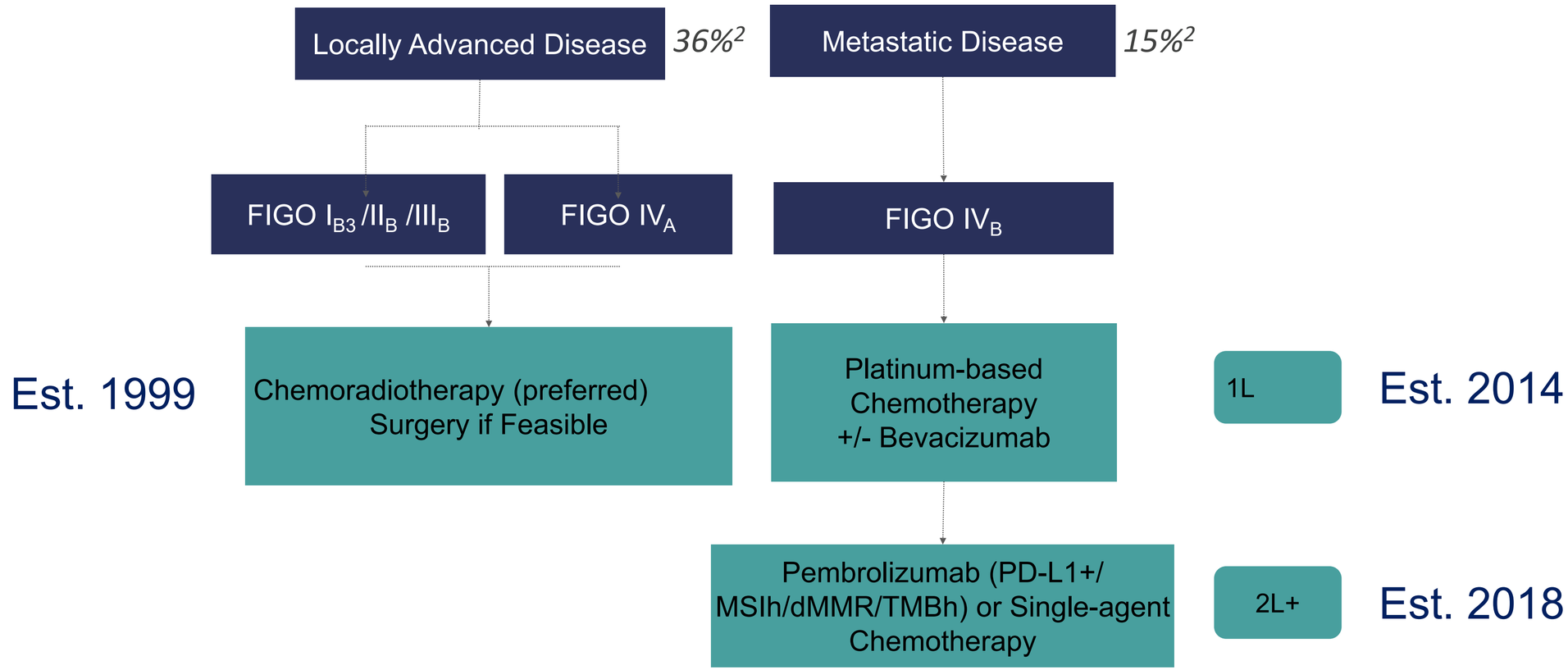
Sequencing Therapies for Cervical Cancer and Future Directions Beyond IO

Leslie M. Randall, MD, MAS
The Diane Harris Wright Professor and Director
Division of Gynecologic Oncology
Virginia Commonwealth University
Cervical Cancer Trials Advisor, GOG Partners

Thursday, September 9, 2021

GOG FOUNDATION®
Transforming the standard of care™

Cervical Cancer: Summary of Current High-Risk Disease Treatment[1]

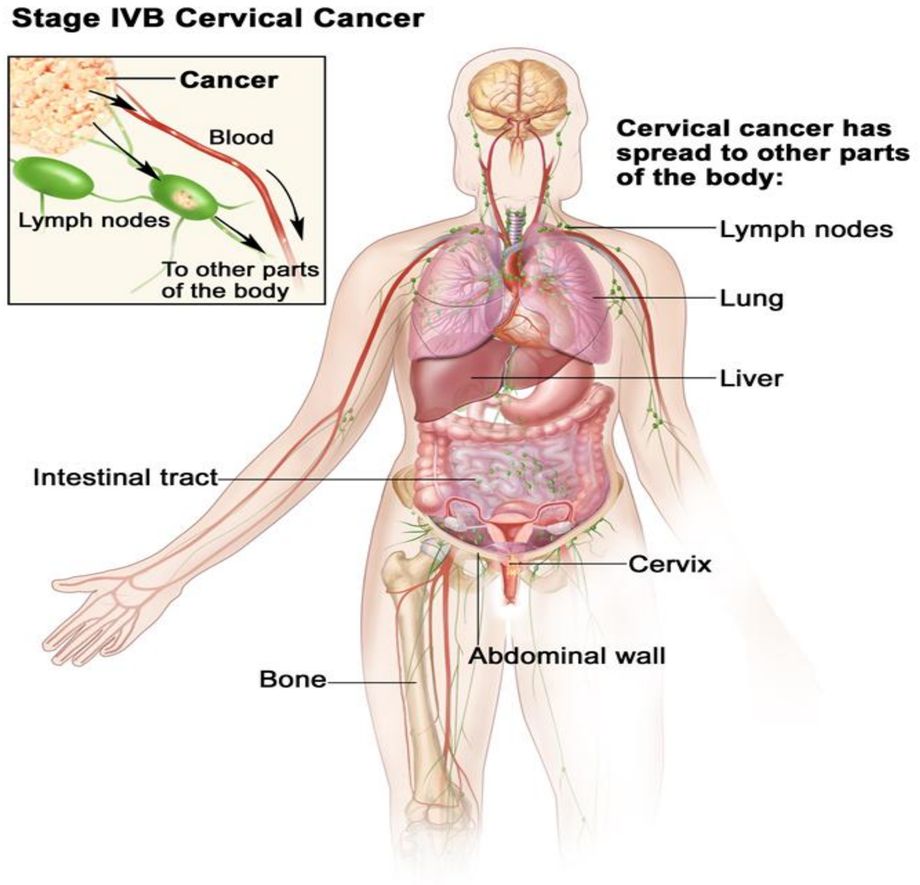


[1] NCCN Cervical Cancer Guidelines v2.2019
[2] SEER Cancer Stat Facts: Cervical Cancer. National Cancer Institute. Bethesda, MD

GOG FOUNDATION®

Locally Advanced, Metastatic and Recurrent Cervical Cancer:
A HIGH UNMET CLINICAL NEED!

- New drug strategy-find activity in later lines of treatment
- Special FDA new drug approval pathways
- Accelerated approval when no standard of care exists
- For cervical ca-after 1st chemotherapy (2L or greater)
- Requires confirmatory trial in earlier line of therapy



Winslow T. www.aacrfoundation.org/CancerTypes/Pages/PDQs/Cervical-Cancer-Treatment-PDQ.aspx. Accessed 15 January 2018.

GOG FOUNDATION

Single-agent anti PD-(L)1 activity, 2L+

Agent	N	ORR (95% CI)	ORR PD-L1+ (95% CI)	ORR PD-L1- (95% CI)
Pembrolizumab[1]	98	14.3% (8.0-22.8)	17.1% (9.7-27.0)	0% (0-21.8)
Cemiplimab[2]	304	16.4% (12.5-21.1)	18.3% (10.6-28.4)	11.4% (3.8-24.6)
Balstilimab[3]	140	15% (10.0-21.8)	20.0% (12.9-29.7)	7.9% (NR)
Socazolimab[4]	94	18.1% (10.9-27.4)	19.6% (10.2-32.4)	20.7% (8.0-39.7)

1. Chung et al. Virtual SGO 2021 2. Tewari KS et al. Virtual IGCS 2021 3. O'Malley DM, et al. Gynecol Oncol. 2021 Aug 24:S0090-8258(21)01316-0. 4. Jusheng et.al Virtual IGCS 2021.

Randomized phase III ICI trials in metastatic/recurrent setting

Frontline ICI trial	Agent (n)	Design	Stratification factors	Primary endpoint(s)
Keynote-826 (NCT03635567)	Pembro (600)	2 arm 1:1 GOG 240 control MD choice bev	• Stage • +/- Bev • PD-L1 status	• PFS BICR • OS
BEATcc (NCT03556839)	Atezo (404)	2 arm 1:1 GOG 240 control Mandatory bev	• Prior CRT • Histology • Chemotherapy Backbone: Cis v Carbo	• OS
FERMATA (NCT03912415)	BCD-100 (316)	2 arm 1:1 GOG 240 control MD choice bev	• Stage • +/- Bev • PDL1 status • Ethnicity	• OS

First Interim IDMC Review

KEYTRUDA® (pembrolizumab) Plus Platinum-Based Chemotherapy With or Without Bevacizumab Significantly Improved OS and PFS Compared to Platinum-Based Chemotherapy With or Without Bevacizumab Alone as First-Line Treatment, Regardless of PD-L1 Status

KENILWORTH, N.J., Jun 22, 2021--(BUSINESS WIRE)--Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced that the pivotal Phase 3 KEYNOTE-826 trial investigating KEYTRUDA, Merck's anti-PD-1 therapy, in combination with platinum-based chemotherapy (paclitaxel plus cisplatin or paclitaxel plus carboplatin) with or without bevacizumab, met its primary endpoints of overall survival (OS) and progression-free survival (PFS) for the first-line treatment of patients with persistent, recurrent or metastatic cervical cancer. Based on an interim analysis conducted by an independent Data Monitoring Committee, KEYTRUDA plus platinum-based chemotherapy with or without bevacizumab demonstrated statistically significant and clinically meaningful improvements in OS and PFS compared to the same platinum-based chemotherapy regimens with or without bevacizumab alone, regardless of PD-L1 status; KEYTRUDA is the first anti-PD-1/PD-L1 therapy to demonstrate this. The safety profile of KEYTRUDA in this trial was consistent with that observed in previously reported studies. Results will be presented at an upcoming medical meeting and will be submitted to regulatory authorities.

https://www.businesswire.com/news/home/20210622005214

BEATcc: Study Design

- Primary Stage IVB, persistent or recurrent carcinoma of the cervix
- Measurable disease by RECIST v1.1
- ECOG-PS: 0-1
- No previous systemic chemotherapy for advanced or recurrent disease
- Available tissue (archival or fresh)
- N=404 pts

R: 1:1

Control Arm

Cis- or carboplatin + paclitaxel + bevacizumab (GOG 240) until disease progression, unacceptable toxicity, death or withdrawal of consent

Experimental Arm

Cis- or carboplatin + paclitaxel + bevacizumab + atezolizumab until disease progression, unacceptable toxicity, death or withdrawal of consent

Primary Endpoint:
Overall survival (OS)

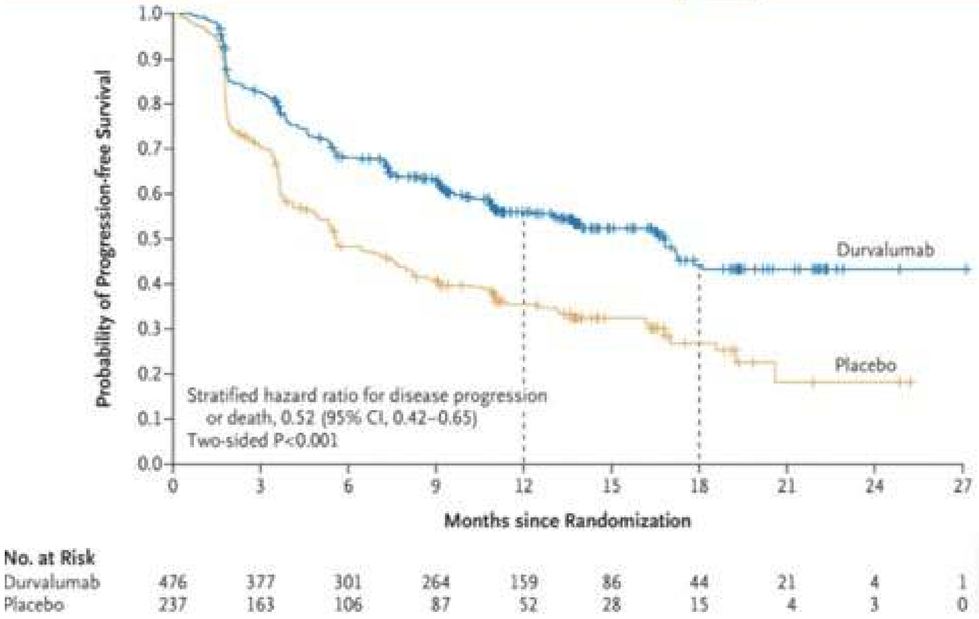
Secondary Endpoints:
- PFS
- ORR
- DOR
- Safety
- HR-QOL

Stratification Factors:
- Prior ChemoRT
- Histology: SCC vs Adeno (including AdenoSquamous)
- Chemotherapy Backbone: Cisplatin vs Carboplatin

ClinicalTrials.gov Identifier: NCT03556839

PACIFIC: Phase III Trial of Durvalumab Post-CRT Maintenance for Locally-advanced, Unresectable NSCLC

Study Population	R	Arms	Efficacy Endpoints
• NSCLC Stage 3 Unresectable • Prior ≥2 cycles of platinum-based Tx with concurrent radiation • N= 713	2:1	→ Durvalumab 10 mg/kg IV Q2W up to 12 months Vs → Placebo	**Primary:** PFS, OS **Secondary:** 12 mo PFS, 18 mo PFS, 24 mo OS, ORR, DOR, Time to death, Time to distant metastasis



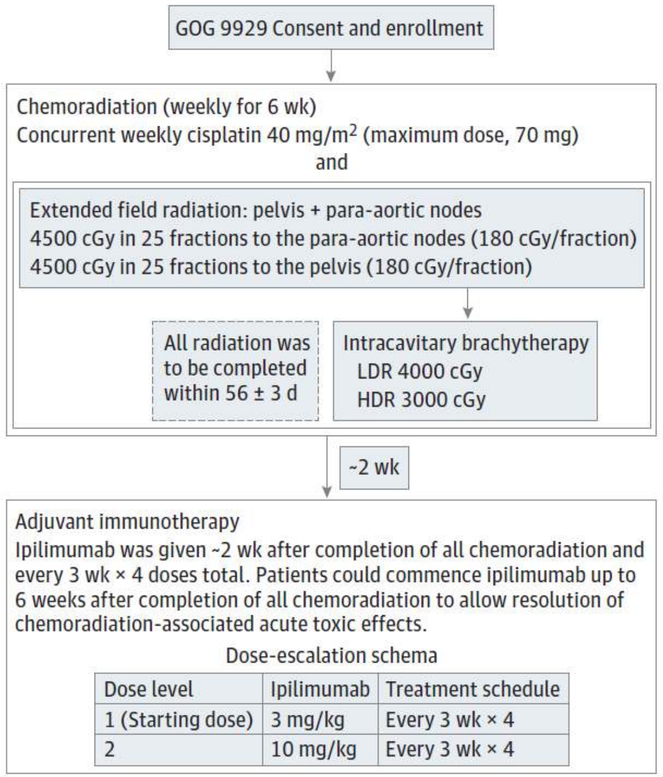
	Durvalumab	Placebo
No of Events/ No of Patients	214/476	157/237
PFS (95% CI)	16.8 (13-18.1)	5.6 (4.6-7.8)
OS (95% CI)	NR (34.7 -NR)	28.7 (22.9-NR)
12 mo PFS (95% CI)	55.9 (51-60.4)	35.3 (29-41.7)
18 mo PFS (95% CI)	44.2 (37.7-50.5)	27 (19.9-34.5)
24 mo OS (95% CI)	66.3 (61.7-70.4)	55.6 (48.9-61.8)

Antonia et al, NEJM 2017; Antonia et al, NEJM 2018

GOG FOUNDATION®

GOG 9929: CRT + ipilimumab (anti-CTLA4)

Figure 1. Study Schema



Dose level	Ipilimumab	Treatment schedule
1 (Starting dose)	3 mg/kg	Every 3 wk × 4
2	10 mg/kg	Every 3 wk × 4

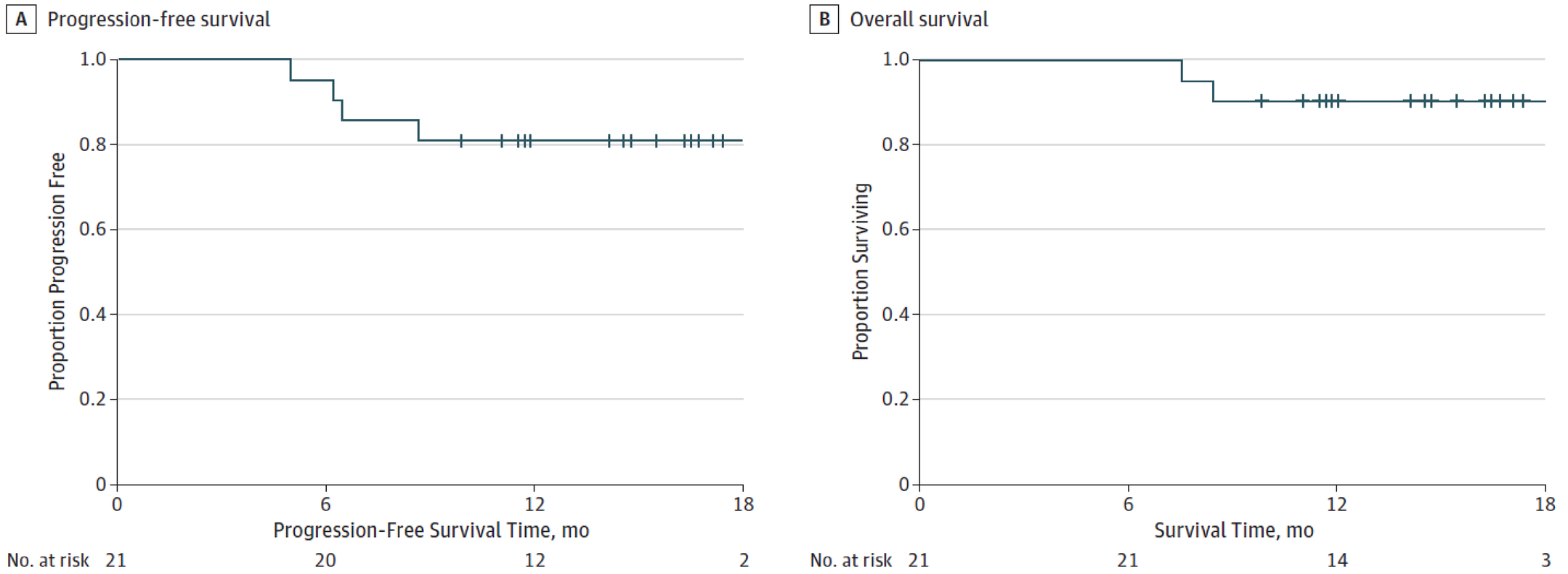
After the maximum tolerated dose was estimated, the expansion cohort started treatment. GOG indicates Gynecology Oncology Group; HDR, high dose rate brachytherapy; and LDR, low dose rate brachytherapy.

Mayadev JS, et al. JAMA Oncol. 2019 Nov 27;6(1):92–9.

GOG FOUNDATION

GOG 9929: PFS/OS

Figure 3. Progression-Free and Overall Survival in Patients Receiving 2 or More Cycles of Ipilimumab

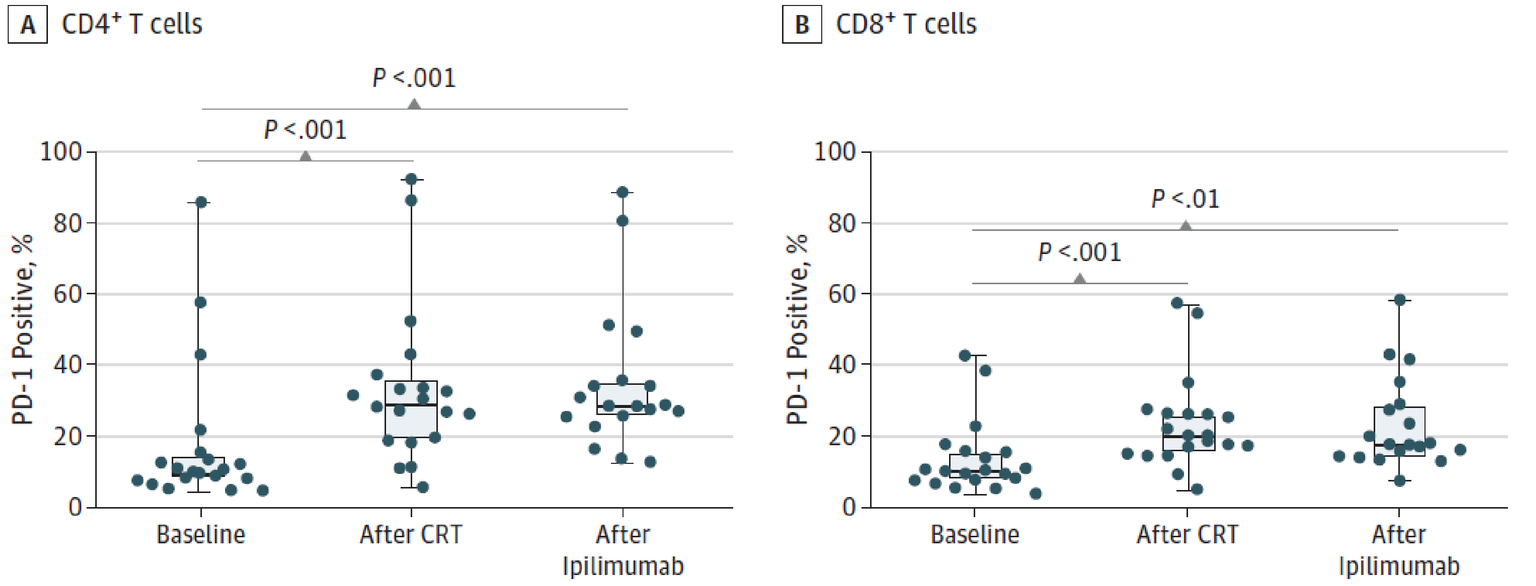


Mayadev JS, et al. JAMA Oncol. 2019 Nov 27;6(1):92–9.

GOG FOUNDATION

On-treatment T-cell activation anti-CTLA4

Figure 4. Expression of Programmed Cell Death 1 (PD-1) After Chemoradiotherapy (CRT) and Ipilimumab Administration



Peripheral blood lymphocytes were phenotyped by multicolor flow cytometry for T-cell activation markers. Both $CD4^+$ and $CD8^+$ T cells were associated with significantly increased expression of PD-1 compared with baseline, and the percentage of PD-1–positive cells was sustained throughout the 12 weeks of ipilimumab treatment. Boxplots show 25th to 75th percentiles, with median (horizontal line in the box) PD-1 expression in all patients (solid circles) with evaluable data. Whiskers indicate minimum and maximum values.

Mayadev JS, et al. JAMA Oncol. 2019 Nov 27;6(1):92–9.

GOG FOUNDATION®

Duska, et al, SGO 2020: 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

GOG FOUNDATION

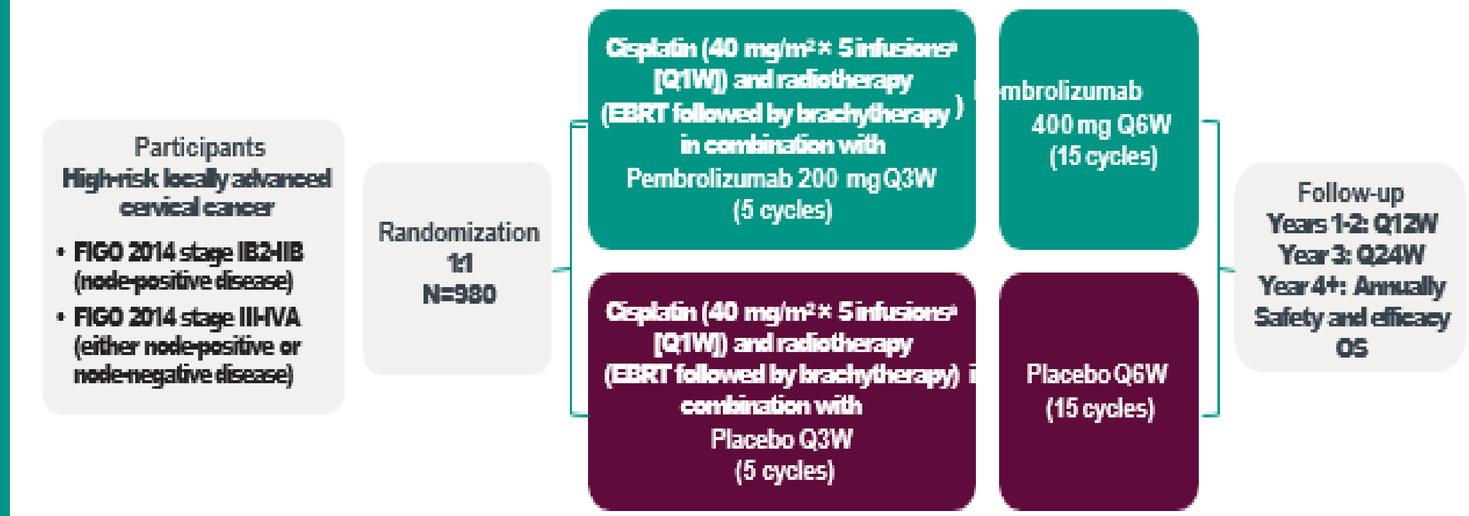
Randomized Phase III ICI Trials in the Locally-advanced Setting

Frontline ICI trial	Population	Agent (n)	Design	Primary endpoint(s)
CALLA (NCT03830866)	•FIGO 2009 IB2-IIB node+ •IIIA-IVA any nodal status •Measurable RECIST v1.1 •ECOG PS: 0-1	Durva (714)	2 arm 1:1 CRT control 24 months	•PFS
ENGOT cx11/GOG 3047/ KEYNOTE-A18 (NCT04221945)	•FIGO 2009 IB2-IIB node+ •IIIA-IVA any nodal status •Measurable RECIST v1.1 •ECOG PS: 0-1	Pembro (980)	2 arm 1:1 CRT control 24 months	•PFS •OS

CRT, chemoradiotherapy; durva, durvalumab; ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, International Federation of Gynecology and Obstetrics; ICI, immune checkpoint inhibitor; OS, overall survival; pembro, pembrolizumab; RECIST, Response Evaluation Criteria in Solid Tumours

GOG-3047/KEYNOTE-A18: Schema

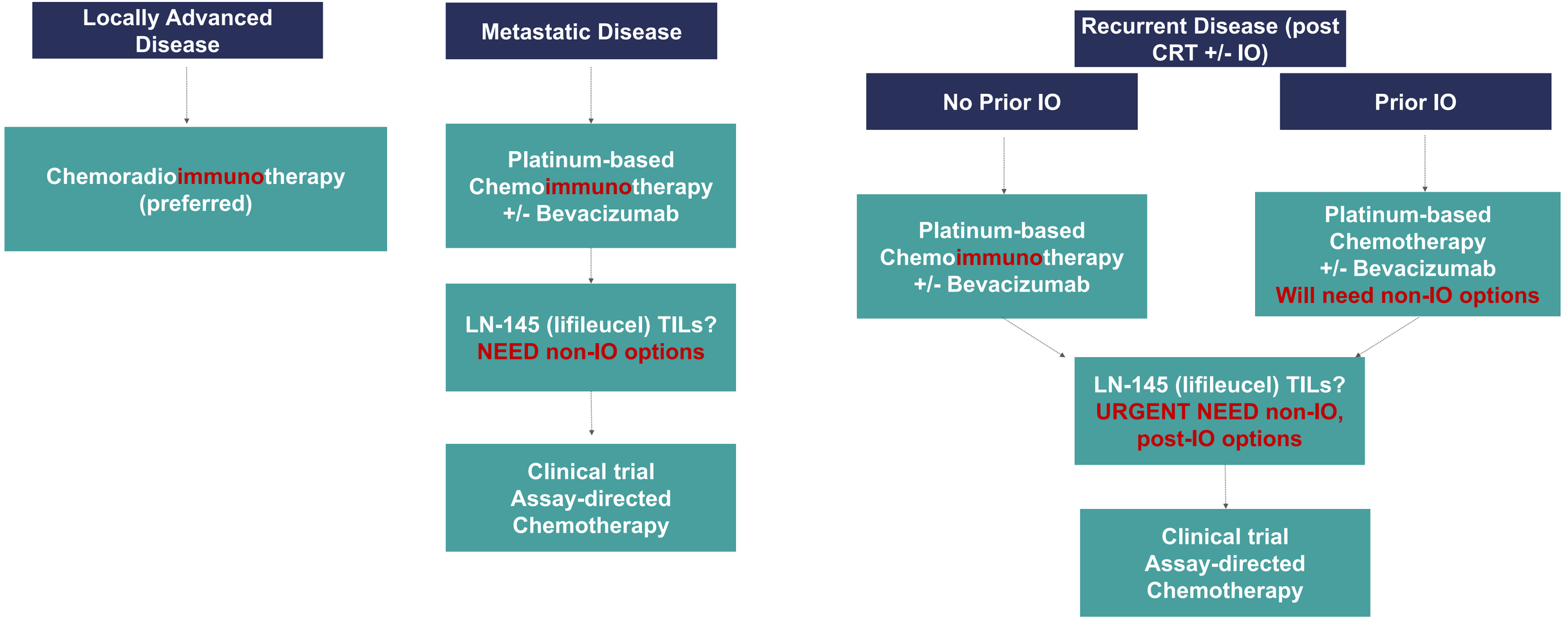
Figure 2. ENGOT-cx11/GOG 3047/KEYNOTE-A18 Study Design



EBRT, external beam radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; IMRT, intensity-modulated radiotherapy; OS, overall survival; QnW, every n weeks; VMAT, volumetric-modulated arc therapy. [a]An optional 6th dose may be administered according to local practice.

GOG FOUNDATION®

Cervical Cancer: Projection of Treatment



GOG FOUNDATION®

Checkpoint/IO After Checkpoint/IO?

- No proof of concept to date
- LN-145 (lifileucel) TILs
- Combinations likely key
- Best response and time to progression on or after initial checkpoint will likely matter
- As urgent as PARPi after PARPi in HGSOC

LN-145 Phase II Trial in Recurrent and/or Metastatic Cervical Carcinoma

A phase II, multicenter study to evaluate the efficacy and safety of adoptive cell therapy using autologous tumor-infiltrating lymphocytes (LN-145) in patients with recurrent, metastatic, or persistent cervical carcinoma

N = 47; Simon's two-stage design

Key Inclusion Criteria:

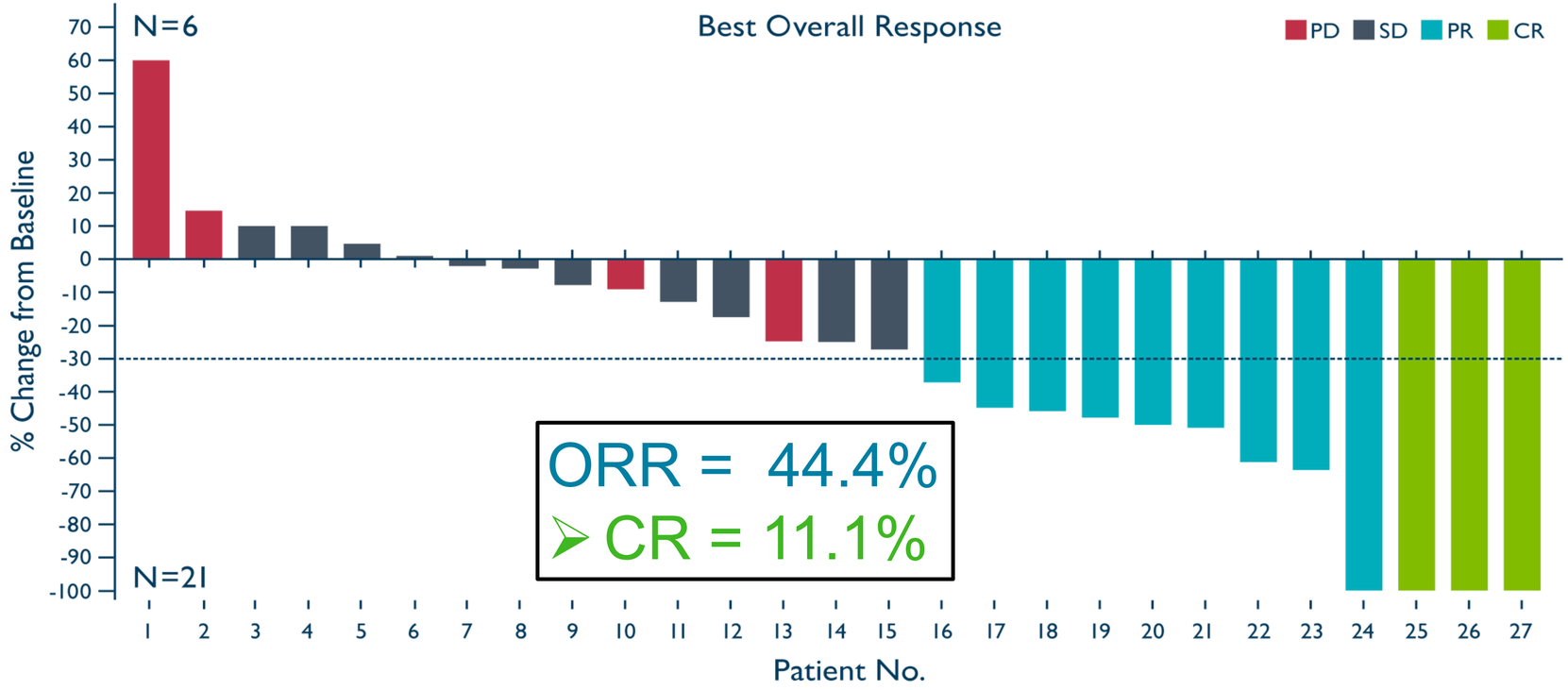
- **Measurable metastatic disease and ≥1 lesion resectable for TIL generation**
- **At least one prior systemic therapy, checkpoint-naïve**
- **Age ≥18**
- **ECOG PS 0-1**
- **Adequate hematologic, cardiac, pulmonary, hepatic, and renal function**

Endpoints:

- **Efficacy and safety**

National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT03108495. Accessed March 13, 2019.

Autologous TILs (LN-145) 2L+
FDA Breakthrough Designation



- 78% of patients had a reduction in tumor burden
- Median follow up is 7.4 months
- Mean number of TIL cells infused: 28 x 10^9
- Median number of IL-2 doses administered was 6.0

NCT03108495; Jazaeri AA et al. *J Clin Onc*. 2019;37(15)2538.

GOG FOUNDATION

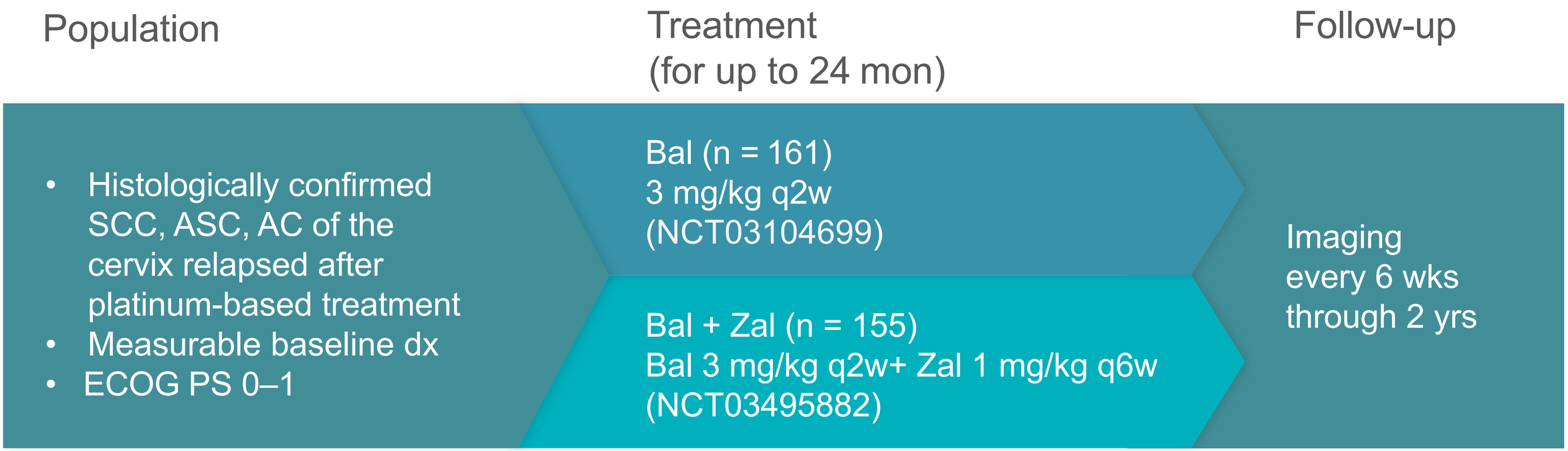
I/O combinations in the pipeline, 2L+

	N	ORR (%) (95% CI)	ORR PD-L1+ (95% CI)	ORR PD-L1- (95% CI)
Nivolumab3 + ipilimumab1[1]	26	23% (9-43.6)	40% (12.2-73.8)	9.1% (0.2-41.3)
Nivolumab1 + ipilimumab3[1]	22	36% (17.2-59.3)	16.7% (2.1-48.4)	57.1% (18.4-90.1)
Balstilimab + Zalifrelimab[2]	143	22% (16-29)	27% (19-37)	11% (4-25)
AK-104 (PD1i/CTLA4i bispecific) [3]	40	--	--	--
Bintrafusp alfa (PDL1i/TGFbi bispecific)[4]	39	28.2% (15-44.9)		
Tiragolumab (+atezolizumab)[5]	160	--	--	--
Socazolimab[6]	94	18.1% (10.9-27.4)	19.6% (10.2-32.4)	20.7% (8.0-39.7)

1. Oaknin ESMO 2019 2. O'Malley DM et al. Virtual ESMO 2020 3. https://clinicaltrials.gov/ct2/show/NCT04380805 4. Strauss et al. JCO 39, 2021 abstr 5509. 5. https://clinicaltrials.gov/ct2/show/NCT04300647. 6. Jusheng et.al Virtual IGCS 2021.

Balstilimab +/- Zalifrelimab

Two Parallel, Single-arm Trials Testing Balstilimab Alone and with Zalifrelimab in Recurrent/Metastatic Cervical Cancer



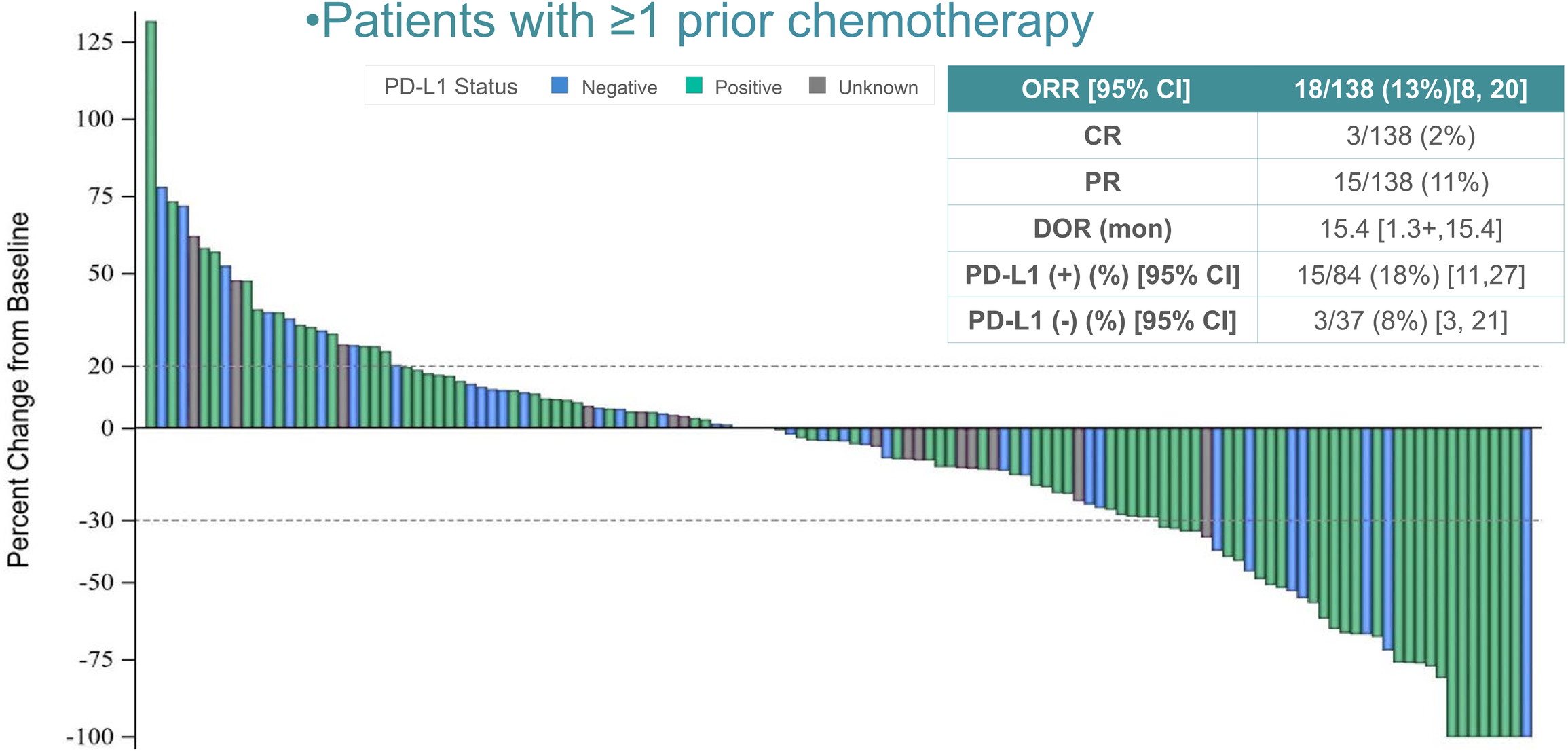
- Primary endpoint: Independent Review Committee (IRC) ORR by RECIST 1.1
- Secondary endpoints: OS, PFS, DOR

O'Malley et al, ESMO 2020

GOG FOUNDATION®

Tumor Response with Balstilimab Monotherapy

- Patients with ≥1 prior chemotherapy

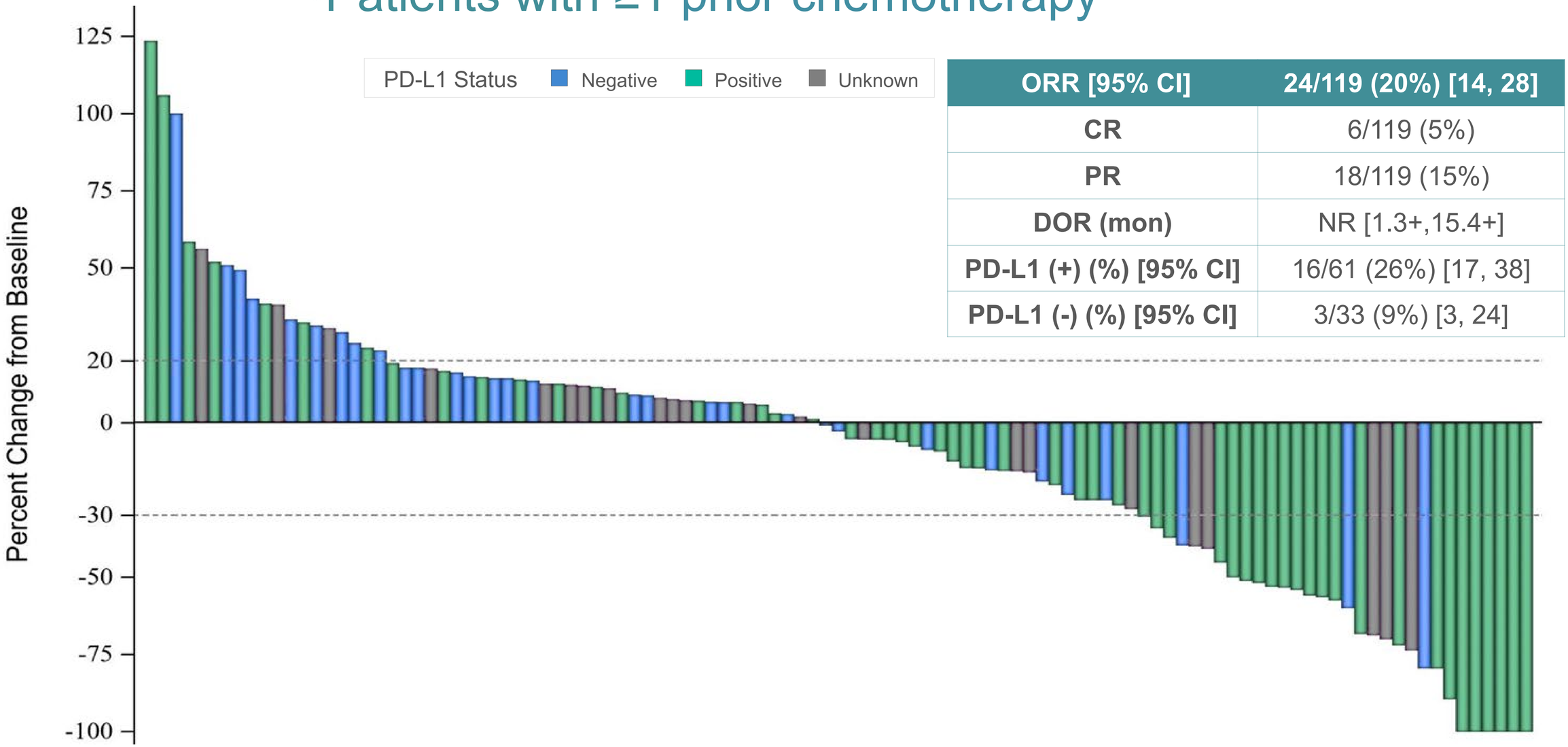


ORR [95% CI]	18/138 (13%)[8, 20]
CR	3/138 (2%)
PR	15/138 (11%)
DOR (mon)	15.4 [1.3+,15.4]
PD-L1 (+) (%) [95% CI]	15/84 (18%) [11,27]
PD-L1 (-) (%) [95% CI]	3/37 (8%) [3, 21]

GOG FOUNDATION

Tumor Response with Balstilimab plus Zalifrelimab

- Patients with ≥1 prior chemotherapy



ORR [95% CI]	24/119 (20%) [14, 28]
CR	6/119 (5%)
PR	18/119 (15%)
DOR (mon)	NR [1.3+,15.4+]
PD-L1 (+) (%) [95% CI]	16/61 (26%) [17, 38]
PD-L1 (-) (%) [95% CI]	3/33 (9%) [3, 24]

O'Malley et al, ESMO 2020

GOG FOUNDATION

FDA Grants Balstilimab/Zalifrelimab Dual Immunotherapy Fast Track Designation in Cervical Cancer

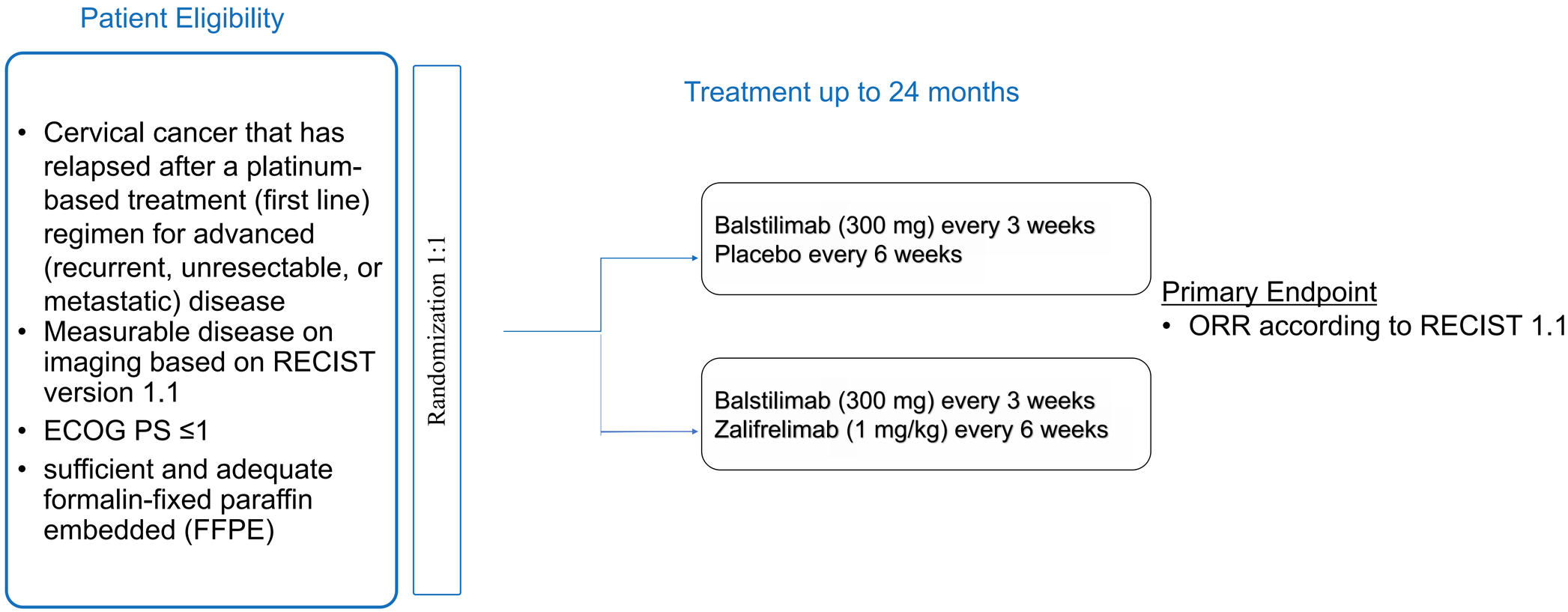
March 12, 2020

Jason M. Broderick

Relevant Topics

The FDA has granted a Fast Track designation to the combination of the PD-1 inhibitor balstilimab and the CTLA-inhibitor zalifrelimab for the treatment of patients with relapsed or refractory metastatic cervical cancer.

GOG-3028 - A Two Arm, Randomized, Non Comparative Blinded Phase 2 Trial of AGEN2034 (anti PD-1) as a Monotherapy or in Combination Therapy with AGEN1884 (anti-CTLA4) or with Placebo in Women with Recurrent Cervical Cancer (Second Line) – RaPiDS



GOG FOUNDATION®

6 Completely Enrolled Studies in Cervical Cancer as of Feb 2021

1. Phase 3: CALLA (Durvalumab with chemotherapy and radiation)*
2. Phase 3: KN-826 (Pembrolizumab added to chemotherapy +/- bevacizumab in 1-L)*
3. Phase 3: EMPOWER- CERVICAL 1 (Cemiplimab vs chemotherapy in 2-L)*
4. Phase 2: innovaTV 204 (Tisotumab vedotin in 2-L)
5. Phase 2: (LN-145 in 2-L)*
6. Phase 2: SKYSCRAPER-04 (Tiragolumab plus atezolizumab in 2-L)*

* Results Pending

Slide courtesy of Dr. Brad Monk

GOG FOUNDATION

6 Completely Enrolled Studies in Cervical Cancer as of April 2021

1. Phase 3: CALLA (Durvalumab with chemotherapy and radiation)*
2. Phase 3: KN-826 (Pembrolizumab added to chemotherapy +/- bevacizumab in 1-L)*
3. Phase 3: EMPOWER- CERVICAL 1 (Cemiplimab vs chemotherapy in 2-L)**
4. Phase 2: innovaTV 204 (Tisotumab vedotin in 2-L)***
5. Phase 2: (LN-145 in 2-L)*
6. Phase 2: SKYSCRAPER-04 (Tiragolumab plus atezolizumab in 2-L)*

*Results Pending
**Results announced
***BLA pending

GOG FOUNDATION®

6 Completely Enrolled Studies in Cervical Cancer as of September 2021

1. Phase 3: CALLA (Durvalumab with chemotherapy and radiation)*
2. Phase 3: KN-826 (Pembrolizumab added to chemotherapy +/- bevacizumab in 1-L)**
3. Phase 3: EMPOWER- CERVICAL 1 (Cemiplimab vs chemotherapy in 2-L)**
4. Phase 2: innovaTV 204 (Tisotumab vedotin in 2-L)***
5. Phase 2: (LN-145 in 2-L)*
6. Phase 2: SKYSCRAPER-04 (Tiragolumab plus atezolizumab in 2-L)*

**Results announced

GOG FOUNDATION®

Thank You!!

lrandall@gog.org

GOG FOUNDATION®
Transforming the standard of care™