CALLA
KEYNOTE A18

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Senior Consultant, HoD
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OVERVIEW

- History of cervical cancer trials
- What is immunotherapy?
- Trials with regard to immunotherapy

LANDONI TO KEYNOTE A18

Meta-analysis
‘19 trials’

2017

Landoni
20 year update

KEYNOTE - 826

2001

2021

OUTBACK

NCI Alert
‘5 trials’

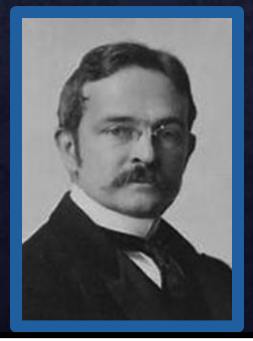
1999

2023

CALLA

1997

Landoni et al.



Dr. Robert Abbe

2024

INTERLACE

KEYNOTE
A18

LANDMARK STEP IN TREATMENT OF CERVICAL CANCER

NCI ALERT Feb 1999

Keyes et al NEJM 1999

England Journal of Medicine

CISPLATIN, RADIATION, AND ADJUVANT HYSTERECTOMY COMPARED WITH RADIATION AND ADJUVANT HYSTERECTOMY FOR BULKY STAGE IB CERVICAL CARCINOMA

HENRY M. KEYS, M.D., BRIAN N. BUNDY, PH.D., FREDERICK B. STEHMAN, M.D., LAILA I. MUDERSPACH, M.D., WELDON E. CHAFE, M.D., CHARLES L. SUGGS III, M.D., JOAN L. WALKER, M.D., AND DEBORAH GERSELL, M.D.

Morris et al NEJM 1999

...9, by the Massachusetts Medical Society

APRIL 15, 1999 NUMBER 15

PELVIC RADIATION WITH CONCURRENT CHEMOTHERAPY COMPARED WITH PELVIC AND PARA-AORTIC RADIATION FOR HIGH-RISK CERVICAL CANCER

MITCHELL MORRIS, M.D., PATRICIA J. EIFEL, M.D., JIANDONG LU, PH.D., PERRY W. GRIGSBY, M.D., CHARLES LEVENBACK, M.D., RANDY E. STEVENS, M.D., MARVIN ROTMAN, M.D., DAVID M. GERSHENSON, M.D., AND DAVID G. MUTCH, M.D.

Peters et al JCO 2000

Concurrent Chemotherapy and Pelvic Radiation Therapy Compared With Pelvic Radiation Therapy Alone as Adjuvant Therapy After Radical Surgery in High-Risk Early-Stage Cancer of the Cervix

By William A. Peters III, P.Y. Liu, Rolland J. Barrett II, Richard J. Stock, Bradley J. Monk, Jonathan S. Berek, Luis Souhami, Perry Grigsby, William Gordon, Jr, and David S. Alberts

Rose et al NEJM 1999

England Journal of Medicine

CONCURRENT CISPLATIN-BASED RADIOTHERAPY AND CHEMOTHERAPY FOR LOCALLY ADVANCED CERVICAL CANCER

PETER G. ROSE, M.D., BRIAN N. BUNDY, PH.D., EDWIN B. WATKINS, M.D., J. TATE THIGPEN, M.D., GUNTHER DEPPE, M.D., MITCHELL A. MAIMAN, M.D., DANIEL L. CLARKE-PEARSON, M.D., AND SAM INSALACO, M.D.

Whitney et al JCO 1999

Randomized Comparison of Fluorouracil Plus Cisplatin Versus Hydroxyurea as an Adjunct to Radiation Therapy in Stage IIB-IVA Carcinoma of the Cervix With Negative Para-Aortic Lymph Nodes: A Gynecologic Oncology Group and Southwest Oncology Group Study

By Charles W. Whitney, William Sause, Brian N. Bundy, John H. Malfetano, Edward V. Hannigan, Wesley C. Fowler, Jr, Daniel L. Clarke-Pearson, and Shu-Yuan Liao

"Concomitant (cisplatin-based) Chemo-radiotherapy should be considered instead of radiotherapy alone in women with cervical cancer"

Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis

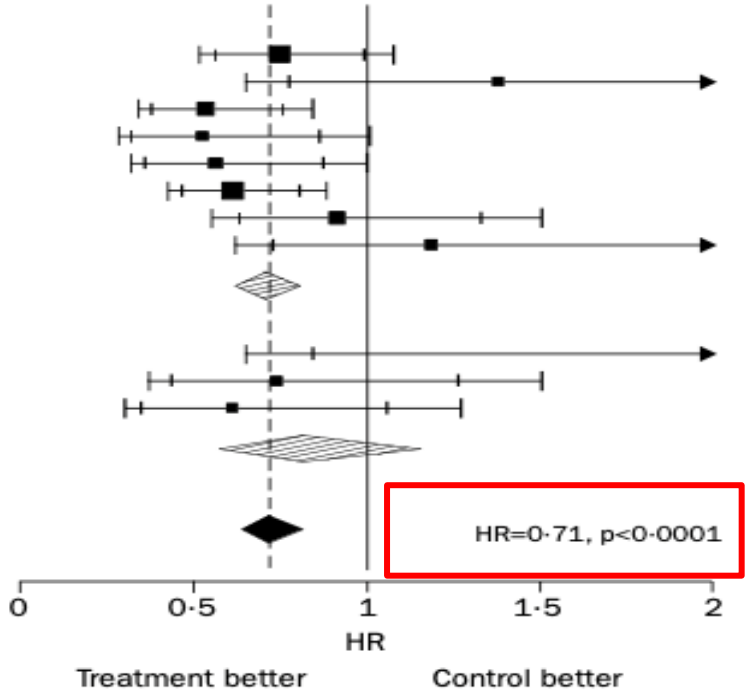
John A Green, John M Kirwan, Jayne F Tierney, Paul Symonds, Lydia Fresco, Mandy Collingwood, Christopher J Williams

Green et al LANCET 2001

- 19 trials
- 17 publications
- 2 unpublished
- 1981-2000
- N = 4580

CT and RT benefit:
- PFS benefit: 16%
- OS benefit: 12%

	Treatment*	Control*	O–E	Variance
Platinum				
Whitney[10]	79/177	108/191	−13·69	45·45
Tseng[20]	23/60	22/62	3·69	11·25
Morris[8]	48/195	71/193	−19·13	29·41
Peters[13]	21/127	36/116	−9·60	14·25
Keys[7]	27/183	49/186	−10·84	17·86
Rose[9]	116/349	89/177	−23·38	45·77
Pearcey[12]	49/127	52/126	−2·38	25·26
Leborgne†	42/75	39/78	2·61	15·02
Subtotal	405/1293	466/1129	−72·72	204·27
Non-platinum				
Hernandez[27]	21/36	6/18	3·56	5·30
Wong (1999)[11]	21/110	34/110	−3·93	12·41
Roberts[14]	20/82	30/78	−5·93	11·45
Subtotal	62/228	70/206	−6·30	29·16
Total	467/1521	536/1335	−79·02	233·43



Overall OS Benefit

Concomitant CT-RT improves OS and PFS and reduces local (OR 0·61, 95% CI 0·51–0·73, p<0·0001)and distant recurrence (OR 0·57, 95% CI 0·46–0·77, p<0·0001) in locally advanced cervical cancer

WHERE DOES SURGERY STAND?

Landoni et al. Lancet 1997

THE LANCET

Articles

Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer

Fabio Landoni, Andrea Maneo, Alessandro Colombo, Franco Placa, Rodolfo Milani, Patrizia Perego, Giorgio Favini, Luigi Ferri, Costantino Mangioni

Landoni et al. JGO 2017 20-year Update

J Gynecol Oncol. 2017 May;28(3):e34
https://doi.org/10.3802/jgo.2017.28.e34
pISSN 2005-0380·eISSN 2005-0399

JGO JOURNAL OF GYNECOLOGIC ONCOLOGY

Original Article

Check for updates

Randomized study between radical surgery and radiotherapy for the treatment of stage IB–IIA cervical cancer: 20-year update

Fabio Landoni,[1] Alessandro Colombo,[2] Rodolfo Milani,[3] Franco Placa,[2] Vanna Zanagnolo,[1] Costantino Mangioni[3]

[1]Division of Gynecology, European Institute of Oncology, Milan, Italy
[2]Division of Radiotherapy, Hospital of Lecco, Lecco, Italy
[3]Obstetrics and Gynecology Clinic, University of Milan-Bicocca, Monza, Italy

OPEN ACCESS

- N = 343
- FIGO IB/ IIA
- Age – 30-70 yr

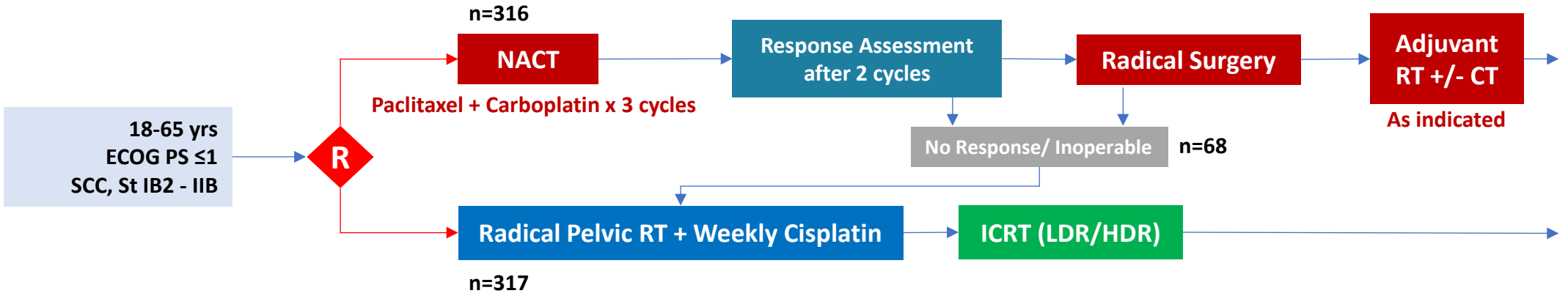
- **Both Surgery or Radiation can be given for early cervical cancer in terms of OS.**
- **Long term FU confirms the best treatment should take into account clinical factors**

For more than a decade,
there was no new significant development

NACT Followed by Radical Surgery Vs Concomitant CT-RT in Patients With Stage IB2, IIA, or IIB Squamous Cervical Cancer: A Randomized Controlled Trial

JCO, 2018
Sudeep Gupta et al
Ph 3 RCT

Comparison of outcome between NACT > Sx and Conc CT-RT in Ca Cervix St IB2-IIB



End Points (ITT)

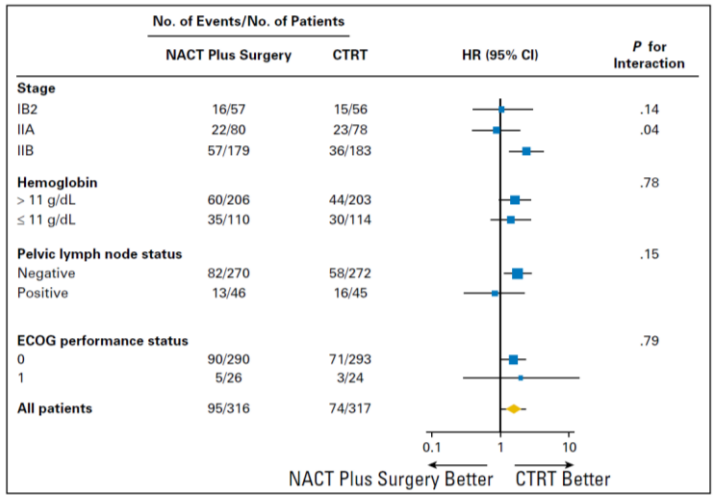
Primary End Point
DFS

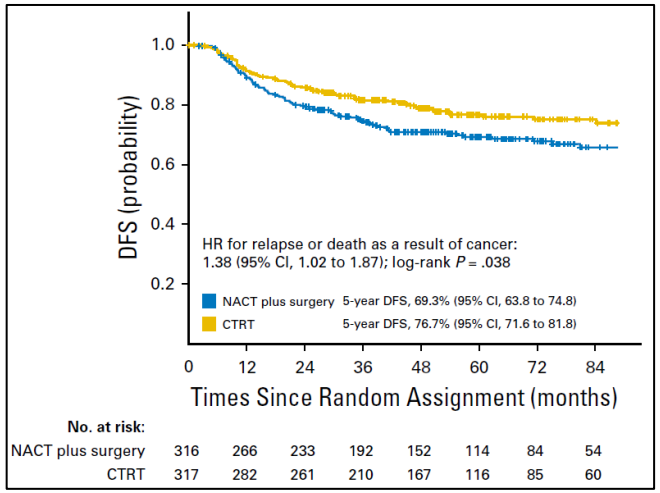
Secondary End Point
OS
Toxicity

R E S U L T S Median follow-up – 58.5 mo

Survival	NACT-Sx	CT-RT	HR	P-value
5yr DFS	69.3%	76.7%	1.38 (1.02-1.87)	0.038
Adjusted HR (Stage/Hb/LN/PS)			1.46 (1.08-1.99)	0.015
5Yr OS	75.4%	74.7%	1.025 (0.75-1.39)	0.87
Recurrence	18.7%	13.6%	-	-

Maximum benefit noted for Stage IIB disease
More Acute Grade 3 and 4 Thrombocytopenia with NACT-Sx
Significant higher Late Vaginal Toxicity with CT-RT (>24mo)





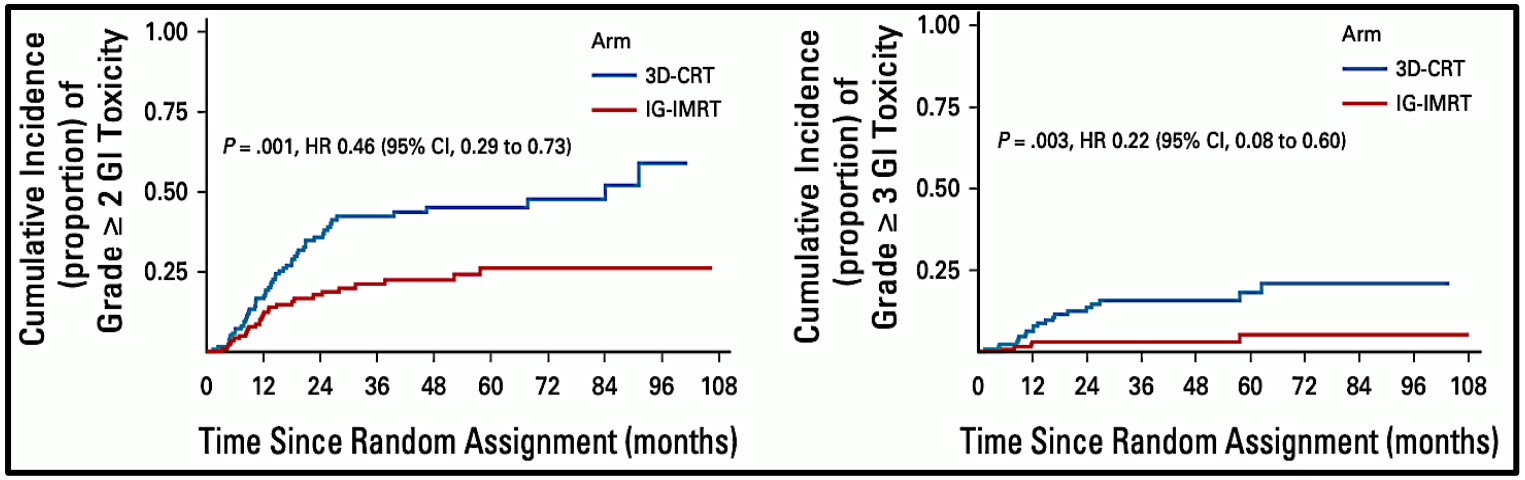
CONCLUSION: Concurrent Chemoradiation showed significantly improved DFS rate compared to NACT - Surgery

Late Toxicity After Adjuvant Conventional Radiation Versus Image-Guided Intensity-Modulated Radiotherapy for Cervical Cancer (PARCER): A Randomized Controlled Trial

Supriya et al et al
JCO, 2021

To compare late toxicity of (IG-IMRT) with (3D-CRT) in cervical cancer undergoing postoperative RT.

- Phase III Trial:
- IG-IMRT or 3D-CRT.
- Primary end point: 3-year grade > 2 late GI toxicity.
- Secondary end points:Acute toxicity, HRQOL, Pelvic relapse-free, DFS & OS.
- 2011-2020
- N= 300, IG-IMRT: 151 and 3D CRT:149
- Median FU: 46 months



Incidence of Grade >/= 2 any late toxicity: 28.1% Vs 48.9% (p: .001)

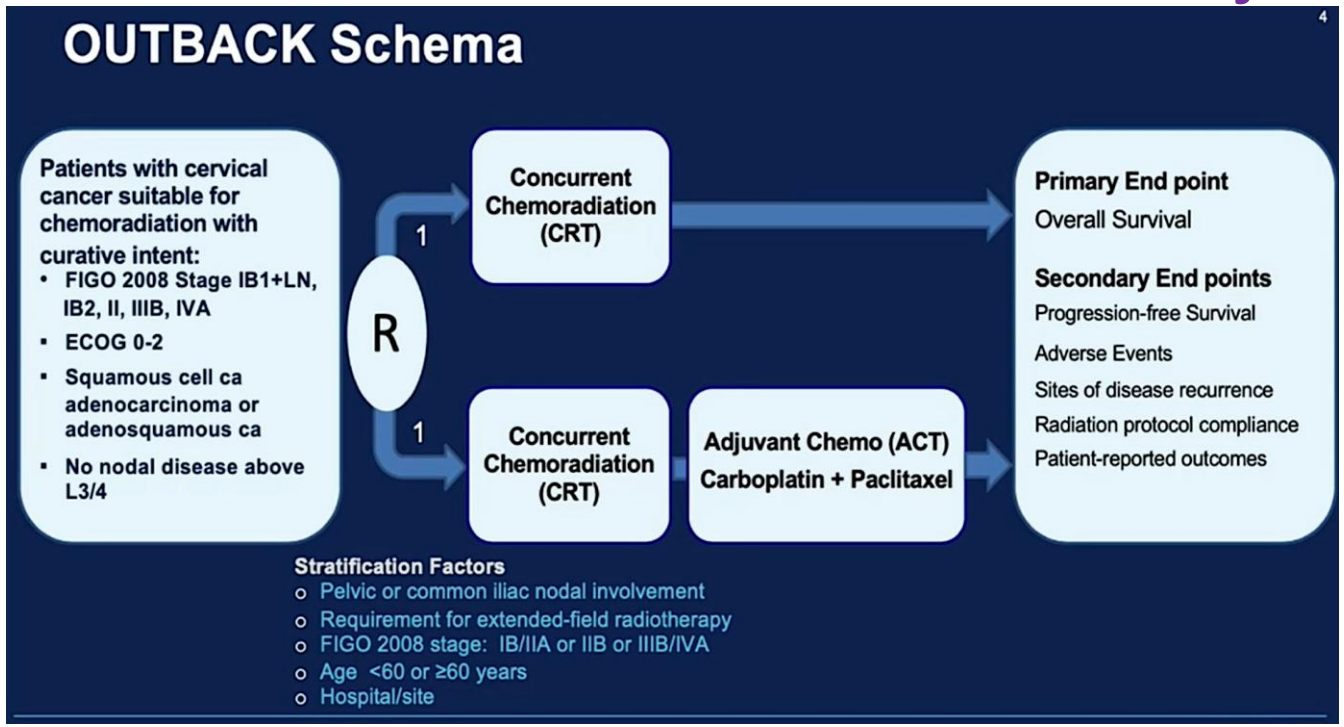
- ❑ Postoperative IG-IMRT results in lower rate of late toxicity.
- ❑ No differences in disease outcomes.
- ❑ IG-IMRT should represent the new standard of care.

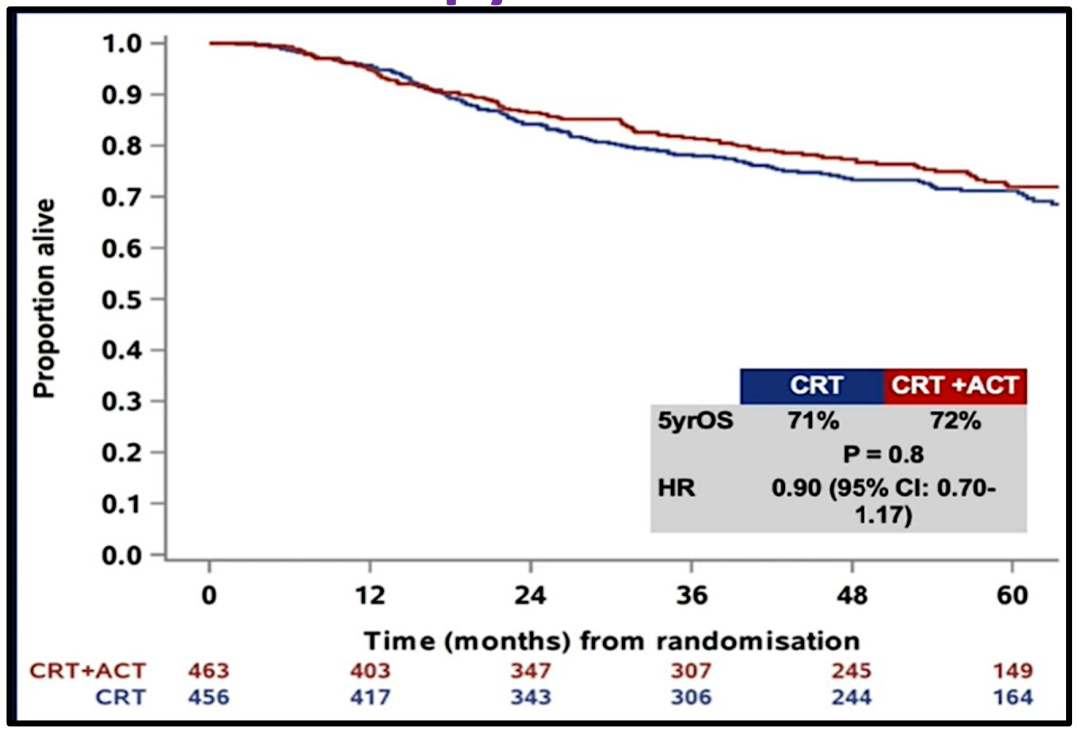
	IG-IMRT	3 DCRT	P value
Pelvic RFS	81.8%	84%	0.55
DFS	76.9%	81.2%	0.89

OUTBACK TRIAL: Phase III trial of adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared.

Lancet 2023

CT-RT followed by chemotherapy Versus Chemotherapy Versus CT-RT alone : Is there a benefit of adjuvant chemotherapy?





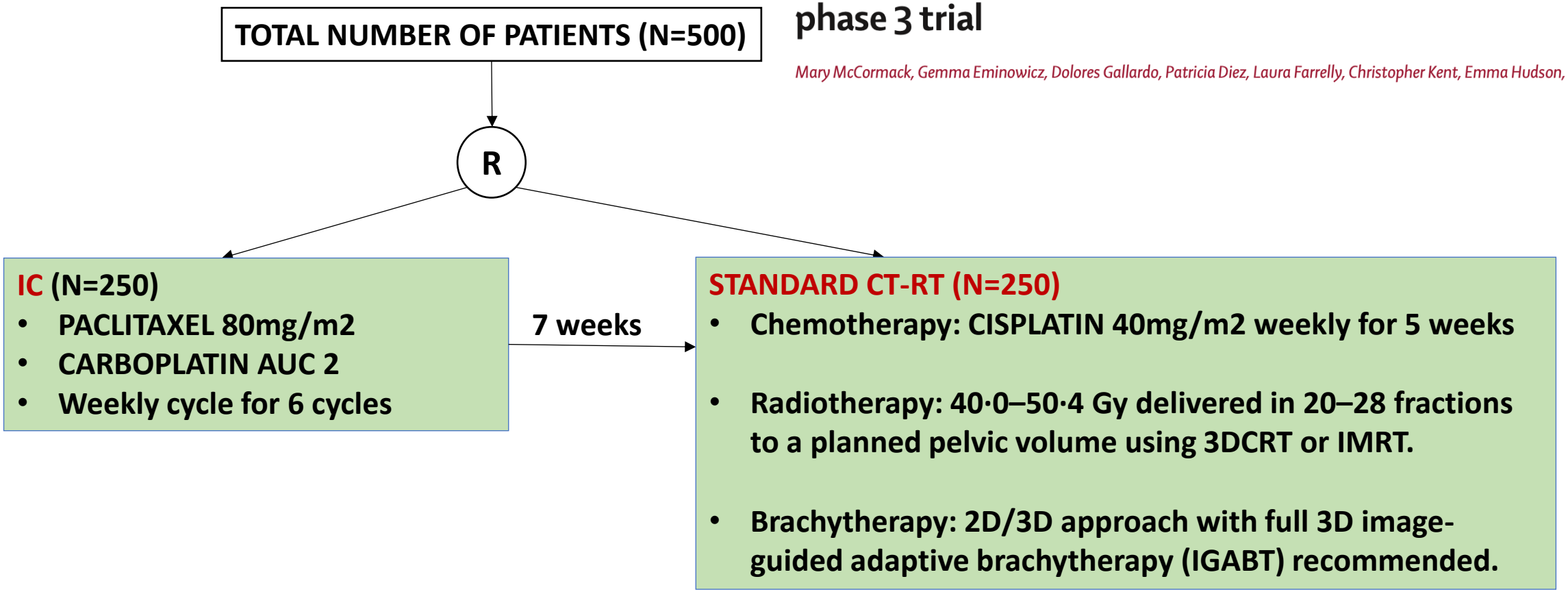
Adjuvant carboplatin and paclitaxel chemotherapy given after standard cisplatin-based chemoradiotherapy for locally advanced cervical cancer *increased short-term toxicity and did not improve overall survival*

Interlace Trial:

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

2024

Mary McCormack, Gemma Eminowicz, Dolores Gallardo, Patricia Diez, Laura Farrelly, Christopher Kent, Emma Hudson, Miguel Panades,



Conclusion of Interlace Trial:

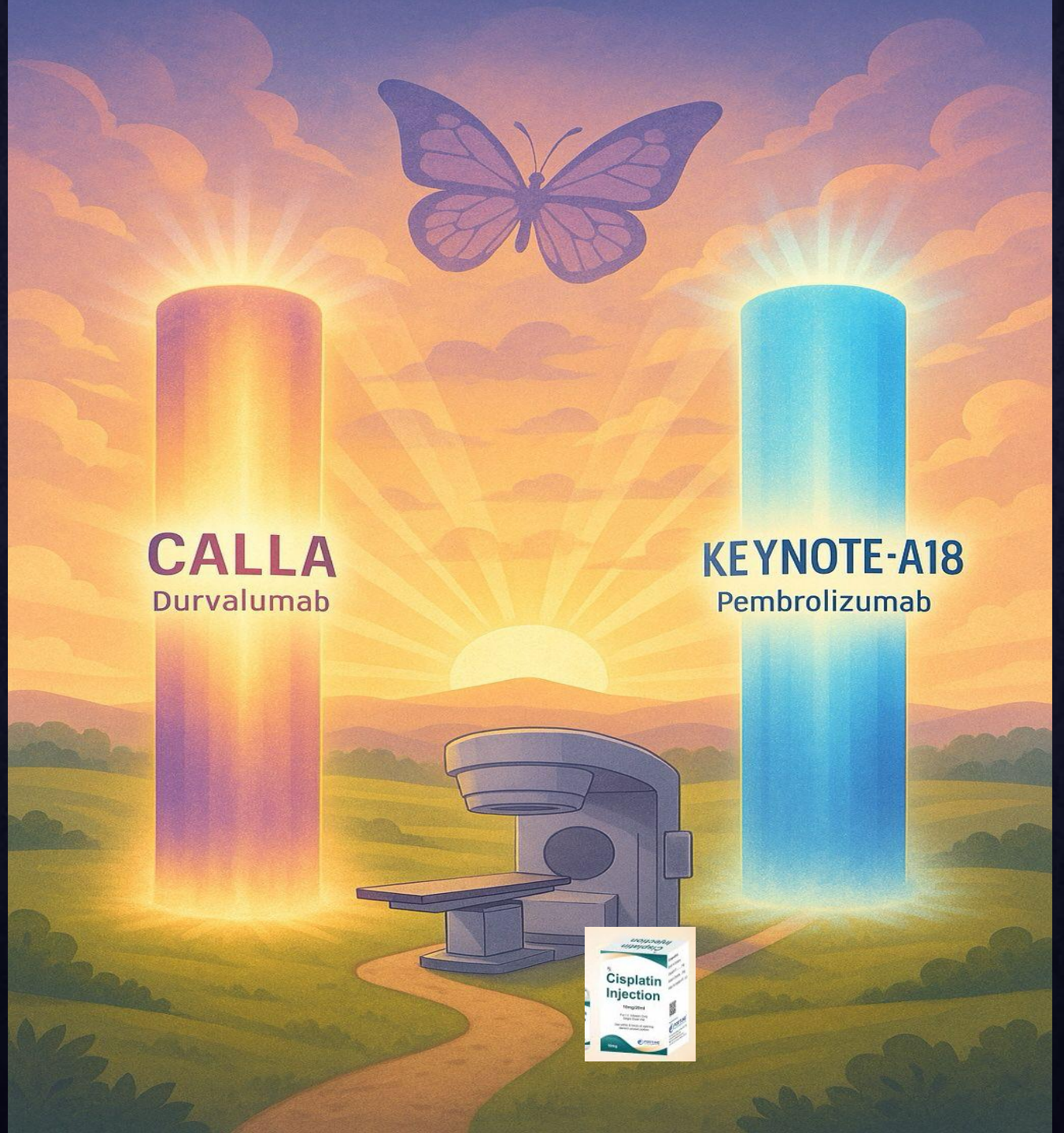
In conclusion, this short-course IC regimen followed within 7 days by CRT improves survival of patients with locally advanced cervical cancer. It should now be considered a standard of care and be included in the design of future trials that explore the incorporation of new agents for the treatment of locally advanced cervical cancer.

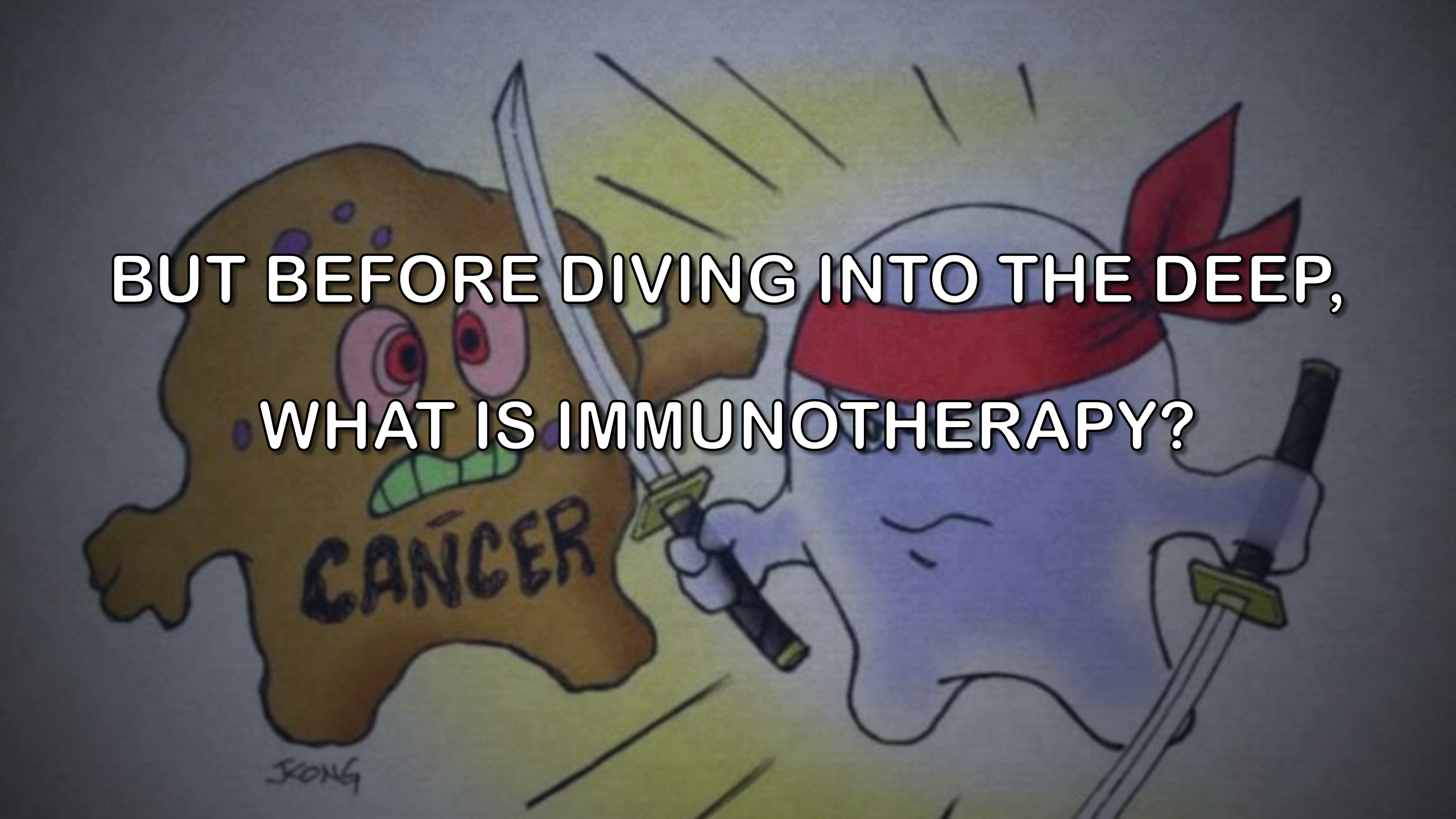
However:

NACT leads to:

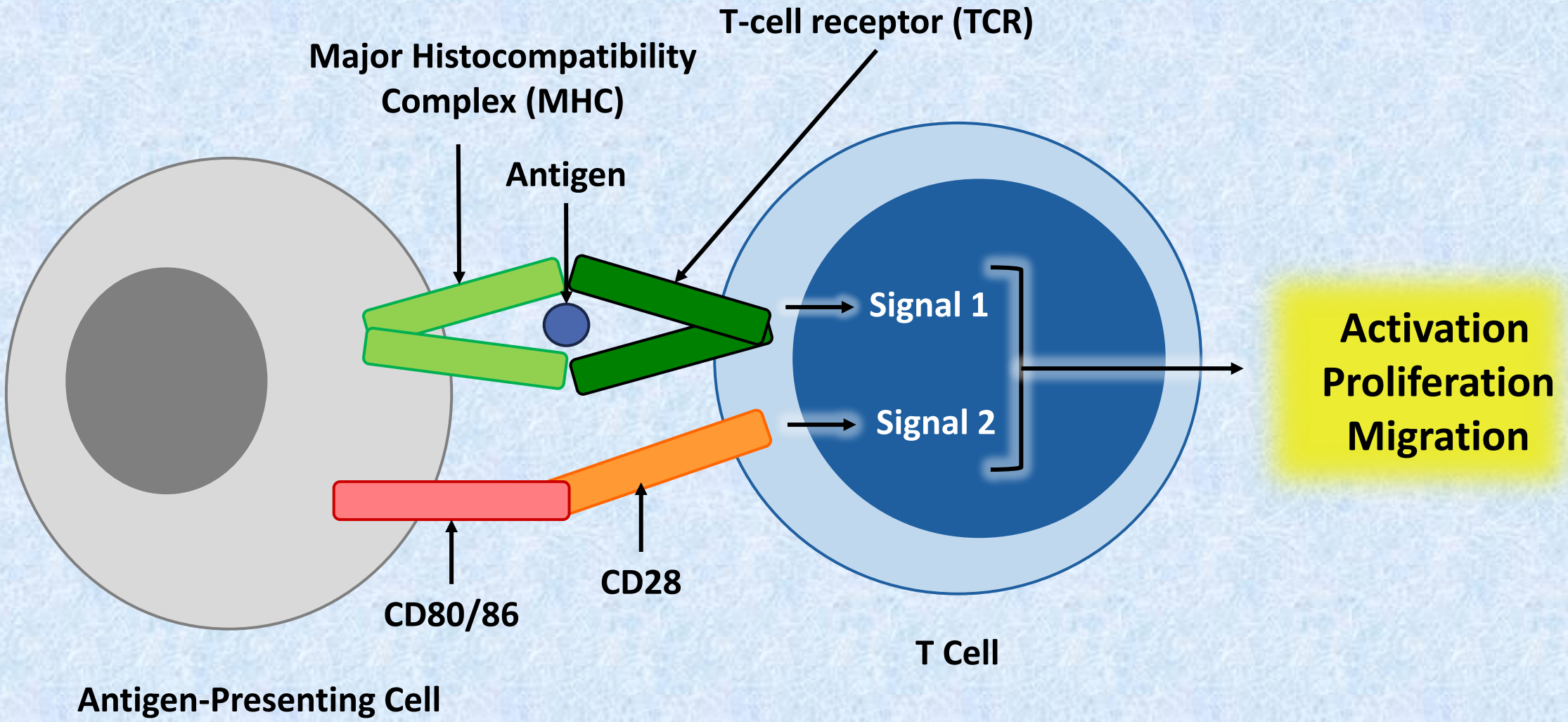
- **Prolong overall treatment time**
- **Reduce compliance to concomitant CT during CRT**
- **Increase in cost of treatment including supportive care**
- **Overall higher morbidity**

NACT needs to explored in high risk locally advanced carcinoma cervix patients with high nodal burden, IIIB & IIIC2 who qualifies for extended field radiation.

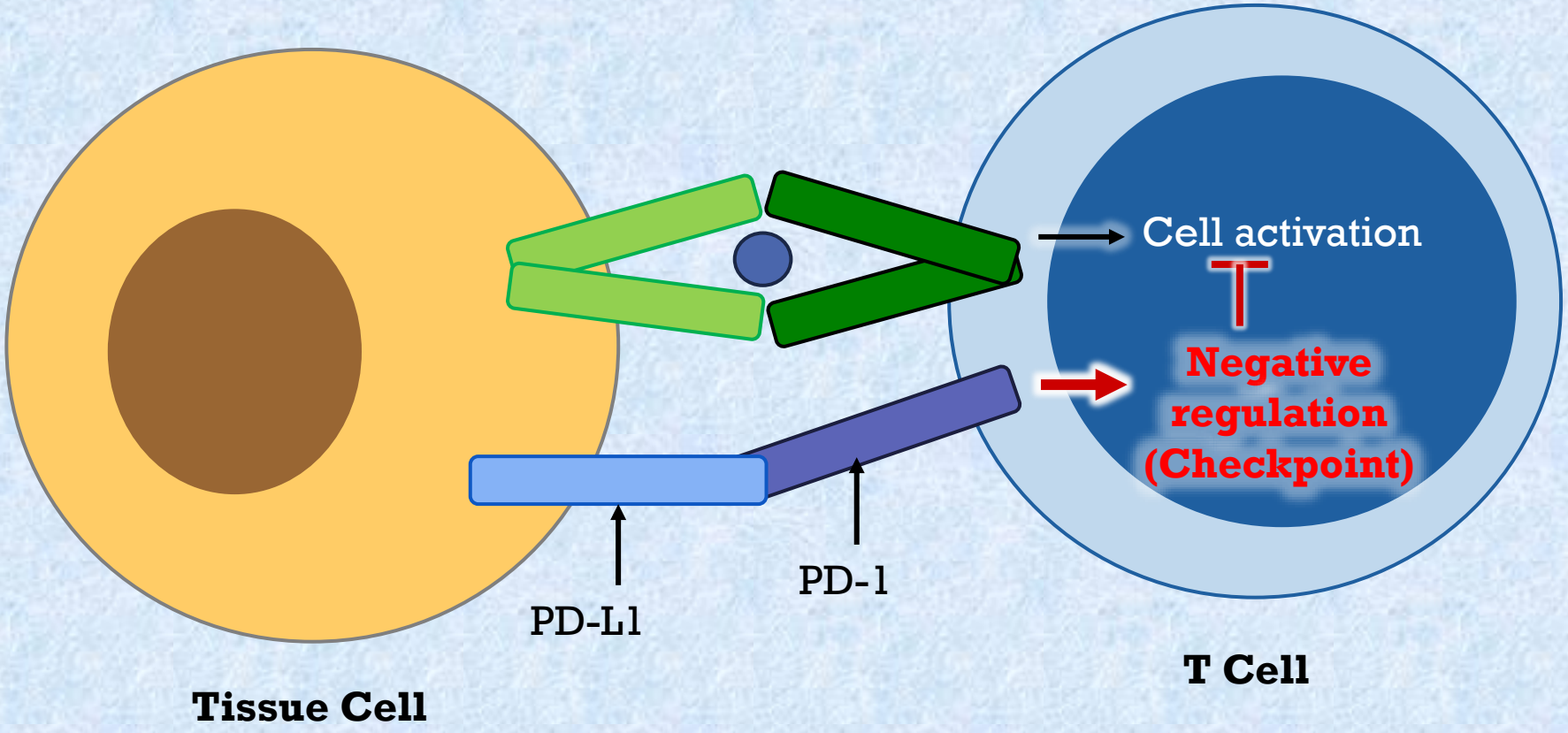

CALLA
Durvalumab
KEYNOTE-A18
Pembrolizumab
Cisplatin Injection


BUT BEFORE DIVING INTO THE DEEP,
WHAT IS IMMUNOTHERAPY?
CANCER
JKONG

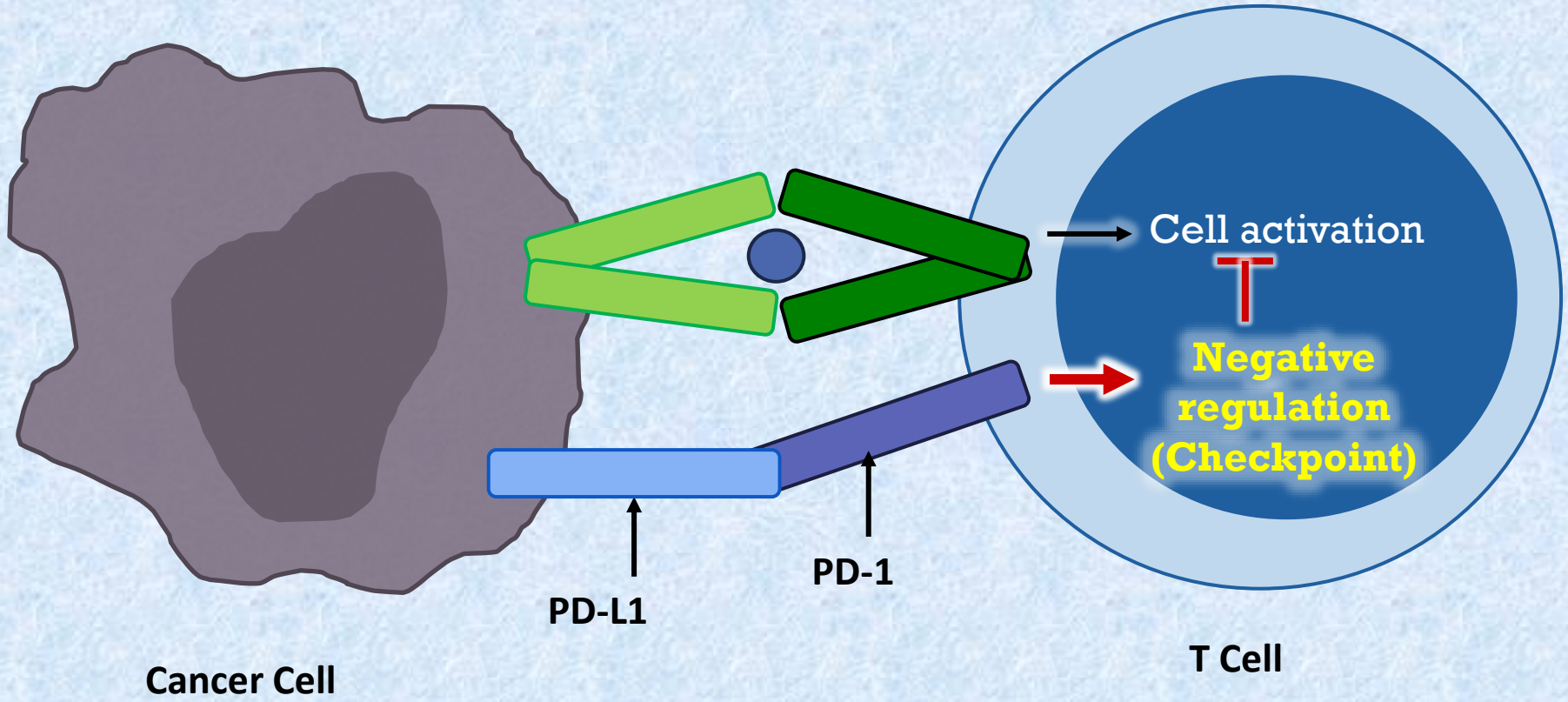
IMMUNE ACTIVATION IN LYMPH NODE



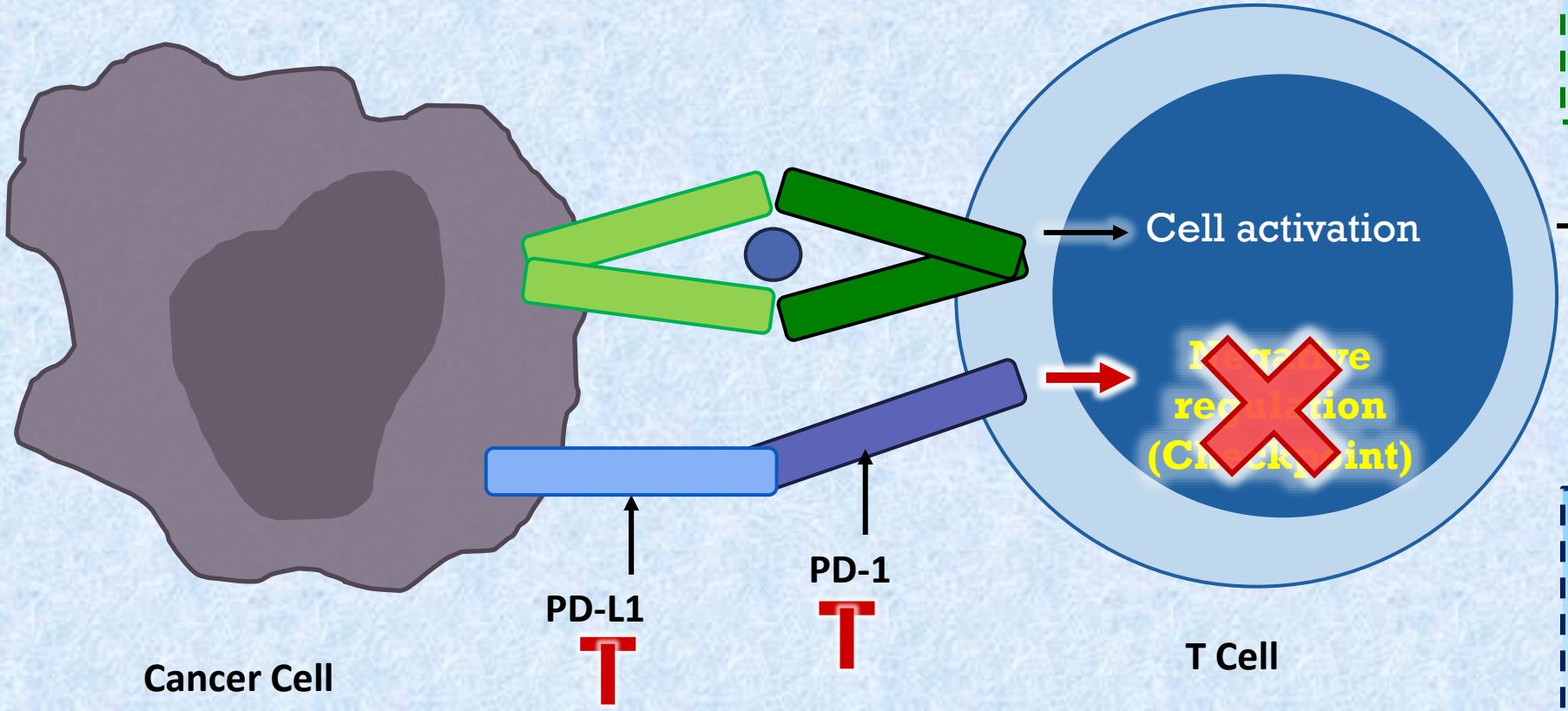
NEGATIVE CHECKPOINT REGULATION IN PERIPHERAL TISSUE



CANCER CO-OPTS THE CHECKPOINT MECHANISM



IMMUNE CHECKPOINT INHIBITORS

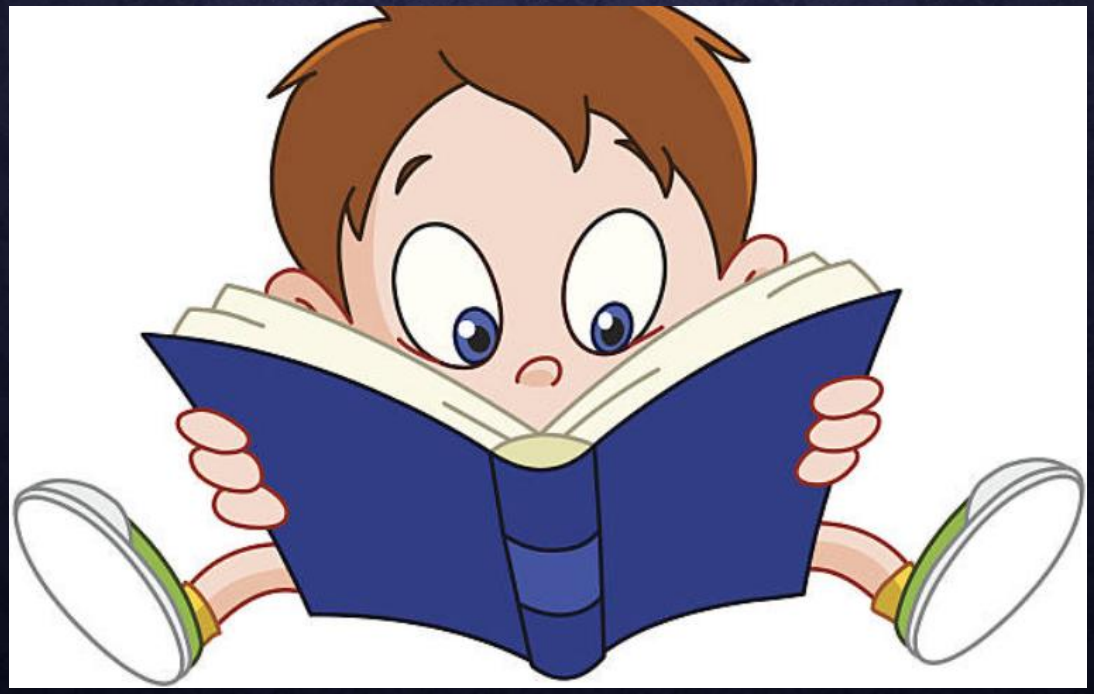


PD-1 inhibitors
- Nivolumab
- Pembrolizumab

- Activation
- Proliferation
- Elimination (cancer cells)

PD-L1 inhibitors
- Atezolizumab
- Durvalumab

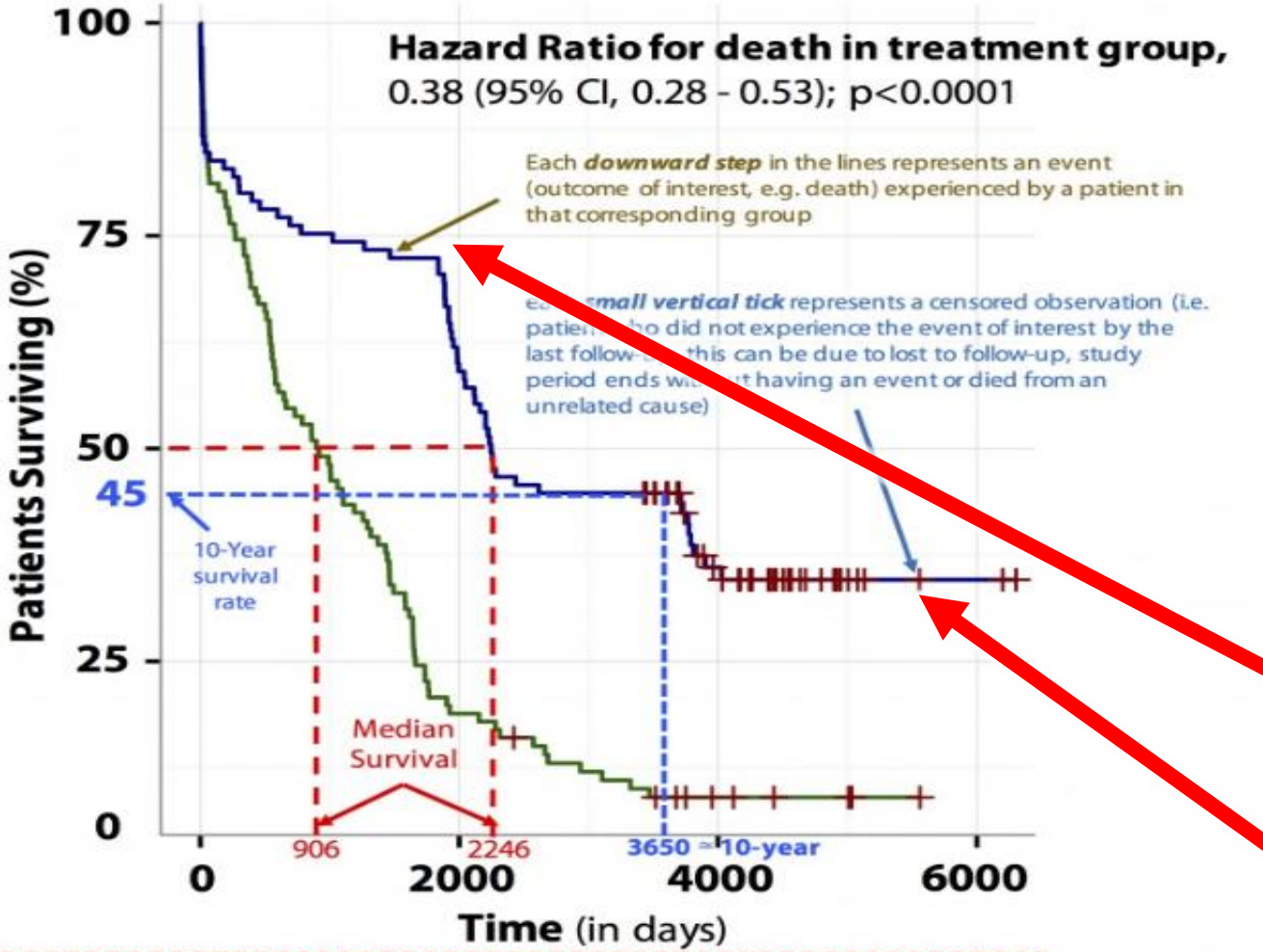
BEFORE WE TALK ABOUT TRIALS, WE SHOULD KEEP IN MIND CERTAIN DEFINITIONS



SURVIVAL DATA

Survival Variables	Definitions	Remarks
Objective Response Rate (ORR)	**Fraction of patients with a *tumor size reduction*** of a predefined amount for a minimum time period	**ORR = sum of patients with PR and CR** (According to FDA)
Progression Free Survival (PFS)	the time of randomization to the time of ***disease progression or death***	**Phase III** Trials (TTP considered only in Phase II Trials)
Overall Survival (OS)	Defined as the time from randomization to ***death***	***Gold standard*** of clinical trial end point

Kaplan Meier Plot



No. at Risk	Number of patients at risk shown below at regular time intervals, as times go, less people remain are at risk			
Placebo	106	20	5	0
Treatment	105	62	25	2

Figure produced by the author using R software

(Blue line represents treatment group and green line represents control group).

- Probabilities are calculated for each interval of time
- Each Downward step indicates an **event**
- Vertical tick – **censored observation**

NOW LET'S SHIFT GEARS

FIRST TRIAL OF CERVICAL CANCER RELATED TO IMMUNOTHERAPY

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer

N. Colombo, C. Dubot, D. Lorusso, M.V. Caceres, K. Hasegawa, R. Shapira-Frommer, K.S. Tewari, P. Salman, E. Hoyos Usta, E. Yañez, M. Gümüş, M. Olivera Hurtado de Mendoza, V. Samouëlian, V. Castonguay, A. Arkhipov, S. Toker, K. Li, S.M. Keefe, and B.J. Monk, for the KEYNOTE-826 Investigators*

Dr. Nicoletto Colombo

Colombo et al.
KEYNOTE 826
NEJM 2021

Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer

Colombo et al.
KEYNOTE 826
NEJM 2021

- N=617
- Phase 3 RCT
- Persistent, Recurrent, or Metastatic Cervical cancer

R

- Platinum based CT + Pembrolizumab ± Bevacizumab
- CT ±Bevacizumab

RESULTS

Arms	Grouping	PFS (mon)	OS (at 24 mon)
CT + Pembro	Median	10.4	53%
	Overall	10.4	50.4%
	CPS≥10	10.4	54.4%
CT	Median	8.2	41.7%
	Overall	8.2	40.4%
	CPS≥10	8.1	44.6%

PFS and OS were significantly longer with Pembrolizumab

WHAT ABOUT IN LOCALLY ADVANCED CERVICAL CANCER?

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

Monk et al.
CALLA
Lancet Oncol
2023

- N=770
- Feb 2019 – Dec 2020
- Phase 3 RCT
- FIGO 2009 IB2-IIB LN+
- ≥ III any LN status
- ECOG PS 0 or 1

R

- CTRT + Durvalumab → Adjuvant Durvalumab
- CTRT

Endpoint

- Primary – PFS
- Secondary
  - OS
  - ORR
  - OS & PFS – TAP ≥1%

- RT – 45 Gy/ 25#/5 wks → BT (HDR – 27.5-30 Gy, LDR – 35-40 Gy)
- Cisplatin – 40 mg/m^2 q1wk; Carboplatin – AUC 2 q1wk
- Durvalumab – 1500 mg q4wk (24 cycles) – during and after RT

	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%)
White	130 (34%)	125 (33%)
Black	10 (3%)	12 (3%)
Other	93 (24%)	100 (26%)
Ethnicity		
Non-Hispanic	210 (55%)	221 (57%)
Hispanic	175 (46%)	164 (43%)
Region of enrolment		
Central and South America	176 (46%)	165 (43%)
Central and East Asia	151 (39%)	144 (37%)
Eastern Europe and Russia	49 (13%)	57 (15%)
USA	8 (2%)	18 (5%)
South Africa	1 (<1%)	1 (<1%)
ECOG performance status score		
0	265 (69%)	255 (66%)
1	119 (31%)	130 (34%)
2	1 (<1%)	0
Histological type		
Squamous carcinoma	322 (84%)	320 (83%)
Adenocarcinoma	55 (14%)	58 (15%)
Adenosquamous carcinoma	8 (2%)	7 (2%)
FIGO 2009 stage*		
IB2	19 (5%)	20 (5%)
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%)

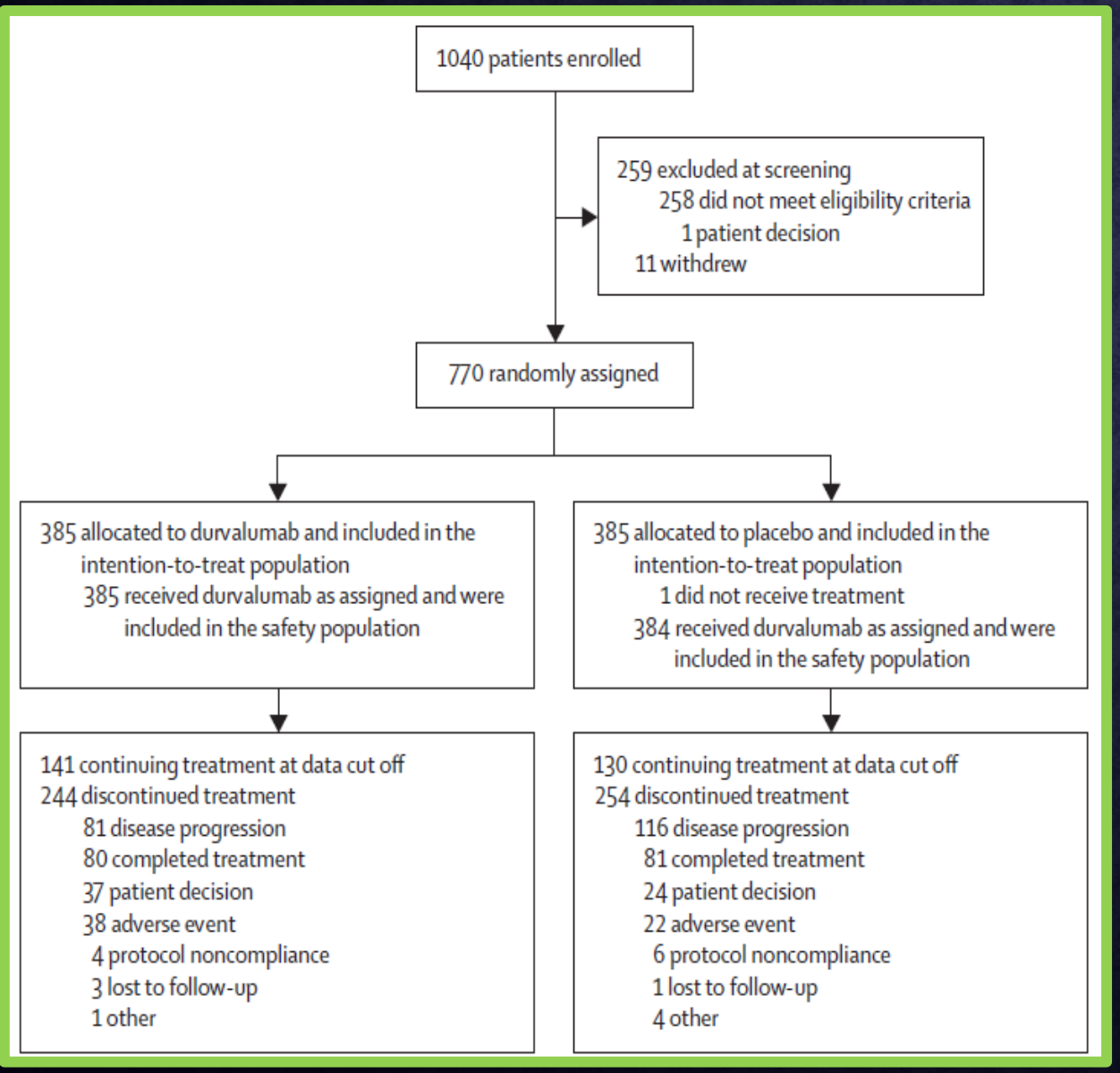
Inclusion Criteria

- Women aged 18 years or older
- Untreated histologically confirmed cervical adenocarcinoma, squamous carcinoma, or adenosquamous carcinoma
- FIGO 2009 IB2-IIB node +ve, IIIA-IVA (any LN status)
- ECOG PS 0 or 1

Exclusion Criteria

- H/o Hysterectomy
- Previous exposure to immune-mediated therapy
- Severe Co-morbidities
- Auto-immune or inflammatory disorder
- Immuno-deficiency
- Active TB/Hepatitis

CONSORT

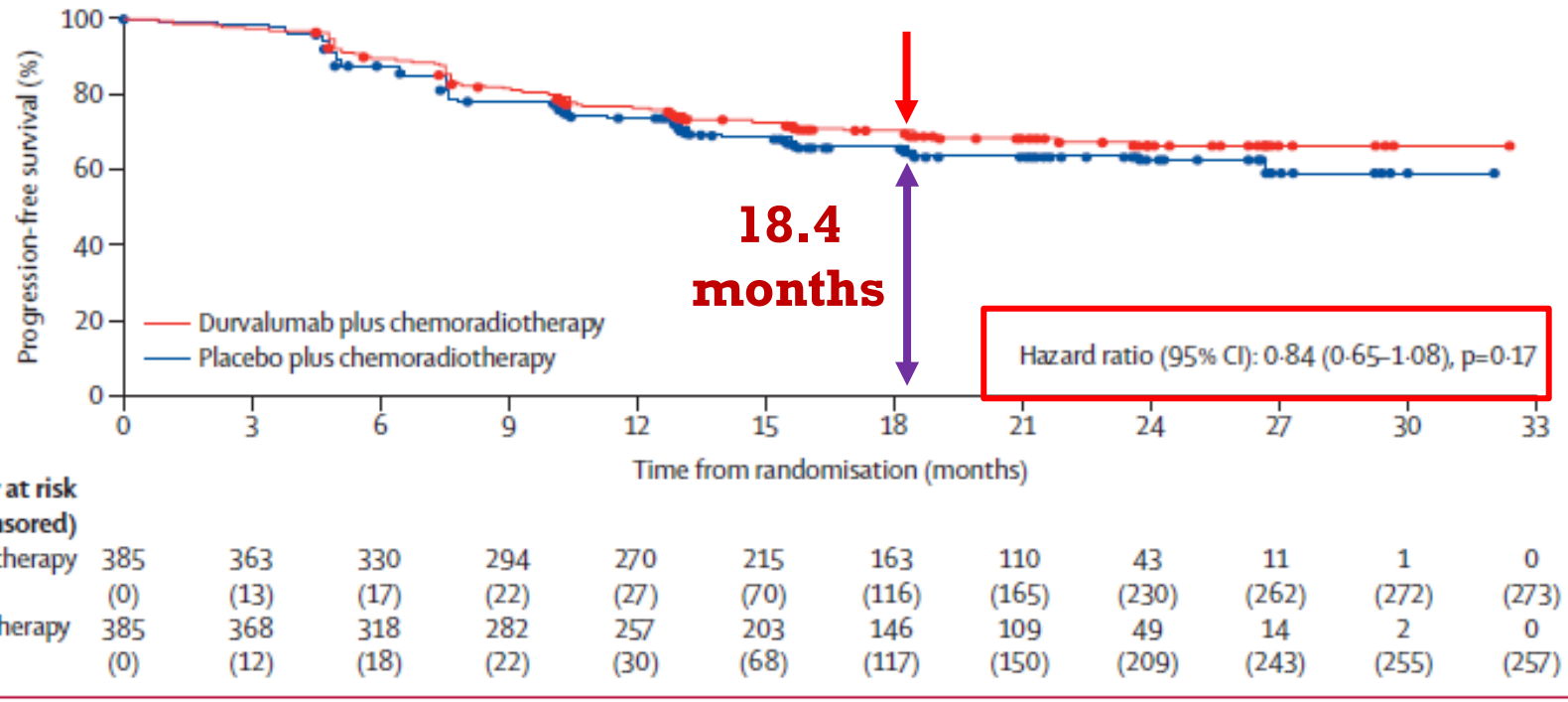


STATISTICAL ANALYSIS

- **90% power** to demonstrate **superiority** for PFS
- PFS, OS and duration of response estimated as per the **Kaplan-Meier** method
- **Two sided α=0.05,** assumed true PFS **HR 0.65, 11% increase** in proportion of progression free patients
- **Stratified log rank test** – determine effect of durvalumab vs placebo (adjusted for disease stage and region)
- Magnitude of effect summarized with HR and 95% CI using a **stratified Cox proportional hazards model** and Efron's method of tie handling

-Median age 49y (IQR 41-57)
-Median FU (18.5 vs 18.4 mon)

RESULTS



leier plot of progression-free survival
urvival, as per Response Evaluation Criteria in Solid Tumors version 1.1 as assessed by investigator or histopathological confirmation of local
n. Data maturity was 31%.

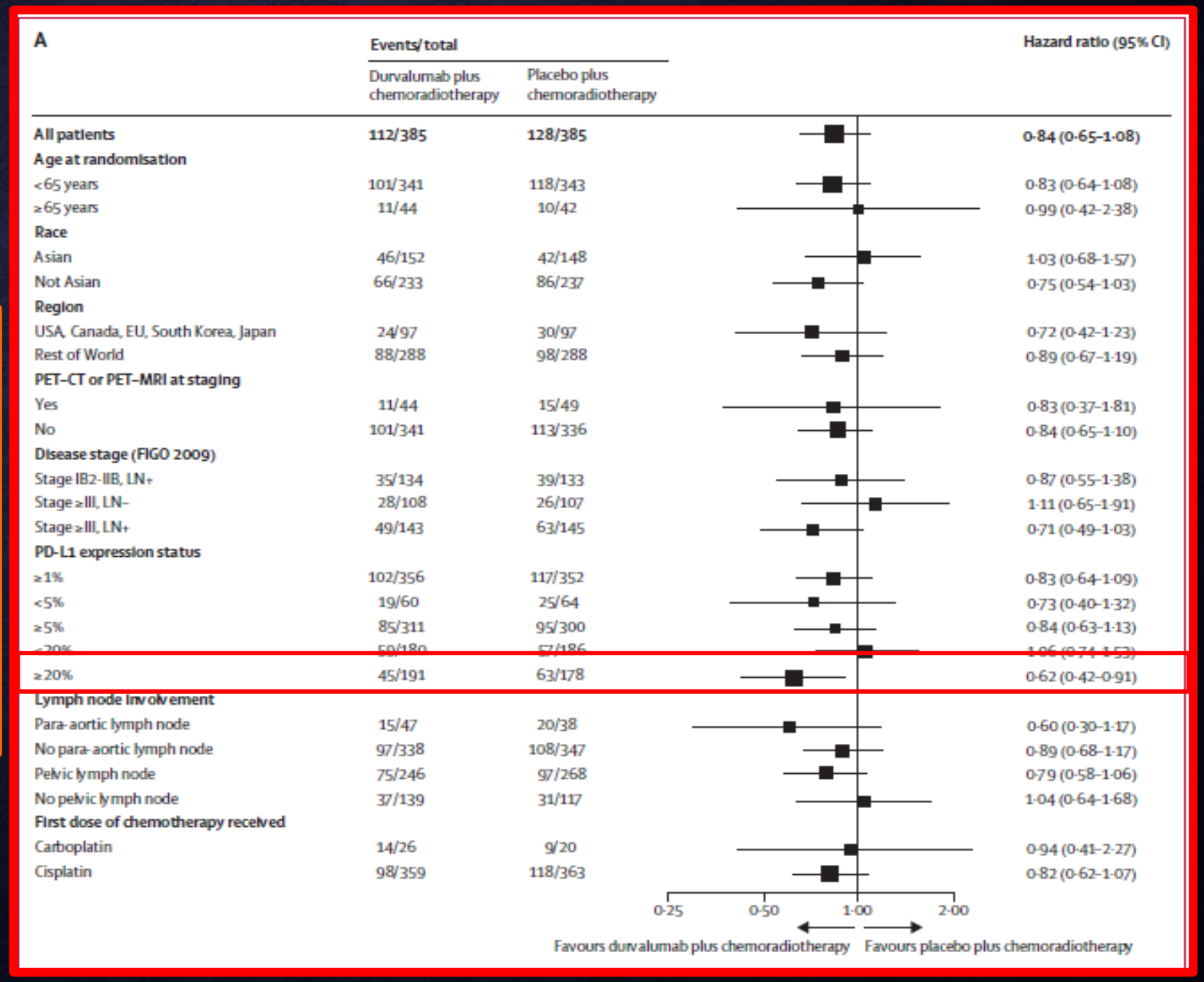
		CTRT + Durva	CTRT
PFS	Overall	HR – 0.84 (95%CI 0.65-1.08), p=0.17	
	12 mon	76% (71.3-80)	73.3% (68.4-77.5)
	24 mon	65.9% (59.8-71.4)	62.1% (56.2-67.4)

Sub-group analysis showed:

- **PD L1 ≥20% → HR 0.62 (0.42-0.91)**

	Durvalumab plus chemoradiotherapy (n=385)	Placebo plus chemoradiotherapy (n=385)
Objective response rate†	318 (83%)	310 (81%)
Complete response	165 (43%)	155 (40%)
Partial response	153 (40%)	155 (40%)
Stable disease‡	19 (5%)	14 (4%)
Progressive disease	35 (9%)	49 (13%)
Not evaluable for response§	13 (3%)	12 (3%)
Duration of response, months	NC (17·3–NC)	NC (13·7–NC)
Local progression events	42 (11%)	40 (10%)
Distant progression events	52 (14%)	69 (18%)
Secondary malignancy events	5 (1%)	4 (1%)

ORR was similar between both arms

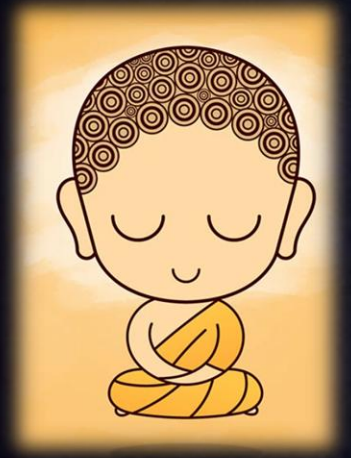


Adverse Events		CTRT+Durva	CTRT
Grade 3-4 events	Anemia	199 (52%)	196 (51%)
	Low WBC	39 (10%)	49 (13%)
T/T related events	Serious	Anemia 15(4%)	Leucopenia (4 (1%))
		RT Proctitis (6 (2%))	Low ANC
		Febrile Neutropenia (5 (1%))	Low platelet
		Genital Fistula (4(1%))	
RT Toxicities	<1 y	291 (76%)	287 (75%)
	≥1 y	37 (10%)	36 (9%)

Huge data! Hence, a short summary

ADVERSE EVENTS

	Durvalumab plus chemoradiotherapy (n=385)				Placebo plus chemoradiotherapy (n=384)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Nausea	188 (49%)	5 (1%)	0	0	182 (47%)	2 (1%)	0	0
Anaemia	102 (27%)	55 (14%)	2 (1%)	0	111 (29%)	42 (11%)	1 (<1%)	0
Diarrhoea	141 (37%)	6 (2%)	0	0	161 (42%)	0	0	0
Vomiting	83 (22%)	3 (1%)	0	0	94 (25%)	2 (1%)	0	0
Decreased appet	67 (17%)	4 (1%)	0	0	54 (14%)	1 (<1%)	0	0
Decreased neutr t	43 (11%)	25 (7%)	2 (1%)	0	47 (12%)	29 (8%)	7 (2%)	0
eased white ell count	30 (8%)	35 (9%)	4 (1%)	0	36 (9%)	45 (12%)	4 (1%)	0
	36 (9%)	25 (7%)	1 (<1%)	0	33 (9%)	13 (3%)	2 (1%)	0
	31 (8%)	22 (6%)	0	0	25 (7%)	22 (6%)	1 (<1%)	0
Decreased platelet count	35 (9%)	7 (2%)	1 (<1%)	0	52 (14%)	9 (2%)	1 (<1%)	0
Fatigue	36 (9%)	0	0	0	56 (15%)	3 (1%)	0	0
Hypomagnesaemia	33 (9%)	2 (1%)	1 (<1%)	0	29 (8%)	2 (1%)	1 (<1%)	0
Lymphopenia	6 (2%)	22 (6%)	6 (2%)	0	6 (2%)	13 (3%)	4 (1%)	0
Weight decreased	31 (8%)	1 (<1%)	0	0	34 (9%)	1 (<1%)	0	0
Hypokalaemia	25 (7%)	6 (2%)	0	0	22 (6%)	4 (1%)	4 (1%)	0
Urinary tract infection	26 (7%)	4 (1%)	0	1 (<1%)	23 (6%)	2 (1%)	0	0
Thrombocytopenia	27 (7%)	2 (1%)	1 (<1%)	0	25 (7%)	1 (<1%)	0	0
Radiation proctitis	21 (6%)	5 (1%)	1 (<1%)	0	23 (6%)	1 (<1%)	0	0
Alanine aminotransferase increased	24 (6%)	0	0	0	25 (7%)	3 (1%)	0	0
Hyperthyroidism	22 (6%)	2 (1%)	0	0	8 (2%)	0	0	0
Aspartate aminotransferase increased	21 (6%)	0	0	0	16 (4%)	2 (1%)	0	0
Abdominal pain	17 (4%)	3 (1%)	0	0	24 (6%)	2 (1%)	0	0
Blood creatinine increased	18 (5%)	0	0	0	14 (4%)	2 (1%)	0	0
Gastroenteritis radiation	16 (4%)	2 (1%)	0	0	7 (2%)	1 (<1%)	0	0
Arthralgia	16 (4%)	1 (<1%)	0	0	10 (3%)	2 (1%)	0	0
Hyponatraemia	15 (4%)	2 (1%)	0	0	16 (4%)	1 (<1%)	0	0
Lymphocyte count decreased	1 (<1%)	7 (2%)	7 (2%)	0	5 (1%)	20 (5%)	9 (2%)	0
Vaginal haemorrhage	12 (3%)	2 (1%)	0	0	14 (4%)	2 (1%)	0	0
Gamma-glutamyl transferase increased	11 (3%)	2 (1%)	0	0	13 (3%)	3 (1%)	0	0
Colitis	8 (2%)	3 (1%)	1 (<1%)	0	5 (1%)	0	0	0
Hypocalcaemia	10 (3%)	1 (<1%)	0	0	12 (3%)	1 (<1%)	1 (<1%)	0
Proctitis	8 (2%)	3 (1%)	0	0	4 (1%)	1 (<1%)	0	0
Acute kidney injury	4 (1%)	3 (1%)	0	0	2 (1%)	1 (<1%)	0	0



TO CONCLUDE…

Strengths

- First Phase 3 RCT studying immune checkpoint inhibitor in locally advanced cervical cancer
- Improved PFS in PD L-1 ≥ 20 with durvalumab
- Provided base for further studies

Limitations

- No overall PFS seen
- F/U time was short to provide 5 y OS or PFS
- Benefit of PFS not analysed with respect to LN status

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): a randomised, double-blind, phase 3 clinical trial

Lorusso et al. KEYNOTE A18 Lancet 2024

- N=1060
- Jun 2020 – Dec 2022
- Phase 3 RCT
- FIGO 2014 IB2-IIB LN+ III-IVA any LN status
- ECOG PS 0 or 1
- SCC, Adenoca, Adenosq. Ca

R

CTRT + Pembrolizumab → **Adjuvant Pembrolizumab**

CTRT (Cisplatin 40mg/m²)

Pembro 200mg q3wks x 5# → 400mg q6wks x 15 cycles

Endpoint

- **Primary – PFS & OS**
- **Secondary**
  - ORR
  - PFS (24 mon & RECIST v1.1)
  - OS & PFS (PDL1 Status)
  - Safety

- IMRT/VMAT vs Non-IMRT/Non-VMAT
- IB2-IIB (LN+) vs III-IVA
- RT dose (EBRT+Brachy) - <70 Gy vs ≥70 Gy

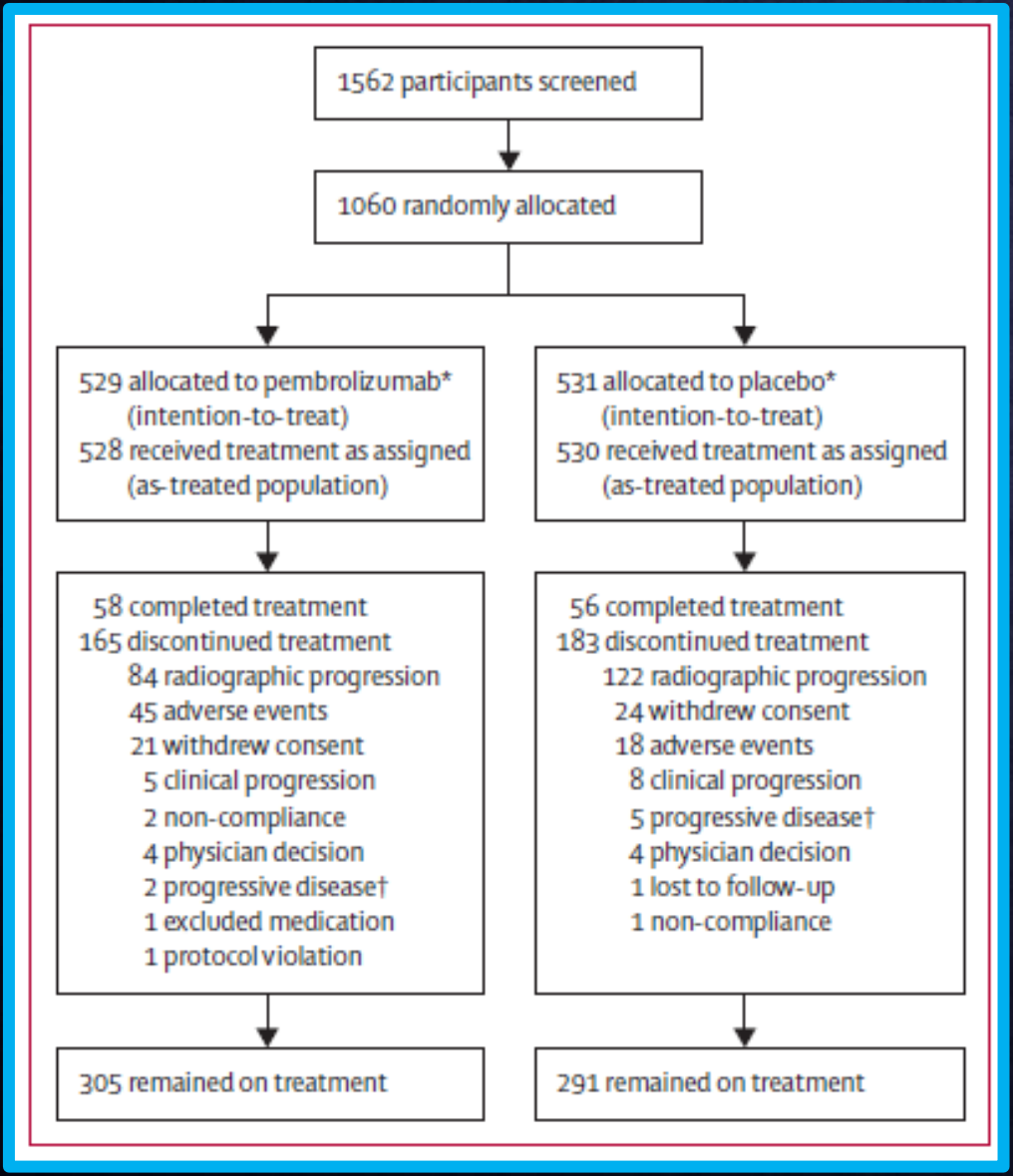
Inclusion Criteria

- Women aged 18 years or older
- Locally advanced histologically confirmed cervical adenocarcinoma, squamous carcinoma, or adenosquamous carcinoma
- FIGO 2014 IB2-IIB node +ve, III-IVA (any LN status)
- ECOG PS 0 or 1
- Adequate Organ Function

Exclusion Criteria

- H/o previous systemic therapy
- Previous exposure to immunotherapy
- Definitive surgery
- Previous H/o Radiation

CONSORT



STATISTICAL ANALYSIS

- PFS and OS estimated using the non-parametric **Kaplan-Meier** method
- **Stratified log rank test** - determine between group differences in PFS and OS
- Magnitude of difference assessed using a **stratified Cox proportional hazards model** and Efron's method of tie handling
- Consistency of PFS treatment effect in sub-groups assessed by means of **HR and 95% CI** using the non-stratified **Cox proportional hazards**
- One-sided **α=0.025**, test PFS superiority

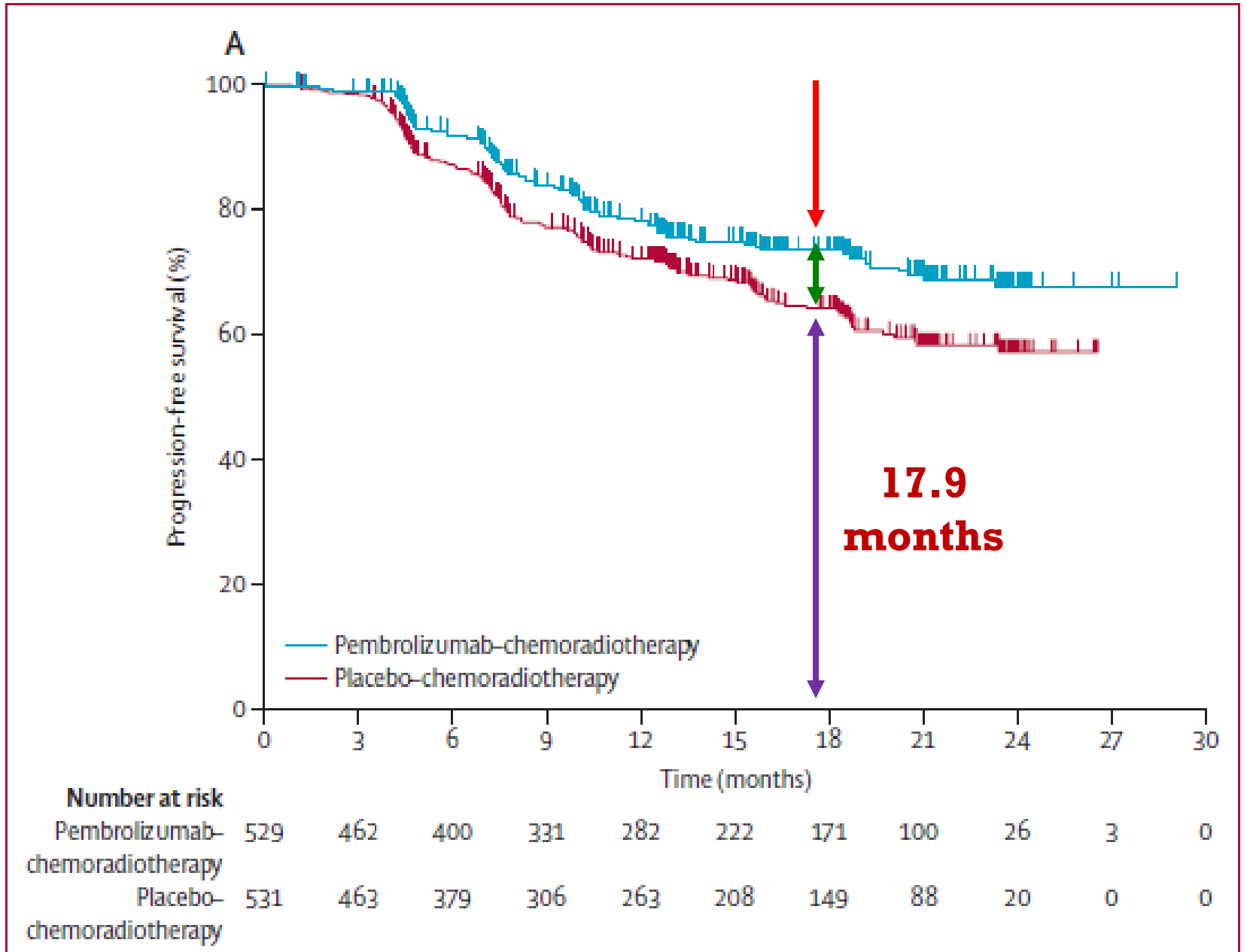
RESULTS

- Median age 49y (40-57) vs 50y (41-59)
- Median FU 17.9 months (IQR 11.3-22.3) for both groups

- Enrollment done from 176 medical centres in 30 countries (including resource-poor countries)

	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%)

Demographic Data

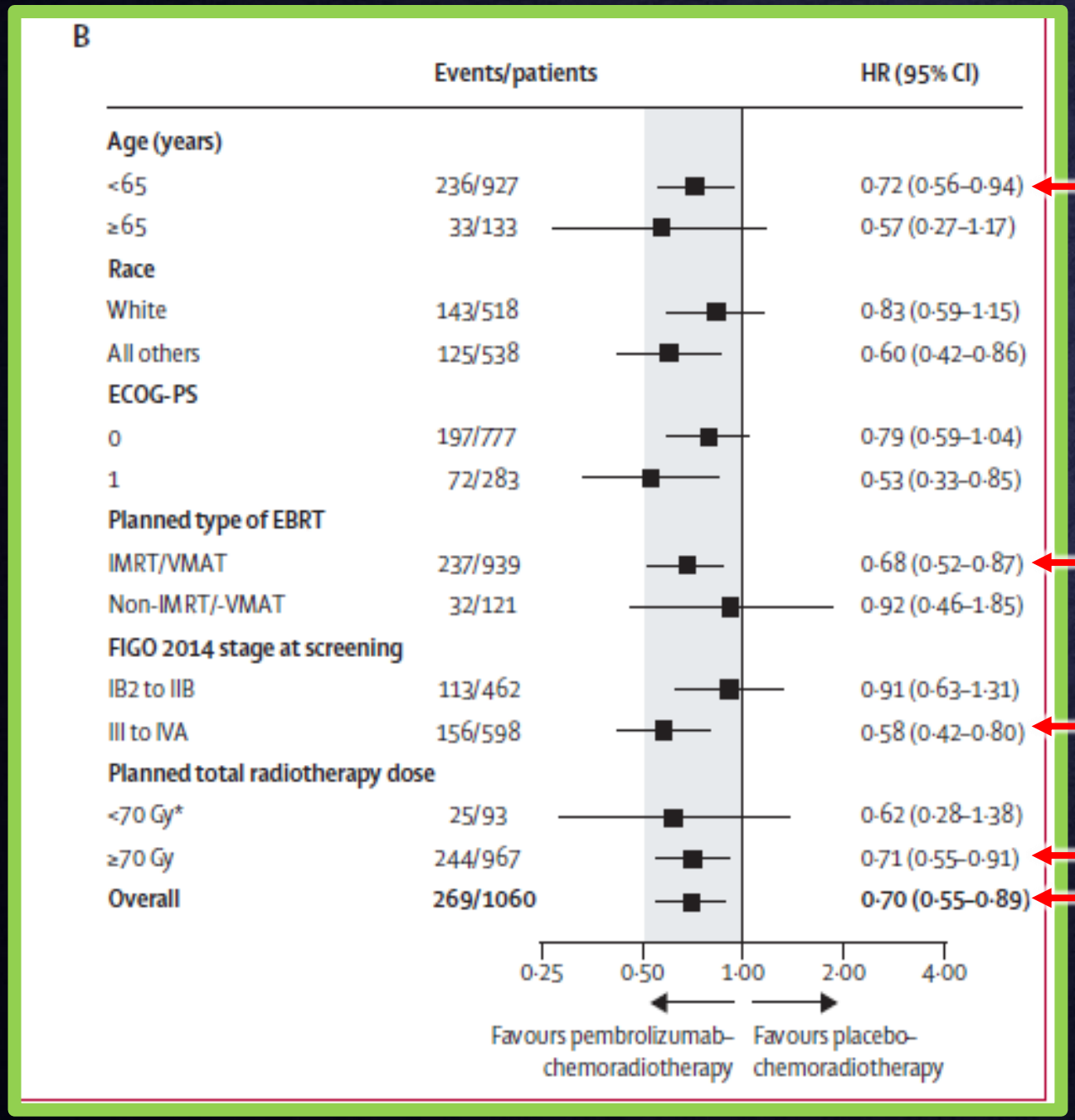


-Statistically significant PFS HR 0.70 (0.55-0.89), p=0.002

-PFS (24 mon) - 68%(62-73) vs 57% (51-63)

Note:

- First interim analysis (237 events - deaths or disease progression)



- PFS for PD-L1+ve (CPS≥1) → HR 0.72 (0.56-0.92)
- ORR – 413(79%) vs 369(76%)
- Median duration of response has not been reached
- Response duration ≥ 12 months → 172 (81%) vs 153 (77%)
- Median total cervix physical dose – 76 Gy
- Median total cervix EQD2 – 87 Gy

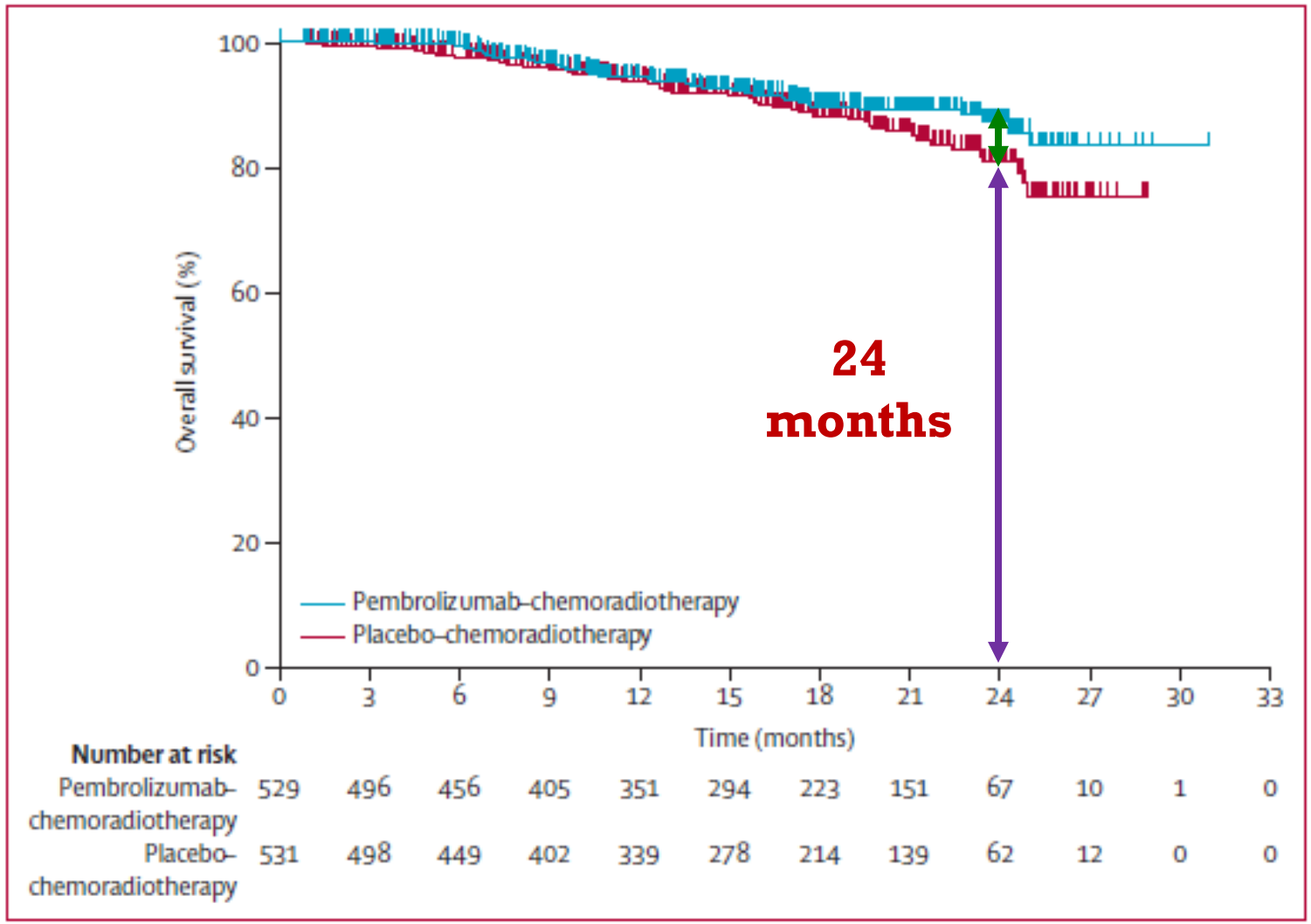


Figure 3: **Overall survival**
Kaplan–Meier estimates of overall survival in the intention-to-treat population. Tick marks indicate censoring of data.

- OS at 24 mon – 87% (82-91) vs 81% (75-86)
- Median OS was not reached in either group

Dr. Linda R. Duska

LBA5504 Oral Abstract Session

Pembrolizumab with chemoradiotherapy in patients with high-risk locally advanced cervical cancer: Final analysis results of the phase 3, randomized, double-blind ENGOT-cx11/GOG-3047/KEYNOTE-A18 study.

Linda R. Duska, Yang Xiang, Kosei Hasegawa, Pier Angelo Ramos-Elias, Paolo Rodolfo Valdez Barreto, Alejandro Acevedo, Felipe José Silva Melo Cruz, Valeria Saevets, Rudolf Lampé, Limor Helpman, Jalid Sehouli, Flora Zagouri, Yong Man Kim, Peng Liu, Karin Sayuri Yamada, Sarper Toker, Sandro Pignata, Domenica Lorusso, on behalf of the ENGOT-cx11/GOG-3047/KEYNOTE-A18 Investigators; University of Virginia School of Medicine, Charlottesville, VA; Department of Obstetrics and Gynecology, National Clinical Research Center for Obstetric & Gynecologic Diseases, Peking Union Medical College Hospital, Beijing, China; Saitama Medical University International Medical Center, Hidaka, Japan; Integra Cancer Institute, Edificio Integra Medical Center, Guatemala City, Guatemala; Hospital de Alta Complejidad de La Libertad Virgen de La Puerta, Trujillo, Peru; Oncocentro, Valparaiso, Chile; Instituto Brasileiro de Controle do Câncer, São Paulo, Brazil; Chelyabinsk Regional Clinical Center of Oncology and Nuclear Medicine, Chelyabinsk, Russian Federation; University of Debrecen, Faculty of Medicine, Department of Obstetrics and Gynecology, Debrecen, Hungary; Sheba Medical Center, Tel Aviv University Faculty of Medical and Health Sciences, Ramat Gan, Israel; Department of Gynecology with Center for Oncological Surgery, Charité - Universitätsmedizin Berlin, and North-Eastern German Society of Gynaecologic Oncology (NOGGO) and AGO Study Group, Berlin, Germany; Alexandra Hospital, Athens, Greece; Asan Medical Center, University of Ulsan, Seoul, South Korea; Merck & Co., Inc., Rahway, NJ; Department of Urology and Gynecology, Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, Napoli, Italy; Fondazione Policlinico Universitario A Gemelli IRCCS, and Humanitas San Pio X, Milan, Italy

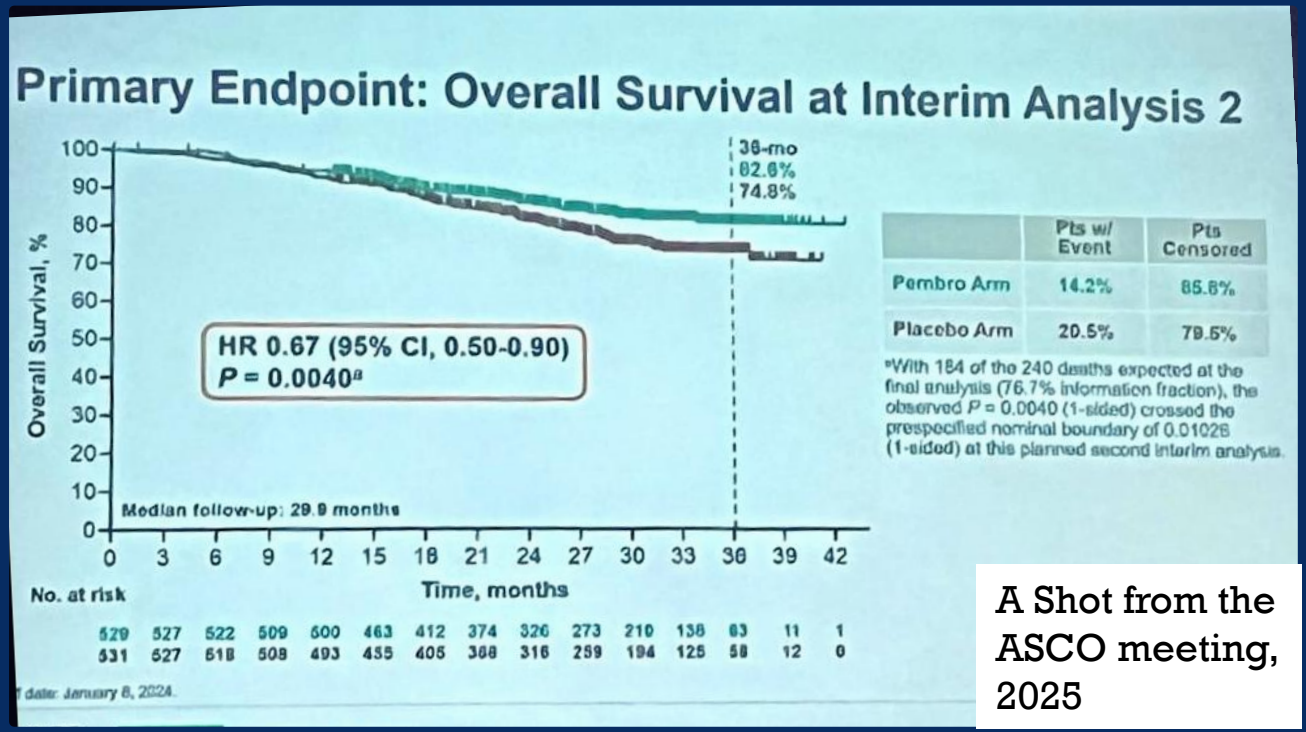
Final and 2nd interim analyses were presented at ASCO meeting, 2025 in Chicago, Illinois, USA

Summary of PFS and OS in ENGOT-cx11/GOG-3047/KEYNOTE-A18.

	Final Analysis 07JAN25		Interim Analysis 2 08JAN24	
	Pembro + CCRT	Pbo + CCRT	Pembro + CCRT	Pbo + CCRT
OS, median (95% CI)	NR (NR-NR)	NR (NR-NR)	NR (NR-NR)	NR (NR-NR)
36-mo OS	81.8%	74.4%	82.6%	74.8%
HR (95% CI)	0.73 (0.57-0.94)		0.67 (0.50-0.90); *P*=0.0040	
PFS, median (95% CI)	47.6 (47.6-NR)	47.5 (41.0-NR)	NR (NR-NR)	NR (32.0-NR)
24-mo PFS	70.6%	59.7%	70.6%	58.6%
HR (95% CI)	0.72 (0.59-0.87)		0.68 (0.56-0.84)	

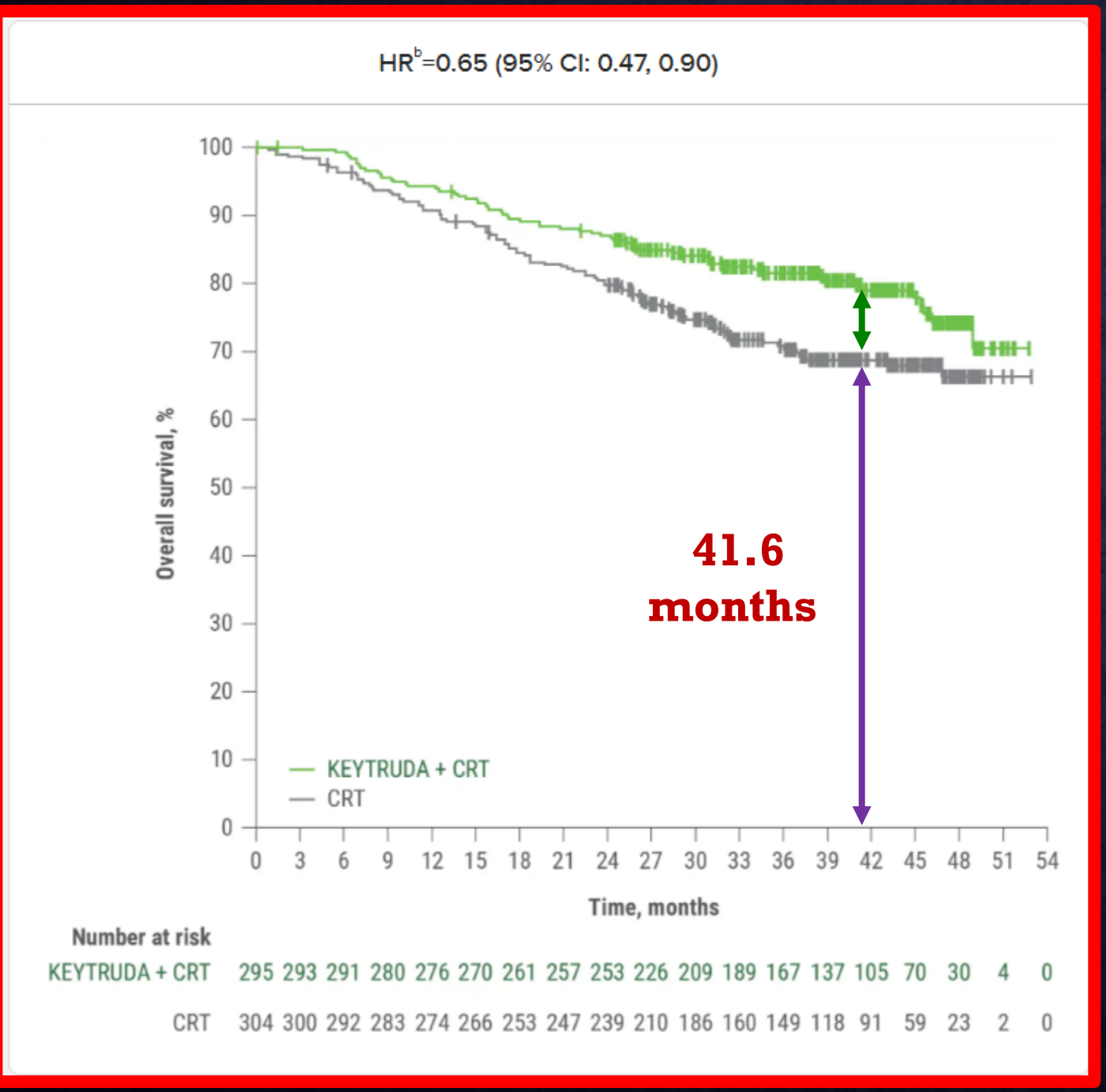
NR=not reached.

- Median follow up of **41.6 months** (IQR 24.8 – 55.0)
- 86 patients had received post-progression immunotherapy; of those, 64 received Pembrolizumab (details not mentioned)



A Shot from the ASCO meeting, 2025

- Statistically Significant OS (2nd interim analysis) – **HR 0.67 (0.50-0.90), p=0.0040**
- OS (Final Analysis) – HR 0.73 (0.57-0.94)
- PFS (in 2nd interim analysis and Final analysis) were HR 0.72 (0.59-0.87) and 0.68 (0.56-0.84) respectively



OS in FIGO 2014 III-IVA

- HR 0.65 (95%CI 0.47-0.90)

But there is no mention regarding p value

ADVERSE EVENTS

No grade 5 immune-mediated adverse events

	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
Leukopenia	125 (24%)	67 (13%)	92 (17%)	57
Platelet count decreased	116 (22%)	25 (5%)	108 (20%)	13
Neutropenia	113 (21%)	56 (11%)	92 (17%)	51
Immune-mediated adverse event‡	167 (32%)	21 (4%)	54 (10%)	5
Hypothyroidism	102 (19%)	3 (<1%)	24 (5%)	6
Hyperthyroidism	60 (11%)	2 (<1%)	11 (2%)	0
Colitis	14 (3%)	4 (<1%)	9 (2%)	4
Thyroiditis	11 (2%)	1 (<1%)	1 (<1%)	0

Adverse Events		CTRT+ Pembro	CTRT
T/T emergent events	Total	525 (99%)	526 (99%)
	Grade≥3	394 (75%)	364 (69%)
	Serious	91 (17%)	65 (12%)
Potentially immune-mediated	Total	167 (32%)	54 (10%)
	Grade≥3	21 (4%)	5 (<1%)

Strengths

- First Phase 3 RCT to report a statistically significant OS with PD-1 inhibitor and CTRT in locally advanced cervical cancer
- Statistically significant PFS
- Potential role for addition of Pembrolizumab with CTRT

Limitations

- Interim Analysis – short F/U period (more time required)
- Benefit of PFS was not analysed with respect to LN status
- Investigator-assessed PFS prone to bias
- The funder of the study was involved at multiple stages – Sponsor bias

LET'S SUMMARISE

KEYNOTE-018: PEMBROLIZUMAB + CRT → MAINTENANCE

- Demonstrated significant PFS & OS improvement in locally advanced cervical cancer.
- Benefit consistent across PD-L1 subgroups
- Established as new standard of care : Immunotherapy + CRT followed by maintenance
- Lesson: Synergistic effect when IO is integrated with curative CT-RT.

CALLA: DURVALUMAB + CRT → MAINTENANCE

- Negative trial : No significant improvement in PFS or OS
- Possible reasons:
  - Targeted only PD-L1 (not PD-1)
  - Long 2-year maintenance → higher attrition
  - Ambitious HR assumption in trial design
- Lesson: Not all checkpoint inhibitors are equal
- Success depends on biology, biomarker selection & trial design.

KEYNOTE-018 vs CALLA: The Lesson

KEYNOTE-018:

- Practice-Changing
- Survival Benefit
- New Standard of Care

CALLA :

- Negative Trial
- No OS/PFS Benefit
- Lessons in Design & Biology

Immunotherapy is here to stay: But
Smart Design + Right Agent = Success in Cervix Cancer

THANK YOU

Acknowledgements:

- Dr Abhay
- Dr Asesh
- Dr Pooja Nandwani Patel