Oncology in the Real World: A Daylong Multitumor Educational Symposium in Partnership with the American Oncology Network

A CME/MOC- and NCPD-Accredited Event

Saturday, October 14, 2023
9:30 AM – 5:00 PM PT

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Moderators

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

CO-MODERATOR
Stephen "Fred" Divers, MD
Chief Medical Officer
American Oncology Network
Hot Springs, Arkansas

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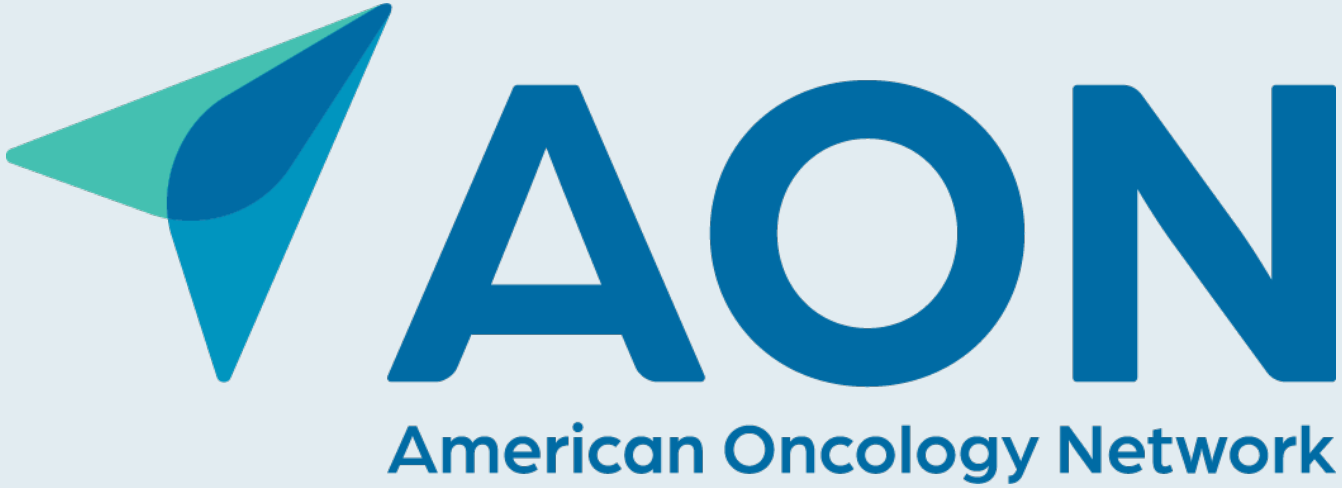

Welcome AON Members!

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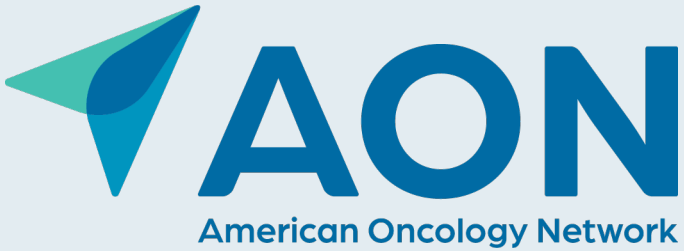
+



MiBA (Meaningful Insights Biotech Analytics) is not your average data company.

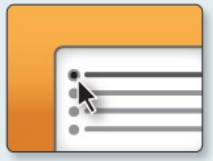
MiBA is a healthcare AI technology company launched with a mission to close the feedback loop between physicians, patients, and industry partners. The CME program is sponsored with MiBA data insights, from AON practices.

MiBA has a clear vision to improve data quality by unlocking the power of data to fuel decisions, education and improve patient care.

Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the premeeting survey.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

Complete Your Evaluation: Tap the CME/NCPD Evaluation button to complete your evaluation electronically to receive credit for your participation.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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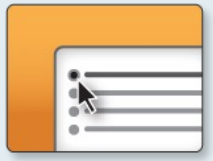
Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.



Answer Survey Questions: Complete the premeeting survey at the beginning of each module.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME/NCPD Credit: CME and NCPD credit links will be provided in the chat room at the conclusion of the program. MOC and ONCC credit information will be emailed to attendees within the next 2-3 business days.

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Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Breast Cancer

A 3-Part CME Satellite Symposium Series Held in Conjunction with the 2023 San Antonio Breast Cancer Symposium®

ER-Positive Metastatic Breast Cancer

Tuesday, December 5, 2023

7:15 PM – 9:15 PM CT

Localized HER2-Negative Breast Cancer

Wednesday, December 6, 2023

7:15 PM – 9:15 PM CT

HER2-Low Breast Cancer

Thursday, December 7, 2023

7:15 PM – 8:45 PM CT

Moderator

Neil Love, MD

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Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Hematologic Cancers

A 4-Part CME Friday Satellite Symposium Series Preceding the 65th ASH Annual Meeting and Exposition

Friday, December 8, 2023

Follicular, Mantle Cell and Hodgkin Lymphoma
7:30 AM – 10:00 AM PT

Diffuse Large B-Cell Lymphoma
11:30 AM – 1:30 PM PT

Chronic Lymphocytic Leukemia
3:15 PM – 5:15 PM PT

Multiple Myeloma
7:00 PM – 9:00 PM PT

Moderator
Neil Love, MD

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JOIN US IN 2024 FOR THE RETURN OF

The Annual
National General Medical Oncology Summit

A Multitumor CME/MOC- and NCPD-Accredited Educational Conference Developed in Partnership with Florida Cancer Specialists and Research Institute

MARCH 22-24, 2024

JW Marriott Miami Turnberry

To Learn More or to Register, Visit
www.ResearchToPractice.com/Meetings/GMO2024

Oncology in the Real World: A Daylong Multitumor Educational Symposium in Partnership with the American Oncology Network

A CME/MOC- and NCPD-Accredited Event

Saturday, October 14, 2023
9:30 AM – 5:00 PM PT

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Overview

Module 1: 9:30 AM – 10:30 AM — Lymphoma

Module 2: 10:30 AM – 11:30 AM — Urothelial Bladder Cancer and Renal Cell Carcinoma

Break: 11:30 AM – 11:50 AM

Module 3: 11:50 AM – 12:50 AM — Hepatobiliary and Pancreatic Cancers

Lunch: 12:50 AM – 1:30 PM

Module 4: 1:30 PM – 2:30 PM — Gynecologic Cancers

Module 5: 2:30 PM – 3:30 PM — Multiple Myeloma

Break: 3:30 PM – 3:50 PM

Module 6: 3:50 PM – 4:50 PM — HER2-Positive and Triple-Negative Breast Cancer

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Questions and Comments: Front-line treatment without chemotherapy

Dr Michael Wang (Houston, Texas)

Wednesday, July 19, 2023

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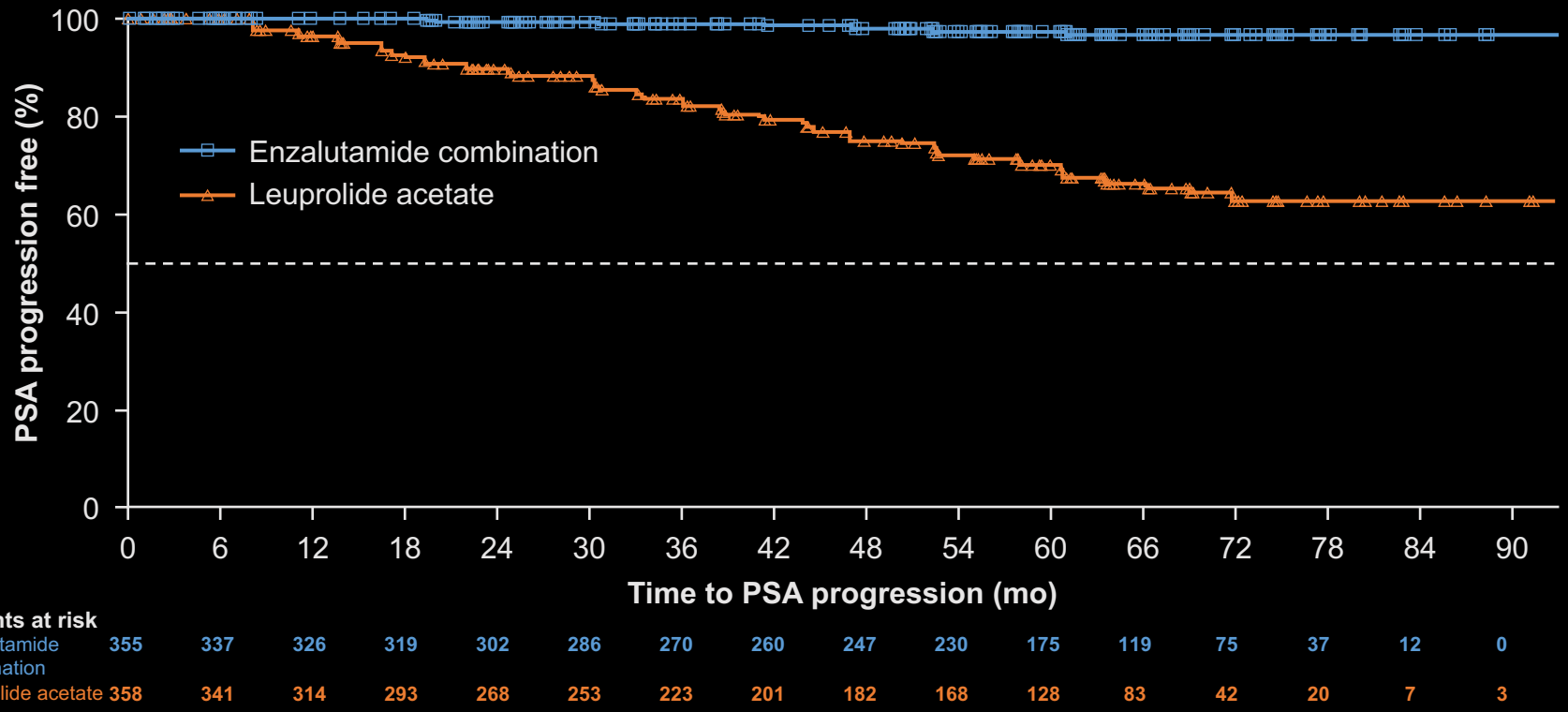
AUA 2023
CHICAGO ✶ APR 28-MAY 1

Key secondary endpoint — Time to PSA progression for enzalutamide combination vs. leuprolide acetate



Patients at risk

Enzalutamide combination	355	337	326	319	302	286	270	260	247	230	175	119	75	37	12	0
Leuprolide acetate	358	341	314	293	268	253	223	201	182	168	128	83	42	20	7	3

	Enzalutamide combination (n = 355)	Leuprolide acetate (n = 358)
Events, n (%)	8 (2)	93 (26)
Median time to PSA progression (95% CI), mo	NR (NR)	NR (NR)

HR (95% CI): 0.07 (0.03–0.14); *P*<0.0001[a]

Data cutoff: January 31, 2023. Symbols indicate censored data. [a]The HR was based on a Cox regression model with treatment as the only covariate stratified by screening PSA, PSADT, and prior hormonal therapy as reported in the IWRS; relative to leuprolide acetate <1 favoring enzalutamide combination; the two-sided *P*-value is based on a stratified log-rank test.

Shore N et al. AUA 2023;Abstract LBA02-09.

Neil Love, MD

Paul G Richardson, MD

8-30-2023

Agenda

Module 1 — Lymphoma: *Drs Flowers and LaCasce*

Module 2 — Urothelial Bladder Cancer and Renal Cell Carcinoma:
Drs Hutson and Sonpavde

Module 3 — Hepatobiliary and Pancreatic Cancers:
Prof Borad and Dr El-Khoueiry

Module 4 — Gynecologic Cancers: *Drs Monk and Moore*

Module 5 — Multiple Myeloma: *Drs Krishnan and Orlowski*

Module 6 — HER2-Positive and Triple-Negative Breast Cancer:
Drs Hurvitz and McArthur

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Lymphoma Faculty

Christopher R Flowers, MD, MS
Chair ad Interim, Division of Cancer Medicine
Professor, Department of Lymphoma/Myeloma
The University of Texas
MD Anderson Cancer Center
Houston, Texas

Ann S LaCasce, MD, MMSc
Director, Dana-Farber/Mass General Brigham
Fellowship in Hematology/Oncology
Associate Professor of Medicine
Harvard Medical School
Lymphoma Program
Dana-Farber Cancer Institute
Boston, Massachusetts

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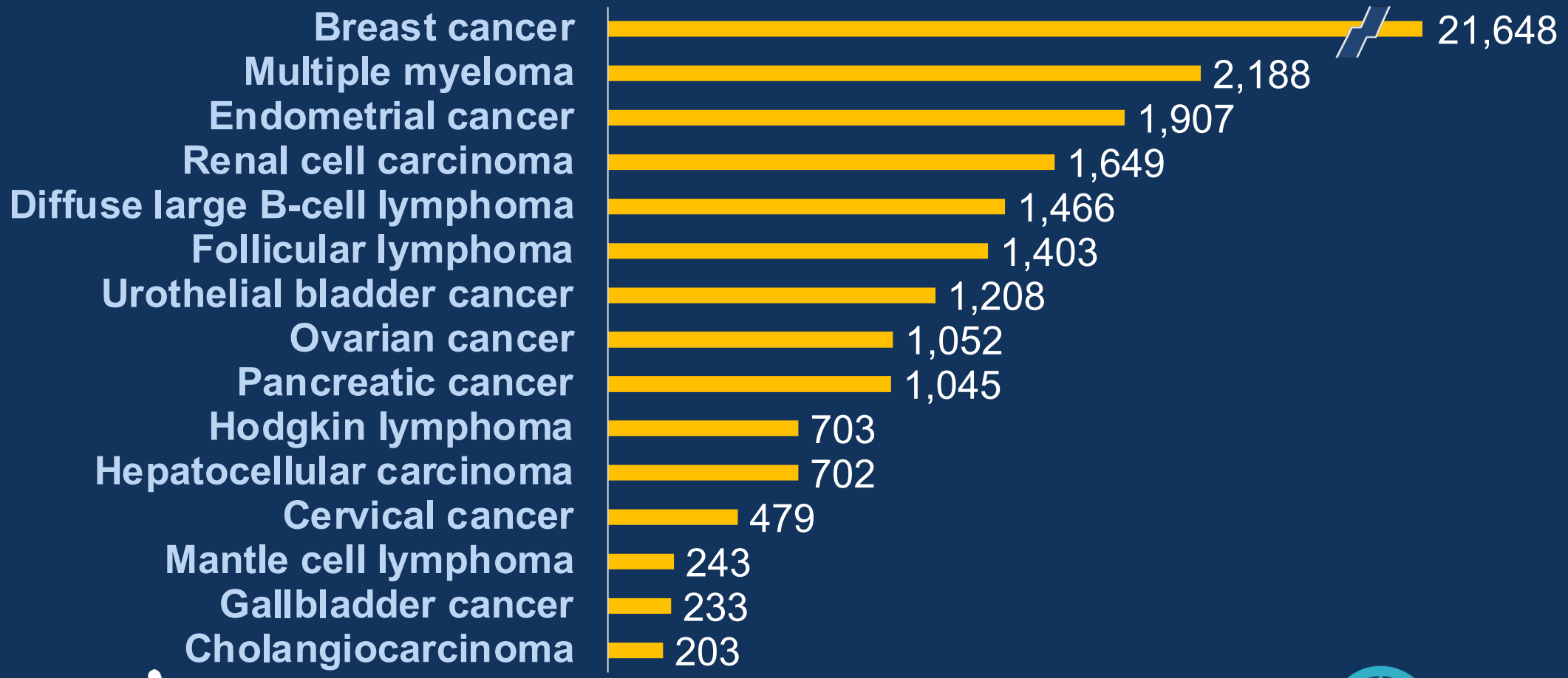
Snapshot of AON Practice
Patients Seen in the Last 12 months



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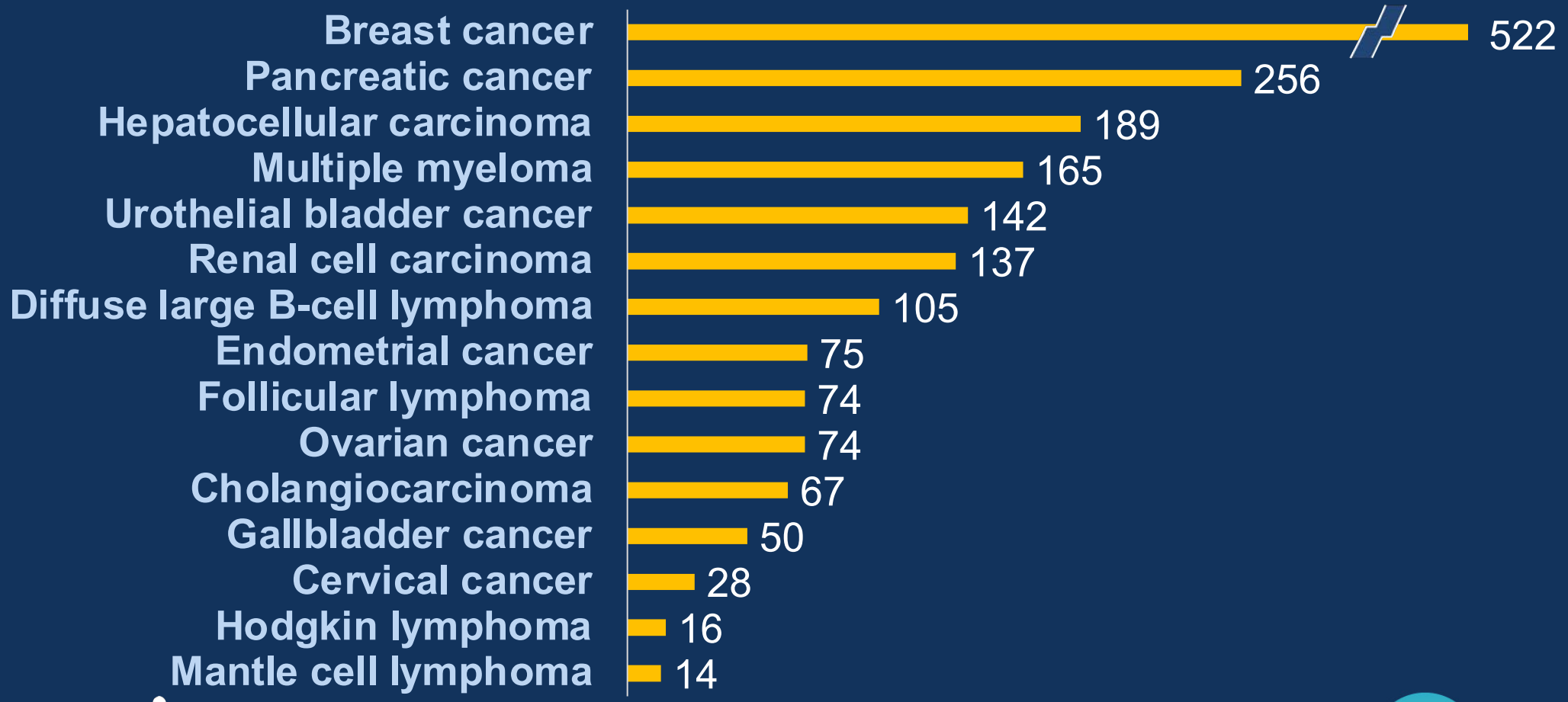
Snapshot of AON Practice
Patient Deaths in the Last 12 months



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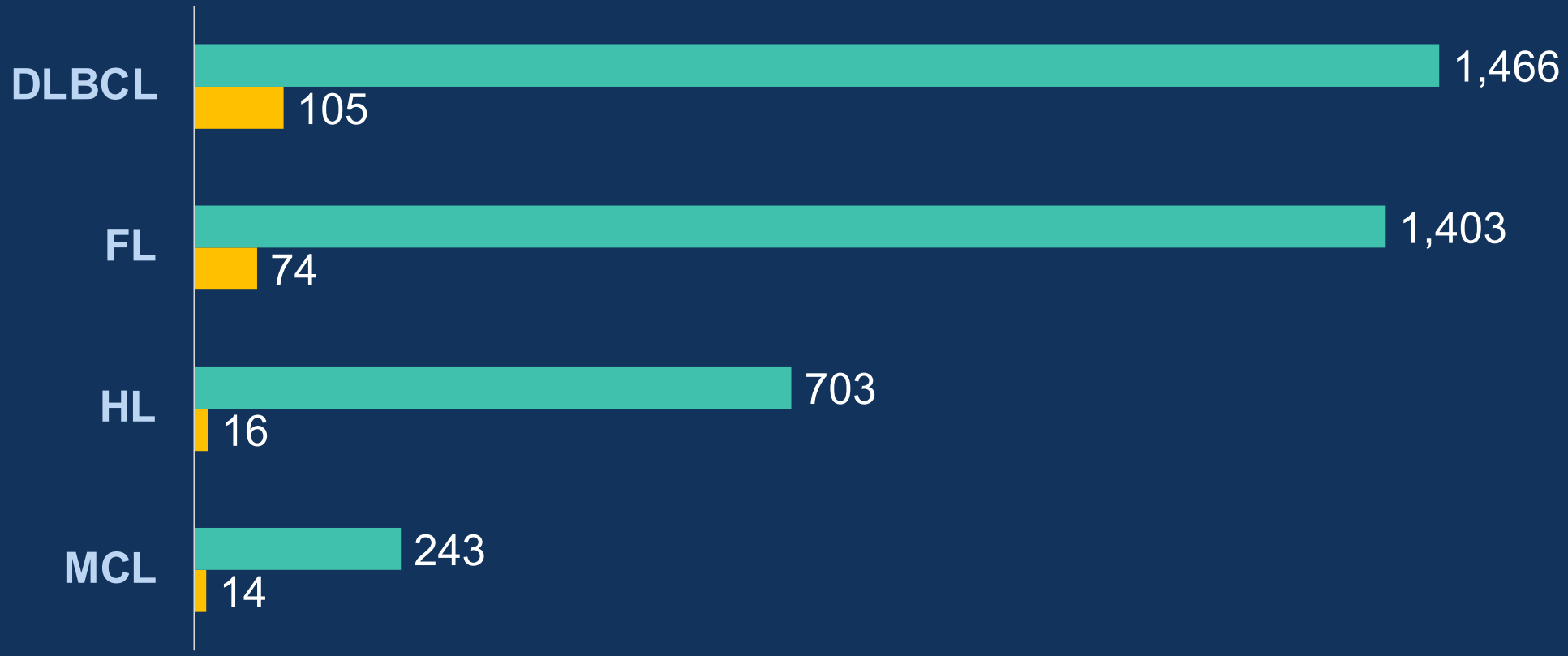
Snapshot of AON Practice
Module 1: Lymphoma



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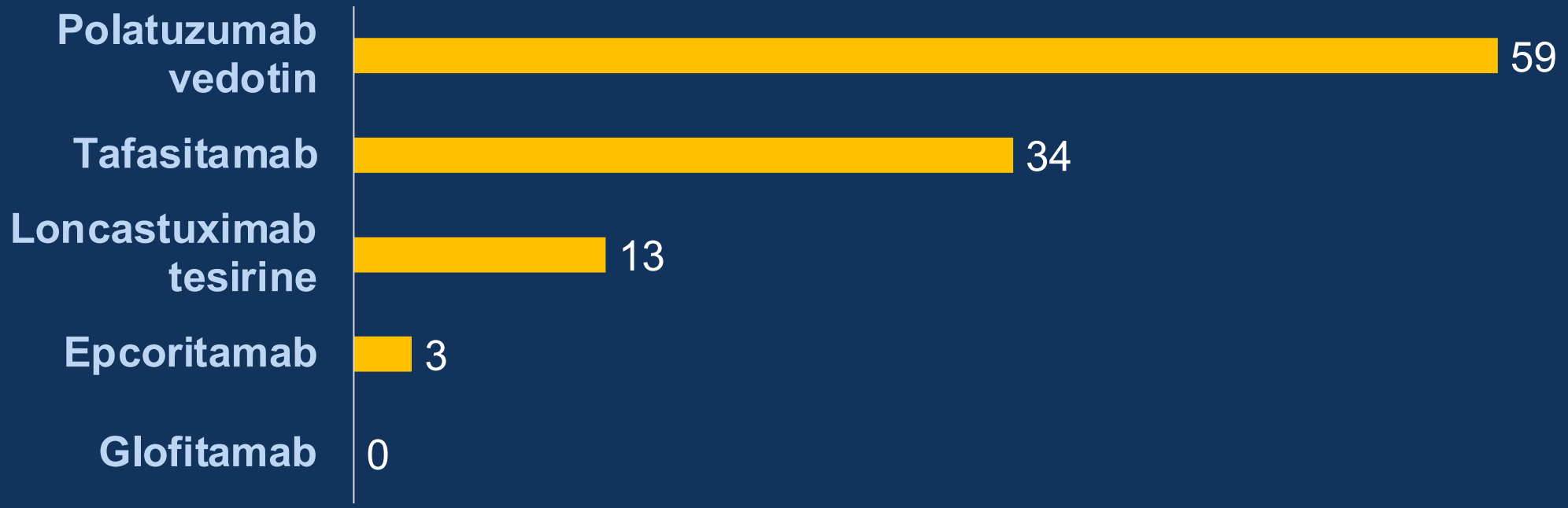
Snapshot of AON Practice
Diffuse Large B-Cell Lymphoma

Select Treatments Received



Clinical Trial Participation

Number of clinical trials	16
Total patients enrolled	46

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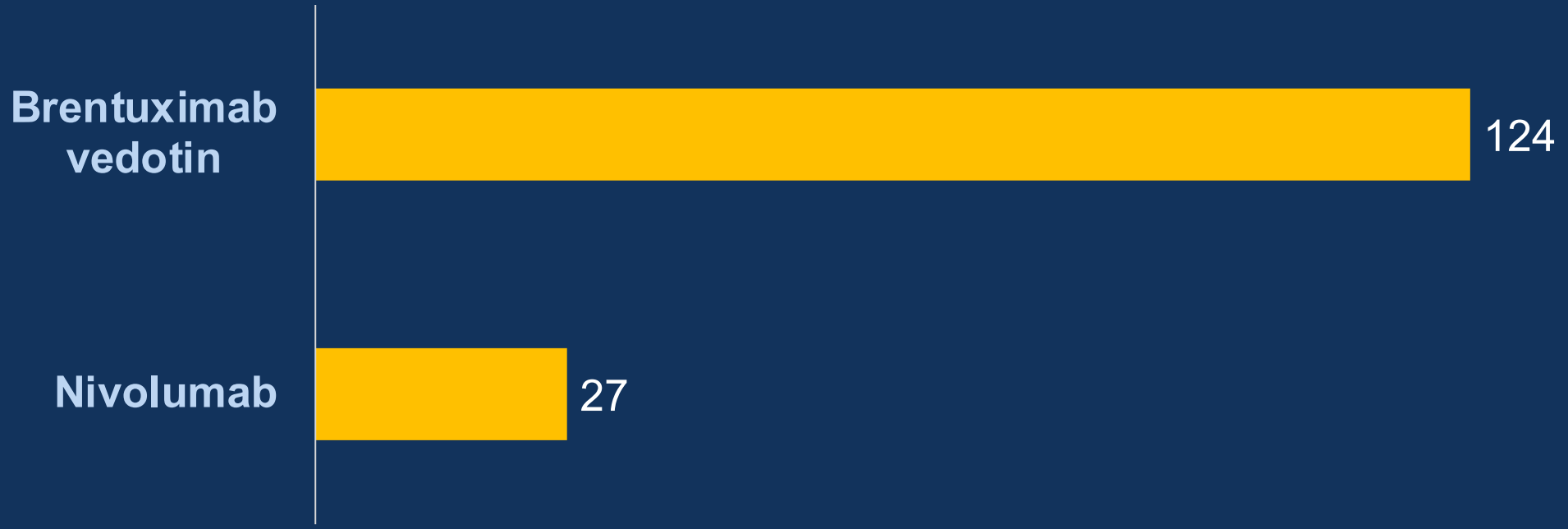
Snapshot of AON Practice
Hodgkin Lymphoma

Select Treatments Received



Clinical Trial Participation

Number of clinical trials	7
Total patients enrolled	11

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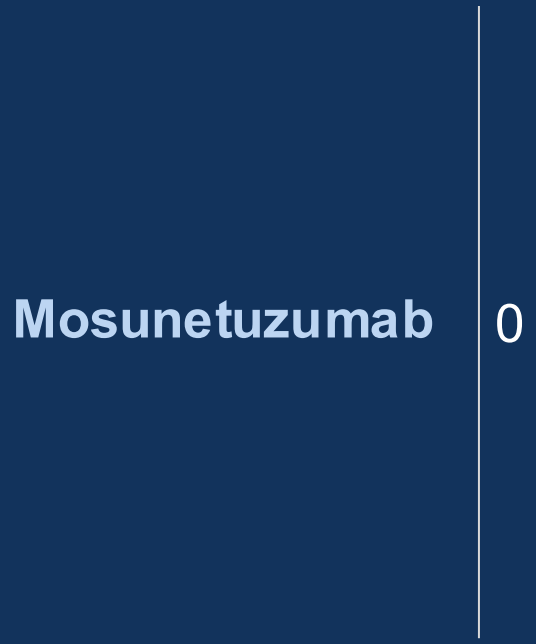
Snapshot of AON Practice
Follicular Lymphoma

Select Treatments Received



Clinical Trial Participation

Number of clinical trials	15
Total patients enrolled	25

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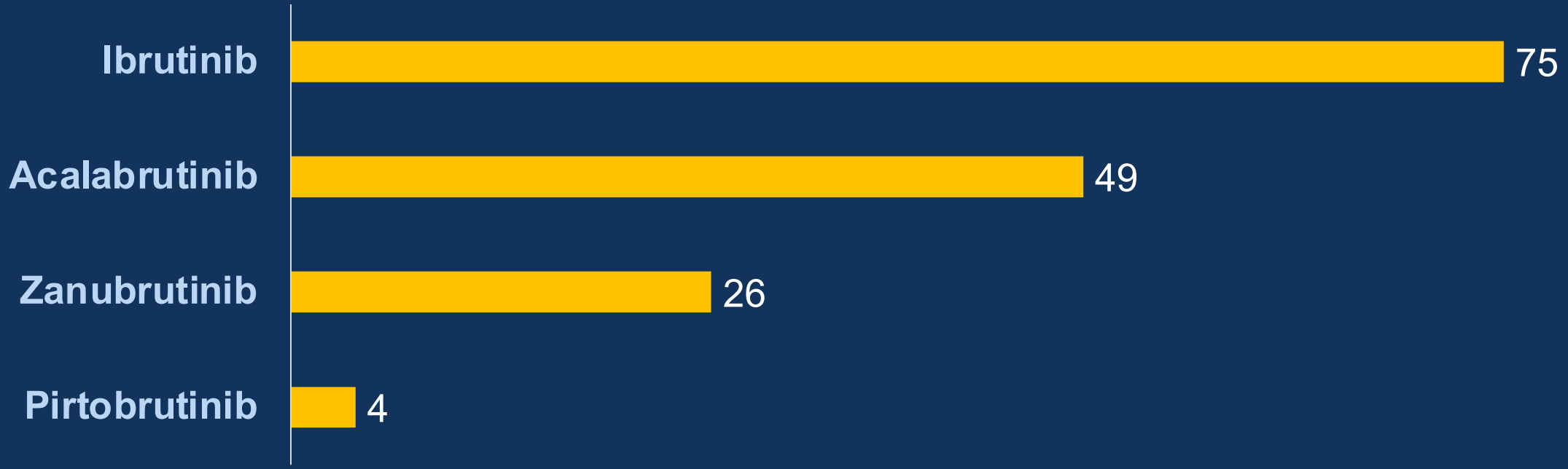
Snapshot of AON Practice
Mantle Cell Lymphoma

Select Treatments Received



Clinical Trial Participation

Number of clinical trials	4
Total patients enrolled	10

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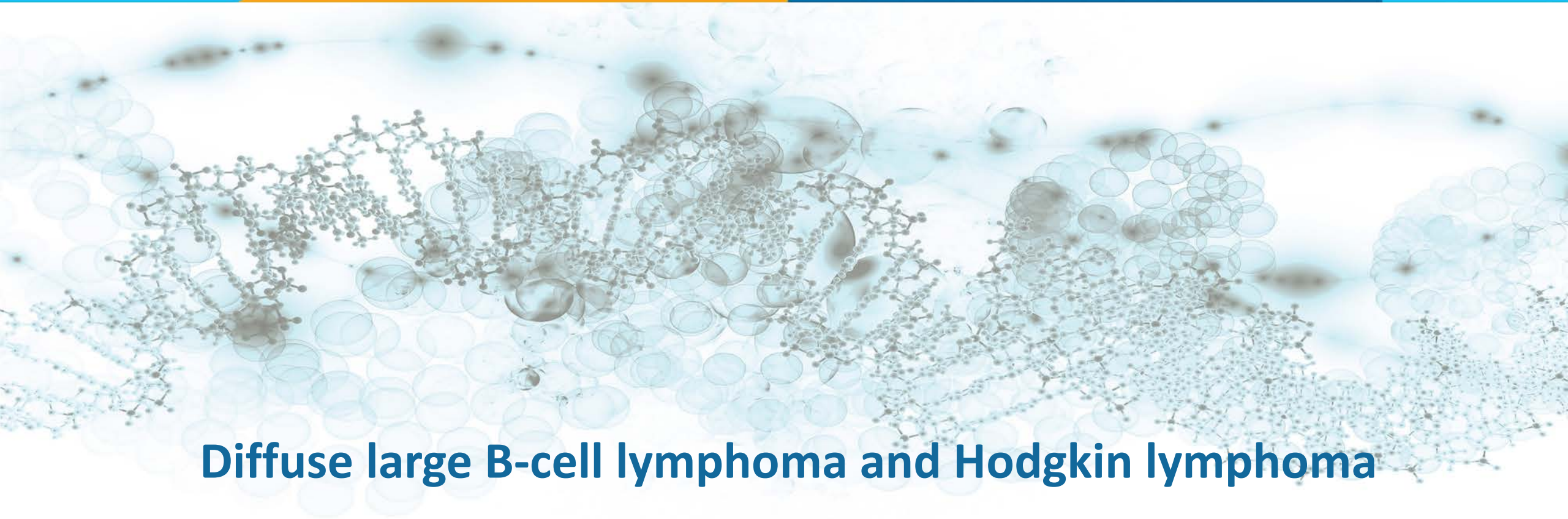
Dana-Farber Cancer Institute



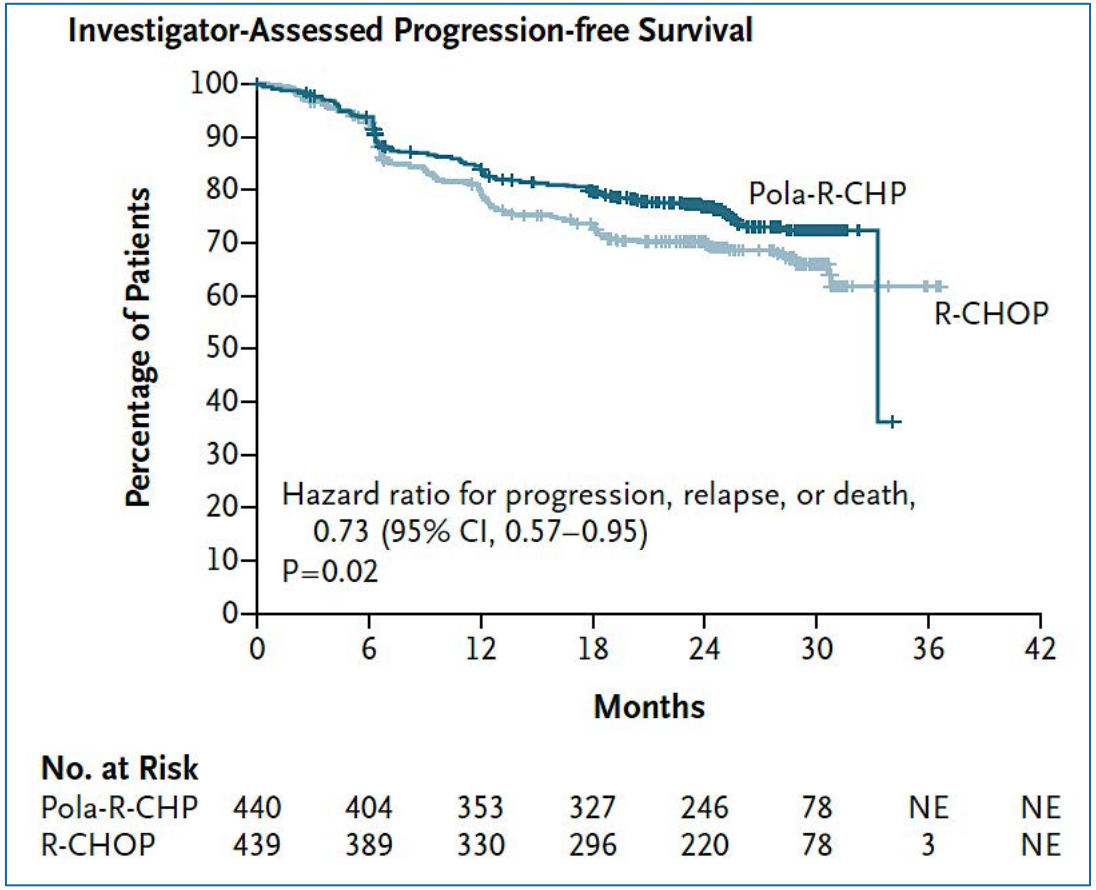
Diffuse large B-cell lymphoma and Hodgkin lymphoma

Ann S. LaCasce, MD, MMSc

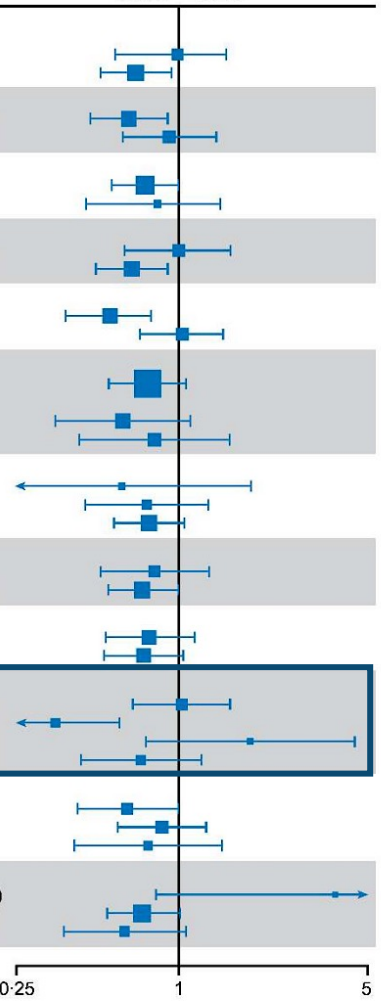
Dana-Farber
Cancer Institute

Diffuse large B-cell lymphoma

Pola-R-CHP vs R-CHOP in DLBCL with IPI ≥ 2 with improved PFS



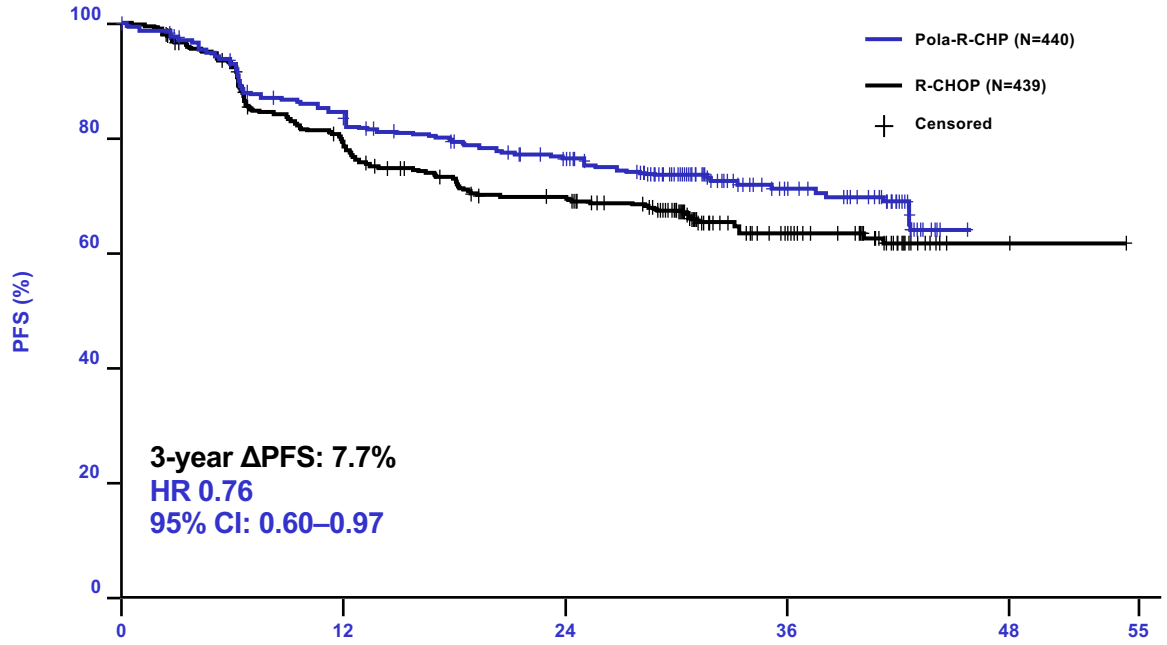
Baseline Risk Factors	Total N	Pola-R-CHP (N=440) n	Pola-R-CHP (N=440) 2-year Rate	R-CHOP (N=439) n	R-CHOP (N=439) 2-year Rate	Hazard Ratio	95% Wald CI
Age group							
≤60	271	140	74·1	131	71·9	0·9	(0·6 to 1·5)
>60	608	300	77·9	308	69·5	0·7	(0·5 to 0·9)
Sex							
Male	473	239	75·9	234	65·9	0·7	(0·5 to 0·9)
Female	406	201	77·7	205	75·2	0·9	(0·6 to 1·4)
ECOG PS							
0–1	737	374	78·4	363	71·2	0·8	(0·6 to 1·0)
2	141	66	67·2	75	65·0	0·8	(0·5 to 1·4)
IPI score							
IPI 2	334	167	79·3	167	78·5	1·0	(0·6 to 1·6)
IPI 3–5	545	273	75·2	272	65·1	0·7	(0·5 to 0·9)
Bulky disease							
Absent	494	247	82·7	247	70·7	0·6	(0·4 to 0·8)
Present	385	193	69·0	192	69·7	1·0	(0·7 to 1·5)
Geographic region							
Western Europe, United States, Canada, and Australia	603	302	78.6	301	72.0	0.8	(0·6 to 1·1)
Asia	160	81	74.3	79	65.6	0.6	(0·4 to 1·5)
Rest of world	116	57	70.8	59	67.3	0.9	(0·6 to 1·5)
Ann Arbor stage							
I–II	99	47	89·1	52	85·5	0·6	(0·2 to 1·8)
III	232	124	80·7	108	73·6	0·8	(0·5 to 1·3)
IV	548	269	72·6	279	66·1	0·8	(0·6 to 1·1)
Baseline LDH							
≤ULN	300	146	78·9	154	75·6	0·8	(0·5 to 1·3)
>ULN	575	291	75·4	284	67·2	0·7	(0·5 to 1·0)
No. of extranodal sites							
0–1	453	227	80·2	226	74·5	0·8	(0·5 to 1·1)
≥2	426	213	73·0	213	65·8	0·7	(0·5 to 1·0)
Cell-of-origin							
GCB	352	184	75·1	168	76·9	1·0	(0·7 to 1·5)
ABC	221	102	83·9	119	58·8	0·4	(0·2 to 0·6)
Unclassified	95	44	73·0	51	86·2	1·9	(0·8 to 4·5)
Unknown	211	110	73·8	101	64·3	0·7	(0·4 to 1·2)
Double expressor by IHC							
DEL	290	139	75·5	151	63·1	0·6	(0·4 to 1·0)
Non DEL	438	223	77·7	215	75·7	0·9	(0·6 to 1·3)
Unknown	151	78	76·0	73	69·8	0·8	(0·4 to 1·5)
Double- or triple-hit lymphoma							
Yes	45	26	69·0	19	88·9	3·8	(0·8 to 17·6)
No	620	305	76·8	315	70·3	0·7	(0·5 to 1·0)
Unknown	214	109	78·5	105	66·4	0·6	(0·4 to 1·1)



Tilly et al. NEJM 2022

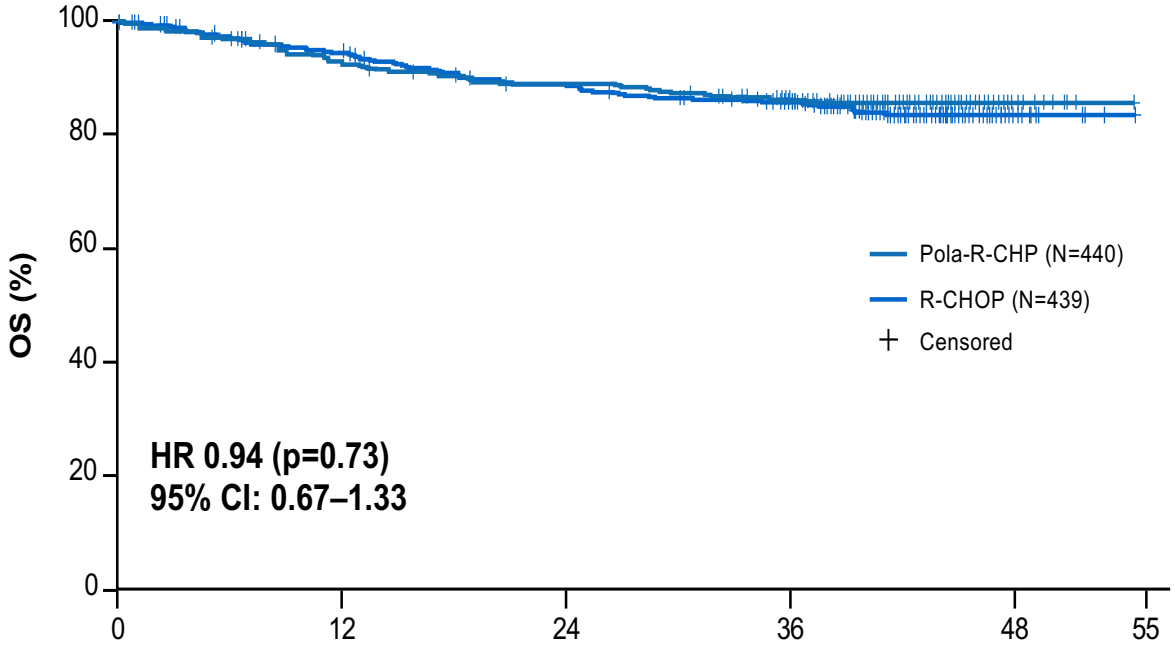
POLARIX: Updated Survival Analyses

PFS : Updated results
Median follow-up: 39.7 months



No. of patients at risk										
Pola-R-CHP	440	405	354	331	313	242	103	66	0	0
R-CHOP	439	390	331	300	284	222	94	59	2	1

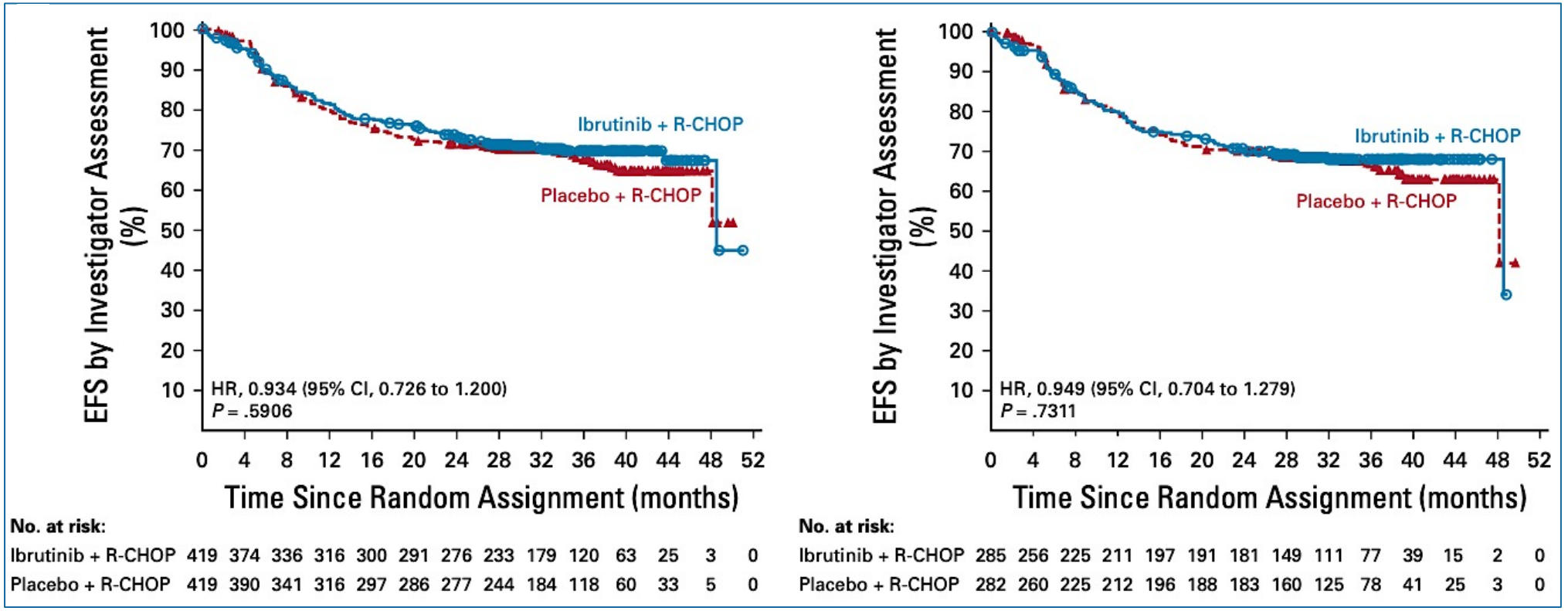
Updated results (CCOD: June 15, 2022)
Median follow-up: 39.7 months



No. of patients at risk										
Pola-R-CHP	440	423	398	387	379	371	338	129	13	1
R-CHOP	439	415	403	382	372	361	329	124	18	1

Herrera AF et al. ASH 2022;Abstract 542.

R-CHOP +/- ibrutinib in non-GCB DLBCL: did not meet primary endpoint in ABC subtype



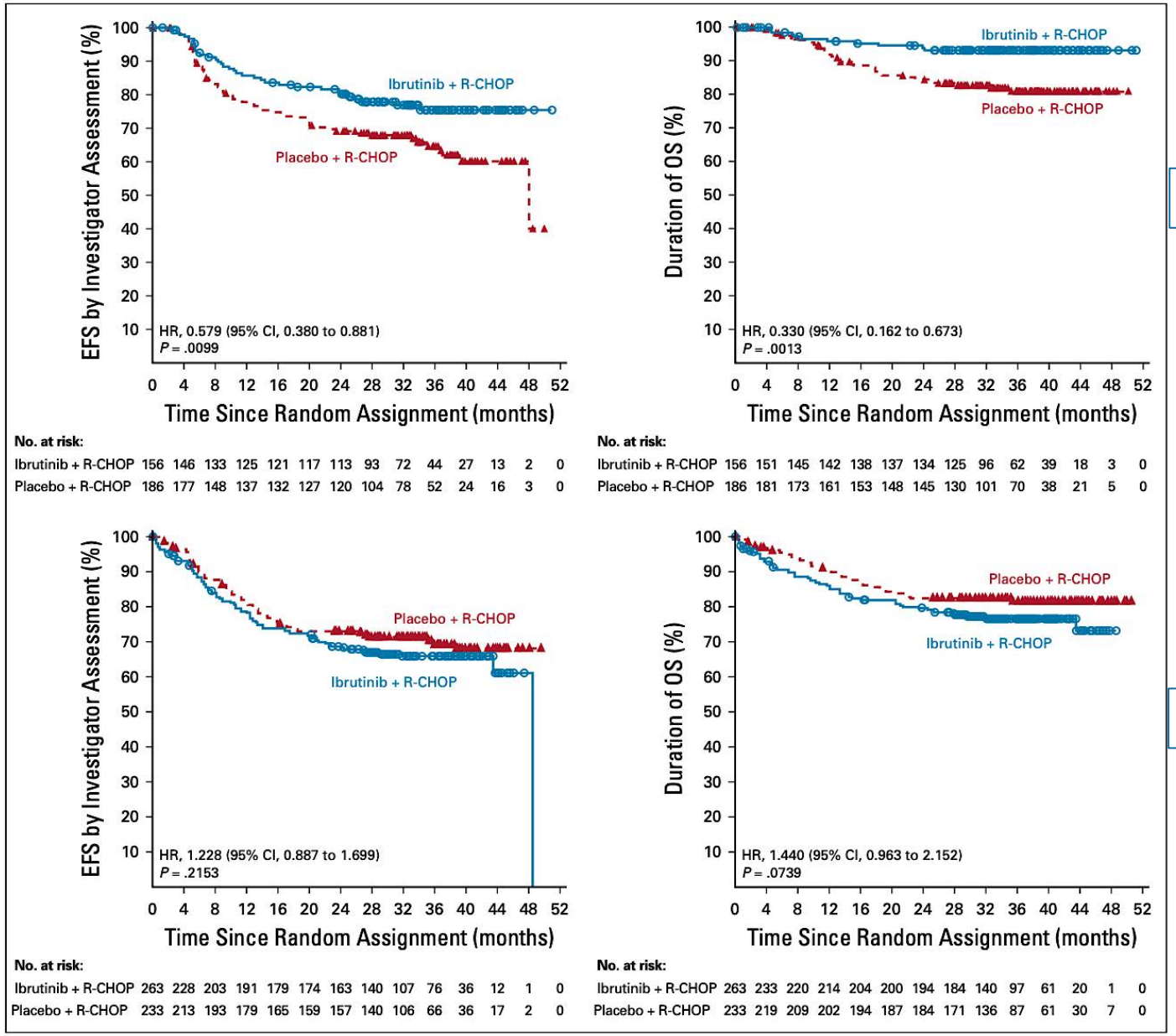
ITT population

ABC subtype

Younes et al. JCO. 2019

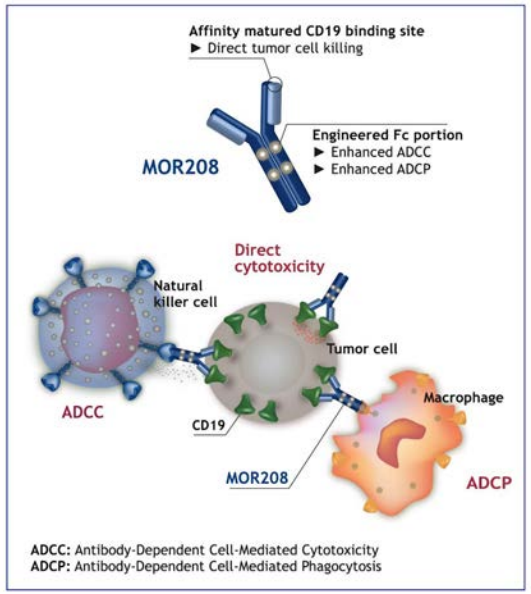
Patients ≥ 60 increased toxicity and inferior outcomes

Two randomized studies on-going with R-CHOP +/- acalabrutinib (REMoDL-A and ESCALADE)



Younes et al. JCO. 2019

Tafasitamab plus lenalidomide: long term outcomes

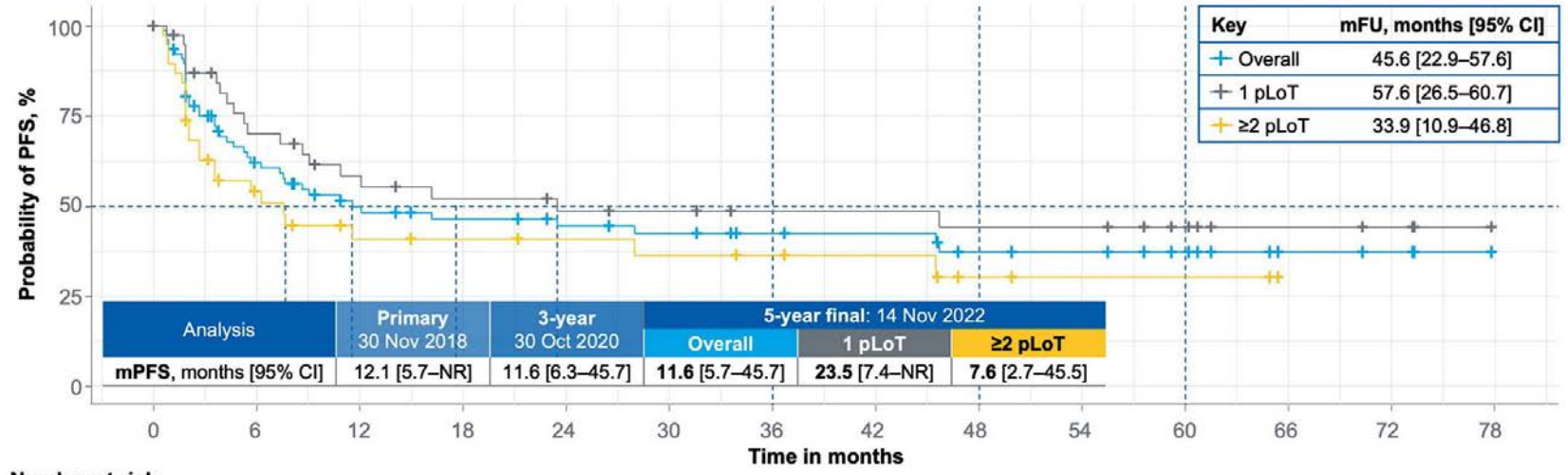


Median prior therapies: 2
50% with 1 prior tx

60% of patients received one year of both agents.

46% required dose reduction of lenalidomide and 22% permanently discontinued.

PFS in the FAS and in subgroups according to number of pLoT



Analysis	Primary 30 Nov 2018	3-year 30 Oct 2020	5-year final: 14 Nov 2022 Overall	1 pLoT	≥2 pLoT
mPFS, months [95% CI]	12.1 [5.7–NR]	11.6 [6.3–45.7]	**11.6** [5.7–45.7]	**23.5** [7.4–NR]	**7.6** [2.7–45.5]

Number at risk:

Overall	80	42	30	26	23	21	18	17	13	12	9	4	3	0
1 pLoT	40	25	19	16	14	13	11	11	10	10	7	4	3	0
≥2 pLoT	40	17	11	10	9	8	7	6	3	2	2	0	0	0

Primary Analysis — **ORR: 60%** **CR: 43%**

Follow-Up Analysis — **ORR: 58%** **CR: 40%**

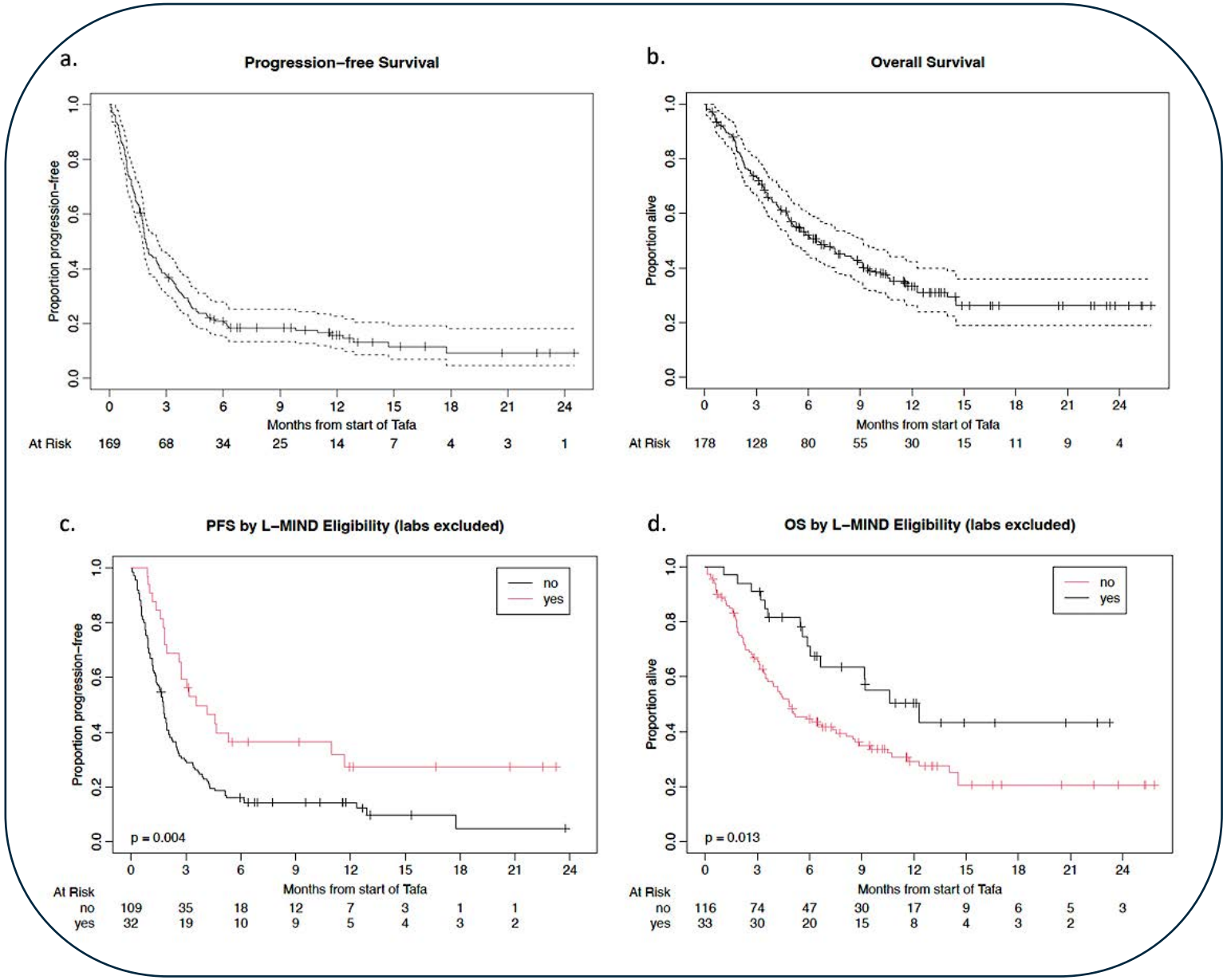
Analysis	Primary 30 Nov 2018	3-year 30 Oct 2020	5-year final: 14 Nov 2022 Overall	1 pLoT	≥2 pLoT
mDoR, months [95% CI]	21.7 [21.7–NR]	43.9 [26.1–NR]	**NR** [33.8–NR]	**NR** [9.1–NR]	**NR** [26.1–NR]

Salles et al. Lancet Onc 2020

Duell et al. Haematolgica 2023

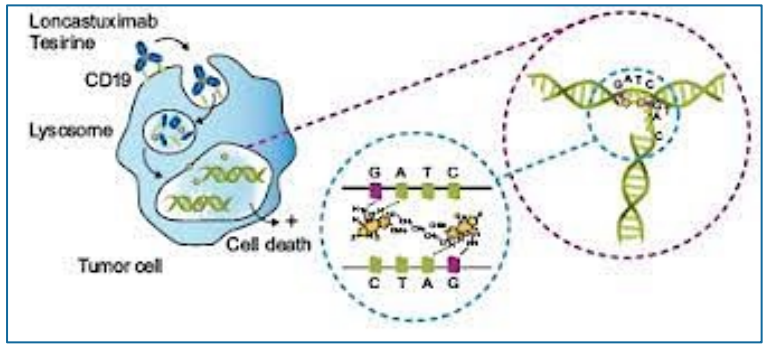
“Real world” tafasitamab plus lenalidomide

ORR: 31%
CR: 19%
m PFS 1.9 m



Qualls et al. Blood 2023

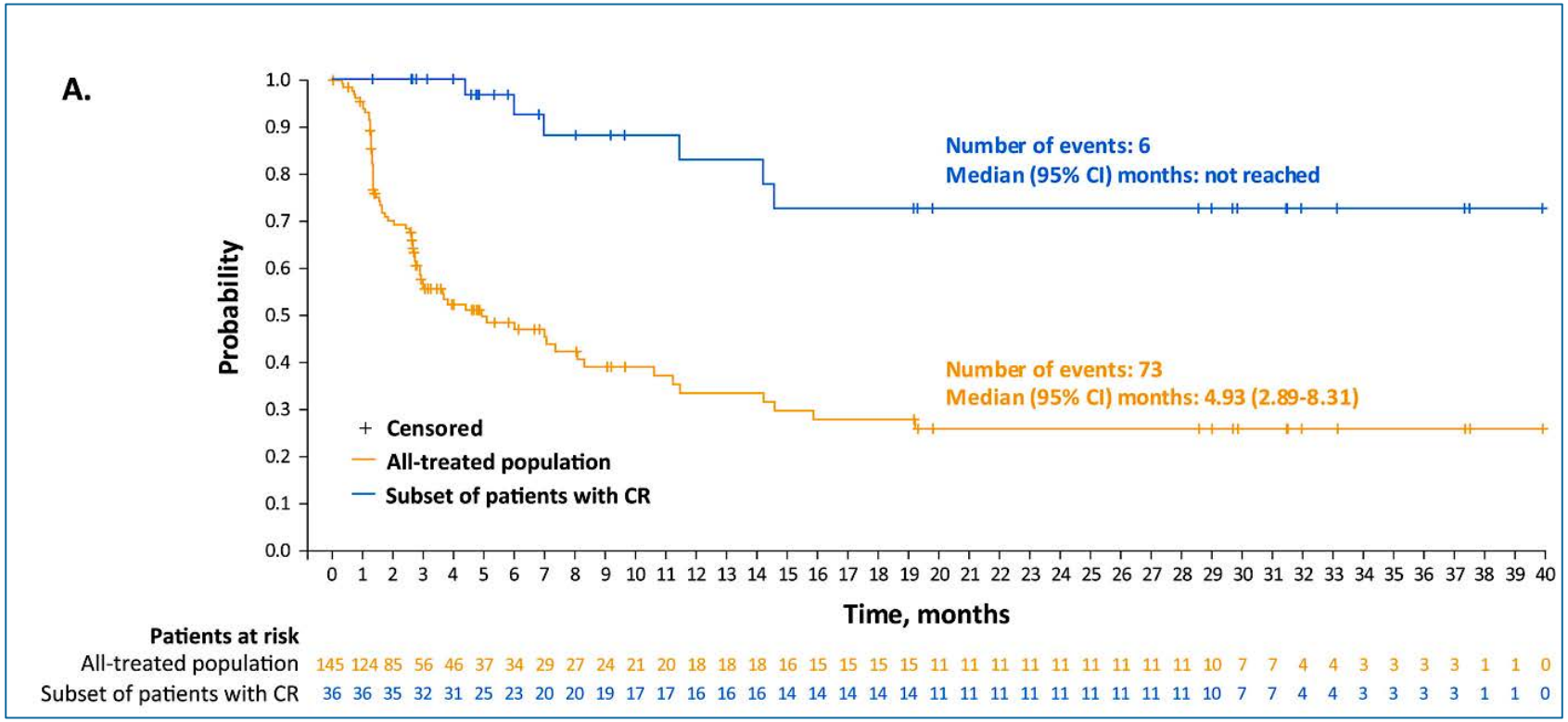
Loncastuximab tesirine phase 2 study: long term outcomes



n=145
Median 3 prior therapies
Relapsed 30%
Refractory 58%
Prior auto 14%
Prior CAR-T 9%

AEs:
Cytopenias
F+N (3%)
Transaminitis
Pleural effusion (11%)

PFS



ORR 48%
CR 25%

Caimi et al. Lancet Oncol 2021; Caimi et al. Haematologica 2023

Discontinuation of the Phase II LOTIS-9 Clinical Trial of Loncastuximab Tesirine-lpyl and Rituximab for Unfit or Frail Patients with Previously Untreated DLBCL

Press Release: July 20, 2023

Plans were announced to discontinue the Phase 2 LOTIS-9 clinical trial evaluating loncastuximab tesirine-lpyl and rituximab (Lonca-R) for unfit or frail patients with previously untreated diffuse large B-cell lymphoma (DLBCL).

“Given the challenges of defining the addressable segment of the difficult-to-treat unfit or frail DLBCL patient population, including many patients with significant active underlying co-morbidities, the benefit-risk profile does not support continuation of the LOTIS-9 trial.

Following a meeting yesterday, the US Food and Drug Administration placed a partial clinical hold on the trial for new patient enrollment but will allow patients already on therapy who are deriving clinical benefit to remain on therapy after being reconsented. Following treatment of any reconsenting patients, the Company will conduct the necessary steps to conclude the trial and does not plan to continue studying this regimen in the unfit or frail previously untreated DLBCL patient population.”

https://ir.adctherapeutics.com/press-releases/press-release-details/2023/ADC-Therapeutics-Announces-Plan-to-Discontinue-the-Phase-2-LOTIS-9-Clinical-Trial-of-ZYNLONTA-loncastuximab-tesirine-lpyl-and-Rituximab-in-Unfit-or-Frail-Previously-Untreated-DLBCL-Patients/default.aspx

RTP RESEARCH TO PRACTICE

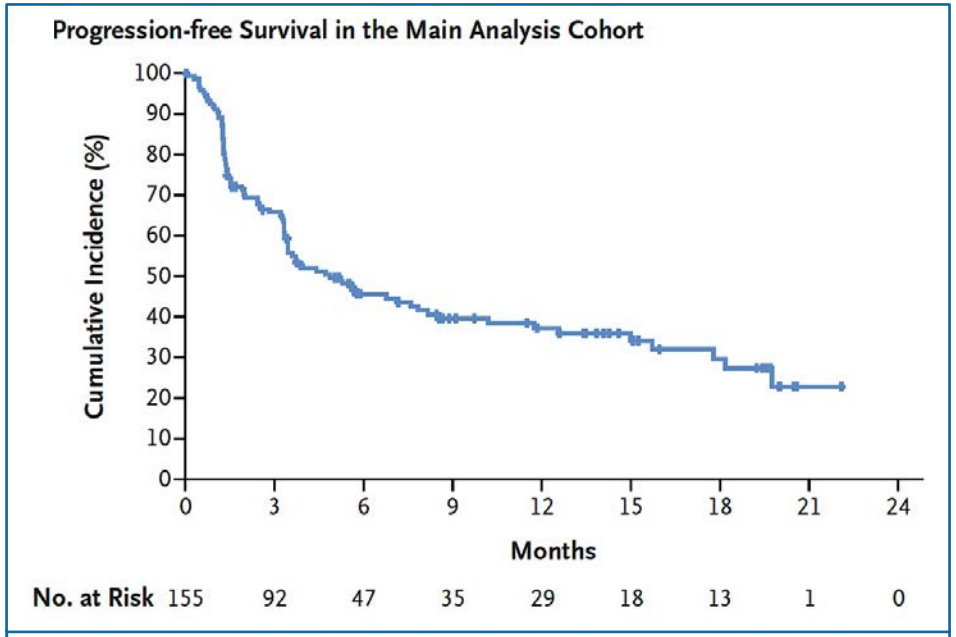
Glofitamab in relapsed/ refractory DLBCL

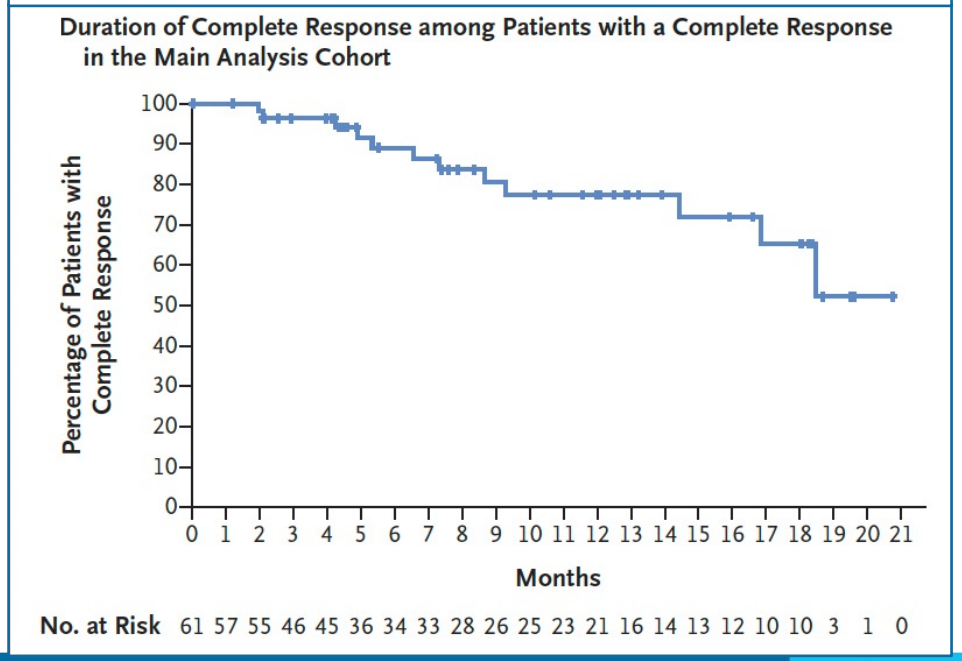
Previous lines of therapy	
Median no. of lines (range)	3 (2–7)
Only 2 previous lines — no. (%)	62 (40)
≥3 previous lines — no. (%)	92 (60)
Previous therapy for lymphoma — no. (%)	
Anti-CD20 antibody	154 (100)
Anthracycline	149 (97)
CAR T-cell therapy	51 (33)

12 cycles

ORR 52%
CR 39%

CRS 63%
≥ 2 16%
ICANS 8%





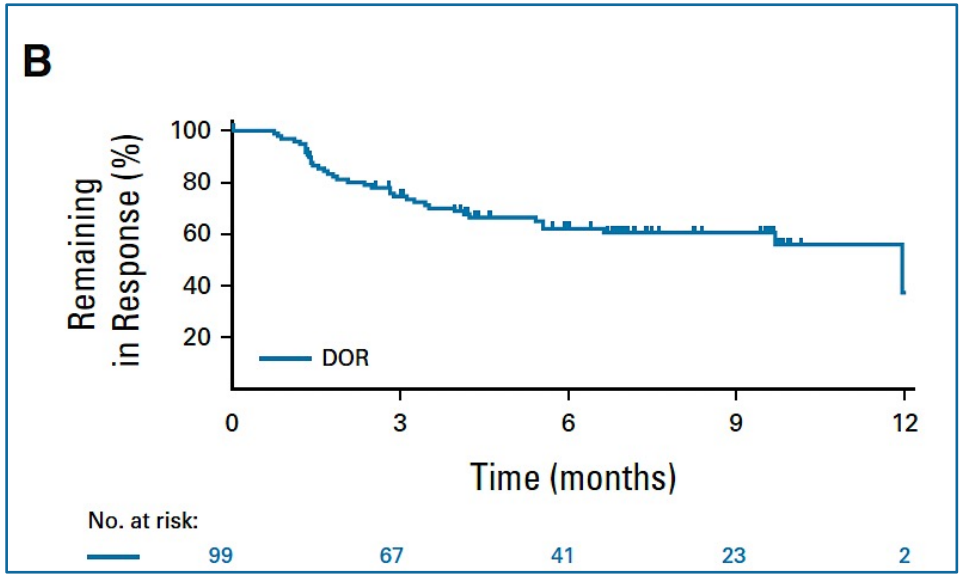
Dickinson et al. NEJM 2022.

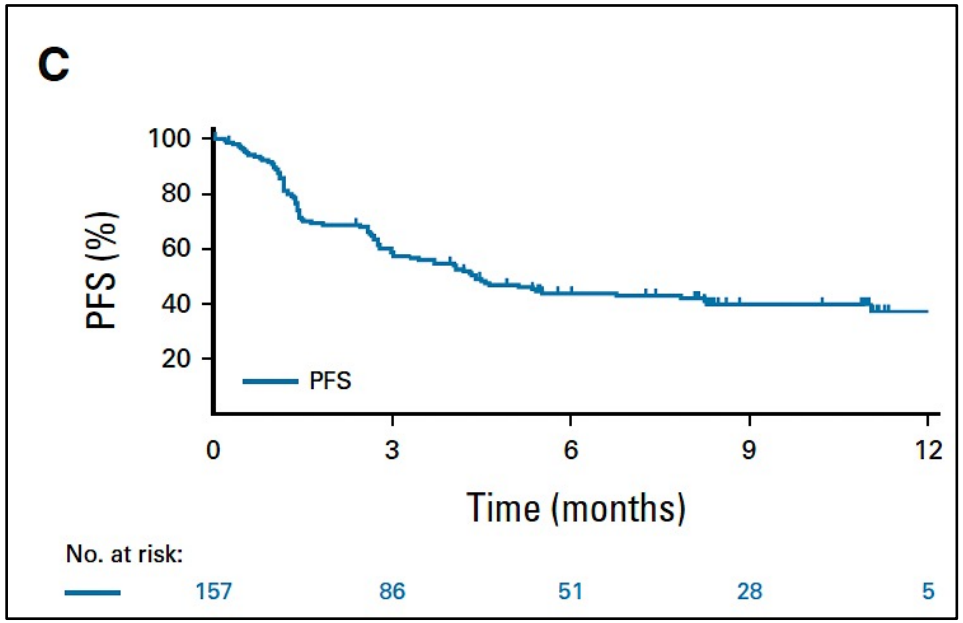
Epcoritamab in relapsed/ refractory DLBCL

Characteristic	Patients (N = 157)
Prior lines of antilymphoma therapy, No. (%)	
2	46 (29.3)
3	50 (31.8)
≥ 4	61 (38.9)
Primary refractory disease,[c] No. (%)	96 (61.1)
Refractory to last systemic therapy,[c] No. (%)	130 (82.8)
Refractory to ≥ 2 consecutive lines of therapy,[c] No. (%)	119 (75.8)
Prior autologous stem-cell transplant, No. (%)	31 (19.7)
Relapsed within 12 months after prior autologous stem-cell transplant, No./n (%)	18/31 (58.1)
Prior CAR T-cell therapy, No. (%)	61 (38.9)
Progressed within 6 months of CAR T-cell therapy, No./n (%)	46/61 (75.4)
Prior anthracycline therapy, No. (%)	154 (98.1)
First line	139 (88.5)
Second line	16 (10.2)

ORR 63%
CR 39%

CRS 49.7%
≥ 3 2.5%
ICANS 6.4%





Thieblemont et al. JCO 2022

ELM-2: Objective Response Rate with Odronextamab for R/R DLBCL

Best overall response	Independent central review N=130*	Investigator evaluation N=130*
Objective response rate (ORR)†	**49.2%** [95% CI 40.4%–58.1%]	**50.0%** [95% CI 41.1%–58.9%]
Complete response	**30.8%**	**36.2%**
Partial response	18.5%	13.8%
Stable disease	3.8%	3.1%
Progressive disease	22.3%	21.5%

Week 12 response assessment by independent central review	1/20 step-up regimen N=67	0.7/4/20 step-up regimen N=63
ORR	46.3% [95% CI: 34.0–58.9%]	42.9% [95% CI: 30.5–56.0%]
Complete response	26.9%	20.6%

- 63% of responders achieved a complete response
- Consistent efficacy observed at Week 12 regardless of Cycle 1 step-up regimen

- Median opportunity of follow-up: 21.3 months (range 2.6–29.8)

Kim WS et al. ASH 2022;Abstract 444.

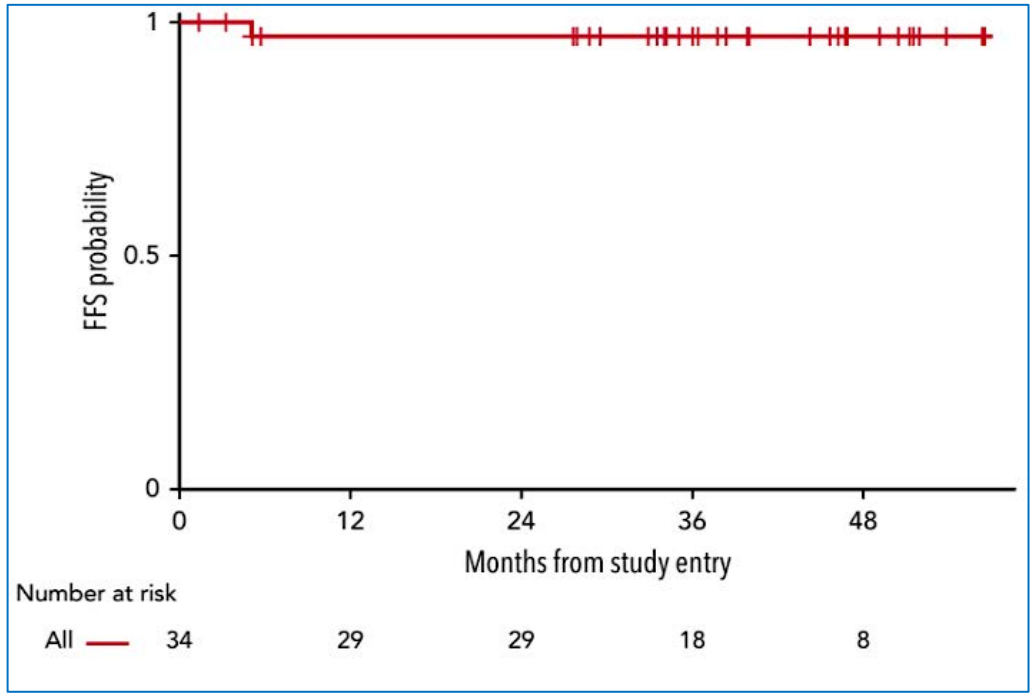
RTP RESEARCH TO PRACTICE

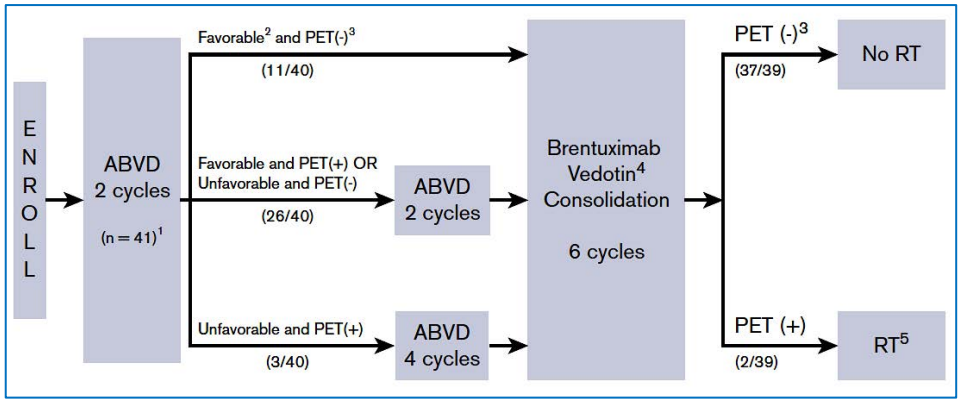
Dana-Farber
Cancer Institute

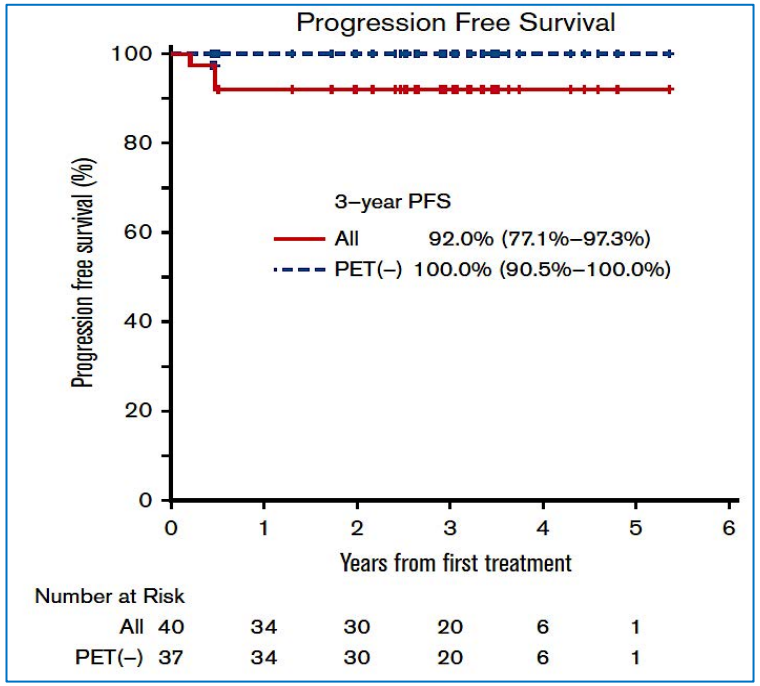
Hodgkin lymphoma

BV + chemotherapy with high PFS in small phase 2 studies

Time point	Overall response	CR	Partial response
Monotherapy lead-in	34 (100; 89.7-100)	18 (52.9; 35.1-70.2)	16 (47.1; 29.8-64.9)
Cycle 2	33 (97.1; 84.7-99.9)	33 (97.1; 84.7-99.9)	0 (0; 0-10.3)
End of treatment	31 (91.2; 76.3-98.1)	31 (91.2; 76.3-98.1)	0 (0; 0-10.3)



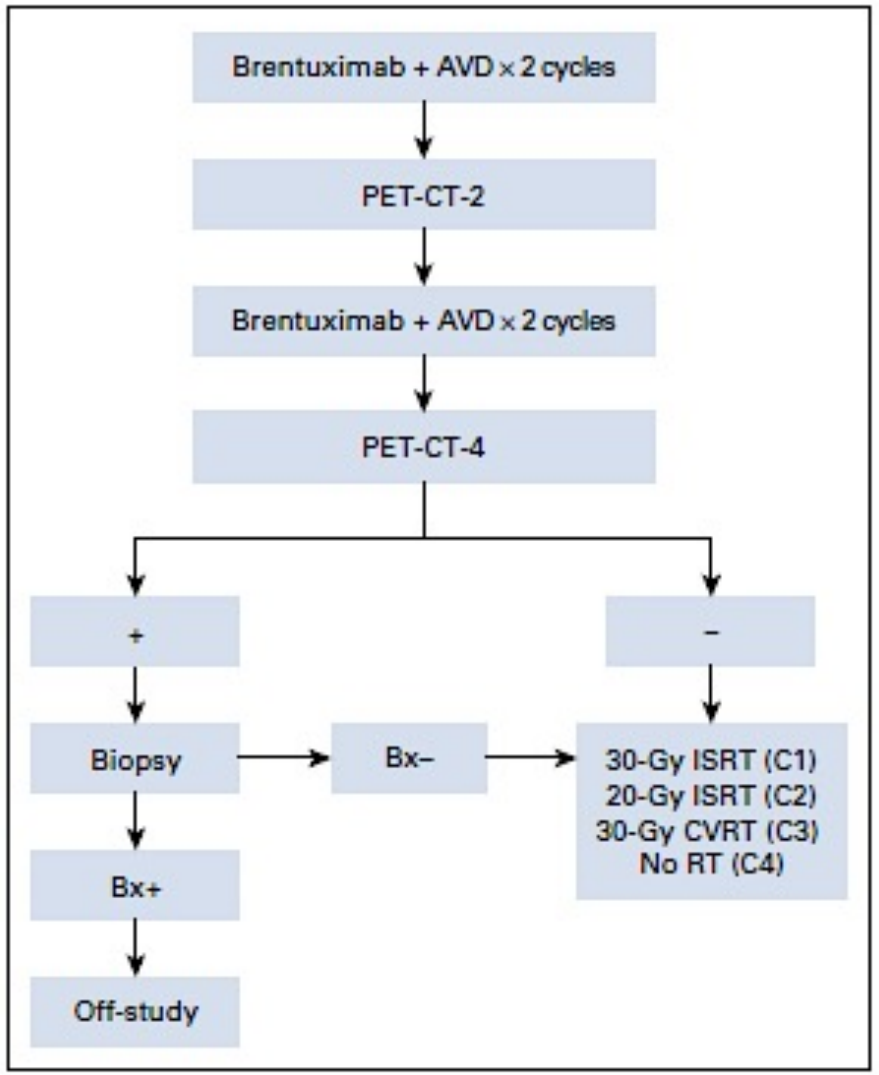


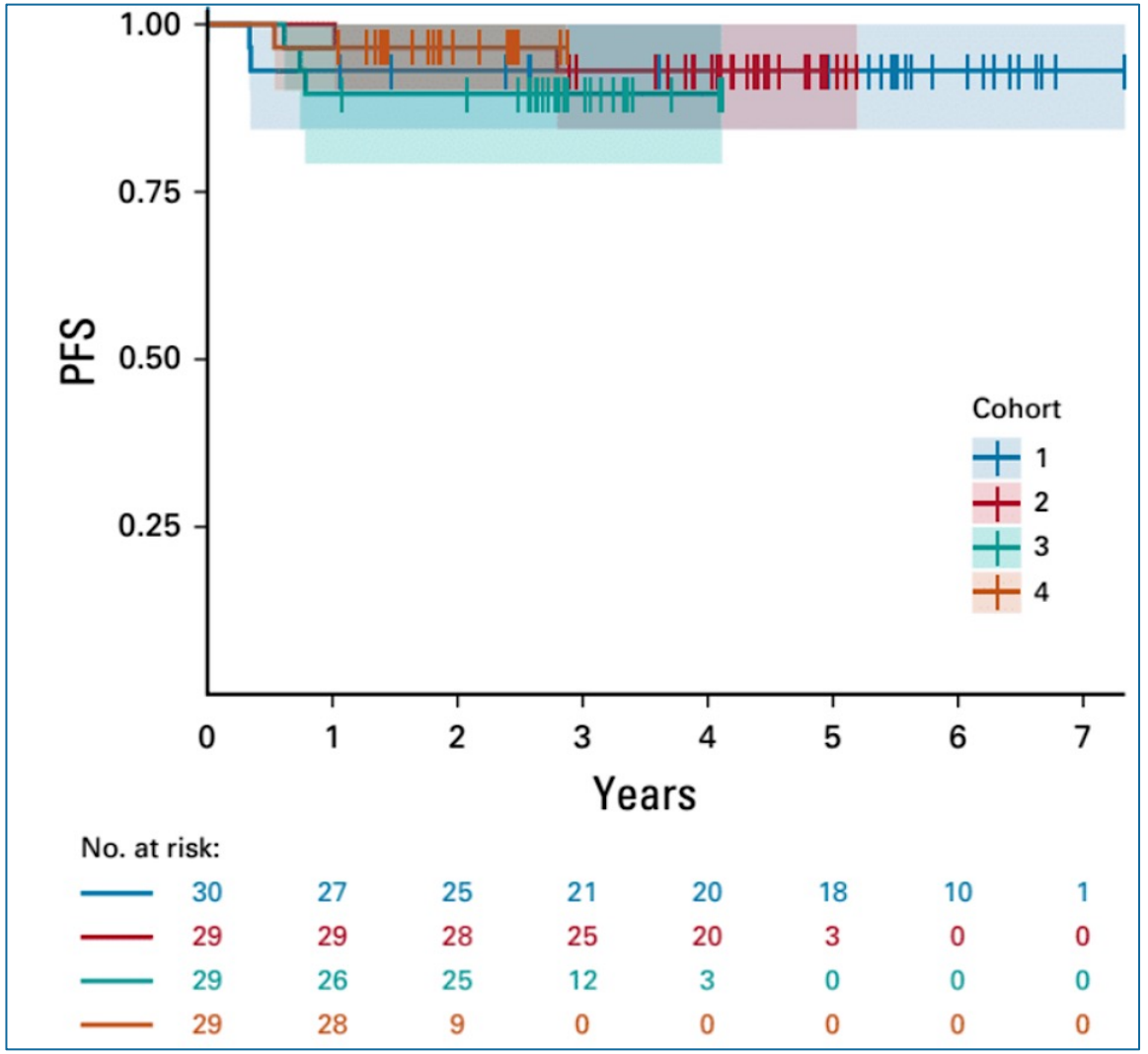


Abramson et al. Blood 2019

Park et al. Blood Adv 2020

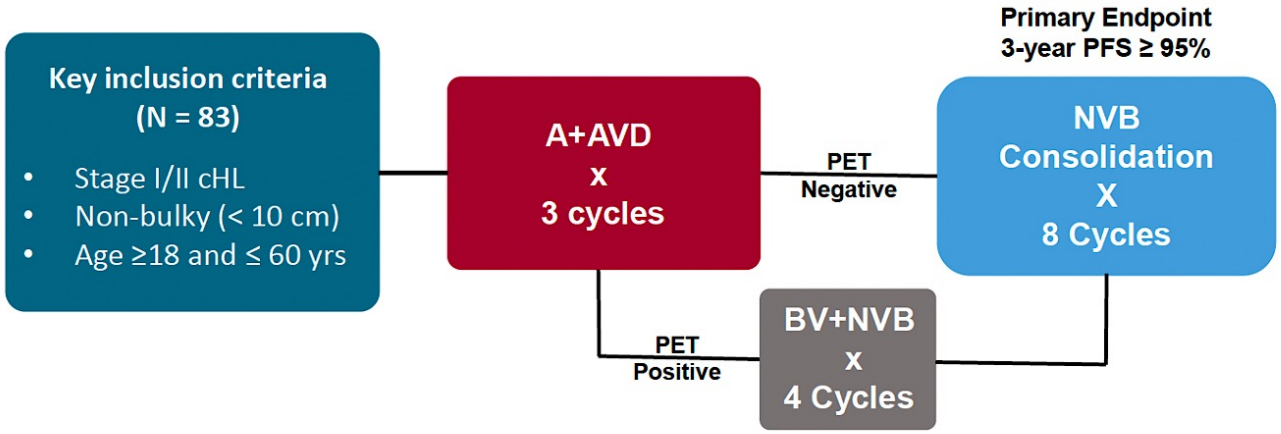
BV-AVD +/- RT with excellent outcomes in unfavorable HL



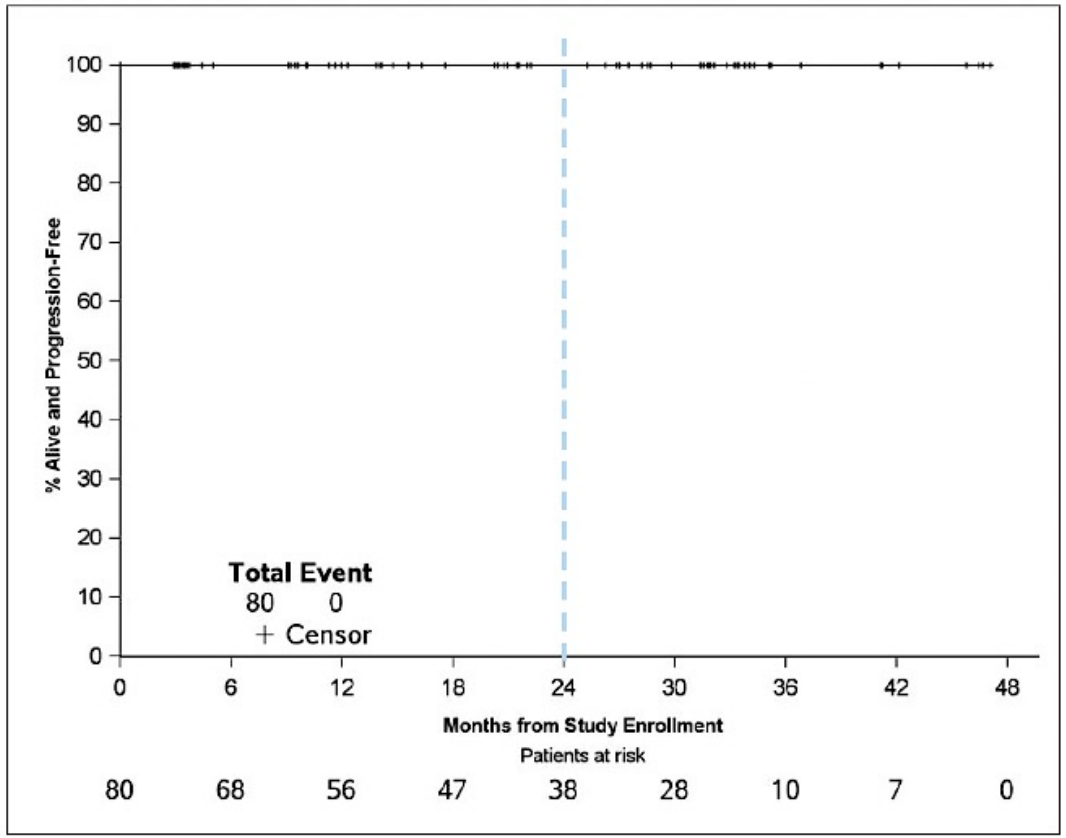


Kumar et al. JCO 2021

BV+AVD followed by nivolumab in limited stage HL

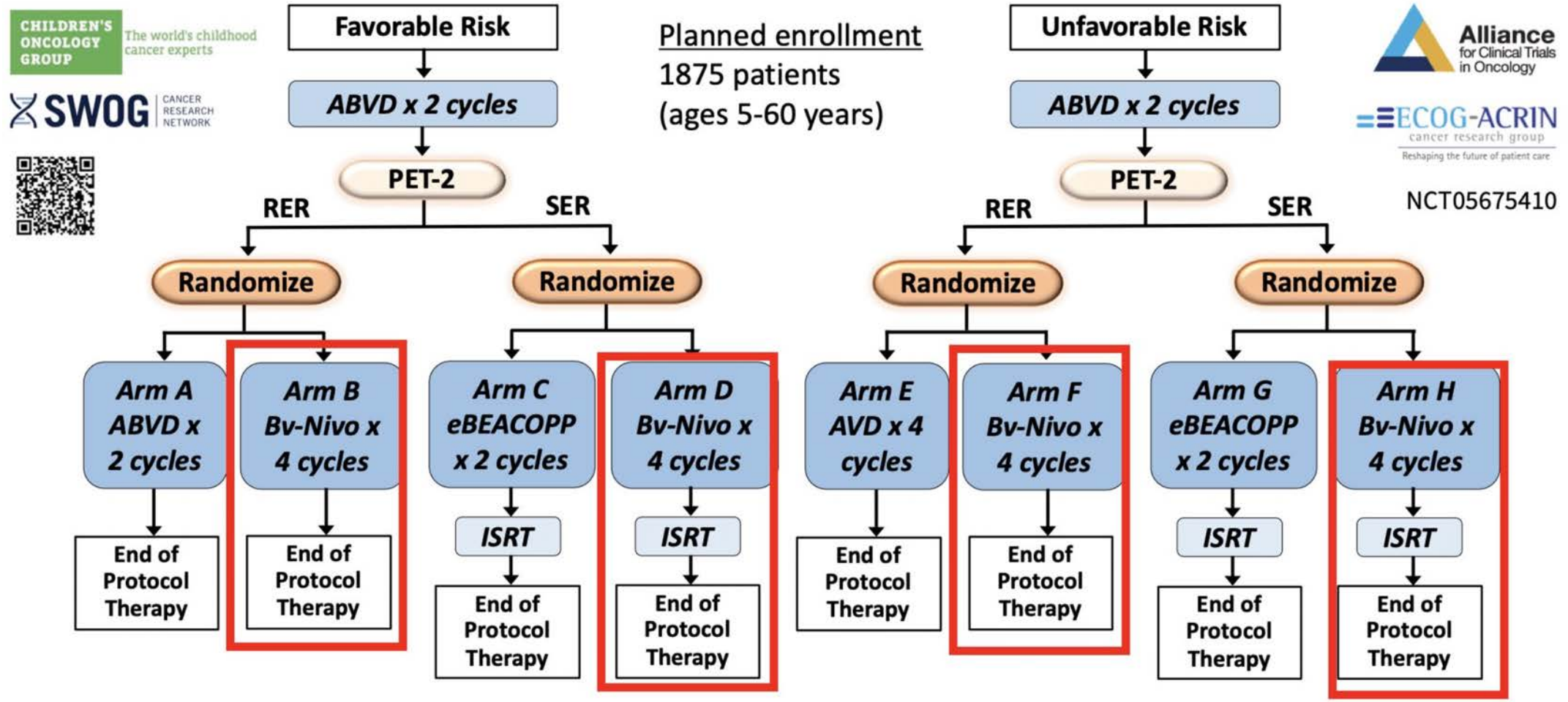


N=80
Stage 1: 9 (11%)
Stage 2: 71 (89%)
B sx: 26 (33%)



Park et al. ASH 2022

Standard therapy vs. immuno-oncology for children and adults with newly diagnosed stage I and II classic HL: AHOD 2131



BV-AVD with improved OS (4.5% absolute with median f/u 6 yrs)

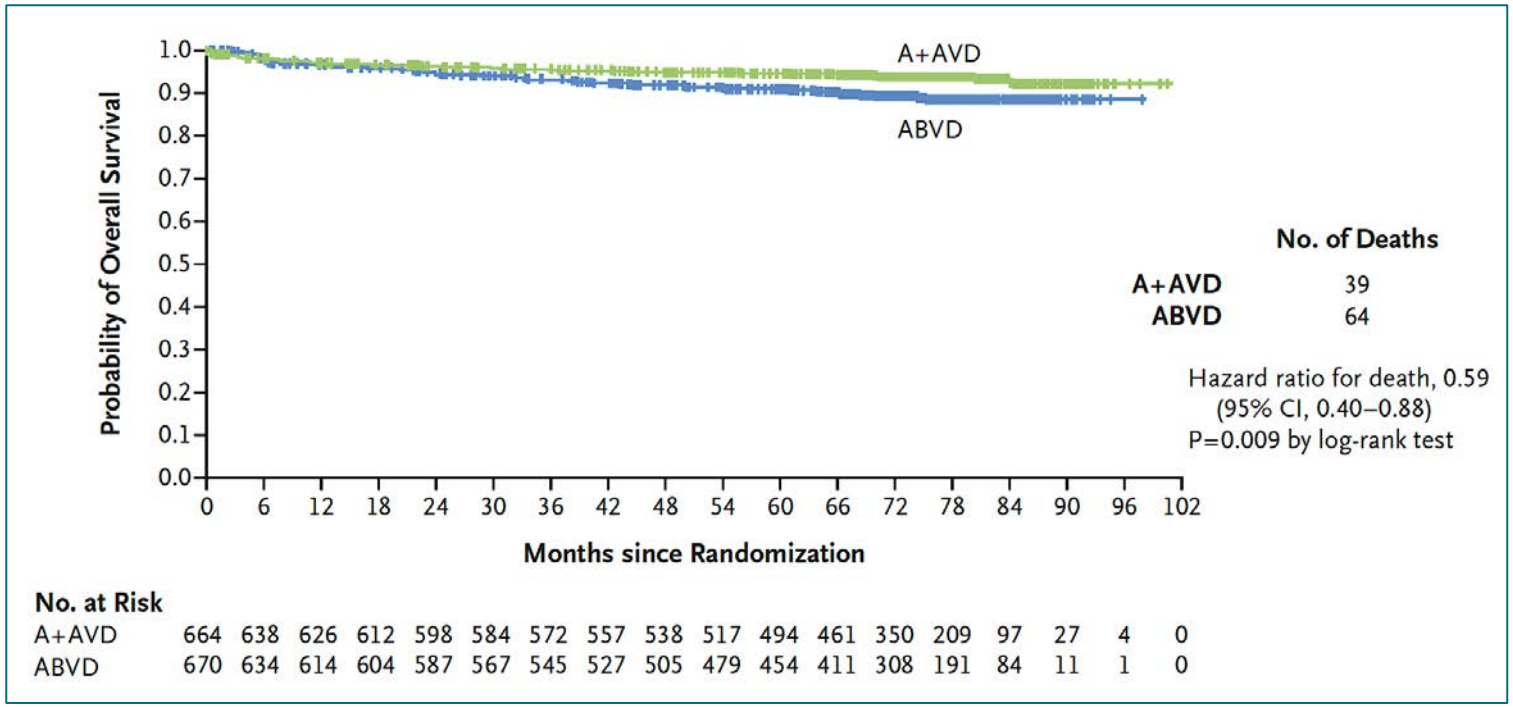


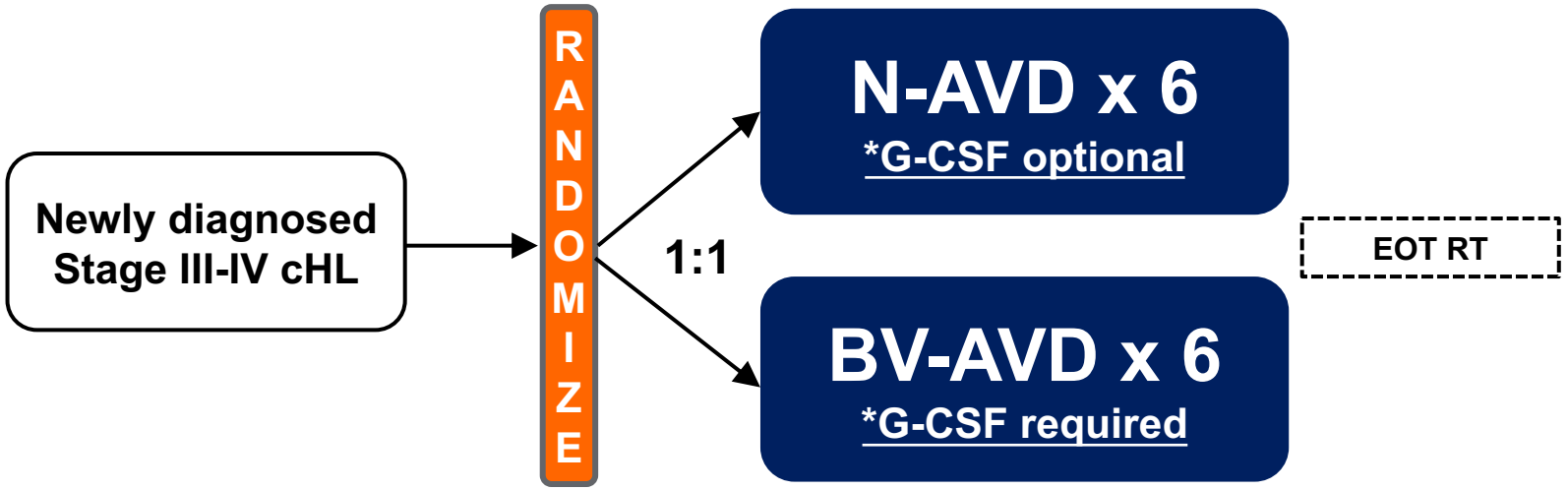
Table 1. Summary of Causes of Death (Safety Population).*

Cause of Death	A+AVD (N=662)	ABVD (N=659)
Any cause — no. (%)	39 (5.9)	64 (9.7)
Hodgkin's lymphoma or complications — no.	32	45
Second cancer — no.	1	11
Other cause — no.	6	8
Unknown cause	1	5†
Accident or suicide	3	0
Covid-19	0	1
Heart failure	1	1
Intracranial hemorrhage	1	0
Lower respiratory tract infection	0	1

Caution: PN and bone pain

Ansell et al. NEJM 2022

S1826: study design and eligibility criteria



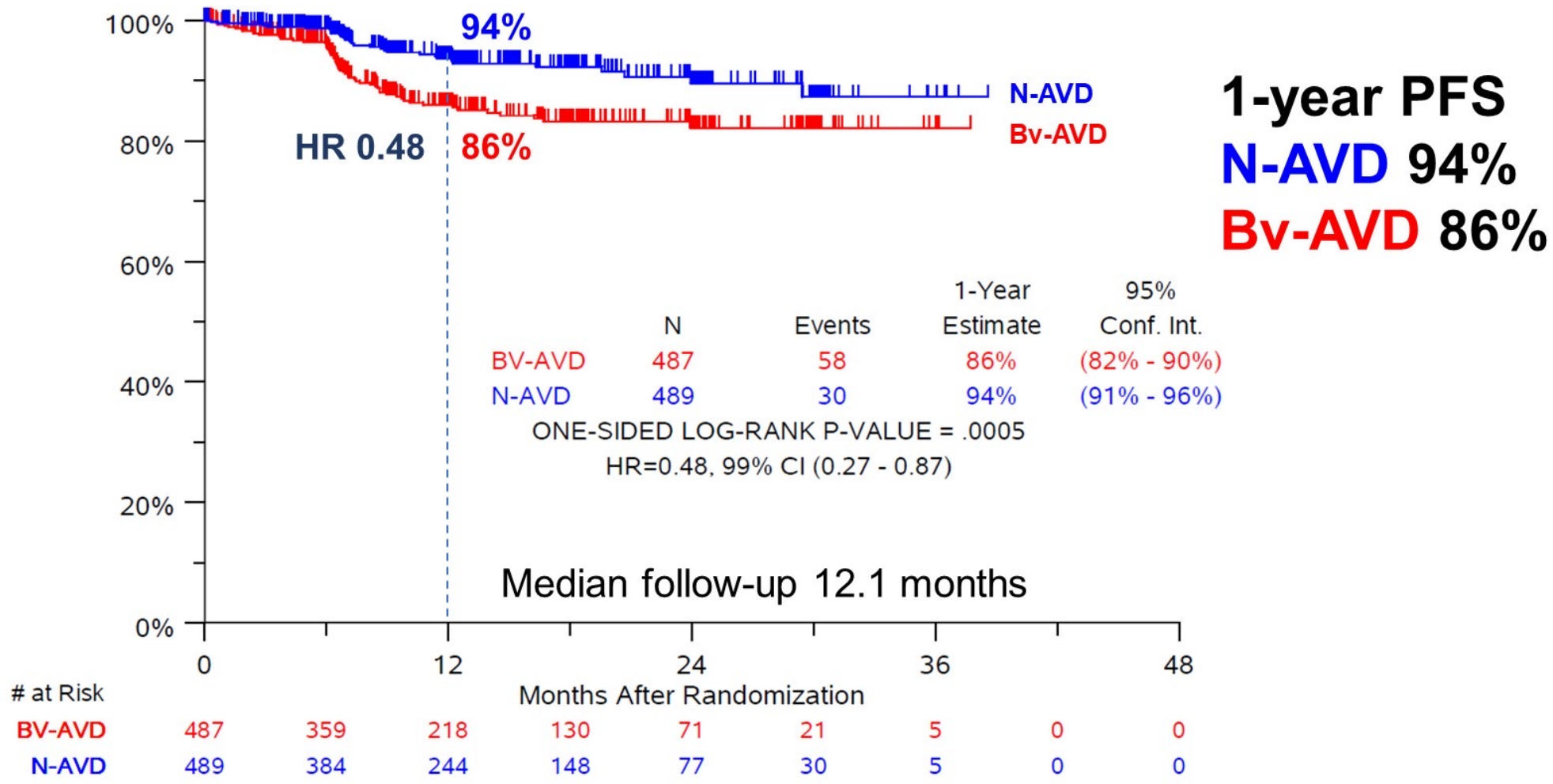
Key Inclusion

- Age ≥ 12 years old
- HIV+ eligible, if controlled
- Zubrod PS 0-2 (Peds: Lansky)
- LVEF ≥ 50% (or SF ≥ 27%)

Key Exclusion

- Interstitial lung disease or pneumonitis
- Peripheral neuropathy ≥ Gr2
- Active autoimmune disease

Primary endpoint met: superior PFS of nivolumab-AVD vs BV-AVD



1-year PFS
N-AVD 94%
Bv-AVD 86%

Herrera et al. ASCO 2023

Results favor N-AVD with regard to short-term toxicities

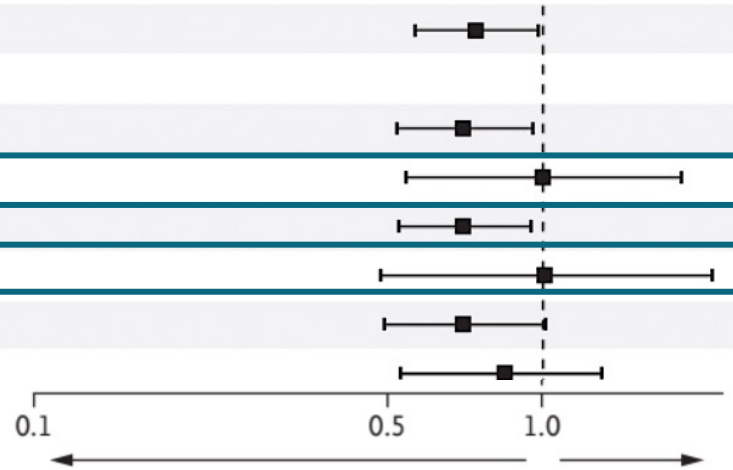
	Received g-csf	Febrile neutropenia	Thyroid dysfunction	ALT increased	Peripheral sensory neuropathy	Peripheral motor neuropathy	Discontinued N or BV
N-AVD	54%	5%	10%	32%	29%	4%	11%
BV-AVD*	95%	7%	1%	41%	55%	7%	22%

* Growth factor support mandated per protocol

What about older patients with cHL?

14% ≥ 60 y

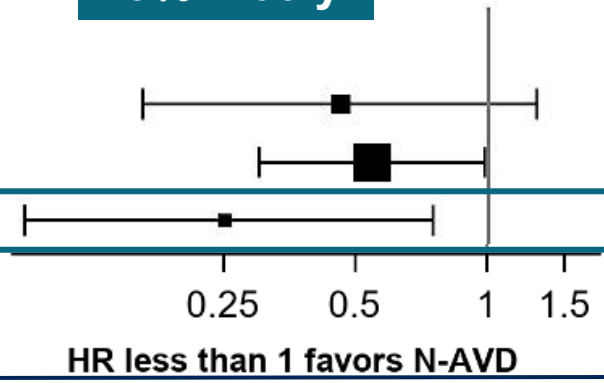
Subgroup	A+AVD	ABVD	Hazard Ratio (95% CI)
	no. of events/total no. (%)		
Overall	117/664 (17.6)	146/670 (21.8)	0.77 (0.60–0.98)
Age			
<60 yr	93/580 (16.0)	117/568 (20.6)	0.73 (0.56–0.96)
≥60 yr	24/84 (28.6)	29/102 (28.4)	1.01 (0.59–1.73)
<65 yr	99/604 (16.4)	128/608 (21.1)	0.74 (0.57–0.96)
≥65 yr	18/60 (30.0)	18/62 (29.0)	1.01 (0.53–1.95)
<45 yr	70/451 (15.5)	83/423 (19.6)	0.73 (0.53–1.01)
≥45 yr	47/213 (22.1)	63/247 (25.5)	0.86 (0.59–1.26)



Echelon 1

10% > 60 y

Subgroup	N + AVD Events/N (%)	BV + AVD Events/N (%)	HR (95% CI)	P Value
Age				
12 - 17 y	6/120 (5.0)	12/117 (10.3)	0.48 (0.18, 1.27)	0.140
18 - 60 y	19/323 (5.9)	32/323 (9.9)	0.56 (0.32, 0.98)	0.042
> 60 y	5/46 (10.9)	14/47 (29.8)	0.27 (0.10, 0.76)	0.013

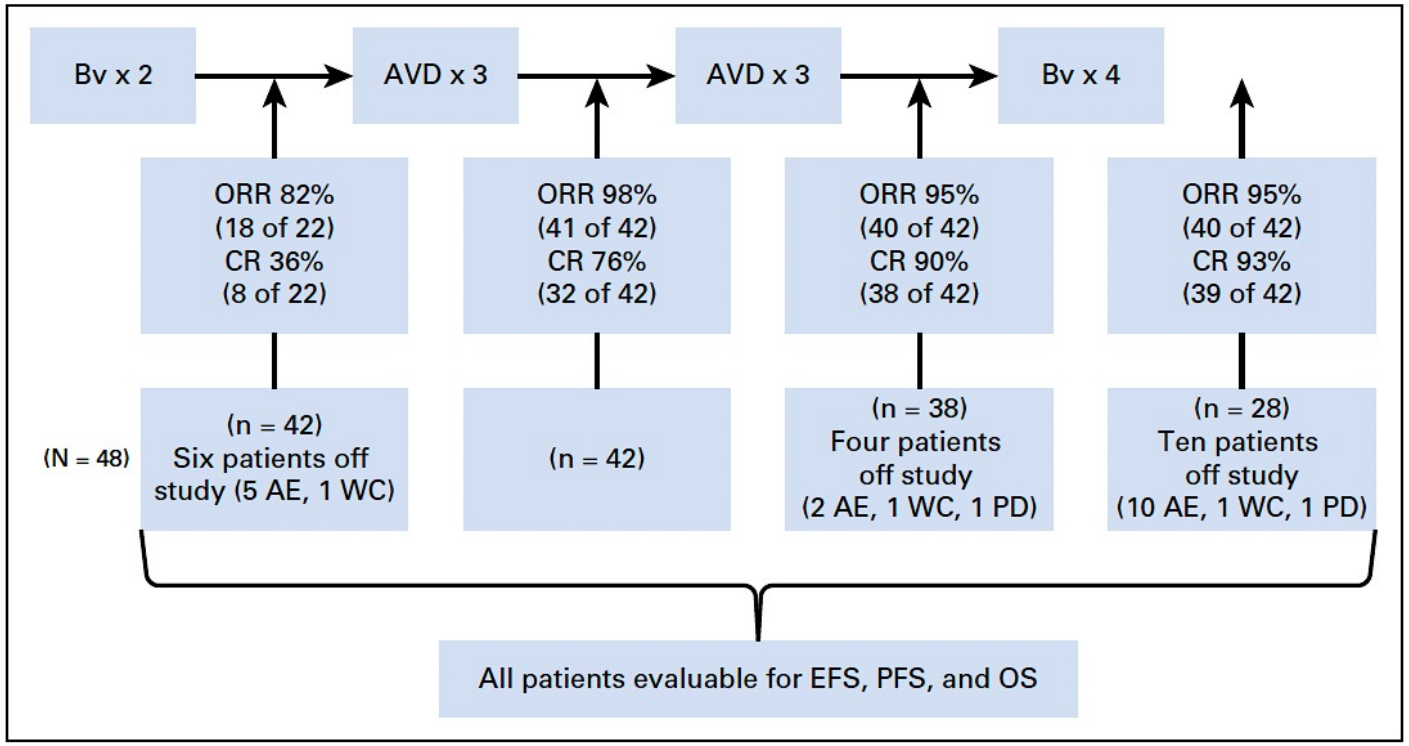


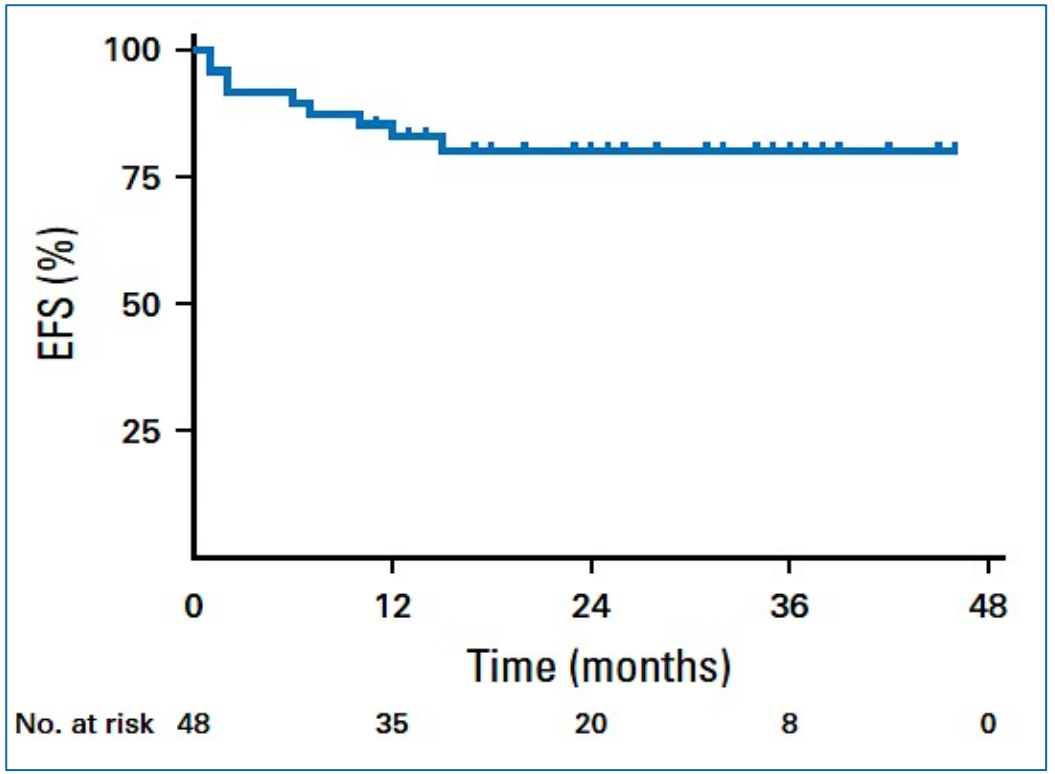
S1826

Herrera et al. ASCO 2023

Connors et al. NEJM 2017

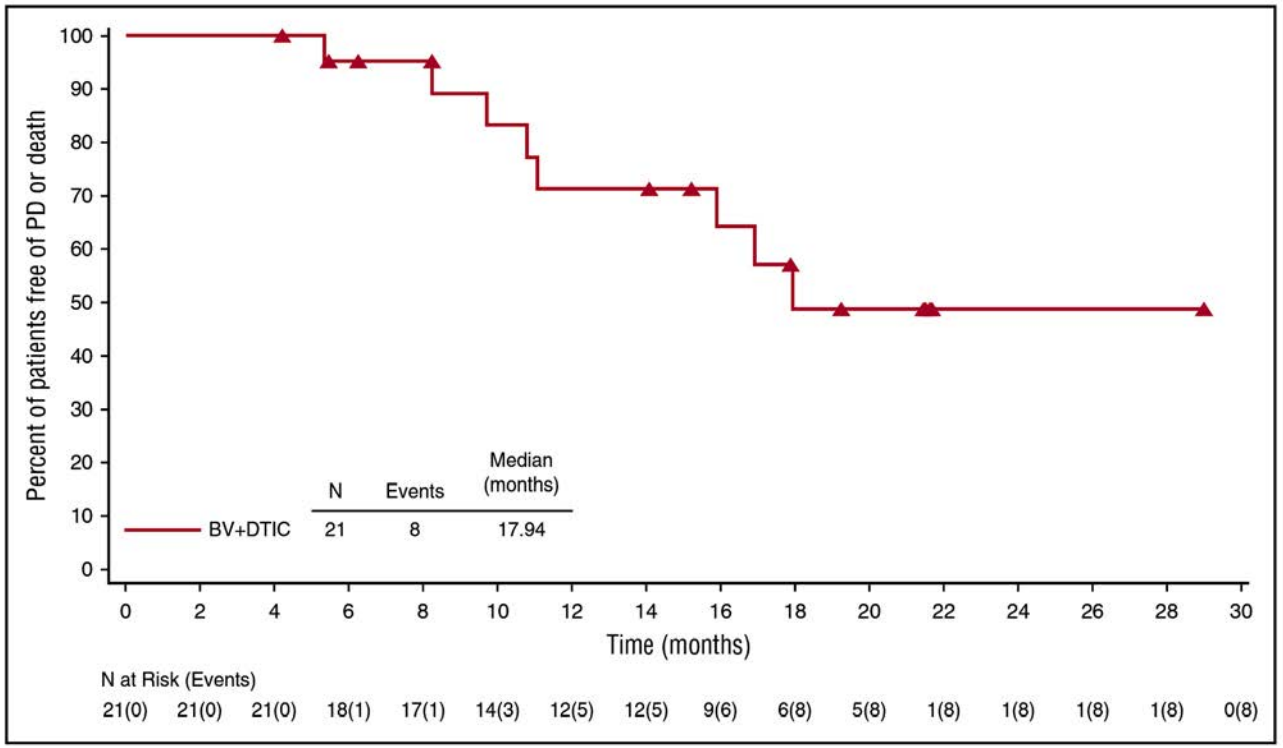
Sequential BV-AVD in elderly patients with stage IIB/IIX or III/IV HL

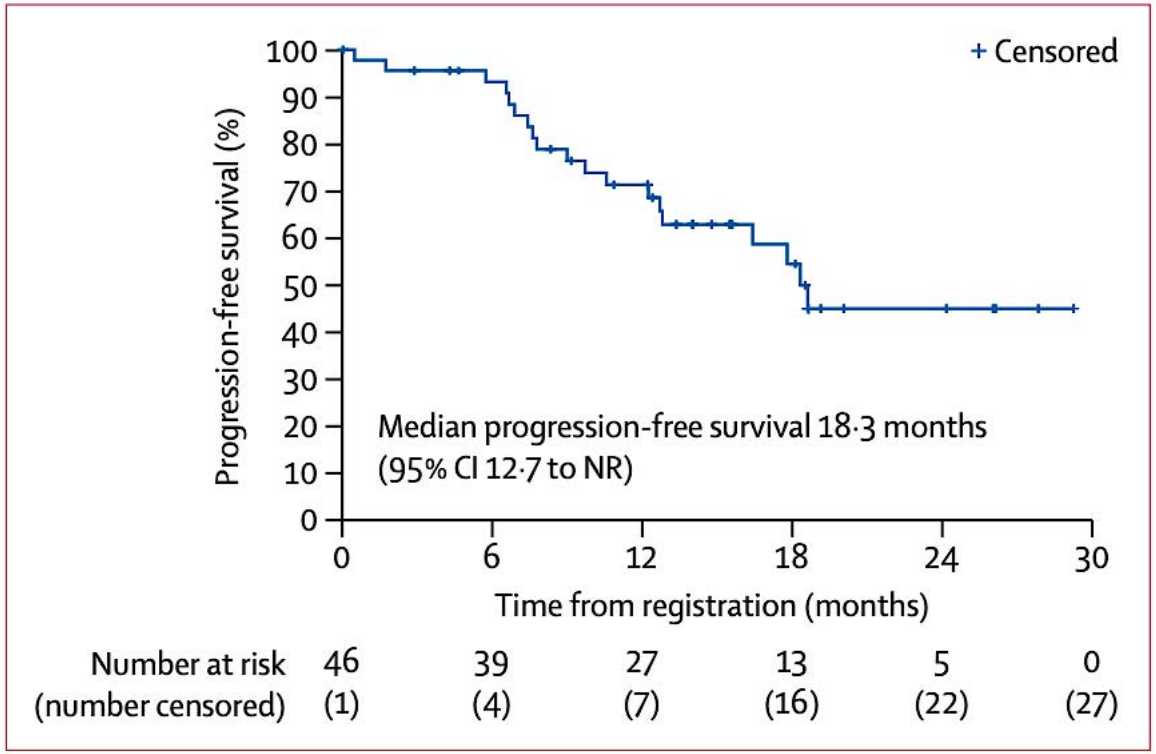




Evens et al. JCO 2018

BV+DTIC and BV+nivolumab in elderly patients with untreated HL

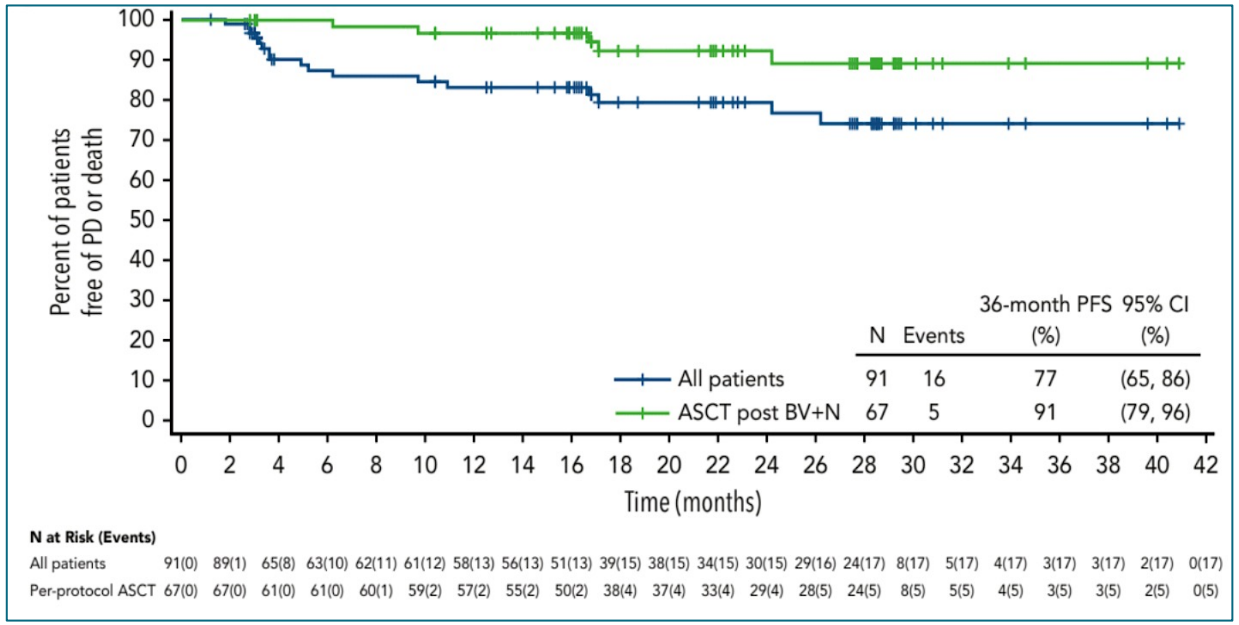


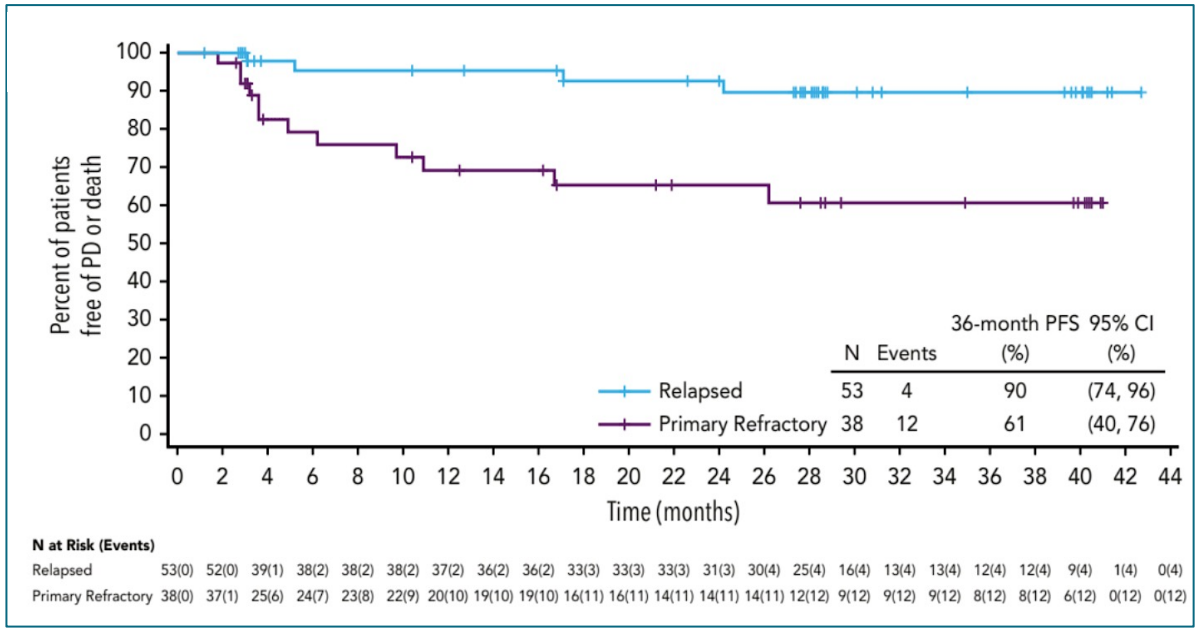


Friedberg et al. Blood 2017

Cheson et al. Lancet Hem 2020

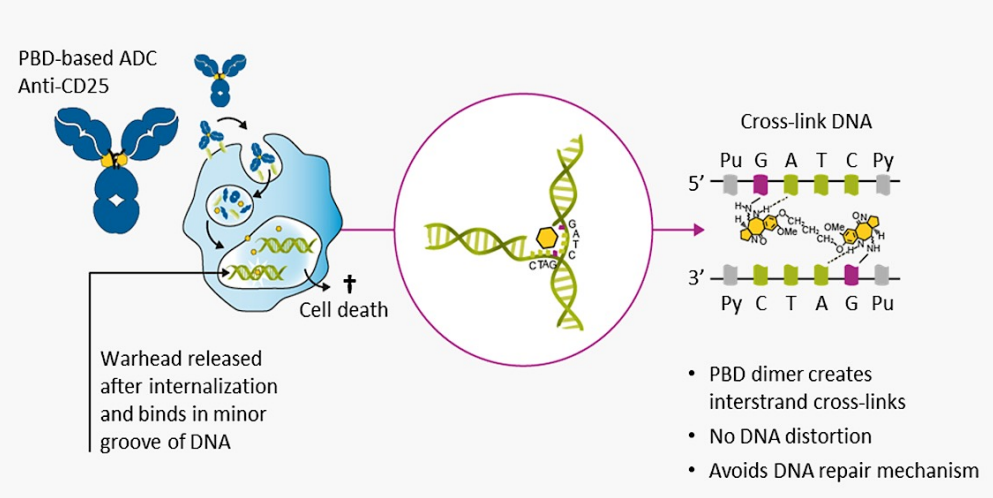
BV plus nivolumab first salvage with favorable PFS

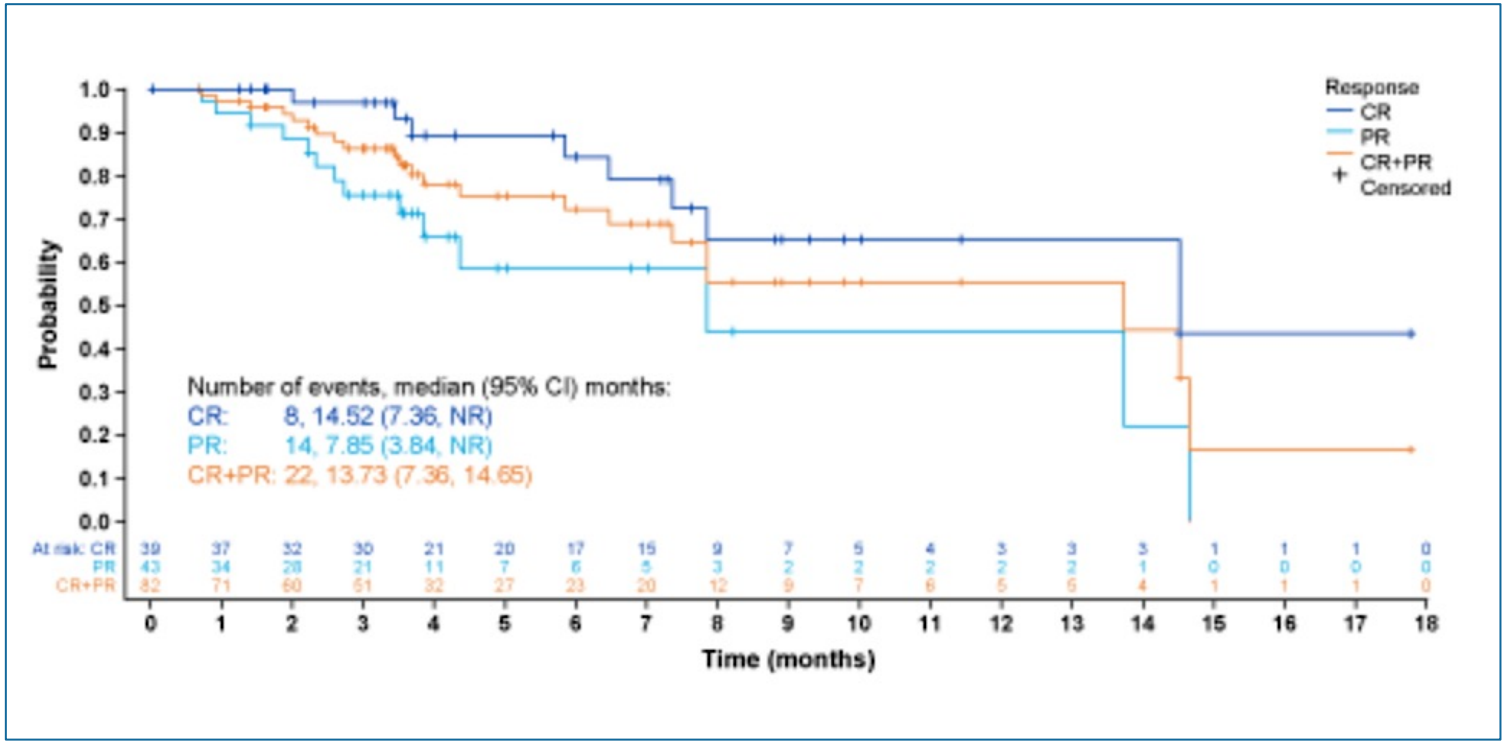




Advani et al. Blood 2021

Camidanlumab tesirine: updated phase 2 results





Eligible: ≥3 prior lines
median 6
n=117

ORR 70 %
CR 33%
Med 6 prior lines
mDOR 13.7 m
mPFS 9.1 m

GBS/polyradiculopathy in 8 pts (6.8%)
Other TRAE: rash, fever, cytopenias

Carlo-Stella et al. EHA 2022 / Herrera et al. ASH 2022

CD30 CAR-T generated using allogeneic EBV specific T-cells

N=16 patients

Median 5 prior lines of therapy

ORR 75% (CR 38%)

Persistence of CAR-T approx. 1 week despite lymphodepletion

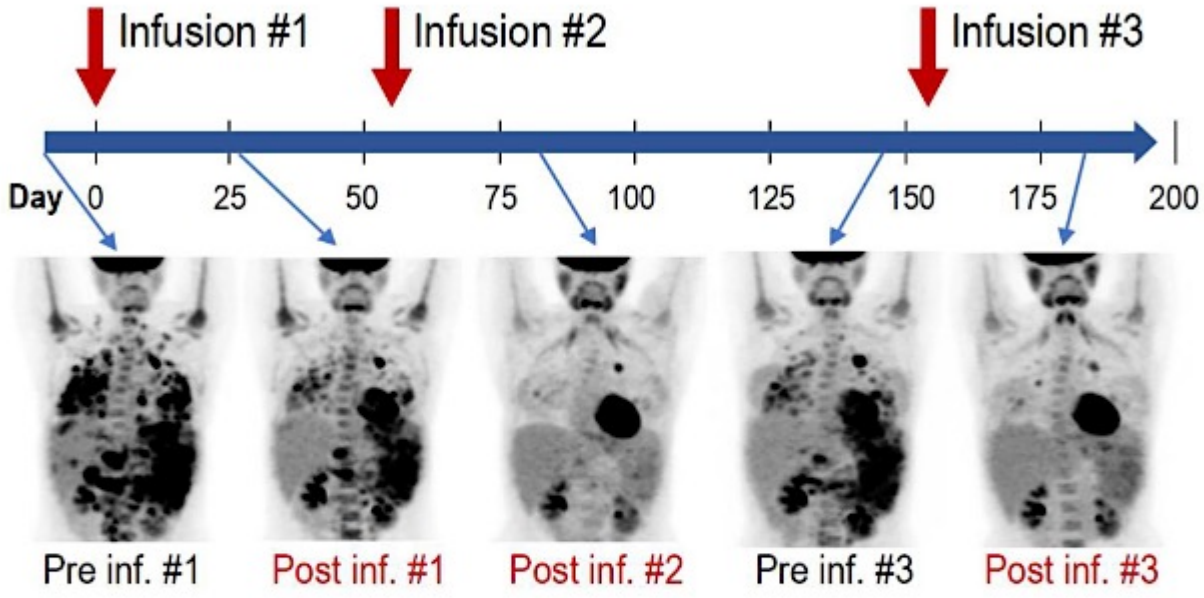


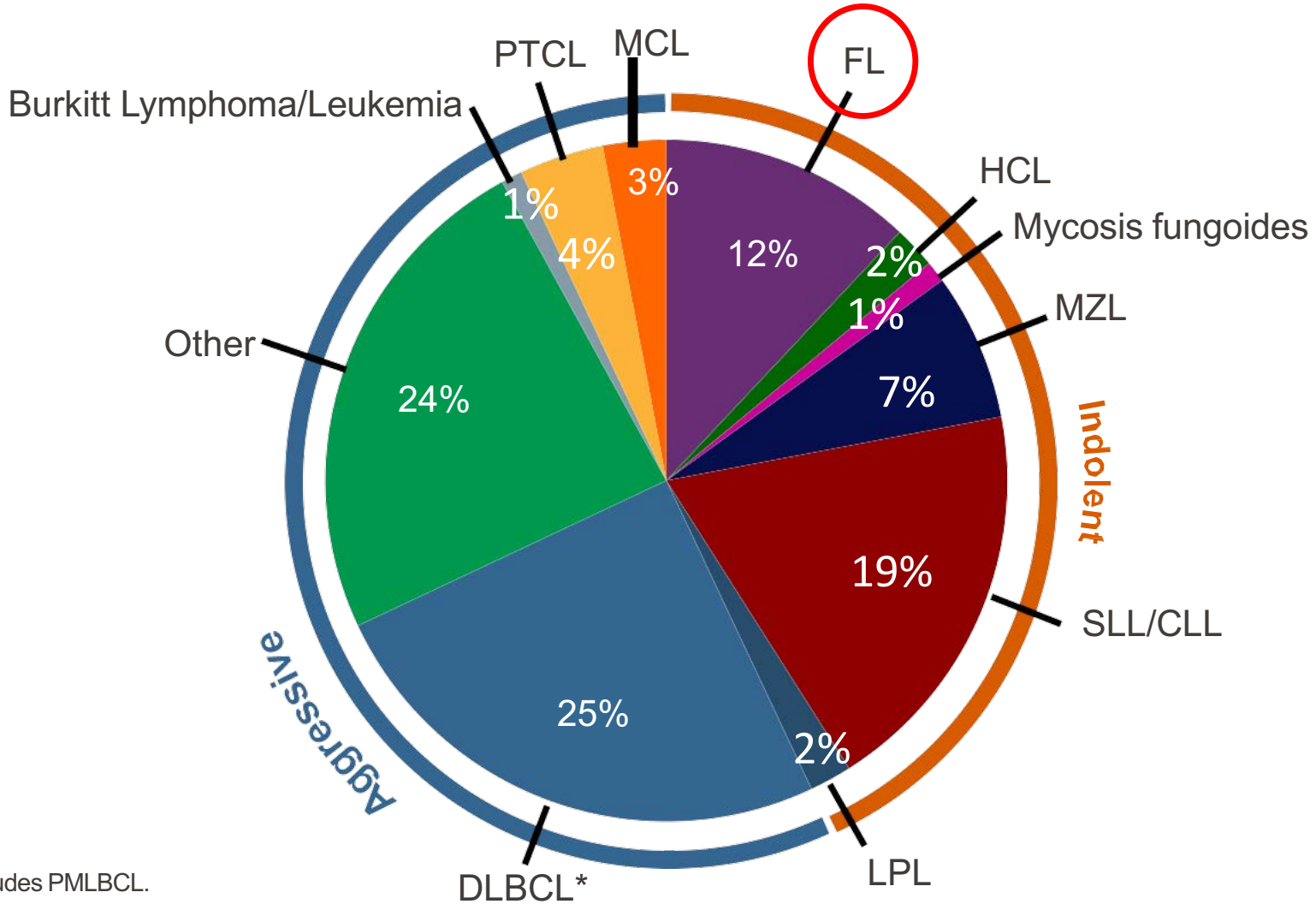
Figure 1. Clinical responses in patient who had high tumor burden and received 3 CD30.CAR-EBVST infusions at DL3. The timeline shows timing of infusions and diagnostic PET/CT scans, evidencing PR after each infusion.

Ramos et al. ICML 2023

Optimizing Therapy in FL and MCL

Christopher Flowers, MD, MS, FASCO
Chair, Professor
Department of Lymphoma/Myeloma

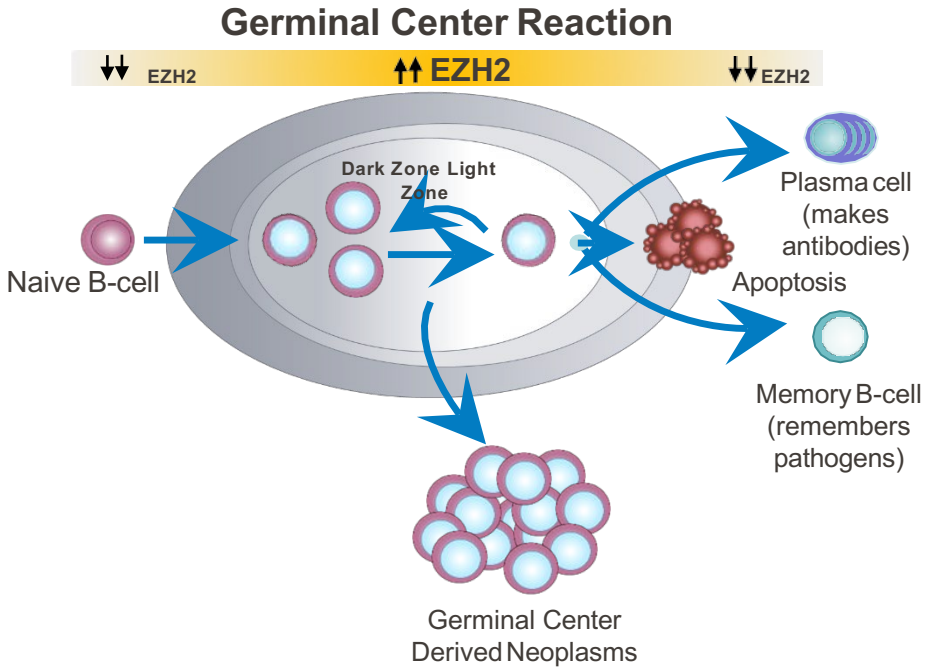
Distribution of NHL Subsets

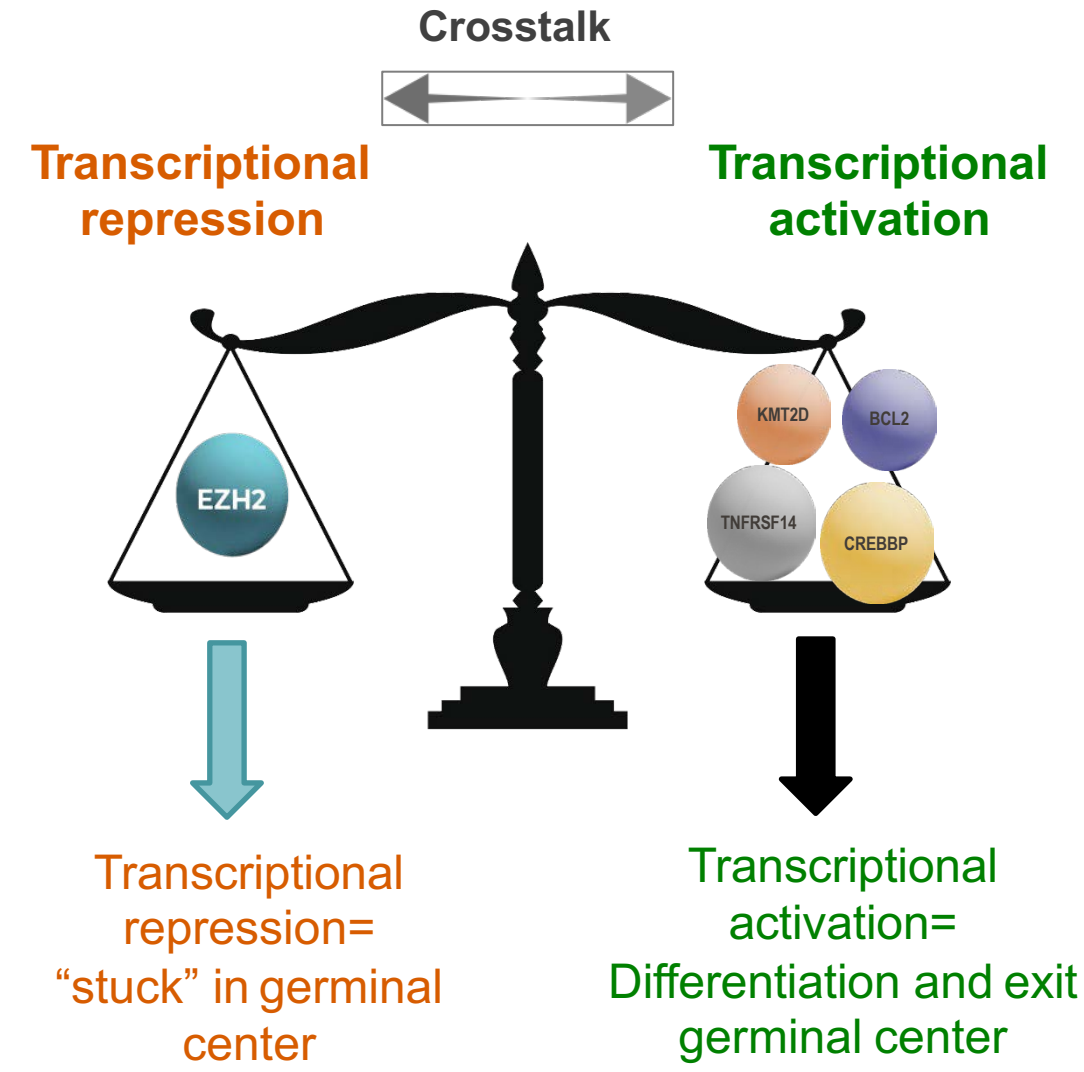


*Includes PMLBCL.

Teras LR, et al. *CA Cancer J Clin*. 2016;66:443-459

Tazemetostat: Follicular Lymphoma and *EZH2*





- EZH2 an epigenetic regulator of gene expression and cell fate decisions[1]
- EZH2 is required for normal B-cell biology and germinal center formation[2]
  - Oncogenic mutations in EZH2 suppress exit from germinal state and "lock" B cells in this state thereby transforming into a cancer[2]

1. Gan L et al. *Biomark Res*. 2018;6:10. 2. Béguelin W et al. *Cancer Cell*. 2013;23:677-692.

Tazemetostat for R/R FL
Phase 2, Open-Label, Multicenter Study

Response in the MT *EZH2* Cohort

Response in MT EZH2 (n=45)	IRC	INV
ORR, n (%) [95% CI[a]]	31 (69) [53, 82]	35 (78) [63, 89]
CR, n (%)	6 (13)	4 (9)
PR, n (%)	25 (56)	31 (69)
SD, n (%)	13 (29)	10 (22)
PD, n (%)	1 (2)	0

- 44 of 45[b] (98%) patients with evidence of tumor reduction, by IRC
- mPFS, 13.8 mos (95% CI, 10.7-22.0)

Response in the WT *EZH2* Cohort

Response in WT EZH2 (n=54)	IRC	INV
ORR, n (%) [95% CI[a]]	19 (35) [23, 49]	18 (33) [21, 48]
CR, n (%)	2 (4)	3 (6)
PR, n (%)	17 (31)	15 (28)
SD, n (%)	18 (33)	16 (30)
PD, n (%)	12 (22)	16 (30)
NE/missing/unknown,[b] n (%)	5 (9)	4 (7)

- 37 of 49[c] (69%) patients with evidence of tumor reduction, by IRC
- mPFS, 11.1 mos (95%CI, 3.7-`14.6)

[a]By Brookmeyer and Crowley method. [b]4 subjects with missing post-baseline values and 1 subject with poor image. [c]Best overall response based on Cheson (2007) criteria for lymphomas.

Morschhauser F et al. *Lancet Oncol.* 2020;21:1433-1444.

Tazemetostat: Safety Profile

	Treatment-emergent adverse events			Treatment-related adverse events		
	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4
Nausea	23 (23%)	0	0	19 (19%)	0	0
Diarrhea	18 (18%)	0	0	12 (12%)	0	0
Alopecia	17 (17%)	0	0	14 (14%)	0	0
Cough	16 (16%)	0	0	2 (2%)	0	0
Asthenia	15 (15%)	3 (3%)	0	13 (13%)	1 (1%)	0
Fatigue	15 (15%)	2 (2%)	0	11 (11%)	1 (1%)	0
Upper respiratory tract infection	15 (15%)	0	0	1 (1%)	0	0
Bronchitis	15 (15%)	0	0	3 (3%)	0	0
Abdominal pain	12 (12%)	1 (1%)	0	2 (2%)	0	0
Headache	12 (12%)	0	0	5 (5%)	0	0
Vomiting	11 (11%)	1 (1%)	0	6 (6%)	0	0
Back pain	11 (11%)	0	0	0	0	0
Pyrexia	10 (10%)	0	0	2 (2%)	0	0

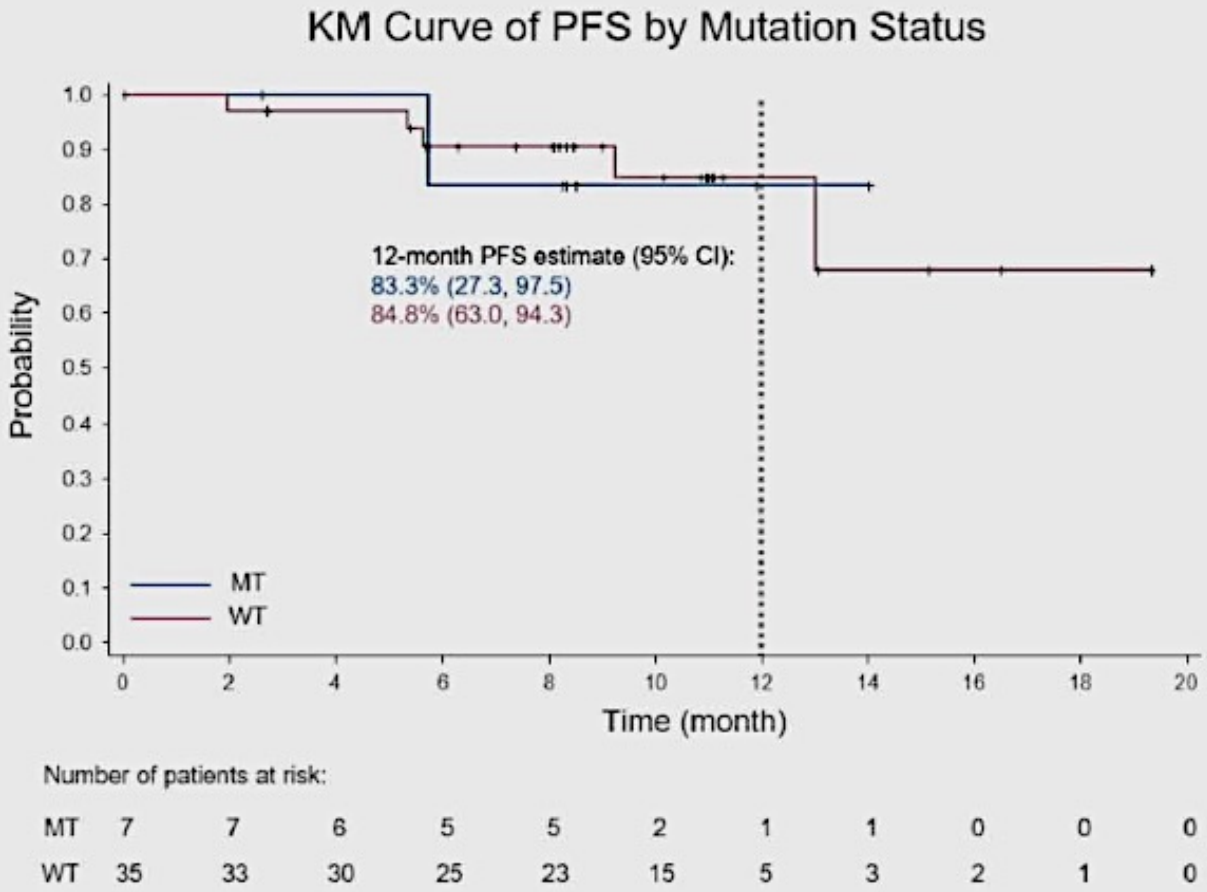
- 5% of all patients discontinued treatment
- 9% had dose reductions due to treatment-related AEs

Morschhauser et al, 2020.

SYMPHONY-1 Phase Ib/III Study: Tazemetostat with Lenalidomide/Rituximab for R/R FL

Best Overall Response,[a] % (n)	WT (n=33)	MT (n=7)
ORR	97.0 (32)	100 (7)
Complete response	45.5 (15)	71.4 (5)
Partial response	51.5 (17)	28.6 (2)
Stable disease	3.0 (1)	0

- ORR was 97.0% in patients with WT *EZH2* (n=32)
- ORR was 100% in patients with MT *EZH2* (n=7)
- mPFS and mDOR were not reached



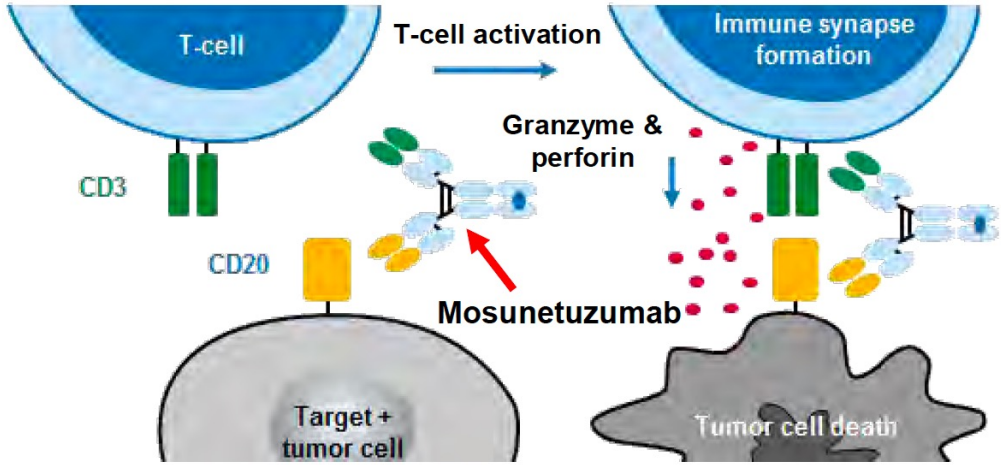
WT = wild type; MT = mutated; mPFS = median progression-free survival; mDOR = median duration of response

Batlevi CL et al. ASH 2022;Abstract 954.

Mosunetuzumab

- Mosunetuzumab **(first-in-class)** is approved in the EU and is under Priority Review by the FDA, for the treatment of **relapsed/refractory follicular lymphoma (R/R FL)** after ≥2 prior systemic therapies[1,2]
  - **ORR 80%, CR 60%,** majority maintaining response after 18 months[3]
  - Consistent benefit in patients with double-refractory disease and POD24[3]
  - **Off-the-shelf, fixed-duration** treatment that can be administered in the **outpatient** setting[3]

Mosunetuzumab: CD20xCD3 T-cell-engaging bispecific antibody that redirects T cells to engage and eliminate malignant B cells[4,5]



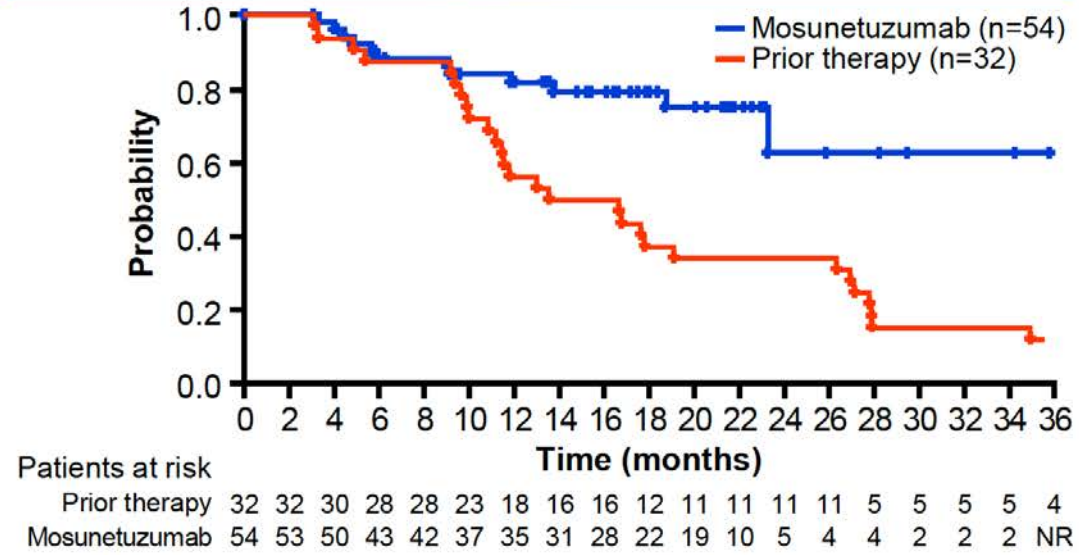
We present updated results after a median 28.3 months of follow-up (cut-off: July 8, 2022)

1. Lunsumio SmPC: https://www.ema.europa.eu/en/medicines/human/EPAR/lunsumio;
2. Lunsumio Filing Acceptance: https://www.roche.com/media/releases/med-cor-2022-07-06; 3. Budde LE, et al. Lancet Oncol 2022;23:1055–1065;
4. Sun LL, et al: Sci Transl Med 2015;7:287ra70; 5. Hernandez G, et al. ASH 2019; poster presentation (P-1585).

Bartlett NL et al. ASH 2022;Abstract 610.

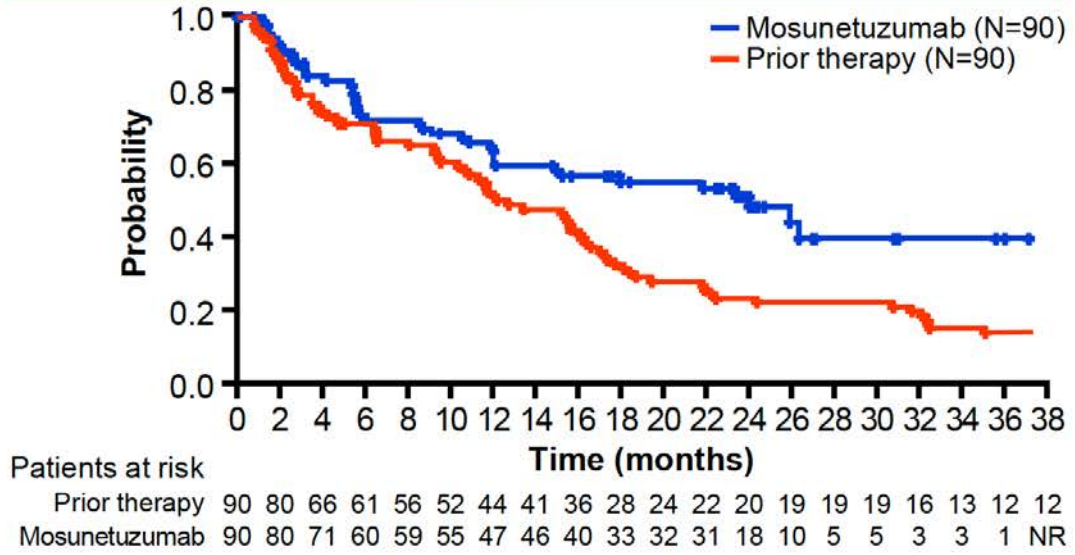
Updated Phase II Results: Duration of Complete Response (DOCR) and PFS with Mosunetuzumab versus Last Prior Therapy for R/R FL

DOCR



	Mosunetuzumab (n=54)	Last prior therapy (n=32)
Median DOCR, months (95% CI)	**NR** (23–NR)	**15** (11–26)

PFS



	Mosunetuzumab (N=90)	Last prior therapy (N=90)
Median PFS, months (95% CI)	**24** (12–NR)	**12** (10–16)

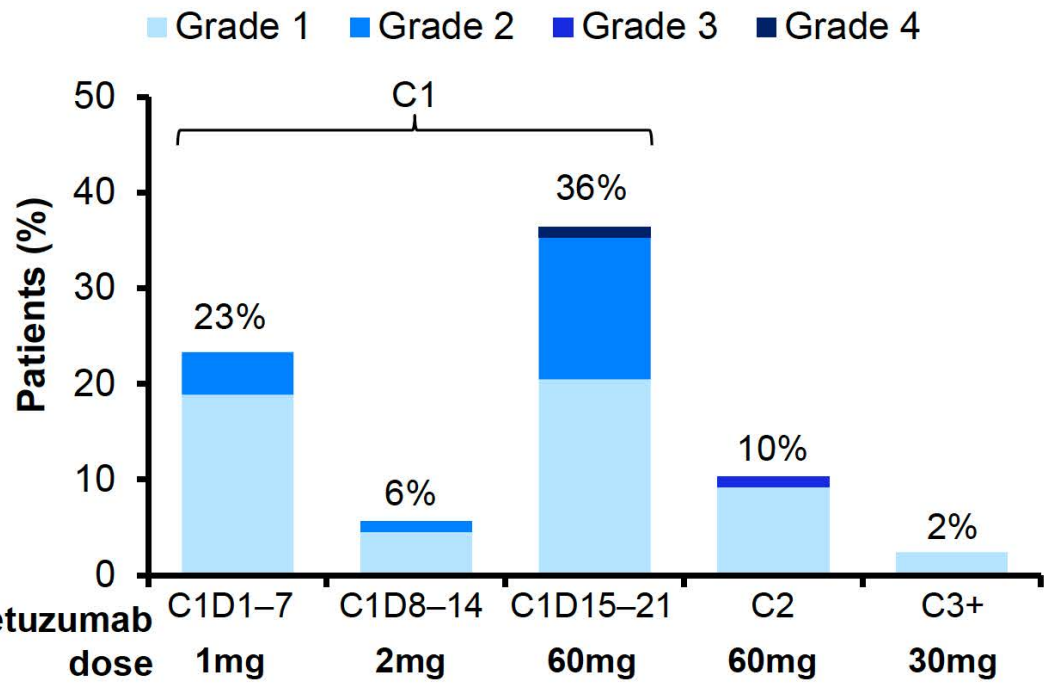
Extended DOCR and 12-month improvement in median PFS with mosunetuzumab compared with last prior therapy

Bartlett NL et al. ASH 2022;Abstract 610.

Mosunetuzumab CRS Summary

CRS by ASTCT criteria[1]	N=90
CRS (any grade)	44%
Grade 1	26%
Grade 2	17%
Grade 3	1%
Grade 4	1%
Median time to CRS onset, hours (range)	
C1D1	5.2 (1.2–24)
C1D15	27 (0.1–391)
Median CRS duration, days (range)	3 (1–29)
Corticosteroids for CRS management	11%
Tocilizumab for CRS management	8%
Events resolved	100%

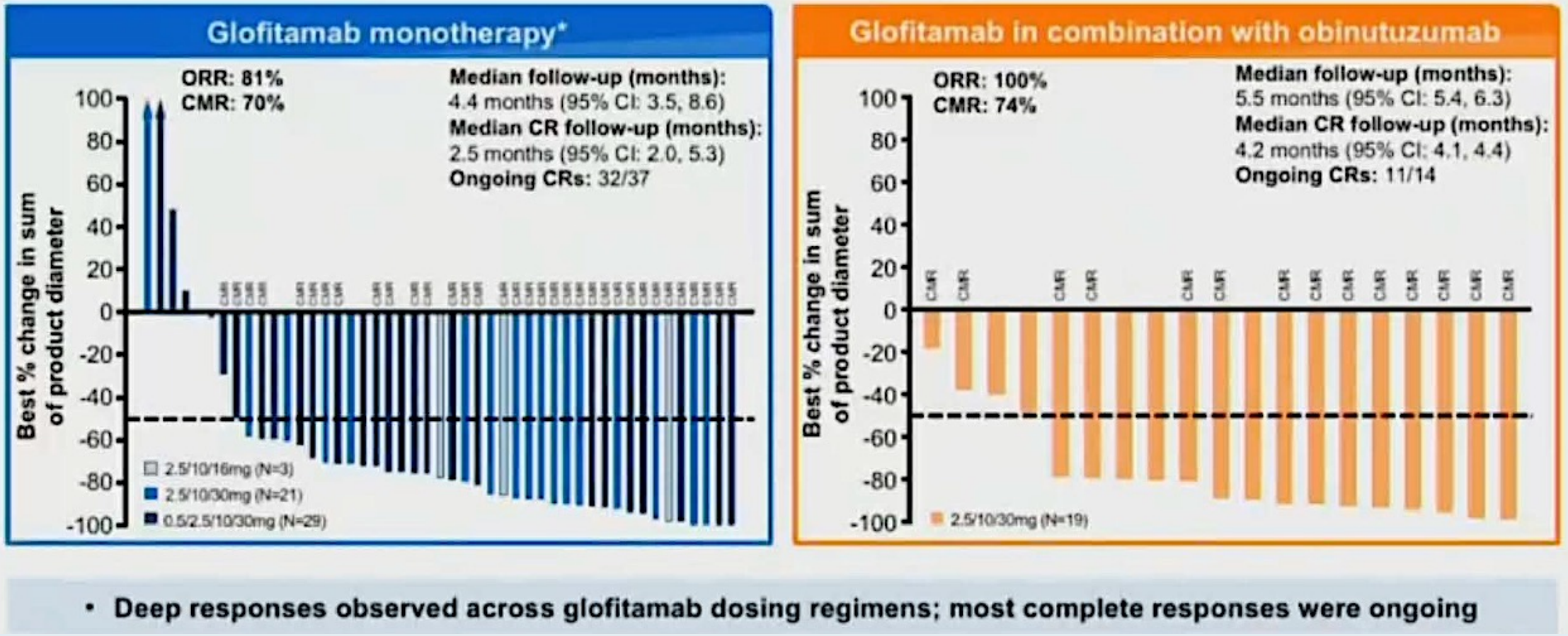
CRS by cycle and grade



CRS was predominantly low grade and during Cycle 1
All CRS events resolved; no new events were reported with 10 months of additional follow-up

1. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–638.

Phase I/II Study of Glofitamab as Monotherapy or in Combination with Obinutuzumab for R/R FL



- **Deep responses observed across glofitamab dosing regimens; most complete responses were ongoing**

- Myelosuppression was more common with the combination
- CRS rates were high and comparable, and cases were mainly low grade

Morschhauser F et al. ASH 2021;Abstract 128.

RTP RESEARCH TO PRACTICE

ELM-2: Efficacy of Odronextamab in Cohort of Patients with R/R FL

Best overall response	Independent central review N=121*	Investigator evaluation N=121*
Objective response rate (ORR)†	**81.8%** [95% CI: 73.8–88.2%]	81.8% [95% CI: 73.8–88.2%]
Complete response	**75.2%**	70.2%
Partial response	6.6%	11.6%
Stable disease	5.8%	2.5%
Progressive disease	4.1%	5.8%

Week 12 response assessment by independent central review	1/20 step-up regimen N=68	0.7/4/20 step-up regimen N=53
ORR	72.1% [95% CI: 59.9–82.3%]	75.5% [95% CI: 61.7–86.2%]
Complete response	61.8%	71.7%

- Majority of R/R FL patients achieved a complete response
- 92% of responders were complete responders
- Consistent efficacy observed at Week 12 regardless of Cycle 1 step-up regimen

- Median opportunity of follow-up: 22.4 months (range 2.6–33.0)

Kim TM et al. ASH 2022;Abstract 949.

Positive Topline Results Announced for Phase I/II EPCORE NHL-1 Trial for Patients with Relapsed/Refractory Follicular Lymphoma

Press Release: June 27, 2023

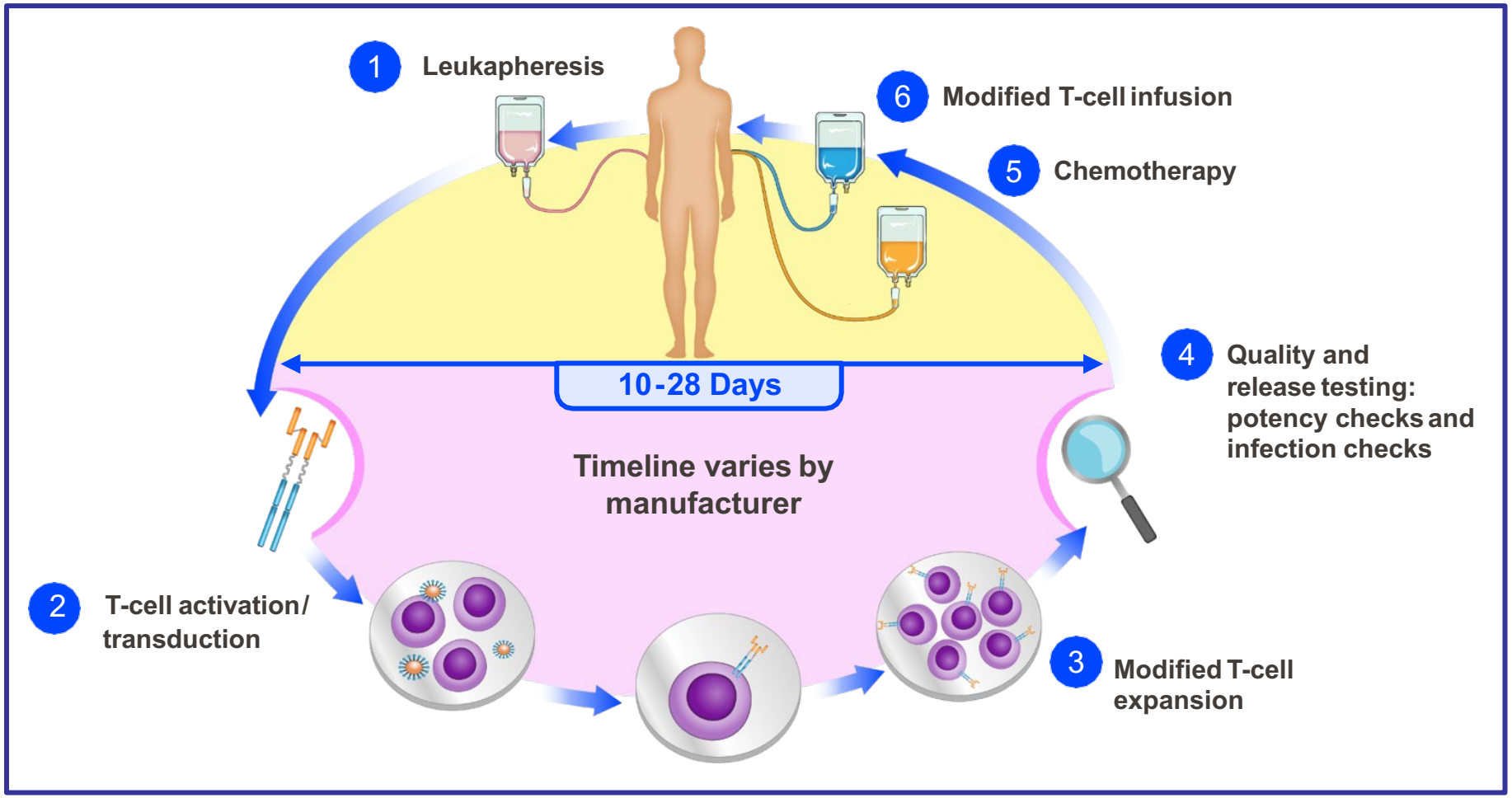
"Topline results were announced from the follicular lymphoma (FL) cohort of the Phase 1/2 EPCORE™ NHL-1 clinical trial evaluating epcoritamab, an investigational T-cell engaging bispecific antibody administered subcutaneously. The study cohort includes 128 adult patients with relapsed or refractory (R/R) FL who received at least two or more lines of systemic therapy. 70.3 percent of patients were double refractory to an anti-CD20 monoclonal antibody and an alkylating agent.

No new safety signals were observed with epcoritamab in this study at the time of this analysis. The most common treatment-emergent adverse event was cytokine release syndrome (CRS) with 66.4 percent (1.6 percent Grade 3 or higher). The optimization part of the trial is continuing to evaluate alternative step-up dosing regimens to help further mitigate the risk of CRS, preliminary data are encouraging.

Full results from the study will be submitted for presentation at a future medical meeting."

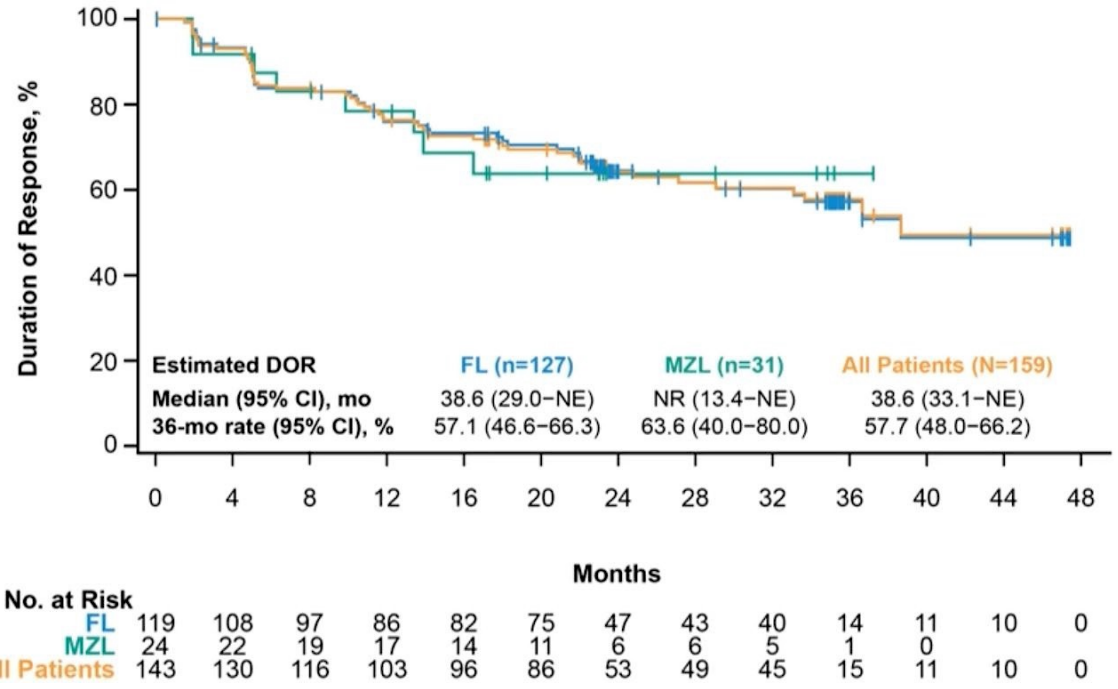
https://news.abbvie.com/news/press-releases/abbvie-and-genmab-announce-positive-topline-results-from-phase-12-epcore-nhl-1-trial-evaluating-epcoritamab-duobody-cd3xcd20-in-patients-with-relapsedrefractory-follicular-lymphoma-fl.htm

Overview of CAR-T Therapy

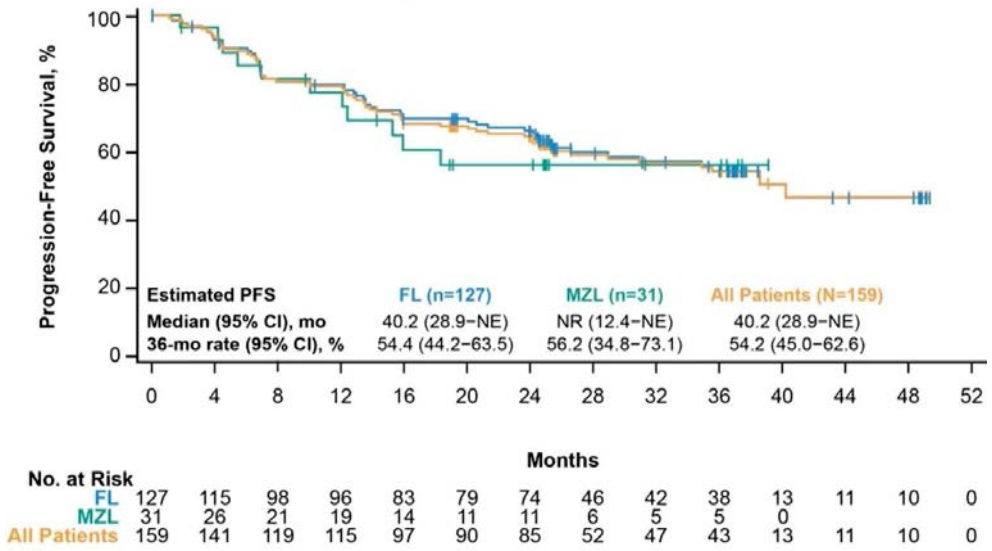


ZUMA-5 Outcomes: DOR, PFS, OS — ASH 2022

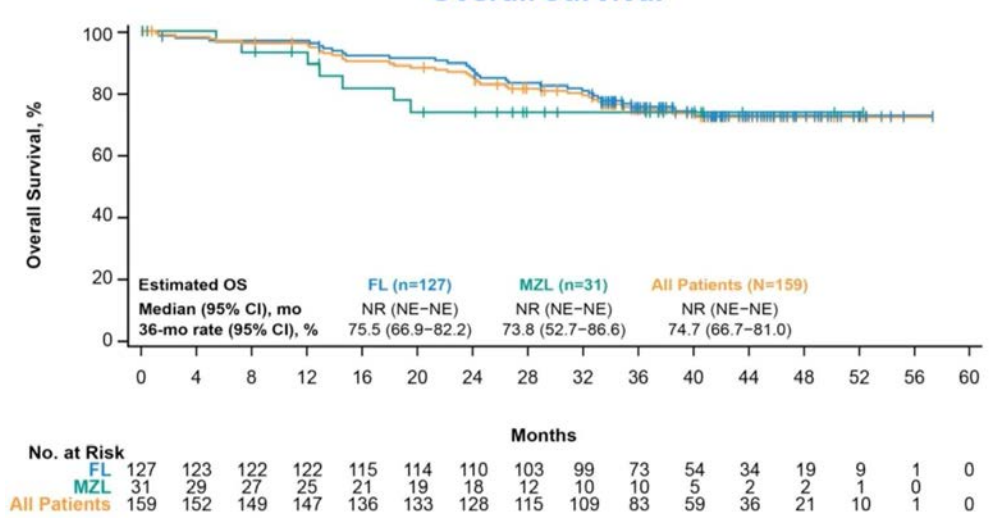
Duration of Response



Progression-Free Survival[a]



Overall Survival



Neelapu SS et al. ASH 2022. Abstract 4660.

ELARA: Long-Term Outcomes with Tisagenlecleucel for R/R FL

Endpoint in Efficacy Analysis Set (IRC Assessment)	% (95% CI) N=94
CRR[a]	68 (58-77)[b]
ORR[c]	86 (78-92)[b]

- High ORR (86%) and CRR (69%) are consistent with the primary analysis[1]

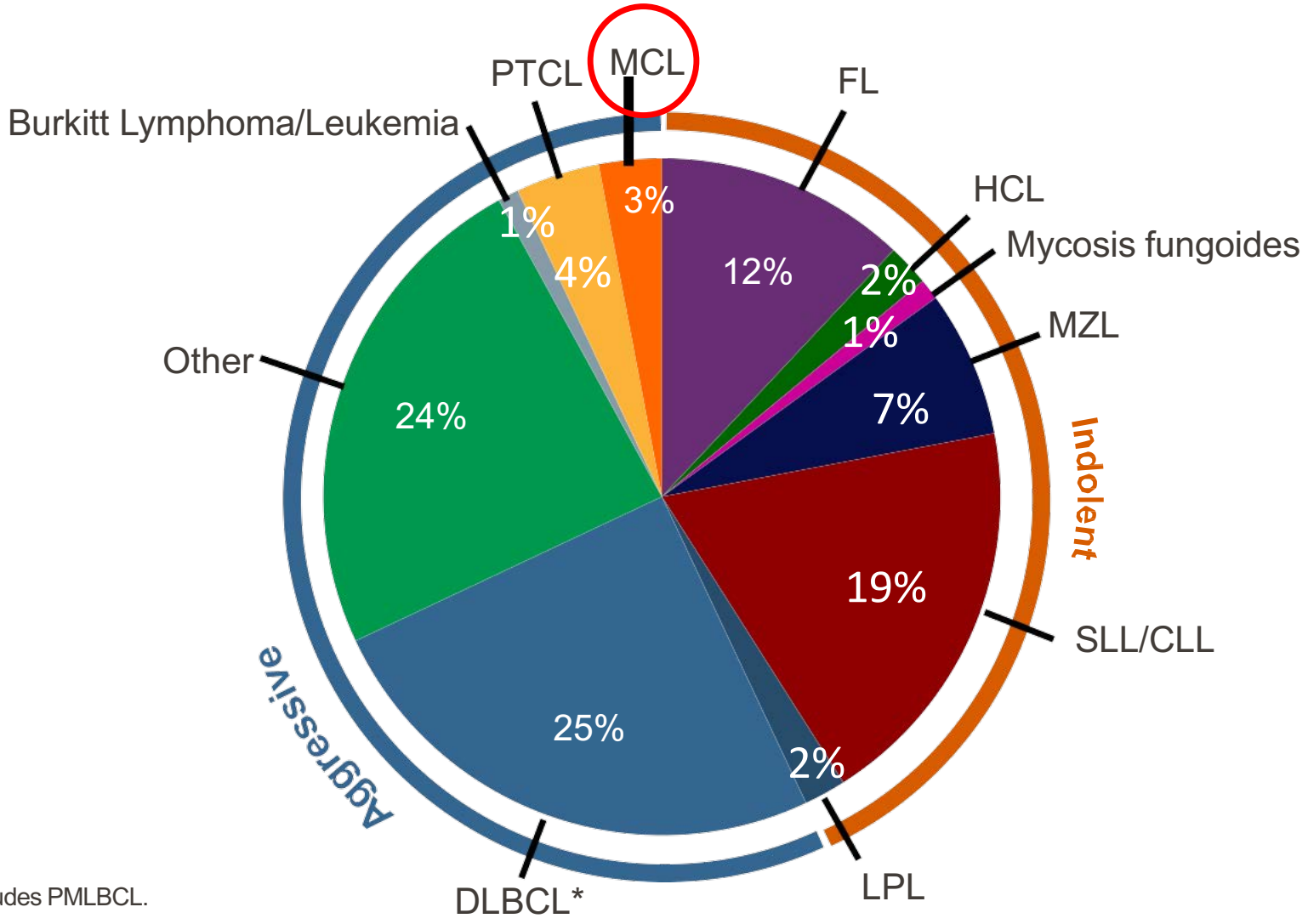
Baseline Disease Characteristic	All Patients n (%) N=97	CRR % (95% CI)	ORR % (95% CI)
POD24	61 (63)	59 (46-71)	82 (70-91)
High metabolic tumor volume[d]	20 (21)	40 (19-64)	75 (51-91)
Bulky disease[e]	62 (64)	65 (51-76)	86 (74-93)
Double refractory	65 (67)	66 (53-77)	85 (74-92)
High FLIPI (≥3)	57 (59)	61 (48-74)	81 (68-90)

- High rates of durable responses were observed in most patients in high-risk disease subgroups who have poor prognosis with current non-CAR-T cell therapies

- Median duration of response, PFS and OS were not reached after a median follow-up of 29 months
- No new safety signals were observed

Dreyling M et al. ASH 2022;Abstract 608.

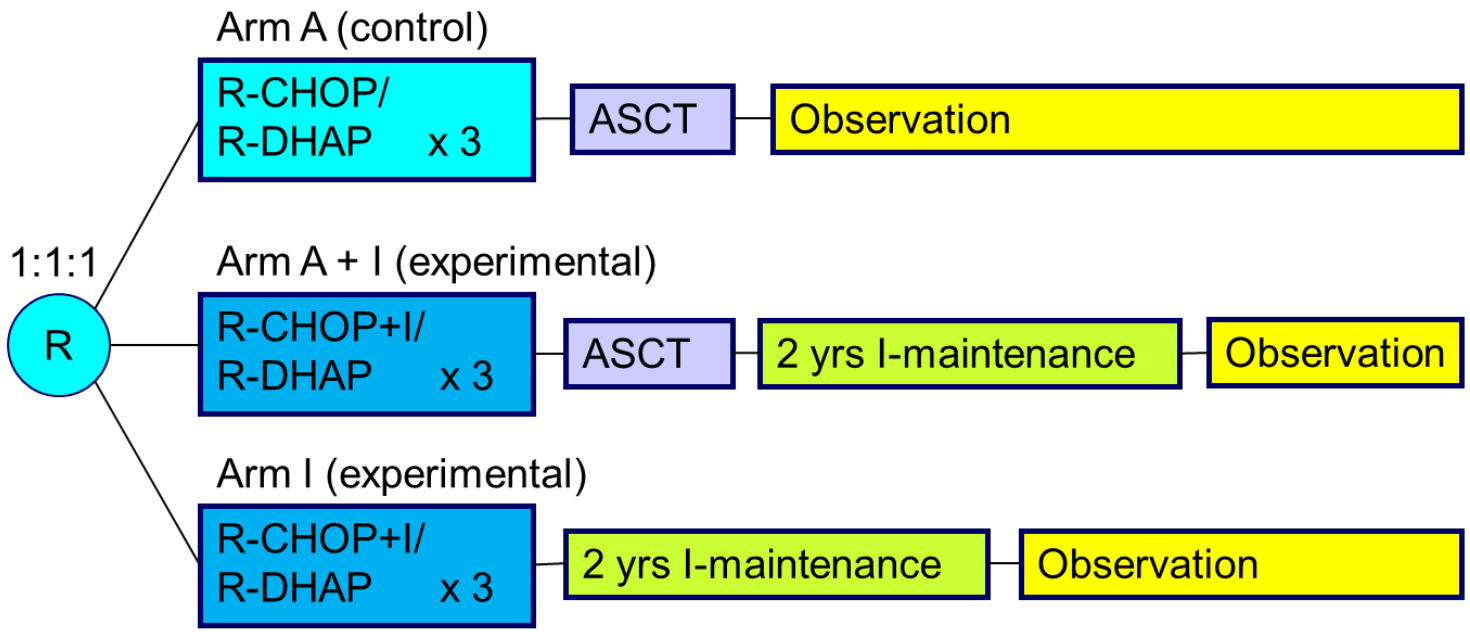
Distribution of NHL Subsets



*Includes PMLBCL.

Teras LR, et al. *CA Cancer J Clin*. 2016;66:443-459

TRIANGLE: Ibrutinib + R-CHOP/R-DHAP ± ASCT ± Ibrutinib Maintenance



Test 1: FFS Superiority of A+I vs. A

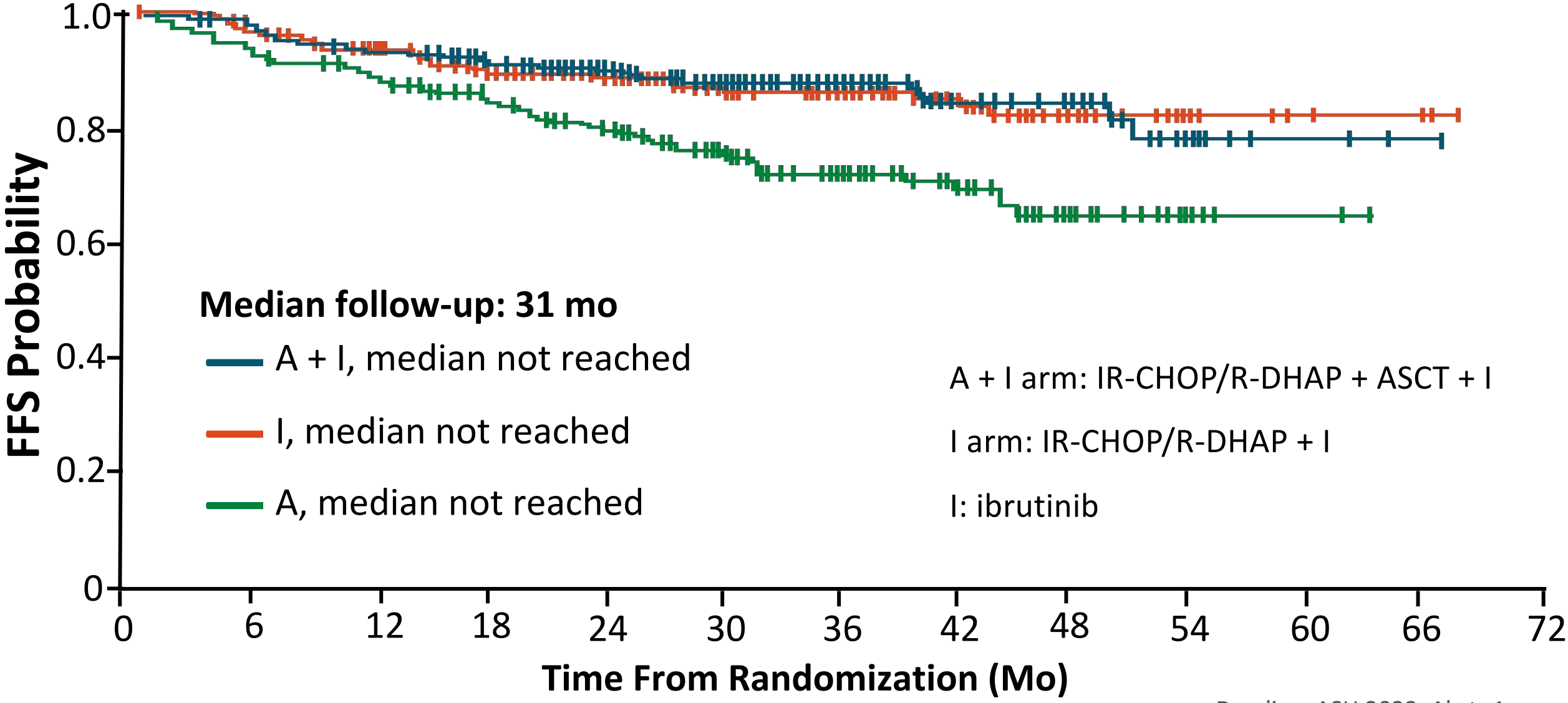
Test 2: FFS Superiority of A vs. I

Test 3: FFS Superiority of A+I vs. I

FFS = failure-free survival

Dreyling M et al. ASH 2022;Abstract 1.

TRIANGLE: FFS (Primary Endpoint)



Dreyling. ASH 2022. Abstr 1.

SHINE: A Randomized, Double-Blind, Phase III Study

Patients

- Previously untreated MCL
- ≥ 65 years of age
- Stage II to IV disease
- No planned stem cell transplant

Stratification factor

- Simplified MIPI score (low vs intermediate vs high)

N = 523

R 1:1

BR induction for 6 cycles → **if CR or PR** → **R**ituximab maintenance every 8 weeks for 12 cycles

Ibrutinib 560 mg (4 capsules daily) until PD or unacceptable toxicity

BR induction for 6 cycles → **if CR or PR** → **R**ituximab maintenance every 8 weeks for 12 cycles

Placebo (4 capsules daily) until PD or unacceptable toxicity

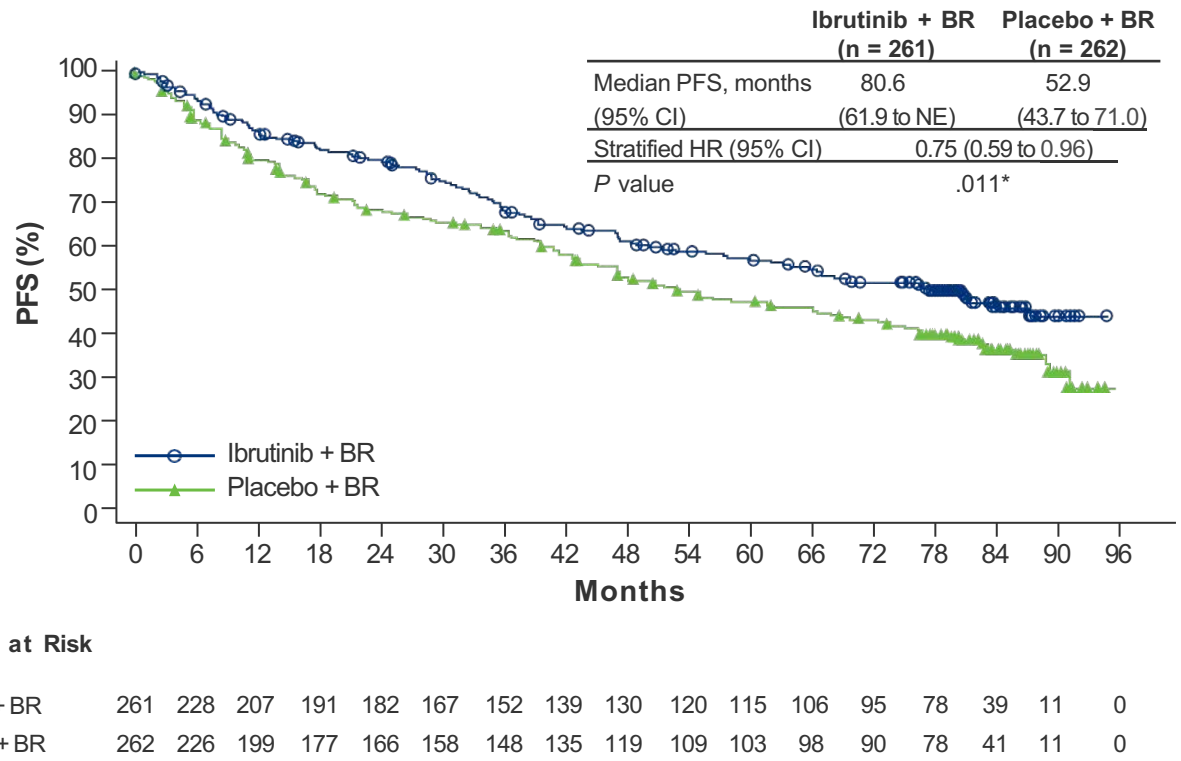
Enrolled between May 2013 and November 2014 at 183 sites

Primary end point: PFS (investigator-assessed) in the ITT population

Key secondary end points: response rate, time to next treatment, overall survival, safety

Induction: Bendamustine 90 mg/m^2 Days 1 and 2, Rituximab 375 mg/m^2 Day 1, Q4W. A cycle is defined as 28 days.
CR, complete response; ITT, intent-to-treat; MIPI, Mantle Cell Lymphoma International Prognostic Index; PD, progressive disease; PFS, progression-free survival; PR, partial response.
Wang ML, et al. N Engl J Med. 2022;386:2482-2494.

Primary Endpoint of Improved PFS Was Met



- **Significant improvement in median PFS by 2.3 years** (6.7 vs 4.4 years)
- **25% reduction** in risk of PD or death

	BR + I	BR + P
ORR	89.7	88.5
CR	65.5	57.6
PR	24.1	30.9

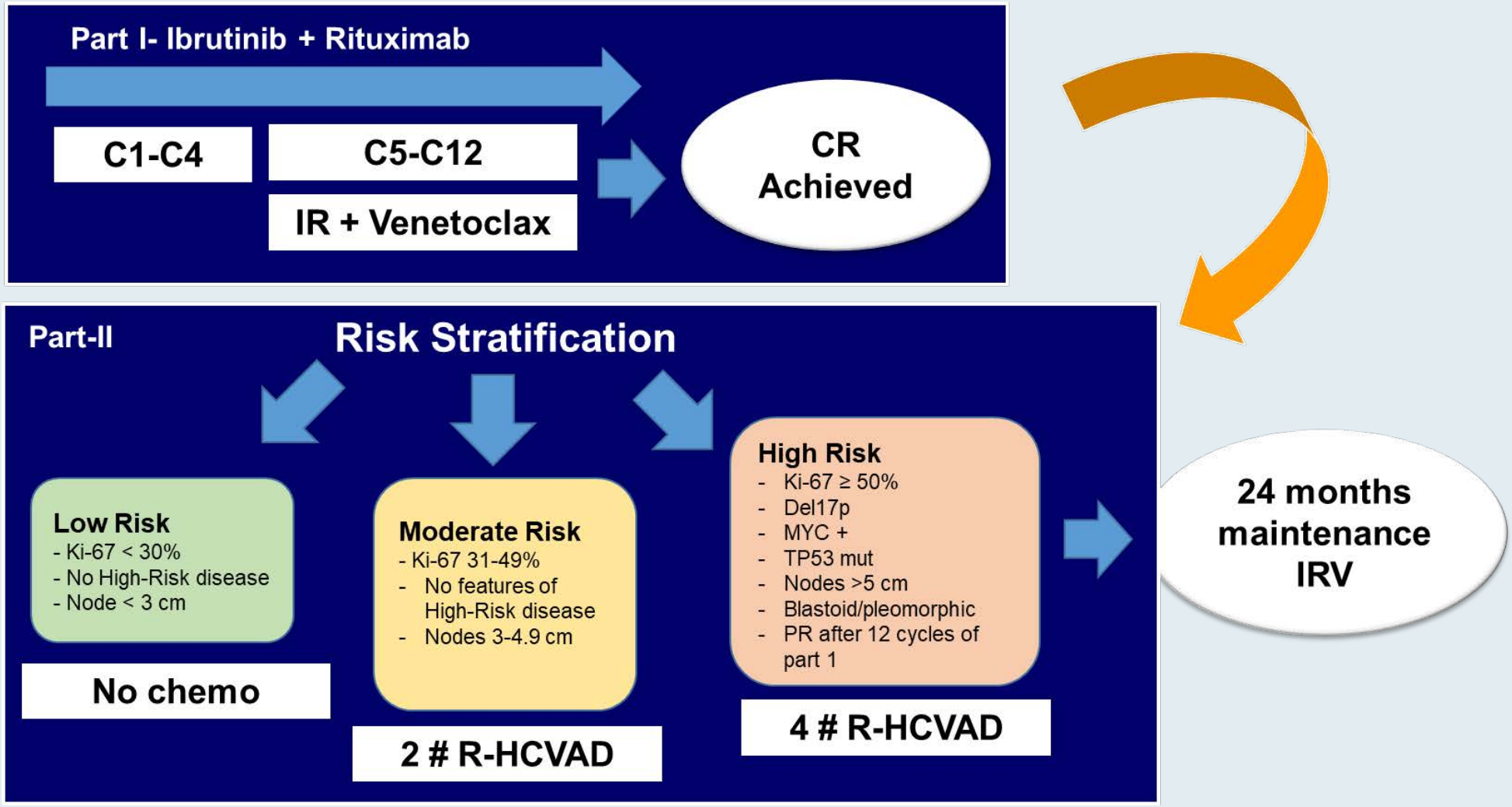
HR, hazard ratio; NE, not evaluable.
*Significance boundary for superiority was $P < .023$.
Wang ML, et al. N Engl J Med. 2022;386:2482-2494.

Ibrutinib

- November 2013, FDA granted accelerated approval to ibrutinib for MCL based on ORR of 65.8% in multicenter, single-arm phase 2 study
- Confirmatory phase 3 SHINE met primary end point of PFS, but ibrutinib + BR had more toxicity vs the control regimen.

- April 2023, voluntary withdrawal of the accelerated approvals of ibrutinib for MCL in patients who have received at least 1 prior therapy, and MZL in patients who require systemic therapy and have received at least 1 prior anti-CD20-based therapy

Phase II Window II Trial: Ibrutinib/Rituximab and Venetoclax (IRV) Followed by R-hyper-CVAD for Young Patients with Untreated Mantle Cell Lymphoma



Wang M et al. ICML 2023;Abstract 101.

WINDOW-2 Trial Responses

Response (ITT)	All patients
Part A – IR Best response	N (%)
Evaluable patients	46
ORR	44 (88)
CR	23 (46)
Part A – IRV Best response	
Evaluable patients	46
ORR	46 (96)
CR	46 (92)

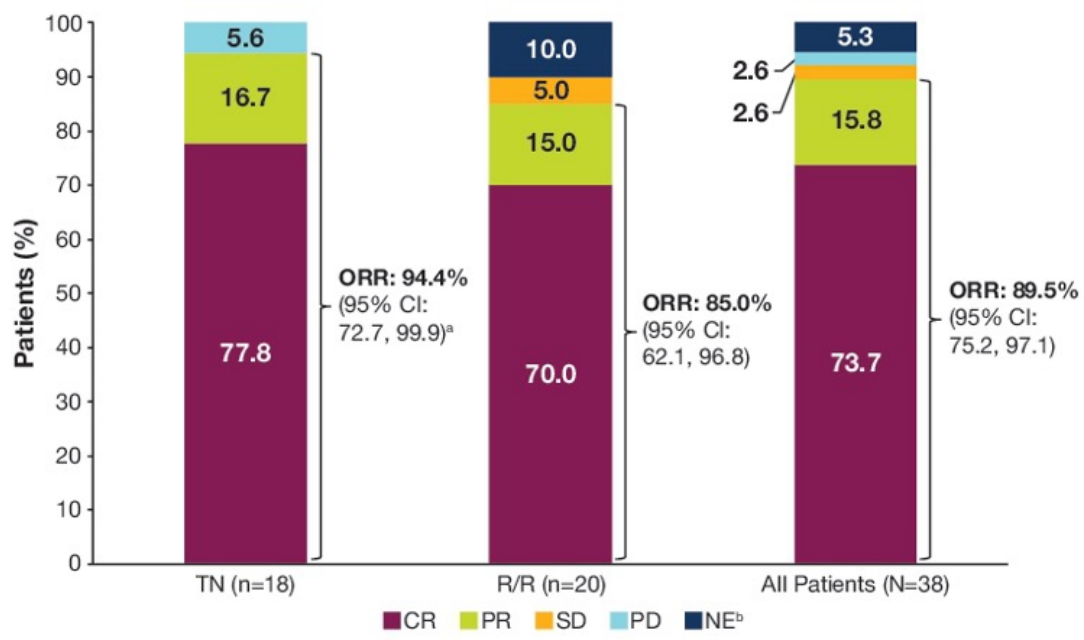
- **Two pts had isolated GI/BM disease with CR on part A**
- **Best response to IRV was 100% and CR of 100% (no ITT)**
- **The median number of cycles of triplet IRV to reach best response was 8 cycles (range 2-12)**

Median number of cycles of chemo R-HCVAD was 2 (range 0-4); 3 pts got only one cycle of chemo and discontinued due to AEs; ORR and CR with part B (no ITT) 100%

Wang M et al. ICML 2023;Abstract 101.

Phase Ib Study of Acalabrutinib with Bendamustine/Rituximab (ABR) for Patients with MCL: Results From Treatment-Naïve (TN) Cohort

Investigator Assessed ORR by Lugano Criteria



Maximum Change from Baseline in SPD – TN Cohort

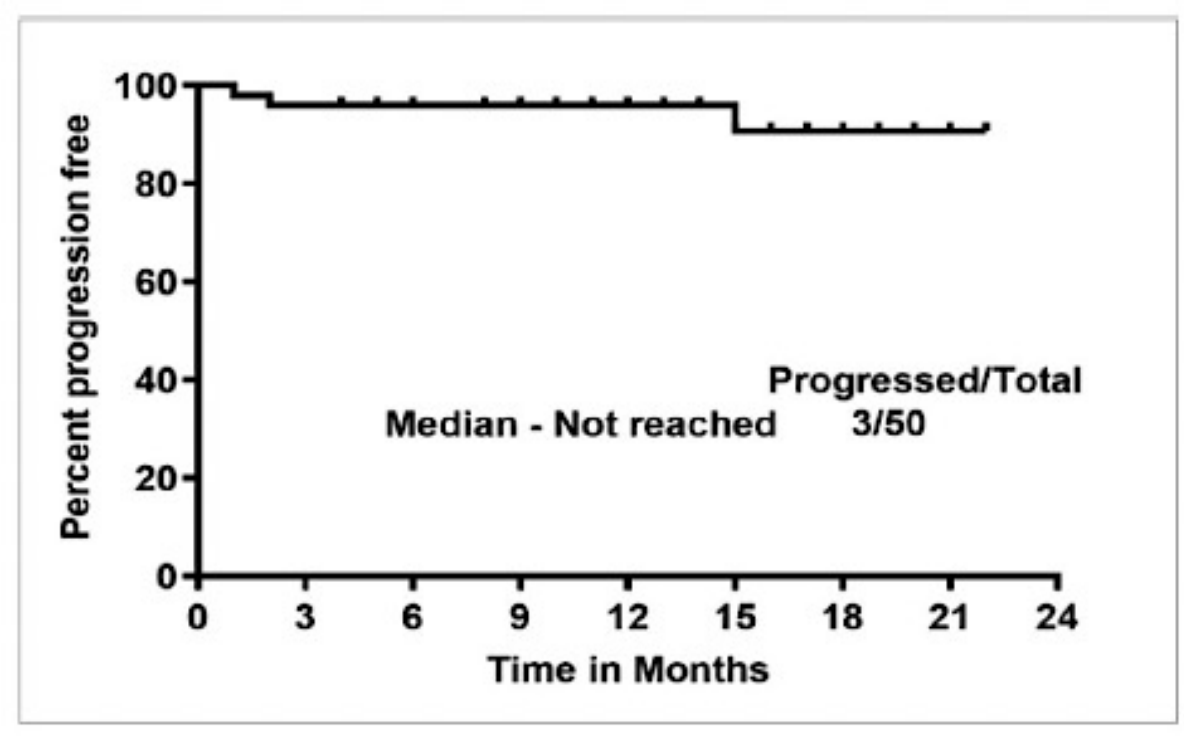
- After median follow-up of 47.6 mo, median PFS and OS were not reached in the TN cohort
- Results support ongoing Phase III ECHO trial of ABR versus BR in patients with TN MCL (NCT02972840)

Philips T et al. ASCO 2023;Abstract 7546.

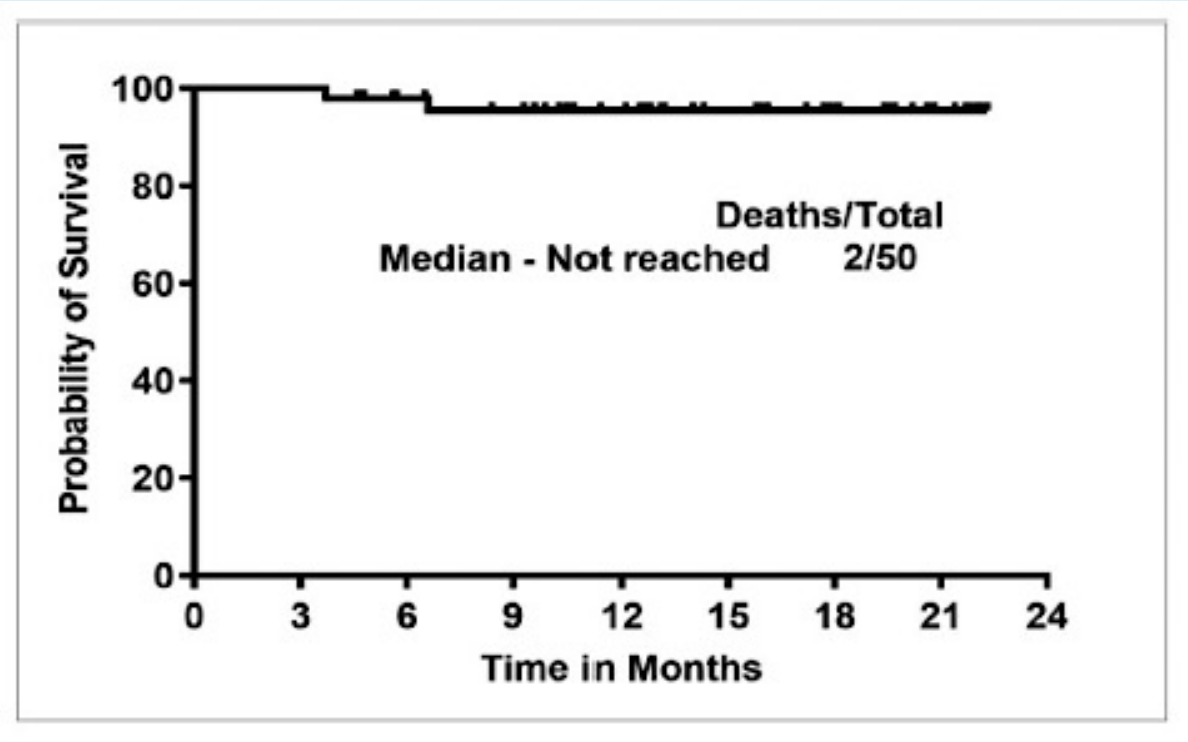
RTP RESEARCH TO PRACTICE

Progression-Free Survival (PFS) and Overall Survival (OS) with Acalabrutinib/Rituximab as First-Line Therapy for Older Patients with MCL

PFS



OS

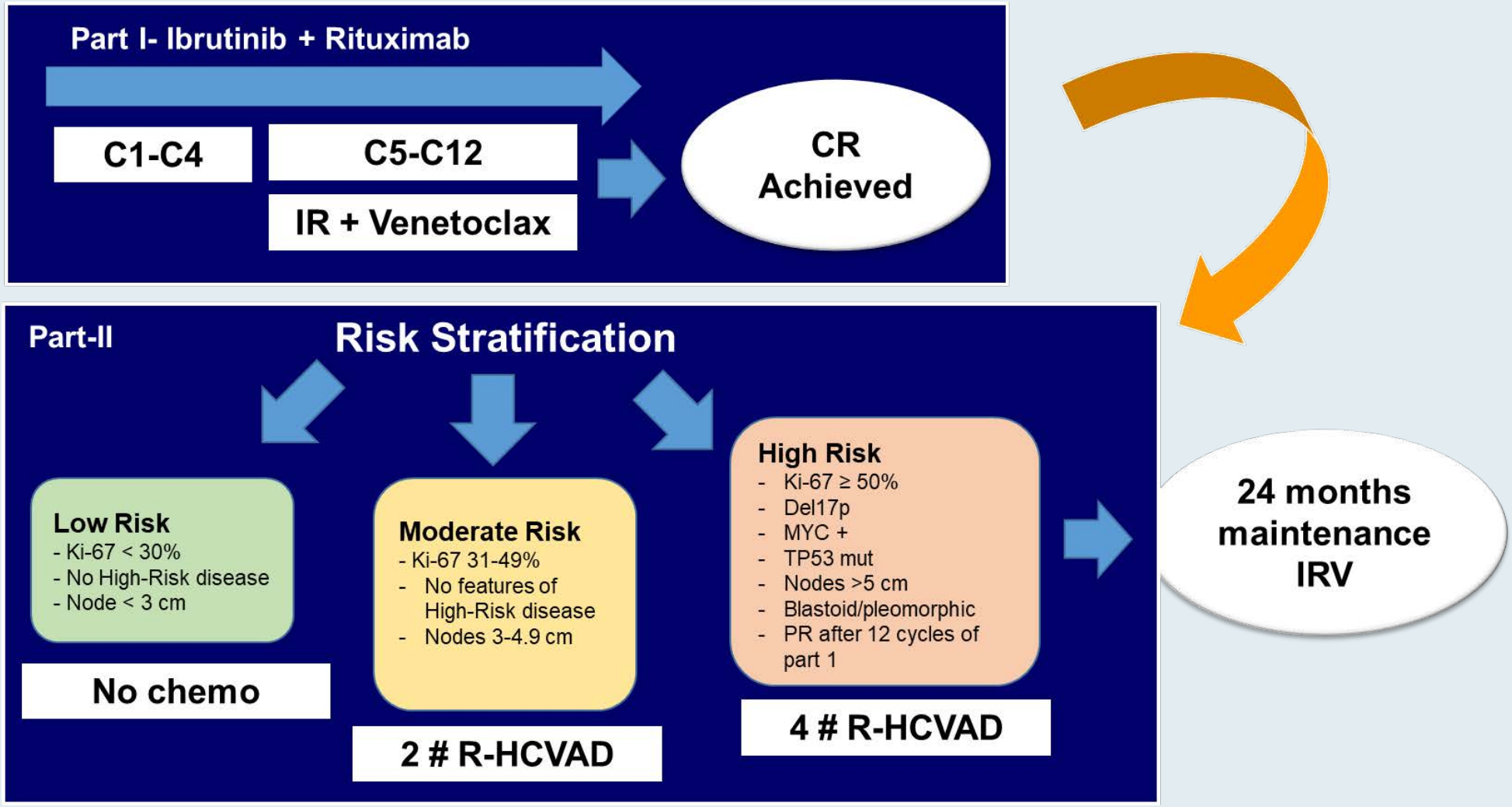


Response: ORR = 94% (CR = 90%, PR = 4%), nonevaluable = 6%

Jain P et al. ICML 2023;Abstract 099.

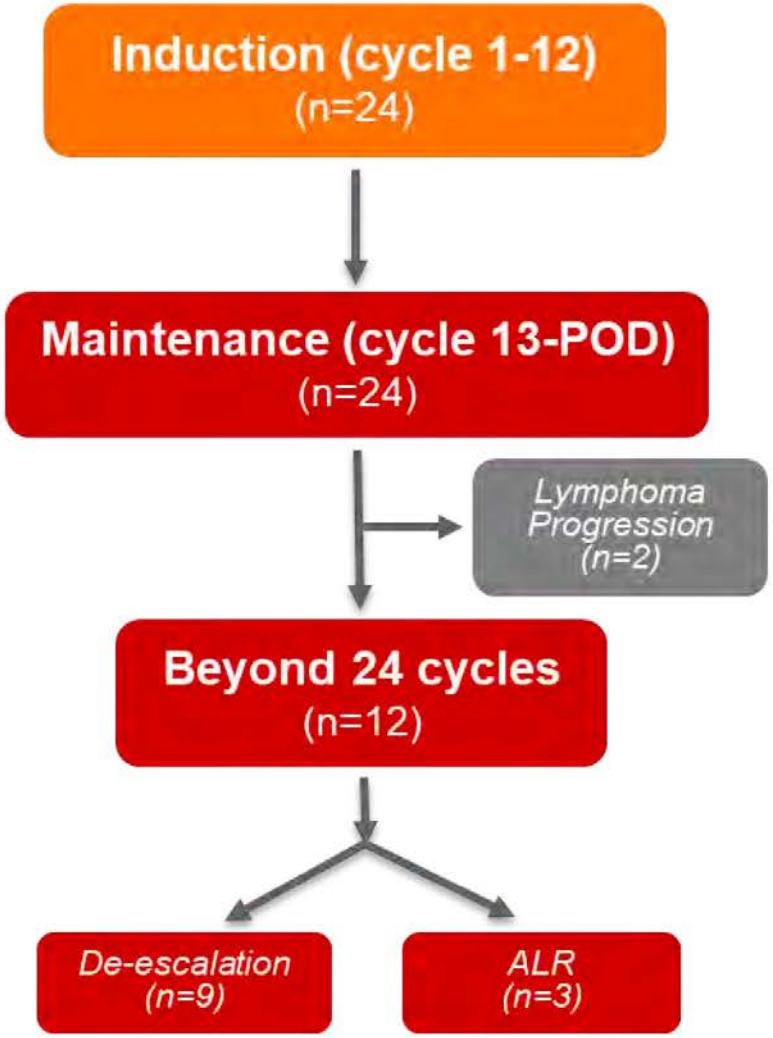
RTP RESEARCH TO PRACTICE

Phase II Window II Trial: Ibrutinib/Rituximab and Venetoclax (IRV) Followed by R-hyper-CVAD for Young Patients with Untreated Mantle Cell Lymphoma



Wang M et al. ICML 2023;Abstract 101.

Objective Responses to Acalabrutinib/Lenalidomide/Rituximab

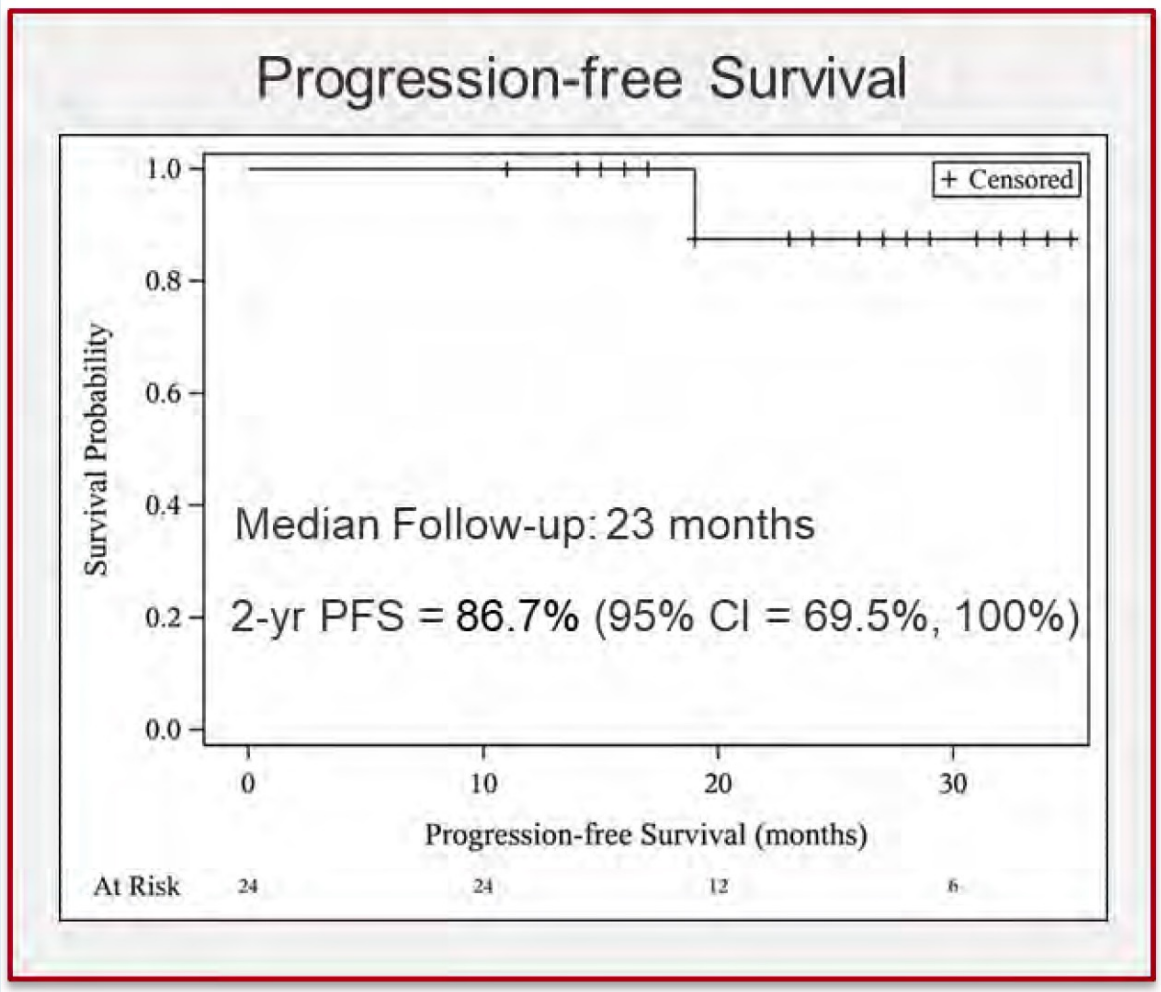


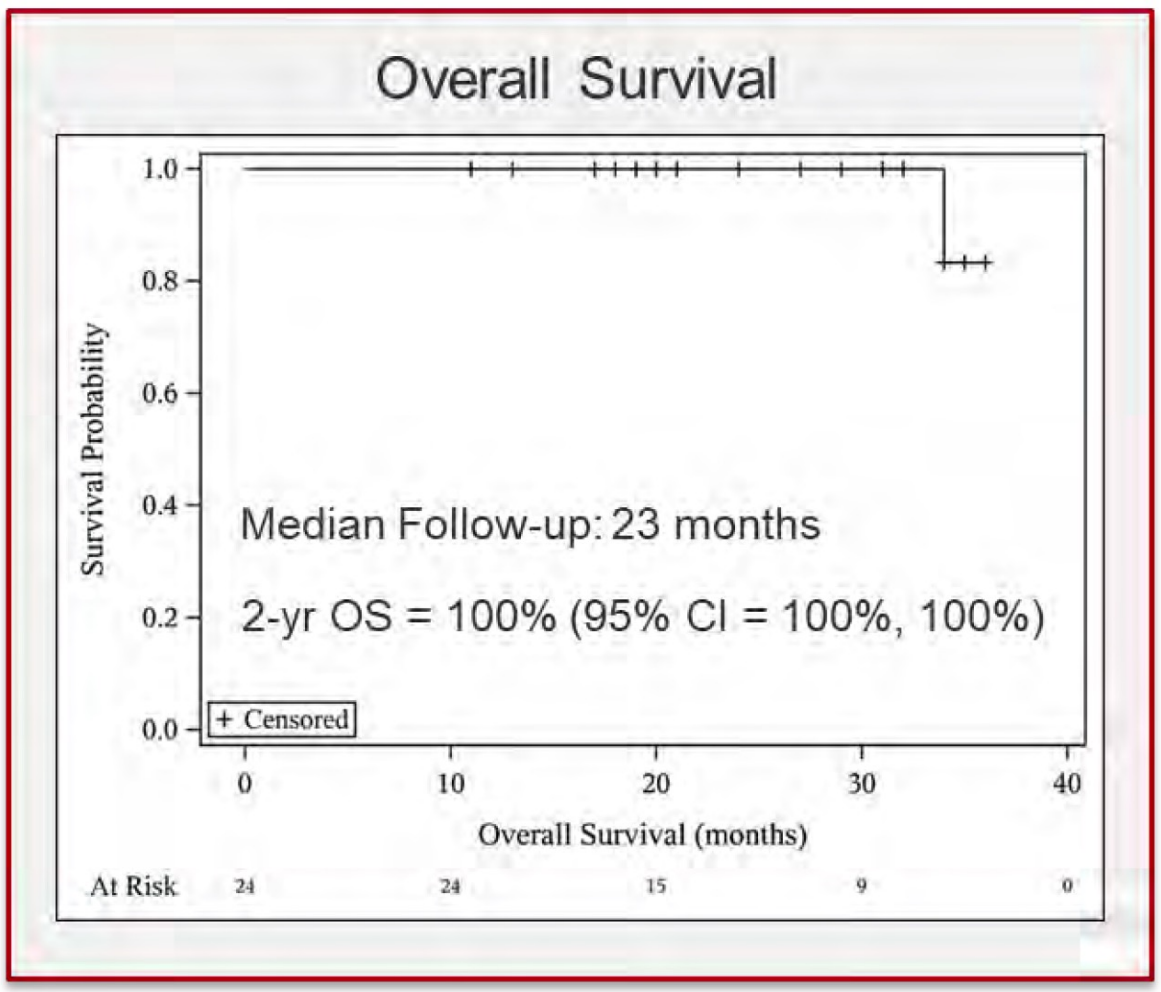
Response	End of Induction* (12 cycles)	
	No. Pt	ITT
ORR	24	100%
CR	20	**83%**
PR	4	17%
SD	0	0
PD	0	0
Median Follow-up	23 months (range 12-36)	

"*": EOI following 12 cycles of treatment; response per Lugano criteria

Ruan J et al. ASH 2022;Abstract 73.

Survival Analyses with Acalabrutinib/Lenalidomide/Rituximab

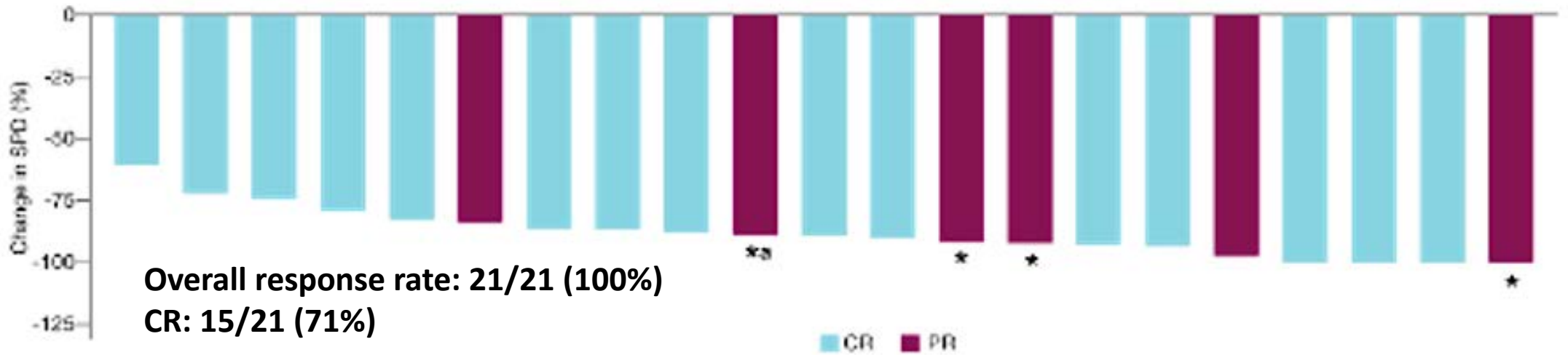




Ruan J et al. ASH 2022;Abstract 73.

RTP RESEARCH TO PRACTICE

Acalabrutinib with Venetoclax and Rituximab for Patients with Treatment-Naïve MCL



Overall response rate: 21/21 (100%)
CR: 15/21 (71%)

ECI Category, % (n) ECI Subcategory	N=21	
	Any Grade	Grade ≥3
Infections	61.9 (13)	38.1 (8)*
Neutropenia	42.9 (9)	33.3 (7)
Hemorrhage Major hemorrhage	33.3 (7) 0	0 0
Cardiac events Atrial fibrillation	19 (4) 0	0 0
Hypertension	4.8 (1)	4.8 (1)

*5 of 8 grade ≥3 infections were COVID-19 related.

Wang ML et al. ASH 2021;Abstract 2416; Wang M et al. *Blood* 2022;140 (Supplement 1):6477-9.

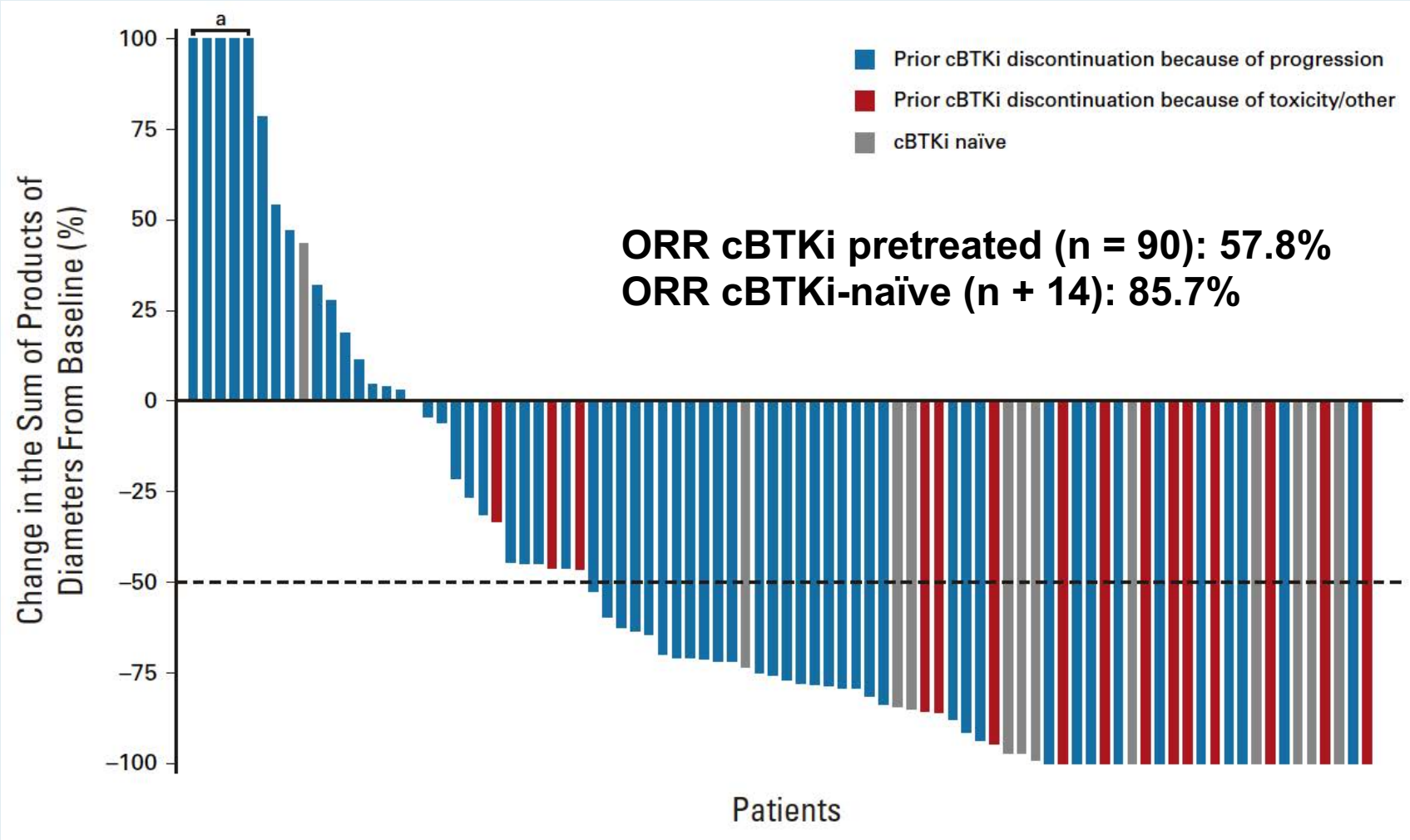
RTP RESEARCH TO PRACTICE

Summary of Investigator-Assessed Efficacy with Zanubrutinib for R/R MCL

Efficacy endpoint	N = 86
Overall response rate	83.7%
Best response	
CR	77.9%
PR	5.8%
SD	1.2%
PD	9.3%
Discontinued before treatment assessment	5.8%
Median time to response	2.7 mo
Median time to CR	2.8 mo
Median response duration	NE
Event-free rate at 30 mo	57.3%

Song Y et al. *Blood* 2022;139(21):3148-58.

BRUIN 1/2: Efficacy of Pirtobrutinib for Patients with cBTKi-Pretreated and cBTKi-Naïve MCL

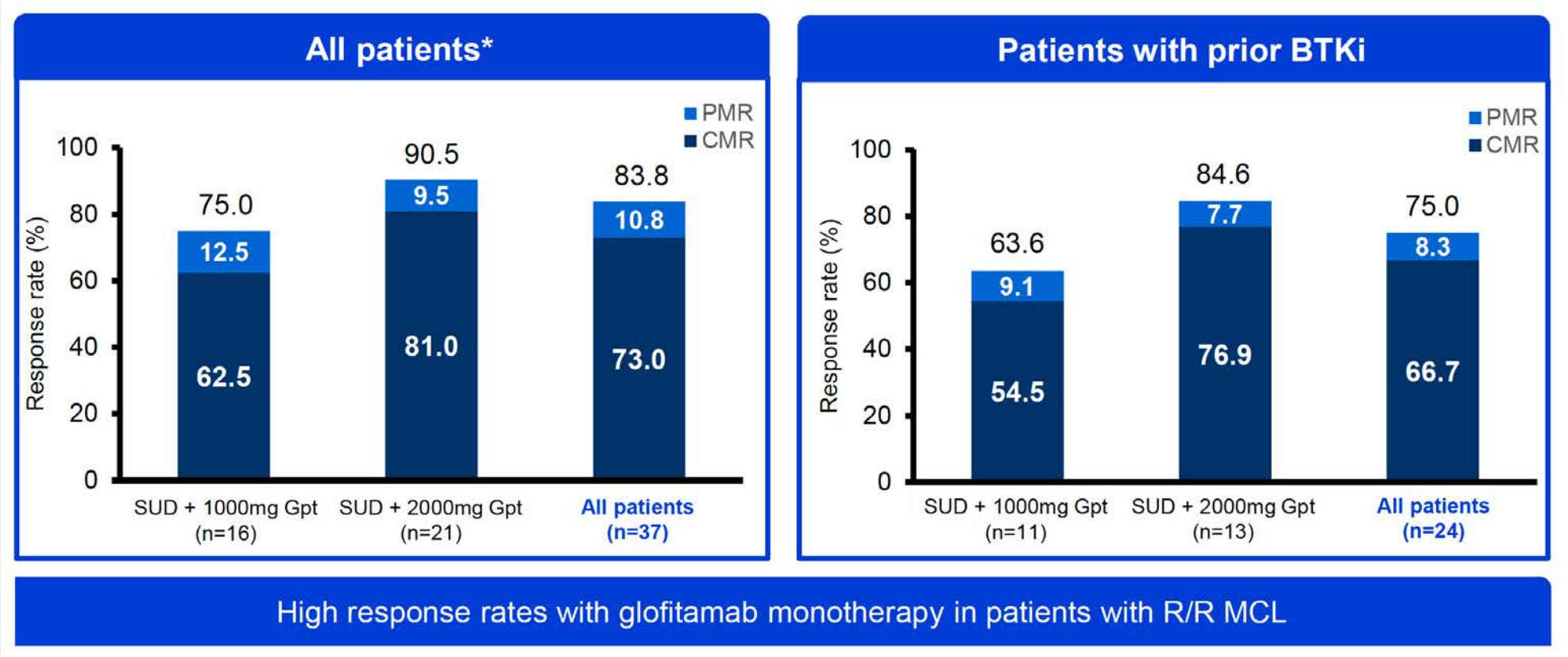


cBTKi = covalent Bruton tyrosine kinase inhibitor; ORR = overall response rate

Wang ML et al. *J Clin Oncol* 2023; May 16;[Online ahead of print].

Glofitamab Monotherapy for Patients with Heavily Pre-Treated R/R MCL

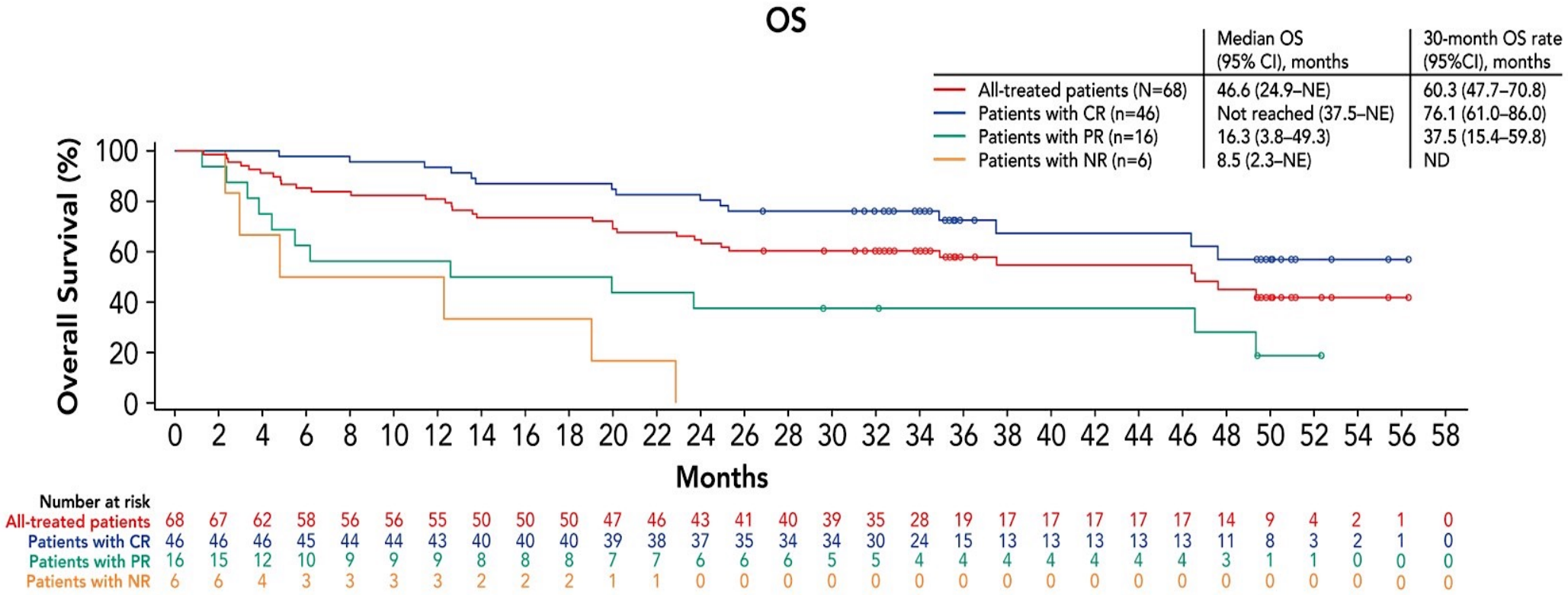
- Patients received obinutuzumab pretreatment (Gpt) to mitigate CRS



- Any grade CRS was 75.7%, with majority of the cases being Grade 1/2
- No Grade 4 CRS events were observed, and higher Gpt dose was associated with a lower rate of CRS

Phillips T et al. ASH 2022;Abstract 74; Phillips T et al. SOHO 2023;Abstract MCL-467.

ZUMA-2, 3-Year Follow Up

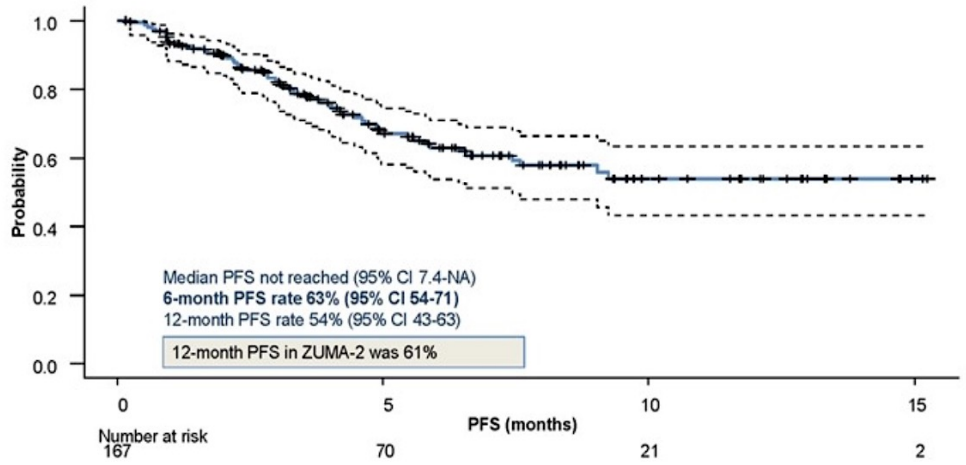


- The median progression-free survival (PFS) was 25.8 months, as shown in the full poster
- In the ITT population (data not shown), the median PFS was 24.0 months and the median OS was 47.4 months

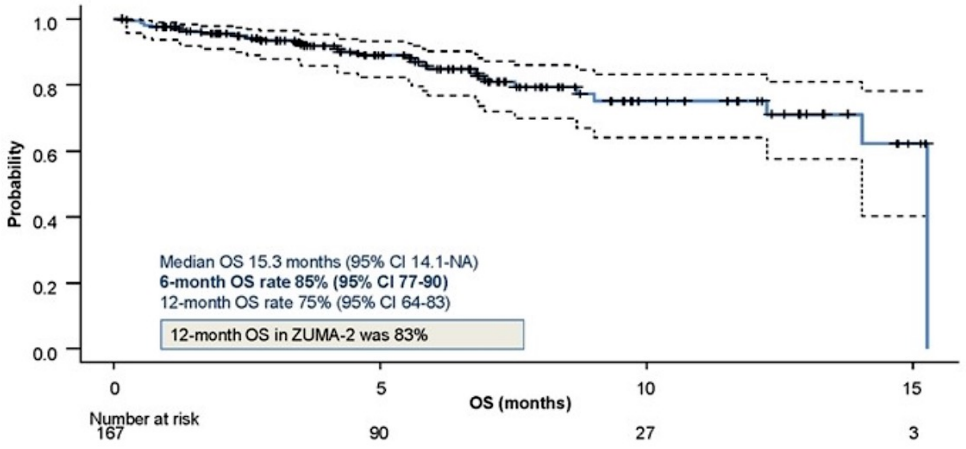
Median OS among treated patients was 46.6 months and was not reached among those who achieved CR.

US CAR T-Cell Consortium

PROGRESSION-FREE SURVIVAL



OVERALL SURVIVAL



	CRS, n (%)	ICANS, n (%)	ZUMA-2 CRS (%)	ZUMA-2 NE (%)
Total	147 (90%)	100 (61%)	91%	63%
Max Grade*				
1-2	135 (82%)	48 (29%)	76%	32%
3-4	11 (7%)	52 (32%)	15%	31%
5	1 (1%)			
Days to onset	4 (0-13)	6 (1-18)	2 (1-13)	7
Days to max Grade	5 (0-30)	7 (1-18)	-	-
Duration	5 (1-33)	6 (1-144+)	11	12

*CRS grading: ASTCT (n=13), Lee (n=2), CARTOX (n=1);
ICANS grading: ASTCT (n=14), CTCAE (n=1), CARTOX (n=1).
CRS = cytokine release syndrome;
ICANS = immune effector cell-associated neurotoxicity syndrome;
NE = neurological events.

Incidence of CRS and ICANS similar

Wang M, et al. J Clin Oncol. 2022;40:7518-7518.

Oncology in the Real World: A Daylong Multitumor Educational Symposium in Partnership with the American Oncology Network

A CME/MOC- and NCPD-Accredited Event

Saturday, October 14, 2023
9:30 AM – 5:00 PM PT

RTP
RESEARCH
TO PRACTICE

Agenda

Module 1 — Lymphoma: *Drs Flowers and LaCasce*

Module 2 — Urothelial Bladder Cancer and Renal Cell Carcinoma:
Drs Hutson and Sonpavde

Break: 11:30 AM – 11:50 AM

Module 3 — Hepatobiliary and Pancreatic Cancers:
Prof Borad and Dr El-Khoueiry

Module 4 — Gynecologic Cancers: *Drs Monk and Moore*

Module 5 — Multiple Myeloma: *Drs Krishnan and Orlowski*

Module 6 — HER2-Positive and Triple-Negative Breast Cancer:
Drs Hurvitz and McArthur

RTP
RESEARCH
TO PRACTICE

Urothelial Bladder Cancer and Renal Cell Carcinoma Faculty

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Director, GU Oncology Program
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Charles A Sammons Cancer Center
Baylor University Medical Center
Professor of Medicine
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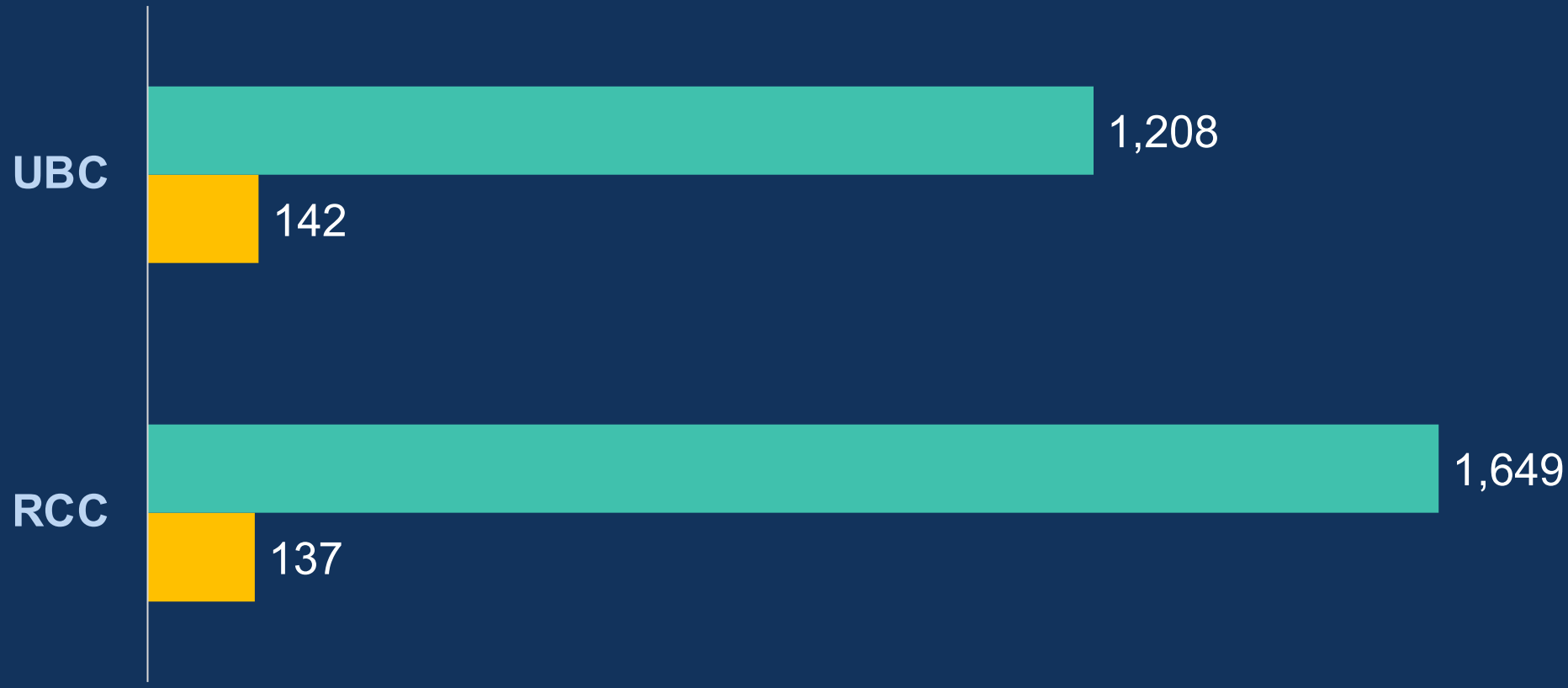
Cancer Research
AdventHealth Cancer Institute
Professor of Medicine
University of Central Florida
Orlando, Florida

RTP
RESEARCH
TO PRACTICE

Snapshot of AON Practice
Module 2: UBC and RCC



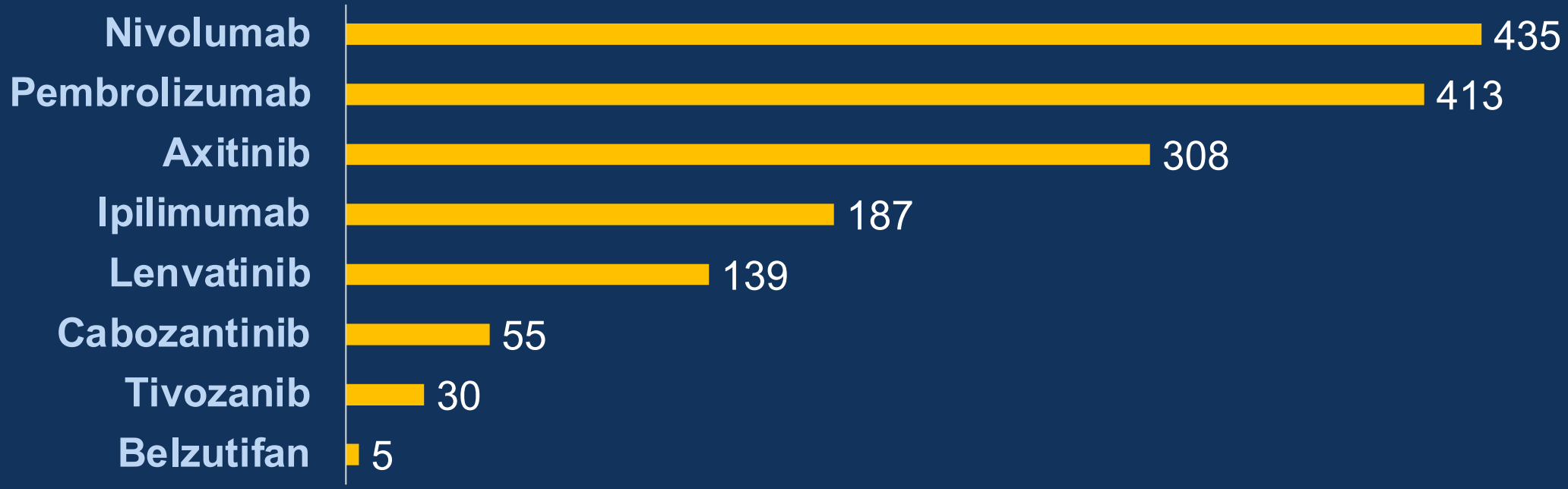
MIBA

THE AON CLINICAL SUMMIT 2023

Collaborate. Innovate. Celebrate.

Snapshot of AON Practice
Renal Cell Carcinoma

Select Treatments Received



Clinical Trial Participation

Number of clinical trials	15
Total patients enrolled	31

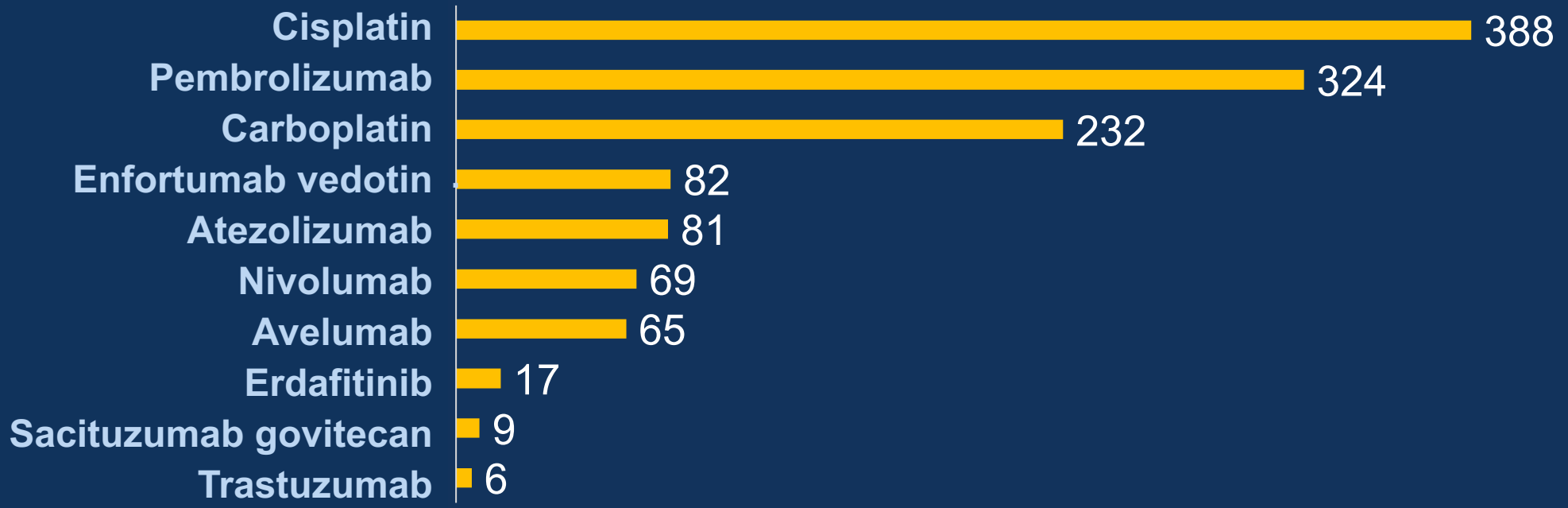
MIBA

THE AON CLINICAL SUMMIT 2023

Collaborate. Innovate. Celebrate.

Snapshot of AON Practice
Urothelial Bladder Cancer

Select Treatments Received



Clinical Trial Participation

Number of clinical trials	13
Total patients enrolled	18

MIBA

THE AON CLINICAL SUMMIT 2023

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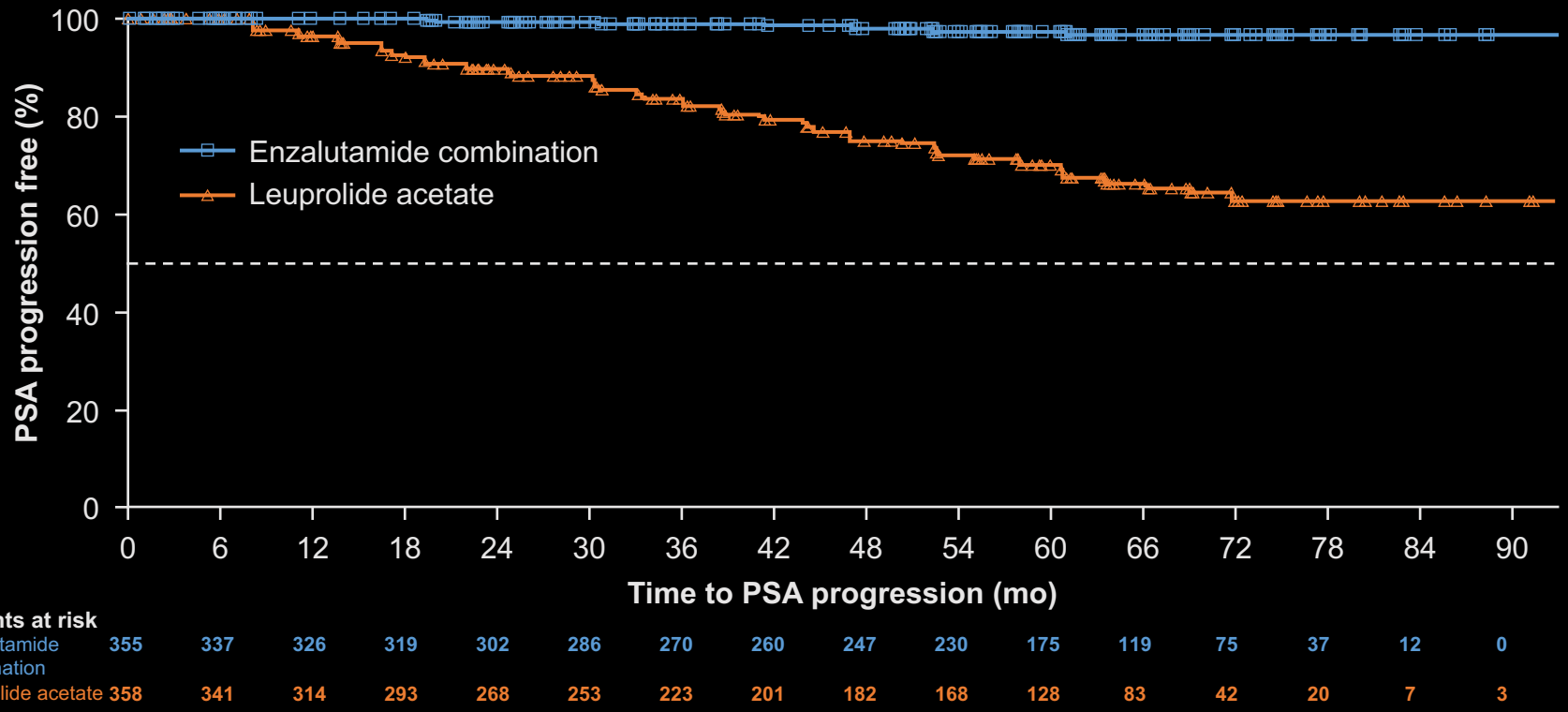
AUA 2023
CHICAGO ✶ APR 28-MAY 1

Key secondary endpoint — Time to PSA progression for enzalutamide combination vs. leuprolide acetate



Patients at risk

Enzalutamide combination	355	337	326	319	302	286	270	260	247	230	175	119	75	37	12	0
Leuprolide acetate	358	341	314	293	268	253	223	201	182	168	128	83	42	20	7	3

	Enzalutamide combination (n = 355)	Leuprolide acetate (n = 358)
Events, n (%)	8 (2)	93 (26)
Median time to PSA progression (95% CI), mo	NR (NR)	NR (NR)

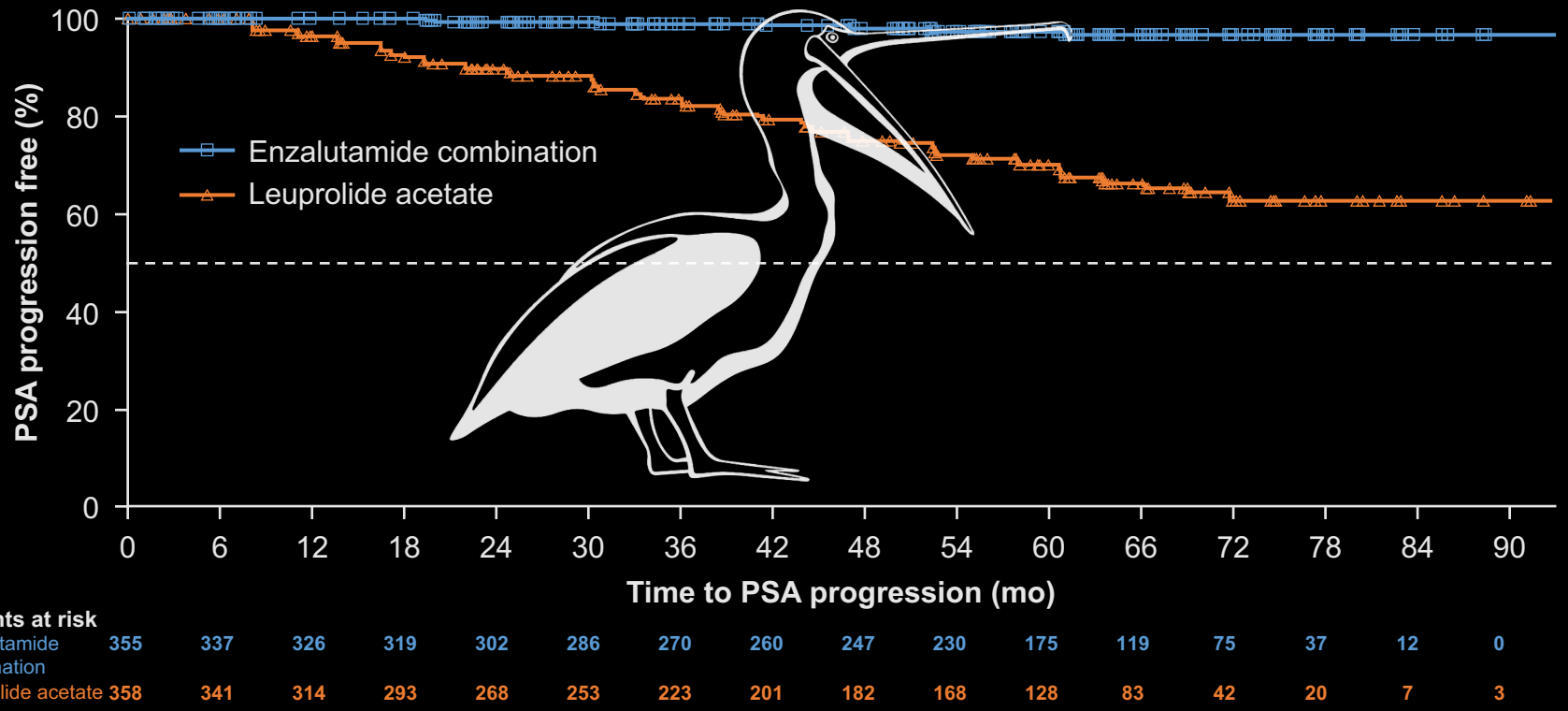
HR (95% CI): 0.07 (0.03–0.14); *P*<0.0001[a]

Data cutoff: January 31, 2023. Symbols indicate censored data. [a]The HR was based on a Cox regression model with treatment as the only covariate stratified by screening PSA, PSADT, and prior hormonal therapy as reported in the IWRS; relative to leuprolide acetate <1 favoring enzalutamide combination; the two-sided *P*-value is based on a stratified log-rank test.

Shore N et al. AUA 2023;Abstract LBA02-09.

AUA 2023
CHICAGO ✶ APR 28-MAY 1

Key secondary endpoint — Time to PSA progression for enzalutamide combination vs. leuprolide acetate



Patients at risk

Enzalutamide combination	355	337	326	319	302	286	270	260	247	230	175	119	75	37	12	0
Leuprolide acetate	358	341	314	293	268	253	223	201	182	168	128	83	42	20	7	3

	Enzalutamide combination (n = 355)	Leuprolide acetate (n = 358)
Events, n (%)	8 (2)	93 (26)
Median time to PSA progression (95% CI), mo	NR (NR)	NR (NR)

HR (95% CI): 0.07 (0.03–0.14); *P*<0.0001[a]

Data cutoff: January 31, 2023. Symbols indicate censored data. [a]The HR was based on a Cox regression model with treatment as the only covariate stratified by screening PSA, PSADT, and prior hormonal therapy as reported in the IWRS; relative to leuprolide acetate <1 favoring enzalutamide combination; the two-sided *P*-value is based on a stratified log-rank test.

Shore N et al. AUA 2023;Abstract LBA02-09.

NAVIGATING THE RCC TREATMENT LANDSCAPE

Thomas E Hutson, DO, PharmD, FACP

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Director, GU Oncology Program
Co-Director, Urologic Cancer
Research and Treatment Center

Texas Oncology, PA
Baylor-Sammons Cancer Center
Dallas, Texas
Texas AM HSC College of Medicine
US Oncology/ SCRI

FIGHT CANCER
TEXAS ONCOLOGY

TEXAS ONCOLOGY
More breakthroughs. More victories.

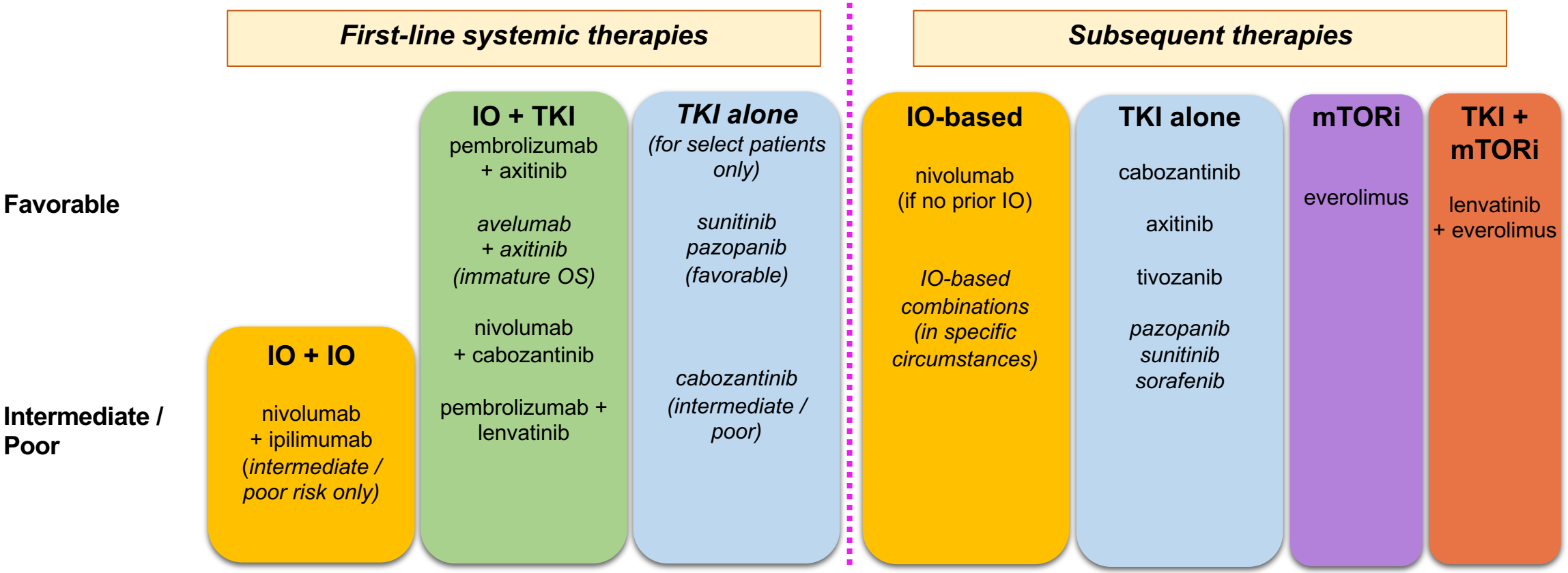
Studies of Adjuvant IO in RCC

Trial	Sample Size	Inclusion Criteria	Treatment	Primary Endpoint	Expected Results
KEYNOTE-564[1]	994	pT2G4, pT3aG3-4, pT3b-T4Gx, pTxN1, pTxNxM1 (resected to NED within 1 year); clear cell	Pembrolizumab vs placebo	DFS	**Median DFS not reached in both study arms HR, 0.68; P=0.002**
IMmotion010[2]	778	pT2G4, pT3aG3-4, pT3b-T4Gx, pTxN1, pTxNxM1 (resected to NED*); clear cell	Atezolizumab vs placebo	DFS	**ESMO 2022 NS DFS HR 0.93; P=0.4950**
CheckMate-914[3]	1600	pT2aG3-4N0, pT2b-T4GxN0, pTxGxN1; clear cell	Nivolumab + ipilimumab vs. nivolumab + placebo vs placebo *(6 months)*	DFS	**ESMO 2022 *Part A (Nivo+Ipi)* NS DFS HR, 0.92; P=0.5347**
PROSPER RCC[4]	766	cT2Nx, cTxN1, cTxNxM1 (resected to NED); any RCC histology	Nivolumab vs observation	EFS	**ESMO 2022 NS DFS HR, 0.97; P=0.43 Trial stopped for futility**
RAMPART[5]	1750	Leibovich score 3-11; any RCC histology	Durvalumab + tremelimumab vs durvalumab vs observation	DFS, OS	7/2024

*Metachronous pulmonary, lymph node, or soft tissue recurrence >12 months from nephrectomy.
DFS, disease-free survival; EFS, event-free survival; NED, no evidence of disease; RCC, renal cell carcinoma; OS, overall survival; NS, non-significant.
1. Choueiri TK et al. *N Engl J Med*. 2021;385:683-694. 2. NCT03024996. 3. NCT03138512. 4. NCT03055013. 5. NCT03288532.

Systemic therapies for clear cell RCC

Braun et al, ASCO 2023

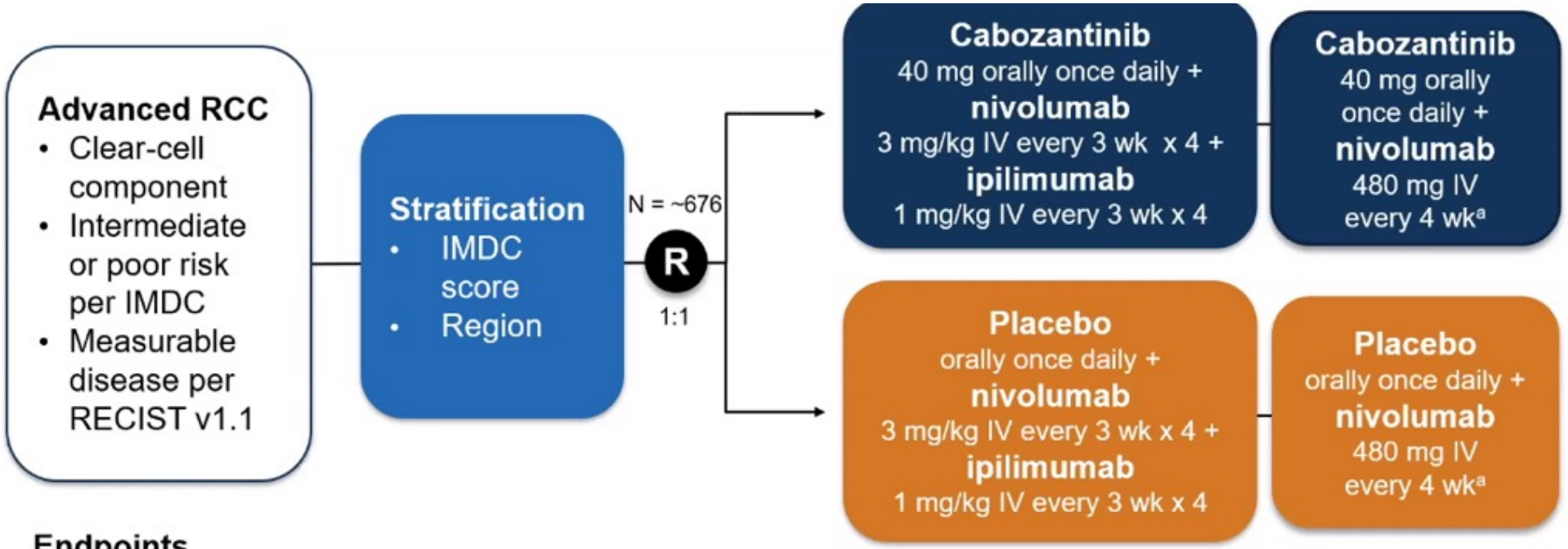


First-line IO Combination Trials in mRCC (ITT)

	CheckMate 214 (Ipi/Nivo)[1] (n=550 vs n=546)	KEYNOTE-426 (Axi/Pembro)[2] (n=432 vs n=429)	CheckMate 9ER (Cabo/Nivo)[3] (n=323 vs n=328)	CLEAR (Len/Pembro)[4] (N=355 vs n=357)
OS HR mOS, months	**0.72** 55.7 vs 38.4	**0.84** 47.2 vs 40.8	**0.70** 49.5 vs 35.5	**0.79** 53.7 v. 54.3
Landmark OS	**60%** at 3 years (est.) **48%** at 5 years	**63%** at 3 years **42%** at 5 years	**59%** at 3 years	**66%** at 3 years
PFS HR mPFS, months	**0.86** **12.3** vs 12.3	**0.69** **15.7** vs 11.1	**0.59** **16.6** vs 8.4	**0.47** **23.9** vs 9.2
Landmark PFS	32% (3 years; est.) 30% (5 years)	29% (3 years) 18% (5 years)	23% (3 years)	37% (3 years)
ORR, %	**39** vs 32	**61** vs 40	**56** vs 28	**71** vs 37
CR, %	**12** vs 3	**12** vs 4	**13** vs 5	**18** vs 4
Med f/u, months	**68**	**67**	**44**	**48**
Primary PD, %	**18**	**12**	**7**	**5**

1. Motzer et al. Cancer 2022
2. Rini et al. ASCO 2023
3. Bottaro et al. CITM 2023
4. Motzer et al. ASCO 2023

Phase 3 COSMIC 313 Clinical Trial of Study of First-line Cabozantinib + Nivolumab + Ipilimumab



Endpoints

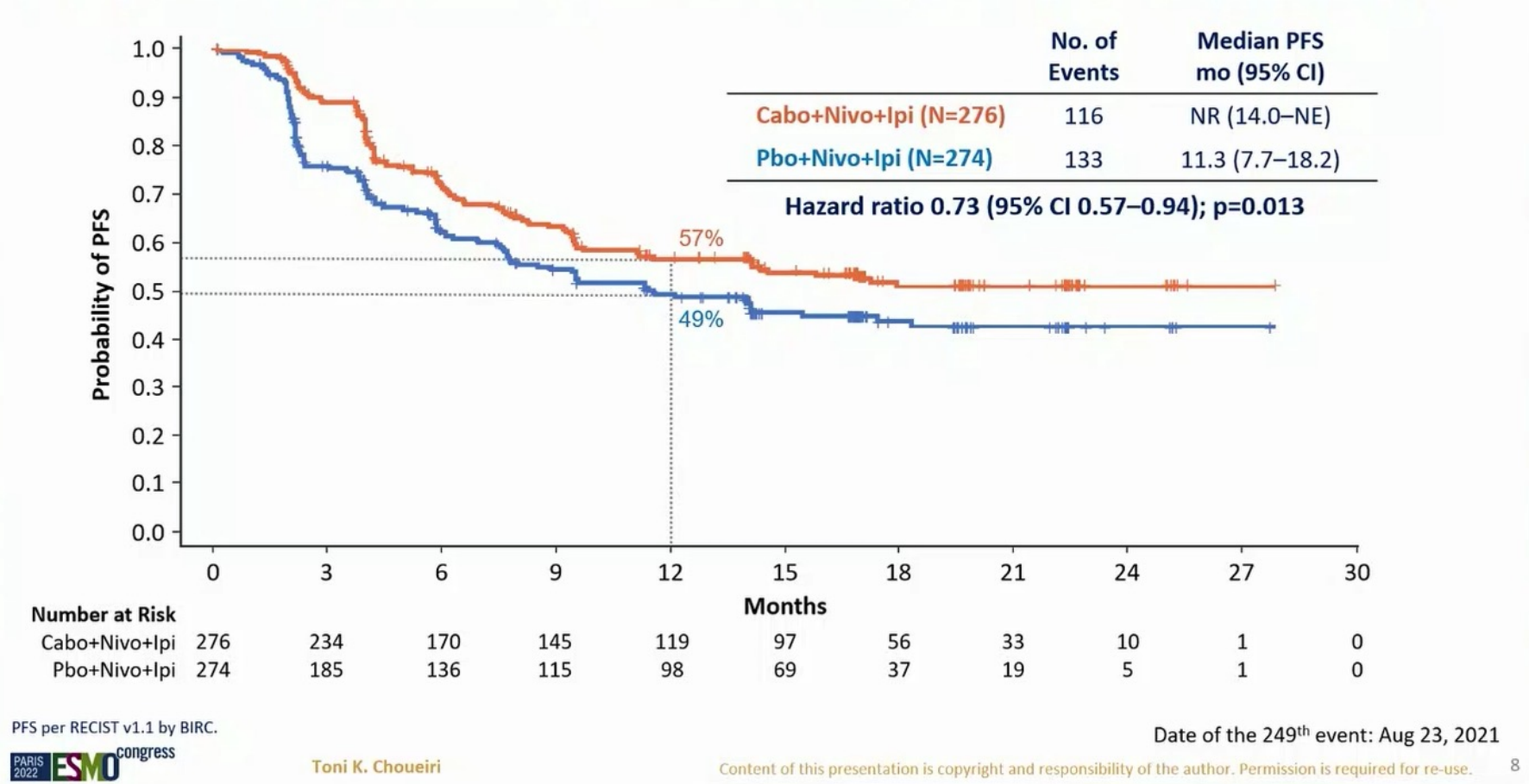
- **Primary:** PFS per RECIST 1.1 by BIRC
- **Key secondary:** OS
- Tumor assessment every 8 wk (RECIST v1.1)[b]
- Treatment until loss of clinical benefit[c] or intolerable toxicity

- Median age: 61 y
- 75% IMDC Int
- 65% prior nephrectomy

No Crossover allowed

NCTID NCT03937219

COSMIC-313: PFS Final Analysis of First 550 Patients Randomized (PITT Population)—Median follow-up, 20.2 Mo



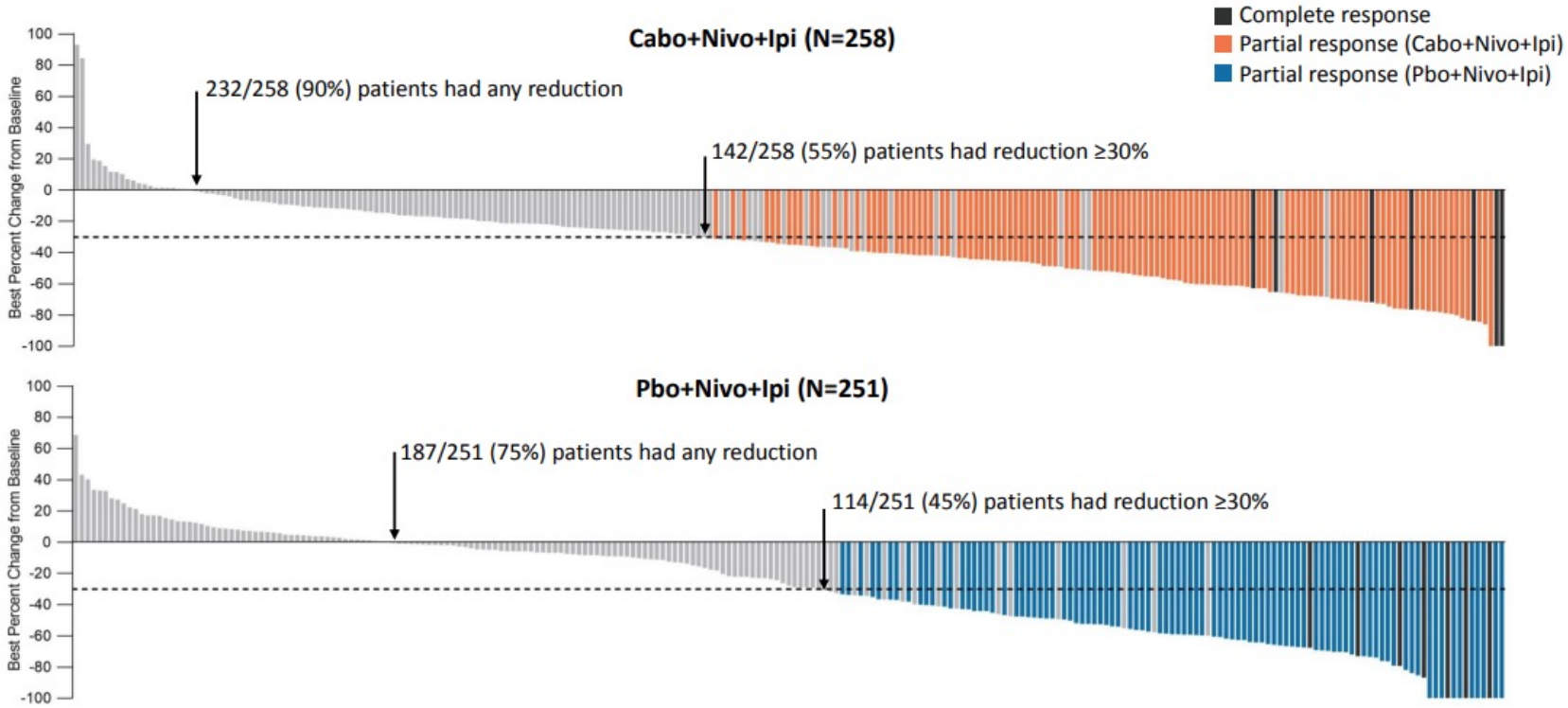
	C+N+I (n=276)	N+I (n=274)
ORR, %	**43**	**36**
CR	3	3
PR	41	32
SD	43	36
PD	8	20
DCR	86	72
mDOR	NR	NR

DCR, disease control rate.

Choueiri T, et al. ESMO 2022. Abstract LBA8; Choueiri TK et al. NEJM 2023;388:1767-78.

COSMIC-313: Responses in PFS ITT Population[a] per RECIST v1.1 by BIRC

Best Change From Baseline in SoD of Target Lesions per RECIST v1.1 by BIRC



Tumor response per RECIST v1.1 by BIRC

	C+N+I (n=276)	N+I (n=274)
ORR	**43**	**36**
CR	3	3
PR	41	32
SD	43	36
PD	8	20
DCR	86	72
mDOR	NR	NR

Data cut off: Jan 31, 2022.

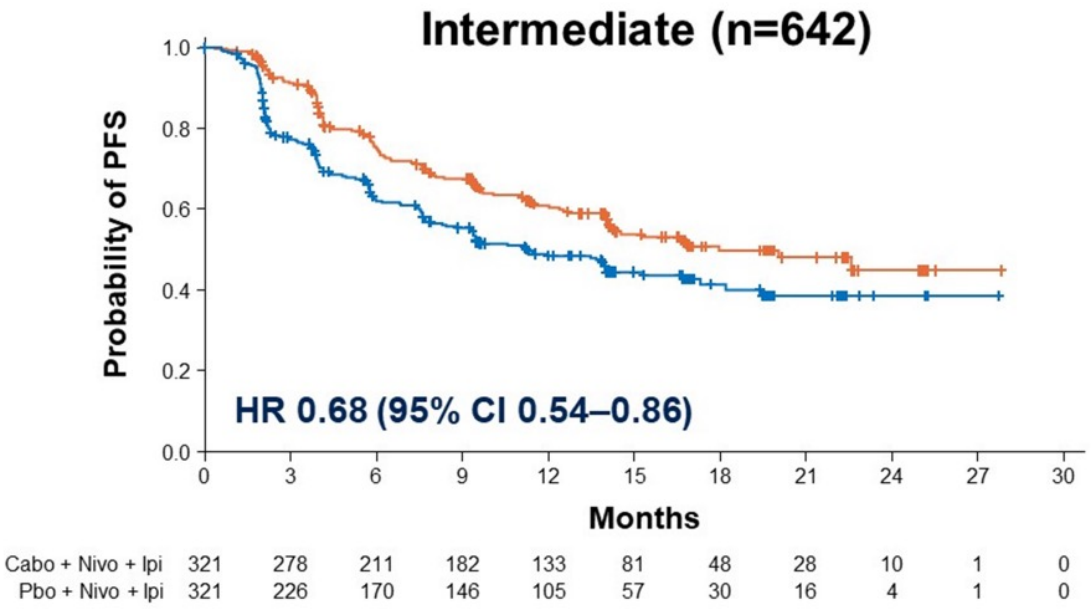
a. The PFS ITT population is the first 550 patients randomized.

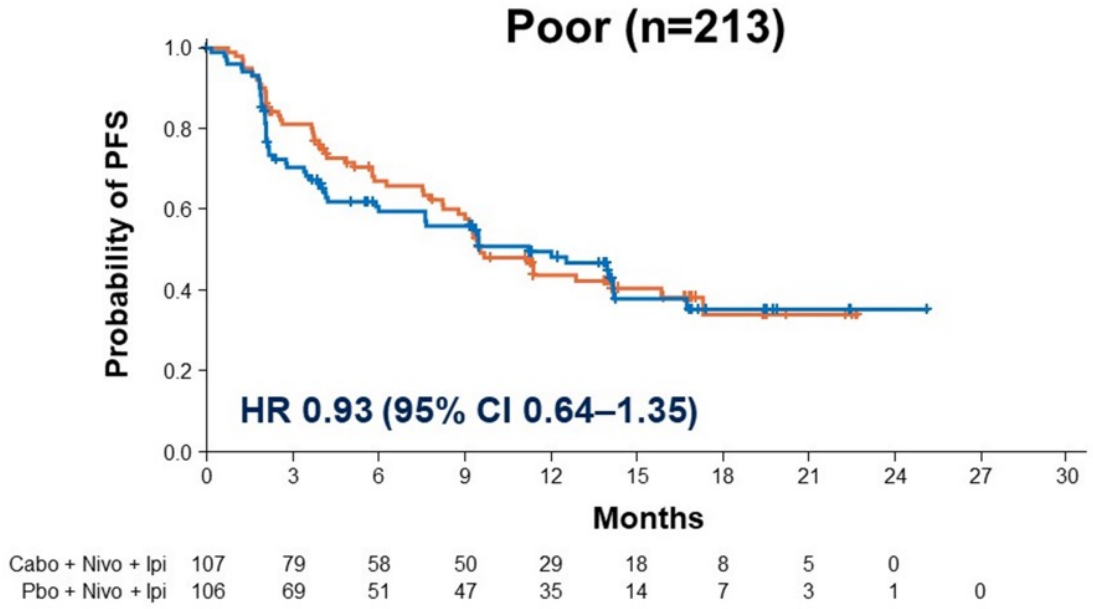
b. Patients in the PITT population with at least one baseline and post-baseline assessment.

Choueiri T, et al. ESMO 2022. Abstract LBA8.

COSMIC-313: Efficacy in Intermediate- and Poor-Risk Subgroups

- Subgroup analyses of PFS and response consistent with overall PITT population; results suggest greater benefit for int-risk group vs poor-risk group





- No major differences in exposure that can explain the differing efficacies seen in intermediate- vs poor-risk subgroups with triplet
- AEs led to discontinuation more frequently in intermediate-risk vs poor-risk in triplet arm

Median follow up, 17.7 mo; 855 pts, 402 PFS events, data cutoff: Jan 31, 2022

Powles T, et al. ASCO GU Ca Symp 2023. Abstract 605; Choueiri TK et al. NEJM 2023;388:1767-78.

NCCN Guidelines Version 1.2024: Kidney Cancer

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

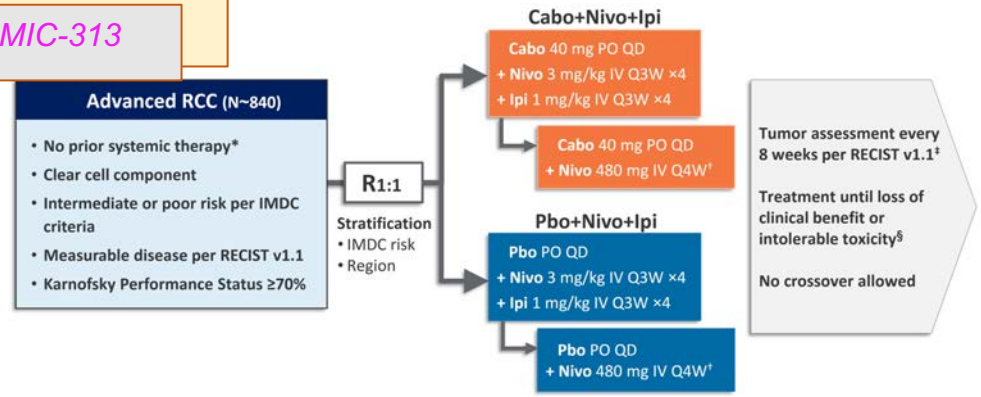
FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY			
Risk	**Preferred Regimens**	**Other Recommended Regimens**	**Useful in Certain Circumstances**
Favorable[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b] (category 1) • Lenvatinib + pembrolizumab[b] (category 1)	• Axitinib + avelumab[b] • Cabozantinib (category 2B) • Ipilimumab + nivolumab[b] • Pazopanib • Sunitinib	• Active surveillance[c] • Axitinib (category 2B) • High-dose IL-2[d] (category 2B)
Poor/ intermediate[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b] (category 1) • Ipilimumab + nivolumab[b] (category 1) • Lenvatinib + pembrolizumab[b] (category 1) • Cabozantinib	• Axitinib + avelumab[b] • Pazopanib • Sunitinib	• Axitinib (category 2B) • High-dose IL-2[d] (category 3) • Temsirolimus[e] (category 3)

NCCN. Kidney Cancer. V1.2024. Oct 11, 2023.

Next steps for front-line ccRCC?

Triplet therapy?

COSMIC-313



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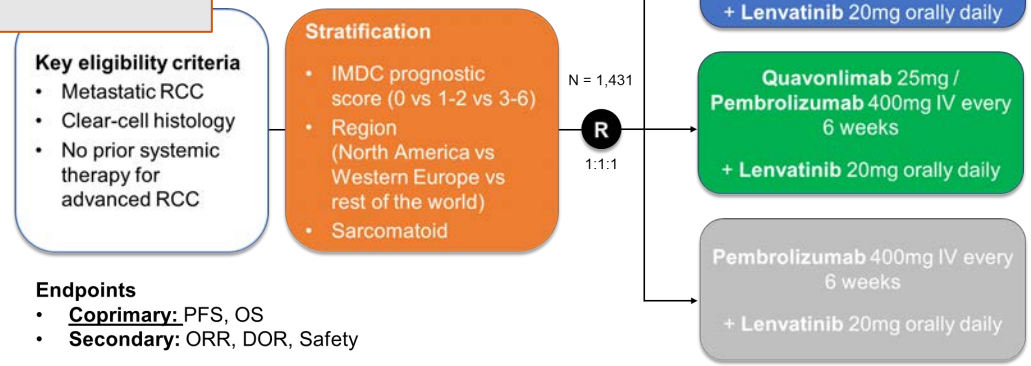
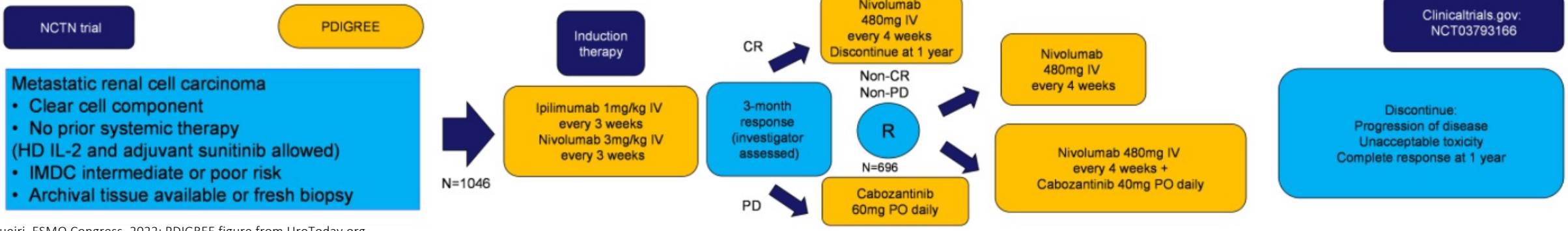


Adaptive trial designs

PDIGREE



Choueiri, ESMO Congress, 2022; PDIGREE figure from UroToday.org

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY (IN ALPHABETICAL ORDER BY CATEGORY)			
Immuno-oncology (IO) Therapy History Status	**Preferred Regimens**	**Other Recommended Regimens**	**Useful in Certain Circumstances**
IO Therapy Naïve	• None	• Axitinib + pembrolizumab[b] • Cabozantinib • Cabozantinib + nivolumab[b] • Ipilimumab + nivolumab[b] • Lenvatinib + everolimus • Lenvatinib + pembrolizumab[b] • Nivolumab[b]	• Axitinib • Everolimus • Pazopanib • Sunitinib • Tivozanib[f] • Belzutifan (category 2B) • Bevacizumab[g] (category 2B) • High-dose IL-2 for selected patients[d] (category 2B) • Temsirolimus[e] (category 2B) • Axitinib + avelumab[b] (category 3)
Prior IO Therapy	• None	• Axitinib • Cabozantinib • Lenvatinib + everolimus • Tivozanib[f]	• Axitinib + pembrolizumab[b] • Cabozantinib + nivolumab[b] • Everolimus • Ipilimumab + nivolumab[b] • Lenvatinib + pembrolizumab[b] • Pazopanib • Sunitinib • Belzutifan (category 2B) • Bevacizumab[g] (category 2B) • High-dose IL-2 for selected patients[d] (category 2B) • Temsirolimus[e] (category 2B) • Axitinib + avelumab[b] (category 3)

[b] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[d] Patients with excellent performance status and normal organ function.
[e] The poor risk model used in the global ARCC trial to direct treatment with temsirolimus included at least 3 of the following 6 predictors of short survival: <1 year from the time of diagnosis to start of systemic therapy, Karnofsky performance status score 60–70, hemoglobin <LLN, corrected calcium >10 mg/dL, LDH >1.5 times the ULN, and metastasis in multiple organs. Hudes G, et al. N Engl J Med 2007;356:2271-2281.
[f] For patients who received ≥2 prior systemic therapies.
[g] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

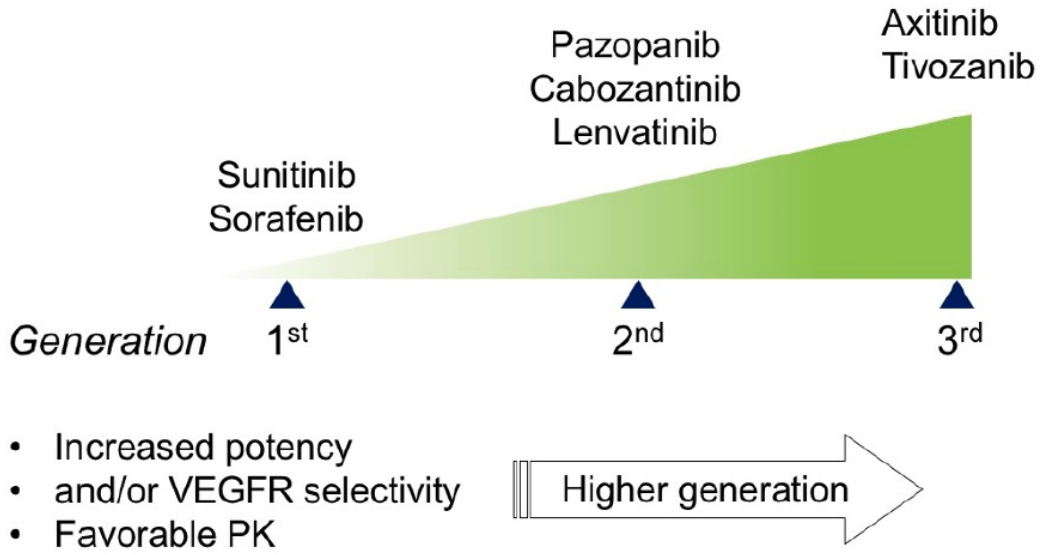
Second-Line Therapy Options

	Nivolumab vs evero[2] N = 821	Cabozantinib vs evero[3] N = 658	Lenvatinib + evero vs lenvatinib or evero[4] N = 153
Trial	**Phase 3 CheckMate-025**	**Phase 3 METEOR**	Phase 2 Study 205
Patient population	TKI-refractory (72% 1 prior)	TKI-refractory (71% 1 prior)	TKI-refractory (100% 1 prior)
Primary end point	OS	PFS (IRC)	PFS (INV)
Risk, favorable/int/poor	35/49/16	45/42/12	24/37/39
ORR, %	25	17	43
PFS, mo	4.6	7.4 (HR 0.51; 95% CI, 0·41–0·62; P <.0001)	14.6 (HR, 0.40; 95% CI, 0.24-0.68; P = .0005 vs evero)
OS, mo	25.0 (HR, 0.73; 95% CI, 0.57-0.93; P =.002)	21.4	25.5
Dose reductions	N/A	62%	71%
AE discontinuation	8%	12%	24%
Toxicity	18% G3 1% G4 (tx-related)	71% G3/4	57% G3 14% G4

AE, adverse event; discontinuation; evero, everolimus; tx, treatment.

1. Rini et al., *Lancet*. 2011;378:1931; 2. Motzer et al., *N Engl J Med*. 2015;373:1803;
3. Choueiri et al., *Lancet Oncol*. 2016;17:917-927; 4. Motzer et al., *Lancet Oncol*. 2015;16:1473

VEGF-TKI Properties



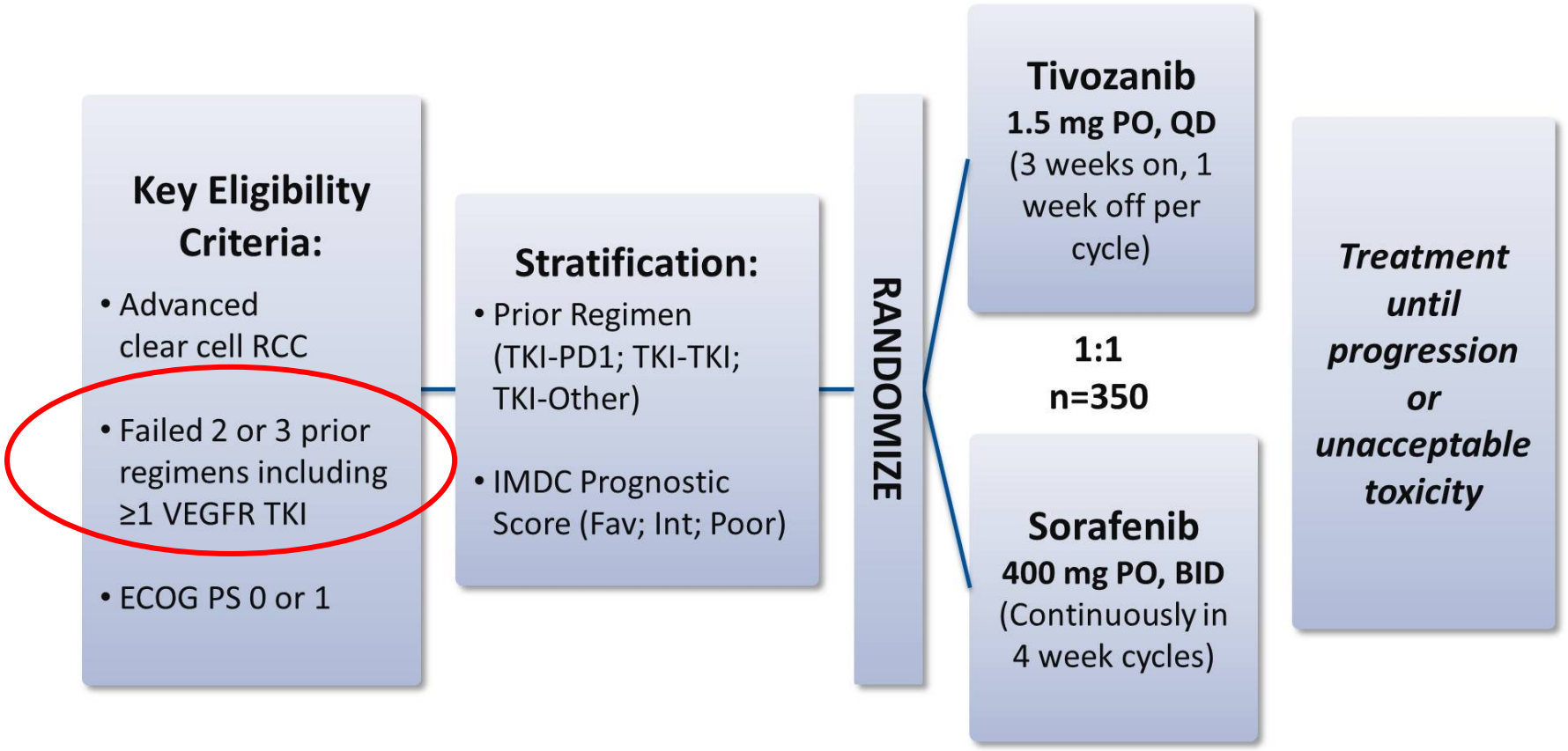
PD Properties

Drug name	Selectivity	Generation	Potency (IC_{50}, nM)						Other targets	$t_{1/2}$ (h)
			VEGFR-1	VEGFR-2	VEGFR-3	PDGFR-β	c-Kit	FGFR-1		
Tivozanib	Yes	III	0.2–30	0.2–6.5	0.2–15	1.7–49	1.6–78	530	RET, FGFR-2/3	80.9
Axitinib	Yes	III	0.1–1.2	0.2–0.3	0.1–0.3	1.6–1.7	1.6–1.7	231	PDGFRα	2–5
Pazopanib	Yes	II	7–15	8–30	2–47	14–215	2.4–74	14–80	PDGFRα	31
Lenvatinib	No	II	1.3	0.74	0.71	NR	11	22	PDGFRα, RET, FGFR-2/4	28
Cabozantinib	No	II	12.2	0.04–14.0	6	575	4.6–752	NA	c-MET, RET, AXL, FLT3, TRKB, TIE-2	55–102
Sunitinib	No	I	2–21	10–38	3–30	8–75	1–40	437–880	PDGFRα, RET, FLT3, CSF-1R	40–60
Sorafenib	No	I	9	28–90	7–20	68	68–1862	64–580	RET, FLT3, RAF	25–48

IC_{50}: concentration required for 50% inhibition. The comparison of the pharmacological potencies among VEGFR-TKIs should be done with caution due to different assays and conditions used (e.g., inhibition of recombinant receptor tyrosine kinase activity in cell-free kinase assays or VEGF-induced phosphorylation of intracellular VEGFR in cell-based assays). NR: not reported. References: [16,18,44,94–98].

Fogli S, et al. Cancer Treat Rev. 2020;84:101966.

Phase 3 TIVO-3: Study Design



Primary endpoint: PFS (BICR)
Secondary endpoints: OS, ORR, DOR, and safety

Rini BI, et al. GU Ca Symp 2019. Abstract 541.
Rini BI, et al. *Lancet Oncol*. 2020;21:95-104.

Phase 3 TIVO-3: Baseline Characteristics

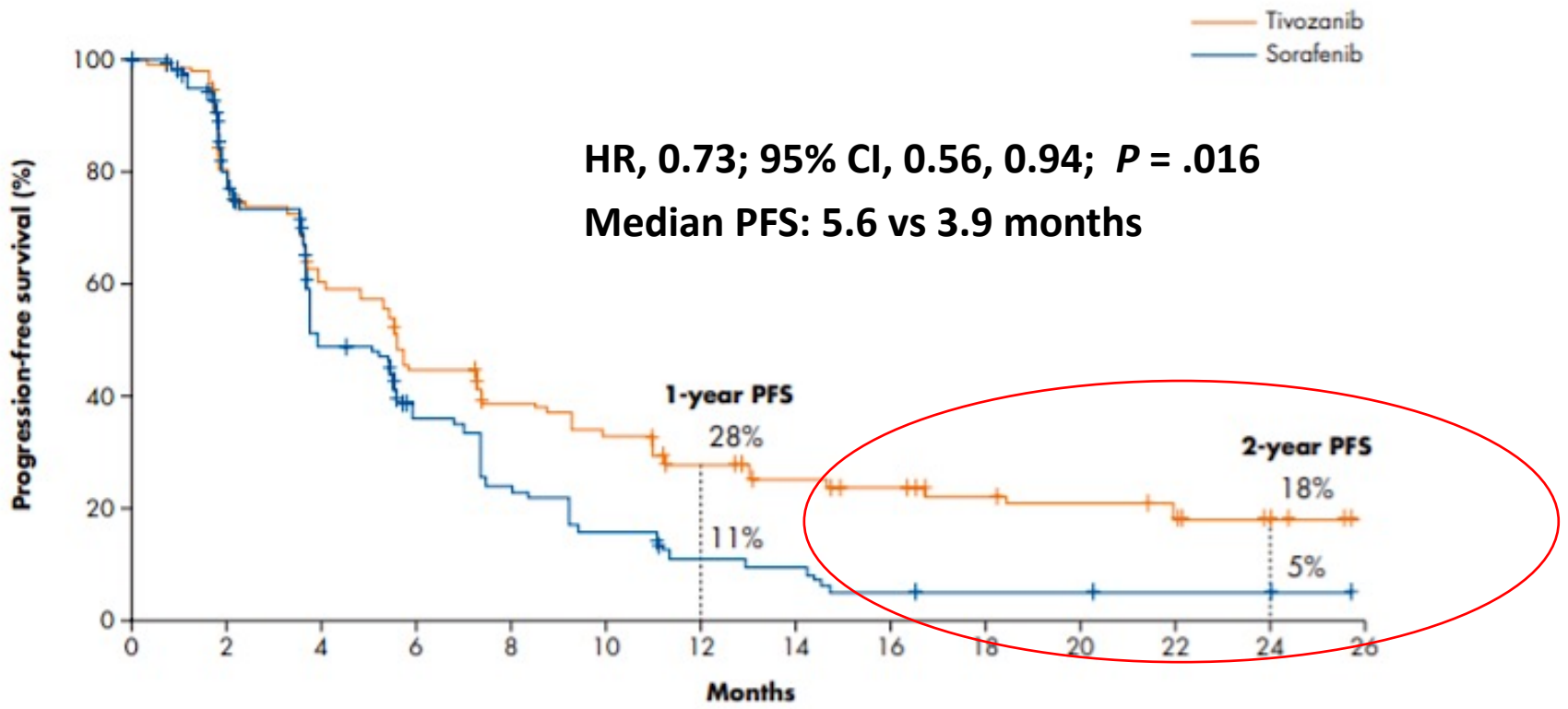
Characteristics	Tivozanib (N=175)	Sorafenib (N=175)
Median age, years	62	64
Male, %	72	73
IMDC Prognostic Risk, %		
Favorable	19	21
Intermediate	62	60
Poor	18	19
ECOG Performance Status, % (0/1)	(49/50)	(47/48)
Region, % (NA/EU)	(18/82)	(15/85)
Prior Lines of Therapy, % (2/3)	(62/38)	(59/41)
Prior Treatment Regimen, %		
TKI-PD1	27	25
TKI-TKI	45	46
TKI-Other	28	29

- Age: 35% between age 65 and 75; 10% were over 75
- Time from initial diagnosis: 50 months, both arms
- Time from most recent relapse: 1 month, both arms

Data cutoff: Jan 15, 2021

Verzoni E, et al. ASCO 2021. Abstract 4546. Escudier B, et al. ASCO 2021. Abstract e16553.

TIVO-3: PFS (ITT) by Blinded Radiologic Review—Primary Analysis



HR, 0.73; 95% CI, 0.56, 0.94; *P* = .016

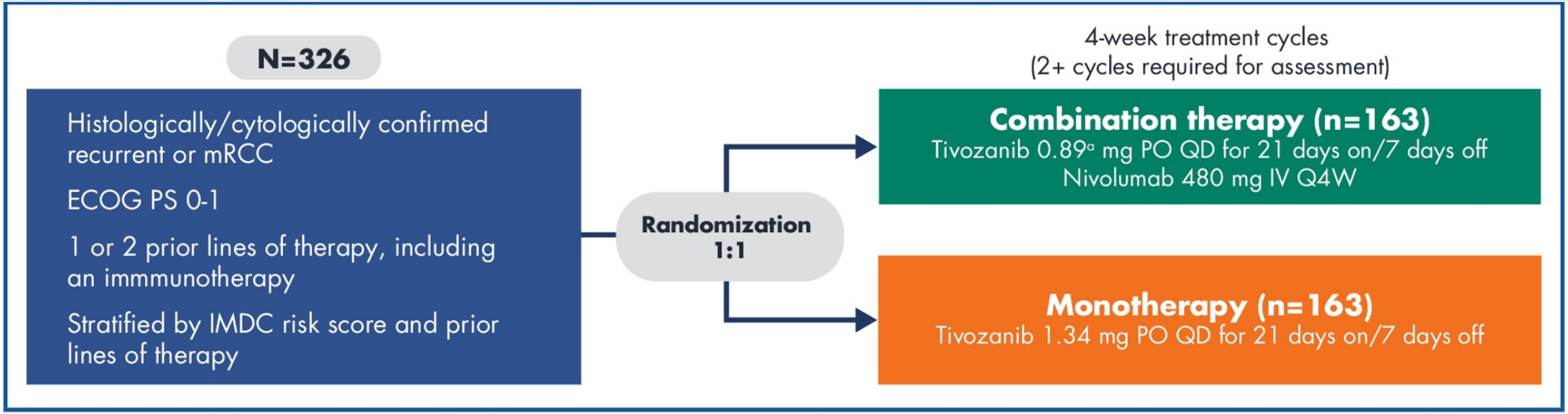
Median PFS: 5.6 vs 3.9 months

- Tivozanib active in patients who received prior axitinib (a similarly potent and selective VEGFR-TKI)
- Prior axitinib does not influence tivozanib tolerability in 3rd and 4th line of therapy
- 1-year duration of response: 71% tivozanib vs 46% sorafenib

Median follow-up of 19 months; data cutoff: Oct 4, 2018.

Pal S, et al. *Eur Urol*. 2020;78(6):783-785. Rini BI, et al. GU Ca Symp 2021.

TiNivo-2: Ongoing Phase III Trial of Tivozanib plus Nivolumab Compared to Tivozanib Alone in Patients with RCC Following 1 or 2 Lines of Therapy Where At Least One Line Has an Immune Checkpoint Inhibitor



[a]Protocol amendment in February 2022 reduced dose of tivozanib from 1.34 to 0.89 mg when combined with nivolumab. This amendment was not the result of any clinical outcomes seen in the conduct of the TiNivo-2 trial, which has enrolled 2 patients thus far. The growing body of evidence in combination trials suggest that the risk-benefit may be optimized at a reduced dose in the combination.
1L, first line; 2L, second line; ECOG PS, Eastern Cooperative Oncology Group performance status; IMDC, International Metastatic RCC Database Consortium; IV, intravenous; mRCC, metastatic renal cell carcinoma; PO, orally; Q4W, every 4 weeks; QD, once daily; TKI, tyrosine kinase inhibitor.

Primary Endpoint: PFS assessed by blinded independent radiological review (until PD [≈ 30 months] as measured by RECIST v1.1

Coueiri TK et al. 2022 *Genitourinary Cancers Symposium*; Abstract TPS405.

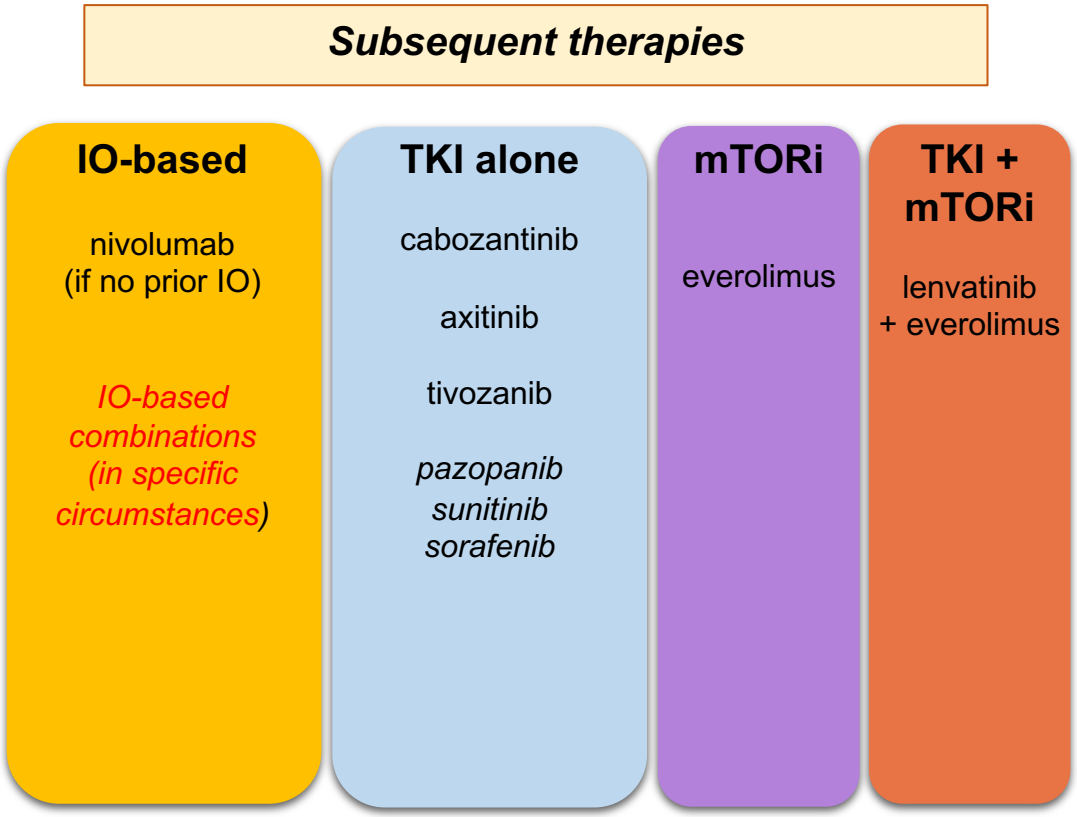
RTP RESEARCH TO PRACTICE

Discussion for oral abstract session: genitourinary cancer – kidney and bladder

Braun et al, ASCO 2023

Abstract LBA4500 (Choueiri):

Efficacy and safety of atezolizumab plus cabozantinib vs cabozantinib alone after progression with prior immune checkpoint inhibitor (ICI) treatment in metastatic renal cell carcinoma (RCC): Primary PFS analysis from the phase 3, randomized, open-label CONTACT-03 study.



Phase III CONTACT-03 study

Choueiri et al, ASCO 2023

Key eligibility criteria

- Advanced/metastatic clear cell or non–clear cell[a] RCC with or without a sarcomatoid component
- Radiographic progression on or after prior ICI treatment
  - ICI as adjuvant, 1L or 2L (single agent or in combination with another permitted agent)
  - ICI in the immediately preceding line of therapy

R
1:1

N=522

Atezolizumab 1200 mg IV q3w + Cabozantinib 60 mg daily PO

Cabozantinib 60 mg daily PO

Stratification factors

- **IMDC risk group**
  0 vs 1-2 vs ≥3
- **Histology**
  Dominant clear cell without sarcomatoid vs dominant non-clear cell without sarcomatoid vs any sarcomatoid[b]
- **Most recent line of ICI**
  Adjuvant vs 1L vs 2L

Primary endpoints

- Independent centrally-assessed PFS[c]
- OS

Key secondary endpoints

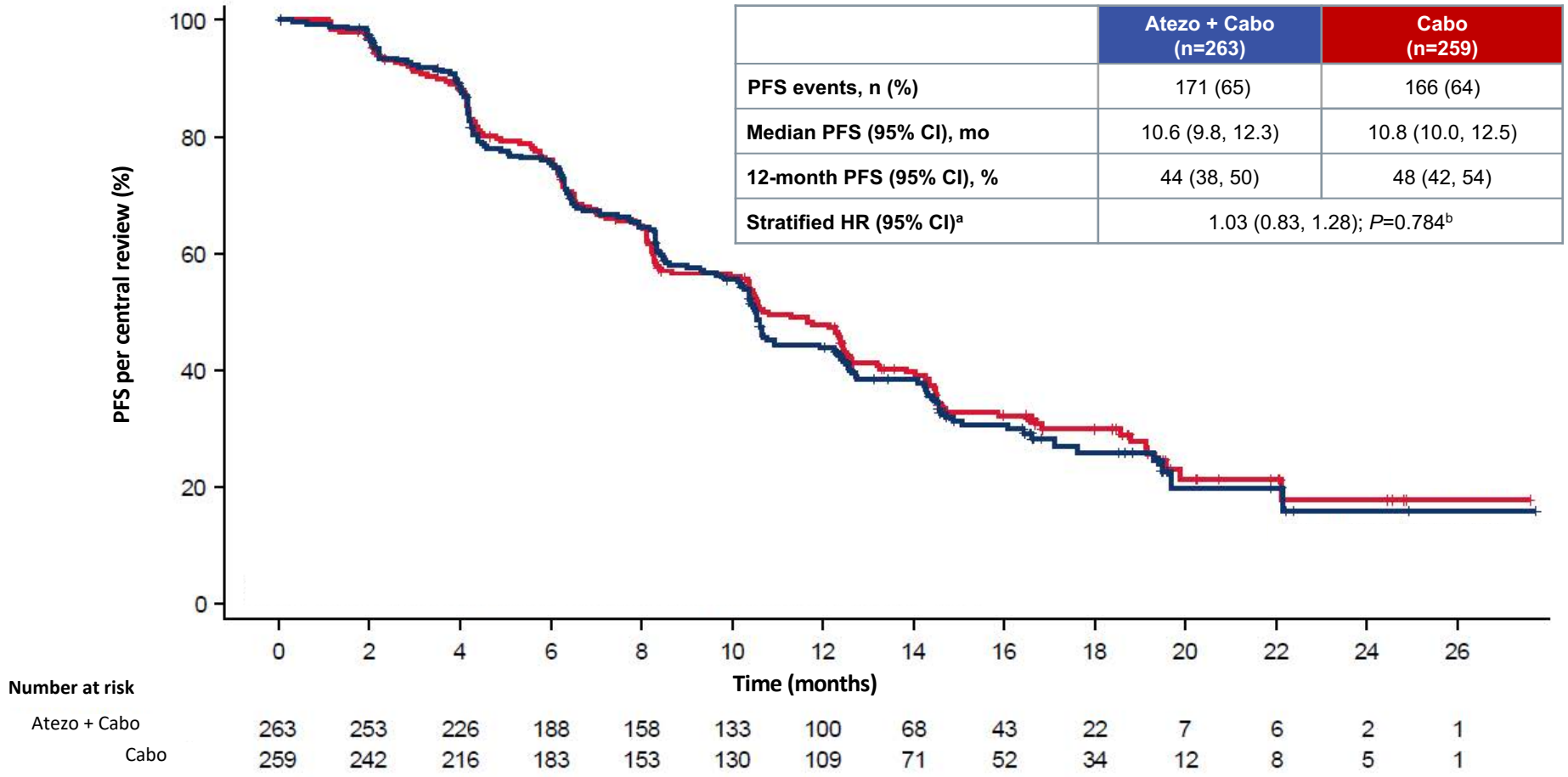
- Investigator-assessed PFS[c]
- ORR (per central review and per investigator)[c]
- Duration of response (per central review and per investigator)[c]
- Safety

ClinicalTrials.gov ID, NCT04338269. IMDC, International Metastatic RCC Database Consortium. Patients were enrolled between July 28, 2020 and December 27, 2021.
[a] Papillary, chromophobe or unclassified (chromophobe requires sarcomatoid differentiation). [b] Clear cell or non-clear cell. [c] Assessed according to RECIST 1.1.

Primary analysis of centrally reviewed PFS (primary endpoint)

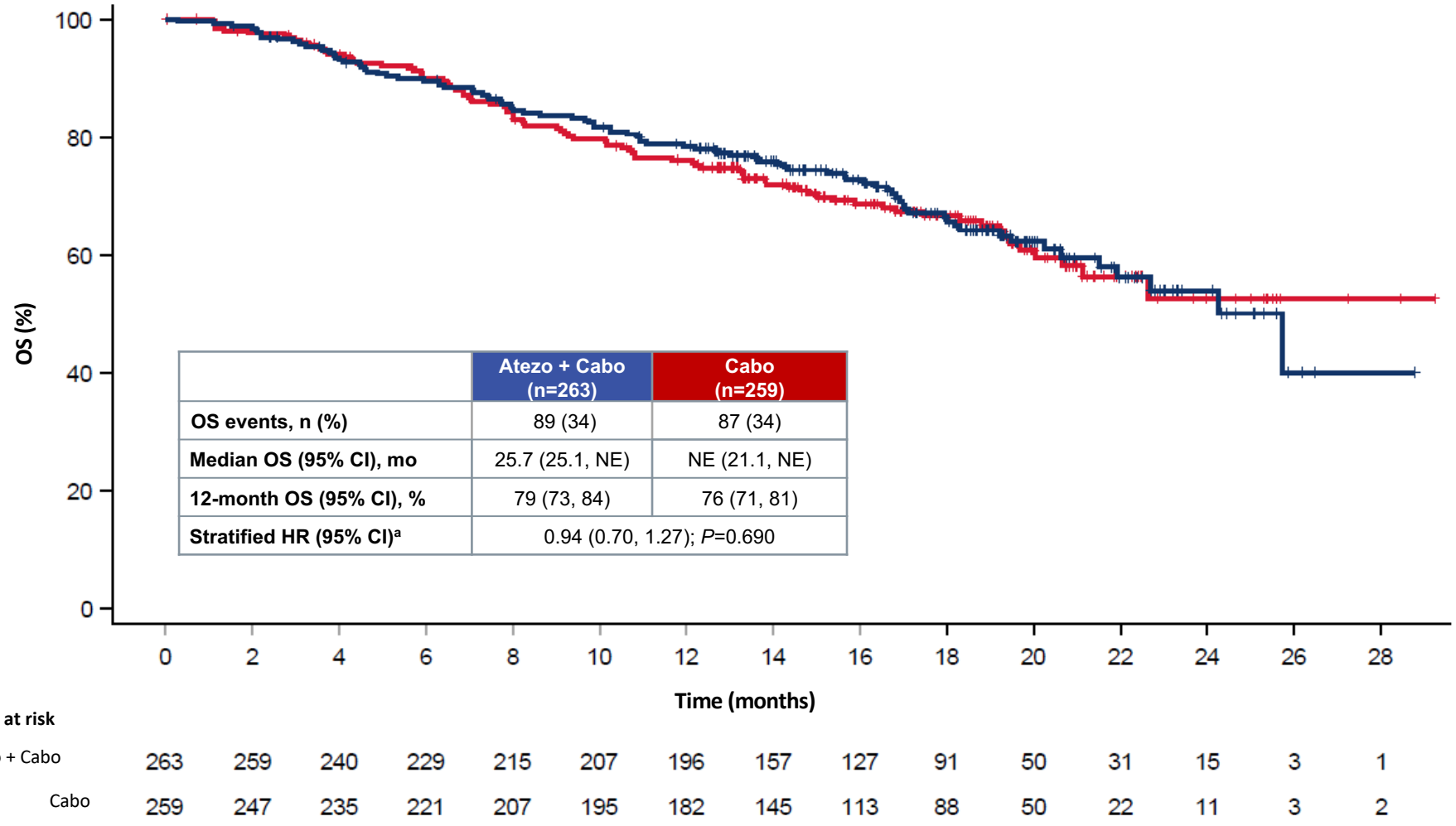
Choueiri et al, ASCO 2023

	Atezo + Cabo (n=263)	Cabo (n=259)
PFS events, n (%)	171 (65)	166 (64)
Median PFS (95% CI), mo	10.6 (9.8, 12.3)	10.8 (10.0, 12.5)
12-month PFS (95% CI), %	44 (38, 50)	48 (42, 54)
Stratified HR (95% CI)[a]	1.03 (0.83, 1.28); *P*=0.784[b]	



[a] Stratified for IMDC risk group. [b] Not significant at α=0.02.

Interim analysis of OS (primary endpoint)



	Atezo + Cabo (n=263)	Cabo (n=259)
OS events, n (%)	89 (34)	87 (34)
Median OS (95% CI), mo	25.7 (25.1, NE)	NE (21.1, NE)
12-month OS (95% CI), %	79 (73, 84)	76 (71, 81)
Stratified HR (95% CI)[a]	0.94 (0.70, 1.27); *P*=0.690	

[a] Stratified for IMDC risk group.

Limitations of CONTACT-03

Braun et al, ASCO 2023

- **Anti-PD-L1 instead of anti-PD-1**
  Anti-PD-L1 may be less active in RCC

- **IO re-challenge is *immediately* after prior IO**
  Long-term PD-1 receptor occupancy
  Does not answer delayed re-challenge

- **Very few patients treated after adjuvant pembrolizumab**
  Does not answer question of optimal treatment after adjuvant IO (need trials for this)

Phase III LITESPARK-005 Trial of Belzutifan Meets Primary Endpoint for Certain Patients with Previously Treated Advanced RCC

Press Release – August 18, 2023

Topline results were announced from LITESPARK-005, the first positive Phase III trial investigating belzutifan, an oral hypoxia-inducible factor-2 alpha (HIF-2α) inhibitor. LITESPARK-005 is evaluating belzutifan for the treatment of adult patients with advanced renal cell carcinoma (RCC) who have experienced disease progession after PD-1/L1 checkpoint inhibitor and vascular endothelial growth factor-tyrosine kinase inhibitor (VEGF-TKI) therapies.

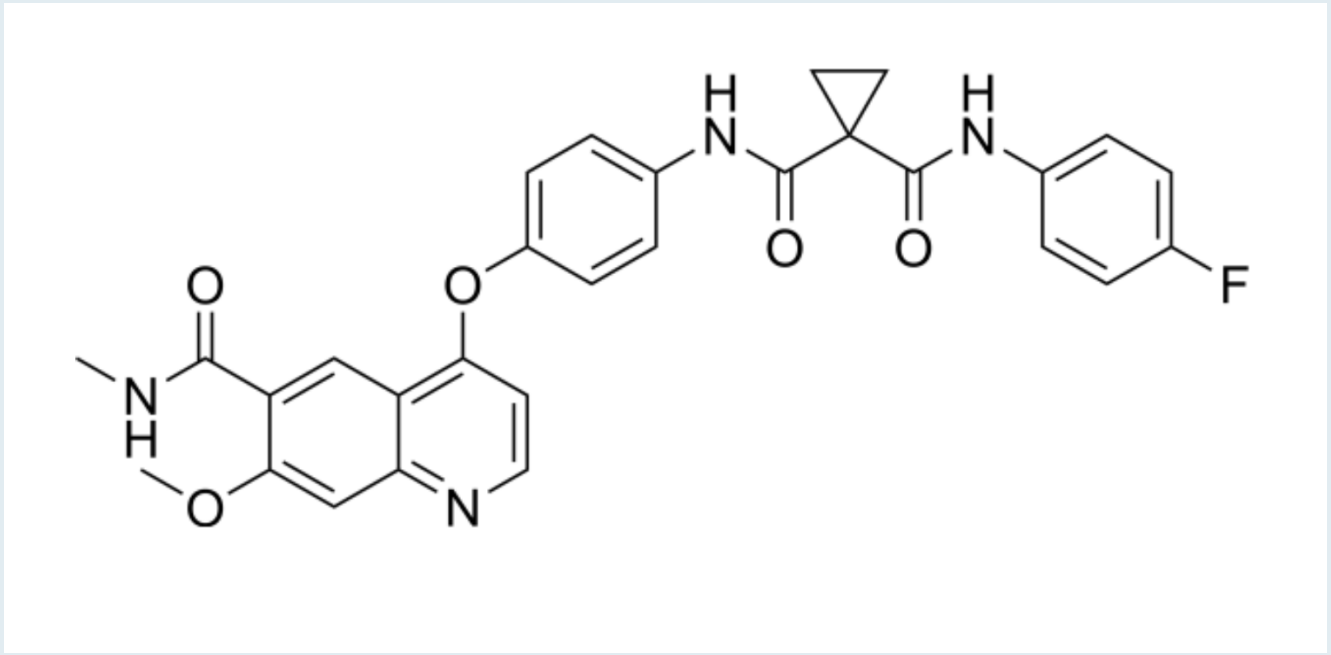
“In the trial, belzutifan showed a statistically significant and clinically meaningful improvement in progression-free survival (PFS) compared to everolimus, based on a pre-specified interim analysis conducted by an independent Data Monitoring Committee. A statistically significant improvement in the trial’s key secondary endpoint of objective response rate (ORR) was also demonstrated. A trend toward improvement in overall survival (OS), a dual primary endpoint, was observed; however, this result did not reach statistical significance. OS will be tested at a subsequent analysis. The safety profile of belzutifan in this trial was consistent with that observed in previously reported studies. Results will be presented at an upcoming medical meeting and shared with regulatory authorities.”

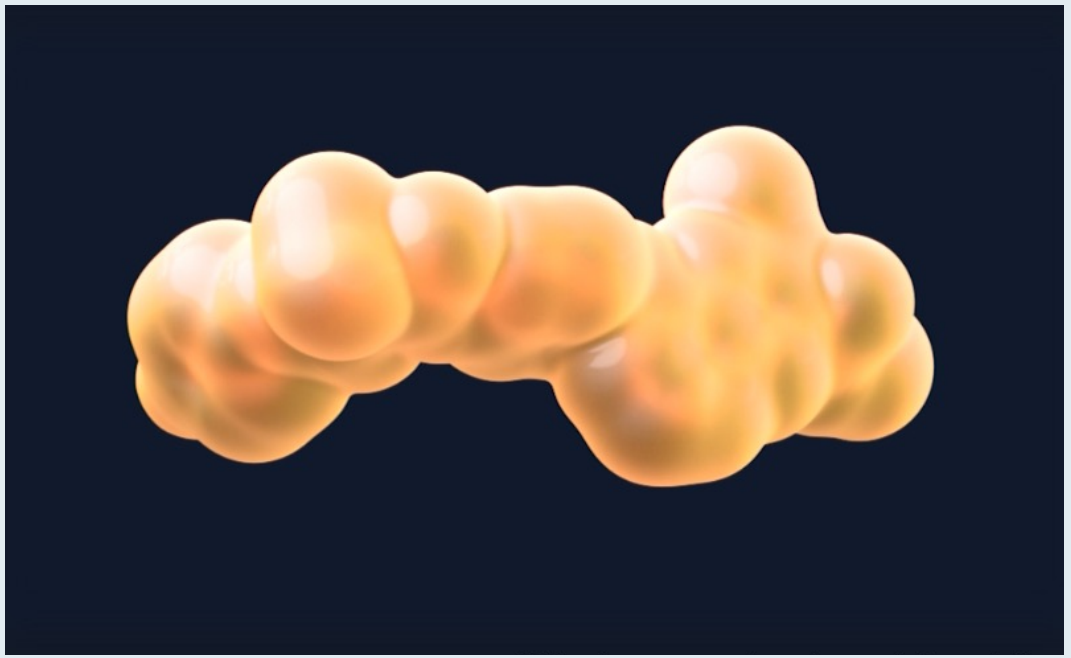
The recommended belzutifan dosage is 120 mg administered orally once daily with or without food.

https://www.merck.com/news/merck-announces-welireg-belzutifan-phase-3-litespark-005-trial-met-primary-endpoint-of-progression-free-survival-in-certain-previously-treated-patients-with-advanced-renal-cell-carcinoma/

Zanzalintinib: Mechanism of Action

- Zanzalintinib is designed to inhibit multiple receptor tyrosine kinases (RTKs), including VEGFR, MET, TAM kinases (AXL and ER) and other kinases implicated in the growth and spread of cancer.

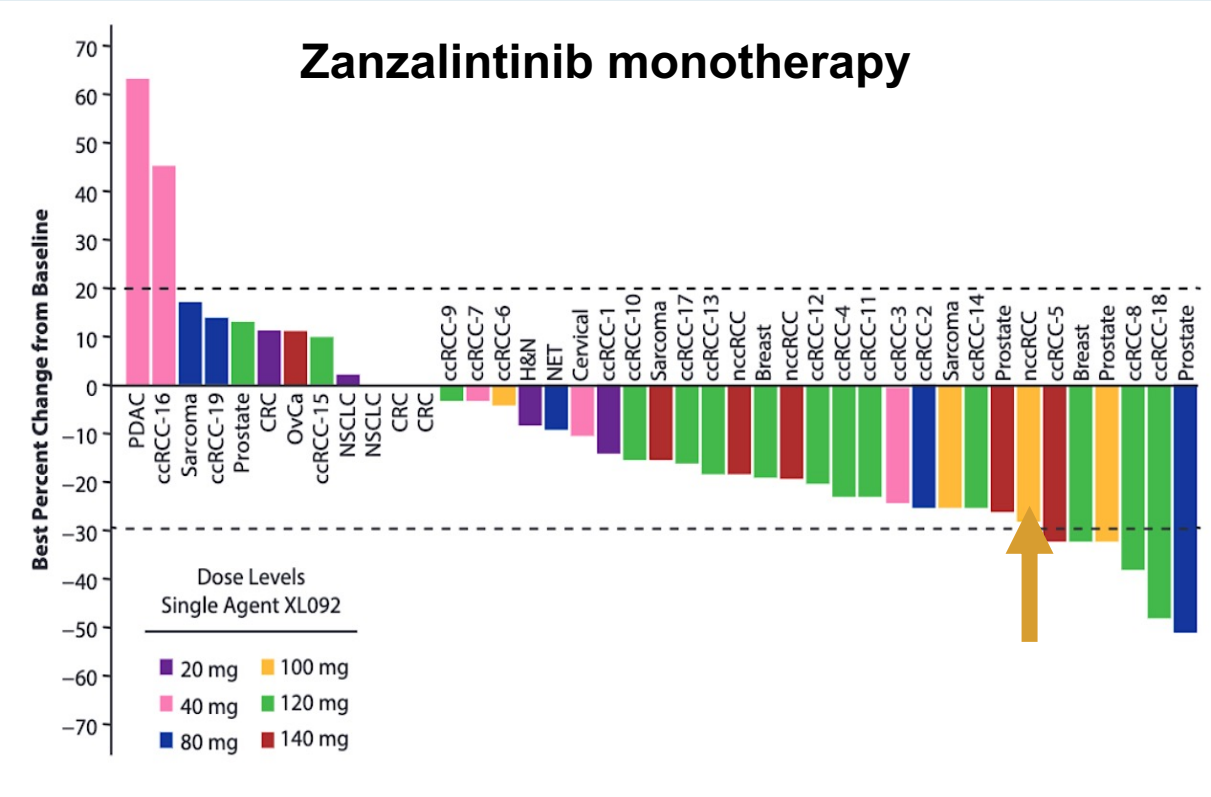


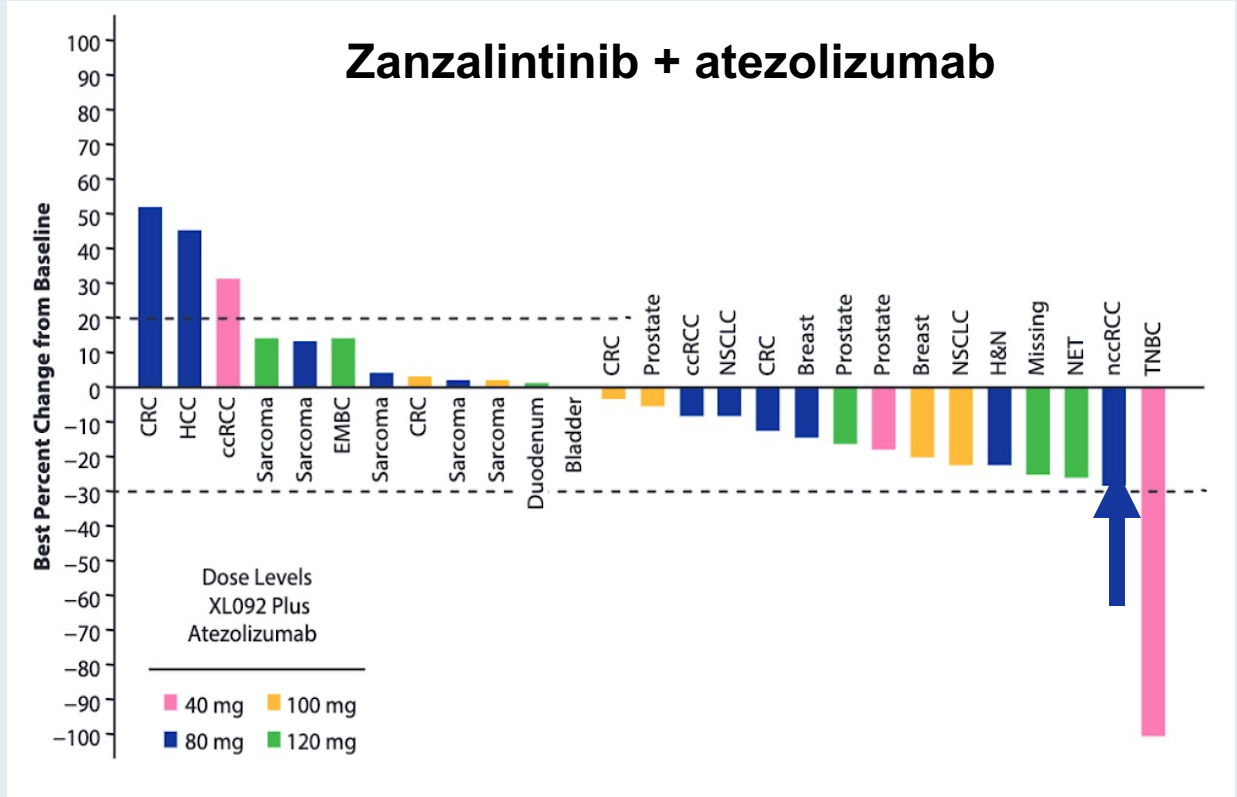


https://www.exelixismedicalaffairs.com/explore-our-pipeline/explore-xl092/

RTP RESEARCH TO PRACTICE

STELLAR-001: Phase 1 Dose-Escalation and Expansion Study of Zanzalintinib (XL092) Alone or in Combination in Locally Advanced or Metastatic Solid Tumors





Sharma M et al. ESMO 2022;Abstract 481P.

RTP RESEARCH TO PRACTICE

STELLAR-304: A Randomized Open-Label Phase III Study of Zanzalintinib (XL092) and Nivolumab versus Sunitinib Malate for Advanced or Metastatic Non-Clear Cell RCC

Key Eligibility Criteria

- Unresectable, advanced, or metastatic nccRCC (papillary, unclassified, and translocation subtypes); sarcomatoid features allowed
- Measurable disease
- No prior systemic anticancer therapy for unresectable locally advanced or metastatic nccRCC
  - One prior systemic adjuvant therapy, excluding sunitinib, allowed if recurrence ≥6 months after last dose

Key Endpoints

Multiple Primary Endpoints

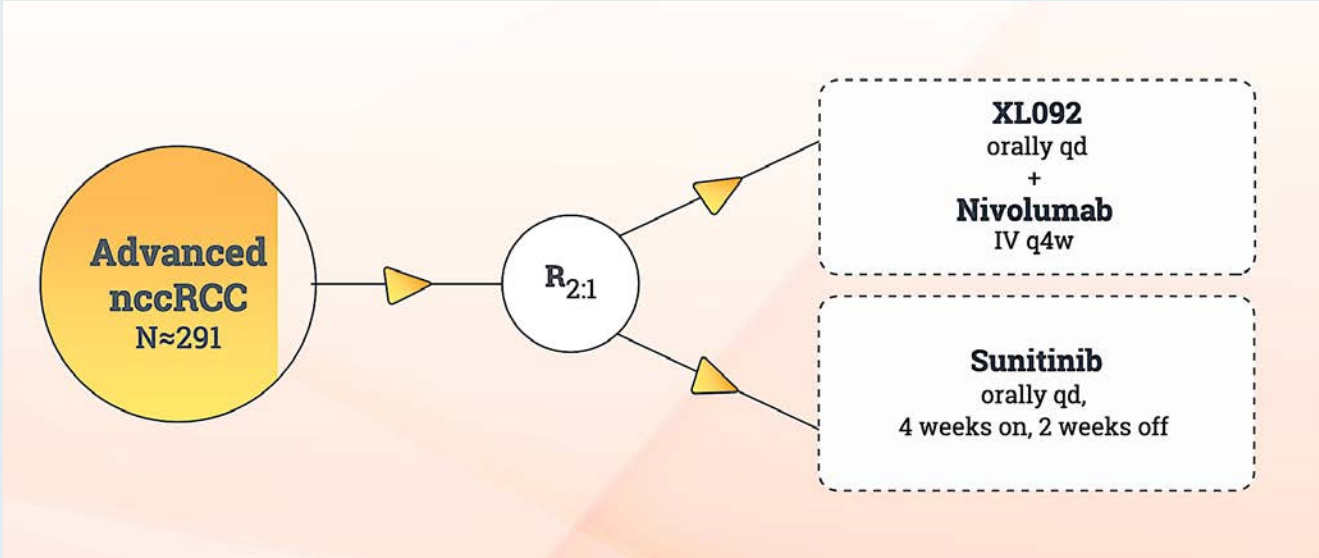
- PFS by BIRC
- ORR by BIRC

Secondary Endpoint

- OS

Additional Endpoints

- DOR by BIRC
- PFS, ORR, and DOR by investigator
- PROs accessed by FKSI-19 and EQ-5D-5L



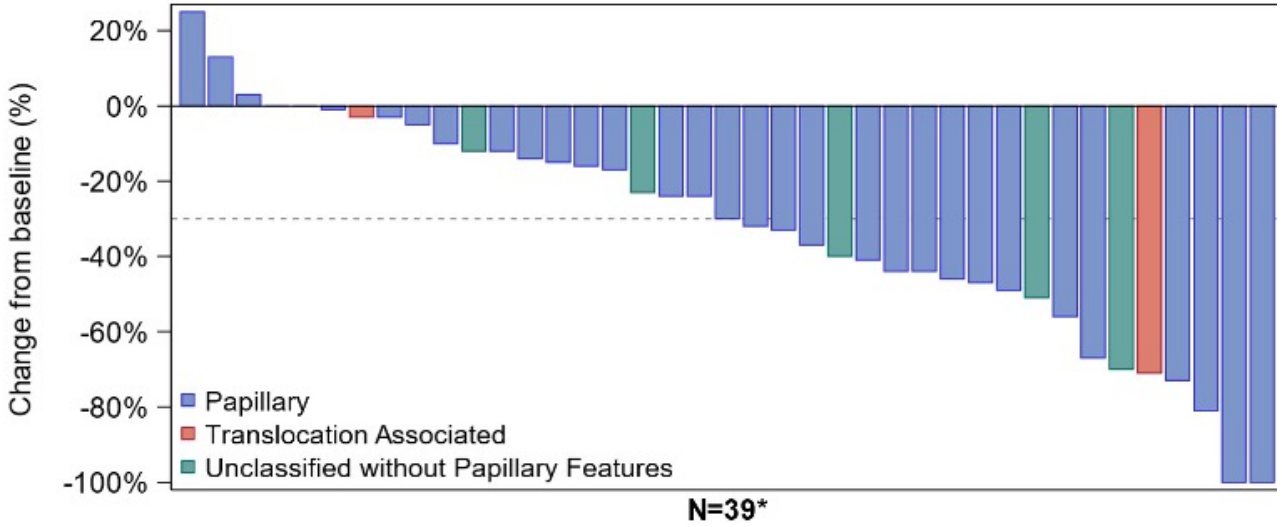
https://www.stellarclinicaltrials.com/stellar-304

RTP RESEARCH TO PRACTICE

Updated Results from a Phase II Study of Nivolumab with Cabozantinib for Non-Clear Cell RCC

	1st line (any histology, N=26)	2nd line (any histology, N=14)	Papillary* (32)	Unclassified w/o papillary features (6)	Translocation-assoc. (2)
ORR	54% (33, 73)	36% (13, 65)	47% (30, 64)	50% (12, 88)	50% (1, 99)
CR	1 (4%)	0	1 (3%)	0	0
PR	13 (50%)	5 (36%)	14 (44%)	3 (50%)	1 (50%)
SD	12 (46%)	7 (50%)	16 (50%)	2 (33%)	1 (50%)
PD	0	2 (14%)	1 (3%)	1 (17%)	0
Med. PFS, months (95% CI)	11 (7, 19)	13 (5, 16)	13 (7, 16)	8 (1, *NE*)	14 (5, 23)

*Includes 16 unclassified with papillary features, 11 high grade papillary and 5 FH-deficient RCC.



*One patient with rapid clinical progression and unevaluable lesions excluded from the figure

- Adverse events in the non-clear cell RCC population were consistent with the observed adverse event profile of this combination for clear cell RCC

Lee C-H et al. ASCO 2023;Abstract 4537.

COSMIC-021 Extended 3-Year Follow-Up of Cohort 10: Tumor Response per Investigator Assessment with Cabozantinib and Atezolizumab for Patients with Non-Clear Cell RCC

	nccRCC (N=32)
ORR, % (n, 95% CI)	31 (10, 16.1–50.0)
Best overall response, n (%)	
Confirmed complete response	0
Confirmed partial response	10 (31)
Stable disease	20 (63)
Progressive disease	2 (6)
Disease control rate, % (n, 95% CI)	94 (30, 79.2–99.2)
Time to response, median (range), months	2.7 (1.2–6.9)
Duration of response, median (95% CI), months	8.1 (2.4–18.1)

Objective response rate = confirmed complete response + confirmed partial response.
Disease control rate = confirmed complete response + confirmed partial response + stable disease.

McGregor BA et al. Genitourinary Cancers Symposium 2023;Abstract 684.

KEYNOTE-B61: Best Overall Response with First-Line Pembrolizumab and Lenvatinib for Non-Clear Cell RCC

	All patients (N=158)	Papillary histology (n=93)	Chromophobe histology (n=29)	Unclassified histology (n=21)	Translocation histology (n=6)	Other histology (n=9)
Confirmed objective response	78 (49%; 41–57)	50 (54%; 43–64)	8 (28%; 13–47)	11 (52%; 30–74)	4 (67%; 22–96)	5 (56%; 21–86)
Confirmed disease control†	130 (82%; 75–88)	79 (85%; 76–92)	20 (69%; 49–85)	19 (90%; 70–99)	5 (83%; 36–100)	7 (78%; 40–97)
Confirmed clinical benefit‡	113 (72%; 64–78)	69 (74%; 64–83)	18 (62%; 42–79)	15 (71%; 48–89)	5 (83%; 36–100)	6 (67%; 30–93)
Best overall response						
Confirmed complete response	9 (6%)	8 (9%)	0	0	0	1 (11%)
Confirmed partial response	69 (43%)	42 (45%)	8 (28%)	11 (52%)	4 (67%)	4 (44%)
Stable disease	52 (33%)	29 (31%)	12 (41%)	8 (38%)	1 (17%)	2 (22%)
Progressive disease	17 (11%)	9 (10%)	4 (14%)	2 (10%)	1 (17%)	1 (11%)
Not evaluable§	1 (1%)	0	1 (3%)	0	0	0
Not assessed¶	10 (6%)	5 (5%)	4 (14%)	0	0	1 (11%)

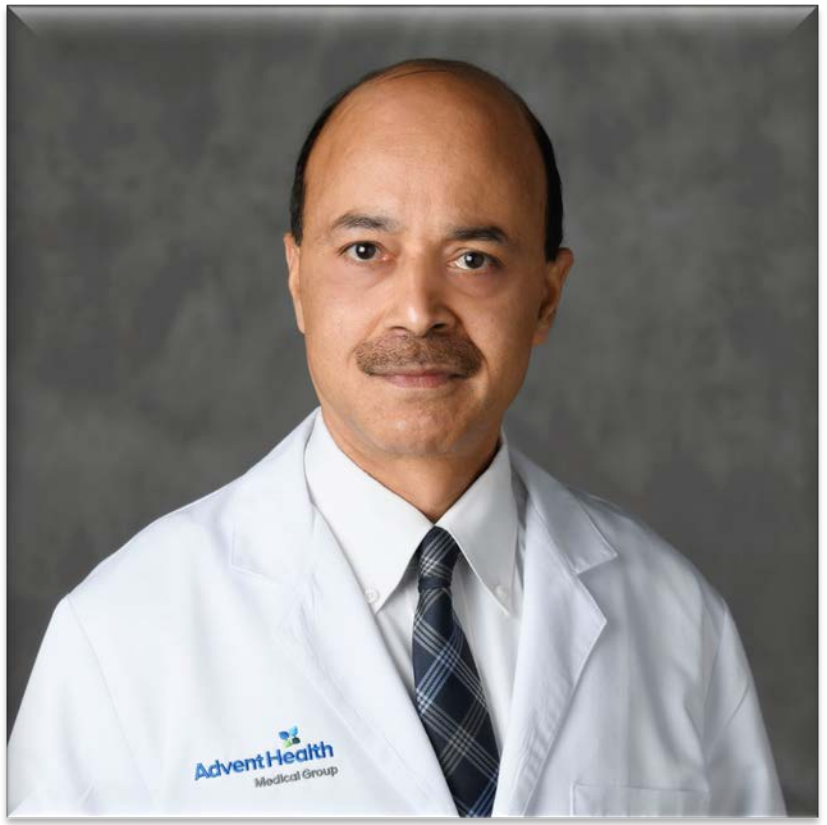
Data are n (%; 95% CI) or n (%). RECIST=Response Evaluation Criteria in Solid Tumours. *RECIST (version 1.1) was adjusted to allow a maximum of ten target lesions in total and five per organ if a larger number of target lesions was needed to adequately represent tumour burden. †Confirmed complete response, partial response, or stable disease of any duration. ‡Confirmed complete response, partial response, or stable disease for at least 6 months. §Post-baseline assessment available but not evaluable. ¶No post-baseline assessment available.

Albiges L et al. *Lancet Oncol* 2023;24;881-91.

RTP RESEARCH TO PRACTICE

Guru P. Sonpavde, MD

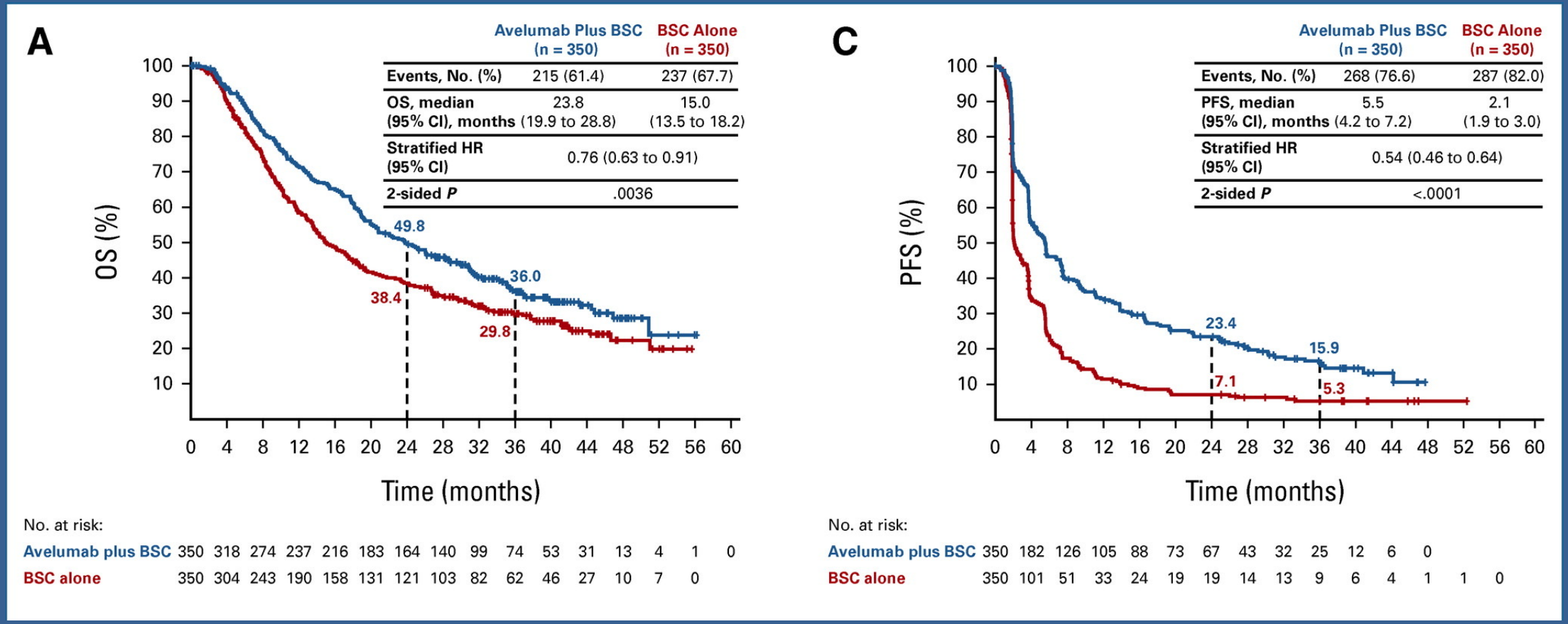
Director Genitourinary Medical Oncology
Phase I Clinical Research
Christopher K. Glanz Chair, Bladder Cancer Research
AdventHealth Cancer Institute
Professor of Medicine, University of Central Florida
Orlando, Florida



AdventHealth
Cancer Institute

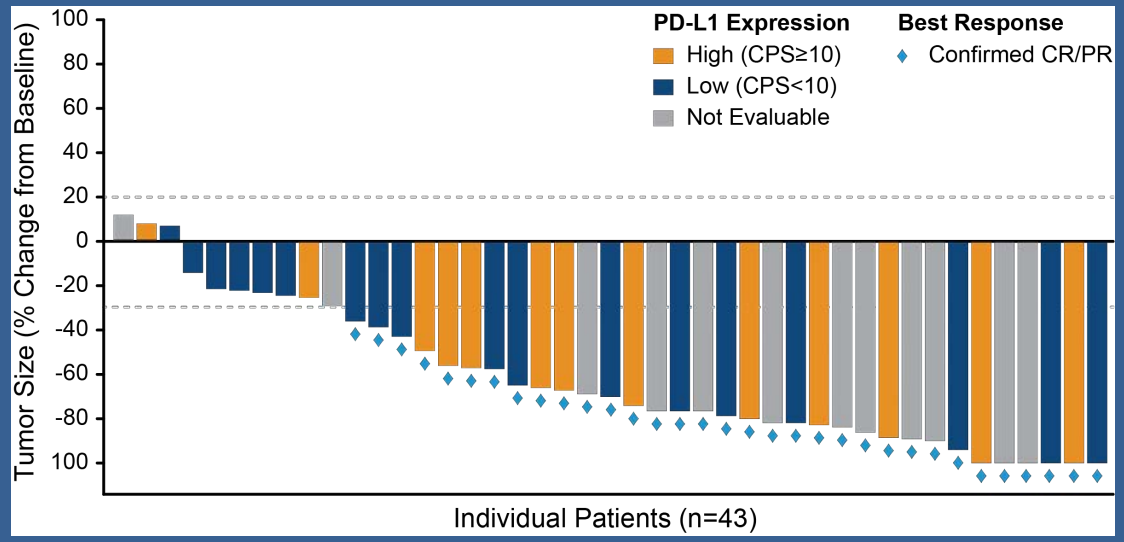
UNIVERSITY OF CENTRAL FLORIDA
1963

Avelumab First-Line Maintenance for Advanced Urothelial Carcinoma: Results From the JAVELIN Bladder 100 Trial After ≥2 Years of Follow-Up



Powles T, et al. J Clin Oncol 2023 Jul 1;41(19):3486-3492.

Enfortumab Vedotin + Pembrolizumab as first-line therapy for cisplatin-ineligible advanced UC (EV-103 cohorts A and K): accelerated approval in USA



Confirmed ORR 95% CI	73.3% (33/45) (58.1, 85.4)
Complete response	15.6% (7/45)
Partial response	57.8% (26/45)

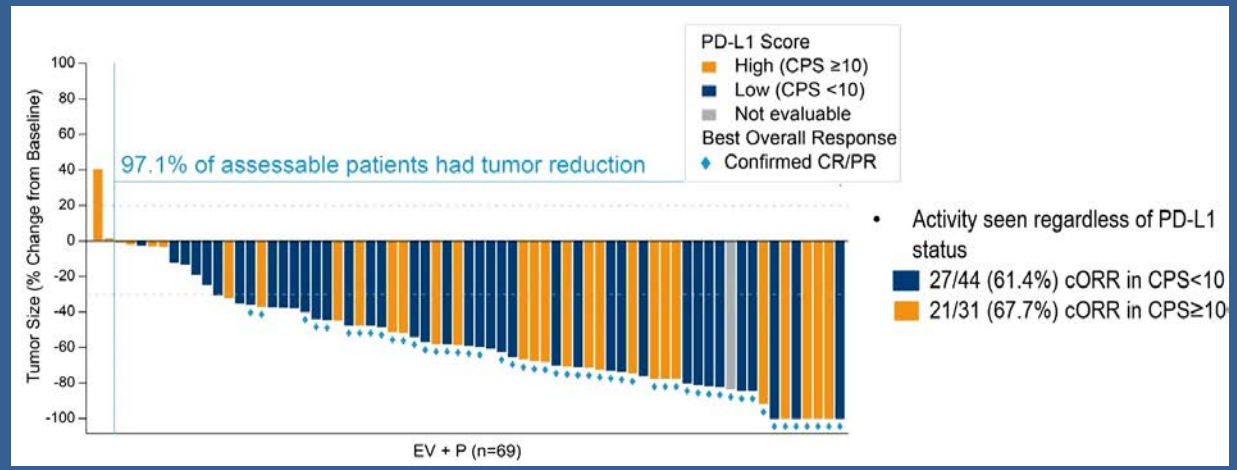
Median DOR =25.6 mo

Median PFS =12.3 mo

24-mo OS=56.3%

Benefit regardless of PD-L1

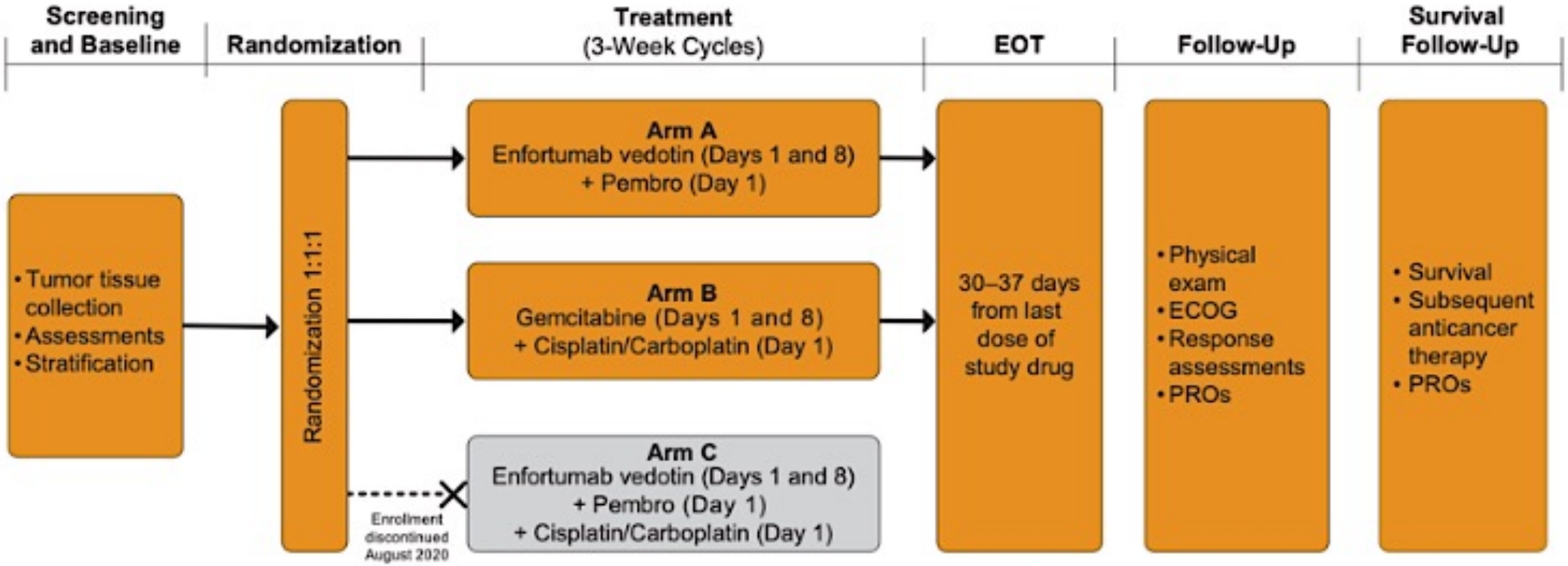
Hoimes C, et al. JCO 2022



	EV+P (N=76)	EV Mono (N=73)
Confirmed ORR, n (%) (95% CI)	49 (64.5) (52.7, 75.1)	33 (45.2) (33.5, 57.3)
Best overall response, n (%)		
Complete Response	8 (10.5)	3 (4.1)
Partial Response	41 (53.9)	30 (41.1)
Stable Disease	17 (22.4)	25 (34.2)
Progressive Disease	6 (7.9)	7 (9.6)
Not Evaluable	3 (3.9)	5 (6.8)
No Assessment	1 (1.3)	3 (4.1)
Median time to objective response (range), mos	2.07 (1.1, 6.6)	2.07 (1.9, 15.4)
Median number of treatment cycles (range)	11.0 (1, 29)	8.0 (1, 33)

Rosenberg JE, et al. ESMO Congress September 2022

EV-302 phase III trial



EOT= End of Treatment; Pembro=pembrolizumab; PROs=patient reported outcomes

- Stratification Factors for Randomization: cisplatin eligibility (eligible/ineligible), liver metastases (present/absent), PD-L1 expression (high/low)
- Follow-up until disease progression, death, consent withdrawal, or study closure

September 22, 2023 05:00AM Eastern Daylight Time

BOTHELL, Wash & Tokyo– (Business WIRE)– Manufacturers today announced positive topline results from the Phase 3 EV-302 clinical trial (also known as KEYNOTE-A39) for Enfortumab vedotin-efjv in combination with pembrolizumab versus chemotherapy in patients with previously untreated locally advanced or metastatic urothelial cancer (Ia/mUC), a form of bladder cancer that has spread to surrounding organs or muscles, or other parts of the body. The EV-302 trial enrolled patients with previously untreated Ia/mUC who were eligible for cisplatin- or carboplatin-containing chemotherapy regardless of PD-L1 status.

"Over two hundred thousand deaths from urothelial cancer are reported worldwide annually, making it a major cause of morbidity and mortality. The topline results from EV-302 are encouraging for patients with advanced-stage urothelial cancer, which is aggressive and associated with devastating outcomes."

The EV-302 study met its dual primary endpoints of overall survival (OS) and progression-free survival (PFS), compared to chemotherapy. An Independent Data Monitoring Committee determined that OS crossed the pre-specified efficacy boundary at interim analysis. The safety results of the combination are consistent with those of enfortumab vedotin in combination with pembrolizumab previously reported in cisplatin-ineligible patients with Ia/mUC.

Please see Important Safety Information at the end of this press release including BOXED WARNING for Enfortumab vedotin-ejfv.

CheckMate 901 phase III trial

Manufacturer Provides Update on CheckMate-901 Trial Evaluating Nivolumab plus Ipilimumab as First-Line Treatment for Patients with Unresectable or Metastatic Urothelial Carcinoma
05/16/2022

CATEGORY: Corporate/Financial News

PRINCTEON, NJ -- (BusinessWire) – The manufacturer today announced the Phase 3 CheckMate-901 trial, comparing nivolumab plus ipilimumab to standard-of-care chemotherapy as a first-line treatment for patients with untreated unresectable or metastatic urothelial carcinoma, did not meet the primary endpoint of overall survival (OS) in patients whose tumor cells express PD-L1 ≥1% at final analysis. The company remains blinded to the data, and an independent Data Monitoring Committee recommended that the trial continue to assess other primary and secondary endpoints. No new safety signals were observed at the time of analysis.

- Cisplatin-eligible or ineligible patients with unresectable or mUC
- No prior systemic therapy for unresectable or mUC

Cisplatin-ineligible

Cisplatin-eligible

R 1:1

R 1:1

Arm: A
- Nivolumab + Ipilimumab (Q3W up to 4 doses)
- Followed by Nivolumab (Q4W up to 24 months)[a]

Arm: B
- Gemcitabine + Cisplatin or Gemcitabine + Carboplatin (Q3W up to 6 cycles)

Arm: C
- Nivolumab + Gemcitabine + Cisplatin (Q3W up to 6 cycles)
- Followed by Nivolumab (Q4W up to 24 months)[b]

Arm: D
- Gemcitabine + Cisplatin (Q3W up to 6 cycles)

Primary endpoints

OS in PD-L1+ patients receiving nivolumab +ipilimumab vs gemcitabine + cisplatin/carboplatin

OS in cisplatin-ineligible patients receiving nivolumab +ipilimumab vs gemcitabine + carboplatin

PFS, OS in cisplatin-eligible patients receiving nivolumab + gemcitabine + cisplatin vs gemcitabine + cisplatin

Nivolumab in Combination with Cisplatin-Based Chemotherapy Shows Overall Survival and Progression-Free Survival Benefit for Cisplatin-Eligible Patients with Unresectable or Metastatic Urothelial Carcinoma in the Phase 3 CheckMate-901 Trial

JUL 11, 2023

Checkmate-901 is the first and only Phase 3 trial with an immunotherapy-based combination to demonstrate a survival benefit compared to standard-of-care cisplatin-based combinations in the first-line treatment of this patient population

PRINCETON, N.J.—(BUSINESS WIRE)– The manufacturer today announced that the sub-study of the Phase 3 CheckMate-901 trial met the dual primary endpoints of overall survival (OS) and progression-free survival (PFS) as assessed by Blinded Independent Central Review (BICR) at final analysis. Results of the sub-study showed that nivolumab in combination with cisplatin-based chemotherapy followed by nivolumab monotherapy demonstrated statistically significant benefits in OS and PFS compared to standard-of-care cisplatin-based combinations as a first-line treatment for patients with unresectable or metastatic urothelial carcinoma who are eligible for cisplatin-based chemotherapy. The combination of nivolumab with cisplatin-based chemotherapy in first-line urothelial carcinoma had a tolerable safety profile consistent with the known safety profiles of the individual components of the regimen. No new safety concerns have been identified.

Presidential 2

Date Sun, 22.10.2023
Time 16:30 - 18:15
Chairs Andres Cervantes (Valencia, Spain), Silke Gillessen (Bellinzona, Switzerland)
Room Madrid Auditorium - Hall 6
Session Type Proffered Paper session

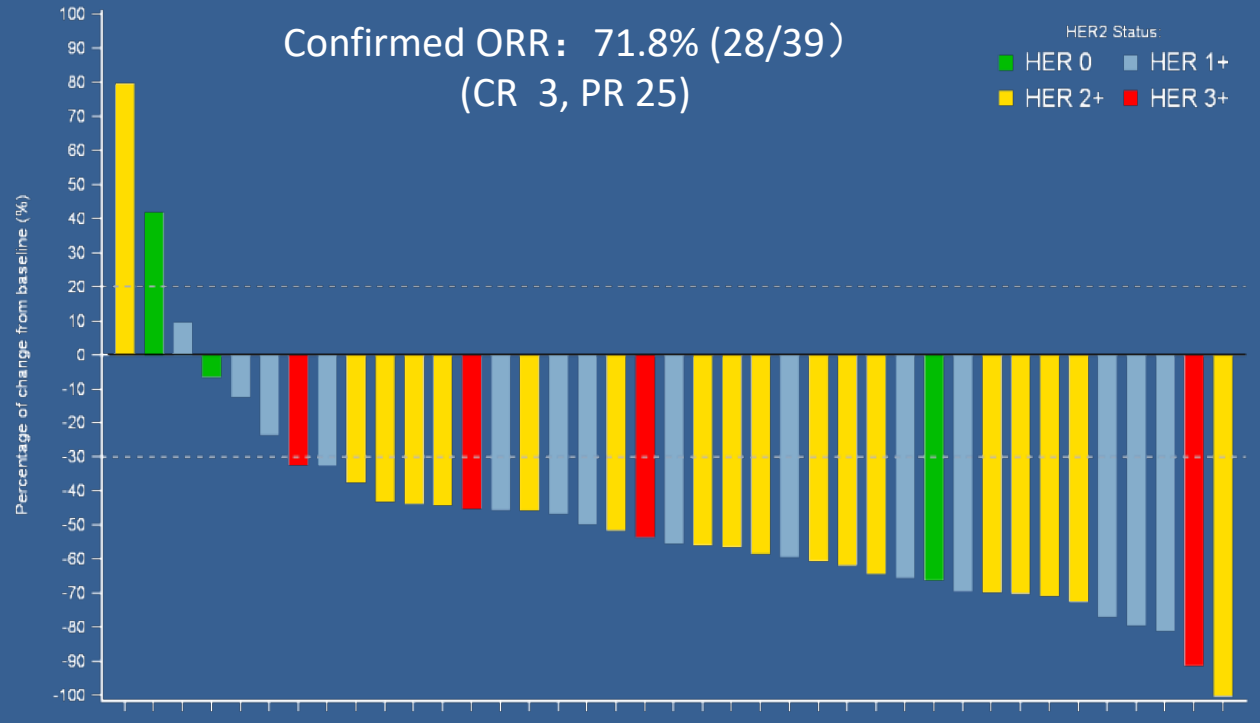
Proffered Paper session

LBA7 - Nivolumab plus gemcitabine-cisplatin versus gemcitabine-cisplatin alone for previously untreated unresectable or metastatic urothelial carcinoma: results from the phase 3 CheckMate 901 trial

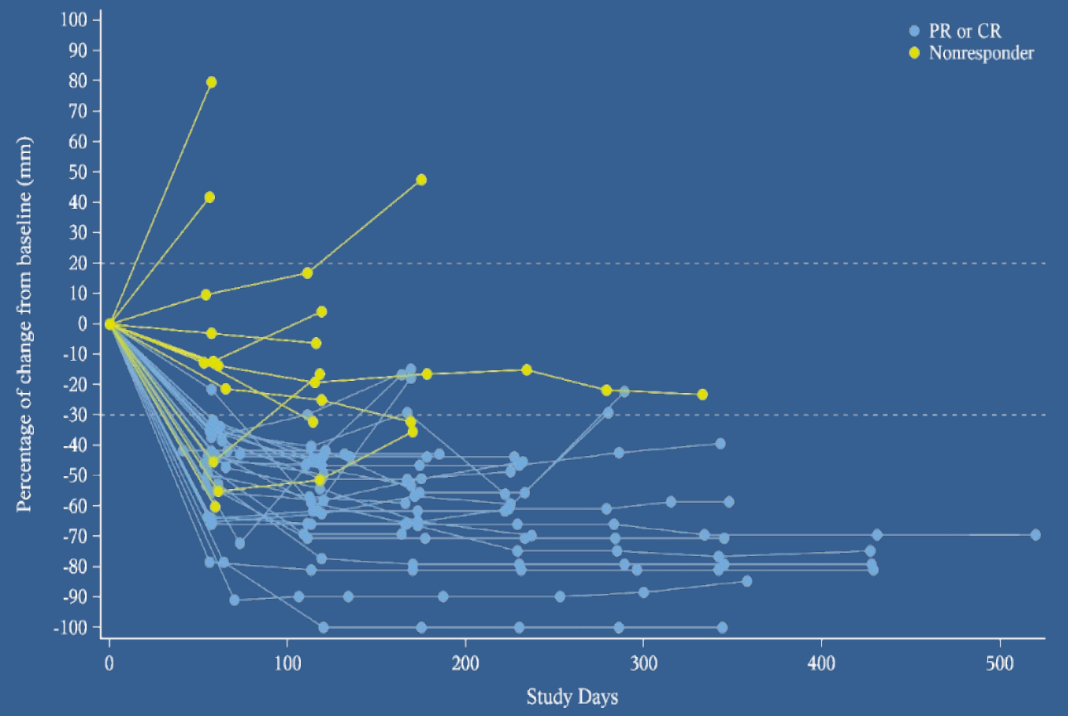
Presentation Number LBA7
Speakers Michiel S. Van der Heijden (Amsterdam, Netherlands)

Disitamab Vedotin (RC-48 ADC) (Her2 targeting ADC with MMAE toxin & cleavable linker) **+ Toripalimab** (PD1 inhibitor) is **active in mUC**

Confirmed ORR： 71.8% (28/39）
(CR 3, PR 25)



Prior systemic treatment (n,%)	
0 Line	**25 (60.98%)**
≥1 Lines	**16 (39.02%)**



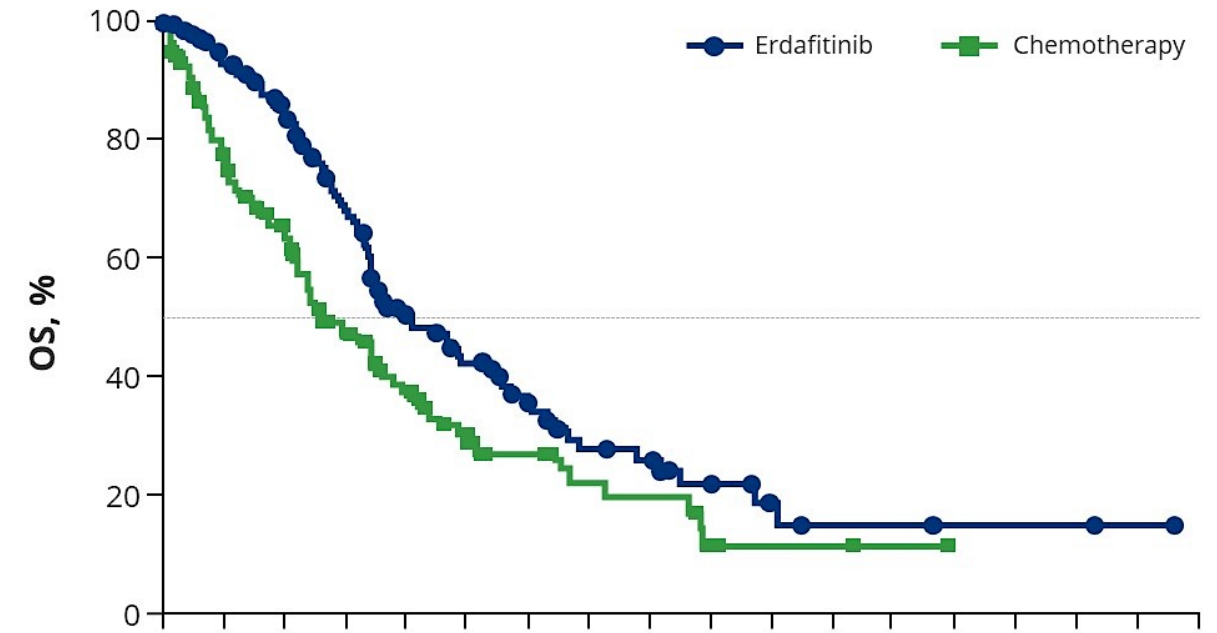
ORR appeared higher in those with HER2 2-3+ (~86%) disease

Sheng et al. ASCO 2022, abstract 4518

Ongoing First-Line Phase III Trials in Advanced UC

Trial	Strategy	Experimental Arm(s)	Standard Arm	Endpoint
CM-901	PD-1 + CTLA-4	Nivo + Ipi*	Gem-Platinum	OS in cis-inelig OS in PD-L1+
	Chemo-IO (substudy)	Gem-Cis-Nivo	Gem-Cis	PFS, OS
NILE	PD-L1 +/- CTLA-4 (+ Chemo)	Durvalumab + Gem-Plat OR Durva + Treme + Gem-Plat	Gem-Platinum	PFS, OS
EV-302	EV + PD1	EV + Pembrolizumab	Gem-Platinum	PFS, OS
NCT05302284 (Her2+)	Her2 ADC + PD1	Disitamab Vedotin + Toripalimab	Gem-Platinum	PFS, OS
MAIN-CAV Maintenance	PD-L1+VEGF	Avelumab + Cabozantinib	Avelumab	OS

Overall Survival for Erdafitinib Was Superior to Investigator's Choice of Chemotherapy



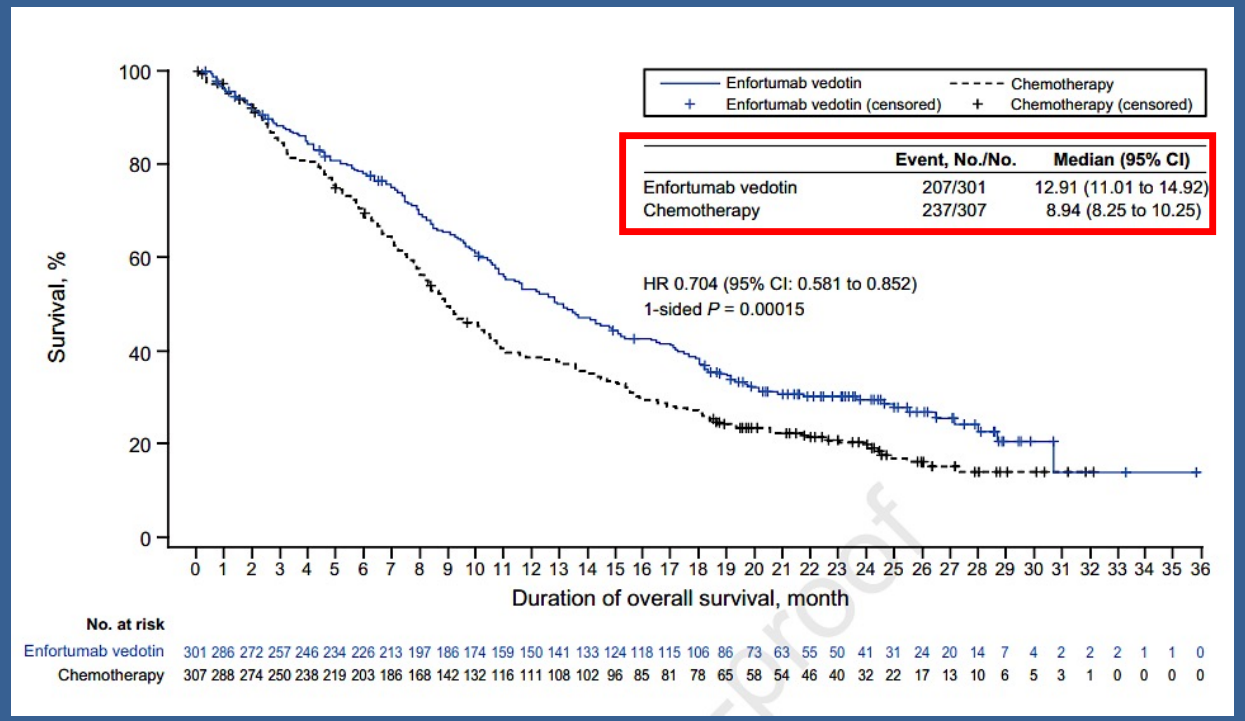
No. at risk																		
Erdafitinib	136	117	97	74	46	35	25	17	15	9	5	3	3	2	2	2	1	0
Chemotherapy	130	87	66	43	30	18	13	9	8	3	2	2	1	0	0	0	0	0

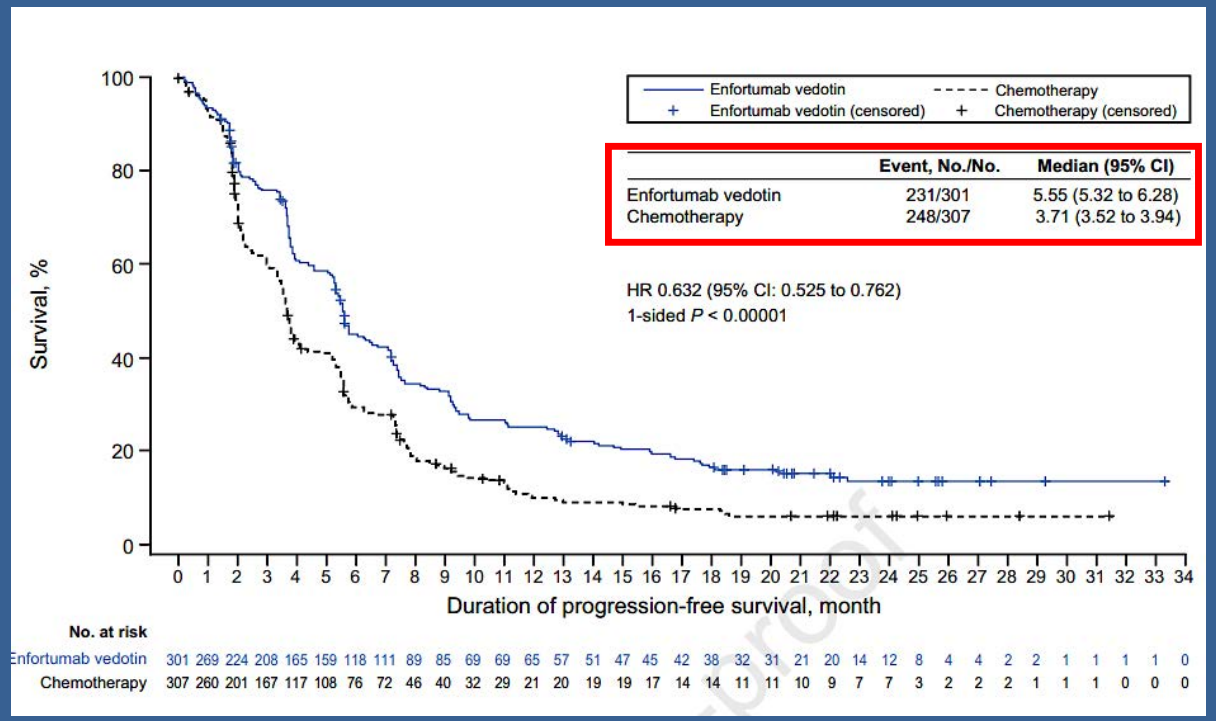
- Median follow-up was 15.9 months
- Median OS was 12.1 months for erdafitinib versus 7.8 months for chemotherapy
- Erdafitinib reduced the risk of death by 36% versus chemotherapy
  - HR, 0.64 (95% CI, 0.47-0.88; *P* = 0.005)[a]
- Based on these interim analysis results, the IDMC recommended to stop the study, unblind data, and cross over patients from chemotherapy to erdafitinib

CI, confidence interval; HR, hazard ratio; IDMC, independent data monitoring committee; OS, overall survival.
[a]The significance level for stopping for efficacy was p=0.019, corresponding to a HR of 0.69.

Loriot Y, et al. ASCO 2023.

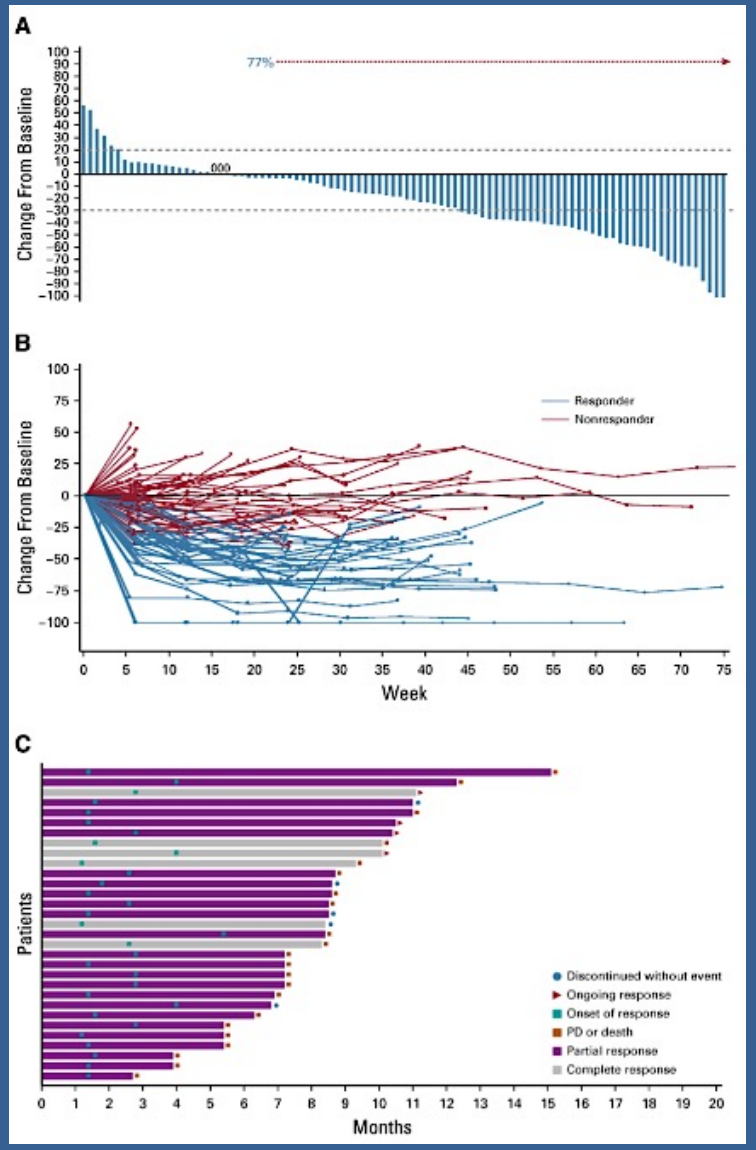
Enfortumab Vedotin following platinum and PD1/L1 inhibitors: EV301 update





Rosenberg JE, et al. Ann Oncol 2023 Sep 5;S0923-7534(23)00832-3.

Sacituzumab Govitecan following platinum and PD1/L1 inhibitors



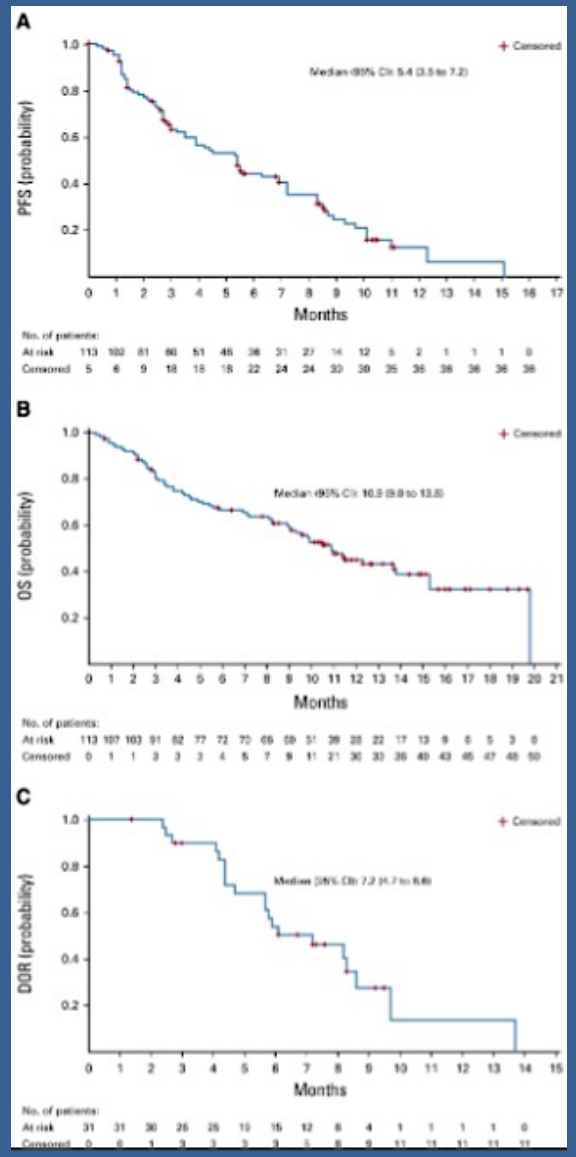
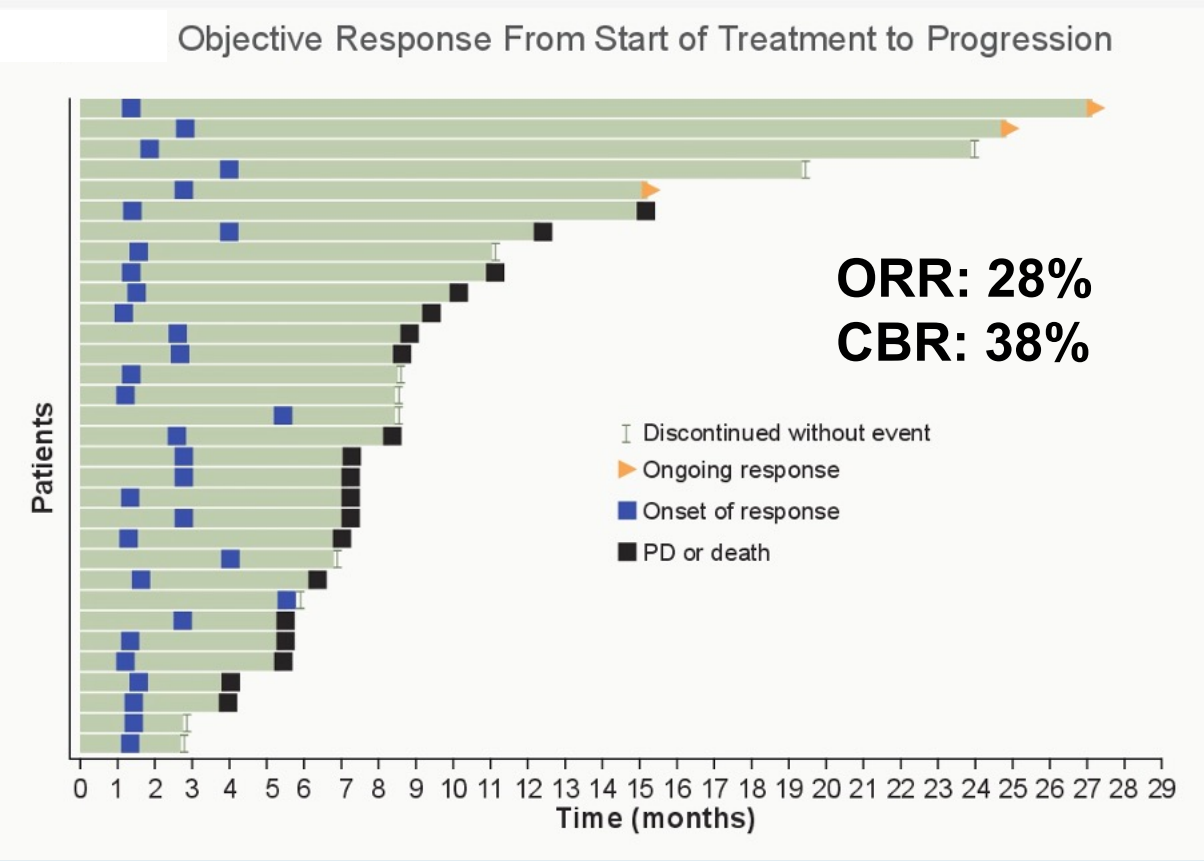


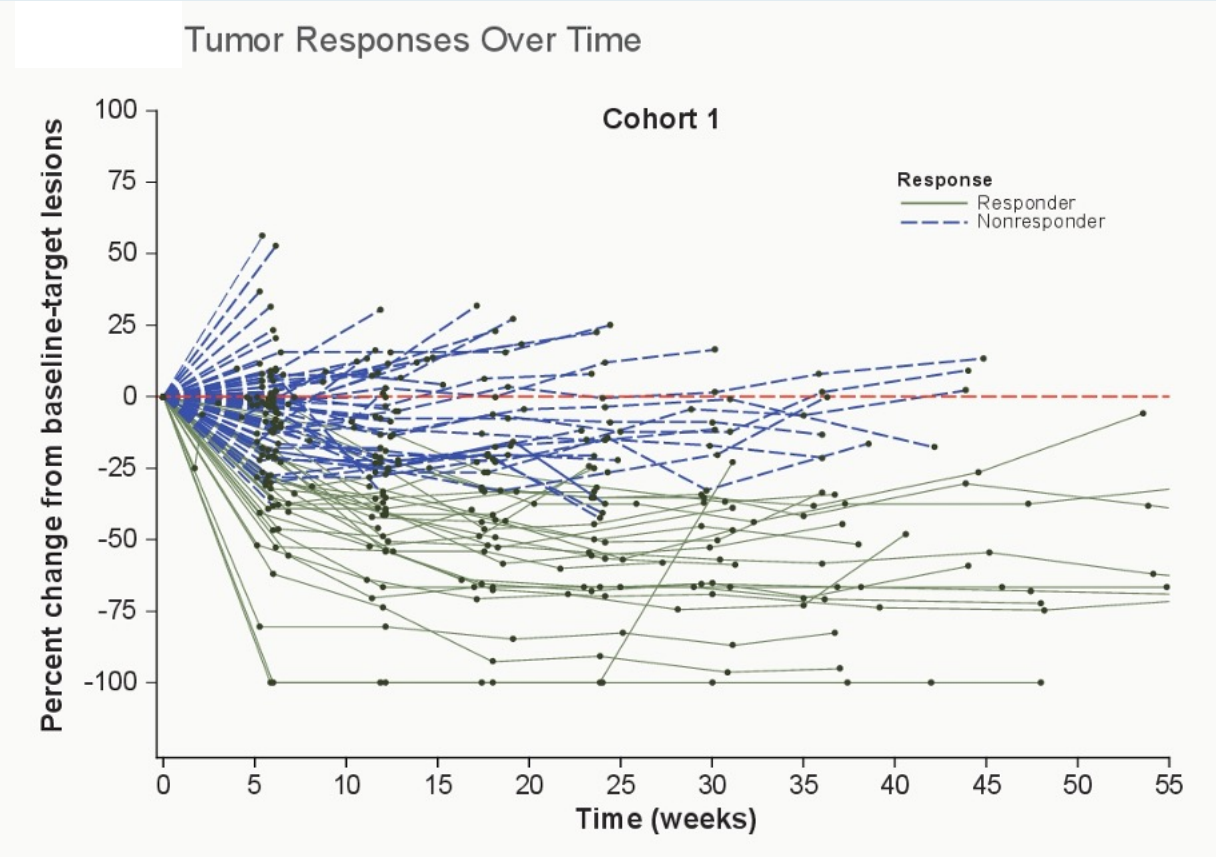
TABLE 2. Summary of Treatment Efficacy

Variable	(N = 113)
Best response, No. (%)	
CR	6 (5)
PR	25 (22)
SD	38 (34)
PD	21 (19)
Not evaluable	8 (7)
Not assessed[a]	15 (13)
ORR	
No. of patients	31
% patients (95% CI)	27 (19 to 37)
CBR[b]	
No. of patients	42
% patients (95% CI)	37 (28 to 47)
Time to onset of response (months)	
Median	1.6
Range	1.2-2.9
Median DOR (months)	
Median	7.2
95% CI	4.7 to 8.6
Range	1.4-13.7

Tagawa S, et al. J Clin Oncol 2021 Aug 1;39(22):2474-2485.

TROPHY U-01 (Cohort 1 — Third-Line After Platinum and Immunotherapy): Response

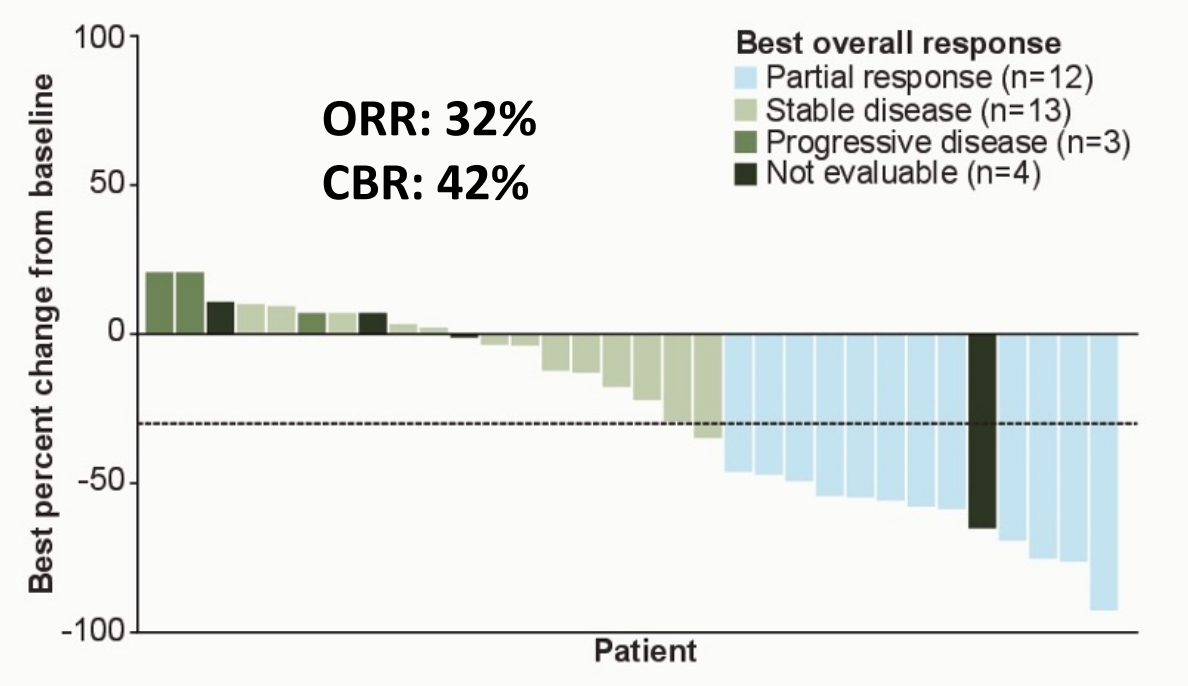


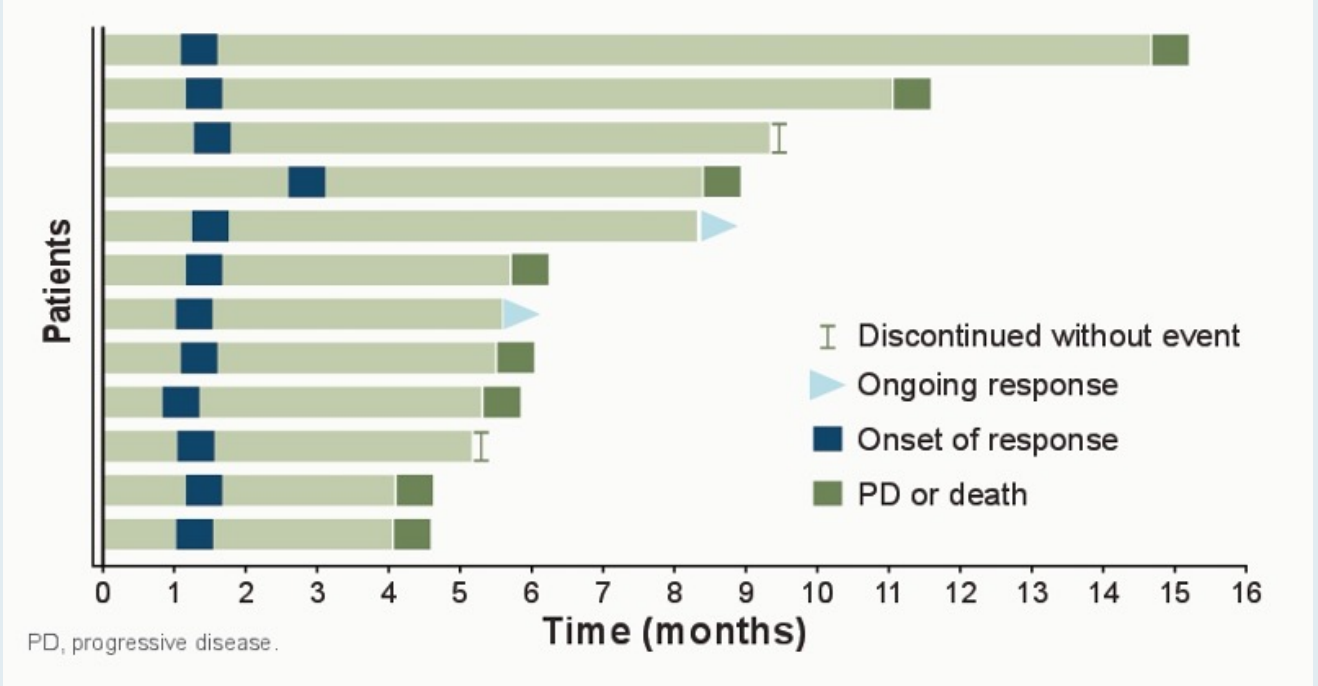


Tagawa ST et al. Genitourinary Cancers Symposium 2023;Abstract 526.

RTP RESEARCH TO PRACTICE

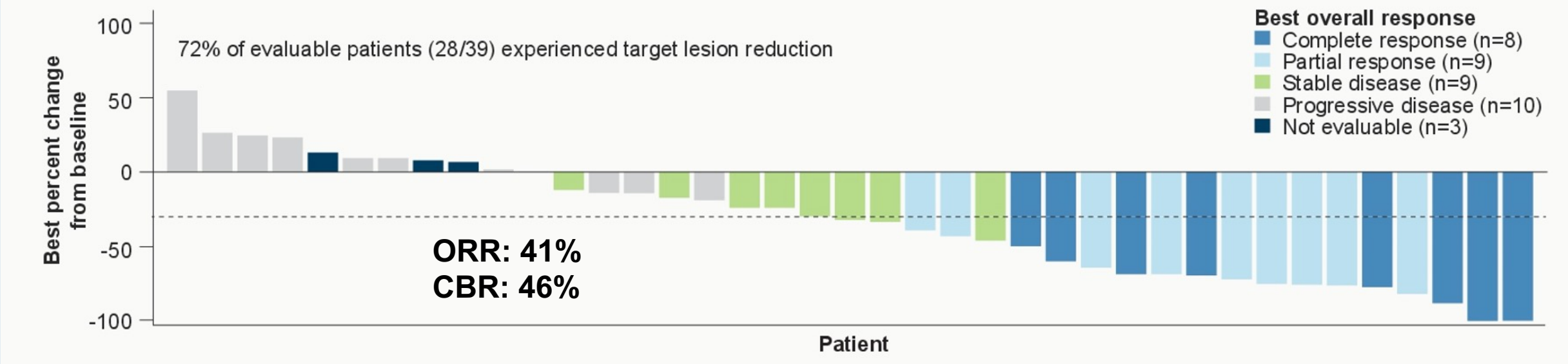
TROPHY U-01 (Cohort 2 — Second-Line Platinum-Ineligible After Immunotherapy): Response

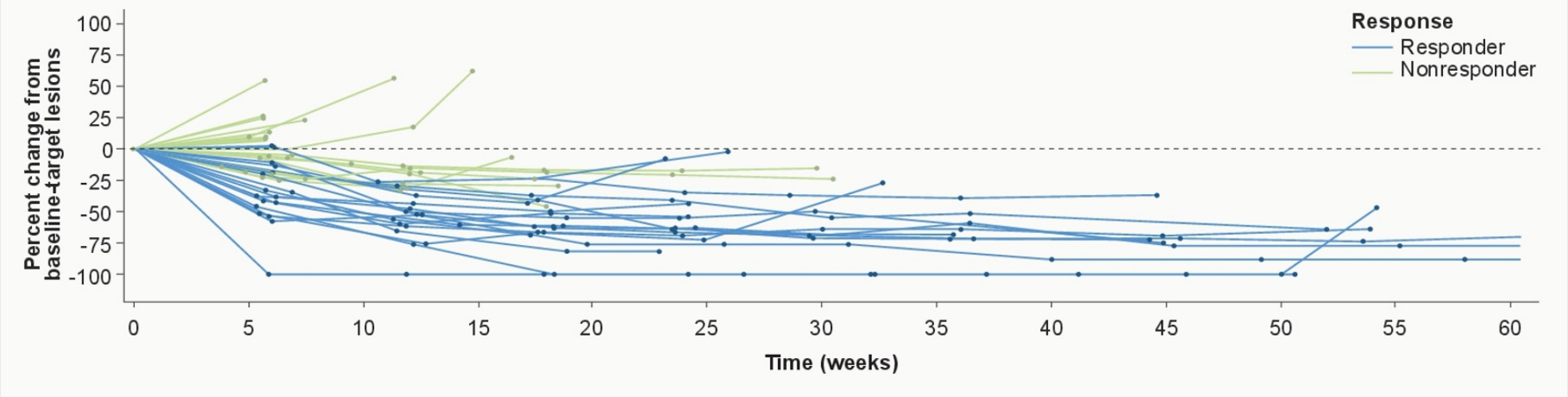




Petrylak DP et al. Genitourinary Cancers Symposium 2023;Abstract 520.

TROPHY U-01 (Cohort 3 — Second-Line Sacituzumab Govitecan and Pembrolizumab): Response





Grivas P et al. Genitourinary Cancers Symposium 2023;Abstract 518.

RTP RESEARCH TO PRACTICE

Urothelial Carcinoma Therapy (with emerging therapy)

Treatment	First-Line	Second-line	Post-platinum & PD1/L1	Late salvage
Cisplatin-eligible	•GC→Avelumab •ddMVAC→Avelumab •MVAC→Avelumab GC+Nivolumab emerging EV+Pembro emerging	<u>Post-platinum</u> •Erdafitinib (FGFR2/3) •Pembrolizumab (or nivolumab or avelumab) •EV (cis-ineligible) <u>Post-PD1/L1 inhibitor</u> •Gem-Carbo •Erdafitinib (pending regulatory review for FGFR2/2 altered) •EV (cis-ineligible)	•EV •SG •Erdafitinib	•Taxane •Vinflunine
Cisplatin-ineligible	•Gem-Carbo →Avelumab •EV+Pembrolizumab			
Platinum-ineligible	•Pembrolizumab			

EV: Enfortumab Vedotin, SG: Sacituzumab Govitecan

Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: DESTINY-PanTumor02 interim results

Her2 IHC 2-3+tumors

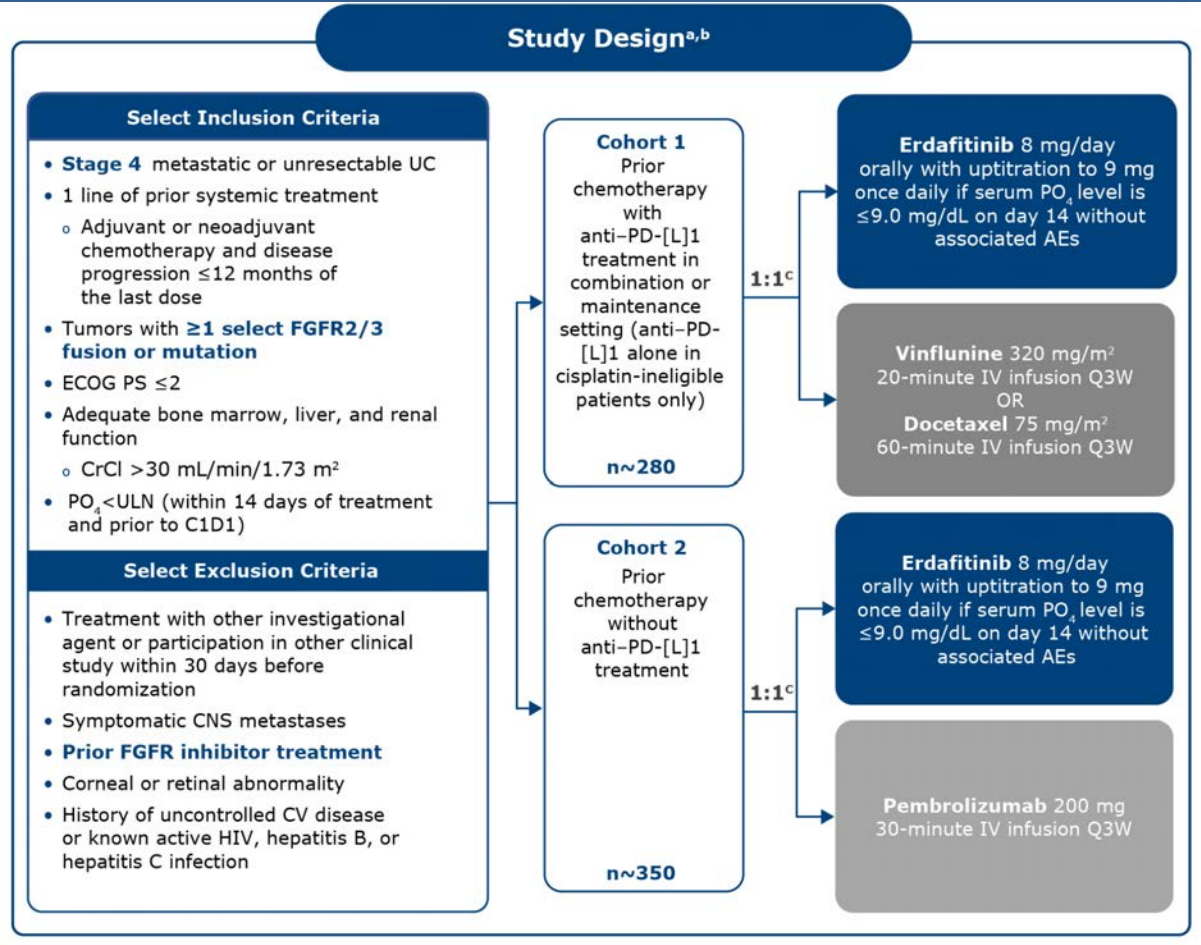
Efficacy endpoints: ORR, DCR and DOR

		Cervical (n=40)	Endometrial (n=40)	Ovarian (n=40)	BTC (n=41)	Pancreatic (n=25)	Bladder (n=41)	Other (n=40)	All patients (N=267)
Investigator assessment									
ORR, n (%)		20 (50.0)	23 (57.5)	18 (45.0)	9 (22.0)	1 (4.0)	16 (39.0)	12 (30.0)	99 (37.1)
Best overall response, n (%)	Complete response	2 (5.0)	7 (17.5)	4 (10.0)	1 (2.4)	0	1 (2.4)	0	15 (5.6)
	Partial response	18 (45.0)	16 (40.0)	14 (35.0)	8 (19.5)	1 (4.0)	15 (36.6)	12 (30.0)	84 (31.5)
	Stable disease	11 (27.5)	12 (30.0)	13 (32.5)	23 (56.1)	16 (64.0)	16 (39.0)	20 (50.0)	111 (41.6)
	Progressive disease	7 (17.5)	4 (10.0)	7 (17.5)	7 (17.1)	7 (28.0)	7 (17.1)	3 (7.5)	42 (15.7)
	Not evaluable	1 (2.5)	0	1 (2.5)	0	0	0	1 (2.5)	3 (1.1)
DCR[a], n (%)		27 (67.5)	32 (80.0)	28 (70.0)	27 (65.9)	9 (36.0)	29 (70.7)	30 (75.0)	182 (68.2)
Median DOR, months (95% CI)		9.8 (4.2–NE)	NR (9.9–NE)	11.3 (4.1–NE)	8.6 (2.1–NE)	NR	8.7 (4.3–11.8)	NR (4.1–NE)	11.8 (9.8–NE)
Independent central review: ORR, n (%)		16 (40.0)	21 (52.5)	17 (42.5)	11 (26.8)	3 (12.0)	17 (41.5)	13 (32.5)	98 (36.7)

Analysis of response and DCR was performed in patients who received ≥1 dose of T-DXd (n=267). Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd (n=99).
[a]Confirmed complete response, confirmed partial response or stable disease at or after 11 weeks.
BTC, biliary tract cancer; CI, confidence interval; DCR, disease control rate; DOR, duration of response; ICR, independent central review; NE, not estimable; NR, not reached; ORR, objective response rate.

Phase III trials evaluating salvage agents

THOR



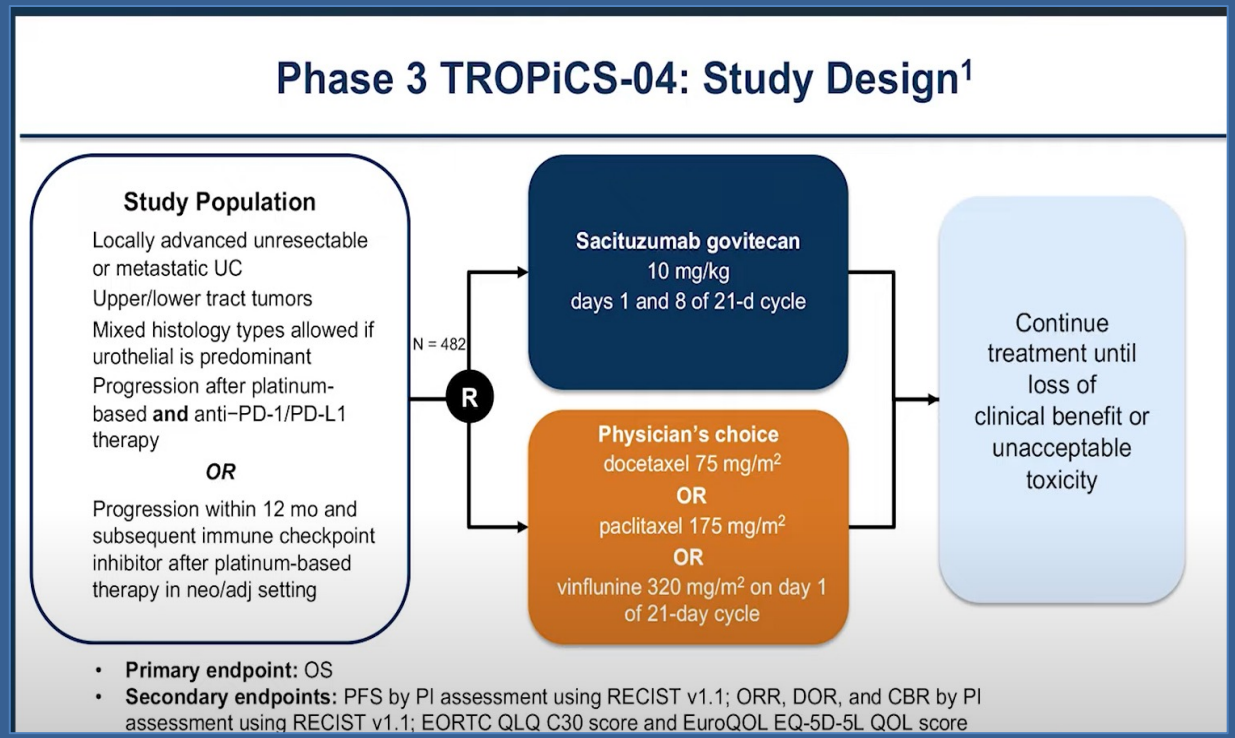
Proffered Paper session

2359O - Phase 3 THOR Study: Results of Erdafitinib (erda) vs Pembrolizumab (pembro) in Pretreated Patients (pts) With Advanced or Metastatic Urothelial Cancer (mUC) With Select Fibroblast Growth Factor Receptor Alterations (FGFRalt)

Presentation Number 2359O

Speakers Arlene O. Siefker-Radtke (Houston, United States of America)

MADRID 2023 ESMO congress

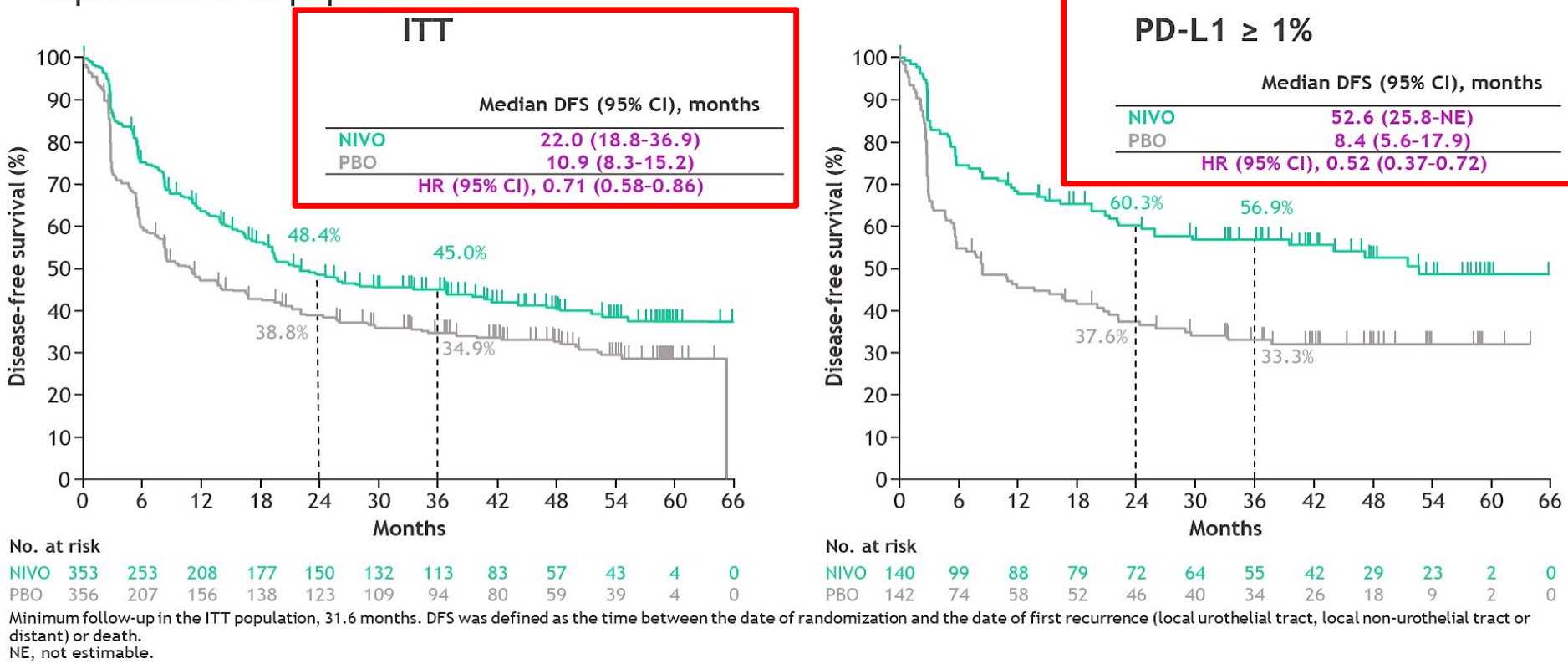


CheckMate 274: Adjuvant nivolumab v placebo for high-risk muscle-invasive urothelial carcinoma

CheckMate 274

Disease-free survival (primary endpoint)

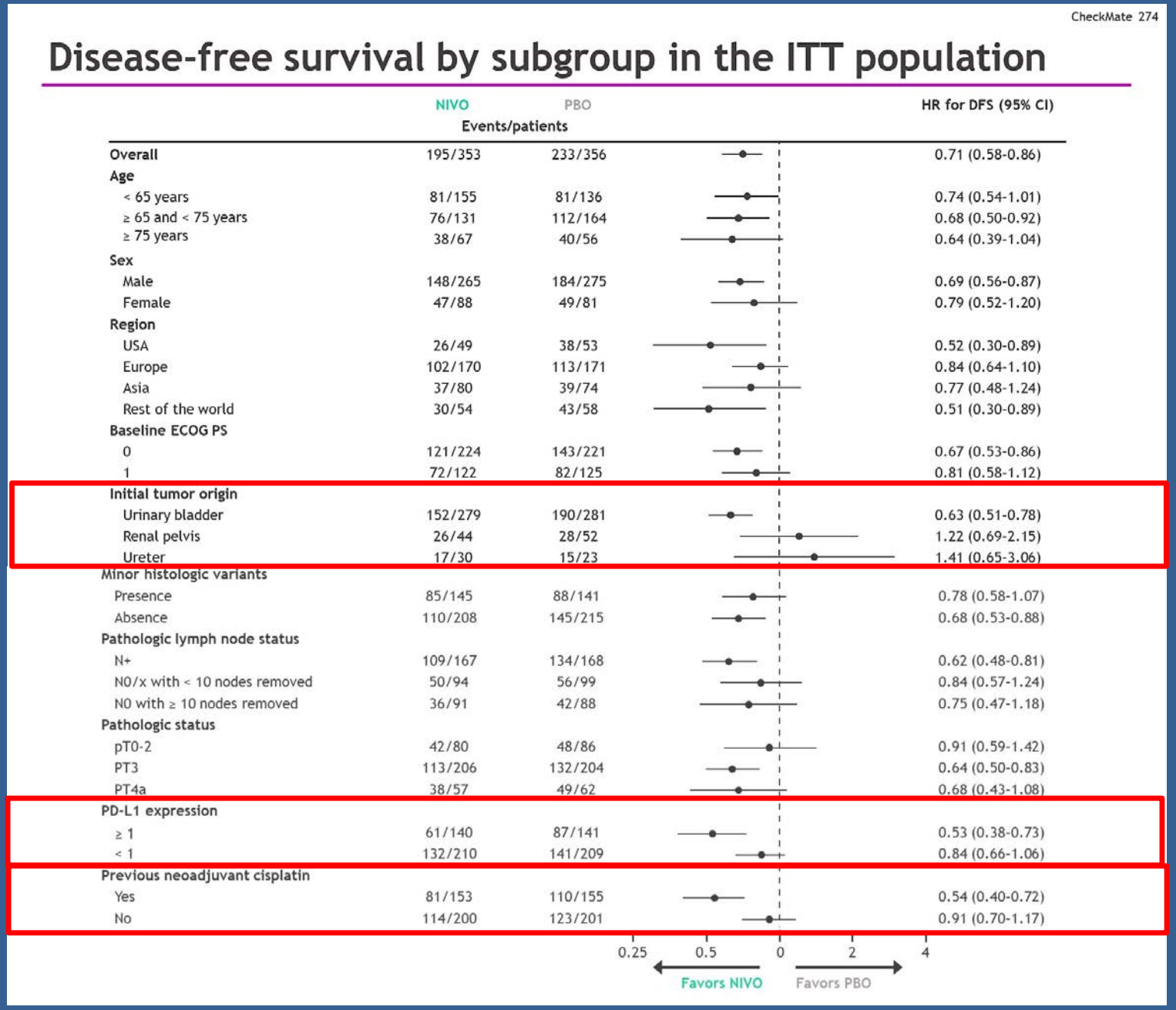
- Continued DFS benefit was observed with NIVO versus PBO both in the ITT and tumor PD-L1 expression ≥ 1% populations



Minimum follow-up in the ITT population, 31.6 months. DFS was defined as the time between the date of randomization and the date of first recurrence (local urothelial tract, local non-urothelial tract or distant) or death.
NE, not estimable.

No survival benefit reported yet (approved in USA for all-comers, but in EU for PD-L1+ only)

Bajorin D, et al. GU ASCO Feb 2021, NEJM Jun 2021, Galsky M, et al, GU-ASCO 2023



CheckMate 274: Adjuvant nivolumab v placebo: sub-analyses

Bajorin D, et al. GU ASCO Feb 2021, NEJM Jun 2021, Galsky M, et al. GU-ASCO 2023

NEWS RELEASE

Pembrolizumab Met Primary Endpoint of Disease-Free Survival (DFS) in Certain Patients With Muscle-Invasive Urothelial Carcinoma (MIUC) After Surgery

10/5/2023

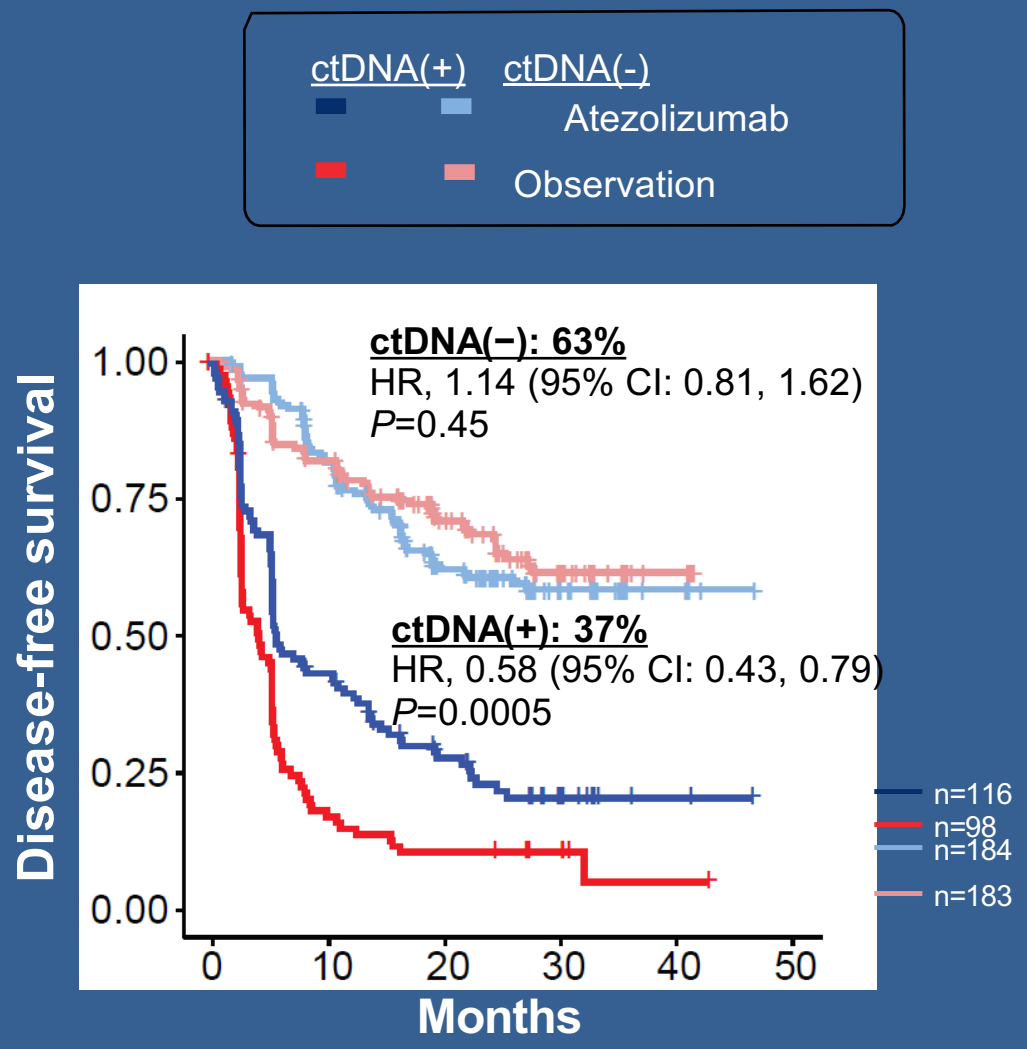
Pembrolizumab significantly improved DFS as adjuvant therapy versus observation for patients with localized MIUC and locally advanced urothelial carcinoma

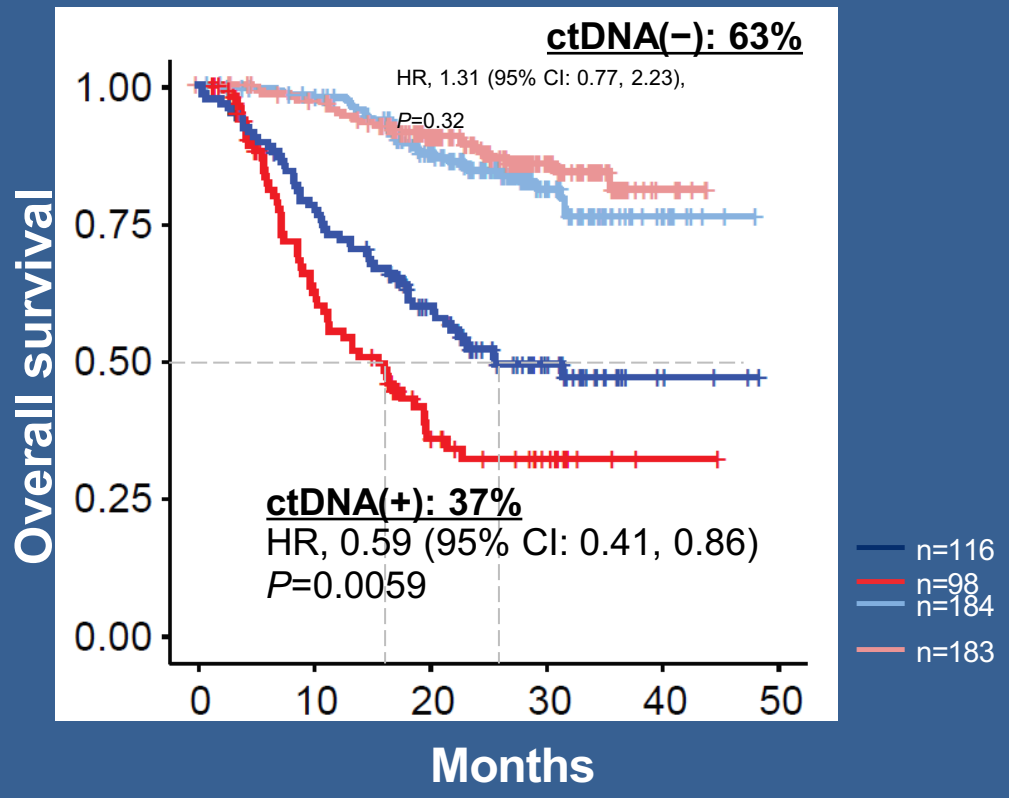
First positive study for pembrolizumab as adjuvant therapy for these patients

RAHWAY, N.J. – (BUSINESS WIRE)– The manufacturer today announced that the Phase 3 AMBASSADOR (A031501) trial (KEYNOTE-123) evaluating pembrolizumab, an anti-PD-1 therapy, met one of its dual primary endpoints of disease-free survival (DFS) for the adjuvant treatment of patients with localized muscle-invasive urothelial carcinoma (MIUC) and locally advanced urothelial carcinoma versus observation. At a pre-specified interim analysis review conducted by an independent Data Monitoring Committee, pembrolizumab demonstrated a statistically significant and clinically meaningful improvement in DFS-versus observation in these patients after surgery. The trial will continue to evaluate its other dual primary endpoint of overall survival (OS). The safety profile of pembrolizumab in this trial was consistent with that observed in previously reported studies; no new safety signals were identified. Results will be presented at an upcoming medical meeting and discussed with regulatory authorities.

Minimal residual disease using post-op ctDNA to select for adjuvant atezolizumab: retrospective IMvigor010 analysis- ctDNA(+) patients had improved DFS and OS with atezo

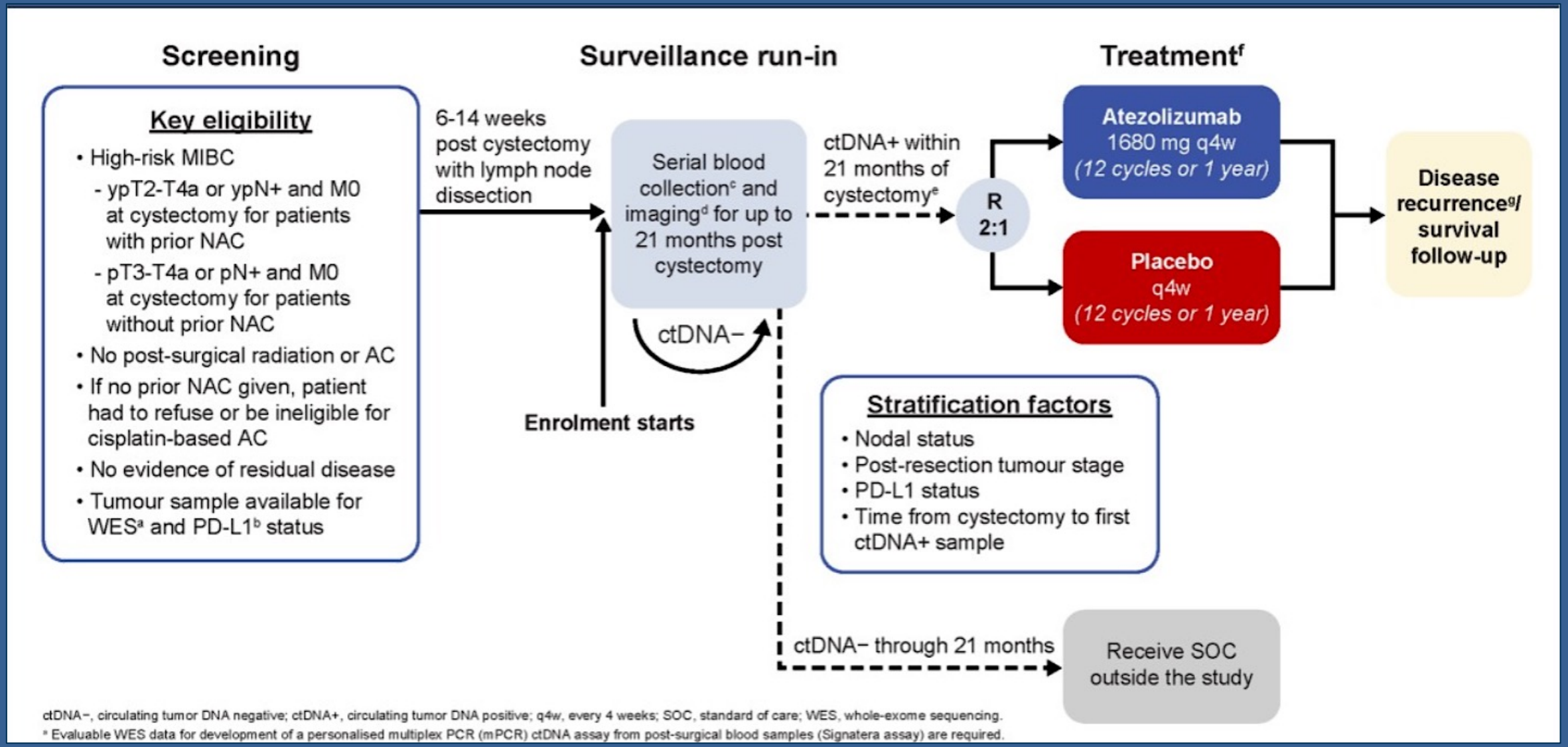
	ctDNA(+) patients	
	Atezolizumab	Observation
Median DFS (95% CI), mo	5.9 (5.6, 11.2)	4.4 (2.9, 5.6)
Median OS (95% CI), mo	25.8 (20.5, NR)	15.8 (10.5, 19.7)





Powles T, ESMO IO 12/2020, Nature 2021; 2021 Jul;595(7867):432-437

IMvigor011: post-op **atezolizumab** (up to 2 years) **if MRD turns +**



ctDNA−, circulating tumor DNA negative; ctDNA+, circulating tumor DNA positive; q4w, every 4 weeks; SOC, standard of care; WES, whole-exome sequencing.
[a] Evaluable WES data for development of a personalised multiplex PCR (mPCR) ctDNA assay from post-surgical blood samples (Signatera assay) are required.

Neoadjuvant Phase III Trials in muscle-invasive urothelial carcinoma

Trial ID	Sponsor	Primary endpoint (s)	Control arm	Experimental arm
CISPLATIN-ELIGIBLE				
NCT03661320	BMS	pCR, EFS	GC / Split Dose-GC	Control + Nivolumab + Placebo ~~Control + Nivolumab + Linrodostat~~
NCT03732677	Astrazeneca	pCR, EFS	GC / Split Dose-GC	Control + Durvalumab
NCT03924856	Merck	pCR (all, PD-L1+) EFS (all, PD-L1+)	GC + Placebo	Control + Pembrolizumab
NCT04700124	Merck, Seagen	pCR EFS	GC	EV + Pembrolizumab
CISPLATIN-INELIGIBLE				
2018-002676-40	BMS	pCR, EFS	-	Nivolumab ~~Nivolumab + NKTR-214~~
NCT03924895	Merck	pCR (all, PD-L1+) EFS (all, PD-L1+)	-	Pembrolizumab Pembrolizumab + EV
NCT04960709	Astrazeneca	pCR EFS	-	Durvalumab + EV Durvalumab + Tremelimumab + EV

Conclusions: therapy for urothelial carcinoma

- First-line therapy remains platinum-based chemotherapy followed by avelumab maintenance but may undergo dramatic changes in landscape following positive results for EV+pembrolizumab (all-comers) and GC-Nivolumab (cisplatin-eligible) in Phase III trials.
- Erdafitinib efficacy was validated in a Phase III trial showing improved OS (vs. chemo) as salvage therapy in those with FGFR3/2 activating mutations/fusions (OS vs pembro awaited).
- Her2 targeting agents are being vigorously evaluated in those with mUC and Her2 IHC+ tumors (Disitamab Vedotin + Pembro 1L, Trastuzumab Deruxtecan salvage)
- Adjuvant nivolumab is approved for high-risk muscle-invasive urothelial carcinoma and the use of ctDNA to select patients is evolving (data for adjuvant pembro awaited).
- The neoadjuvant therapy landscape is likely to change in the near-future when results of GC+PD1/L1 inhibitors and EV+Pembro are reported.
- **Trials evaluating new therapies should be preferred.**

Oncology in the Real World: A Daylong Multitumor Educational Symposium in Partnership with the American Oncology Network

A CME/MOC- and NCPD-Accredited Event

Saturday, October 14, 2023
9:30 AM – 5:00 PM PT

RTP
RESEARCH
TO PRACTICE

We are taking a short break!

The program will resume at 11:50 AM PT

Up Next…

Prof Mitesh Borad and Dr Anthony El-Khoueiry discuss the management of hepatobiliary and pancreatic cancers

Please complete Part 2 of the premeeting survey

RTP
RESEARCH
TO PRACTICE

Oncology in the Real World: A Daylong Multitumor Educational Symposium in Partnership with the American Oncology Network

A CME/MOC- and NCPD-Accredited Event

Saturday, October 14, 2023
9:30 AM – 5:00 PM PT

RTP
RESEARCH
TO PRACTICE

Agenda

Module 1 — Lymphoma: *Drs Flowers and LaCasce*

Module 2 — Urothelial Bladder Cancer and Renal Cell Carcinoma:
Drs Hutson and Sonpavde

Module 3 — Hepatobiliary and Pancreatic Cancers:
Prof Borad and Dr El-Khoueiry

Lunch Break: 12:50 AM – 1:30 PM

Module 4 — Gynecologic Cancers: *Drs Monk and Moore*

Module 5 — Multiple Myeloma: *Drs Krishnan and Orlowski*

Module 6 — HER2-Positive and Triple-Negative Breast Cancer:
Drs Hurvitz and McArthur

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RESEARCH
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Hepatobiliary and Pancreatic Cancers Faculty

Mitesh J Borad, MD
Professor of Medicine
Mayo Clinic College of Medicine and Science
Program Leader, Gene and Virus Therapy Program
Mayo Clinic Comprehensive Cancer Center
Director, Precision Cancer Therapeutics Cancer Program
Mayo Clinic Comprehensive Cancer Center
Scottsdale, Arizona

Anthony El-Khoueiry, MD
Associate Professor of Medicine
Associate Director for Clinical Research
Phase I Program Director
USC Norris Comprehensive Cancer Center
Los Angeles, California

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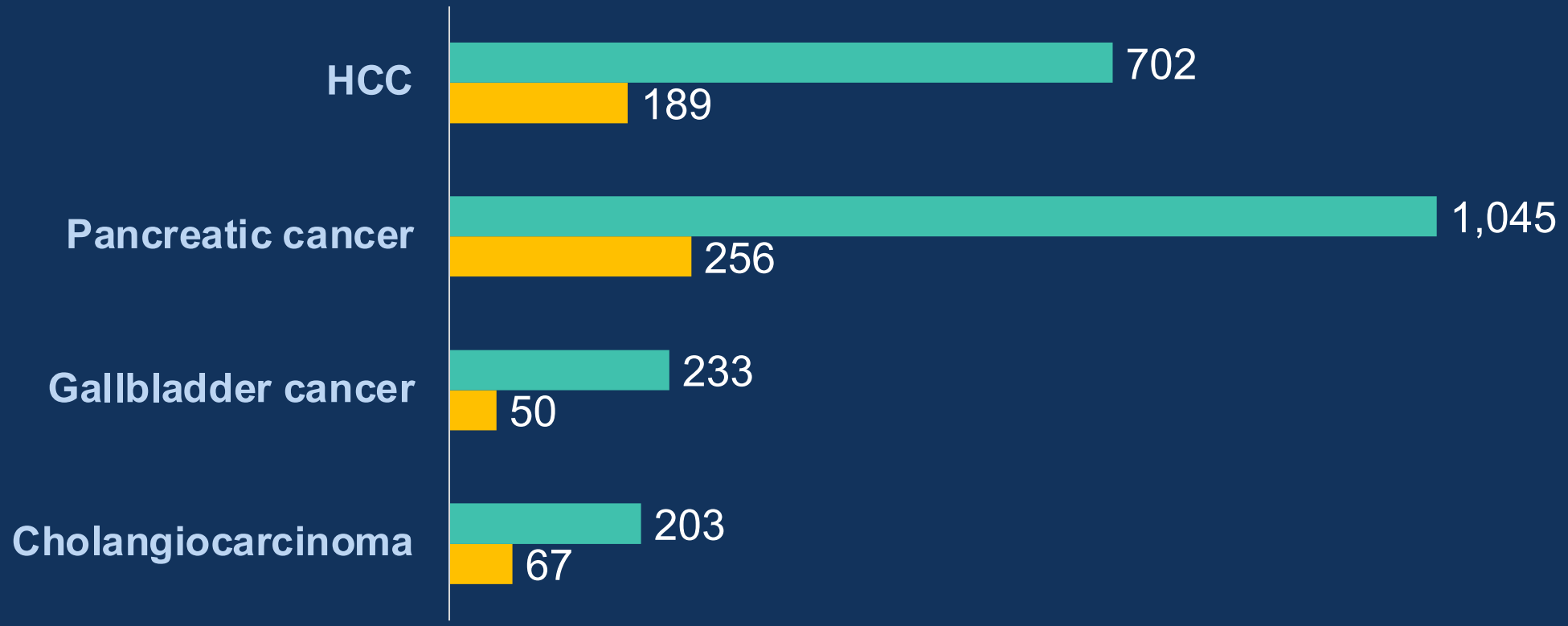
RESEARCH
TO PRACTICE

Snapshot of AON Practice
Module 3: Hepatobiliary and Pancreatic Cancers



MIBA

THE AON CLINICAL SUMMIT 2023

Collaborate. Innovate. Celebrate.

Snapshot of AON Practice
Pancreatic Cancer

Select Treatments Received

Clinical Trial Participation

Number of clinical trials	19
Total patients enrolled	38

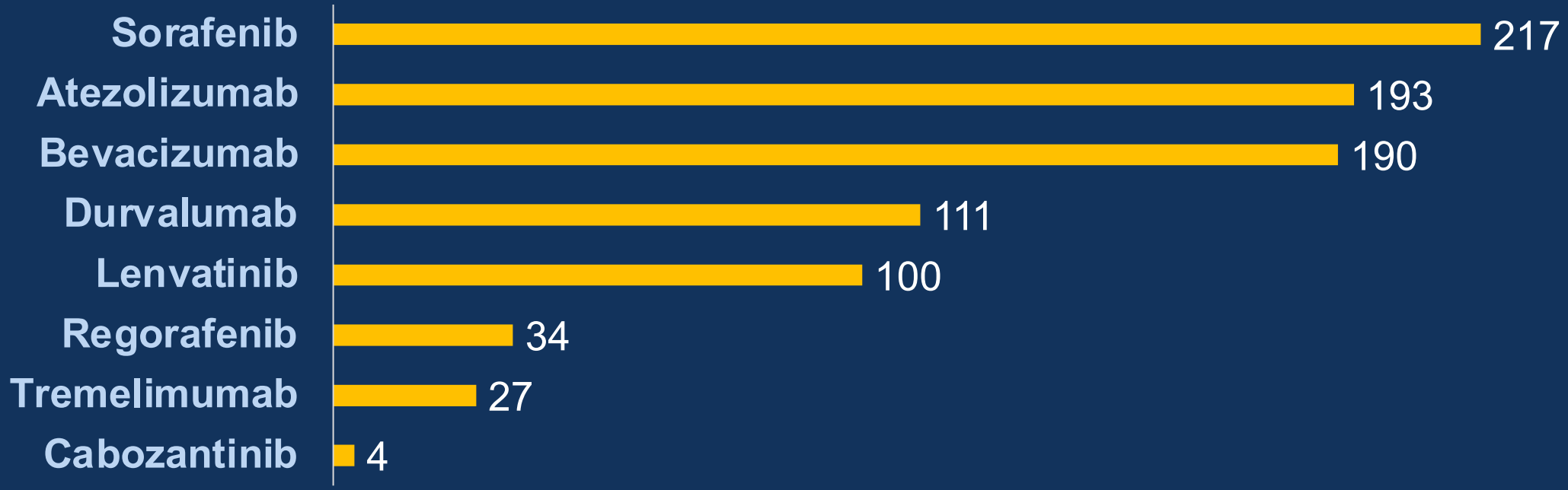
MIBA

THE AON CLINICAL SUMMIT 2023

Collaborate. Innovate. Celebrate.

Snapshot of AON Practice
Hepatocellular Carcinoma

Select Treatments Received



Clinical Trial Participation

Number of clinical trials	3
Total patients enrolled	3

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Snapshot of AON Practice
Cholangiocarcinoma

Select Treatments Received

Clinical Trial Participation

Number of clinical trials	1
Total patients enrolled	1

MIBA

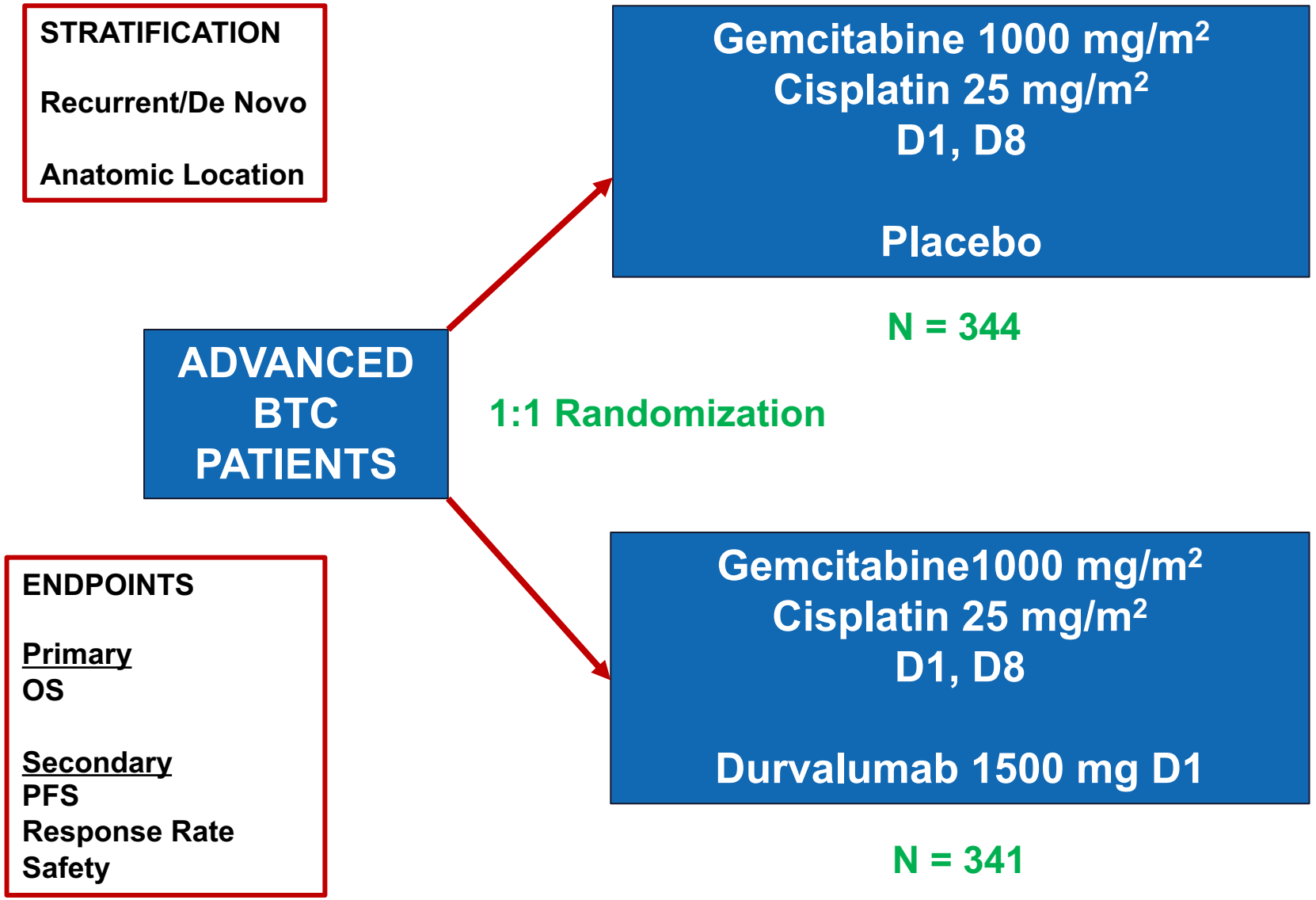
THE AON CLINICAL SUMMIT 2023

Collaborate. Innovate. Celebrate.

Biliary Tract and Pancreatic Cancer

Mitesh J Borad, MD

TOPAZ-1 STUDY



Gemcitabine/Cisplatin +/- Durvalumab: TOPAZ-1 STUDY

OVERALL SURVIVAL = 12.9 vs. 11.3 mth

PFS = 7.2 vs. 5.7 mth

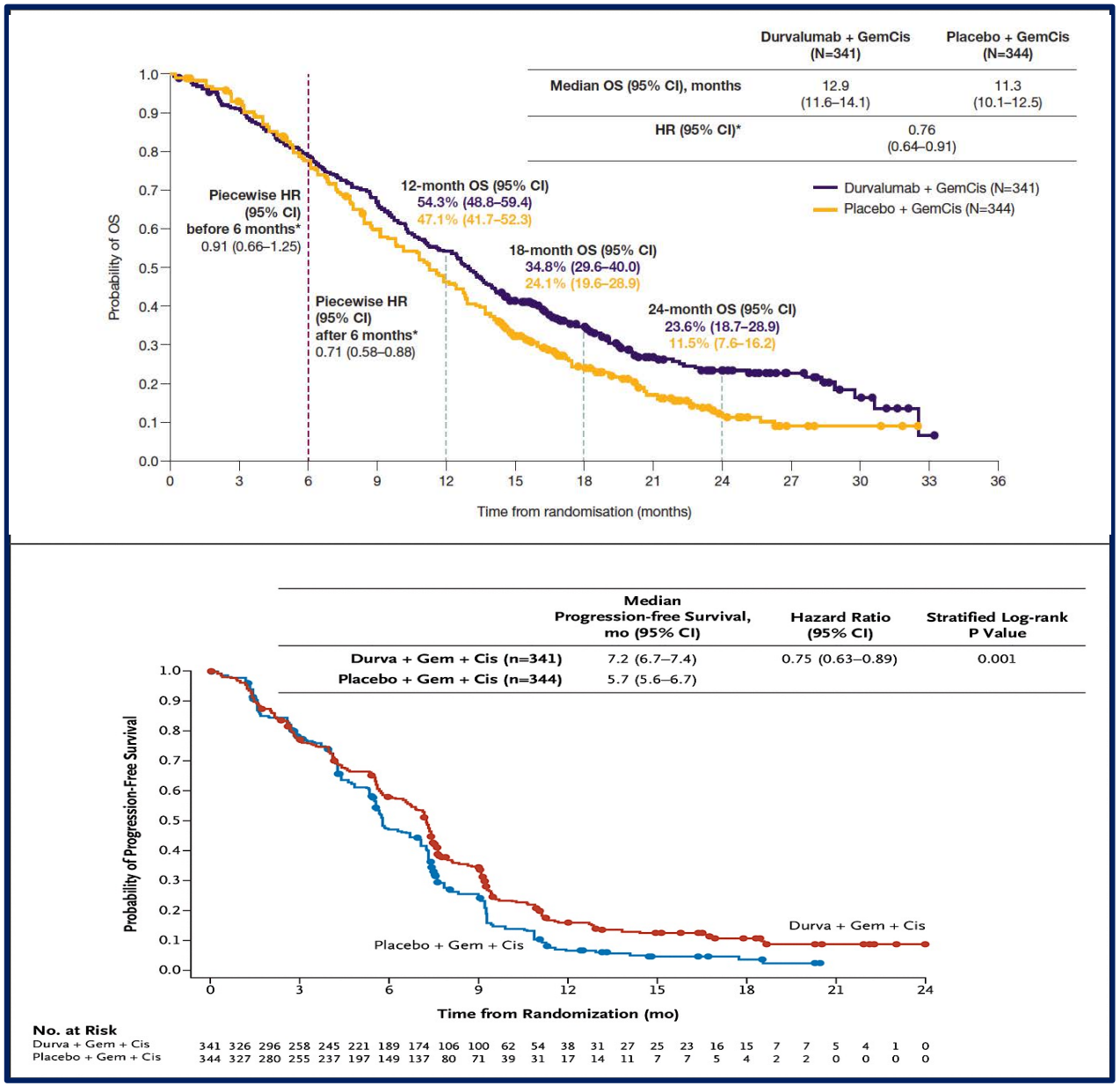
RESPONSE RATE = 26.7% vs. 18.7%

ADVERSE EVENT RATE NOT INCREASED

TIME TO RESPONSE = 1.6 vs. 2.7 mth

DURATION OF RESPONSE = 6.4 vs. 6.2 mth

RESPONSE AT 12 MTH = 26.1% vs. 15%



OH ET AL, NEJM EVID 2022; ESMO 2022;ABSTRACT 56P

KEYNOTE-966 Study Design
Randomized, Double-Blind, Phase 3 Trial

Key Eligibility Criteria

- Histologically confirmed extrahepatic or intrahepatic cholangiocarcinoma or gallbladder cancer
- Unresectable locally advanced or metastatic disease measurable per RECIST v1.1 by investigator review
- No prior systemic therapy[a]
- ECOG PS 0 or 1
- Life expectancy >3 months

R
1:1

Pembrolizumab 200 mg IV Q3W (maximum, 35 cycles)
+
Gemcitabine 1000 mg/m² IV on days 1 and 8 Q3W (no maximum)
+
Cisplatin 25 mg/m² IV on days 1 and 8 Q3W (maximum, 8 cycles)

Placebo IV Q3W for (maximum, 35 cycles)
+
Gemcitabine 1000 mg/m² IV on days 1 and 8 Q3W (no maximum)
+
Cisplatin 25 mg/m² IV on days 1 and 8 Q3W (maximum, 8 cycles)

Stratification Factors

- Geographic region (Asia vs not Asia)
- Disease stage (locally advanced vs metastatic)
- Site of origin (extrahepatic vs gallbladder vs intrahepatic)

- **Primary End Point:** OS
- **Secondary End Points:** PFS, ORR, and DOR assessed per RECIST v1.1 by blinded, independent central review (BICR) and safety

Treatment was continued until disease progression, unacceptable toxicity, investigator decision, or, for pembrolizumab and cisplatin, the maximum number of cycles was reached.
[a]Neoadjuvant or adjuvant chemotherapy was permitted if it was completed ≥6 months before the diagnosis of unresectable or metastatic disease.
ClinicalTrials.gov identifier: NCT04003636.

Gemcitabine/Cisplatin +/- Pembrolizumab: KEYNOTE-966

OVERALL SURVIVAL = 12.7 vs. 10.9 mth

PFS = 6.5 vs. 5.6 mth

RESPONSE RATE = 29% vs. 28%

ADVERSE EVENT RATE NOT INCREASED

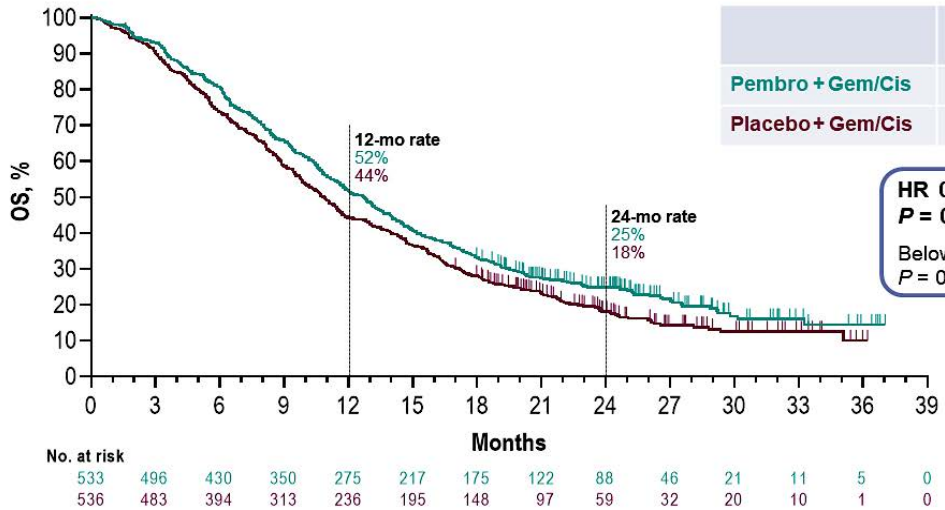
DURATION OF RESPONSE = 8.3 vs. 6.8 mth

RESPONSE AT 12 MTH = 38% vs. 27%

N = 1069 PATIENTS

KELLEY ET AL, LANCET 2023

Overall Survival at Final Analysis



	Pts w/ Event	Median (95% CI), mo
Pembro + Gem/Cis	78%	12.7 (11.5-13.6)
Placebo + Gem/Cis	83%	10.9 (9.9-11.6)

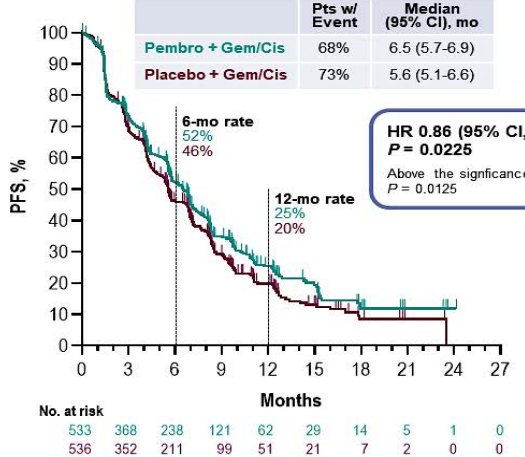
HR 0.83 (95% CI, 0.72-0.95)
***P* = 0.0034**
Below the signficance boundary of *P* = 0.0200

Kelley KEYNOTE-966 AACR 2023

Progression-Free Survival

Interim Analysis 1

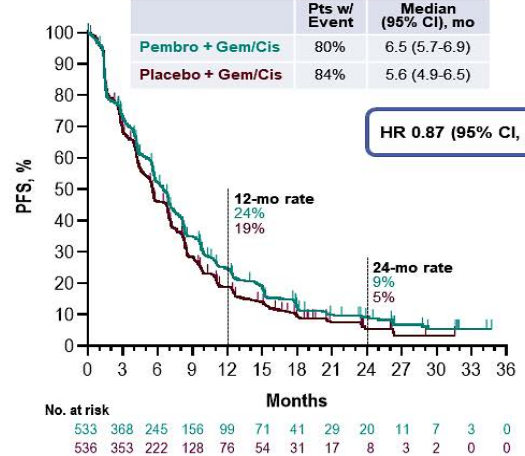
	Pts w/ Event	Median (95% CI), mo
Pembro + Gem/Cis	68%	6.5 (5.7-6.9)
Placebo + Gem/Cis	73%	5.6 (5.1-6.6)



HR 0.86 (95% CI, 0.75-1.00)
***P* = 0.0225**
Above the signficance boundary of *P* = 0.0125

Final Analysis

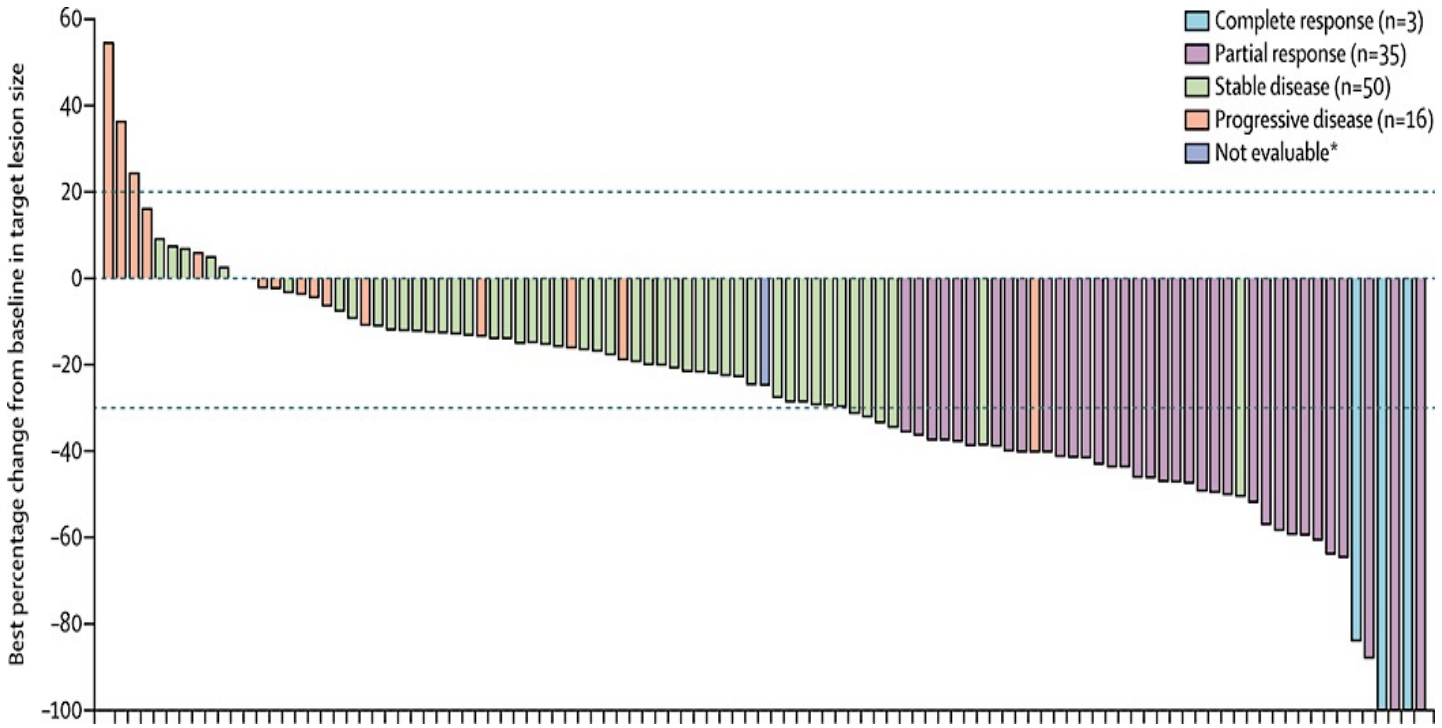
	Pts w/ Event	Median (95% CI), mo
Pembro + Gem/Cis	80%	6.5 (5.7-6.9)
Placebo + Gem/Cis	84%	5.6 (4.9-6.5)



HR 0.87 (95% CI, 0.76-0.99)

PFS was assessed per RECIST v1.1 by BICR.
Data cutoff date: December 15, 2021 (IA1) and December 15, 2022 (FA). IA1 was the prespecified final analysis of PFS. PFS analysis at FA was exploratory.

FIGHT-302: Pemigatinib in FGFR Fusion/Rearrangement+ Cholangiocarcinoma



OVERALL SURVIVAL = 21.1 mth

PFS = 6.9 mth

RESPONSE RATE = 35.5%

TIME TO RESPONSE = 2.7 mth

DURATION OF RESPONSE = 7.5 mth

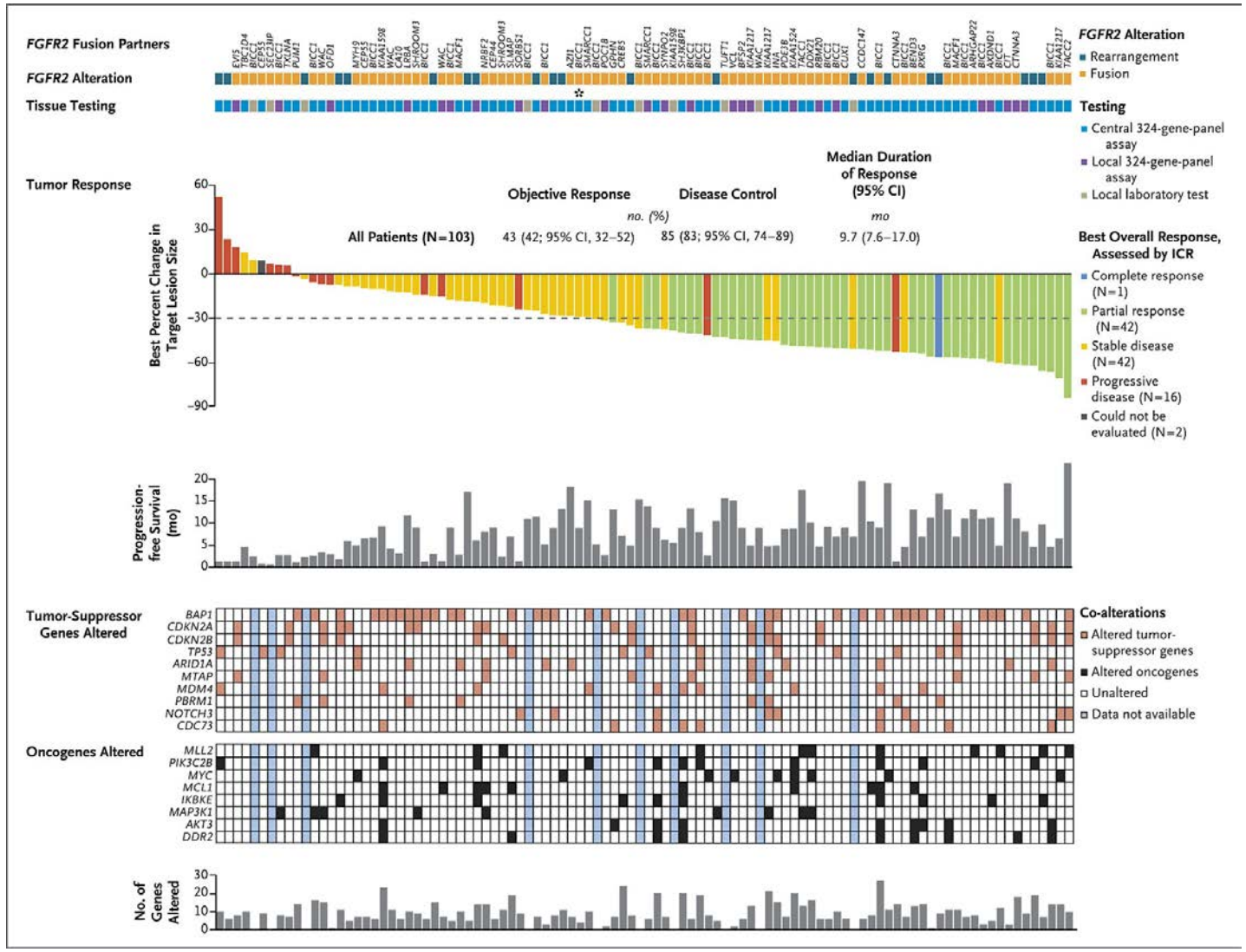
TOXICITIES = Alopecia, hyperphosphatemia, dysgeusia, diarrhea, stomatitis, dry eye, nail changes

N = 107 Patients

13.5 mg oral daily 2 weeks on/one week off dosing

ABOU-ALFA ET AL, LANCET ONC 2020

FOENIX-CCA2: Futibatinib in FGFR Fusion/Rearrangement + Cholangiocarcinoma



OVERALL SURVIVAL = 21.7 mth

PFS = 9 mth

RESPONSE RATE = 42%

TIME TO RESPONSE = 2.5 mth

DURATION OF RESPONSE = 9.7 mth

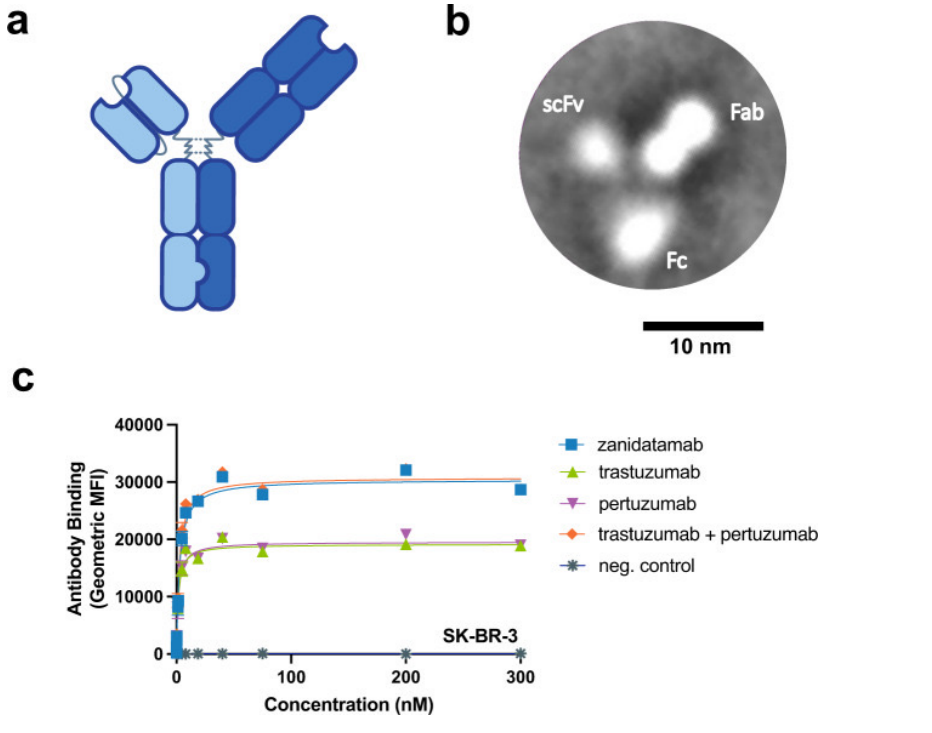
TOXICITIES = Alopecia, hyperphosphatemia, dysgeusia, diarrhea, stomatitis, dry eye, nail changes

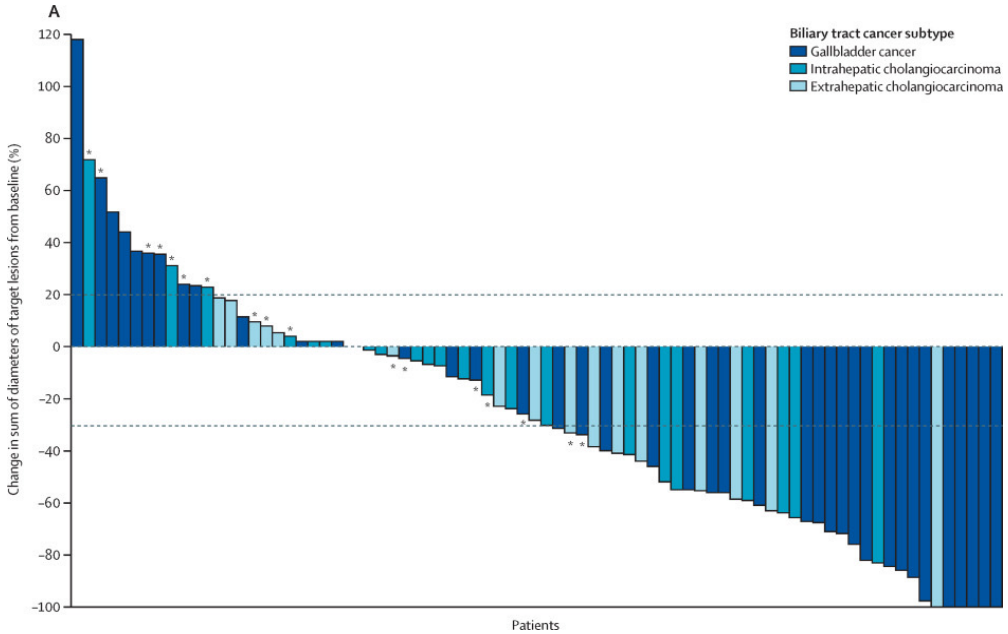
N = 103 Patients

20 mg oral daily dosing

GOYAL ET AL, NEJM 2023; LANCET ONC 2020

ZANIDATAMAB IN BTC





HER2+ (IHC3+ or IHC2+) = HER2 high

RESPONSE RATE = 41% (IHC3+/IHC2+)

TIME TO RESPONSE = 1.8 mth

DURATION OF RESPONSE = 12.9 mth

PFS = 5.5 mth

DISEASE CONTROL RATE = 67.5%

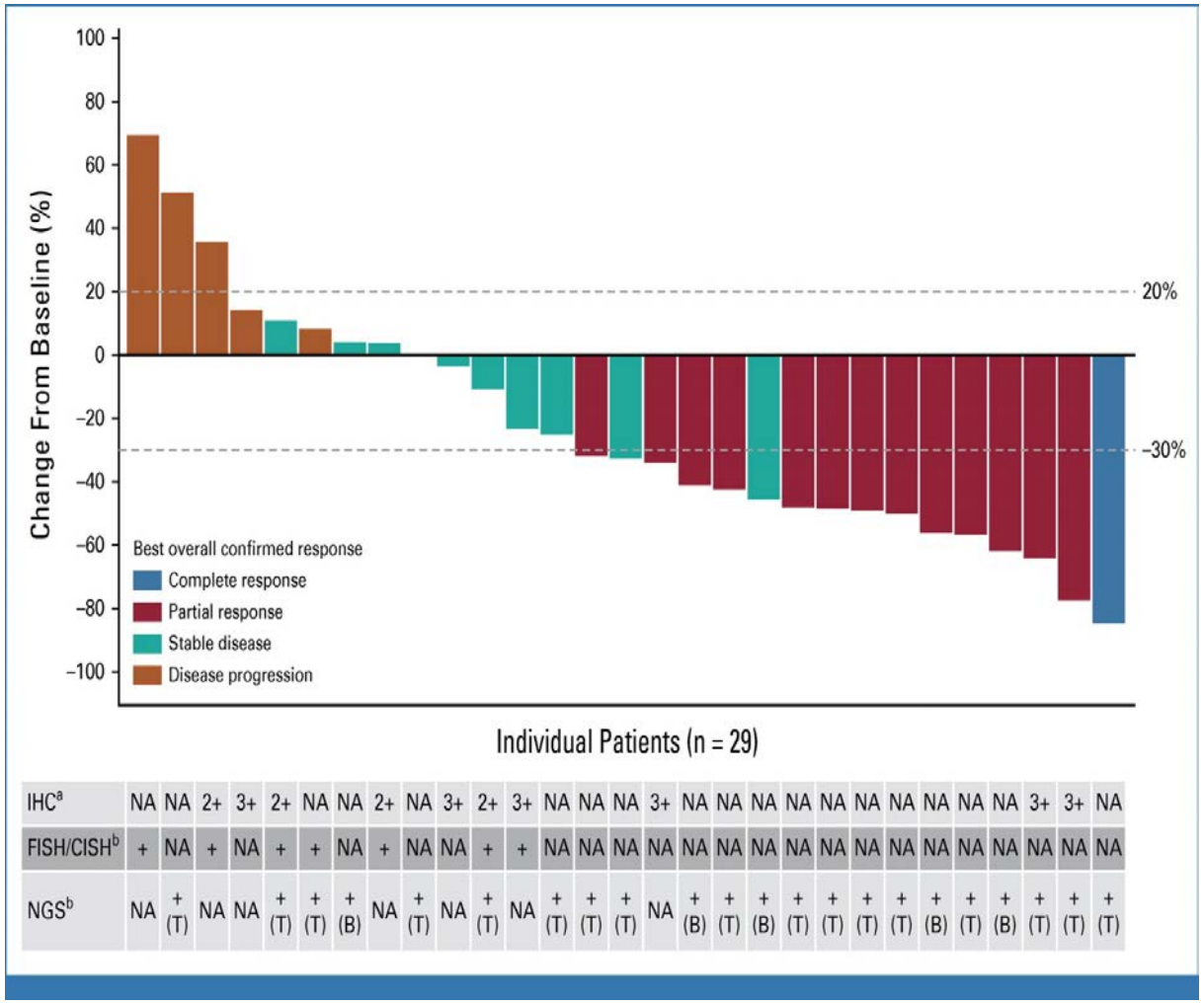
TOXICITIES = Grade ≥3 : Diarrhea (4.6%), decreased ejection fraction (3.4%)

N = 87 Patients (80 IHC3+/IHC2+)

20 mg/kg IV every 2 weeks

HARDING ET AL, LANCET ONC 2023, WEISSER ET AL NATURE COMM 2023

TUCATINIB/TRASTUZUMAB IN BTC



IHC[a]	NA	NA	2+	3+	2+	NA	NA	2+	NA	3+	2+	3+	NA	NA	NA	3+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	3+	3+	NA
FISH/CISH[b]	+	NA	+	NA	+	+	NA	+	NA	NA	+	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
NGS[b]	NA	+ (T)	NA	NA	+ (T)	+ (T)	+ (B)	NA	+ (T)	NA	+ (T)	NA	+ (T)	+ (T)	+ (T)	NA	+ (B)	+ (T)	+ (B)	+ (T)	+ (T)	+ (T)	+ (T)	+ (B)	+ (T)	+ (B)	+ (T)	+ (T)	+ (T)

HER2 NGS amplified, HER2 IHC3+, HER2 ISH+

RESPONSE RATE = 46.7% (IHC3+/IHC2+)

TIME TO RESPONSE = 2.1 mth

PFS = 5.5 mth

DURATION OF RESPONSE = 6 mth

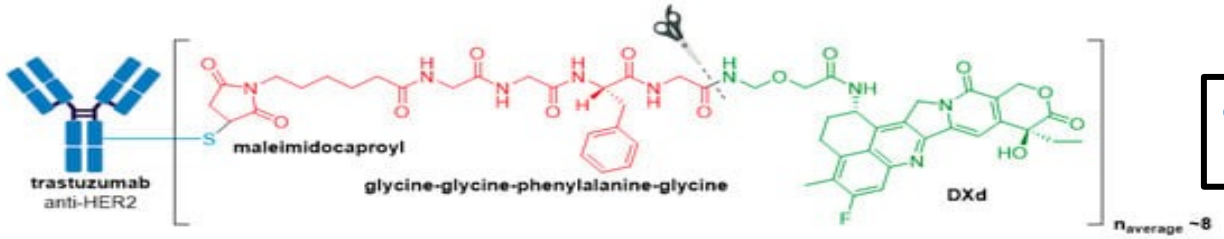
1 YEAR SURVIVAL = 53.6%, MEDIAN OS = 15.5 mth

DISEASE CONTROL RATE = 76.7%

TOXICITIES = Pyrexia, diarrhea

N = 30 Patients (80 IHC3+/IHC2+)

NAKAMURA ET AL, JCO 2023



TRASTUZUMAB DERUXTECAN IN BTC

TONG ET AL, MOLECULES 2021

HER2+ (IHC3+ or IHC2+/ISH+) = HER2 high

OVERALL SURVIVAL = 7.1 mth (HER2-high), 8.9 mth (HER2-low)

PFS = 4.4 mth (HER2-high), 4.2 mth (HER2-low)

RESPONSE RATE = 36.4% (HER2-High), 12.5% (HER2-Low)

TOXICITIES = Anemia, neutropenia, leukopenia, interstitial lung disease (25%)

N = 32 Patients (24 HER2-high, 8 HER2-low)

5.4 mg/kg every 3 weeks

HERB STUDY : OHBA ET AL, ASCO 2022

HER2+ (IHC3+ or IHC2+) = HER2 high

Overall Cohort N = 267, 5.4 mg/kg every 3 weeks

Overall Cohort Resp Rate = 37.1%, 61.3% (IHC3+)

Duration of Response = 11.8 mths (22.1 mths IHC3+)

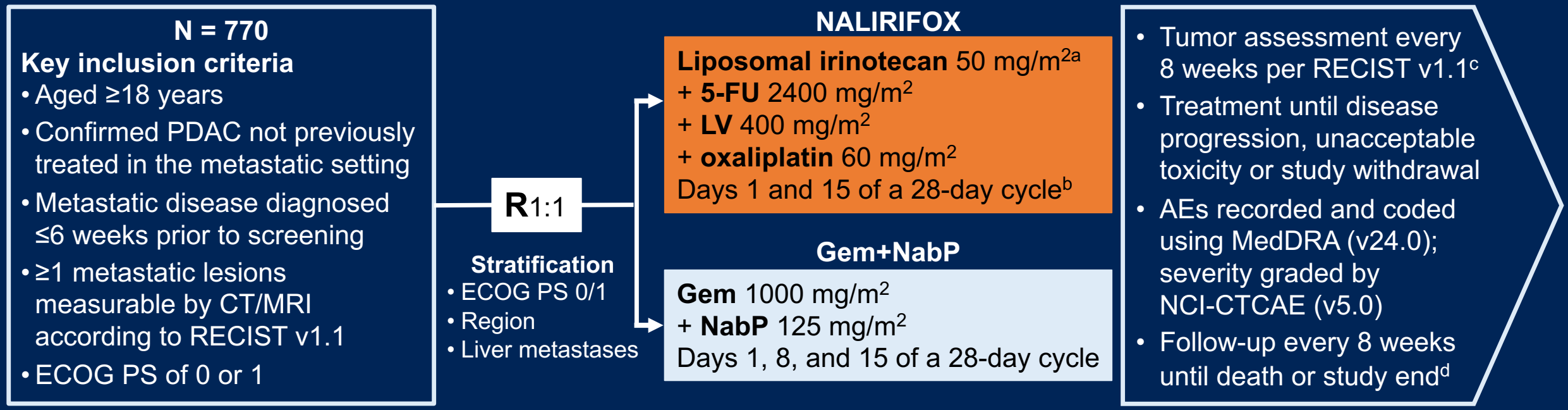
BTC RESPONSE RATE = 22%, 56.3% (IHC3+), 0% (IHC2+)

TOXICITIES = Anemia, neutropenia, leukopenia, interstitial lung disease (6.7%, n = 1 grade 5)

N = 41 Patients

DESTINY PanTumor-02 : MERIC-BERNSTAM ET AL, ASCO 2023

NAPOLI-3: Study design



[a]Dose expressed as irinotecan free base equivalent. [b]Administered sequentially as a continuous infusion over 46 hours beginning on days 1 and 15 of a 28-day cycle (dose delays and oxaliplatin discontinuation were permitted).
[c]Until progressive disease. [d]The study was completed once all patients had discontinued the study treatment and at least 543 OS events had occurred in randomized patients.
5-FU, 5-fluorouracil; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; Gem, gemcitabine; LV, leucovorin; MedDRA, Medical Dictionary for Regulatory Activities; MRI, magnetic resonance imaging; NabP, *nab*-paclitaxel; NALIRIFOX, liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors.

NAPOLI-3 STUDY

OVERALL SURVIVAL = 11.1 vs. 9.2 mth

PFS = 7.4 vs. 5.6 mth

RESPONSE RATE = 41.8% vs. 36.2%

HIGHER GI TOXICITY

DURATION OF RESPONSE = 8.3 vs. 6.8 mth

OS AT 12 MTH = 45.6% vs. 39.5%

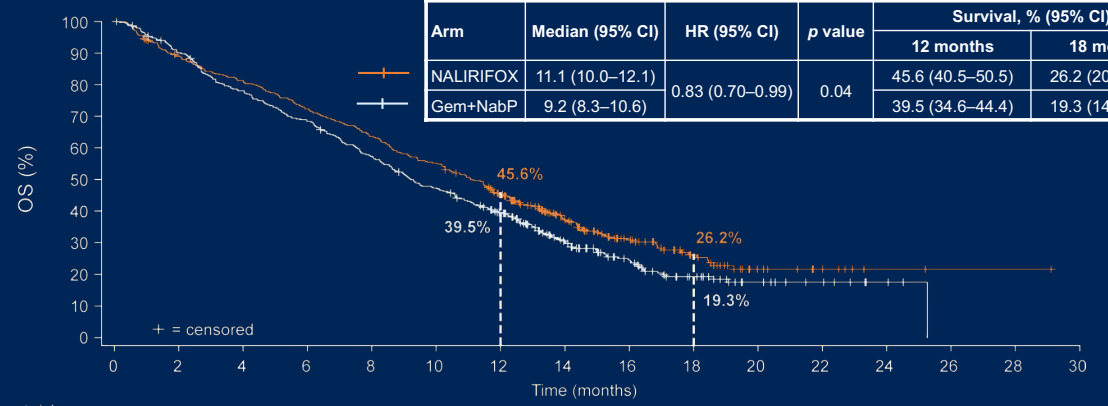
OS AT 18 MTH = 26.2% vs. 19.3%

N = 770 PATIENTS

O'REILLY ET AL, ASCO 2023

NAPOLI 3: OS (ITT population)

Arm	Median (95% CI)	HR (95% CI)	*p* value	Survival, % (95% CI)	
				12 months	18 months
NALIRIFOX	11.1 (10.0–12.1)	0.83 (0.70–0.99)	0.04	45.6 (40.5–50.5)	26.2 (20.9–31.7)
Gem+NabP	9.2 (8.3–10.6)			39.5 (34.6–44.4)	19.3 (14.8–24.2)



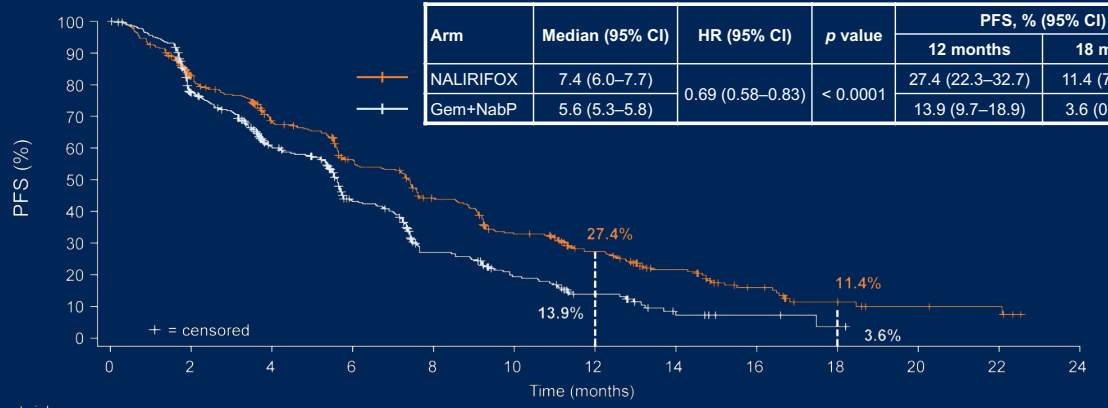
No. at risk:

NALIRIFOX	383	337	308	274	241	209	162	98	59	32	13	7	2	1	1	0
Gem+NabP	387	345	298	261	218	179	140	80	50	28	15	10	3	0	0	0

Hazard ratio and 95% CI based on a Cox proportional hazards regression model, stratified by ECOG PS (0 vs 1), region (North America vs ROW), liver metastases (yes vs no) per IRT. P boundary for efficacy claim *p* value < 0.048.
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; Gem, gemcitabine; HR, hazard ratio; IRT, interactive response technology; ITT, intention-to-treat; NabP, nab-paclitaxel; NALIRIFOX, liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin; OS, overall survival; ROW, rest of world.

NAPOLI 3: PFS per investigator (ITT population)

Arm	Median (95% CI)	HR (95% CI)	*p* value	PFS, % (95% CI)	
				12 months	18 months
NALIRIFOX	7.4 (6.0–7.7)	0.69 (0.58–0.83)	< 0.0001	27.4 (22.3–32.7)	11.4 (7.1–16.9)
Gem+NabP	5.6 (5.3–5.8)			13.9 (9.7–18.9)	3.6 (0.5–12.3)



No. at risk:

NALIRIFOX	383	271	210	164	122	87	61	39	20	9	5	4	0
Gem+NabP	387	267	182	112	60	38	19	6	3	1	0	0	0

Hazard ratio and 95% CI based on a Cox proportional hazards regression model, stratified by ECOG PS (0 vs 1), region (North America vs ROW), liver metastases (yes vs no) per IRT. P boundary for efficacy claim *p* value < 0.048.
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; Gem, gemcitabine; HR, hazard ratio; IRT, interactive response technology; ITT, intention-to-treat; NabP, nab-paclitaxel; NALIRIFOX, liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin; PFS, progression-free survival; ROW, rest of world.

NAPOLI-3: Selected any-cause TEAEs

	NALIRIFOX (n = 370)		Gem+NabP (n = 379)	
Any-cause TEAEs in ≥10% of patients, %[a]	**Any grade**	**Grade 3–4**	**Any Grade**	**Grade 3–4**
Hematologic				
Neutropenia[b] / febrile neutropenia	50.0 / 2.4	23.8 / 2.4	50.6 / 2.6	38.0 / 2.4
Anemia	26.2	10.5	40.4	17.4
Thrombocytopenia[c]	24.0	1.6	40.6	6.1
Non-hematologic				
Diarrhea	70.5	20.3	36.7	4.5
Nausea	59.5	11.9	42.7	2.6
Vomiting	39.7	7.0	26.4	2.1
Hypokalemia	31.6	15.1	12.9	4.0
Peripheral neuropathy[d]	32.9	6.7	30.9	8.7
Paresthesia	11.9	0.3	8.7	0.5
Pyrexia	10.5	0.8	23.0	1.6

[a]Grouped by system organ class (safety population). [b]Includes neutropenia and neutrophil count decreased. [c]Includes thrombocytopenia and platelet count decreased. [d]Includes peripheral neuropathy and peripheral sensory neuropathy.
Gem, gemcitabine; NabP, *nab*-paclitaxel; NALIRIFOX, liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin; TEAE, treatment-emergent adverse event.

GERMLINE BRCA1/BRCA2 IN PANCREATIC CANCER

Germline BRCA1/BRCA2 prevalence : <5%

White patients : 3.3%

Limited evaluation in African American patients (0.2%)

Asian patients (1.7%)

Hispanic patients (0%)

BRCA2 > BRCA 1

PAIELLA ET AL, ESMO OPEN 2023

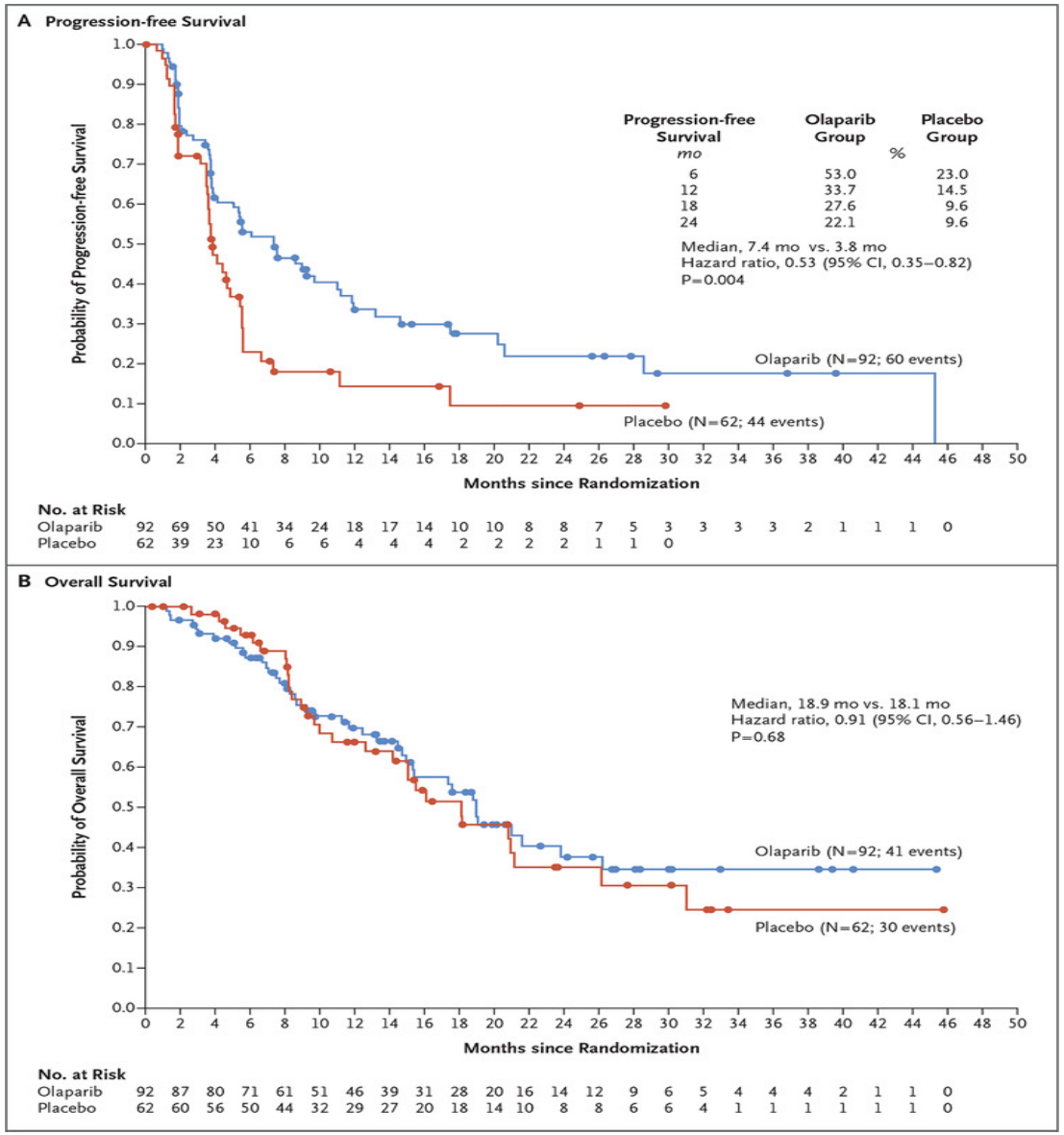
Maintenance Olaparib – POLO Study

N = 154, 3:2 rand, Olaparib 300 mg bid vs placebo

PFS : 7.4 vs. 3.8 mth

OS : 19 vs. 19.2 mth; 3-Yr Survival : 33.9% vs. 17.8%

Toxicity : Fatigue, anemia, nausea, diarrhea/constipation



GOLAN ET AL 2019, NEJM, KINDLER ET AL, JCO 2023

The pivotal, phase 3 PANOVA-3 study: Tumor Treating Fields (TTFields) therapy concomitant with gemcitabine and nab-paclitaxel (GnP) for front-line treatment of locally advanced pancreatic cancer

Hani Babiker[1], Teresa Macarulla[2], Philip Agop Philip[3], Carlos Roberto Becerra[4]; Tomislav Dragovich[5], Vincent J. Picozzi[6]

[1]Mayo Clinic Comprehensive Cancer Center, Jacksonville, FL, USA; [2]Vall d'Hebrón University Hospital and Vall d'Hebrón Institute of Oncology, Barcelona, Spain; [3]Karmanos Cancer Institute, Detroit, MI, USA; [4]Baylor University Medical Center, Dallas, TX, USA; [5]Banner MD Anderson Cancer Center, Gilbert, AZ, USA

INTRODUCTION

- Locally-advanced pancreatic adenocarcinoma has a poor prognosis with existing treatment options[1]
- FOLFIRNOX (leucovorin, 5-fluorouracil, irinotecan, oxaliplatin) or gemcitabine-based chemotherapy are commonly prescribed, but are associated with moderate-to-high systemic toxicity and impaired quality of life (QoL)[2,3]
- Tumor Treating Fields (TTFields) therapy is a noninvasive and localized treatment[4–6] which can be combined with standard of care cancer treatments to enhance efficacy without contributing to systemic toxicity, and has been approved for newly diagnosed and recurrent glioblastoma as well as pleural mesothelioma[7,8]
- TTFields that target pancreatic cells (150 kHz)[9] are produced by the NovoTTF-200T system and delivered using arrays applied to the patient's abdomen (**Figure 1**)

STUDY RATIONALE

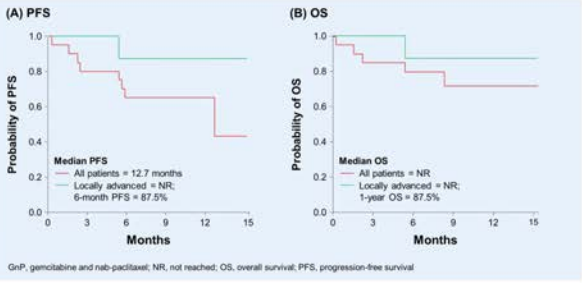
- TTFields therapy in pancreatic cancer is supported by data from preclinical models[9]
  - TTFields treatment (150 kHz) had a long-term anticlonogenic effect on pancreatic cancer cells and enhanced the cytotoxicity of several chemotherapy agents used to treat pancreatic cancer
  - TTFields concomitant with gemcitabine or 5-fluorouracil led to a decrease in tumor volume and weight in hamster pancreatic tumor models vs either chemotherapy agent alone
- The phase 2 pilot PANOVA study (NCT01971281;EF-20) provided preliminary support for the safety and efficacy of TTFields therapy added to gemcitabine or gemcitabine and nab-paclitaxel (GnP) in locally advanced pancreatic and metastatic pancreatic cancer[10]
  - In the total patient population, device usage was 68–78% of the recommended time stated in the protocol (≥18 h/day)
  - In patients receiving TTFields therapy concomitant with GnP, half experienced a TTFields therapy-related skin adverse event (AE), none of these were serious and only 5 patients experienced a grade 3 device-related AE
  - In the locally advanced cohort receiving TTFields therapy concomitant with GnP, the 6-month progression-free survival (PFS) and 1-year overall survival (OS) rates were both 87.5%, while median PFS and OS were not reached (**Figure 2**)

Figure 1. The NovoTTF-200T system applied to deliver TTFields therapy to the abdomen

Two pairs of arrays (1 pair shown applied to the patient) are placed on the abdomen, near the tumor site, and attached to the portable NovoTTF-200T system (2.7 lbs)

Usage information will be provided to patients and physicians to facilitate discussions to optimize outcomes by maximizing time on therapy

Figure 2. (A) PFS and (B) OS in the total population (n = 20), and locally advanced subgroup (n = 8) of patients with pancreatic cancer receiving TTFields therapy + GnP



GnP, gemcitabine and nab-paclitaxel; NR, not reached; OS, overall survival; PFS, progression-free survival

STUDY DESIGN

- TTFields therapy + GnP efficacy and safety in patients with locally advanced pancreatic adenocarcinoma is investigated in this prospective, pivotal, phase 3 study (PANOVA-3, EF-27, NCT03377491) (**Figure 3**)
- Patients will be stratified by performance status and geographical region, and randomly assigned 1:1 to receive TTFields therapy (150 kHz, 18 h/day) concomitant with GnP, or GnP alone

SAMPLE SIZE & STATISTICAL CONSIDERATIONS

- The sample size (N = 556) was estimated per log-rank test comparing time to event in patients treated with TTFields therapy + GnP or GnP alone based on published clinical study data, anticipating that 10% of patients will be censored

KEY INCLUSION CRITERIA

- Diagnosis of unresectable, locally advanced, non-metastatic, *de novo* pancreatic adenocarcinoma (per National Comprehensive Cancer Network)
- Eastern Cooperative Oncology Group performance status ≤2

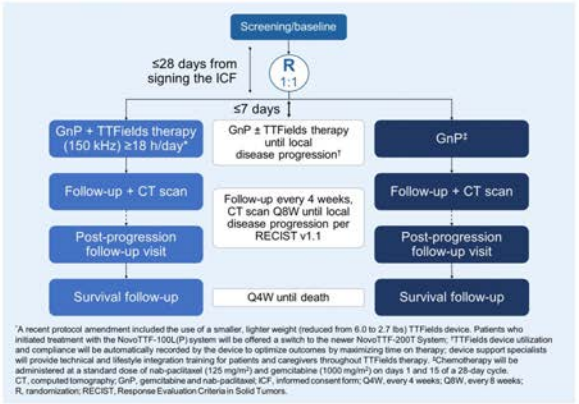
KEY EXCLUSION CRITERIA

- Concurrent antitumor therapy beyond GnP
- Prior treatment
  - palliative treatment to the tumor
  - anti-tumor treatment for any other cancers, within 5 years of enrollment
- Significant comorbidities, contraindicative allergies, pregnancy, or breastfeeding

STUDY ENDPOINTS

- **Primary:** OS; **Secondary:** PFS, local PFS, 1-year survival rate, objective response rate, QoL, pain-free survival, puncture-free survival, resectability rate, and safety

Figure 3. PANOVA-3 study design



*A recent protocol amendment included the use of a smaller, lighter weight (reduced from 6.0 to 2.7 lbs) TTFields device. Patients who initiated treatment with the NovoTTF-100L(P) system will be offered a switch to the newer NovoTTF-200T System; †TTFields device utilization and compliance will be automatically recorded by the device to optimize outcomes by maximizing time on therapy; device support specialists will provide technical and lifestyle integration training for patients and caregivers throughout TTFields therapy. ‡Chemotherapy will be administered at a standard dose of nab-paclitaxel (125 mg/m²) and gemcitabine (1000 mg/m²) on days 1 and 15 of a 28-day cycle.
CT, computed tomography; GnP, gemcitabine and nab-paclitaxel; ICF, informed consent form; Q4W, every 4 weeks; Q8W, every 8 weeks; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors.

STUDY STATUS

- As of February 2023, recruitment has been completed in the following countries:

Australia | Austria | Belgium | Brazil | Canada | China | Croatia | Czech Republic | France | Germany | Hong Kong | Hungary | Israel | Italy | Republic of Korea | Mexico | Poland | Spain | Switzerland | USA

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References

1. He C et al. *Front in Oncol*. 2020;10(6):1–12; **2.** De Jesus et al. *Ther Adv Med Oncol*. 2020;12:1–13; **3.** Gourgou-Bourgade S et al. *J Clin Oncol*. 2013;31(10):23–29; **4.** Mun EJ et al. *Clin Cancer Res*. 2018; 24:266–275; **5.** Kirson ED et al. *Cancer Res*. 2004;64(9):3288–3295; **6.** Voloshin T et al. *Cancers (Basel)*. 2020;12(10):3016; **7.** Novocure. Optune® instructions for use. https://www.optune.com/Content/pdfs/Optune_IFU_8.5x11.pdf (Accessed April 12, 2023); **8.** Novocure. Optune® instructions for use for unresectable malignant pleural mesothelioma. Available from: https://www.optunelua.com/pdfs/Optune-Lua-MPM-IFU.pdf (Accessed April 12, 2023); **9.** Giladi M et al. *Pancreatology*. 2014;14(1):54–63; **10.** Rivera F et al. *Pancreatology*. 2019;19(1):64–72.

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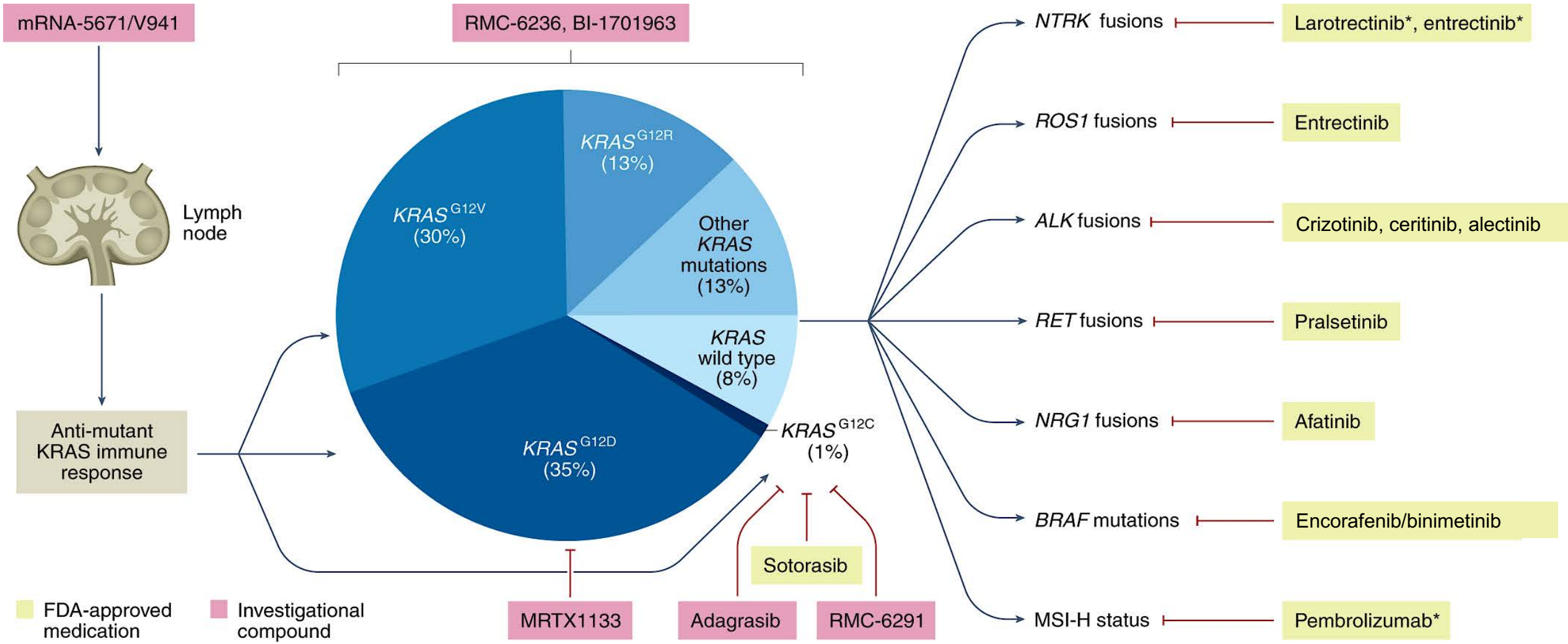
Presented at the 2023 Annual Meeting of the American Society of Clinical Oncology, June 2–6, 2023, Chicago, IL, US

KEY POINTS

- Pivotal Phase 3 Study
- Gemcitabine/*nab*-paclitaxel +/- TTFields randomized 1:1
- Sample Size : N = 556
- Locally Advanced Patients
- Primary Endpoint = Overall Survival
- Secondary Endpoints = PFS, Local PFS, 1 year survival Response Rate, QoL, Pain Free Survival, Puncture Free Survival
- Resectability Rate, Safety
- TTFields @ 150 Hx for >= 18 hours/day
- PANOVA-2 (N = 20, 12 met, 8 Loc Adv)
  Median OS = Not reached (NR), Median OS Loc Adv = NR
  Median PFS = 12.7 months, Median PFS Loc Adv = NR
  6 mth PFS Loc Adv = 87.5%, 6 mth OS Loc Adv = 87.5%
  Cutaneous toxicity in 53% (Grade 3 = 18%, no Grade 4)

OTHER PROMISING AGENTS/TARGETS FOR PANCREATIC CANCER



HOSEIN ET AL, NATURE CANCER 2022

USC Norris Comprehensive Cancer Center
Keck Medicine of USC

Updates on Treatment of Hepatocellular Carcinoma

Anthony El-Khoueiry, MD

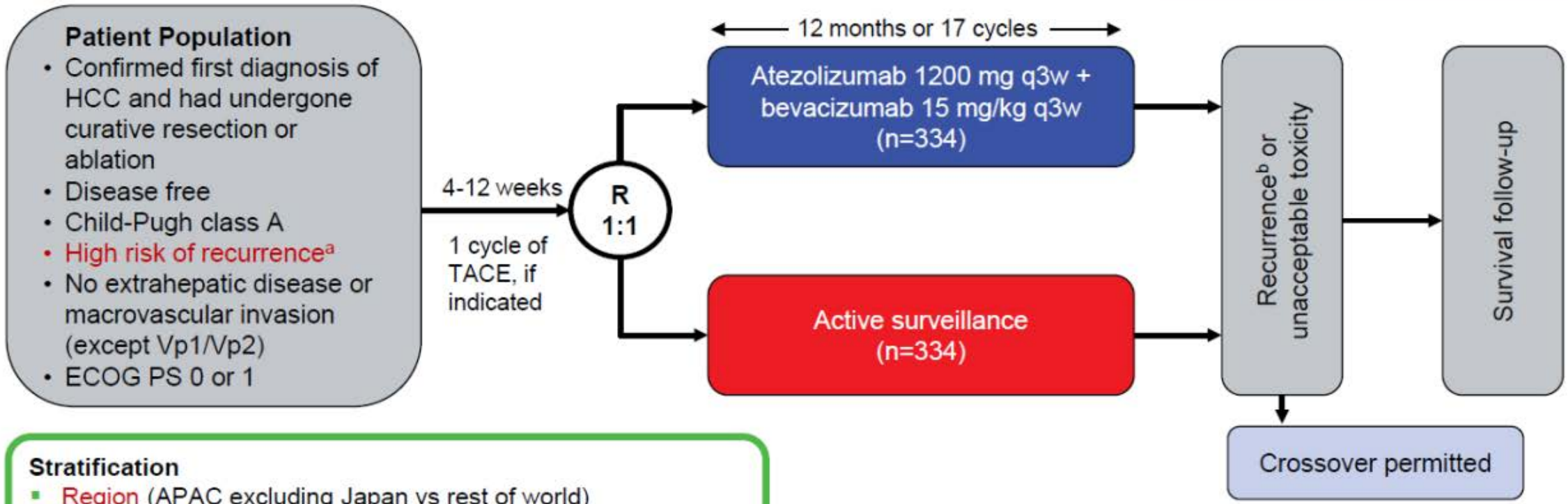
USC Norris Comprehensive Cancer Center

USC Norris Comprehensive Cancer Center
Keck Medicine of USC

New Data in Early-stage HCC

Adjuvant Therapy

IMbrave050 study design



ClinicalTrials.gov, NCT04102098. ECOG PS; Eastern Cooperative Oncology Group performance status; Q3W, every three weeks; R, randomization; TACE, transarterial chemoembolization.

[a] **High-risk features** include: tumor >5 cm, >3 tumors, microvascular invasion, minor macrovascular invasion Vp1/Vp2, or Grade 3/4 pathology.

[b] Intrahepatic recurrence defined by EASL criteria. Extrahepatic recurrence defined by RECIST 1.1.

Chow P et al, AACR 2023

Study endpoints and testing hierarchy

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

Study endpoints

Primary endpoint

- Recurrence-free survival (RFS) assessed by independent review facility (IRF)

Secondary endpoints

- RFS assessed by investigator (INV)
- Time to recurrence assessed per IRF
- Overall survival (OS)

Other endpoint

- Safety

Overall Type I error 0.05 (2-sided) hierarchical testing

IRF-assessed RFS
(interim analysis)

Number of events = 243
Stopping boundary (*P* value) = 0.0195
Target HR = 0.73

If RFS is positive:

OS
(1st interim analysis)
Information fraction = 14.7%
Expected[a] information fraction = 33.5%

Chow P et al, AACR 2023

Baseline characteristics—curative procedures

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

Characteristic	Atezo + bev (n=334)	Active surveillance (n=334)
Resection, n (%)	293 (87.7)	292 (87.4)
Longest diameter of the largest tumor at diagnosis, median (range), cm[a]	5.3 (1.0-18.0)	5.9 (1.1-25.0)
Tumors, n (%)		
1	266 (90.8)	260 (89.0)
2	20 (6.8)	29 (9.9)
3	4 (1.4)	2 (0.7)
4+	3 (1.0)	1 (0.3)
Adjuvant TACE following resection, n (%)	32 (10.9)	34 (11.6)
Any tumors >5 cm, n (%)	152 (51.9)	175 (59.9)
Microvascular invasion present, n (%)	178 (60.8)	176 (60.3)
Minor macrovascular invasion (Vp1/Vp2) present, n (%)	22 (7.5)	17 (5.8)
Poor tumor differentiation (Grade 3 or 4), n (%)	124 (42.3)	121 (41.4)
Ablation, n (%)	41 (12.3)	42 (12.6)
Longest diameter of the largest tumor at diagnosis, median (range), cm	2.5 (1.2-4.6)	2.6 (1.5-4.6)
Tumors, n (%)		
1	29 (70.7)	31 (73.8)
2	11 (26.8)	8 (19.0)
3	1 (2.4)	3 (7.1)

Chow P et al, AACR 2023

Primary endpoint: IRF-assessed RFS was significantly improved with atezo + bev vs active surveillance

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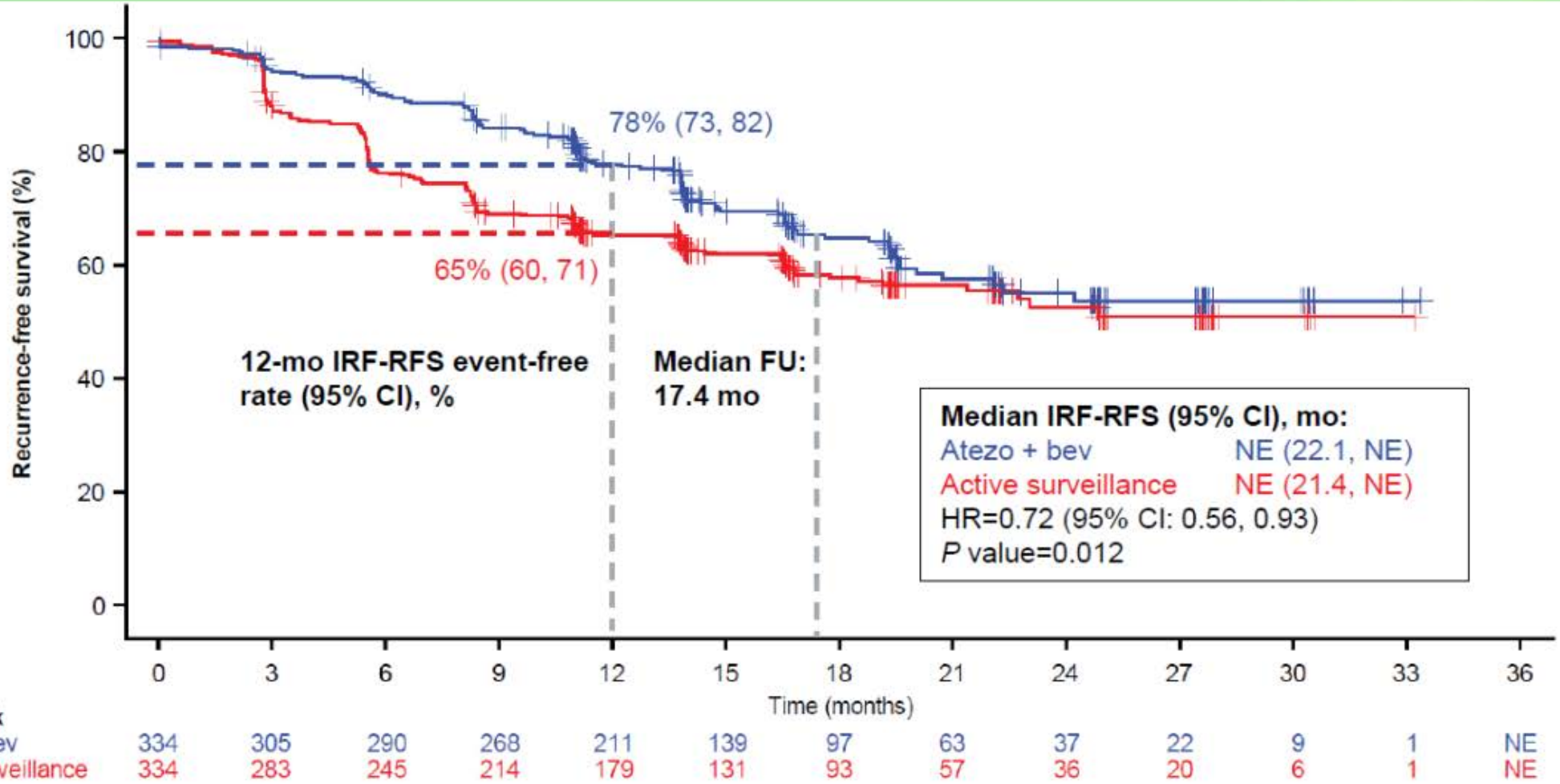


No. at risk													
Atezo + bev	334	305	290	268	211	139	97	63	37	22	9	1	NE
Active surveillance	334	283	245	214	179	131	93	57	36	20	6	1	NE

Clinical cutoff: October 21, 2022; median follow-up duration: 17.4 mo. At clinical cutoff, 110 of 334 patients (33%) in the atezo + bev arm and 133 of 334 (40%) in the active surveillance arm experienced disease recurrence or death.
FU, follow-up; NE, not estimable. HR is stratified. *P* value is a log rank.

Chow P et al, AACR 2023

AE of any grade with an incidence rate of ≥10% in either treatment group by preferred term

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

Event, n (%)	Atezo + bev (n=332)		Active surveillance (n=330)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Proteinuria	154 (46.4)	29 (8.7)	12 (3.6)	0
Hypertension	127 (38.3)	61 (18.4)	10 (3.0)	3 (0.9)
Platelet count decreased	66 (19.9)	15 (4.5)	22 (6.7)	4 (1.2)
Aspartate aminotransferase increased	52 (15.7)	3 (0.9)	18 (5.5)	2 (0.6)
Alanine aminotransferase increased	47 (14.2)	2 (0.6)	18 (5.5)	3 (0.9)
Hypothyroidism	47 (14.2)	0	1 (0.3)	0
Arthralgia	40 (12.0)	1 (0.3)	8 (2.4)	1 (0.3)
Pruritus	40 (12.0)	1 (0.3)	3 (0.9)	0
Rash	40 (12.0)	0	1 (0.3)	0
Blood bilirubin increased	34 (10.2)	1 (0.3)	23 (7.0)	1 (0.3)
Pyrexia	34 (10.2)	0	7 (2.1)	0

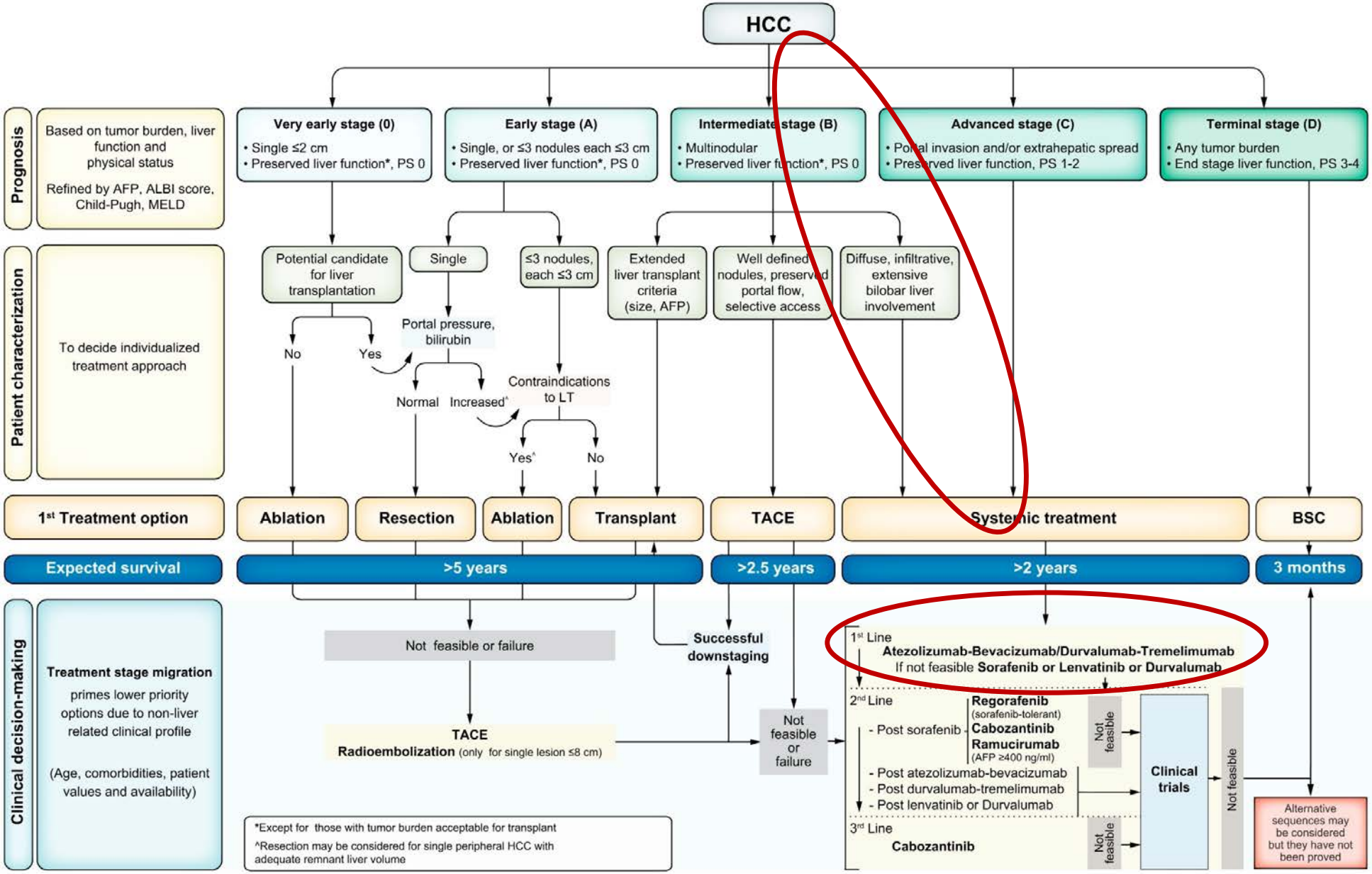
Chow P et al, AACR 2023

USC Norris Comprehensive Cancer Center
Keck Medicine of USC

Advanced HCC

Multiple treatment options and expanding indications

When is systemic therapy indicated for HCC?



Reig M et al, J of Hepatology 2022

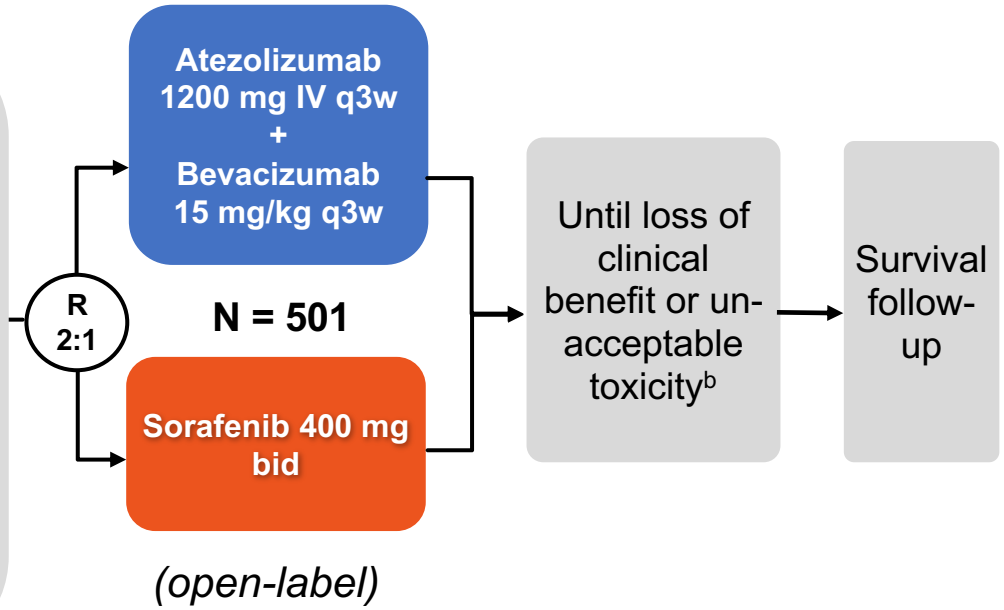
IMbrave150 Study Design

Key eligibility

- Locally advanced or metastatic and/or unresectable HCC
- No prior systemic therapy
- ECOG PS 0-1
- Child-Pugh class A liver function

Stratification

- **Region** (Asia excluding Japan[a]/Rest of world)
- **ECOG** (0/1)
- **Macrovascular invasion** and/or **extrahepatic spread** (Presence/Absence)
- **Baseline AFP** (<400/≥400 ng/mL)



Co-primary endpoints

- OS
- IRF-assessed PFS per RECIST 1.1

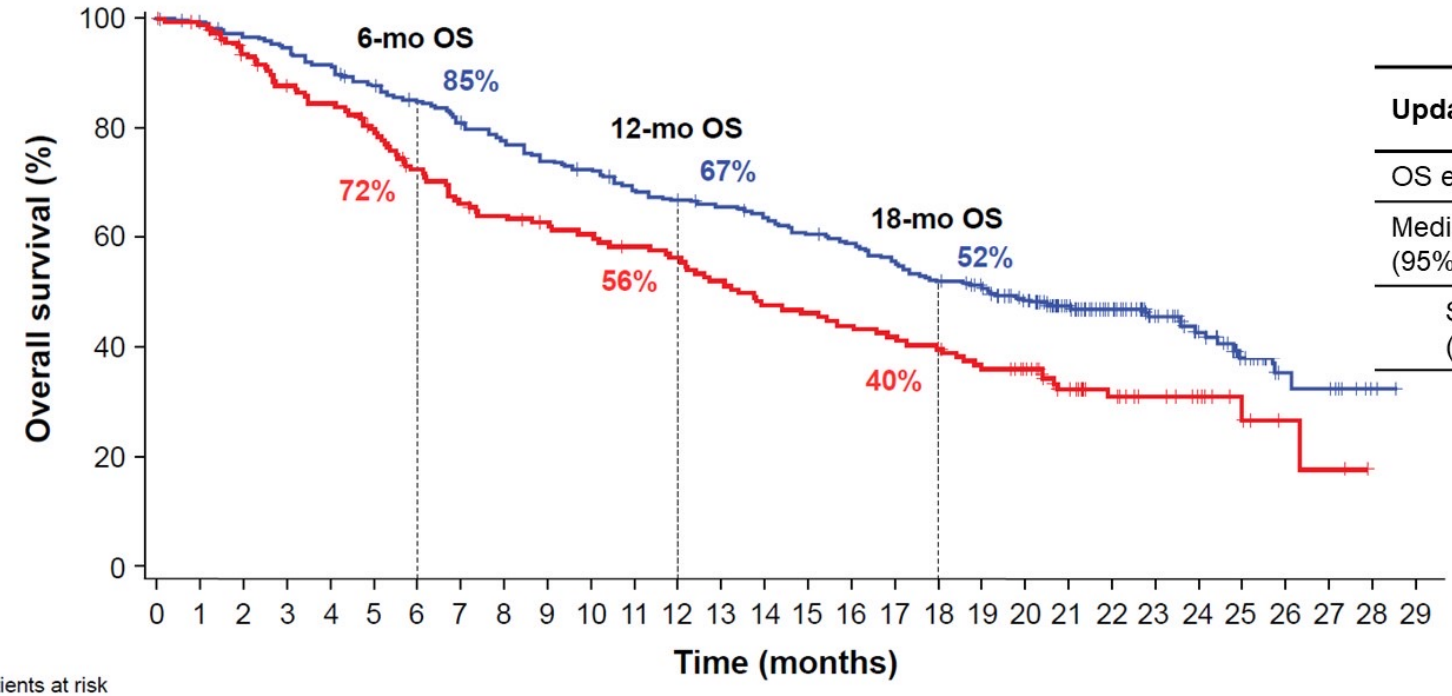
Secondary endpoints included:

- IRF-assessed ORR, DOR per RECIST 1.1 and HCC mRECIST[b]
- PROs: TTD[c] of QOL, physical and role functioning (EORTC QLQ-C30)
- Safety and tolerability assessed based on the nature, frequency and severity of AEs per NCI CTCAE version 4.0

[a] Japan is included in rest of world. [b] Tumor assessment by computed tomography or magnetic resonance imaging was done at baseline and every 6 weeks until 54 weeks, then every 9 weeks thereafter.
[c] Time from randomization to first decrease from baseline of ≥ 10 points maintained for 2 consecutive assessments or 1 assessment followed by death from any cause within 3 weeks.
AFP, α-fetoprotein; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality-of-life questionnaire for cancer; IRF, independent review facility; mRECIST, modified RECIST; NCI, National Cancer Institute; PRO, patient-reported outcomes; QOL, quality of life; TTD, time to deterioration.

IMbrave150

Updated OS



Updated OS	Atezo + Bev (n = 336)	Sorafenib (n = 165)
OS events, n (%)	180 (54)	100 (61)
Median OS, mo (95% CI)	**19.2** (17.0, 23.7)	**13.4** (11.4, 16.9)
Stratified HR (95% CI)[a]	**0.66** (0.52, 0.85) *P* = 0.0009[b]	

No. of patients at risk

Atezo + Bev	336	329	320	312	302	288	276	263	252	240	233	221	214	209	202	192	186	175	164	156	134	105	80	57	42	24	12	11	2	NE
Sorafenib	165	158	144	133	128	119	106	96	92	88	85	81	78	72	66	64	61	58	55	49	44	32	24	18	12	7	3	2	NE	NE

Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo.

[a] Stratification factors included in the Cox model are geographic region (Asia excluding Japan vs Rest of World), AFP level (< 400 ng/mL vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (Yes vs No) per interactive voice/web response system (IxRS).[b] *P* value for descriptive purposes only.

Presented By Richard Finn at 2021 Gastrointestinal Cancers Symposium

Finn et al. New Engl J Med. 2020

HIMALAYA study design

HIMALAYA was a randomised, open-label, multicentre, global, Phase 3 study[1]

Study population

- Adults with confirmed uHCC
- Child-Pugh A
- BCLC B (not eligible for locoregional therapy) or C
- No prior systemic therapy for HCC
- ECOG PS 0–1
- No main portal vein thrombosis
- OGD was not required

Stratification factors

- Aetiology of liver disease: HBV / HCV / nonviral
- Macrovascular invasion: yes / no
- ECOG PS: 0 / 1

R
N=1171

STRIDE (n=393):
tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W

Durvalumab (n=389):
durvalumab monotherapy 1500 mg Q4W

Sorafenib (n=389):
sorafenib 400 mg BID

T75+D (n=153): *arm closed to enrolment**
tremelimumab 75 mg Q4W × 4 doses + durvalumab 1500 mg Q4W

Primary objective

- OS superiority: STRIDE vs sorafenib

Key secondary objectives

- OS noninferiority: durvalumab vs sorafenib
- 36-month OS rate
- PFS, ORR and DCR (investigator-assessed per RECIST v1.1)
- Safety

Multiple testing procedure

OS *superiority* for STRIDE vs sorafenib

OS *noninferiority* for durvalumab vs sorafenib
Noninferiority margin: 1.08

OS *superiority* for durvalumab vs sorafenib

36-month OS rate for STRIDE vs sorafenib

Treatment continued until unacceptable toxicity or any discontinuation criteria were met. Participants with progressive disease who, in the investigator's opinion, continued to benefit from treatment and met the criteria for treatment in the setting of progressive disease could continue treatment. *The T75+D arm was closed following a preplanned analysis of a Phase 2 study. Participants randomised to this arm (n=153) could continue treatment following arm closure. Results from this arm are not reported in this presentation.

BCLC, Barcelona Clinic Liver Cancer; BID, twice a day; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; OGD, oesophagogastroduodenoscopy; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; Q4W, every 4 weeks; R, randomised; RECIST, Response Evaluation Criteria in Solid Tumours; T75+D, tremelimumab 75 mg Q4W × 4 doses + durvalumab 1500 mg Q4W; uHCC, unresectable hepatocellular carcinoma.

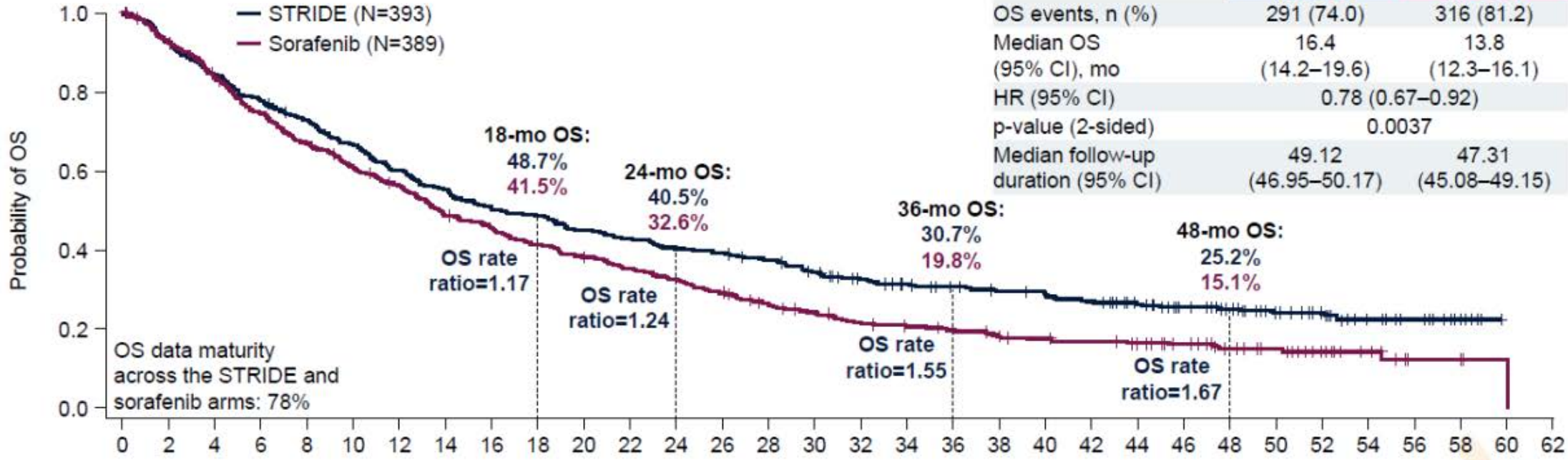
1. Abou-Alfa GK, et al. *NEJM Evid* 2022;1:EVIDoa2100070.

Sangro B et al, World Congress on GI Cancer, 2023

Four-year updated overall survival for STRIDE versus sorafenib

STRIDE demonstrated an unprecedented one in four survival rate at 4 years

	STRIDE (N=393)	Sorafenib (N=389)
OS events, n (%)	291 (74.0)	316 (81.2)
Median OS (95% CI), mo	16.4 (14.2–19.6)	13.8 (12.3–16.1)
HR (95% CI)	0.78 (0.67–0.92)	
p-value (2-sided)	0.0037	
Median follow-up duration (95% CI)	49.12 (46.95–50.17)	47.31 (45.08–49.15)



Number at risk

STRIDE:	393	365	333	308	285	262	235	217	197	190	176	168	158	154	144	131	118	110	103	97	94	88	75	62	54	40	31	19	13	5	0	0
Sorafenib:	389	356	319	283	255	231	211	183	170	155	142	131	121	108	93	83	73	69	64	56	53	50	45	36	28	21	14	9	3	1	1	0

OS HRs and 95% CIs were calculated using a Cox proportional hazards model adjusting for treatment, aetiology, ECOG PS and MVI. The 36-mo OS rate had a nominal 2-sided p-value of 0.0006.
Updated analysis data cut-off: 23 January 2023.

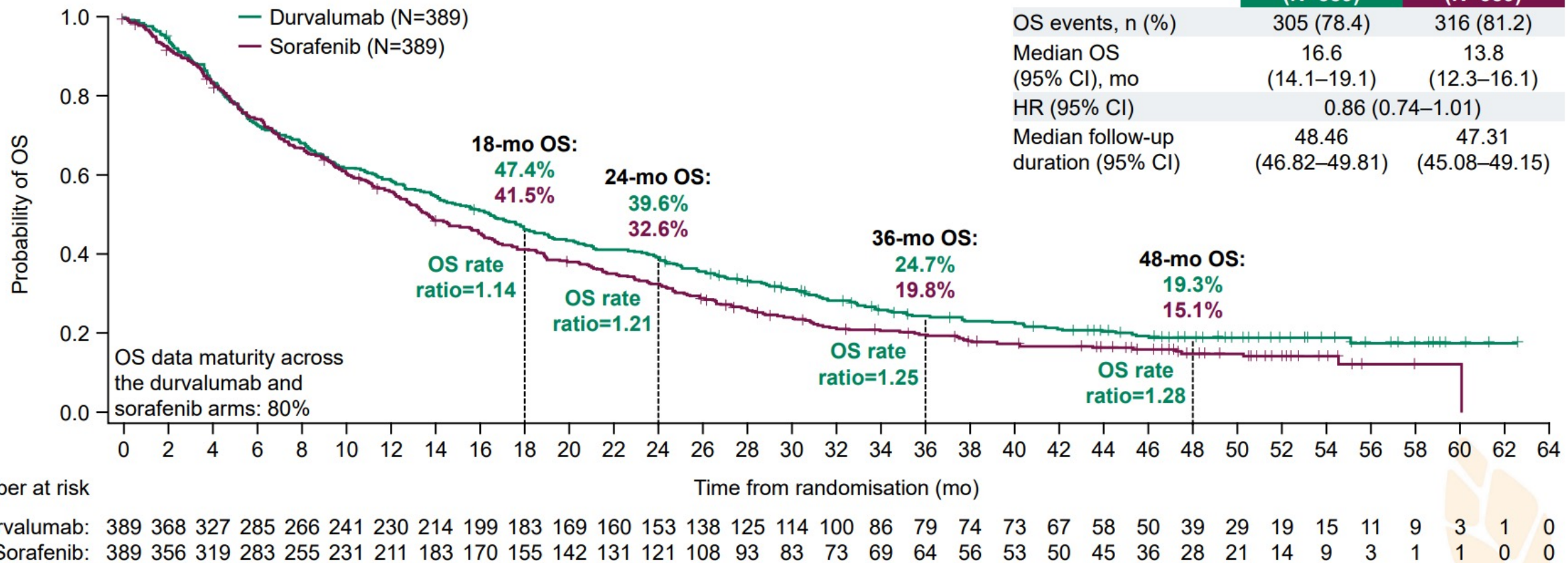
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; mo, month; MVI, macrovascular invasion; OS, overall survival; PS, performance status.

Sangro B et al, World Congress on GI Cancer, 2023

Four-year updated overall survival for durvalumab versus sorafenib

With further follow-up, durvalumab was not inferior to sorafenib, consistent with the primary analysis[1]

	Durvalumab (N=389)	Sorafenib (N=389)
OS events, n (%)	305 (78.4)	316 (81.2)
Median OS (95% CI), mo	16.6 (14.1–19.1)	13.8 (12.3–16.1)
HR (95% CI)	0.86 (0.74–1.01)	
Median follow-up duration (95% CI)	48.46 (46.82–49.81)	47.31 (45.08–49.15)



Number at risk

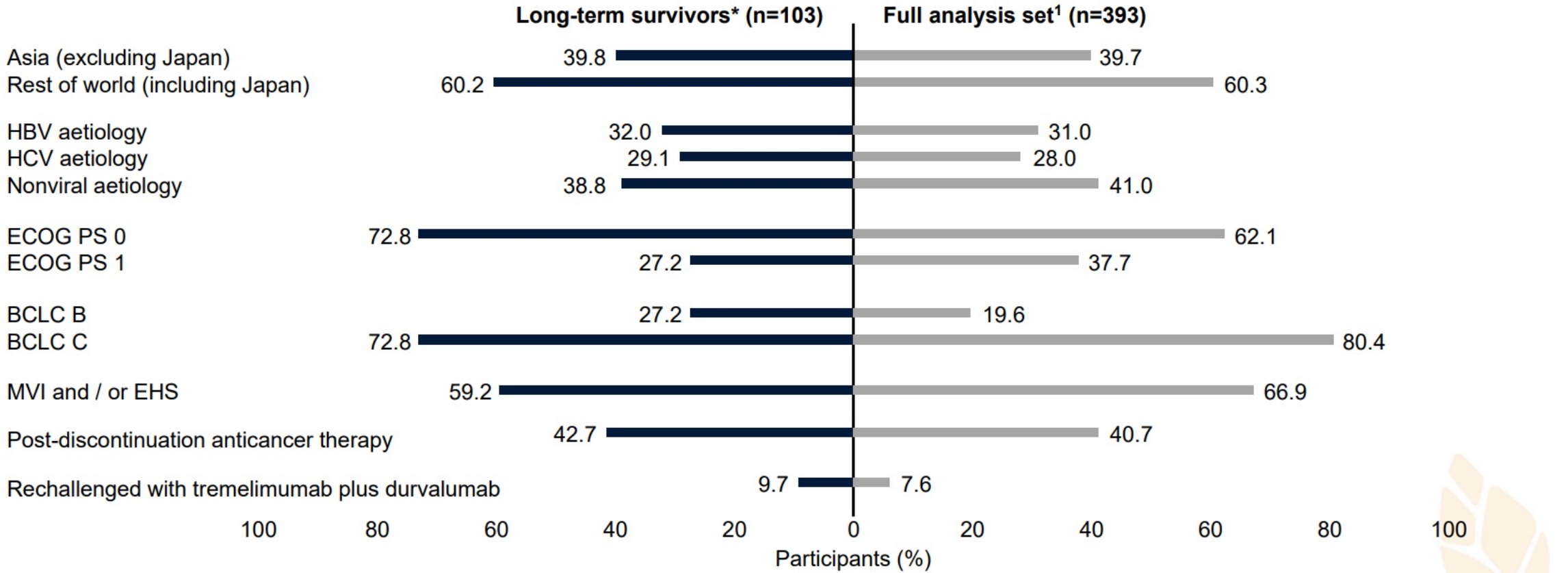
Durvalumab:	389	368	327	285	266	241	230	214	199	183	169	160	153	138	125	114	100	86	79	74	73	67	58	50	39	29	19	15	11	9	3	1	0
Sorafenib:	389	356	319	283	255	231	211	183	170	155	142	131	121	108	93	83	73	69	64	56	53	50	45	36	28	21	14	9	3	1	1	0	0

OS HRs and 95% CIs were calculated using a Cox proportional hazards model adjusting for treatment, aetiology, ECOG PS and MVI. Noninferiority margin = 1.08. Updated analysis data cut-off: 23 January 2023.
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; mo, month; MVI, macrovascular invasion; OS, overall survival; PS, performance status.
1. Abou-Alfa GK, et al. *NEJM Evid* 2022;1:EVIDoa2100070.

Sangro B et al, World Congress on GI Cancer, 2023

Characterisation of long-term survivors (≥36 months) with STRIDE

All clinically relevant participant subgroups were represented in the long-term survivors; no subgroup drives long-term survival



HBV: participants who tested positive for HBsAg or anti-HBcAb with detectable HBV DNA; HCV: participants who tested positive for HCV or had history of HCV infection; Nonviral: no active viral hepatitis identified. Viral aetiology, MVI and / or EHS determined at screening. BCLC determined at study entry.

*Long-term survivors were defined as participants surviving ≥36 months beyond randomisation. An exploratory, ad hoc analysis was performed to characterise the participants who experienced long-term survival at the updated data cut-off. Updated analysis data cut-off: 23 January 2023.

BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; EHS, extrahepatic spread; HBV, hepatitis B virus; HCV, hepatitis C virus; MVI, macrovascular invasion; PS, performance status.

1. Abou-Alfa GK, et al. *NEJM Evid* 2022;1:EVIDoa2100070.

Sangro B et al, World Congress on GI Cancer, 2023

APPROVED FIRST LINE COMBINATIONS FOR FIRST LINE HCC

	IMbrave150		HIMALAYA	
	Atezo/Bev	Sorafenib	STRIDE	Sorafenib
mOS (mo)	19.2 HR 0.66 (0.52,0.85)	13.4	16.4 HR 0.78 (0.65-0.92)	13.8
mPFS (mo)	6.9 HR 0.65(0.53,0.81)	4.3	3.78 HR 0.9 (0.77-1.05)	4.07
ORR (RECIST 1.1)	30%	11%	20.1%	5.1%
CR	8%		3.1%	
PD	19%		39.9%	
Median DoR (months)	18.1	14.9	22.3	18.4
DCR	74%	55%	60.1%	60.7%
Discontinuation due to AEs	22%		13.4%	
≥ Grade 3 TRAEs	43%		25.8%	
IMAEs requiring steroids	12.2%		20.1%	
All grade bleeding events	25%	17.3%	1.8%	4.8%
Grade 3/4 bleeding events	6.4%	5.8%	0.5%	1.6%

Bleeding events less common in HIMALAYA but trial did exclude patients with main PVT who are at highest risk for bleeding

IS THERE A ROLE FOR SINGLE AGENT PD-1/PD-L1 IN FIRST LINE HCC?

	Nivolumab CheckMate 459 (Superiority Design) NEGATIVE	**Durvalumab HIMALAYA (Non-Inferiority) POSITIVE**	**Tislelizumab RATIONALE-301 (Non-Inferiority) POSITIVE**
mOS (months)	16.4 vs. 14.7	16.6 vs 13.8	15.9 vs 14.1
ORR(%)	15 vs 7	17 vs 5.1	14.3 vs 5.4

CheckMate 040 cohort 5: A phase I/II study of nivolumab in patients with advanced hepatocellular carcinoma and Child-Pugh B cirrhosis

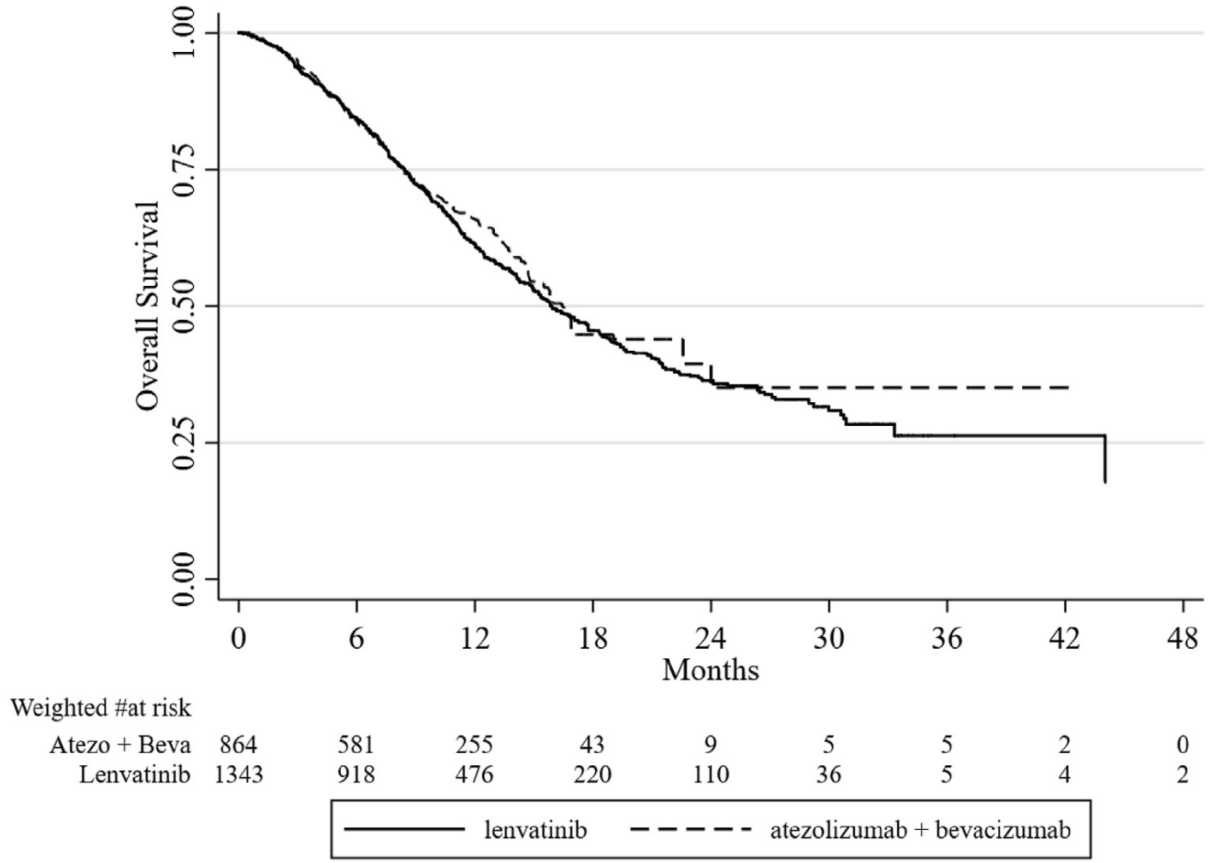
First line treatment option for select patients:
- Poor candidates for combination therapy

Consider for Child Pugh B patients

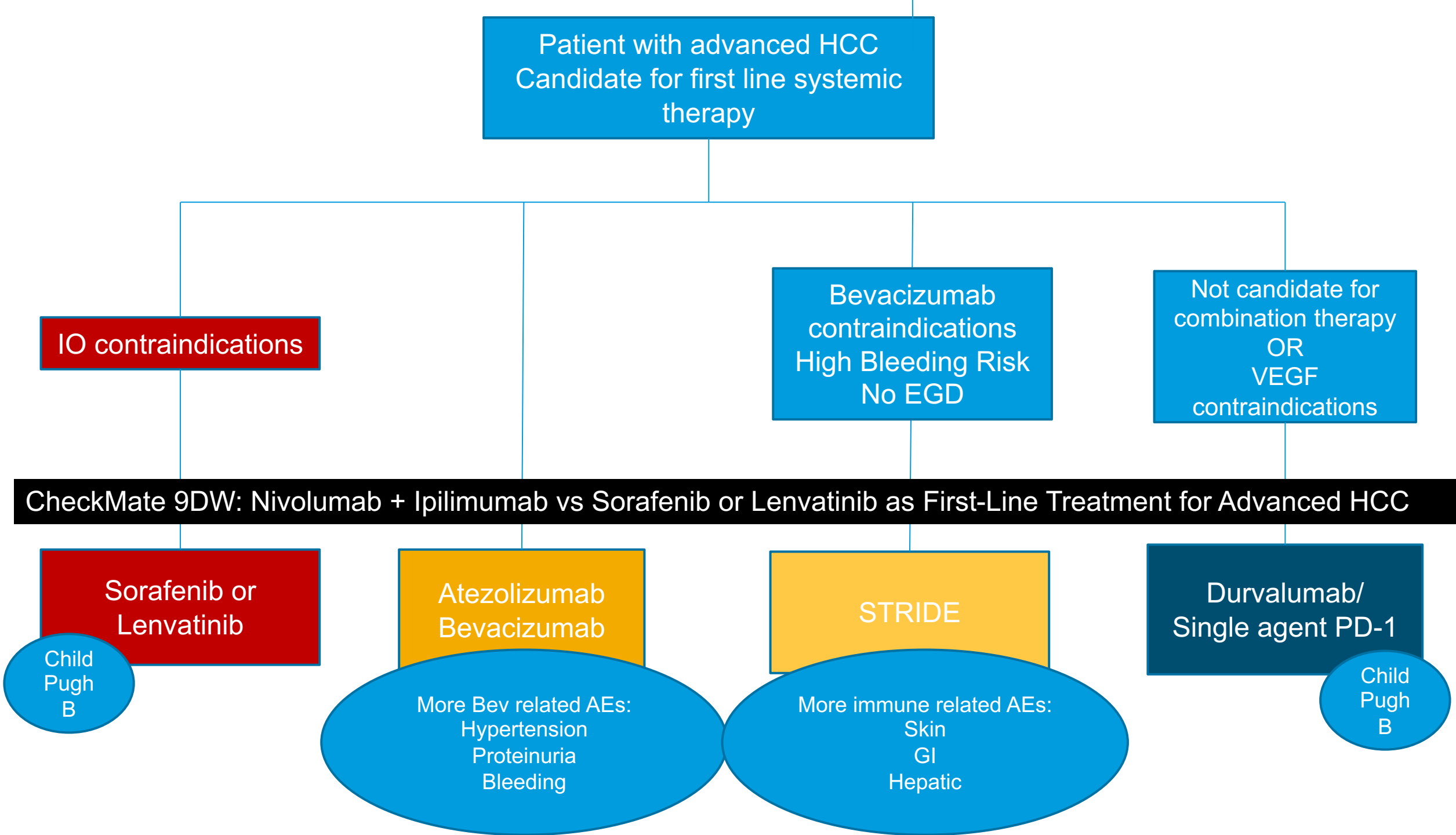
Yau T et al, Lancet Oncol. 2022;; Abou Alfa G et al, ASCO GI 2022; Qin S et al, ESMO 2022; Kudo M et al, J Hepatol 2021

Updated Evidence for Lenvatinib in First Line HCC

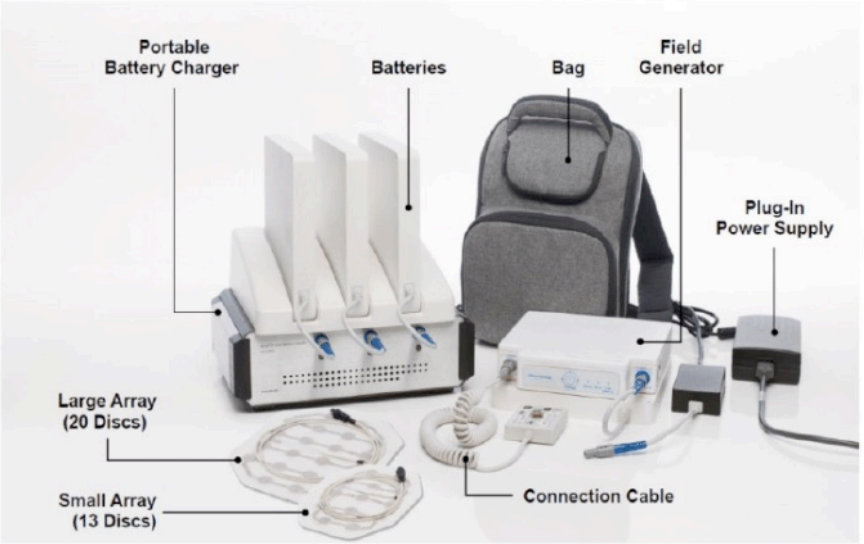
- Retrospective multicenter study of Lenvatinib vs. Atezolizumab/bevacizumab
- 2205 patient analyzed
  - 1341 treated with Lenvatinib
  - 864 treated with Atezolizumab and Bevacizumab
- Clinical features balanced through inverse probability of treatment weighing (IPTW)

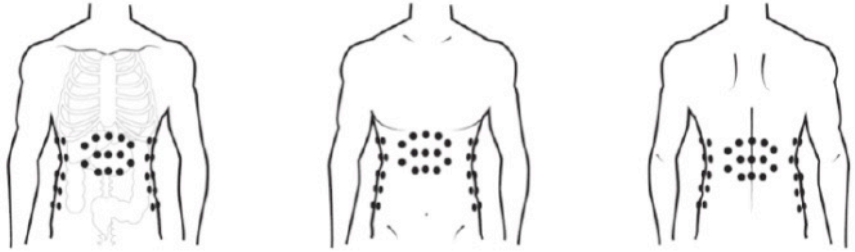


Casadei-Gardini A et al, European J of Cancer 2023


Patient with advanced HCC
Candidate for first line systemic therapy
IO contraindications
Bevacizumab contraindications
High Bleeding Risk
No EGD
Not candidate for combination therapy
OR
VEGF contraindications
CheckMate 9DW: Nivolumab + Ipilimumab vs Sorafenib or Lenvatinib as First-Line Treatment for Advanced HCC
Sorafenib or Lenvatinib
Child Pugh B
Atezolizumab Bevacizumab
More Bev related AEs:
Hypertension
Proteinuria
Bleeding
STRIDE
More immune related AEs:
Skin
GI
Hepatic
Durvalumab/ Single agent PD-1
Child Pugh B

HEPANOVA phase II study: Tumor Treating Fields + Sorafenib





Outcome	TTFields + Sorafenib (n = 21)	TTFields ≥12 Weeks Usage + Sorafenib (n = 11)	Historical Control †
Overall response rate, %	9.5	18	4.5 (p = 0.24) *
Level of response rate, %			
Complete	0	0	-
Partial	9.5	18	-
Stable disease	66.5	73	-
Disease control rate, %	76	91	-
In-field control rate at 1 year, %	9.5	9.1	–

* All evaluable patients vs. historical control. † Table S2. TTFields = Tumor-Treating Fields.

Outcome	TTFields + Sorafenib (n = 27)	TTFields ≥12 Weeks + Sorafenib (n = 11)
OS rate at 1 year, % (95% CI)	30 (11–52)	64 (30–85)
PFS rate at 12 months, % (95% CI)	23 (7–45)	28 (5–58)
Distant metastases-free survival rate at 1 year, % (95% CI)	26 (8–49)	30.5 (5–62)
Median time to progression, months (95% CI)	8.9 (3.1–not reached)	8.9 (5.8–not reached)

CI = confidence interval; OS = overall survival; PFS = progression-free survival; TTFields = Tumor-Treating Fields.

22% ECOG 2
52% Child Pugh B 7/8

Gkika Eleni et al, Cancers 2022

Overview of second line and beyond options

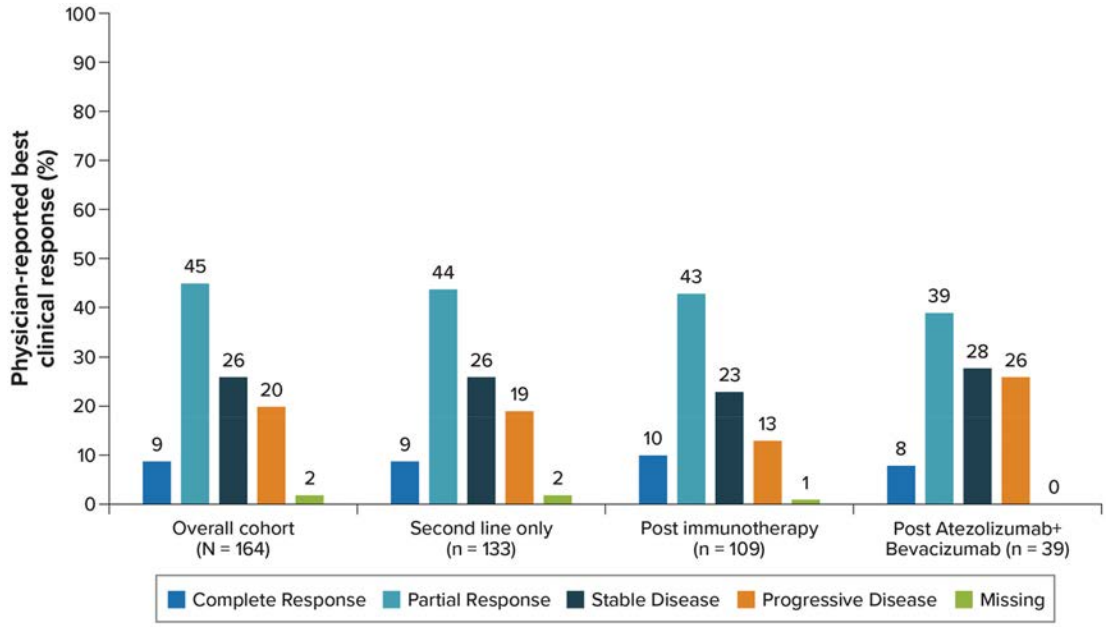
AGENT	Study phase	Prior therapy	Primary Endpoint	Comments
Regorefanib vs. Placebo	Phase 3	Sorafenib	Median OS: 10.6 vs 7.8 mo HR 0.62 (95% CI: 0.50, 0.78)	Eligibility: tolerated sorafenib at 400 mg daily or higher for 20 of last 28 days
Cabozantinib vs. Placebo	Phase 3	Sorafenib (Up to 2 prior lines)	Median OS: 10.2 vs. 8 mo HR 0.76 (95% CI: 0.76-0.92)	30% of patients had 2 prior lines of therapy No requirement for sorafenib tolerability
Ramucirumab vs. Placebo AFP≥ 400	Phase 3	Sorafenib	Median OS: 8.5 vs. 7.3 mo HR 0.710 (0.531-0.949)	
Nivolumab/ Ipilimumab	Phase I/II	Sorafenib (Other lines allowed)	ORR: 32% Median OS: 22.8 mo	Accelerated Approval
Pembrolizumab vs. Placebo	Phase 3	Sorafenib	Keynote 240: 13.9 vs 10.6 mo HR 0.78 (0.61-1.00) Keynote 394: 14.6 vs 13 mo HR 079 (0.63-0.99)	Accelerated Approval

Bruix J et al, Lancet 2017
Abou-Alfa G et al. N Engl J Med. 2018
Zhu A et al, Lancet Oncol 2019

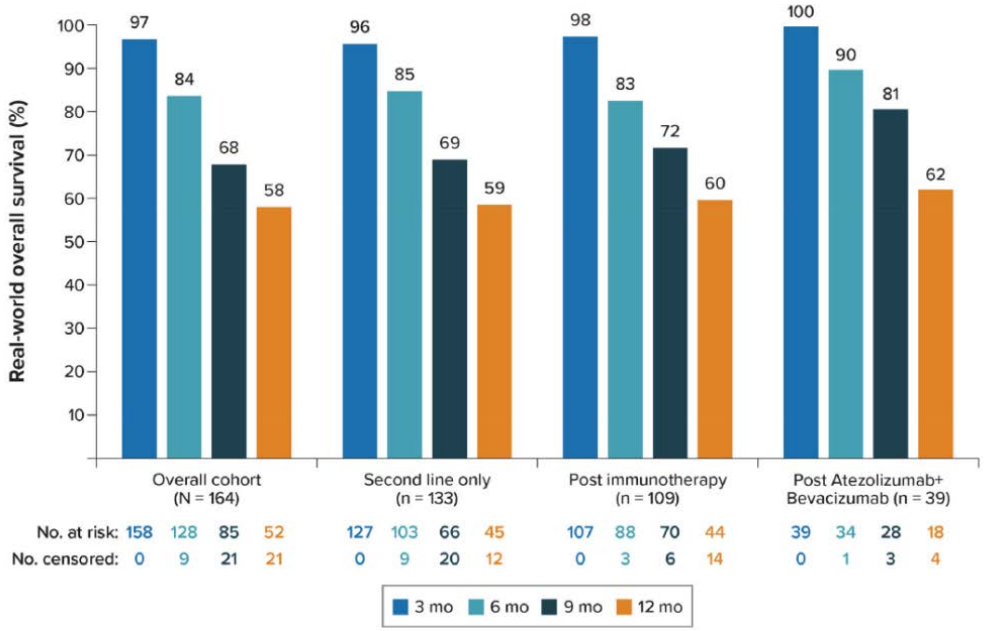
El-Khoueiry A, Lancet. 2017
Finn R et al, ESMO GI 2019

REAL WORLD EVIDENCE: LENVATINIB POST IO

Lenvatinib treatment characteristic	Patients treated with lenvatinib in second or later line (N = 164)	Patients treated with lenvatinib in second line only (n = 133)	Patients treated with lenvatinib postimmunotherapy (n = 109)	Patients treated with lenvatinib postatezolizumab + bevacizumab (n = 39)
Time to initiation from diagnosis of unresectable HCC, months				
Mean (SD)	9.9 (7.5)	8.7 (6.8)	9.9 (7.3)	7.6 (4.3)
Median (Q1, Q3)	8.2 (4.5, 13.8)	7.0 (4.3, 12.0)	8.0 (4.3, 13.7)	7.0 (4.2, 10.1)
First-line treatment prior to lenvatinib, n (%)				
Sorafenib	75 (45.7)	49 (36.8)	25 (22.9)	4 (10.3)
Atezolizumab + bevacizumab	33 (20.1)	33 (24.8)	33 (30.3)	33 (84.6)
Pembrolizumab	31 (18.9)	29 (21.8)	31 (28.4)	0 (0)
Nivolumab	14 (8.5)	14 (10.5)	14 (12.8)	0 (0)
Other[a]	10 (6.1)	7 (5.3)	6 (5.5)	2 (5.1)
Not reported	1 (0.6)	1 (0.8)	0 (0)	0 (0)



Child Pugh B in post IO group: 42.2%



Median OS post Atezo/Bev:14 mo (11.6-NE)

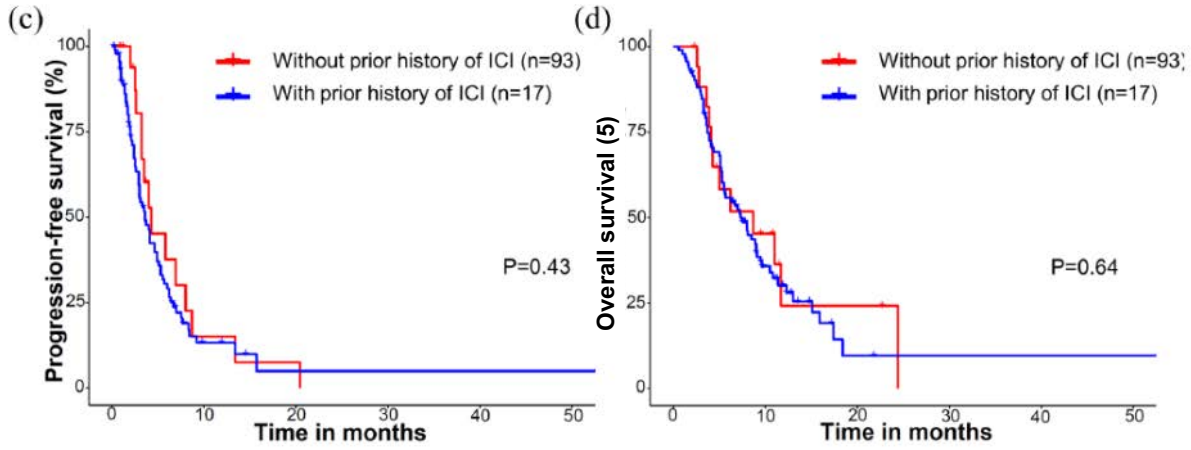
Singal A et al, Cancer Reports 2022

REAL WORLD EVIDENCE: CABOZANTINIB POST IO

	N = 110 (%)
Age (years)	58 (20–77)
Male gender	98 (89.1)
Etiology	
HBV	99 (90.0)
HCV	2 (1.8)
Alcohol	4 (3.6)
Unknown	5 (4.5)
ECOG PS	
0–1	96 (87.3)
2	14 (12.7)
BCLC stage	
C	110 (100.0)
Child–Pugh class	
A	88 (80.0)
B	22 (20.0)
ALBI grade	
1	24 (21.8)
2	69 (62.7)
3	17 (15.5)
Macrovascular invasion	
Yes	51 (46.4)
No	59 (53.6)
⩾3	90 (81.8)
Previous treatments	
Liver transplantation	9 (8.2)
Surgical resection	47 (42.7)
TACE	85 (77.3)
RFA	9 (8.2)
SBRT	46 (41.8)
Previous systemic treatment	
Sorafenib	104 (94.5)
Lenvatinib	26 (23.6)
Regorafenib	91 (82.7)
Ramucirumab	2 (1.8)
Nivolumab	82 (74.5)
Atezolizumab + bevacizumab	10 (9.1)
Durvalumab	2 (1.8)
Pembrolizumab	3 (2.7)
Doxorubicin + cisplatin	3 (2.7)

ALBI, albumin–bilirubin; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; PS, performance status; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolization.
Data are presented as *n* (%) or median (range).

	Overall (n=110)	Child Pugh A (n=88)
ORR	3.6%	4.5%
Stable disease	62.7%	67%
Median OS	7.5 mo (5.5-9.5)	9 mo (7.5-11.7)
Median PFS	3.7 mo (3.1-4.9)	4.3 mo (4-NR)



Bang YH et al, Ther Adv Med Oncol 2022

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Novel Agents in HCC

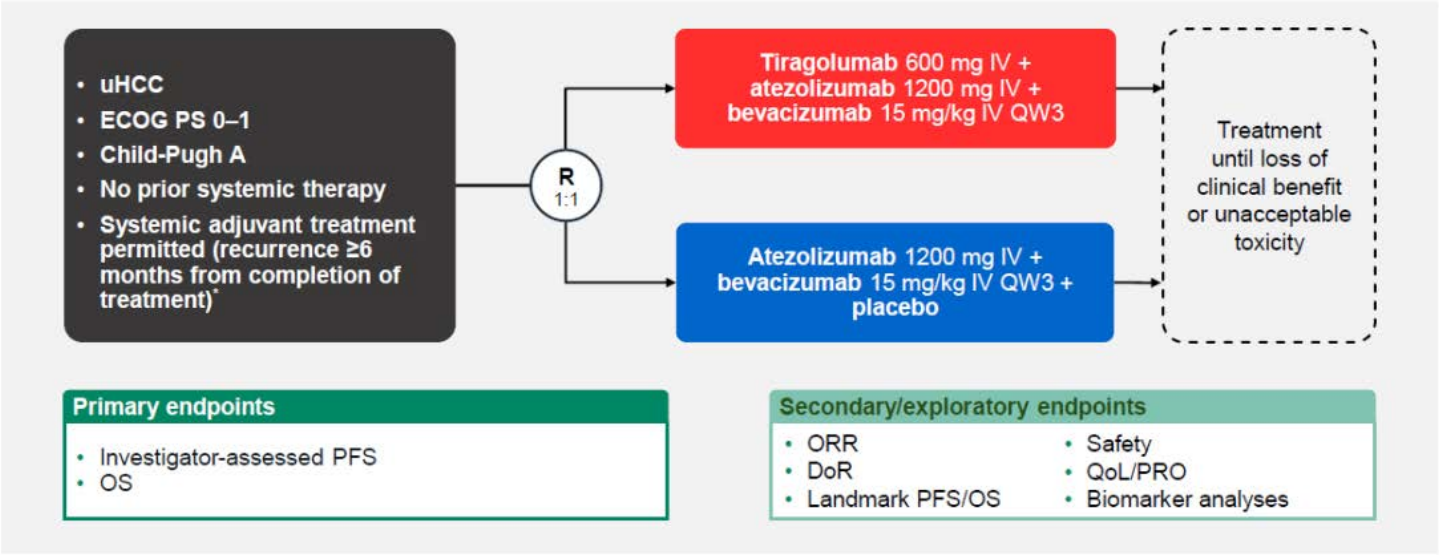
Checkpoints beyond PD-1 and CTLA-4

LAG-3

A Phase 1/2, Safety Confirmation and Double-blind, Placebo-controlled, Randomized Study of Relatlimab in Combination with Nivolumab and Bevacizumab in Treatment-naive Advanced/Metastatic Hepatocellular Carcinoma (RELATIVITY-106)

TIGIT

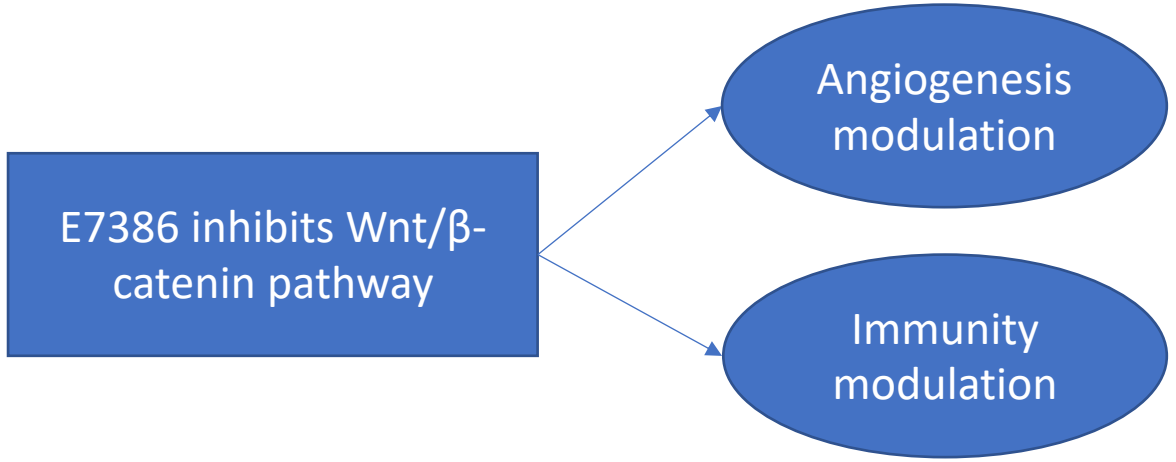
IMbrave152/SKYSCRAPER-14: a phase III, double-blind, placebo-controlled, randomized, global study



Targeting CTNNB1 mutations

E7386-G000-101

An Open-Label, Multicenter, Phase 1 Study of E7386 in Subjects With Selected Advanced Neoplasms



Targeting STAT3

A Phase 1b/2 Multicenter, Open-label Study to Evaluate the Safety and Efficacy of TTI-101 as Monotherapy and in Combination in Participants with Locally Advanced or Metastatic, and Unresectable Hepatocellular Carcinoma

Role in Carcinogenesis	• Mediator of inflammation, injury, fibrosis and cancer • Phosphorylated in 89-100% of HCC
Master Regulator	• Proliferation, resistance to apoptosis, metastasis, angiogenesis • Self renewal of tumor-initiating stem cells
Immune Resistance	• Induction of MDSCs • Promotes M2 macrophages

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Summary and Conclusion

- Checkpoint inhibitor combinations represent the standard first line therapy for advanced HCC
- Tyrosine kinase inhibitors such as sorafenib and lenvatinib remain as alternative options in patients with immunotherapy contraindications or who prefer oral therapy
- Second line therapy after IO combinations is largely empiric
  - Real world evidence may fill important gaps
- Significant drug development efforts under way
  - Novel immunotherapeutics
  - Targeting oncogenic mediators and pathways

Oncology in the Real World: A Daylong Multitumor Educational Symposium in Partnership with the American Oncology Network

A CME/MOC- and NCPD-Accredited Event

Saturday, October 14, 2023
9:30 AM – 5:00 PM PT

RTP
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We are taking a lunch break!

The program will resume at 1:30 PM PT

Up Next…

Drs Bradley Monk and Kathleen Moore discuss the management of gynecologic cancers

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