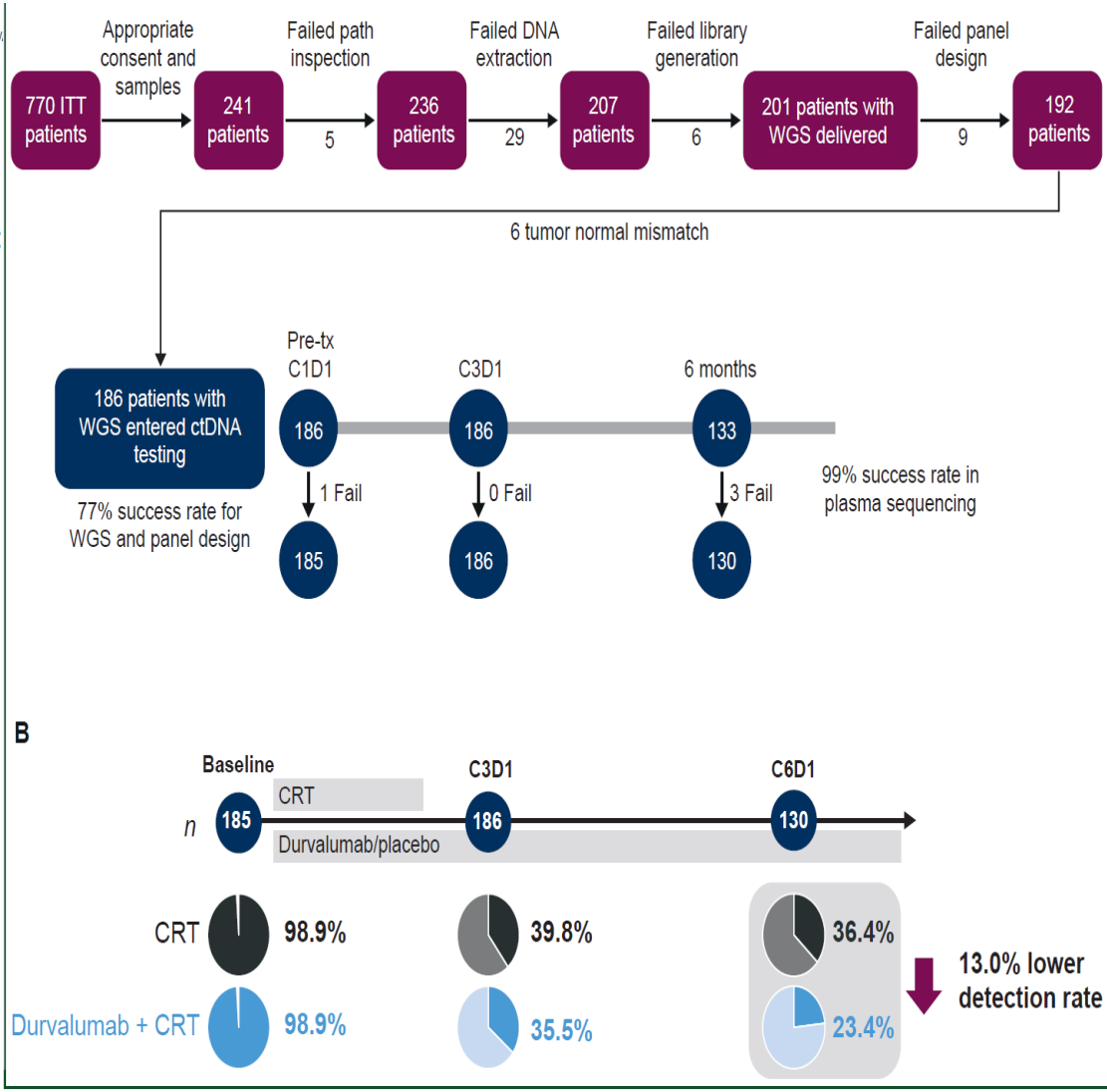
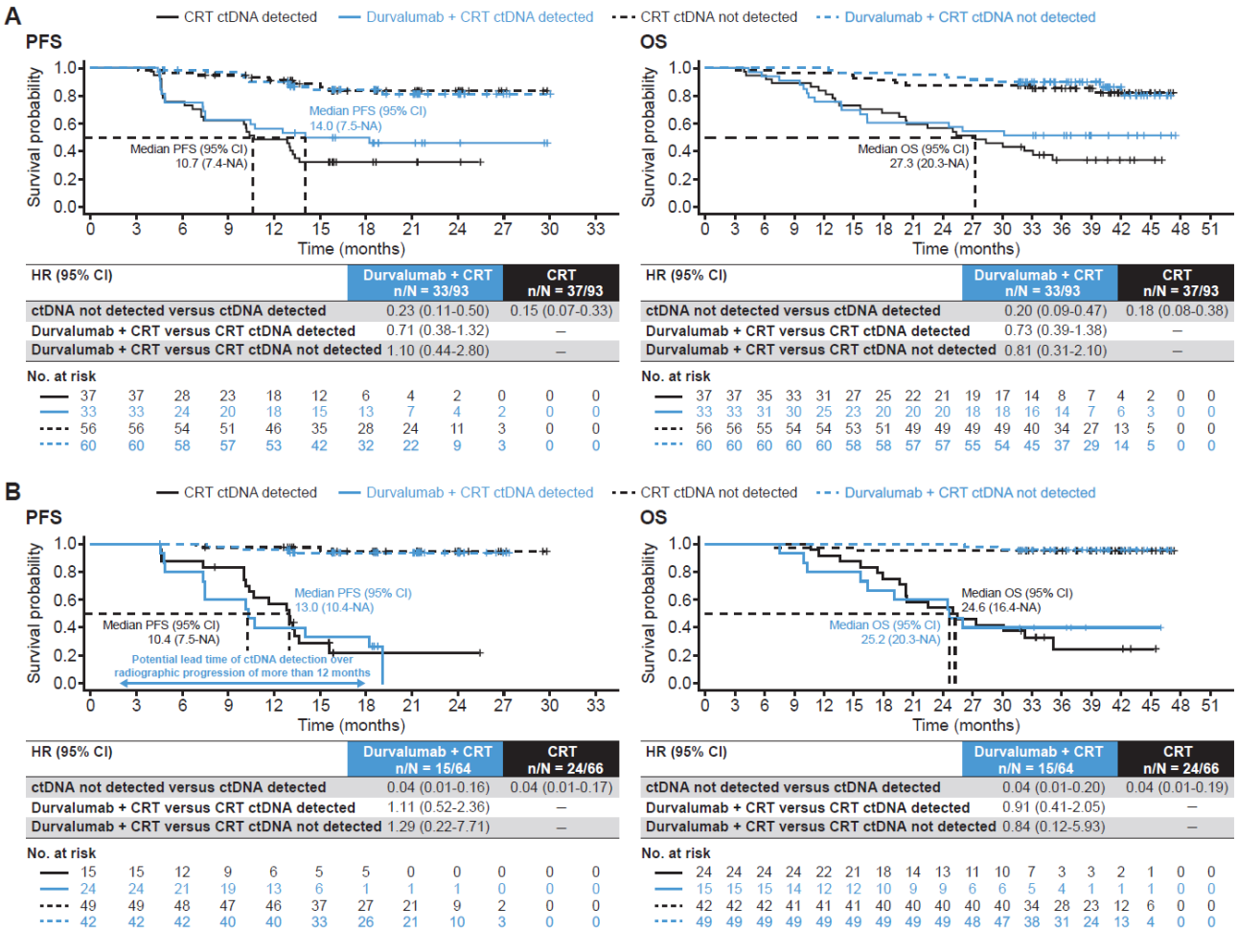


Figure 1. **Sample collection and detection.** (A) Collection, analysis, and data availability. (B) ctDNA detection rates over time. A total of 185 patients had usable samples from C1 and C3, and 129 patients had usable samples at all three time points.
C1D1, cycle 1 day 1; C3D1, cycle 3 day 1; C6D1, cycle 6 day 1; ctDNA, circulating DNA; tx, treatment; WGS, whole genome sequencing.

Subgroup Analyses CALLA trial



Alina Sturdza

Cut off ctDNA levels of 5268.2 parts per million

For low baseline ctDNA at dg, both groups had a good PFS and OS

Detection of ctDNA and cHPV DNA at C3D1 worst prognostic in CRT arm
Pt with high cHPV DNA did better with Durvalumab

Detection of ctDNA levels after completion of treatment suggest incomplete remission
Can show increased risk of recurrence
5.5mths prior to radiographic findings

Stage was the most important pretreatment prognostic factor with respect to OS

Mayadev et al, Annals of Oncology, 2025

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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 version 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 [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

Dual primary endpoints:

- PFS per investigator review
- OS

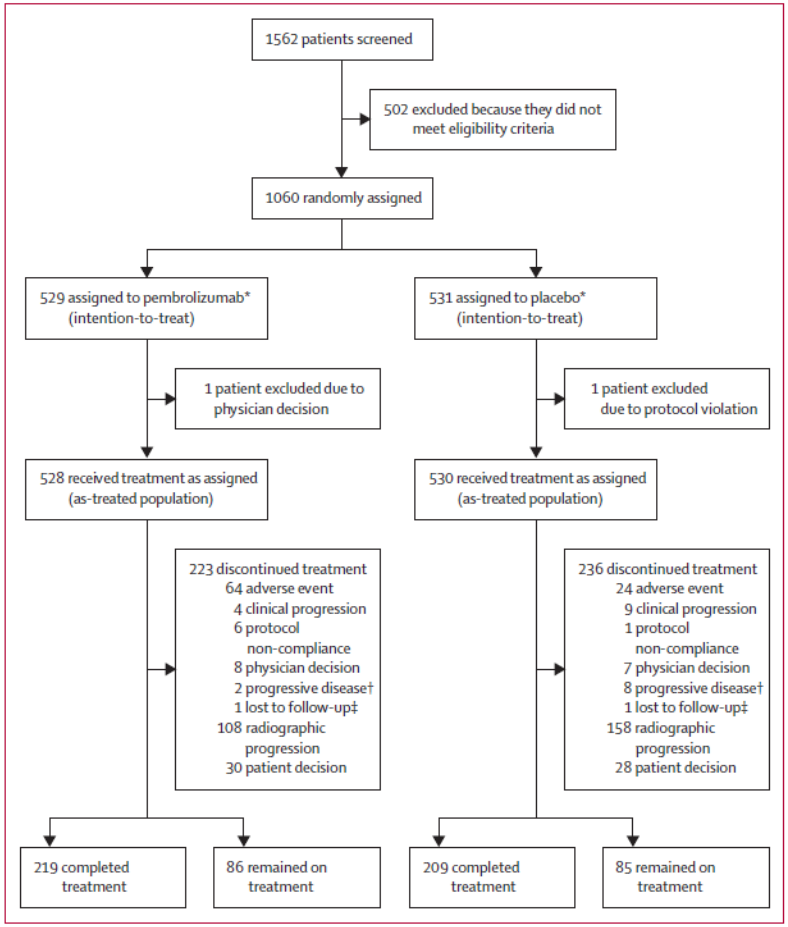
Patients acrued regardless of PDL status

PRO endpoints

- Secondary: change from baseline and overall improvement/stability + improvement in QLQ-C30 GHS/QoL and physical function subscales and QLQ-CX24 symptom-specific scale
- Exploratory: change from baseline and overall improvement/stability + improvement in the EQ-5D-5L VAS

[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.
EBRT, external beam radiotherapy; EQ-5D-5L VAS, European Quality of Life Five Dimension questionnaire visual analogue scale; FIGO, International Federation of Gynecology and Obstetrics; GHS/QoL, global health status/quality of life subscale; Gy, grays; IMRT, intensity-modulated radiotherapy; Q3W, every 3 weeks; Q6W, every 6 weeks; QLQ-C30, quality of life questionnaire core 30; QLQ-CX24, cervical cancer-specific QLQ; RECIST, Response Evaluation Criteria in Solid Tumors; VMAT, volumetric-modulated arc therapy. ENGOT-cx11/GOG-3047/KEYNOTE-A18 ClinicalTrials.gov identifier, NCT04221945.

Results Keynote A18:



Patient population:
1060 patients Randomized 1:1
176 sites, 30 countries, all races
56% Stage III to IVA
62% pelvic lymph nodes +
20% PAN +pelvic
3% PAN only

16% Node negative

Lorusso D, The Lancet, Oct 2024

Results Keynote A18

Median FU: 29.9 Mo
OS@3 years: 82.6% experimental vs 74.8% standard
HR for death: 0.67 (95%CI, p=0040)

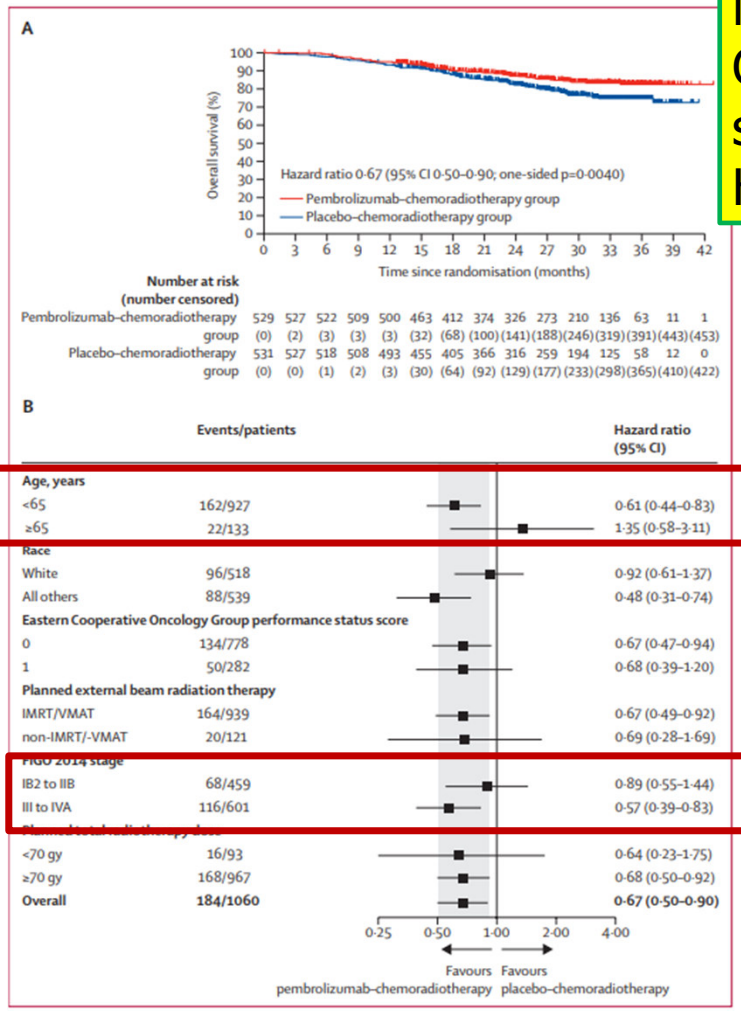


Figure 2: Overall survival
(A) Kaplan-Meier estimates of overall survival in the intention-to-treat population. Tick marks indicate censoring of data. (B) Analysis of overall survival in protocol-specified subgroups of the intention-to-treat population. IMRT=intensity-modulated radiation therapy. VMAT=volumetric modulated arc therapy.

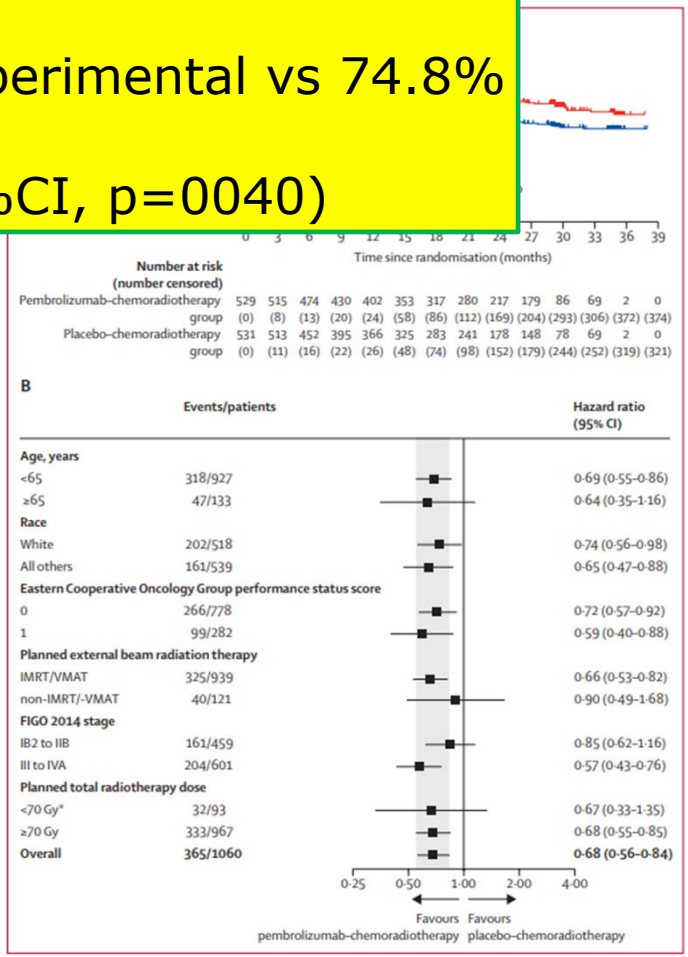


Figure 3: Progression-free survival at the second interim analysis.
(A) Kaplan-Meier estimates of progression-free survival in the intention-to-treat population. Tick marks indicate censoring of data. (B) Analysis of progression-free survival in protocol-specified subgroups of the intention-to-treat population. Progression-free survival was assessed per RECIST version 1.1 by investigator review. IMRT=intensity-modulated radiation therapy. VMAT=volumetric modulated arc therapy. *The patients who received total radiotherapy dose <70 Gy in Japan per Japanese guidelines used the central shielding technique in the pelvic radiotherapy.

Lorusso D, The Lancet, Oct 2024

Results Keynote A18: Side effect profile

	Pembrolizumab–chemoradiotherapy (N=528)		Placebo–chemoradiotherapy (N=530)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any adverse event*	528 (100%)	413 (78%)	526 (99%)	371 (70%)
Anaemia	358 (68%)	122 (23%)	349 (66%)	117 (22%)
Nausea	320 (61%)	8 (2%)	338 (64%)	10 (2%)
Diarrhoea	301 (57%)	27 (5%)	298 (56%)	25 (5%)
White blood cell count decreased	175 (33%)	105 (20%)	186 (35%)	113 (21%)
Neutrophil count decreased	164 (31%)	83 (16%)	152 (29%)	81 (15%)
Vomiting	160 (30%)	5 (1%)	177 (33%)	7 (1%)
Hypomagnesaemia	130 (25%)	15 (3%)	124 (23%)	13 (3%)
Leukopenia	129 (24%)	69 (13%)	98 (9%)	59 (11%)
Neutropenia	123 (23%)	61 (12%)	109 (21%)	57 (11%)
Urinary tract infection	121 (23%)	21 (4%)	146 (28%)	18 (3%)
Constipation	118 (22%)	1 (<1%)	124 (23%)	2 (<1%)
Hypothyroidism	118 (22%)	3 (1%)	36 (7%)	0
Platelet count decreased	118 (22%)	25 (5%)	113 (21%)	15 (3%)
Hypokalaemia	116 (22%)	30 (6%)	92 (17%)	20 (4%)
Alanine aminotransferase increased	115 (22%)	13 (3%)	87 (16%)	7 (1%)
Aspartate aminotransferase increased	106 (20%)	11 (2%)	71 (13%)	3 (1%)
Fatigue	102 (19%)	4 (1%)	113 (21%)	5 (1%)
Decreased appetite	96 (18%)	3 (1%)	106 (20%)	2 (<1%)
Treatment-related adverse event†	512 (97%)	365 (69%)	513 (97%)	325 (61%)
Anaemia	317 (60%)	101 (19%)	296 (56%)	85 (16%)
Nausea	304 (58%)	7 (1%)	317 (60%)	10 (2%)
Diarrhoea	268 (51%)	24 (5%)	271 (51%)	22 (4%)
White blood cell count decreased	173 (33%)	104 (20%)	183 (35%)	111 (21%)
Neutrophil count decreased	156 (30%)	79 (15%)	148 (28%)	78 (15%)
Vomiting	135 (26%)	3 (<1%)	150 (28%)	7 (1%)
Leukopenia	125 (24%)	67 (13%)	92 (17%)	57 (11%)
Platelet count decreased	116 (22%)	25 (5%)	109 (21%)	13 (2%)
Neutropenia	114 (22%)	56 (11%)	94 (18%)	52 (10%)
Hypothyroidism	112 (21%)	3 (<1%)	30 (6%)	0
Immune-mediated adverse event‡	206 (39%)	25 (5%)	90 (17%)	7 (1%)
Hypothyroidism	119 (23%)	3 (<1%)	36 (7%)	0
Hyperthyroidism	64 (12%)	2 (<1%)	15 (3%)	0
Gastritis	22 (4%)	2 (<1%)	20 (4%)	0
Colitis	16 (3%)	4 (<1%)	11 (2%)	4 (<1%)

*Please see the appendix (p 14) for a full table of graded adverse events. †Listed are adverse events that occurred during the treatment period or within 30 days after the treatment period (within 90 days for serious events). The as-treated population included all the patients who had undergone randomisation and received at least one trial treatment. The severity of adverse events was graded according to the Common Terminology Criteria for Adverse Events, version 5.0, of the National Cancer Institute. †Treatment-related adverse events were events that were attributed to a trial treatment by the investigators. Treatment-related adverse events that occurred in at least 20% of the patients in either treatment group are reported. The events are listed in descending order of frequency in the pembrolizumab–chemoradiotherapy group. Patients may have had more than one event. Grade 5 treatment-related adverse events were immune-mediated gastritis (n=1) and large intestine perforation (n=1) in the pembrolizumab–chemoradiotherapy group, and bone marrow failure (n=1) and neutropenic colitis (n=1) in the placebo–chemoradiotherapy. ‡Immune-mediated adverse events were determined according to a list of terms specified by the sponsor, regardless of attribution to any trial treatment by the investigators. Adverse events of interest that occurred in at least 15 patients in either treatment group are reported.

Table 2: **Adverse events that occurred in at least 20% of the patients in the as-treated population**

G3 and more toxicity:
78% experimental arm vs 70% in standard arm
Bone marrow toxicity the highest

Immune-mediated side effects occurred in 39% in experimental arm and 17% in standard arm

Results Keynote A18: PROs

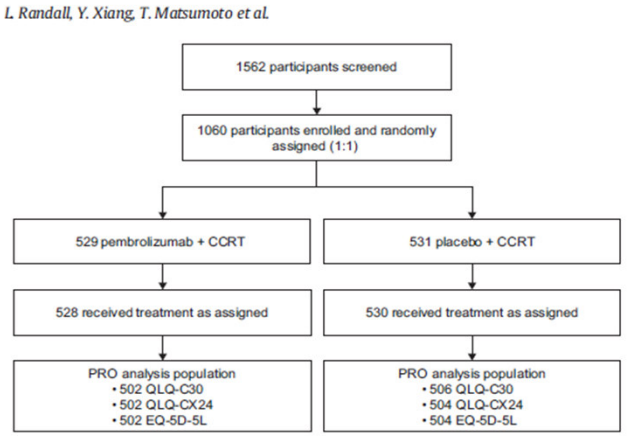
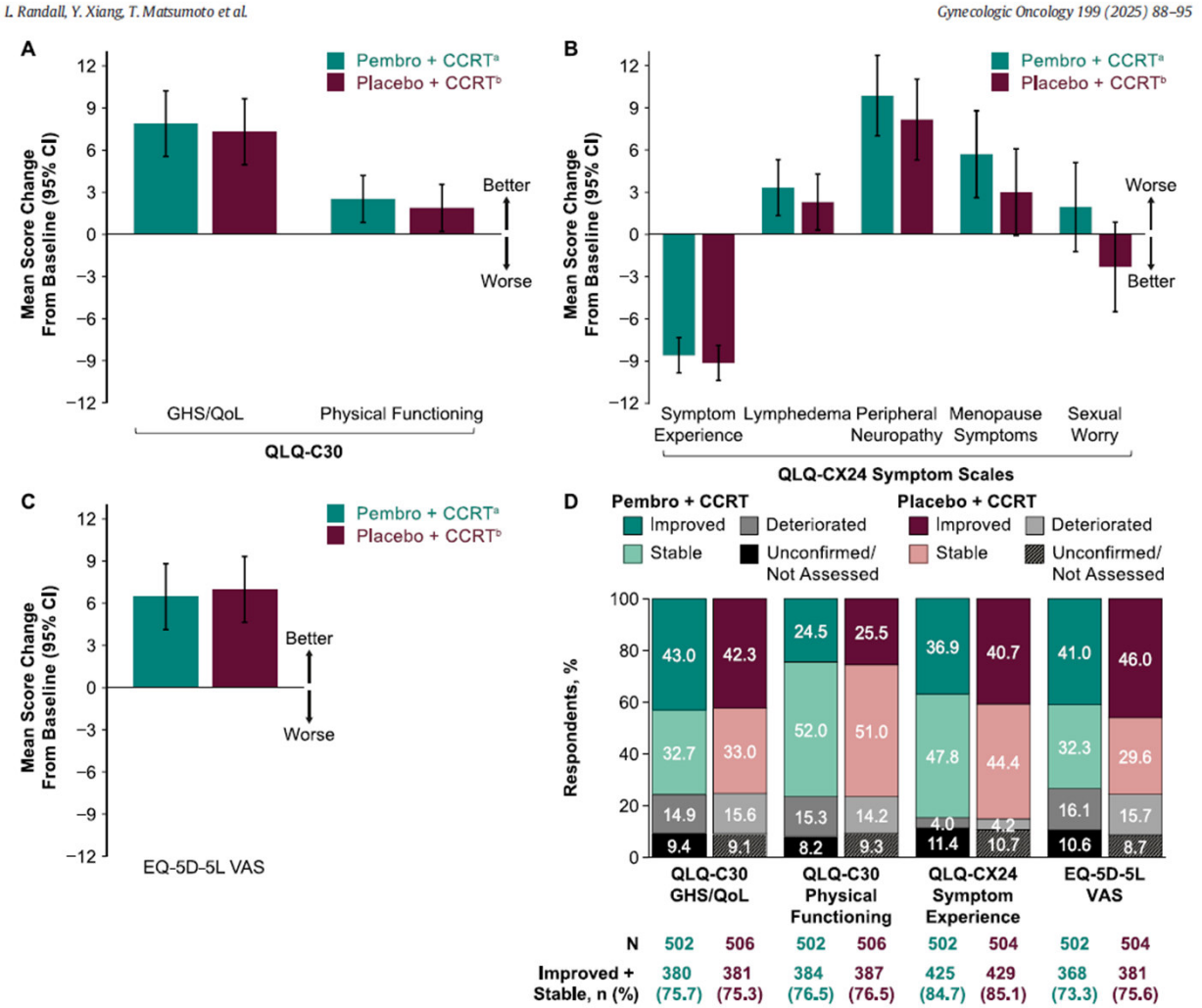


Fig. 1. Participant disposition. PRO analyses were based on the PRO full analysis set population and included all participants who received ≥1 dose of study treatment and completed ≥1 postbaseline PRO assessment. CCRT, concurrent chemoradiotherapy; EQ-5D-5L, EuroQol 5-Dimension 5-Level questionnaire; PRO, patient-reported outcome; QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; QLQ-CX24, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire cervical cancer module.

Pembrolizumab + CCRT did not negatively impact participants' health-related quality of life



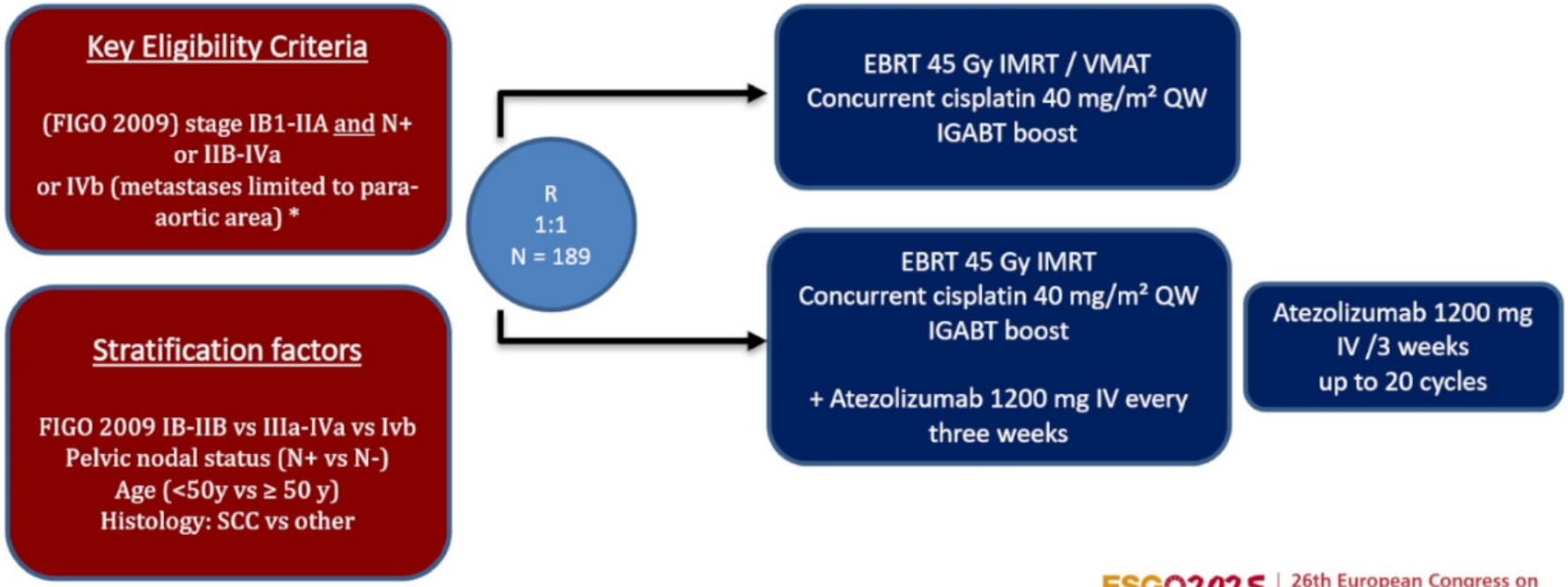
Randall L et al. Gynecologic Oncology, 2025

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ATEZOLACC:
Randomized, open, phase II trial

State of the art radiation in both arms



*based on PET/CT

ESGO2025 Congress | 26th European Congress on Gynaecological Oncology
FEBRUARY 20-23, 2025 | ROME, ITALY

Alina Emiliana Sturdza

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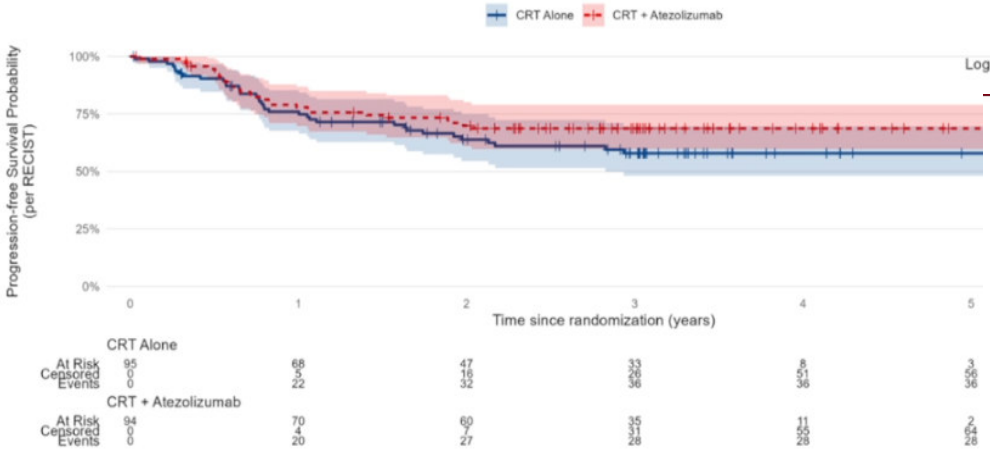
Chargari et al, ESGO Congress, Rome, February 2025

Results: ATEZOLACC

Primary endpoint: 2-y PFS

2-y PFS (95%CI)	
Standard arm	64% [55%; 75%]
Atezo arm	70% [61%; 80%]

HR (95%CI)

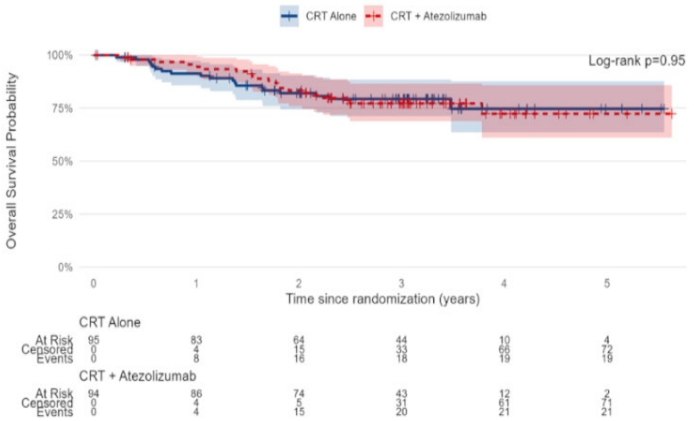


Secondary endpoints

2-y OS (95%CI)	
Standard arm	82% [74%; 90%]
Atezo arm	83% [76%; 91%]

HR (95%CI)
1.01 [0.52; 1.96]

Overall survival



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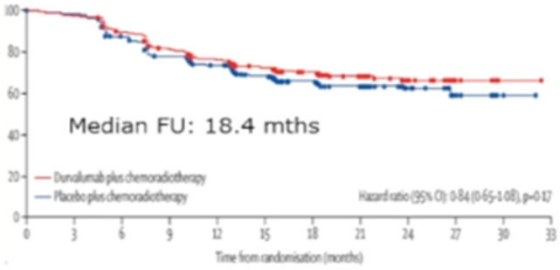
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Chargari et al, ESGO Congress, Rome, February 2025

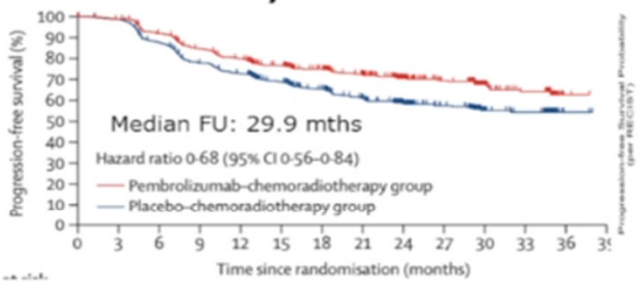
ICI in LACC summary

ICI in locally advanced cervical cancer: PFS

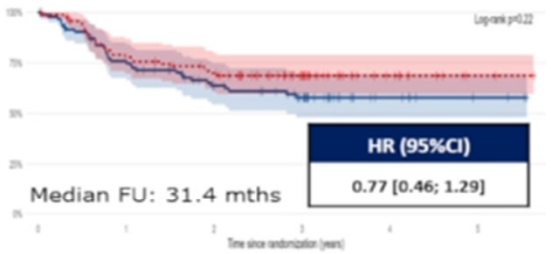
CALLA



Keynote A18



ATEZOLACC



Phase-III randomized double blind	Phase-III randomized double blind	**Phase-II randomized**
Durvalumab **Anti PD-L1**	Pembrolizumab Anti PD-1	Atezoluzimab **Anti PD-L1**
FIGO 2009: IB2-IIB node positive, III-IV	FIGO 2014: IB2-IIB node positive, III-IVa	FIGO 2009: **IB1-IIA node positive, IIB-IV**
N=770; 105 sites 15 countries	N=1060; 176 sites 30 countries	N=189; 24 sites 1 country

Monk B. et al, The Lancet Oncology 2023
Lorusso D. et al, The Lancet, Oct 2024
Chargari C. et al. ESGO Meeting. Feb 2025

The role of ICI and patient selection ist still to be established

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2026

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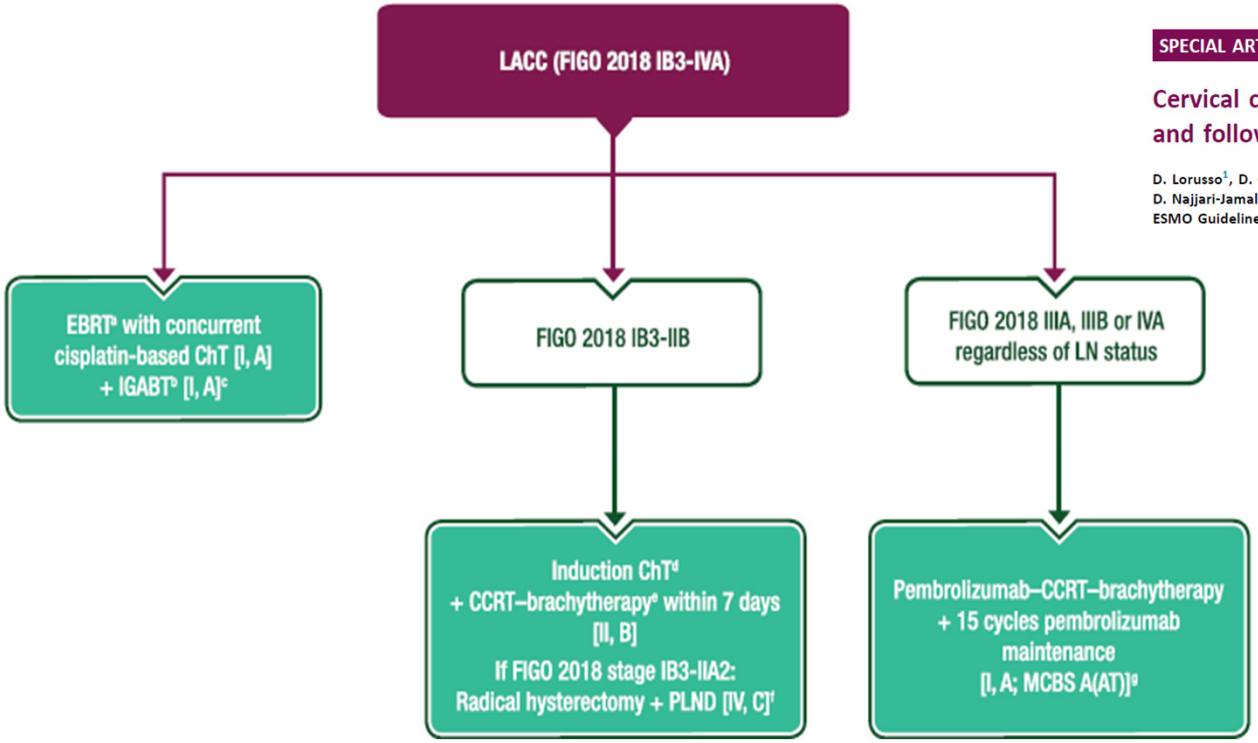
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

SPECIAL ARTICLE

Cervical cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

D. Lorusso[1], D. Cibula[2], I. Colombo[3], A. Félix[4,5], K. Hasegawa[6], J. E. Kurtz[7], S. F. Lax[8], K. Lindemann[9,10], J. Mayadev[11], D. Najjari-Jamal[12], A. Nogueira-Rodrigues[13], R. A. Nout[14], P. T. Ramirez[15], K. S. Tewari[16] & A. Oaknin[17], on behalf of the ESMO Guidelines Committee*



[a]IMRT or VMAT is the recommended EBRT technique [I, A].
[b]MRI-based IGABT is recommended as the standard approach for brachytherapy, and combined IC/IS brachytherapy is recommended for patients with asymmetric or large residual disease [I, A].
[c]The minimal recommended total EQD2 D90 to the HR-CTV should be >85 Gy and the overall treatment should be delivered within 50 days, with a maximum acceptable extension to 56 days [III, A].

[d]Weekly carboplatin—paclitaxel for six cycles.
[e]When IMRT/VMAT and/or IGABT are not available.
[f]An alternative option in specialised sites for carefully selected patients who will likely not need post-operative RT.
[g]ESMO-MCBS v2.0[80] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors.

Questions:

1. Appropriate timing to initiate ICI
2. Biomarkers necessary to identify responders
3. More information about the tumour microenvironment and its real influence on response
4. Which combination of ICI (VGFR?, TKI?), shall CHT be obsolete?
5. Which agents to use after first line ICI
6. ……. …???



Maintanance only

Open-label randomised phase 2 ATOMICC trial

Trial design

- High-risk LACC
  - FIGO 2009 stage IB2, IIA2 or IIB and pelvic LN+
  - FIGO 2009 stage IIIA, IIIB or IVA
  - Any FIGO 2009 stage and para-aortic LN+
- CR/PR after standard concurrent CRT with curative intent
- No prior immune checkpoint inhibitor
- ECOG PS ≤1

CRT completed ≤12 weeks before consenting

R

1:2

- Observation
- Maintenance dostarlimab 500 mg q3w for 4 cycles → 1000 mg q6w for up to 2 years in total

Primary endpoint: PFS per RECIST v1.1

Secondary endpoints: OS, PROs, safety

Stratification factors:

- Histology (squamous vs adenosquamous/adenocarcinoma)
- Response to CRT (CR vs PR)
- FIGO 2009 stage/nodal status (IB2, IIA2 or IIB and pelvic LN+ vs IIIA, IIIB or IVA vs any FIGO 2009 stage and para-aortic LN+)

CR = complete response; ECOG PS = Eastern Cooperative Oncology Group performance status; LN+ = positive lymph nodes; PR = partial response; PRO = patient-reported outcome; q3w = every 3 weeks; q6w = every 6 weeks

Ana Oaknin

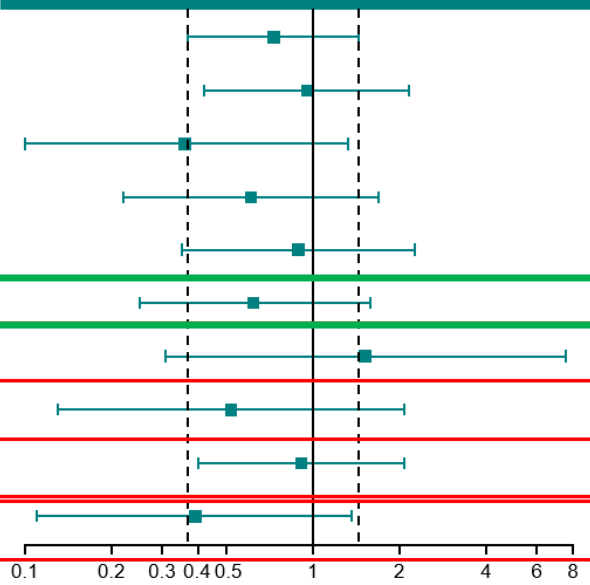
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Open-label randomised phase 2 ATOMICC trial
134 patients from 22 Spanish sites
RCT 1:2

Favours: smaller T with pelvic LN
AD/ADSQ, PAN
Less favorable in SQ Histo
No benefit in very large T

PFS in clinically relevant subgroups

Subgroup	Hazard ratio (95% CI)[a]	Hazard ratio (95% CI)[a]
All patients		0.73 (0.37–1.45)
ECOG PS 0		0.96 (0.42–2.16)
ECOG PS 1		0.36 (0.10–1.33)
PR to CRT		0.61 (0.22–1.69)
CR to CRT		0.89 (0.35–2.27)
FIGO 2009 stage IB2, IIA2 or IIB and pelvic LN+		0.62 (0.25–1.58)
FIGO 2009 stage IIIA, IIIB or IVA		1.52 (0.31–7.53)
Any FIGO 2009 stage and para-aortic LN+		0.52 (0.13–2.08)
Squamous histology		0.91 (0.40–2.08)
Adenosquamous/adenocarcinoma histology		0.39 (0.11–1.37)



[a]Unstratified hazard ratio

Ana Oaknin

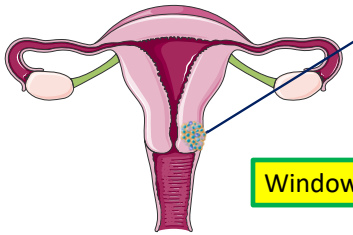
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Neoadj + Concurent + Maintanance

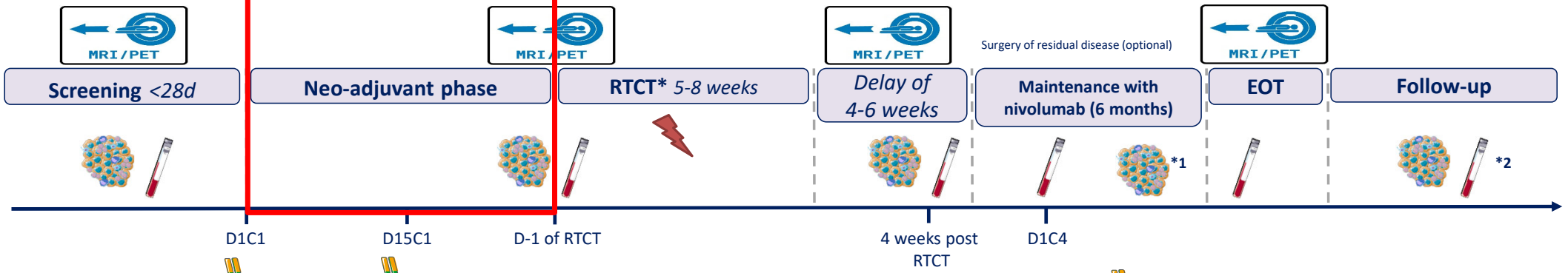
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Phase 2 – COLIBRI-1 inclusion criteria & Study design



Cervical cancer
- Women aged ≥18 years
- Histologically confirmed cervical (adeno)squamous carcinoma
- LACC (FIGO 2018) stage IB3-IVA
- ECOG performance status of 0 or 1
- Multicentric single arm pilot study

Window of oportunity for enhancing the immune response



Nivolumab 3mg/kg

Ipilimumab 1mg/kg

Nivolumab 480mg, q4w

*1 optional *cervical tumor sample during the surgery*

*2 *mandatory blood sample and optional biopsy at progression*

Tumor biopsy

Blood sample

*Chemoradiotherapy Regimen

Platinum agent	Cisplatin 40 mg/m² or carboplatin AUC2 q1w × 5 weeks
EBRT	45 Gy in 25 fractions at 1.8 Gy/fraction, 5 fractions per week
Brachytherapy	High-dose rate: 27.5–30 Gy; Low/pulsed-dose rate: 35–40 Gy

Primary endpoint : To measure the $CD8^+/FOXP3^+$ ratio, in pre- versus post-ICB therapy

Secondary endpoints : - Safety,
- Response rate, **Survival outcomes (3 yrs PFS, OS),**
-Evolution of **immune microenvironment** and **correlation with outcomes**

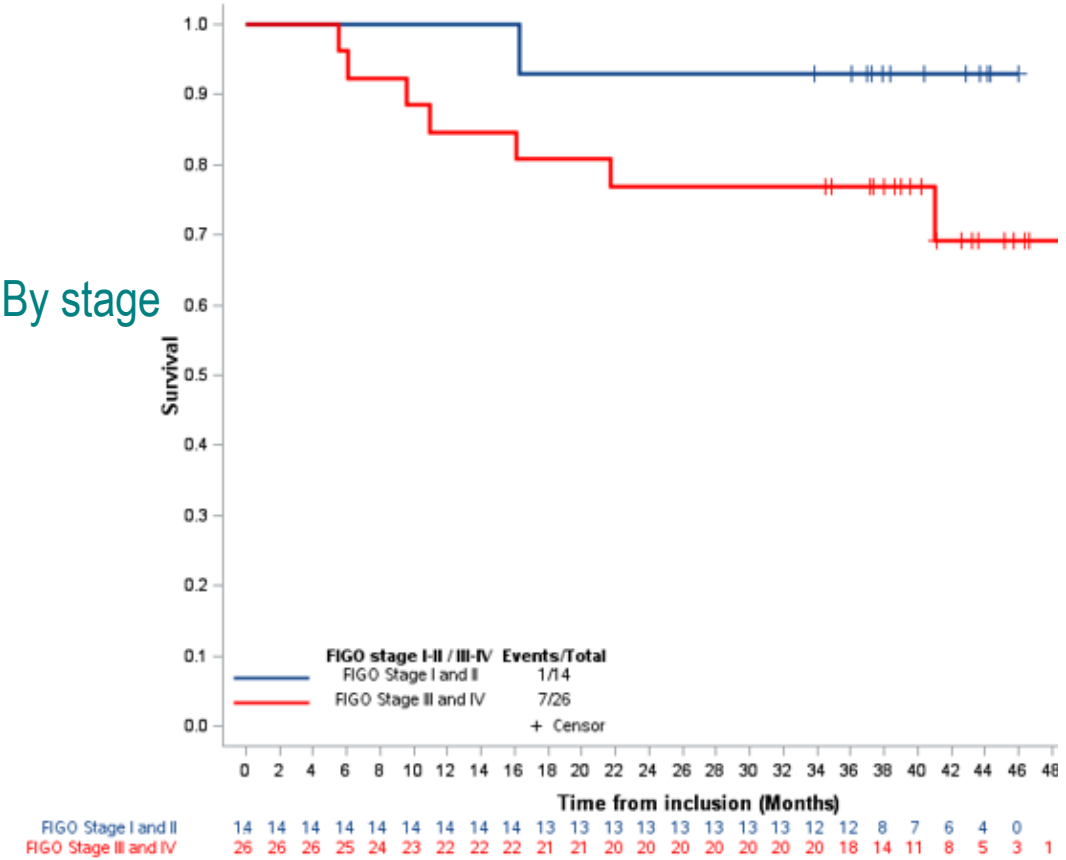
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PRESENTED BY : Florence JOLY

Global PFS and OS AND according to stage

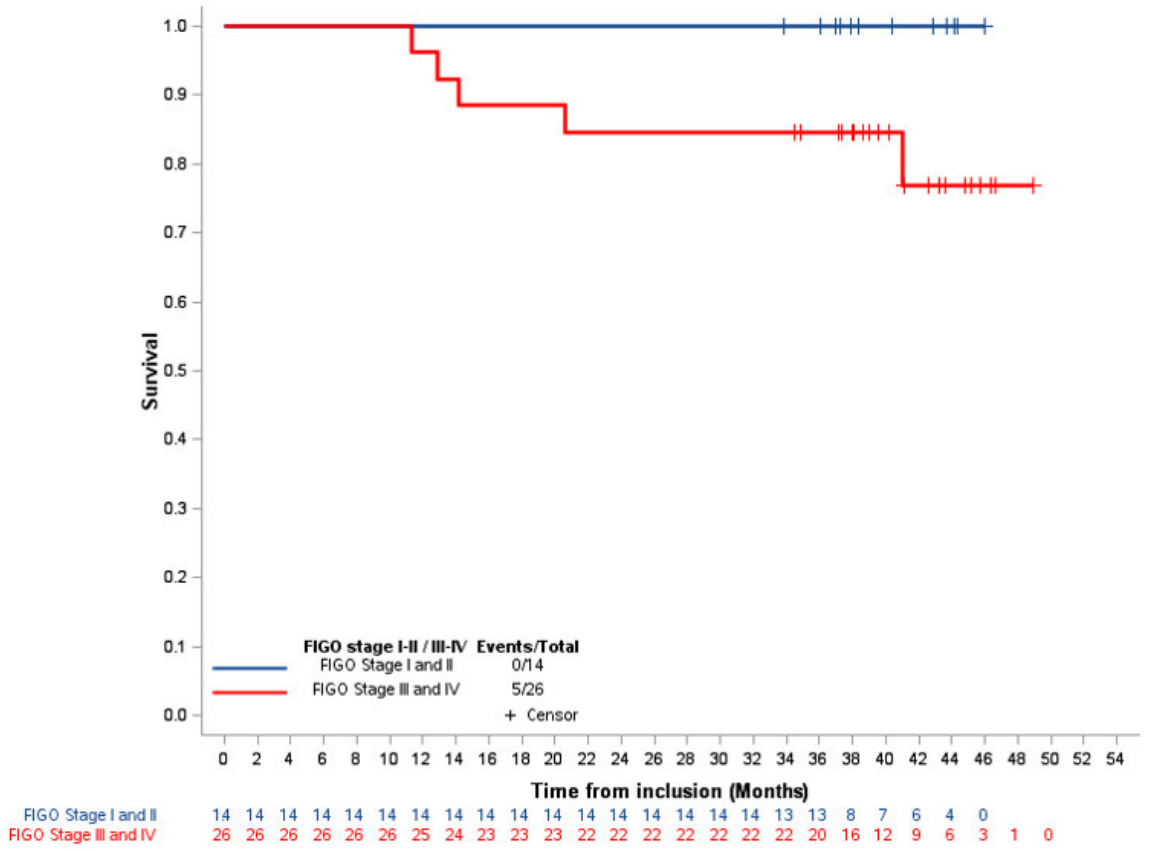
PFS Global 36 months PFS rate = 83% (95%IC 67-91)

By stage



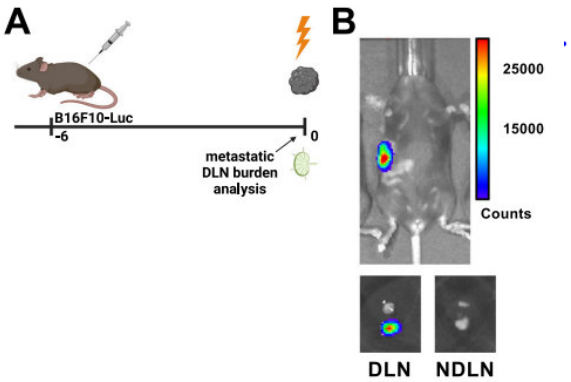
Stage	12 months PFS Rate (95% CI)	36 months PFS Rate (95% CI)
FIGO Stage I and II	100% (100-100)	93% (59-99)
FIGO Stage III and IV	85% (64-94)	77% (56-89)

OS Global 36 months OS rate = 90% (95% IC 76-96)



OS	36 months OS Rate (95% CI)KM
FIGO Stage I and II	100% (100-100)
FIGO Stage III and IV	85% (64-94)

Why???



nature communications

Article

https://doi.org/10.1038/s41467-024-49873-y

Delayed tumor-draining lymph node irradiation preserves the efficacy of combined radiotherapy and immune checkpoint blockade in models of metastatic disease

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Neoadjuvant + Concurrent

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NRG-GY017 (NCT03738228)

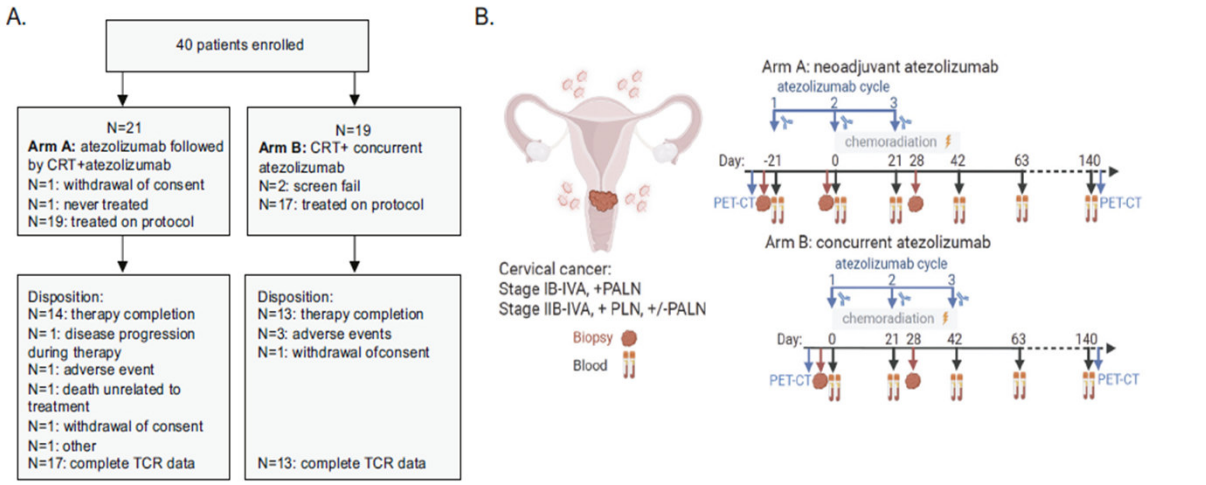


Fig. 1 | Consort diagram and study schema. A Consort diagram of the randomized trial participants and treatment disposition. **B** Study schema with the Arm A and Arm B treatment, imaging, and biospecimen collection timepoints. Created in BioRender. Zamarin, D. (2022) BioRender.com/g30o610.

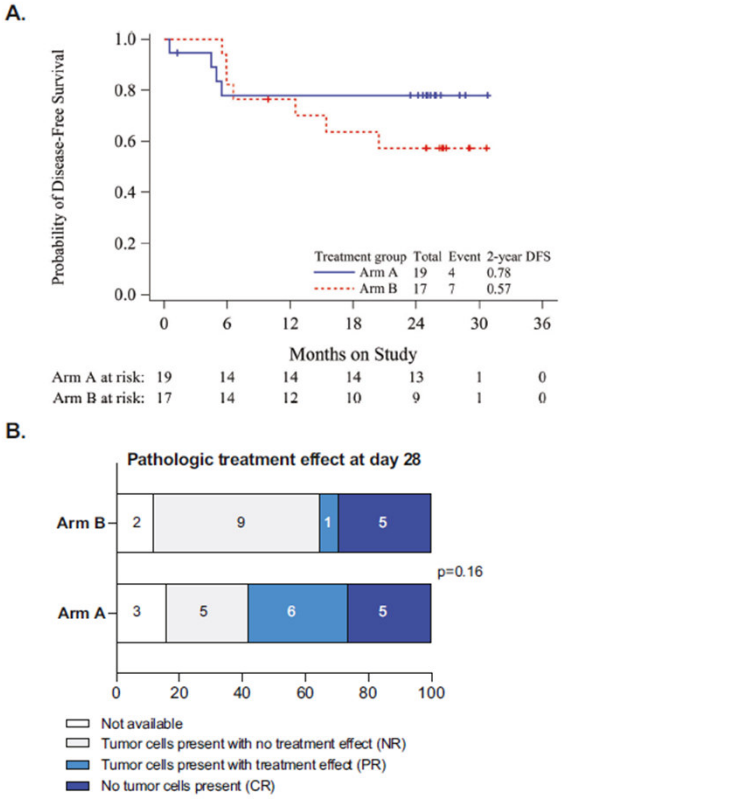


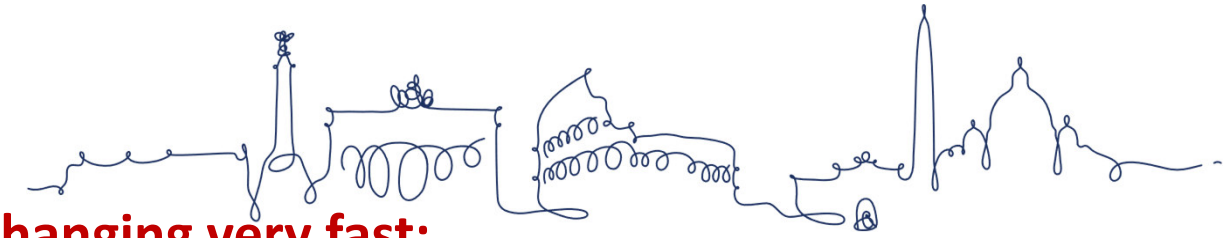
Fig. 2 | Clinical outcomes. A Kaplan–Meier curve for disease-free survival by treatment. **B** Treatment effect in day-28 tumor tissue, 2-sided by Fisher exact test.

Median FU of 25.8 Mo:
DFS at 2 years: 76% vs 56%
No safety signals
Neoadj ICI prior to CRT was associated with clinicaly favourable otcomes

Mayadev J et al., Nature communications, 2024

	ATOMICC trial Dorstalimab maintenance	Colibri-1-GINECO Ind Nivolumab + Ipilimumab +M Nivolumab	Interlace: Induction CHT 500(250/250)	EMBRACE II State of the art IGRT	CALLA (Durvalumab) N=770 (385/385)	Keynote A18 N=1060(529/531) Pembrolizumab	ATEZOLACC N=189 (95/94) Atezolizumab
Patient stage	IB-IVA LN: Pelvic 67/69% PAN 30/26%	IB3-IVA (FIGO2018)	IB1-IVA LN: Pelvic 42%; PAN 0%	IB2-IIBN1, ≥ III, any N LN: Pelvic 74%; PAN 13%	IB2-IIBN1, ≥ III, any N Regardless of PDL status LN: Pelvic 63%; PAN 10%	IB2-IIBN1, ≥ III, any N Regardless of PDL status LN: Pelvic 62%; PAN 23%	IB1-IIA and N1, IIB-IVa any N, IVB with PAN LN: Pelvic or PAO 61%
EBRT	45 Gy	45Gy	45-50.4Gy 40% IMRT	45-50.4Gy IMRT like and 3D conformal	IMRT like 87% (12% 3D conformal) 45-50.4Gy Parametran boost was allowed	45Gy/1,8Gy; IMRT like: 89%	45Gy/1,8Gy; IMRT like: 100%
BT	3D HRCTV-BT	3D-conformal?	70% 2D/3D Point A based	100% MRT based IGABT	62% IGBT	IGBT:100% (CT/MRT based)	IGABT: 100%
Total dose			78Gy to point A	Median minimal dose for D90 HRCTV: 90Gy	72,5- 85Gy	91% ≥ 70Gy	Median minimal dose for D90 HRCTV: 84,4GyGy
Median F/U		40 months	64 mths	44mths	36mths	17.9 mths	
PFS mth Exper arm	At 3 years: **77%**	At 3 years: **83%**	At 5 years: **73%**	At 3 years: **78%**	**65.9%**	**68%**	**70%**
PFS at 24 mth Standard arm	At at 3 years:67%		64%		62.1%	57%	64%
OS at 3 years Exper arm	At 3 years: **86%**	At 3 years: **90%**	At 5 years **80%**	At 3 years: **87%**	NA	**82,6%**	**83% at 2 years**
OS at 3 years Standard arm	At 3 years: 88%		72%		NA	74,8%	82% at 2 years
	Oaknin A. et al ESMO Gyn 2026	Joly F et al., ESMO Gyn 2026	McCormak M. et al., The Lancet,	Pötter et al, ESTRO 2025	Monk B. et al, The Lancet Oncology, 2023	Lorusso D. et al, The Lancet, Oct 2024	Chargari C. et al. ESGO Meeting. Feb 2025

Conclusions:



The landscape of treatment in LACC is changing very fast:

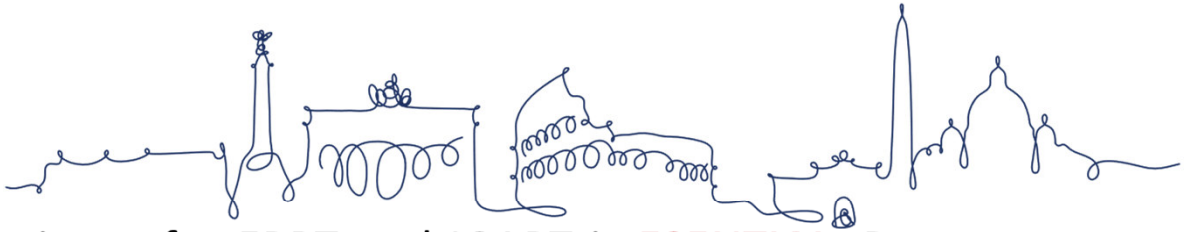
- The outcome in LACC is improving at unprecedented speed, arriving at very high OS at 3/5 years (above 80%)
- Keynote A18 is now standard of care in LACC FIGO2018 IIIA, IIIB, IVA
- ATOMICC trial shows very good results with maintanance Dostarlimab, especially in AC and ADSQ histology and FIGO2009 IB-IIB +N positives
- The COLIBRI 1 study shows encouraging survival outcomes : (3 yrs PFS =83%; 3 yrs OS= 90%) in SQ histology and provides an integrated view of the interplay between tumor/systemic immune parameters, HPV status/ immunity and tumor genomic features for conditioning response/resistance to treatment

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Conclusions:



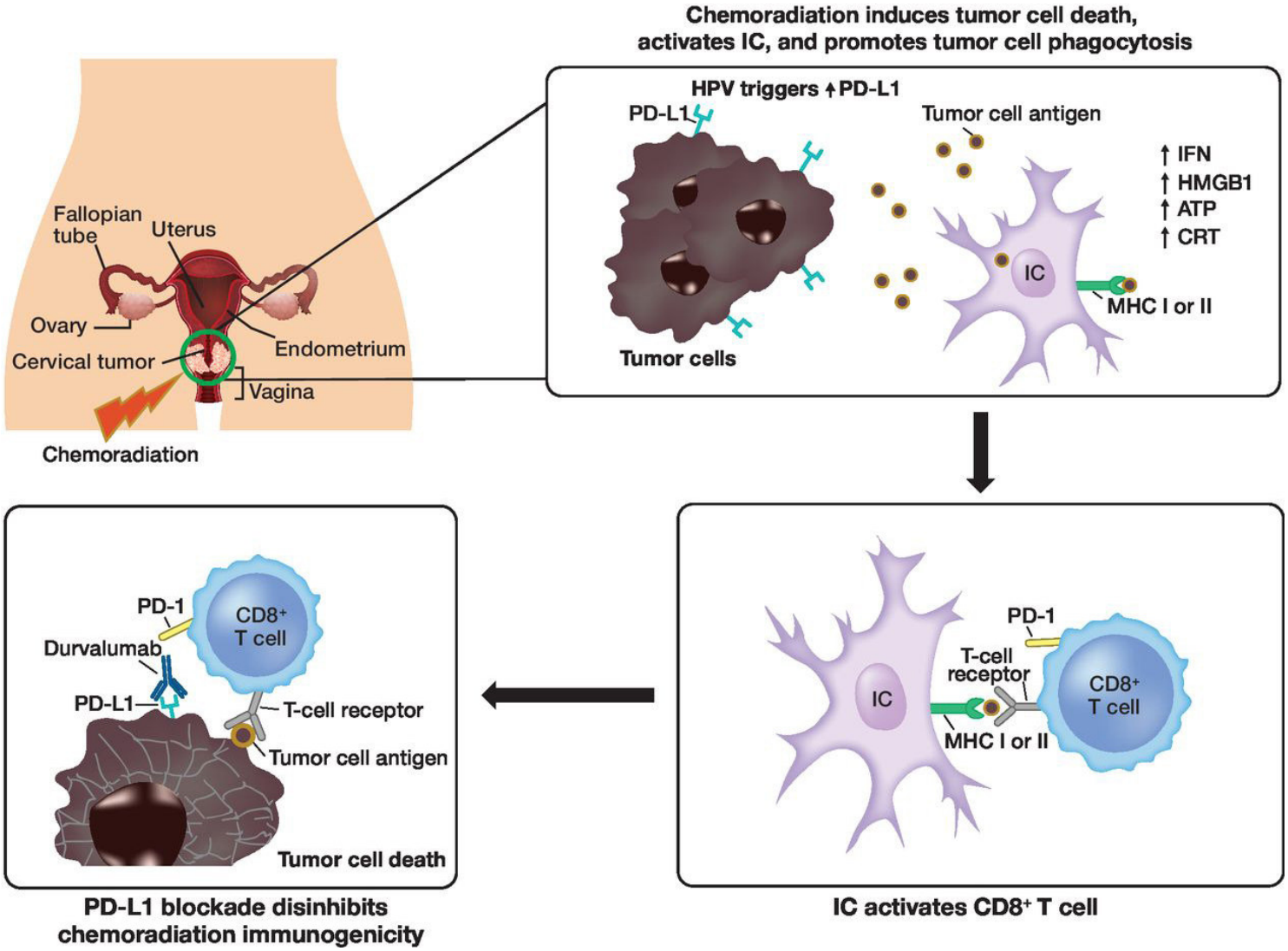
- Modern Radiotherapy including IMRT like techniques for EBRT and IGABT is **ESENTIAL**, Dose to target more than **90 Gy** should be achieved
- Quality of Radiation Therapy is essential in these trials
- Modern LACC trials should include state of the art RT including MRI IGABT
- The use of ICI in induction, concurrent and/or mainatanance setting may eliminate the need of strong CHT and its SE in induction or adj setting
- Better **patient selection**, including exploratory immune subgroups analyses which support the baseline immune activation will lead to further increased therapeutic ratio

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The future is bright and will answer our questions (hopefully)!!!

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Chemoradiation induces tumor cell death,
activates IC, and promotes tumor cell phagocytosis
Fallopian tube
Uterus
Ovary
Cervical tumor
Endometrium
Vagina
Chemoradiation
HPV triggers ↑PD-L1
PD-L1
Tumor cell antigen
↑ IFN
↑ HMGB1
↑ ATP
↑ CRT
IC
MHC I or II
Tumor cells
PD-1
CD8+ T cell
Durvalumab
PD-L1
T-cell receptor
Tumor cell antigen
Tumor cell death
PD-L1 blockade disinhibits chemoradiation immunogenicity
IC
PD-1
T-cell receptor
CD8+ T cell
MHC I or II
IC activates CD8+ T cell

