Emerging opportunities in cervical cancer

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Cervical Cancer: Treatment Landscape

Early Stage FIGO IA1-IB2, IIA — *46%*[2]

Open Radical Surgery Risk-based Adjuvant Treatment

- SHAPE (extrafascial hyst for IA2-IB1)
- SENTICOL (sentinel nodes)
- RACC
- GOG 3043/ROCC (robotic vs open RH)
- GOG 263 (adj CRT intermed risk)
- GOG 724 (outback adj chemo high risk)

Locally Advanced FIGO IB3-IVA — *36%*[2]

Chemoradiotherapy

- NRG GY006 (CRT +/- triapine)
- CALLA (CRT +/- durva)
- GOG 3047/KN A18 (CRT +/-pembro)
- ATOMICC
- ATEZOLACC
- Interlace (chemo induction CRT)

Metastatic (FIGO IVB), Recurrent, Persistent — *15%*[2]

- **CPS <1** → GOG 240
- **CPS ≥1** → KEYNOTE 826
- GOG 3024 Arm H (plt/tisotumab/pembro +/-bev)

Second-line+

- **IO naïve** → CPS ≥1: Pembro; CPS<1: Tisotumab vedotin (+/- pembro)
- **IO exposed** → Tisotumab vedotin

POST IO or CPS <1

[1] NCCN Cervical Cancer Guidelines v2.2019

[2] SEER Cancer Stat Facts: Cervical Cancer. National Cancer Institute. Bethesda, MD

Outline of major IGCS/ESMO updates

- IO for locally advanced disease
  - CALLA
- IO combinations for metastatic disease
  - Checkmate 358
- Alternative targets for recurrent disease
  - SUMMIT

CALLA Study Design

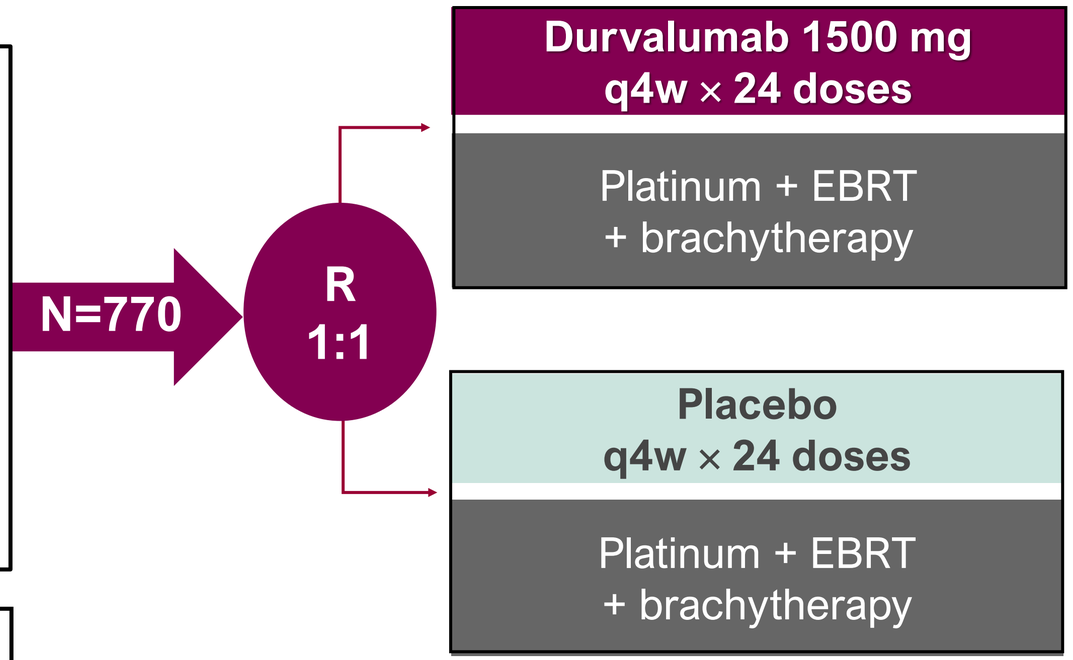
15 countries, **120** sites

Eligible population

- Women aged ≥18 years
- Histologically confirmed cervical adenocarcinoma, squamous carcinoma, or adenosquamous carcinoma
- High-risk LACC (FIGO 2009)
  - Stages IB2 to IIB, node positive (N≥1)
  - Stages IIIA to IVA with any node (N≥0)
- WHO ECOG performance status of 0 or 1

Stratification factors

- Disease stage
  - FIGO Stage IB2–IIB and LN+
  - FIGO Stage ≥III and LN–
  - FIGO Stage ≥III and LN+
- Region of world



Primary Endpoint:

Progression-Free Survival[a] (Investigator-assessed)

Key Secondary Endpoints:

- Overall survival
- Objective response rate
- Duration of response
- Incidence of local or distant progression / 2° malignancy
- Safety and tolerability

Chemoradiotherapy Regimen

Platinum agent	Cisplatin 40 mg/m^2 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

Key Milestones

First patient in	February 2019
Last patient in	December 2020
Data cutoff	January 20, 2022

[a]According to RECIST 1.1 or histopathologic confirmation of local tumor progression.

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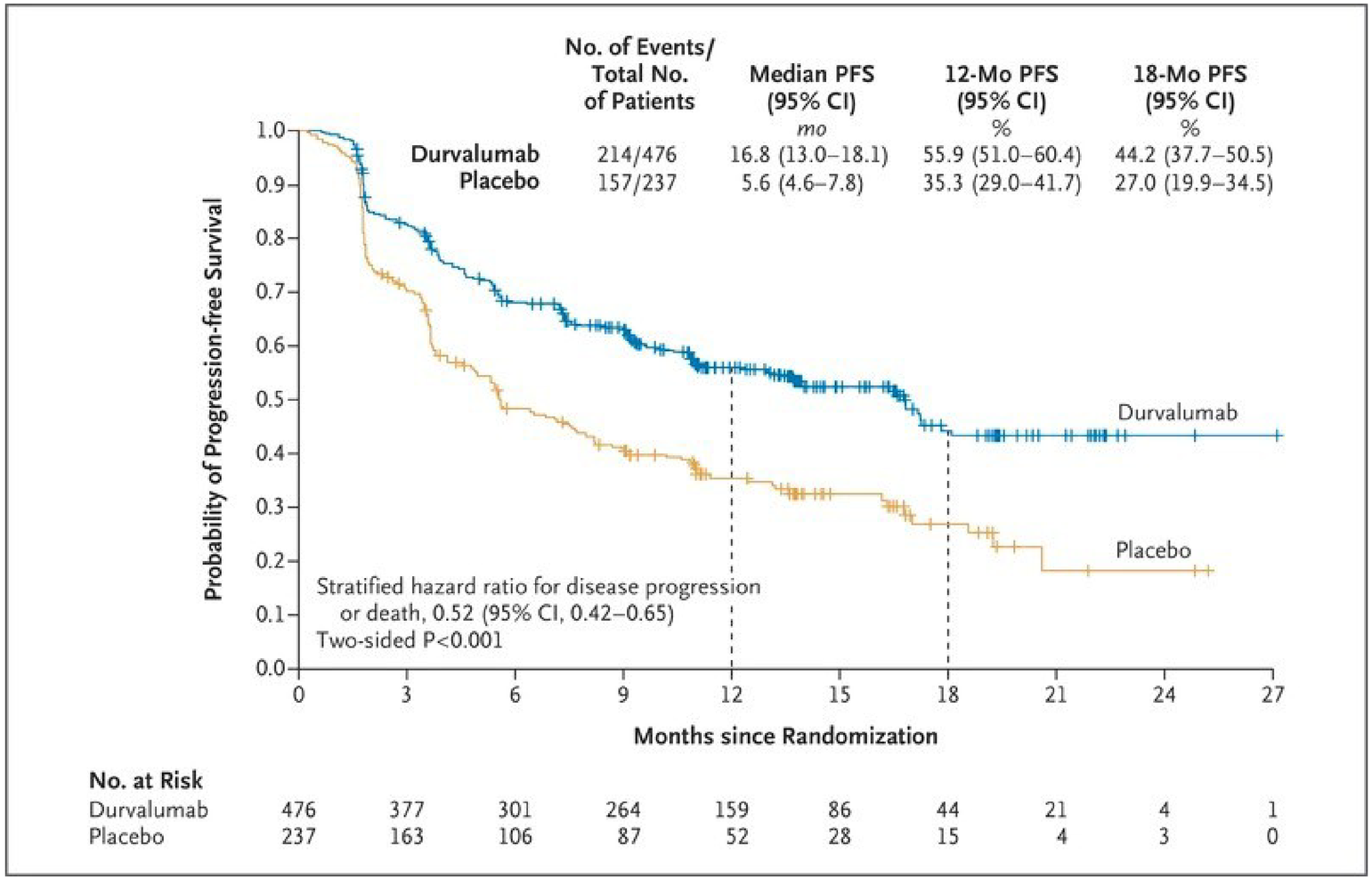
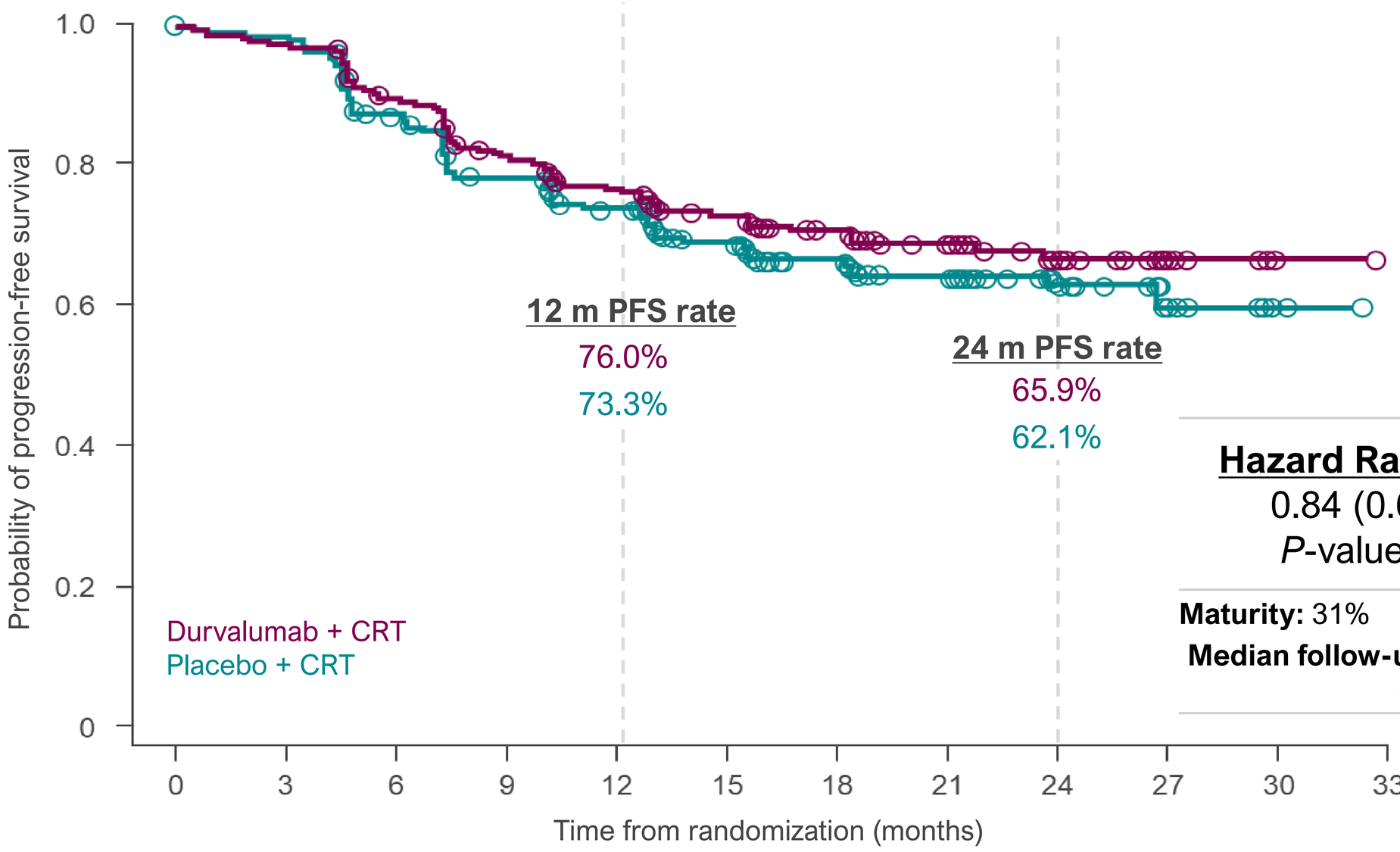
PACIFIC: Anti-PD-L1 therapy post-CRT for locally-advanced lung cancer



Antonia SJ et al. Engl J Med. 2017 Nov 16;377(20):1919-1929.

Primary Endpoint: Progression-Free Survival

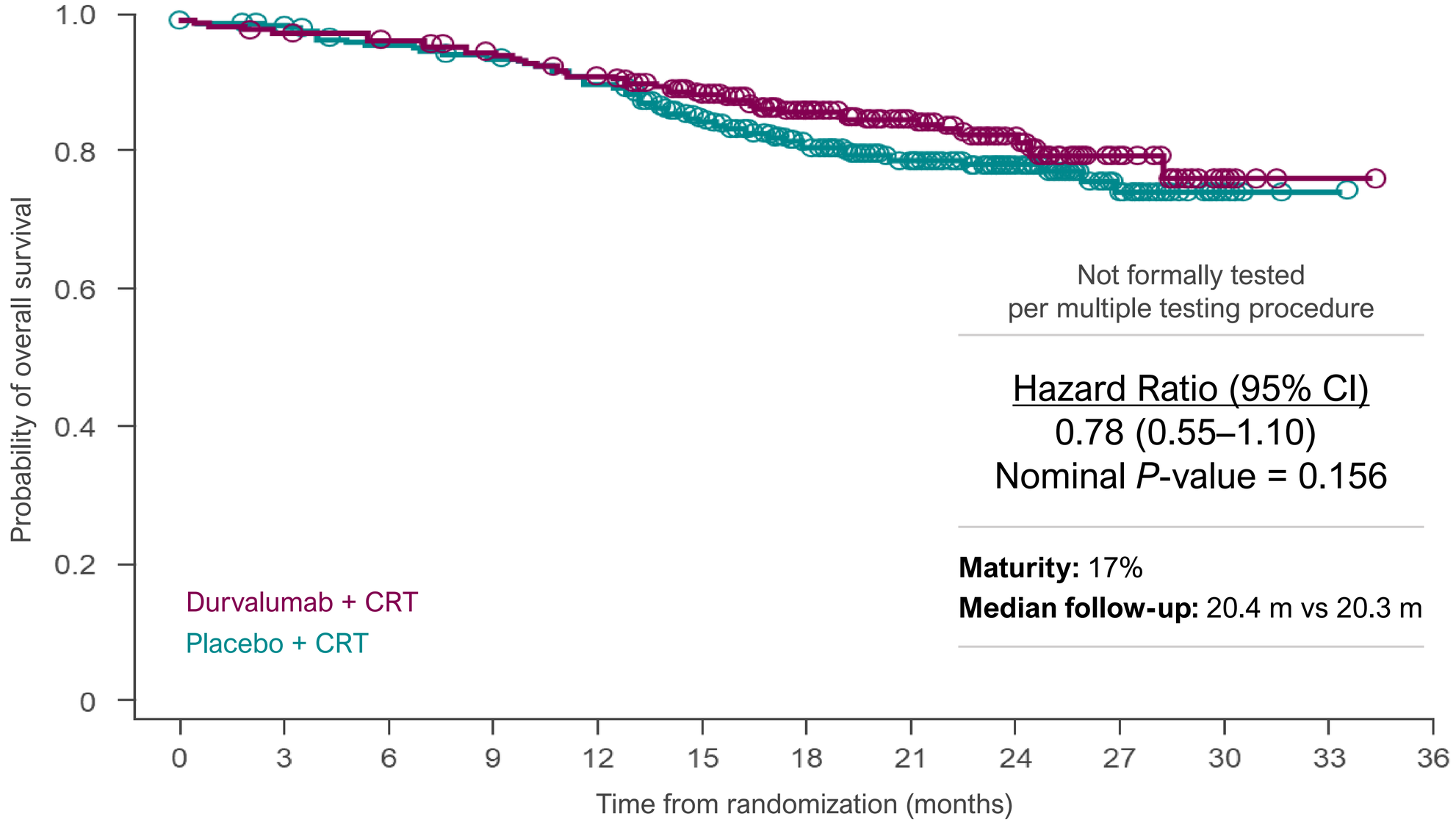


Hazard Ratio (95% CI)
0.84 (0.65–1.08)
P-value = 0.174

Maturity: 31%

Median follow-up: 18.5 m vs 18.4 m

Overall Survival



Randomized Head and Neck SCCa Trials-all negative

Reference	N	Therapy
Javelin 100 HNSCC Lancet Oncol 2021	697	Concurrent CRT+/- avelumab
GORTEC-REACH ESMO 2021	430	Concurrent cetuximab/avelumabRT vs cisRT
PembroRad	131	Concurrent cetuximabRT vs. pembroRT
KEYNOTE 412 ESMO 2022	804	Concurrent CRT+/- pembro

Why a trial with so strong biological rationale failed?

Is it a matter of **strategy**?

Or a matter of **trial**?

?Trial: Demographics

	Durvalumab + CRT (N=385)	Placebo + CRT (N=385)
Median follow-up, months (range)	**18.5 (0–32.6)**	**18.4 (0–32.3)**
Median age, years	**50**	**48**
Race, n (%)		
White	**130 (33.8)**	**125 (32.5)**
Black/African American	**10 (2.6)**	**12 (3.1)**
Asian	**152 (39.5)**	**148 (38.4)**
American Indian/Alaska Native	**47 (12.2)**	**56 (14.5)**
Other	**46 (11.9)**	**44 (11.4)**
Ethnicity, Hispanic/Latino, n (%)	**175 (45.5)**	**164 (42.6)**
Country/Region,[a] n (%)		
Latin America	**176 (45.7)**	**165 (42.9)**
Asia	**151 (39.2)**	**144 (37.4)**
United States/Europe	**40 (10.4)**	**55 (14.3)**
Russian Federation	**17 (4.4)**	**20 (5.2)**

[a]Europe comprises Hungary and Poland only; 1 patient in each arm participated from South Africa.

?Trial: Exposure to Study Treatments

	Durvalumab + CRT (N=385)	Placebo + CRT (N=385)
Durvalumab/placebo relative dose intensity,[a,d] median (range), %	**95.8 (34–104)**	**95.0 (31–100)**
Number of patients who received CRT, n (%)	**385 (100)**	**383 (99.5)**
Number of cycles of cisplatin/carboplatin, n (%)[b,d]		
5 cycles	**199 (51.7)**	**220 (57.3)**
6 cycles	**136 (35.3)**	**126 (32.8)**
EBRT delivered, n (%)	**385 (100)**	**383 (99.5)**
EBRT completed per protocol, n (%)	**371 (96.4)**	**379 (98.4)**
EBRT total dose, median, cGy[c]	**5400**	**5400**
Brachytherapy delivered, n (%)	**366 (95.1)**	**367 (95.3)**
Brachytherapy completed per protocol, n (%)	**363 (94.3)**	**360 (93.5)**
Equivalent EQD2 dose, median, cGy[c]	**8387**	**8387**
Radiotherapy delivered in ≤59 days, n (%)	**278 (72.2)**	**279 (72.5)**

[a]Percentage of the actual dose intensity delivered relative to the intended dose intensity through treatment discontinuation.

[b]1 patient on the durvalumab + CRT arm received >6 cycles of platinum chemotherapy, all other patients not shown in table received <5 cycles.

[c]Reported for ex-Japan population only. Median total EBRT dose reported, Japan patients: w/ midline block (n=50/52), 5400 cGy; w/o midline block (n=2/52), 5960 cGy. Median equivalent EQD2 dose reported, Japan patients: 7027 cGy (durvalumab + CRT); 6926.5 cGy (placebo + CRT). EQD2, equi-effective dose in 2 Gy per fraction.

[d]Safety analysis set; durvalumab + CRT (N=385); placebo + CRT (N=384).

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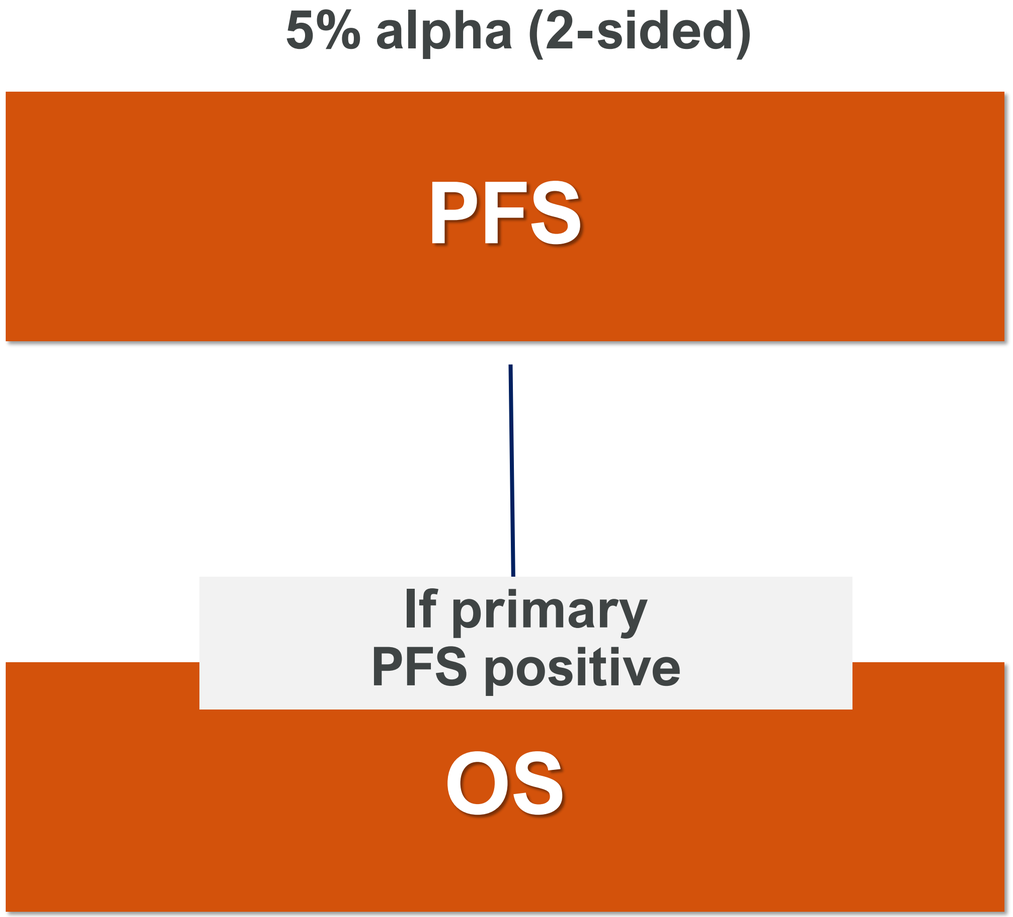
?Trial: Statistical Assumptions

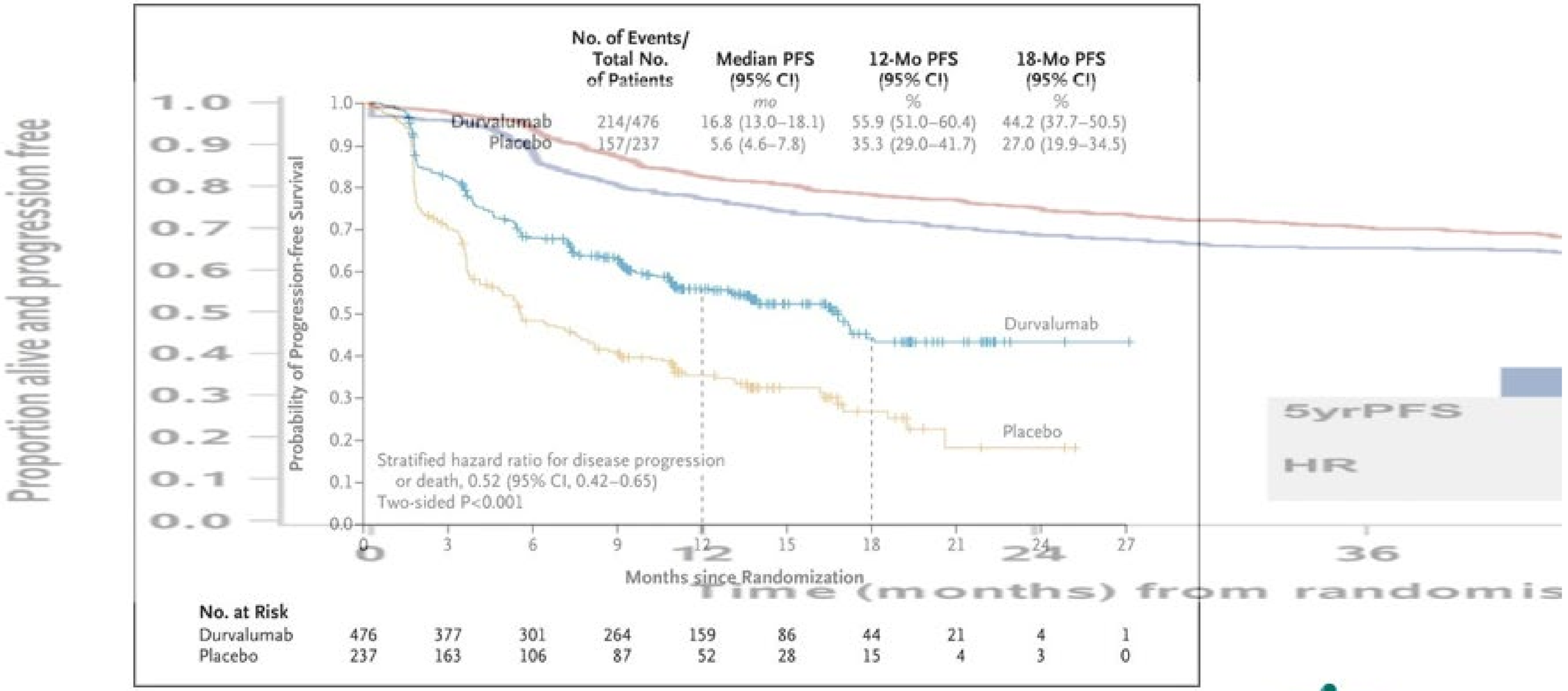
- **PFS Analysis**
  - Intent-to-treat population (ITT)
  - Planned at 32% maturity
  - 90% power with 5% 2-sided alpha to detect a HR of 0.65
  - Known at the time: GOG 120 PFS at 30 months 67%, PA node- population

- **OS Analysis**
  - Interim analysis planned at time of PFS analysis: expected maturity 25%

Data Cutoff: January 20, 2022

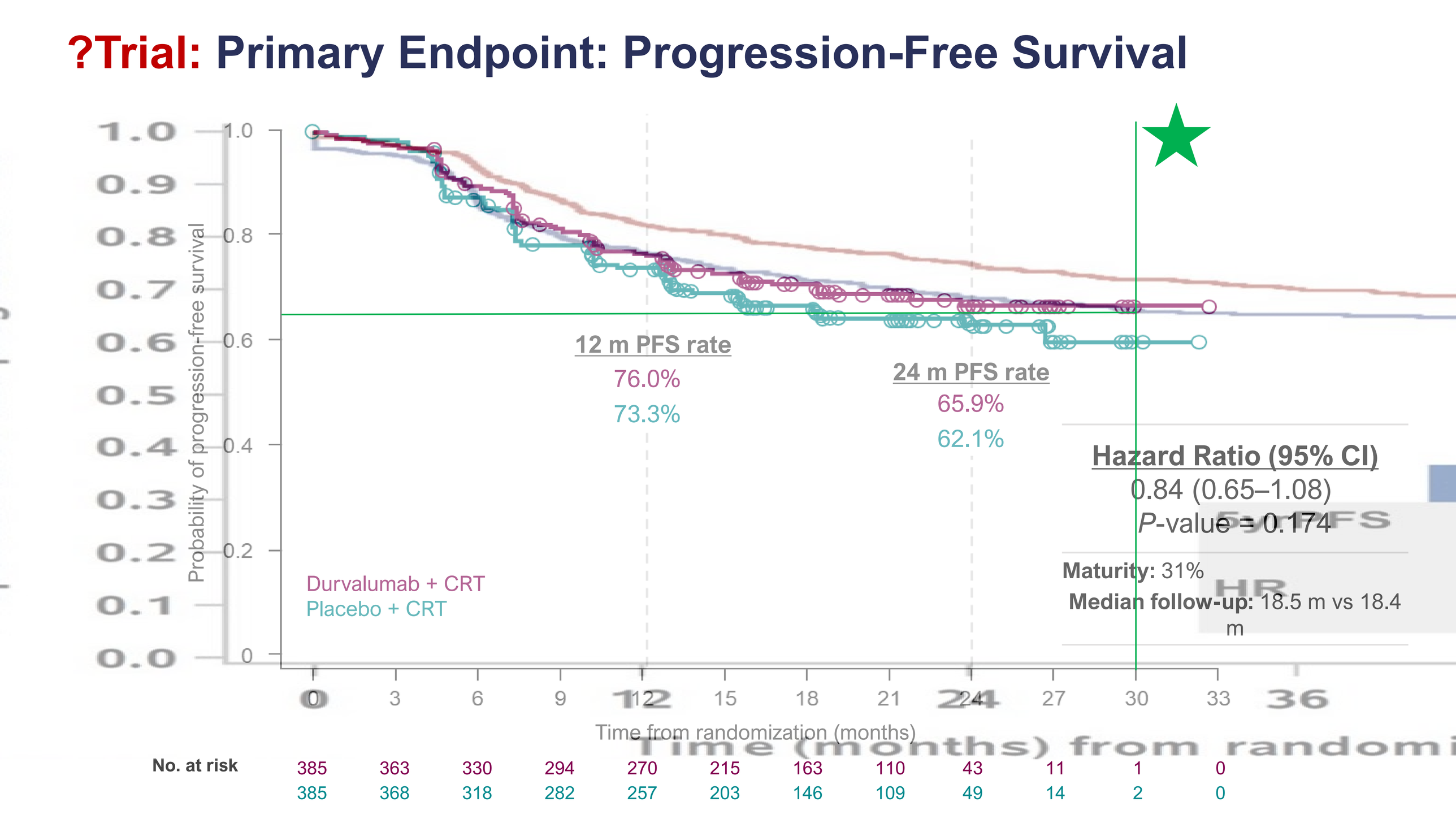


?Trial: PACIFIC: Anti-PD-L1 therapy post-CRT for locally-advanced lung cancer



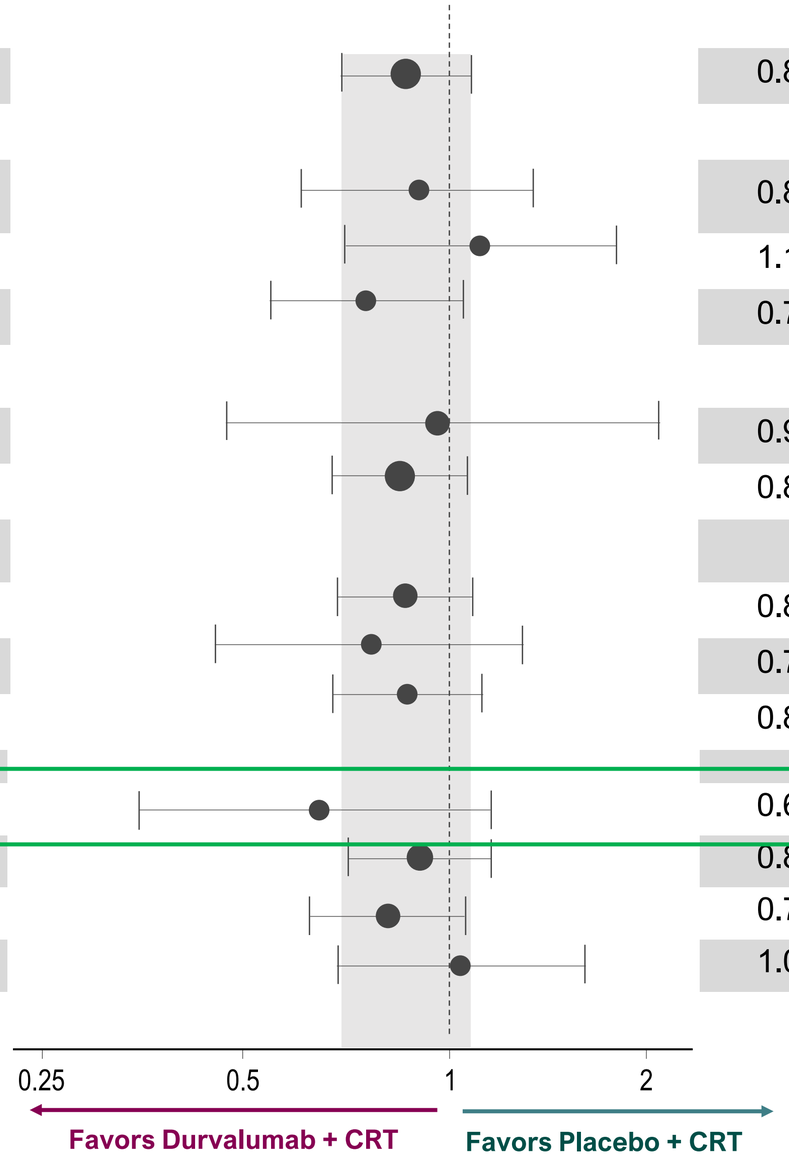
Antonia SJ et al. Engl J Med. 2017 Nov 16;377(20):1919-1929.
Mileshkin L et al. ASCO 2021

?Trial: Primary Endpoint: Progression-Free Survival



?Trial: PFS Subgroup Analysis

	Durvalumab + CRT (Events/Total)	Placebo + CRT (Events/Total)	Hazard Ratio (95% CI)
All patients	112/385	128/385	0.84 (0.65–1.08)
Disease stage (FIGO 2009)			
Stage IB2–IIB, node positive	35/134	39/133	0.87 (0.55–1.38)
Stage ≥III, LN–	28/108	26/107	1.11 (0.65–1.91)
Stage ≥III, LN+	49/143	63/145	0.71 (0.49–1.03)
Chemotherapy received			
Carboplatin	14/26	9/20	0.94 (0.41–2.27)
Cisplatin	98/359	118/363	0.82 (0.62–1.07)
PD-L1 expression status			
≥1%	102/356	117/352	0.83 (0.64–1.09)
<5%	19/60	25/64	0.73 (0.40–1.32)
≥5%	85/311	95/300	0.84 (0.63–1.13)
Lymph nodes			
Para-aortic lymph node	15/47	20/38	0.60 (0.30–1.17)
No para-aortic lymph node	97/338	108/347	0.89 (0.68–1.17)
Pelvic lymph node	75/246	97/268	0.79 (0.58–1.06)
No pelvic lymph node	37/139	31/117	1.04 (0.64–1.68)



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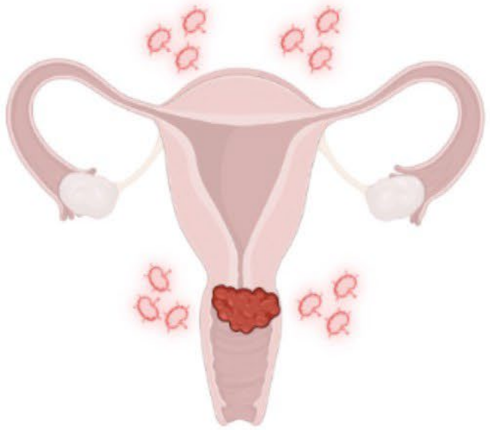
?Strategy: Induction IO for locally-advanced tumors, pre-operative

Reference	Tumor type Stage	N	Therapy	pCR	pPR
PURE-01 JCO 2018	Urothelial III	50	Pembro x 3	42%	54%
NABUCCO Nature Med 2020	Urothelial III	24	Ipi/nivo x 3	46%	58%
RACE IT ESMO 2022	Urothelial III	31	Nivo x 1 then RT Concurrent nivo	39%	58%
Lin et al J Imm Cancer 2022	Rectal T3/T4	30	Short RT CAPOX + camrelizumab x 2	48%	
Cercek NEJM 2022	Rectal T2/T3	14	Dostarlimab x 8	100%	

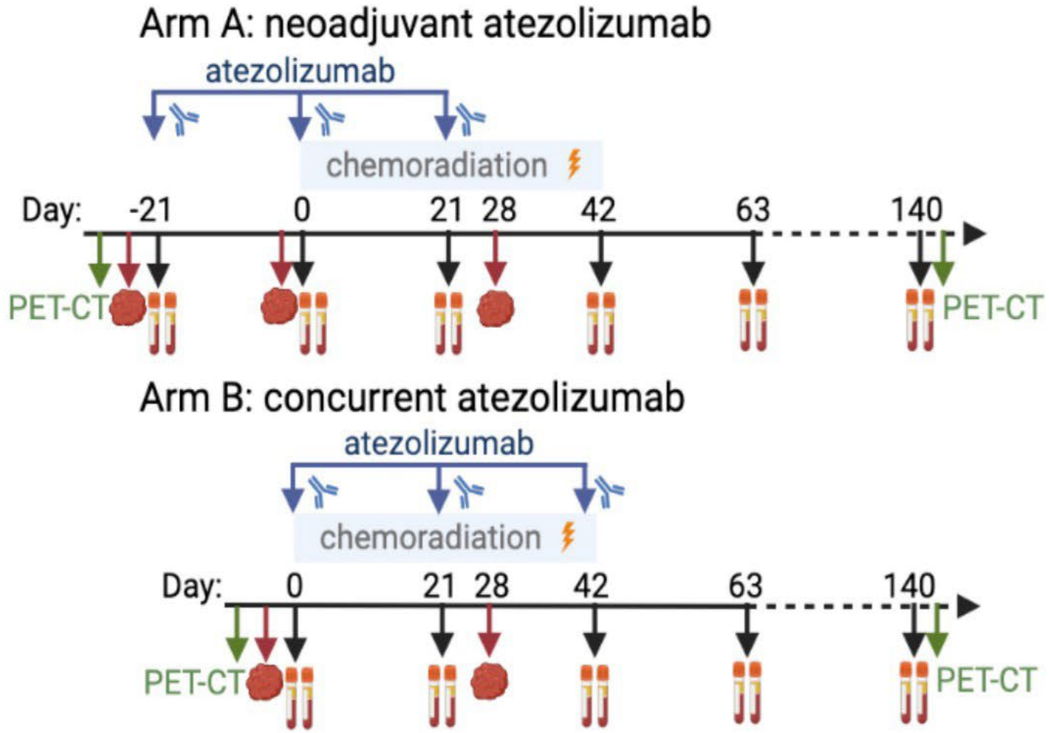
?Strategy: PA node + focus-highest risk



Cervical cancer:
Stage IB-IVA, +PALN
Stage IIB-IVA, + PLN, +/-PALN

Biopsy

Blood



- N=36
- Increase T cell diversity, no diff between arms
- 28% pCR at 1st brachytx
- Higher pre-tx TCR diversity assoc w/pCR
- DFS 12 mo 72%

ANNUAL MEETING ON WOMENS' CANCER®
BUILDING BRIDGES // BREAKING BARRIERS
SGO // PHOENIX, ARIZONA // MARCH 18 – 21, 2022

Mayadev J et al. SGO 2022 Abstract 24

SGO Society of Gynecologic Oncology

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?Strategy: Randomized phase 2 translational study of pembrolizumab during and after CRT

Primary Carcinoma of the Cervix:

Squamous, adenosquamous, adenocarcinoma

Stages IB2-IVA or IB1 wpositive nodes (FIGO 2009)

PET/CT and MRI pelvis

Tissue biopsy and peripheral blood collection

Randomized 1:1

ARM1 (sequential):

CDDP 40 mg/m^2 weekly for 5-6 weeks

Concurrent XRT: EBRT plus brachytherapy

3 cycles of consolidative pembrolizumab: 200 mg every 21 days beginning week 9 for 3 cycles

ARM2 (concurrent):

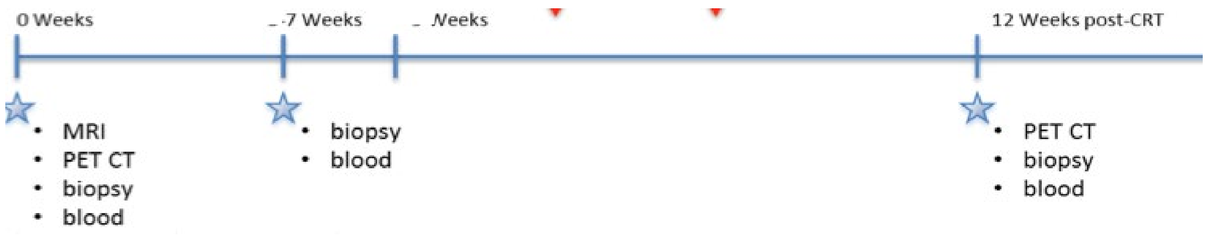
CDDP 40 mg/m^2 weekly for 5-6 weeks

3 cycles of concurrent pembrolizumab: 200 mg every 21 days beginning day 1 for 3 cycles

Concurrent XRT: EBRT plus brachytherapy

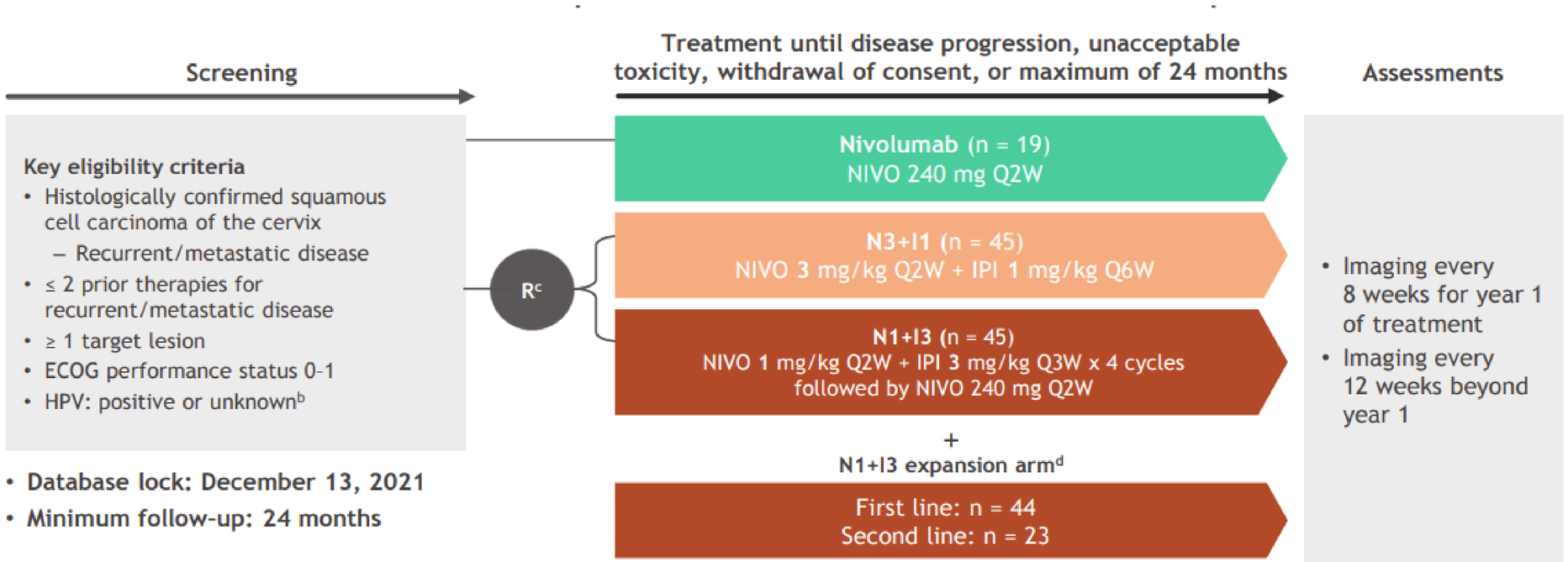
PET/CT required
MRI pelvis (optional)
Tissue biopsy and peripheral blood collection

CRT was SOC per institution, complete in 8 weeks



Duska L, et al. SGO 2020

IO Combos Metastatic Disease
CheckMate 358



- **Database lock: December 13, 2021**
- **Minimum follow-up: 24 months**

Primary endpoint:
- Investigator-assessed ORR

Secondary endpoints:
- DOR
- Investigator assessed PFS
- OS

For all treatment arms, an ORR of ≥ 10% will be considered of clinical interest, and an ORR of ≥ 25% will be considered of strong clinical interest

Investigator-assessed objective response rate

	NIVO	N3+I1 (randomized)			N1+I3 Pooled (randomized + expansion)		
	All (n = 19)	All (n = 45)	1L (n = 18)	≥ 2L (n = 27)	All (n = 112)	1L (n = 69)	≥ 2L (n = 43)
ORR, % (95% CI)	**26 (9-51)**	**31 (18-47)**	**39 (17-64)**	**26 (11-46)**	**38 (29-48)**	**41 (29-53)**	**35 (21-51)**
PD-L1[a] ≥ 1%, responders/evaluable (%)	3/11 (27)	9/25 (36)	4/12 (33)	5/13 (38)	19/53 (36)	13/33 (39)	6/20 (30)
PD-L1[a] < 1%, responders/evaluable (%)	1/7 (14)	3/15 (20)	2/3 (67)	1/12 (8)	11/36 (31)	6/19 (32)	5/17 (29)
Median DOR, months (95% CI)	**NR (35.3-NR)**	**24.4 (8.7-NR)**	**34.6 (6.6-NR)**	**21.1 (7.5-NR)**	**34.1 (11.5-NR)**	**25.6 (9.2-NR)**	**NR (5.2-NR)**

- As expected, more responses were noted in the first- vs second-or-later-line setting
- N1+I3 showed a higher response rate than N3+I1 in both first- and second-or-later-line setting
- Durable responses were observed regardless of tumor PD-L1 status across all treatment arms
  - There are fewer responses seen in patients with PD-L1 < 1% treated with nivolumab monotherapy compared with patients with PD-L1 < 1% treated with nivolumab and ipilimumab

[a]PD-L1 expression by tumor proportion score.

Oaknin A et al ESMO 2022

Other IO combos reported

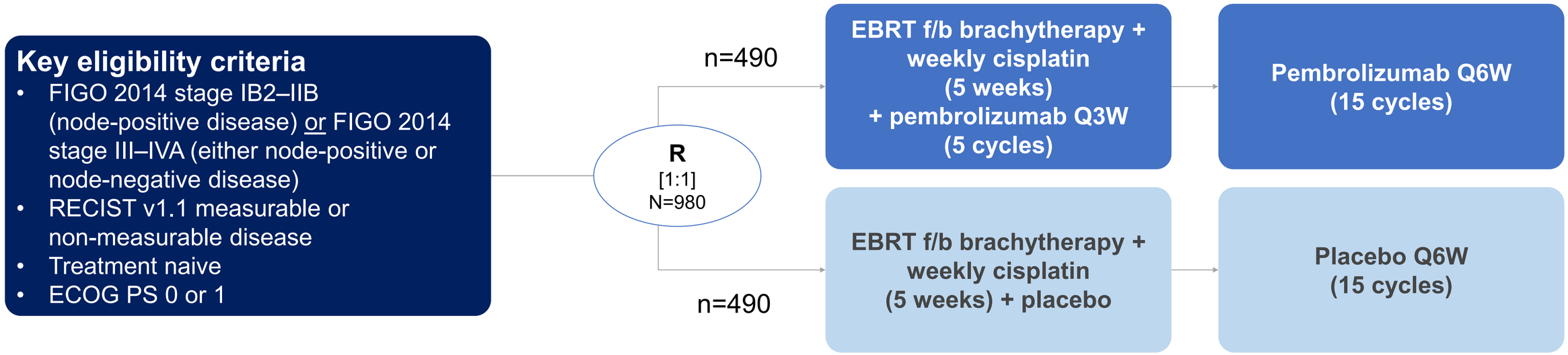
	n	ORR (95% CI)	ORR PDL1+ (95% CI)	ORR PDL1- (95% CI)
Balstilimab +Zalifrelimab[1]	155	25.6% (18.8-33.9)	32.8%	9.1%
Cadonilimab[2]	100	33.0% (23.9-43.1)	43.8% (31.4-56.7)	
Tisotumab vedotin + pembrolizumab[3]	34	38.2% (22.2-56.4)		

1. O'Malley DM et al. JCO 2022
2. Wu XH et al. SGO 2022
3. Vergote I et al. ASCO 2022

Discussion

Ongoing Trials

TBD!: ENGOT-CX11/GOG 3047/KEYNOTE-A18



Stratification factors

- IMRT or VMAT versus non-IMRT and non-VMAT
- Stage at initial diagnosis of cervical cancer (FIGO 2014 Stage IB2–IIB [node-positive disease] vs FIGO 2014 Stage III–IVA [either node-positive or node-negative disease])
- Planned total radiotherapy dose (EBRT + brachytherapy dose) of <70 Gy vs ≥70 Gy

Endpoints

- **Dual primary:** PFS, OS

Key similarities in CALLA and KEYNOTE A-18

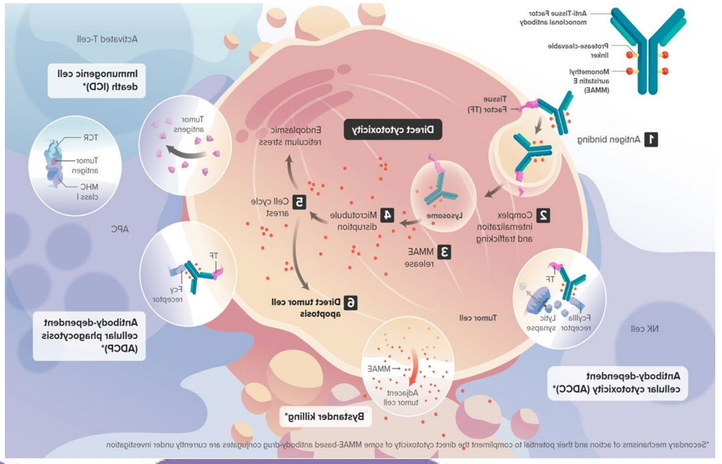
Design	1:1 Randomized phase 3
Approach	IO during and following CRT as maintenance
Enrollment	Global

Key differences in CALLA and KEYNOTE A-18

	CALLA	A-18
Eligibility	Allows 1 pelvic node+	Must have 2 pelvic or aortic node + but allows PET SUV 2.5+
Target	PD-L1	PD1
Agent	Durvalumab	Pembrolizumab
Primary endpoint(s)	PFS	PFS/OS
Stratification factors	Stage Region of world	IMRT/VMAT vs non Total RT dose <70 vs ≥70 Gy Stage (1B2-IIB node + vs III/IVA node +/-)
Enrollment	45% Latin America 40% Asia 10% US/Europe	TBD but different

GOG-3024/ ENGOT-cx8/innovaTV 205

A Phase 1b/2 Open-Label Trial of Tisotumab Vedotin (HuMax®-TF-ADC) Monotherapy and in Combination with Other Agents in Subjects with Recurrent or Stage IVB Cervical Cancer (Amendment 7)



Arm H

Subjects with cervical cancer who have not received prior systemic therapy for recurrent or Stage IVB disease.

- **First line**
- **ECOG 0-1**
- **≥1 measurable lesion disease per RECIST**

1:1

DLT evaluation period.

Enroll and treat 6 subjects (TV + carbo + pembro + BEV only) through Cycle 1

Safety committee review

Expand enrollment to ~30 subjects (TV + carbo + pembro ± BEV)

- First six enrolled patients must be eligible for bevacizumab.
- First six patients will be evaluated by an internal safety committee for dose limiting toxicities (DLT) after their first cycle (approximately 21 days).
  - DLTs <2 patients then enrollment is expanded for a total of approximately 30 patients.
  - DLTs ≥2 patients, enrollment will be paused, and a comprehensive review is conducted.
- At full enrollment, there will be approximately 30 patients (mix of BEV eligible and BEV ineligible).

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NCT03786081

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GOG-3028 - A Two Arm, Randomized, Non Comparative Blinded Phase 2 Trial of Balstilimab +/- Zalifrelimab in Second Line Cervical Cancer

RaPiDS

Patient Eligibility

- Cervical cancer that has relapsed after a platinum-based treatment (first line) regimen for advanced (recurrent, unresectable, or metastatic) disease
- Measurable disease on imaging based on RECIST version 1.1
- ECOG PS ≤1
- sufficient and adequate formalin-fixed paraffin embedded (FFPE)

Randomization 1:1

Treatment up to 24 months

Balstilimab (300 mg) every 3 weeks
Placebo every 6 weeks

Balstilimab (300 mg) every 3 weeks
Zalifrelimab (1 mg/kg) every 6 weeks

Primary Endpoint

- ORR according to RECIST 1.1

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PI: Dave O'Malley

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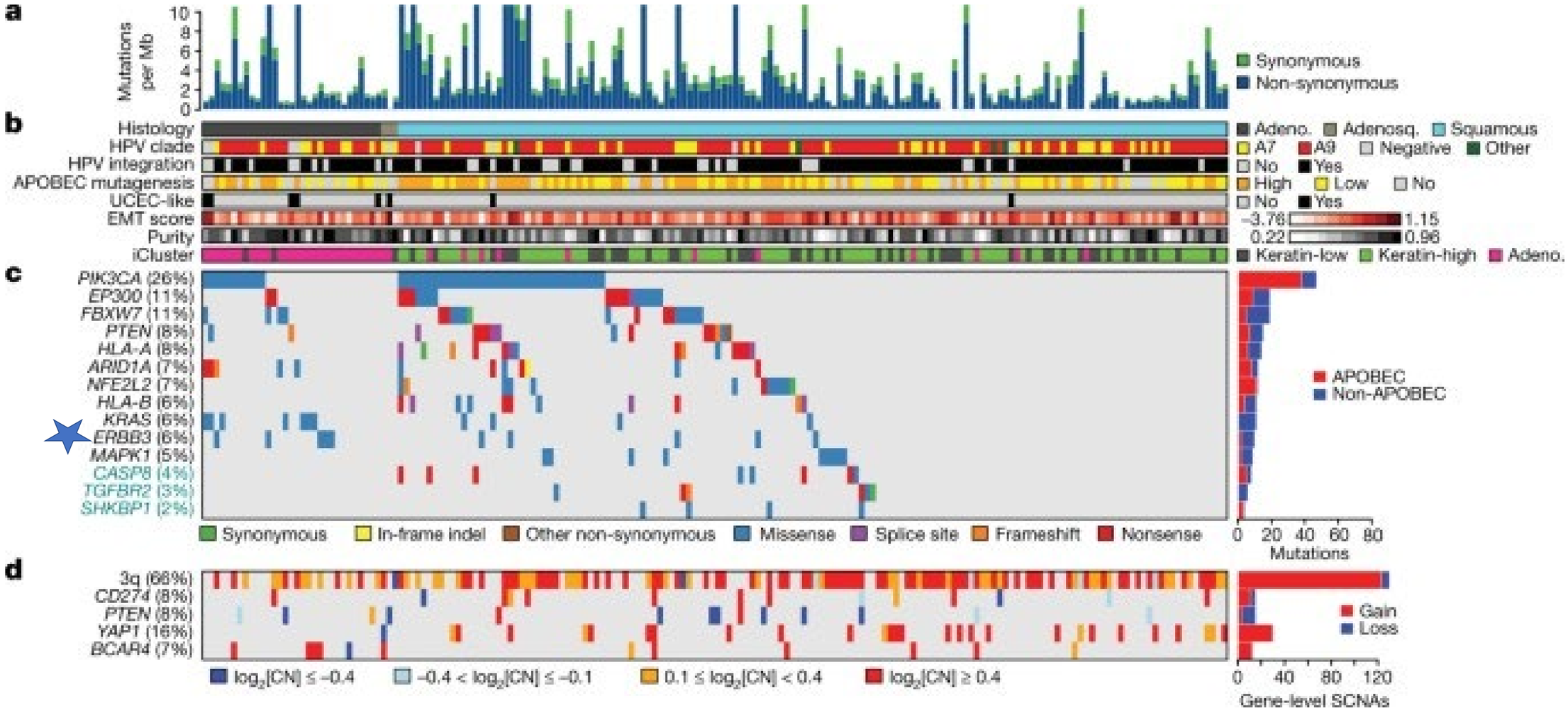
Alternative targets for Metastatic Disease



TCGA Cervix. Nature 2017

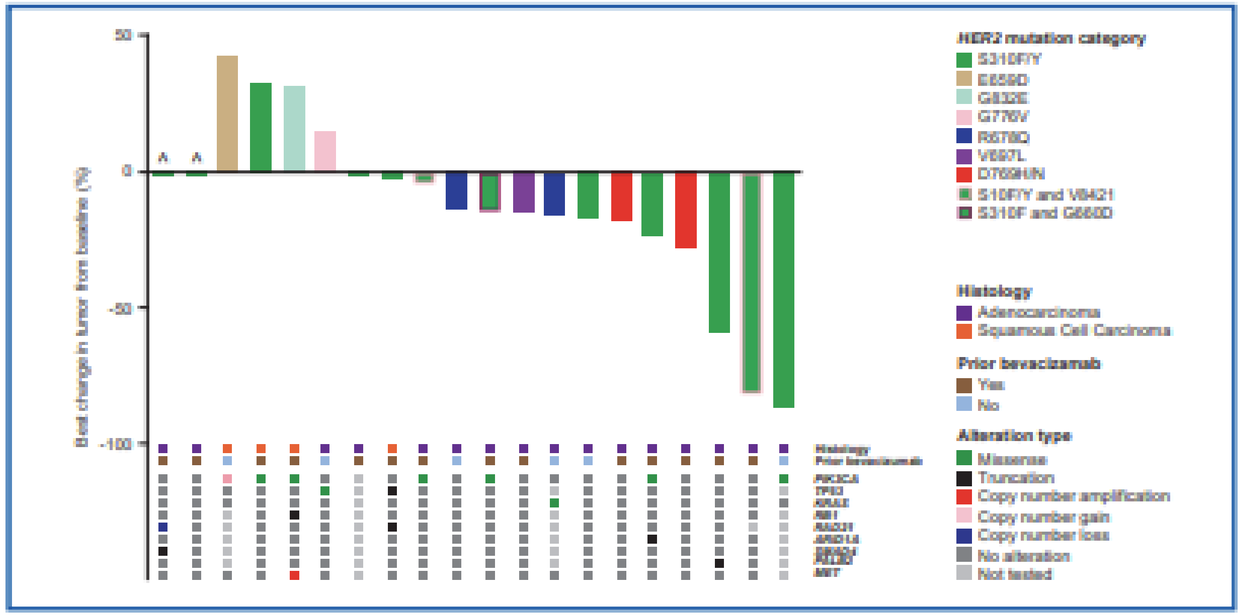
Neratinib in *HER2*-mutant, recurrent/metastatic cervical cancer: updated findings from the phase 2 SUMMIT basket trial

Claire F. Friedman,[1] Anishka D'Souza,[2] Anna Tinker,[3] Elena Corral,[4] Valentina Gambardella,[5] Jonathan Goldman,[6] Sherene Loi,[7] Michelle E. Melisko,[8] Ana Oaknin,[9] Iben Spanggaard,[10] Ari VanderWalde,[11] Aimee L. Frazier,[12] Bo Zhang,[12] Lisa D. Eli,[12] David B. Solit[1]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA; [3]BC Cancer-Vancouver, Vancouver, British Columbia, Canada; [4]Ramón y Cajal University Hospital, Madrid, Spain; [5]Hospital Clínico Universitario de Valenci, Valencia, Spain; [6]The David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [7]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [8]UCSF Early Phase Investigational Therapeutics, University of California San Francisco, San Francisco, CA, USA; [9]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [10]University Hospital, Rigshospitalet, Denmark; [11]West Cancer Center and Research Institute, Germantown, TN, USA; [12]Puma Biotechnology Inc, Los Angeles, CA, USA

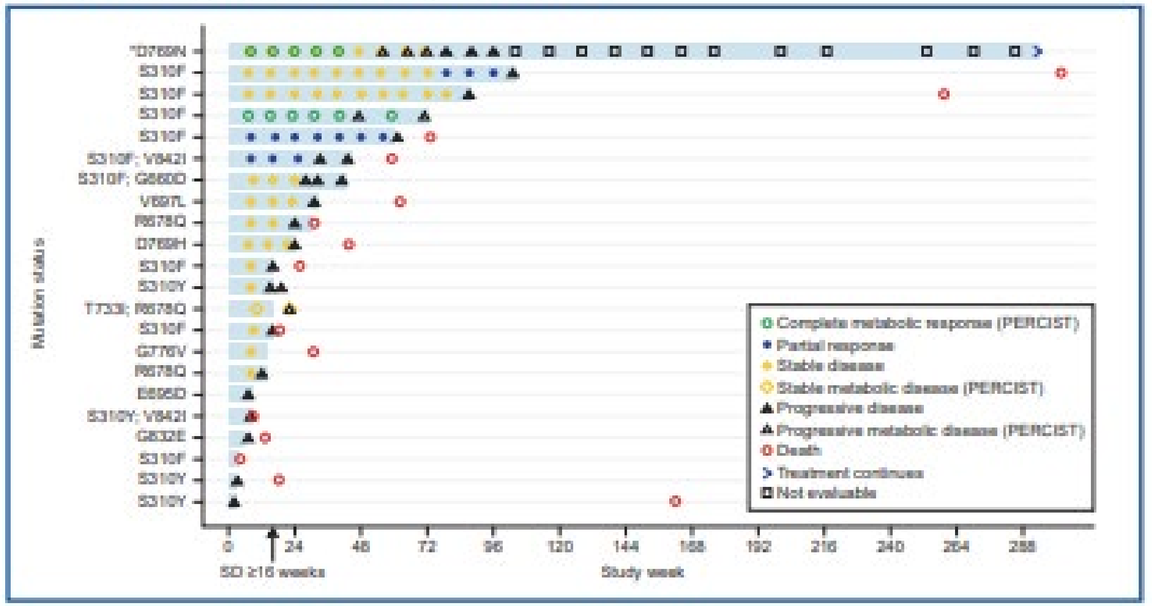
#559P

Figure 4. Individual best change in target lesion from baseline (RECIST-evaluable)



Cut-off date: July 15, 2022. RECIST-evaluable patients at baseline (n=30); 2 other patients not shown were PERCIST evaluable only. Co-mutation data based on local/ enrollment assays.

Figure 3. Individual response by duration of treatment



Cut-off date: July 15, 2022. *Note: Extreme responder had surgical resection at week 96 and so was not evaluable.

Adverse event, n (%)	All adverse events (N=22)		Treatment-related adverse events (N=22)	
	All grades	Grade ≥3*	All grades	Grade ≥3
Patients with at least 1 adverse event	22 (100)	10 (45.5)	19 (84.6)	5 (22.7)
Diarrhea	20 (90.9)	5 (22.7)†	18 (81.8)	5 (22.7)
Constipation	13 (54.5)	0 (0)	2 (9.1)	0 (0)
Nausea	13 (54.5)	0 (0)	9 (40.9)	0 (0)
Decreased appetite	9 (40.9)	0 (0)	4 (18.2)	0 (0)
Vomiting	9 (40.9)	0 (0)	5 (22.7)	0 (0)

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