Current Approaches and Future Strategies in Oncology: A Multitumor Educational Symposium in Partnership with Florida Cancer Specialists and Research Institute

A CME/MOC- and NCPD-Accredited Event

Saturday, October 7, 2023
7:15 AM – 12:30 PM ET

RTP
RESEARCH
TO PRACTICE

Agenda

Module 1 — ER-Positive Breast Cancer: *Drs Burstein and Jhaveri*

Module 2 — Prostate Cancer: *Drs Morgans and Smith*

Module 3 — Non-Small Cell Lung Cancer: *Drs Riely and Wakelee*

Module 4 — Colorectal and Gastroesophageal Cancers:
Drs Bekaii-Saab and Philip

Module 5 — Chronic Lymphocytic Leukemia: *Drs Chanan-Khan and Kahl*

Non-Small Cell Lung Cancer Faculty

Gregory J Riely, MD, PhD
Attending
Memorial Sloan Kettering Cancer Center
New York, New York

Heather Wakelee, MD, FASCO
Professor of Medicine
Chief, Division of Oncology
Deputy Director, Stanford Cancer Institute
President
International Association for the Study of Lung Cancer (IASLC)
Stanford, California

RTP
RESEARCH TO PRACTICE

Case Presentation: 80-year-old woman receiving azacitidine/venetoclax for AML is diagnosed with metastatic adenocarcinoma of the lung (PD-L1 TPS 95%) and receives pembrolizumab

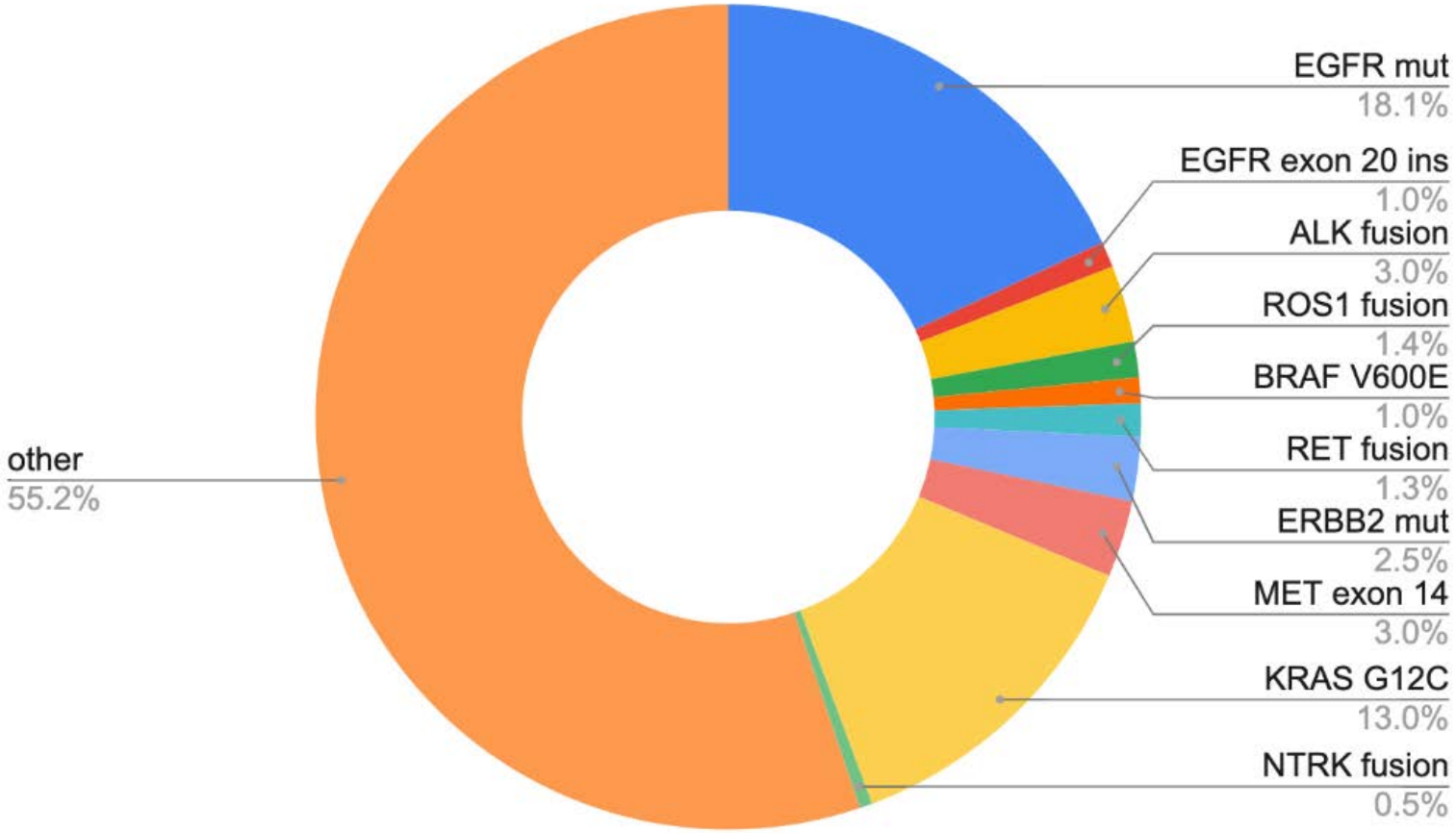
Dr Shachar Peles (Lake Worth, Florida; 10-13-2020)

RTP RESEARCH TO PRACTICE

NSCLC Targeted Therapy

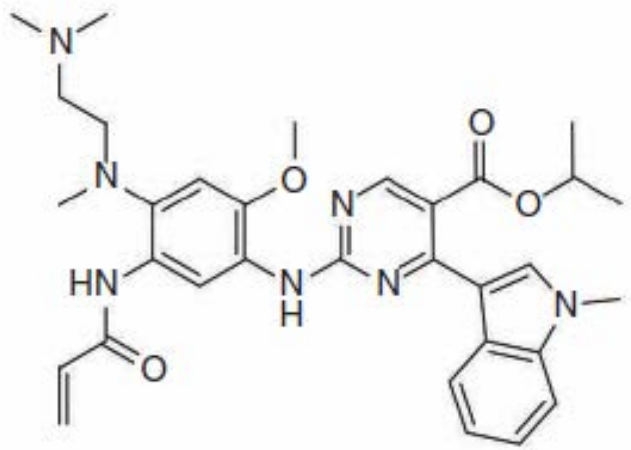
Gregory J Riely, MD, PhD

Lung Cancer Molecular Subtypes with FDA-approved Agents

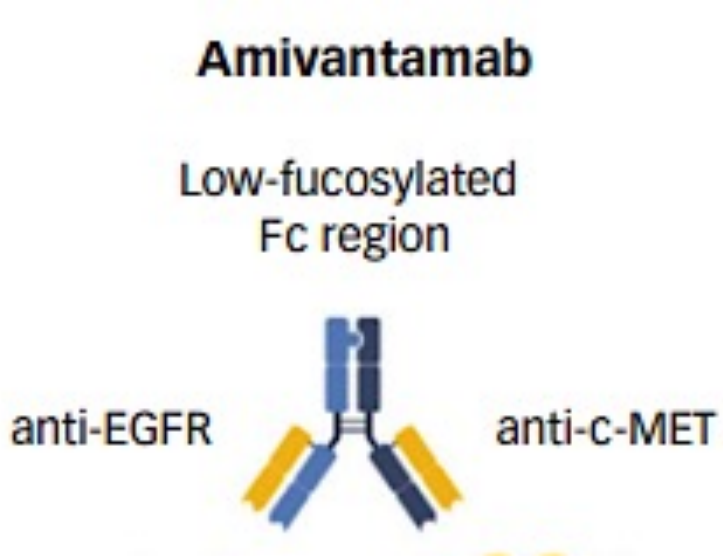


Choudhury NJ, et al. *Clin Cancer Res*. 2023;CCR-23-0580.
Data available at https://genie.cbioportal.org/.

Current Agents for EGFR Exon 20 ins NSCLC



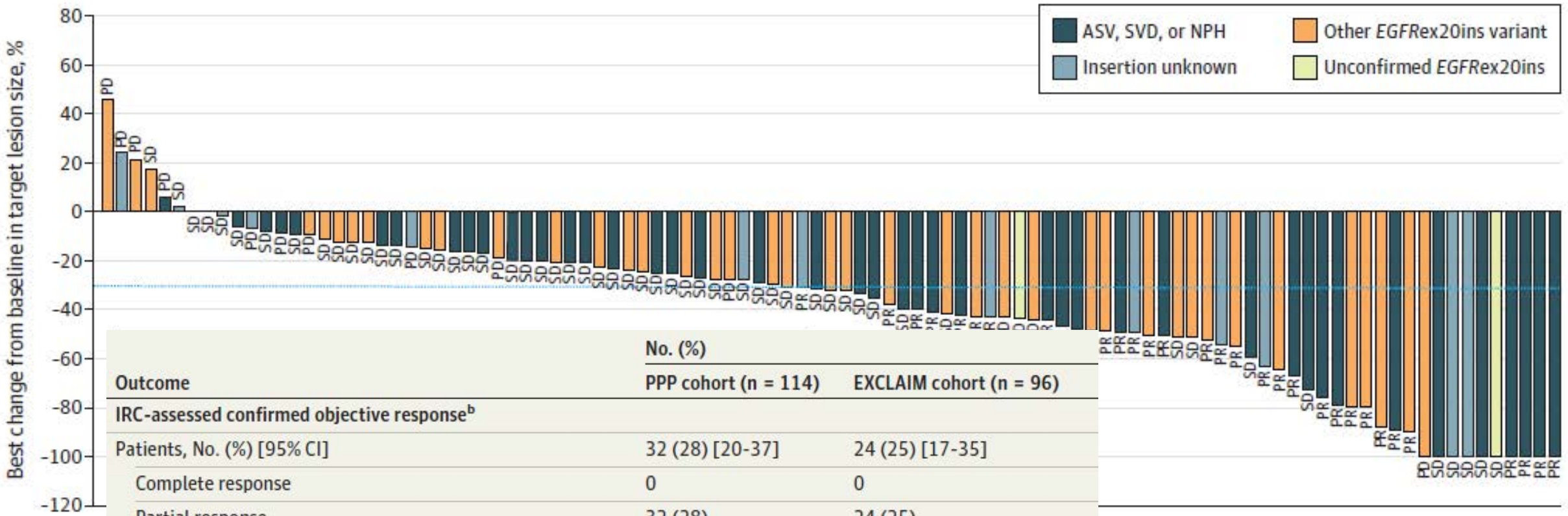
Tyrosine kinase inhibitor
oral



Antibody
IV

Gonzalvez F, et al. *Cancer Discov*. 2021;11(7):1672-1687. Adapted from Guo MZ, et al. Accessed August 31, 2023. https://touchoncology.com/wp-content/uploads/sites/2/2021/08/touchONC_17.1_pp42-47.pdf.

Response to Mobocertinib in Patients with *EGFR* Exon 20 Insertions Treated at 160 mg qd



Outcome	No. (%) PPP cohort (n = 114)	EXCLAIM cohort (n = 96)
IRC-assessed confirmed objective response[b]		
Patients, No. (%) [95% CI]	32 (28) [20-37]	24 (25) [17-35]
Complete response	0	0
Partial response	32 (28)	24 (25)
Stable disease[c]	57 (50)	49 (51)
Not evaluable	12 (11)	10 (10)
Confirmed disease control rate, No. (%) [95% CI][d]	89 (78) [69-85]	73 (76) [66-84]

Zhou J, et al. *JAMA Oncol*. 2021;7(2):263-270.

Mobocertinib in Patients with *EGFR* Exon 20 Insertions Treated at 160 mg qd

Table 3. Safety Overview and Treatment-Related Adverse Events (AEs) of Any Grade Reported in 10% or More or Grade 3 or Higher AEs Reported in 3% or More Among All Patients in the EXCLAIM and PPP Cohorts

	Patients, No. (%)			
	PPP cohort (n = 114)		EXCLAIM cohort (n = 96)	
Adverse event	Any grade	Grade ≥3	Any grade	Grade ≥3
Treatment-related AEs of any grade reported in ≥10% or of grade ≥3 reported in ≥3% of patients				
Diarrhea	104 (91)	24 (21)	89 (93)	15 (16)
Rash	51 (45)	0	43 (45)	0
Paronychia	43 (38)	1 (<1)	37 (39)	1 (1)
Decreased appetite	40 (35)	1 (<1)	31 (32)	1 (1)
Nausea	39 (34)	5 (4)	29 (30)	3 (3)
Dry skin	35 (31)	0	30 (31)	0
Vomiting	34 (30)	3 (3)	25 (26)	1 (1)
Blood creatinine increased	29 (25)	2 (2)	27 (28)	2 (2)
Stomatitis	27 (24)	5 (4)	26 (27)	3 (3)
Pruritus	24 (21)	1 (<1)	19 (20)	1 (1)
Lipase increased	22 (19)	4 (4)	16 (17)	2 (2)
Amylase increased	21 (18)	3 (3)	19 (20)	1 (1)
Dermatitis, acneiform	21 (18)	0	20 (21)	1 (1)
Anemia	20 (18)	1 (<1)	18 (19)	1 (1)
Weight decreased	15 (13)	1 (<1)	13 (14)	0
Alopecia	17 (15)	0	12 (13)	0
Fatigue	16 (14)	3 (3)	12 (13)	2 (2)
Rash, maculopapular	16 (14)	2 (2)	10 (10)	2 (2)
Gastroesophageal reflux disease	14 (12)	0	12 (13)	0
Mouth ulceration	14 (12)	0	14 (15)	0
Electrocardiogram QT prolonged	12 (11)	3 (3)	8 (8)	3 (3)
Rhinorrhea	12 (11)	0	11 (11)	0
Alanine aminotransferase increased	9 (8)	1 (<1)	10 (10)	1 (1)

Common toxicities of EGFR TKI including rash, diarrhea, paronychia

Diarrhea most common/severe adverse event reported, with 91% of people having diarrhea and >20% having grade 3 diarrhea

Zhou J, et al. *JAMA Oncol*. 2021;7(2):263-270.

Voluntary Withdrawal of Indication for Mobocertinib for Metastatic Non-Small Cell Lung Cancer with EGFR Exon 20 Insertion Mutations

Press Release: October 2, 2023

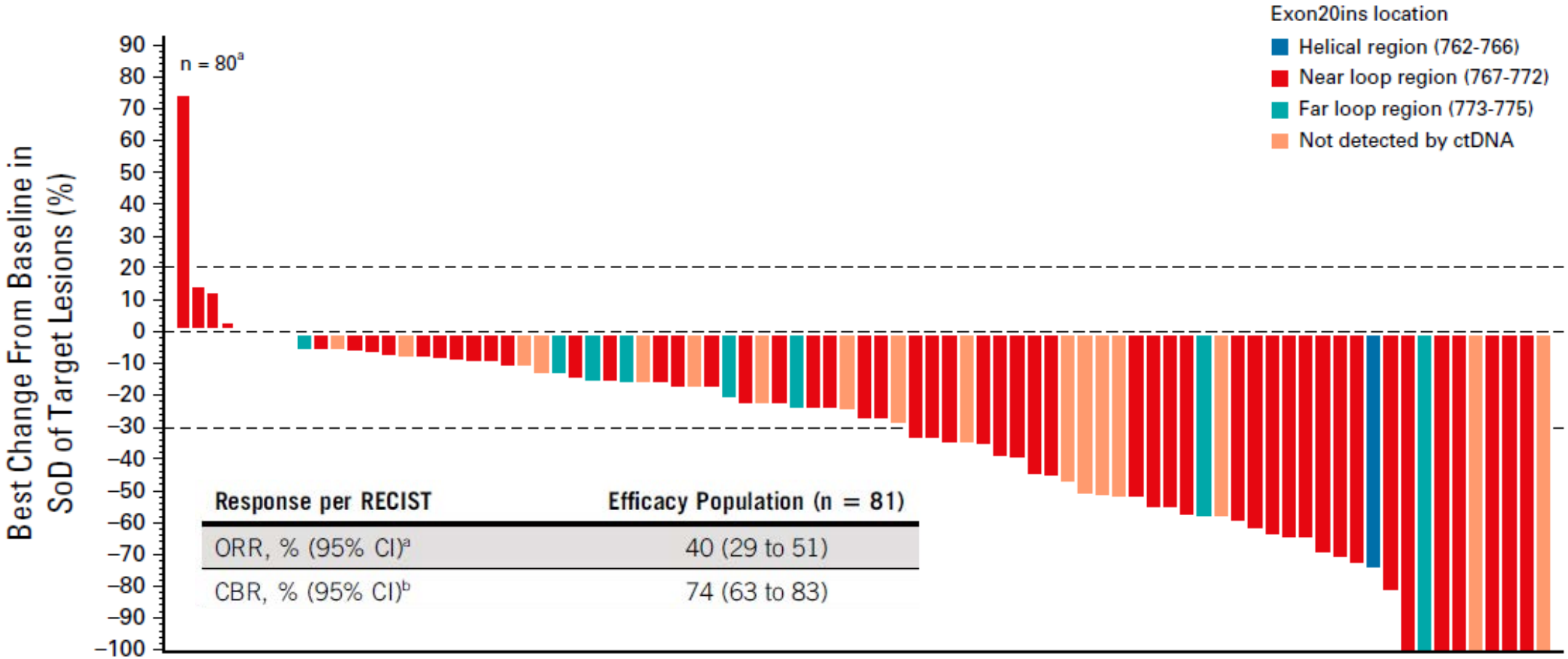
"[The manufacturer of mobocertinib] today announced that, following discussions with the US Food and Drug Administration (FDA), it will be working with the FDA towards a voluntary withdrawal of mobocertinib in the US for adult patients with epidermal growth factor receptor (EGFR) exon20 insertion mutation-positive (insertion+) locally advanced or metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on or after platinum-based chemotherapy. [The company] intends to similarly initiate voluntary withdrawal globally where mobocertinib is approved and is working with regulators in other countries where it is currently available on next steps.

This decision was based on the outcome of the Phase 3 EXCLAIM-2 confirmatory trial, which did not meet its primary endpoint and thus did not fulfill the confirmatory data requirements of the Accelerated Approval granted by the US FDA nor the conditional marketing approvals granted in other countries.

The EXCLAIM-2 trial was a Phase 3, multicenter, open-label study designed to investigate the safety and efficacy of mobocertinib as a monotherapy versus platinum-based chemotherapy in first-line EGFR exon20 insertion+ locally advanced or metastatic NSCLC. No new safety signals were observed in the EXCLAIM-2 trial. Full data from the trial will be presented at an upcoming medical meeting or published in a peer-reviewed journal."

https://www.takeda.com/newsroom/newsreleases/2023/Takeda-Provides-Update-on-EXKIVITY-mobocertinib/

Amivantamab (EGFR – MET bi-specific Ab) in Patients with EGFR Exon 20 Insertion NSCLC



Response per RECIST	Efficacy Population (n = 81)
ORR, % (95% CI)[a]	40 (29 to 51)
CBR, % (95% CI)[b]	74 (63 to 83)

Park K, et al. *J Clin Oncol*. 2021;39(30):3391-3402.

Amivantamab (EGFR – MET bi-specific Ab) in Patients with EGFR Exon 20 Insertion NSCLC

	Safety Population (n = 114), No. (%)				Patients Treated at the RP2D (n = 258), No. (%)			
Most Common AE (≥ 10%)	Total	Grade 1	Grade 2	Grade ≥ 3	Total	Grade 1	Grade 2	Grade ≥ 3
Rash[b]	98 (86)	43 (38)	51 (45)	4 (4)	202 (78)	101 (39)	94 (36)	7 (3)
Infusion-related reaction	75 (66)	9 (8)	63 (55)	3 (3)	167 (65)	21 (8)	140 (54)	6 (2)
Paronychia	51 (45)	28 (25)	22 (19)	1 (1)	104 (40)	50 (19)	51 (20)	3 (1)
Hypoalbuminemia	31 (27)	6 (5)	22 (19)	3 (3)	63 (24)	21 (8)	38 (15)	4 (2)
Constipation	27 (24)	18 (16)	9 (8)	0	58 (23)	36 (14)	22 (9)	0
Nausea	22 (19)	17 (15)	5 (4)	0	55 (21)	40 (16)	14 (5)	1 (0.4)
Dyspnea	22 (19)	12 (11)	8 (7)	2 (2)	52 (20)	28 (11)	13 (5)	11 (4)
Stomatitis	24 (21)	11 (10)	13 (11)	0	50 (19)	33 (13)	17 (7)	0
Peripheral edema	21 (18)	20 (18)	1 (1)	0	50 (19)	43 (17)	5 (2)	2 (1)
Pruritus	19 (17)	11 (10)	8 (7)	0	49 (19)	40 (16)	9 (4)	0
Fatigue	21 (18)	15 (13)	4 (4)	2 (2)	47 (18)	29 (11)	16 (6)	2 (1)
Cough	16 (14)	11 (10)	5 (4)	0	40 (16)	25 (10)	15 (6)	0
Decreased appetite	16 (14)	7 (6)	9 (8)	0	39 (15)	23 (9)	16 (6)	0
Dry skin	18 (16)	18 (16)	0	0	33 (13)	32 (12)	1 (0.4)	0
Increased alanine aminotransferase	17 (15)	15 (13)	1 (1)	1 (1)	30 (12)	22 (9)	5 (2)	3 (1)
Vomiting	12 (11)	10 (9)	2 (2)	0	29 (11)	22 (9)	6 (2)	1 (0.4)
Myalgia	14 (12)	12 (11)	2 (2)	0	28 (11)	23 (9)	5 (2)	0
Dizziness	9 (8)	8 (7)	0	1 (1)	28 (11)	24 (9)	3 (1)	1 (0.4)
Headache	8 (7)	4 (4)	3 (3)	1 (1)	28 (11)	17 (7)	8 (3)	3 (1)
Increased blood alkaline phosphatase	10 (9)	8 (7)	1 (1)	1 (1)	28 (11)	22 (9)	4 (2)	2 (1)
Diarrhea	14 (12)	8 (7)	2 (2)	4 (4)	27 (11)	16 (6)	6 (2)	5 (2)
Back pain	12 (11)	6 (5)	6 (5)	0	26 (10)	13 (5)	11 (4)	2 (1)
Pyrexia	15 (13)	12 (11)	3 (3)	0	26 (10)	21 (8)	5 (2)	0
Hypokalemia	12 (11)	5 (4)	1 (1)	6 (5)	21 (8)	11 (4)	3 (1)	7 (3)

Toxicities common to EGFR inhibitors like rash, paronychia

Infusion related reaction, grade 2 occurs in 55% of patients

Park K, et al. *J Clin Oncol*. 2021;39(30):3391-3402.

Ongoing Trial of Amivantamab in First Line

- Recurrent/Metastatic NSCLC
- EGFR Exon 20 insertion
- **No prior systemic therapy**

N=300

R

carboplatin
pemetrexed

carboplatin
pemetrexed
+
amivantamab

Primary endpoint
PFS by BICR using RECIST v1.1

July 17: Amivantamab-vmjw plus carboplatin and pemetrexed led to a clinically meaningful and statistically significant improvement in progression-free survival

NCT04538664. Accessed August 31, 2023. https://classic.clinicaltrials.gov/ct2/show/NCT04538664.

Ongoing Trial of Mobocertinib in First Line

- Recurrent/Metastatic NSCLC
- EGFR Exon 20 insertion
- **No prior systemic therapy**

N=318

R

mobocertinib

carboplatin or cisplatin + pemetrexed

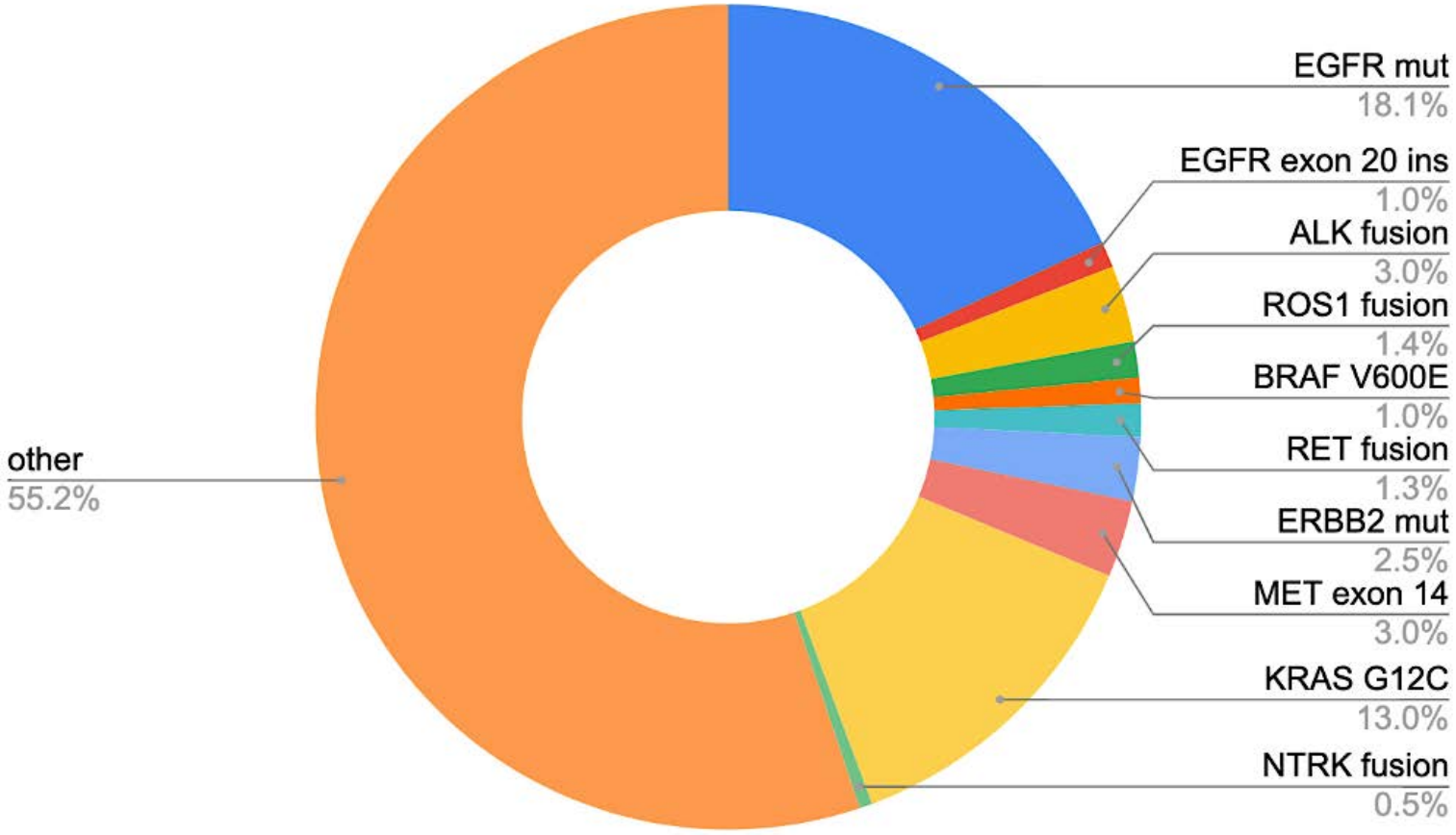
Primary endpoint

- PFS by BICR using RECIST v1.1

July 31: mobocertinib failed to improve progression-free survival

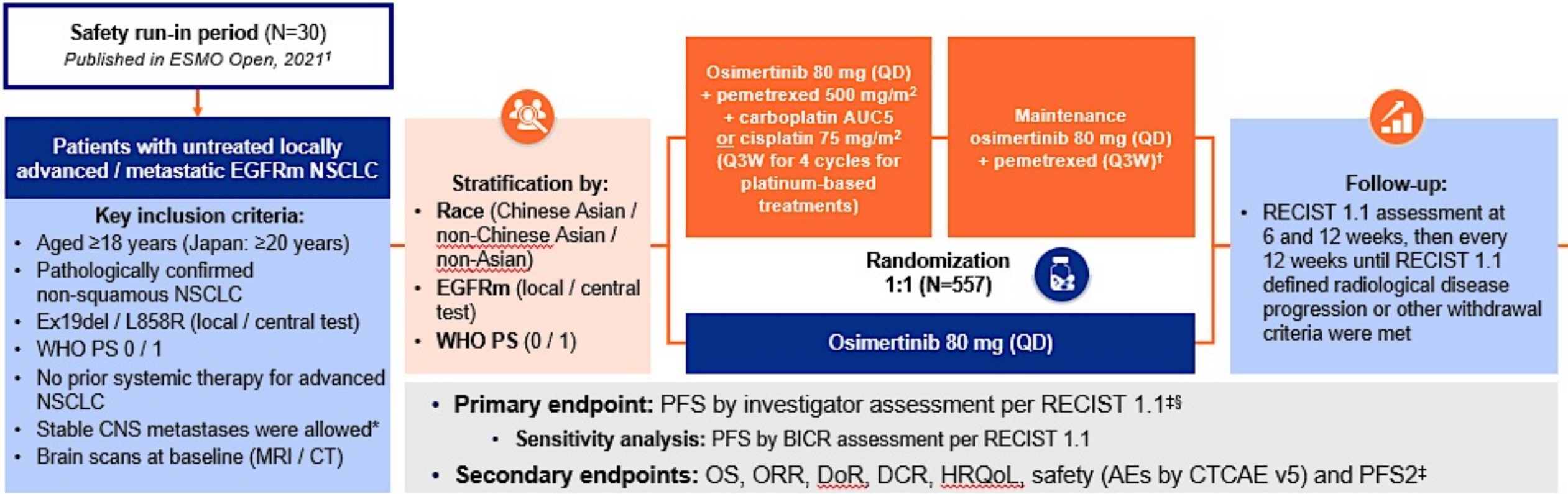
NCT04129502. Accessed August 31, 2023. https://clinicaltrials.gov/study/NCT04129502.

Lung Cancer Molecular Subtypes with FDA-approved Agents



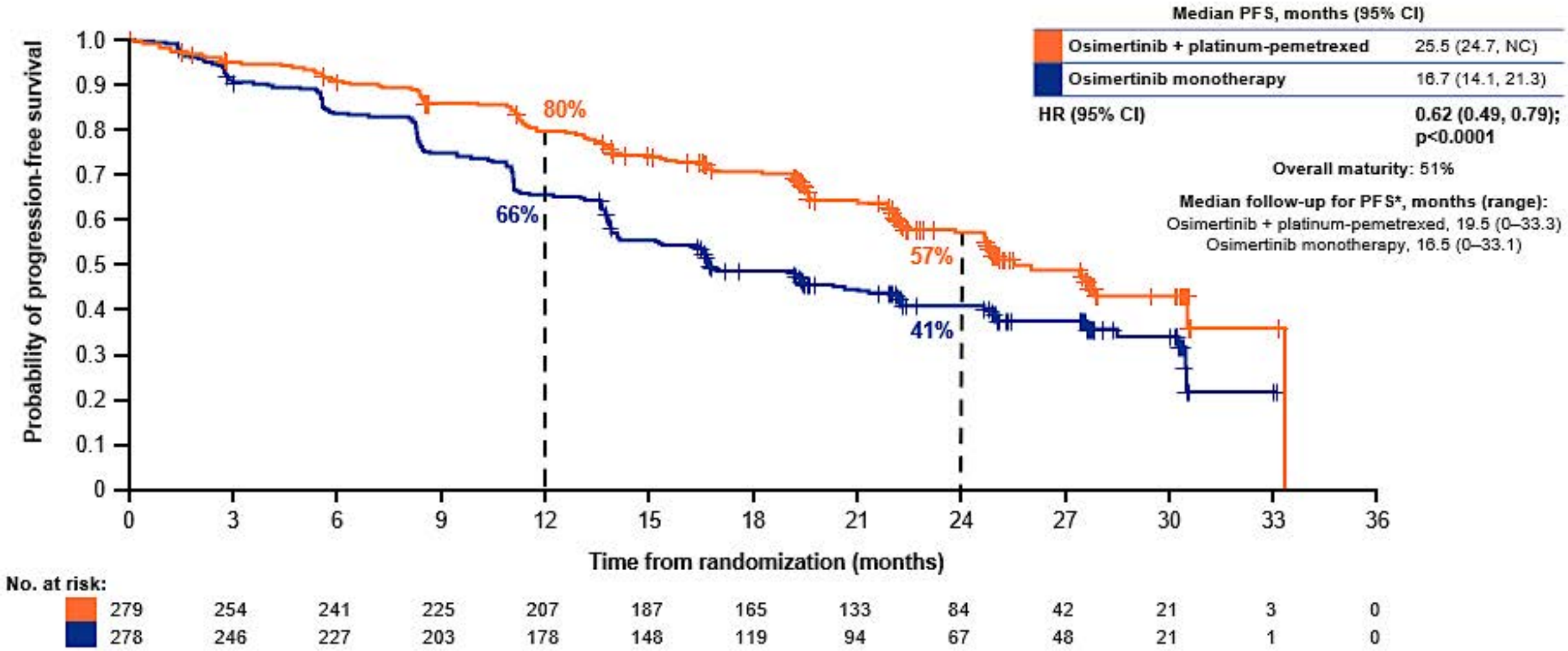
Choudhury NJ, et al. *Clin Cancer Res*. 2023;CCR-23-0580.
Data available at https://genie.cbioportal.org/.

FLAURA2 Phase III study design



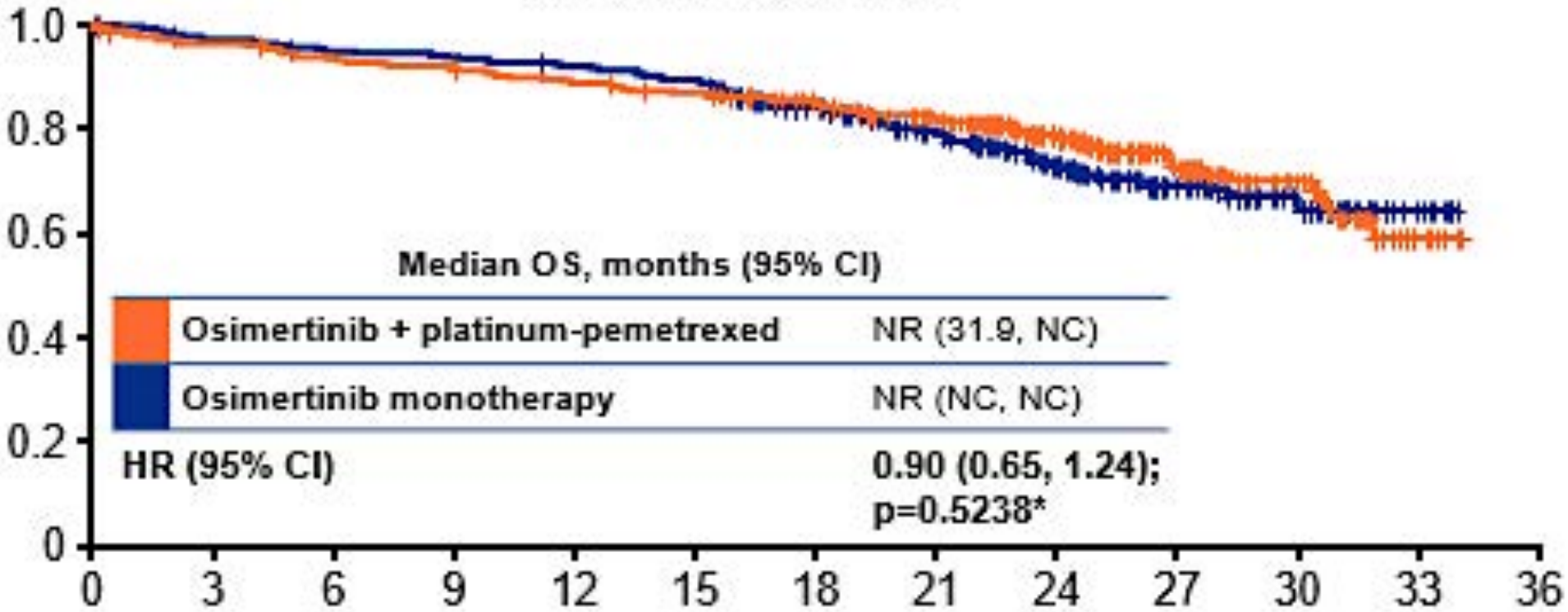
Janne et al WCLC 2023

Does the addition of chemotherapy improve PFS?



Janne et al WCLC 2023

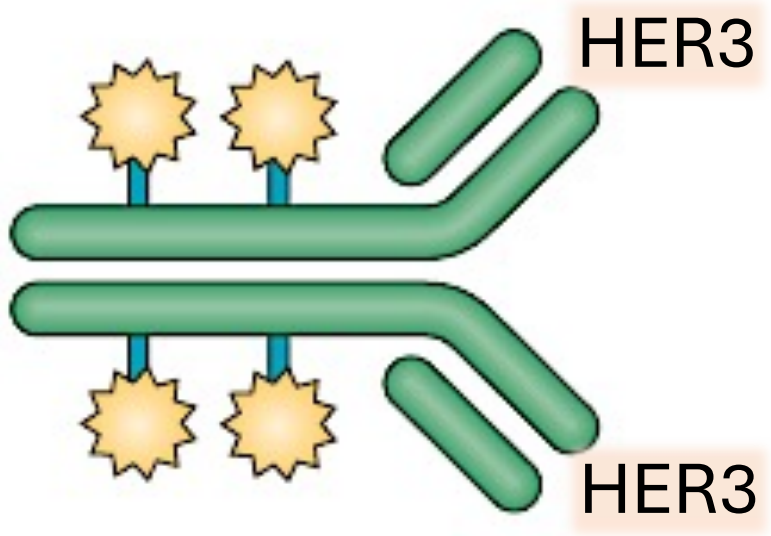
Does the addition of chemotherapy improve OS?



Janne et al WCLC 2023

How do we address resistance to EGFR TKI?

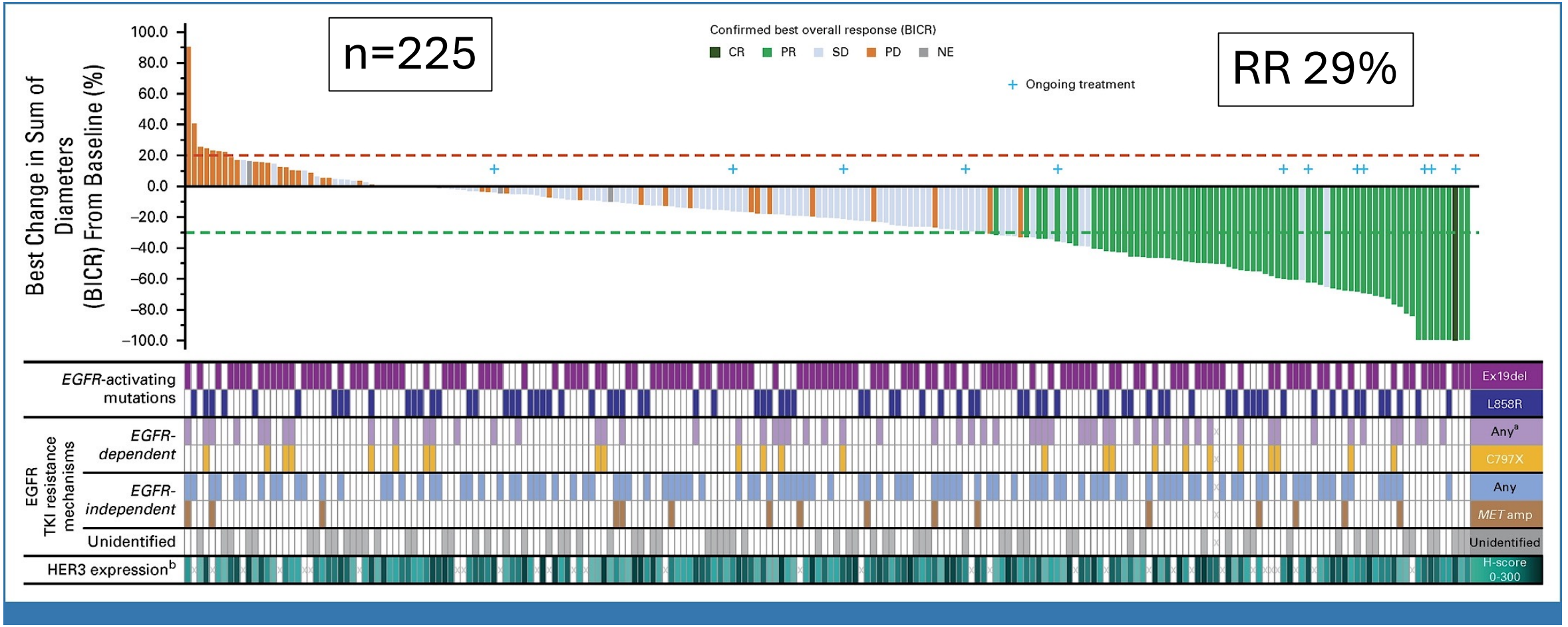
Patritumab Deruxtecan



HER3 targeted Antibody-drug conjugate

Modified from Drago et al, Nat Rev Clin Onc 2021

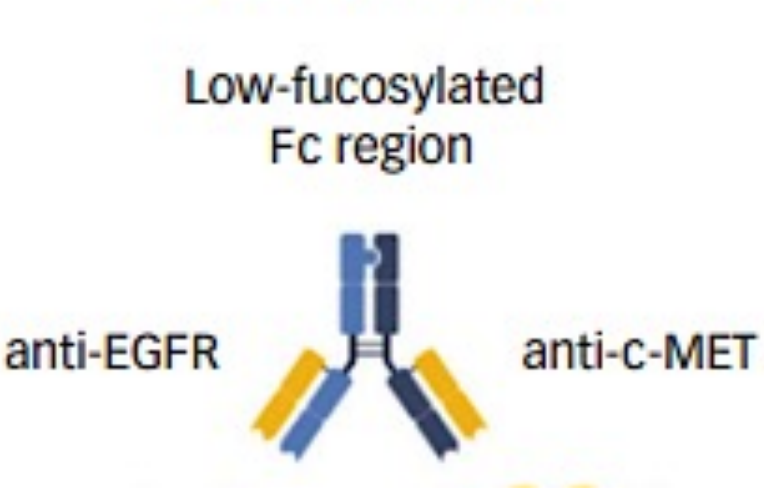
Phase II Trial of Patritumab Deruxtecan (HER3-DXd) in patients with EGFR mut NSCLC after osimertinib



Yu et al, JCO 2023

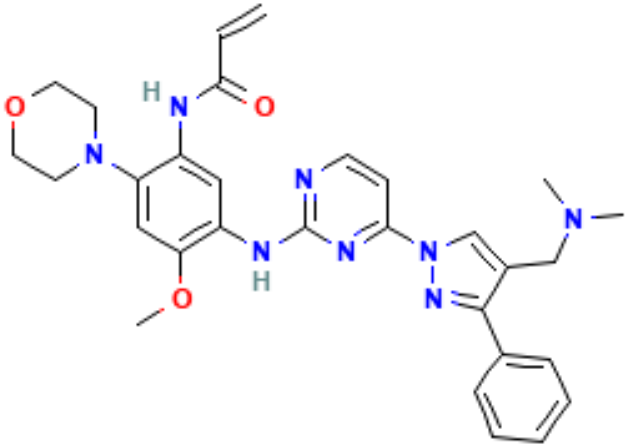
Dual targeting of EGFR

amivantamab



Antibody
IV

lazertinib



3rd gen EGFR TKI
oral

Adapted from: Guo MZ, et al. Touch Oncology; PubChem Compound Summary for CID 121269225, Lazertinib *PubChem*,

Amivantamab + Lazertinib After Osimertinib

Dose Escalation Phase

RP2CD was identified:
Amivantamab 1050 mg (1400 mg if ≥80 kg) IV
plus
Lazertinib 240 mg PO

Dose Expansion Cohorts

Cohort A: *EGFR* ex19del or L858R[b]
Post-osimertinib and platinum-based chemotherapy

Cohort B: *EGFR* ex20ins[b]
Post-standard of care and platinum-based chemotherapy

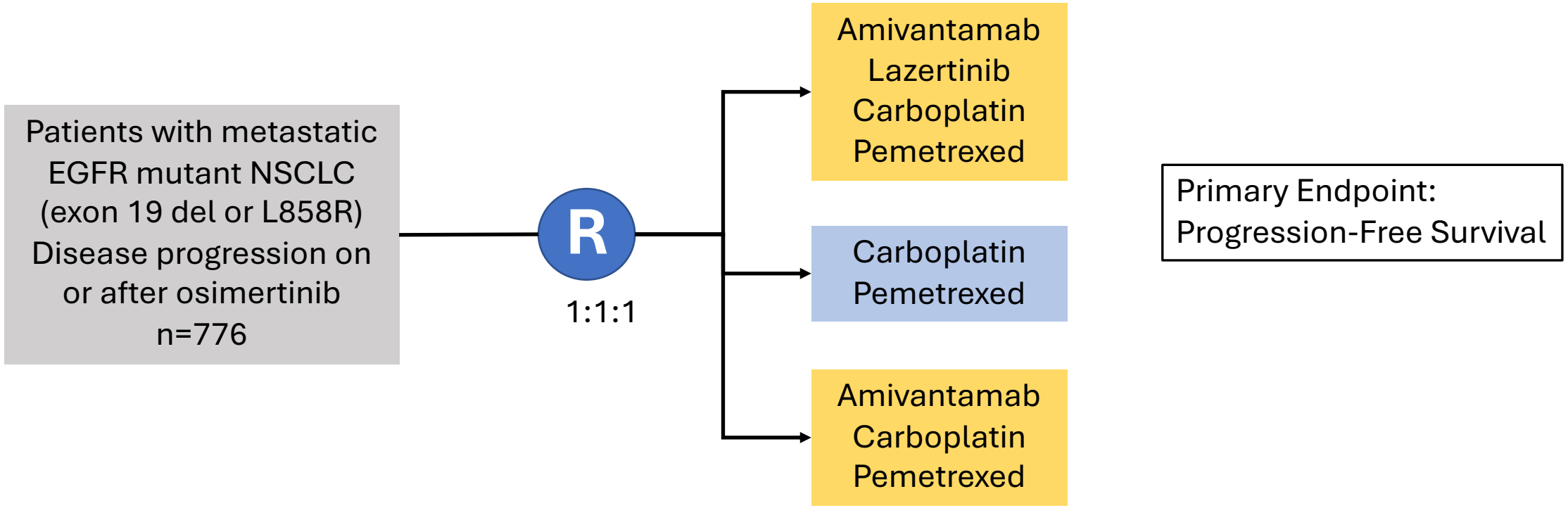
Cohort C: Uncommon *EGFR* mutations[b]
Treatment naïve or post-1st or 2nd generation EGFR TKI

Cohort D: *EGFR* ex19del or L858R
Post-osimertinib, chemotherapy naïve, biomarker validation

	n=101
ORR	30% (95% CI, 21–40)
Median DOR	10.8 months (95% CI, 5.5–NE)
CBR[b]	69% (95% CI, 59–78)
Median PFS	5.7 months (95% CI, 4.0–8.2)
Median OS	Not estimable

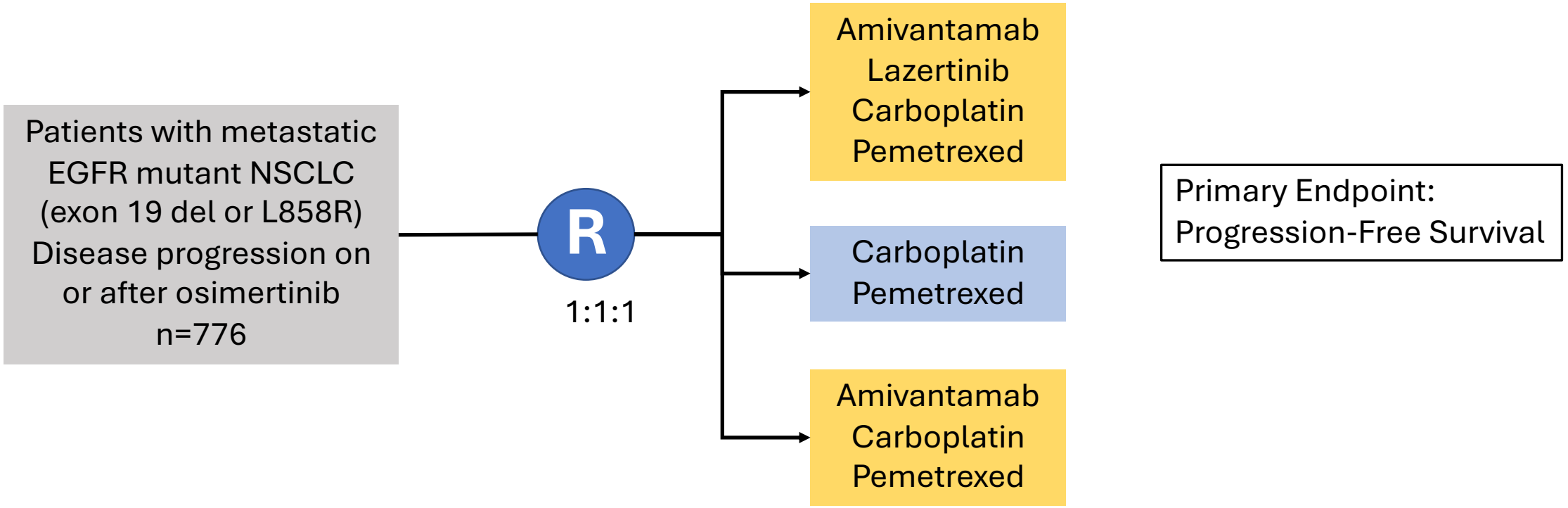
Besse B, et al. Presented at: ASCO 2023.

Can dual targeting of EGFR add to chemotherapy improve outcomes <u>After</u> Osimertinib?



https://classic.clinicaltrials.gov/ct2/show/NCT04988295

Can dual-targeting of EGFR add to chemotherapy improve outcomes After Osimertinib?



September 6:
Announced as positive for both experimental arms

https://classic.clinicaltrials.gov/ct2/show/NCT04988295

Phase III MARIPOSA-2 Trial Meets Dual Primary Endpoint of Progression-Free Survival with Amivantamab with or without Lazertinib for Patients with Metastatic NSCLC with EGFR Mutations After Disease Progression on Osimertinib

Press Release: September 6, 2023

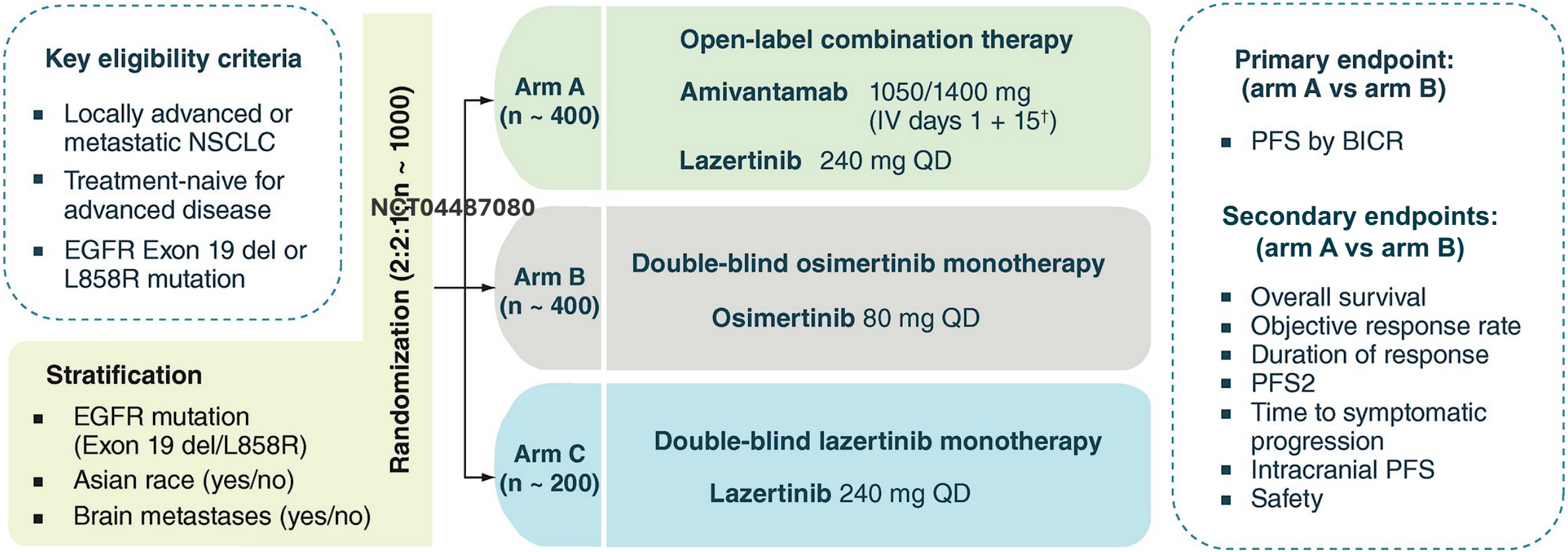
RARITAN, NJ – "[The manufacturer] today announced positive topline results from the three-arm Phase 3 MARIPOSA-2 study evaluating amivantamab-vmjw, a bispecific antibody targeting epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition (MET), given with and without lazertinib, an oral, third-generation EGFR tyrosine kinase inhibitor (TKI), combined with chemotherapy (carboplatin and pemetrexed) versus chemotherapy alone. MARIPOSA-2 enrolled patients with locally advanced or metastatic EGFR exon 19 deletions (ex19del) or L858R substitution NSCLC after disease progression on or after osimertinib. The study met its dual primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in PFS versus chemotherapy alone in both experimental treatment arms. No new safety signals were found for the addition of amivantamab-vmjw to chemotherapy. [The manufacturer] plans to submit these results for presentation at upcoming scientific congresses, including details on secondary endpoints such as overall survival (OS), objective response, duration of response (DoR) and intracranial PFS.

'MARIPOSA-2 provides the first Phase 3 study data of amivantamab-vmjw-based regimens in the broader EGFR-mutated non-small cell lung cancer population,' said Peter Lebowitz, MD, PhD, Global Therapeutic Area Head, Oncology, [Manufacturer]. 'The study builds on the significant innovation of amivantamab-vmjw, a first-in-class bispecific antibody targeting two major oncogenic driver pathways, with clinically meaningful results that may change the treatment paradigm.'"

https://www.prnewswire.com/news-releases/phase-3-mariposa-2-study-meets-dual-primary-endpoint-resulting-in-statistically-significant-and-clinically-meaningful-improvement-in-progression-free-survival-for-rybrevant-amivantamab-vmjw-plus-chemotherapy-with-and-without-la-301919084.html

RTP RESEARCH TO PRACTICE

Can Dual EGFR Blockade + MET Inhibition Delay Resistance as Initial Therapy for Patients with EGFR-mutant NSCLC?



Cho BC, et al. Accessed August 31, 2023. https://www.futuremedicine.com/doi/abs/10.2217/fon-2021-0923

NCT04487080. https://classic.clinicaltrials.gov/ct2/show/NCT04487080.

Phase III MARIPOSA Trial Meets Primary Endpoint of Progression-Free Survival with Amivantamab/Lazertinib versus Osimertinib for Patients with Locally Advanced or Metastatic NSCLC with EGFR Mutations

Press Release: September 28, 2023

"Positive topline results [were announced] from the Phase 3 MARIPOSA study evaluating amivantamab-vmjw, a bispecific antibody targeting epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition (MET), in combination with lazertinib, an oral third-generation EGFR tyrosine kinase inhibitor (TKI), versus osimertinib as first-line treatment in patients with locally advanced or metastatic EGFR-mutated non-small cell lung cancer (NSCLC).

The pivotal Phase 3 MARIPOSA study met its primary endpoint with a statistically significant and clinically meaningful improvement in progression-free survival (PFS) in patients receiving amivantamab-vmjw plus lazertinib compared to osimertinib. The combination of amivantamab-vmjw and lazertinib demonstrated a safety profile consistent with previously reported data on the combination. A planned interim overall survival (OS) analysis showed a trend favoring the combination of amivantamab-vmjw and lazertinib compared to osimertinib. Patients in the study will be followed for subsequent OS analyses, which will determine the statistical and clinical significance of OS."

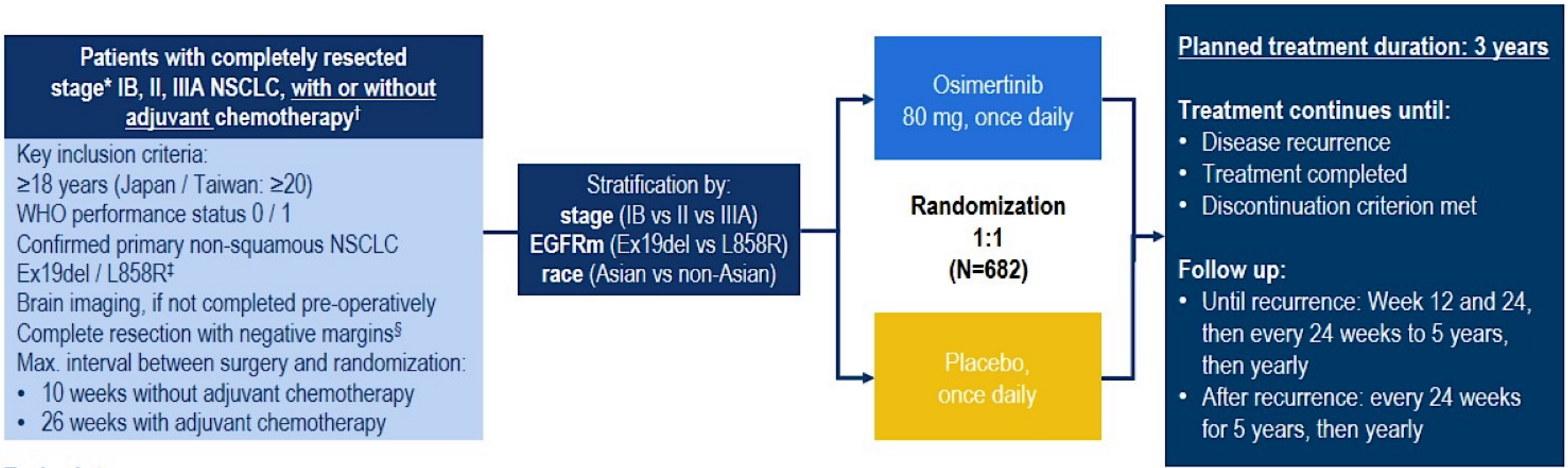
These results, including additional details on select secondary endpoints, will be submitted for presentation at an upcoming scientific congress.

https://www.janssen.com/landmark-phase-3-mariposa-study-meets-primary-endpoint-resulting-statistically-significant

RTP RESEARCH TO PRACTICE

How do we target EGFR in the early stage setting?

ADAURA Phase III double-blind study design



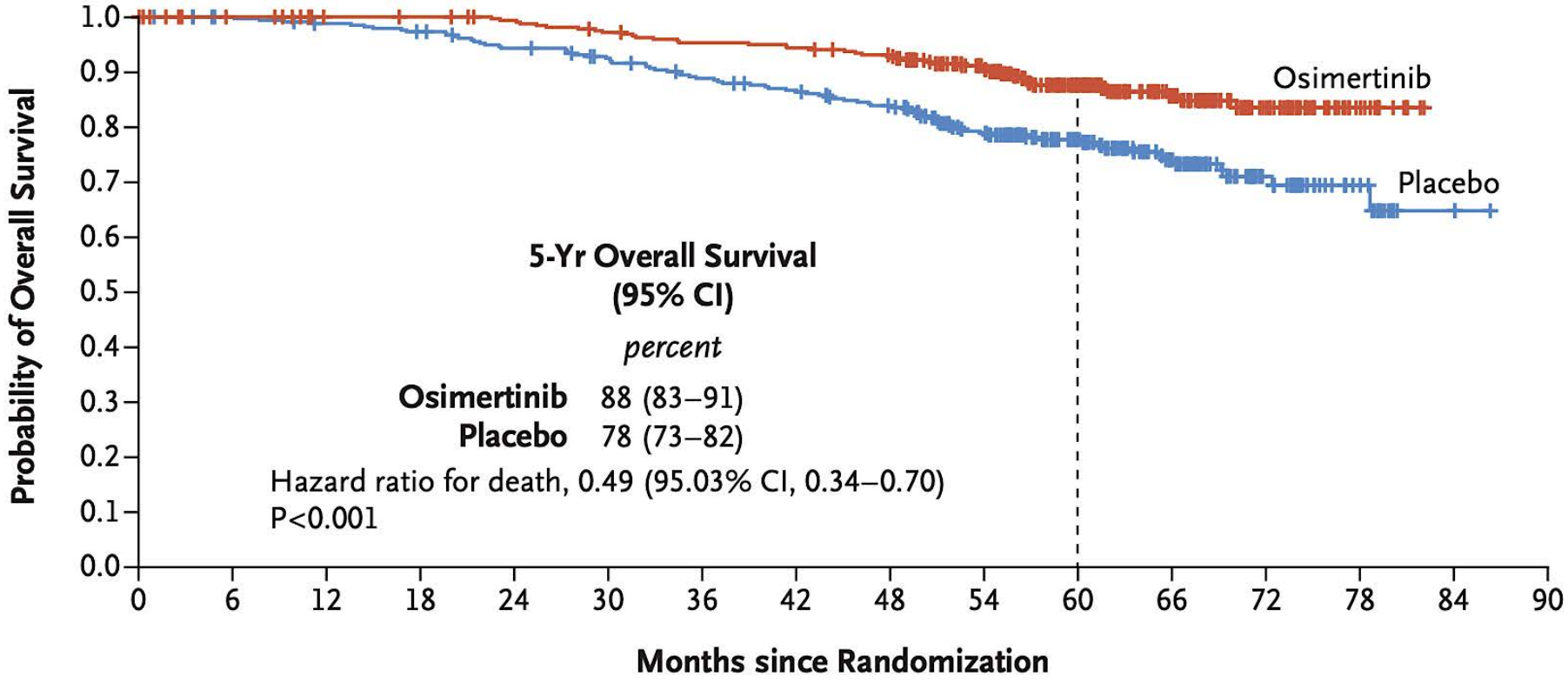
Endpoints

- **Primary**: DFS, by investigator assessment, in stage II/IIIA patients; designed for superiority under the assumed DFS HR of 0.70
- **Secondary**: DFS in the overall population¶, DFS at 2, 3, 4, and 5 years, OS, safety, health-related quality of life

Tsuboi M, et al. NEJM 2023

Three Years of Osimertinib Improves Survival

Patients with Stage IB to IIIA Disease

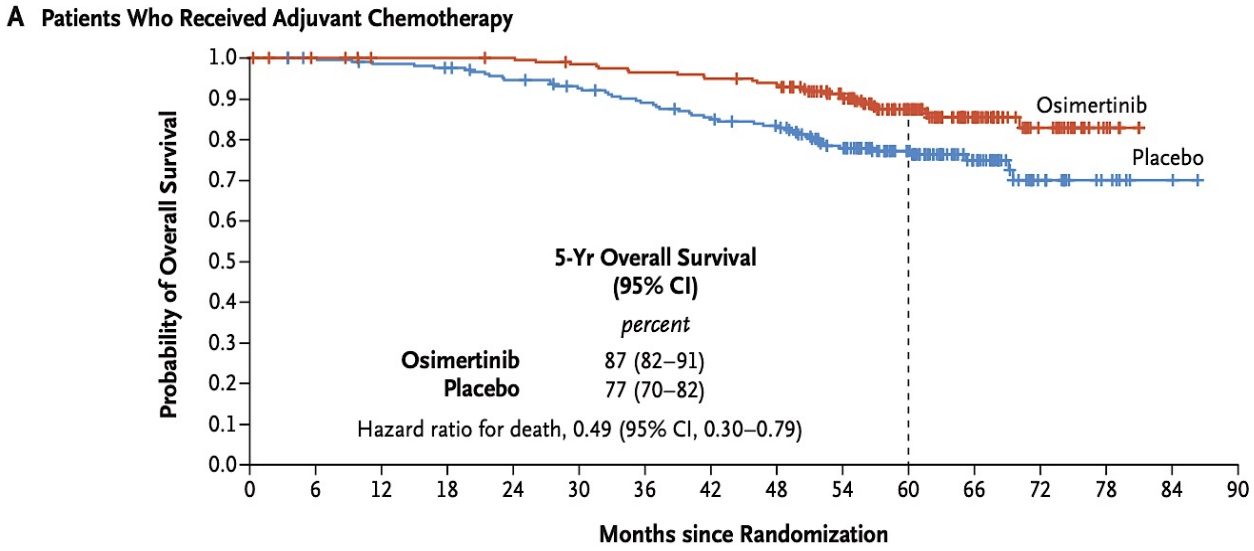


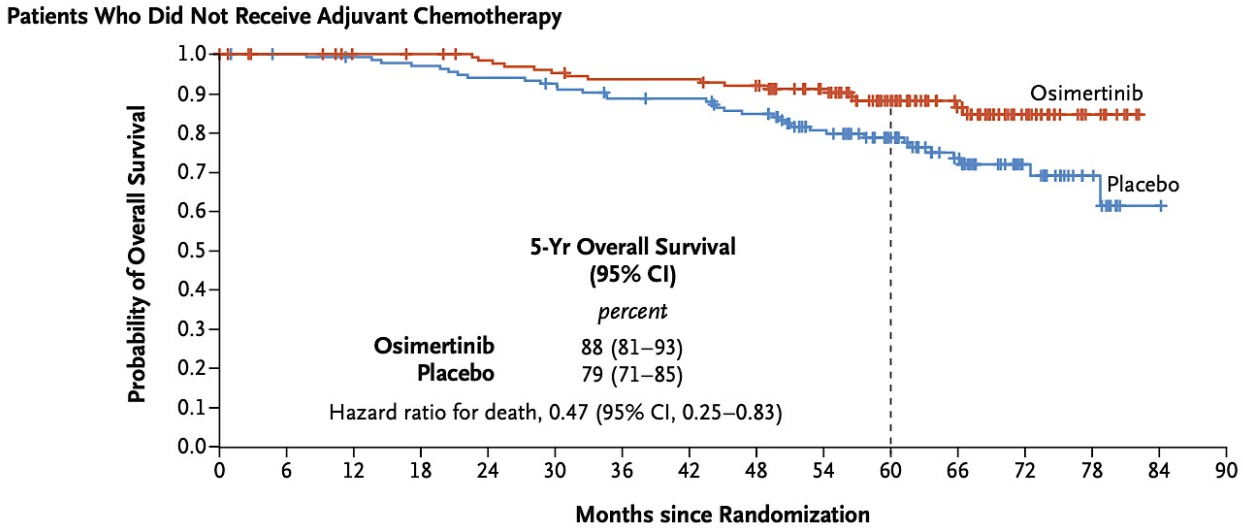
No. at Risk

Osimertinib	339	332	325	324	319	311	304	301	294	252	176	108	50	15	0	
Placebo	343	338	332	326	314	304	290	281	267	223	164	97	44	17	3	0

Tsuboi M, et al. Accessed August 31, 2023. https://www.nejm.org/doi/full/10.1056/NEJMoa2304594.

Do These Patients Still Need Chemo?





But, this is a mix of stages, so the “no chemotherapy” group, had more patients with Stage Ib

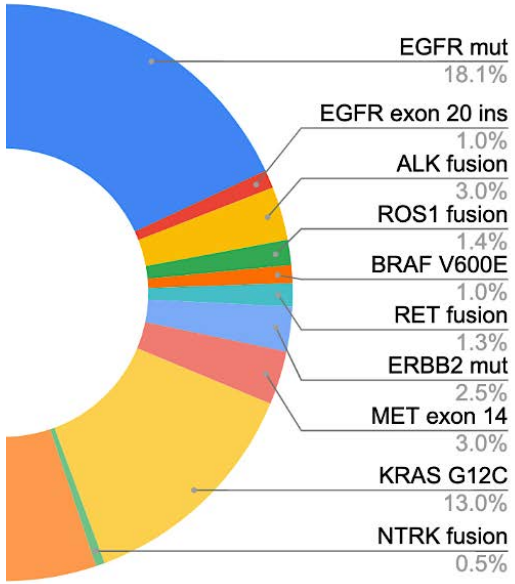
Tsuboi M, et al. Accessed August 31, 2023. https://www.nejm.org/doi/full/10.1056/NEJMoa2304594.

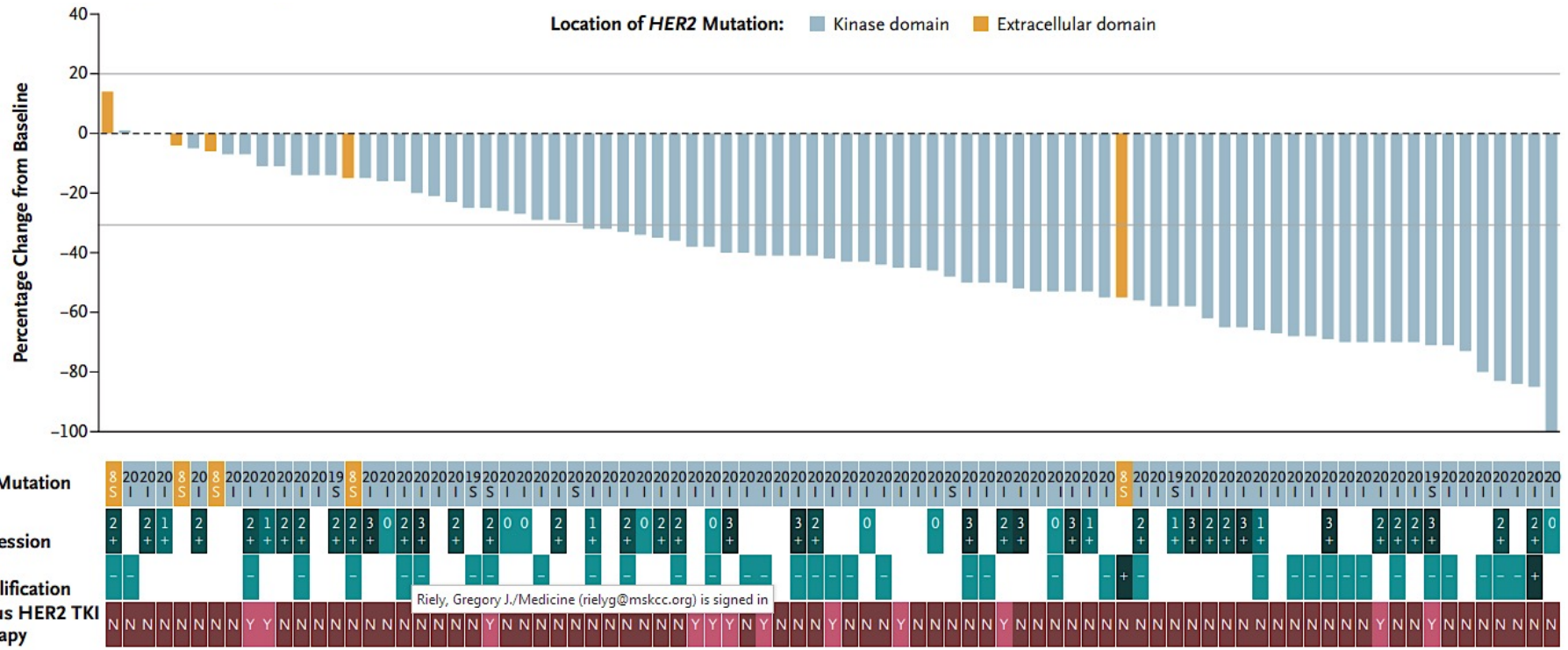
Among Patients with Stage II-III NSCLC

Treatment	5 year OS
No Chemotherapy/placebo	66%
Chemotherapy/placebo	75%
No Chemotherapy/ 3 yrs osimertinib	80%
Chemotherapy/ 3 yrs osimertinib	87%

Tsuboi M, et al. Accessed August 31, 2023. https://www.nejm.org/doi/full/10.1056/NEJMoa2304594.

Trastuzumab Deruxtecan in Patients with Her2 Mutated NSCLC

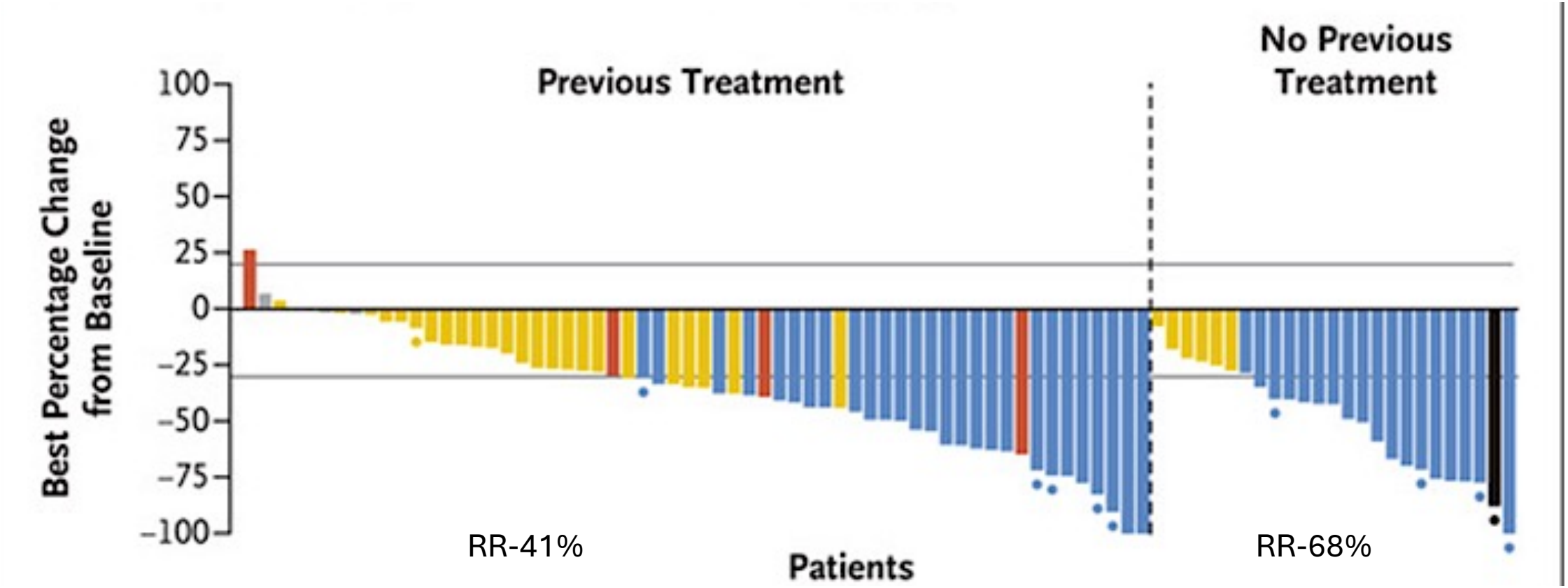




Response Rate -50%
Median PFS – 8 mo
Median OS – 18 mo

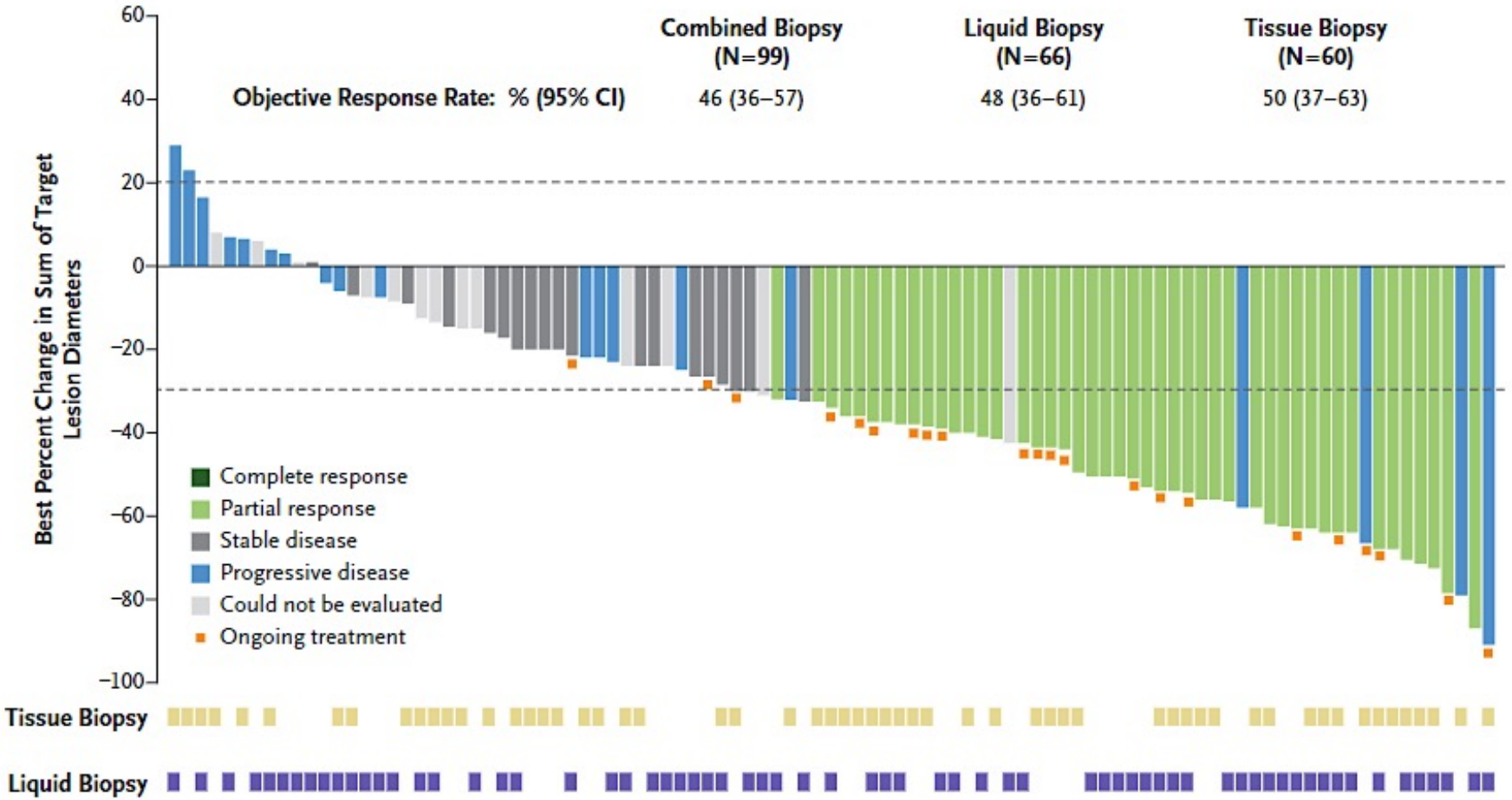
Li et al, NEJM 2022

MET exon 14 NSCLC - capmatinib



Wolf et al, NEJM 2020

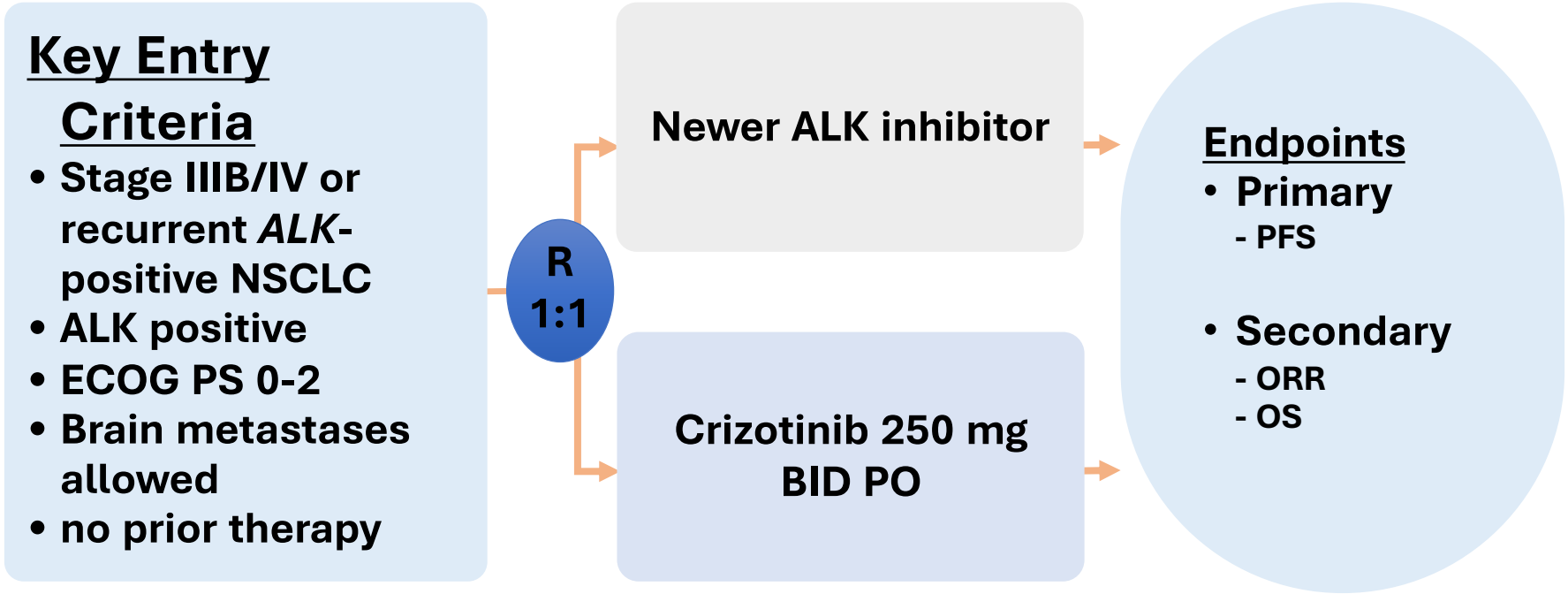
MET exon 14 NSCLC - tepotinib



Response Rate
1st line – 44%
2nd line – 48%

Paik et al, NEJM 2020

Evaluating Newer ALK inhibitors in ALK+ NSCLC

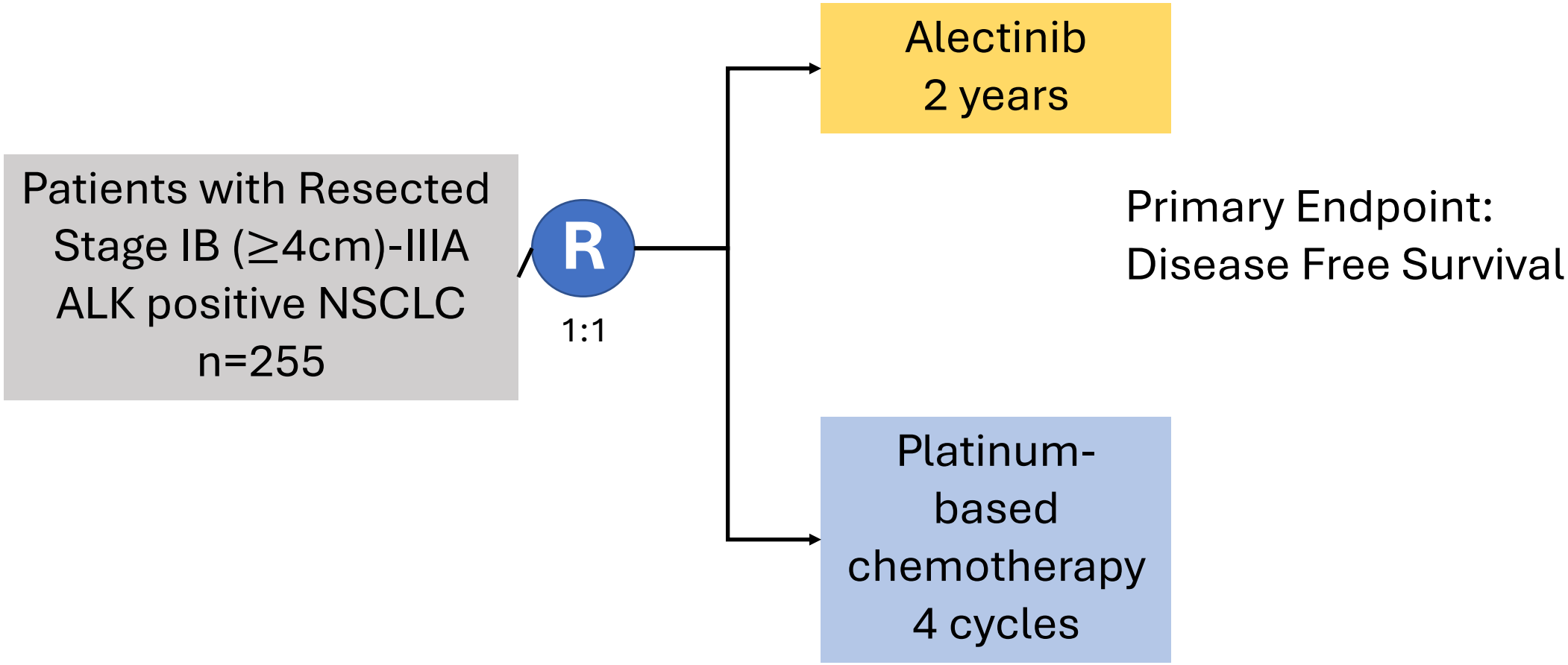


Comparing newer ALK inhibitors in ALK+ NSCLC

	RR (vs crizotinib)	12 month PFS (vs crizotinib)	PFS HR
Alectinib	83% vs 76%*	68% vs 49%	0.47
Brigatinib	74% vs 62%	67% vs 43%	0.43
Lorlatinib	76% vs 58%	78% vs 39%	0.28

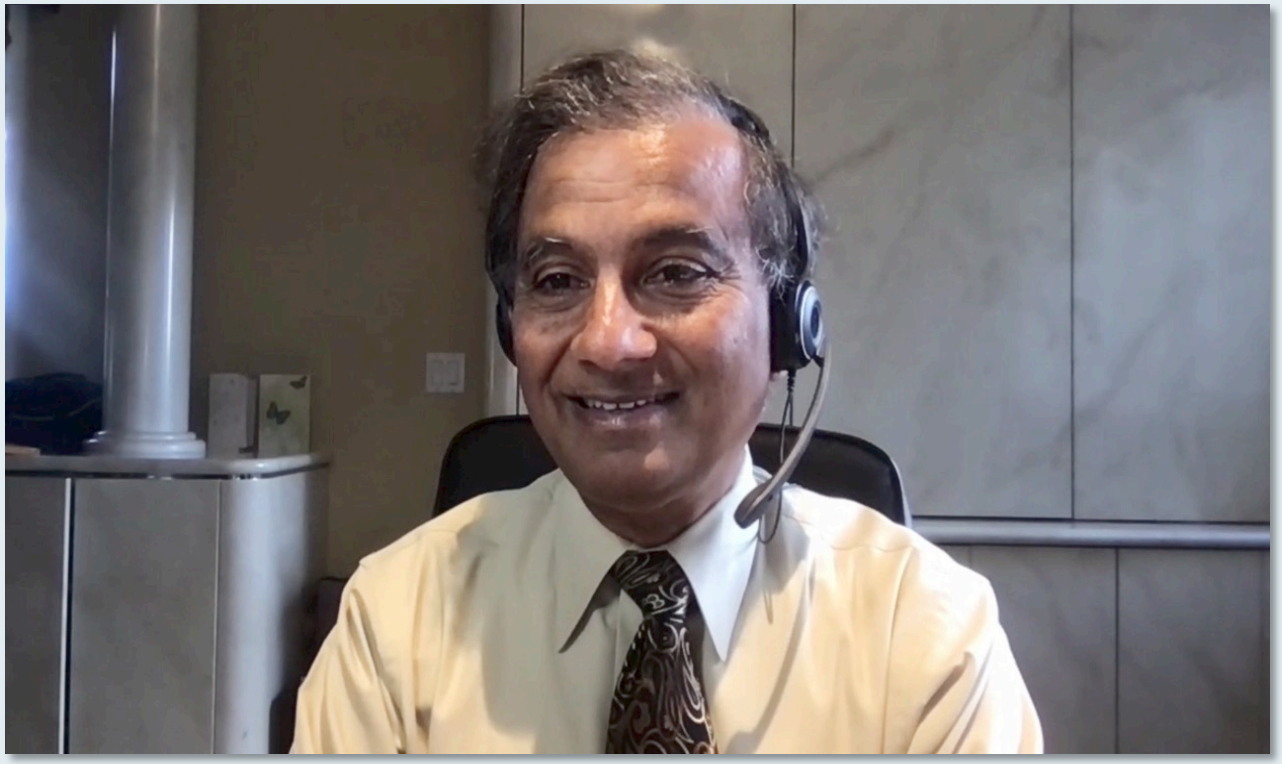
*confirmed objective response rate not reported

Exploring ALK inhibition in early stage disease – the ALINA Trial



Clinical Questions and Cases

Case Presentation: 84-year-old man with PMH of atrial fibrillation and with an LVEF 30% is diagnosed with adenocarcinoma of the lung and an EGFR exon 19 deletion



Dr Sunil Gandhi (Lecanto, Florida; 10-12-2021)

RTP
RESEARCH
TO PRACTICE

Case Presentation: 86-year-old man and former smoker with metastatic adenocarcinoma of the lung and PD-L1 TPS 90% receives pembrolizumab x 1 cycle when NGS reveals an EGFR exon 19 deletion

Dr Susmitha Apuri (Inverness, Florida; 5-11-2021)

RTP RESEARCH TO PRACTICE

Non-Small Cell Lung Cancer
EGFR-Mutant Disease

- **Adjuvant/neoadjuvant targeted therapy: ADAURA (ALINA)**

- **Metastatic EGFR-mutant disease:**
  - **First-line therapy (FLAURA2; amivantamab/lazertinib)**
  - **Later-line therapy: Amivantamab/chemotherapy +/- lazertinib; patritumab deruxtecan**
  - **Metastatic disease with exon 20 insertion mutations (amivantamab, mobocertinib)**

Discussion Question

What was the approximate relative reduction in the risk of death with adjuvant osimertinib in the Phase III ADAURA trial?

Discussion Question

Regulatory and reimbursement issues aside, in general, what adjuvant treatment would you recommend for an otherwise healthy 65-year-old patient with a 4-cm, node-negative nonsquamous NSCLC with an EGFR exon 19 deletion and a PD-L1 TPS of 50%?

Discussion Question

How would you indirectly compare the efficacy of osimertinib to that of amivantamab/lazertinib when administered as first-line therapy for metastatic NSCLC with an EGFR mutation?

Discussion Question

Which adverse events are most frequently observed with amivantamab?

RTP RESEARCH TO PRACTICE

Discussion Question

Which targeted therapies have demonstrated clinical activity in patients who experienced disease progression on osimertinib?

Discussion Question

Patritumab deruxtecan has demonstrated an objective response rate of nearly 30% among patients with EGFR-mutated NSCLC in which clinical scenario?

Discussion Question

What is your preferred initial targeted therapy for a 65-year-old asymptomatic patient with metastatic nonsquamous NSCLC and an EGFR exon 20 insertion mutation?

Discussion Question

Regulatory and reimbursement issues aside, in which line of therapy would you generally offer targeted treatment to a patient with metastatic NSCLC and an EGFR exon 20 insertion mutation?

Case Presentation: 76-year-old woman with PD-L1-low metastatic adenocarcinoma of the lung and a MET exon 14 skipping mutation

Dr Maen Hussein (The Villages, Florida; 9-28-2020)

RTP
RESEARCH
TO PRACTICE

Non-Small Cell Lung Cancer
HER2, MET Exon 14 and BRAF Mutations

- **HER2 (T-DXd)**
  - **Mutant versus overexpressing**
  - **Efficacy and sequencing**
  - **Tolerability (ILD prevention and management)**
- **MET exon 14 skipping mutations**

Discussion Question

Trastuzumab deruxtecan is approved for patients with metastatic NSCLC and which genomic alteration?

Discussion Question

Regulatory and reimbursement issues aside, in which line of therapy would you generally offer targeted treatment to a patient with metastatic nonsquamous NSCLC (PD-L1 TPS 50%) and a HER2 mutation?

Discussion Question

Regulatory and reimbursement issues aside, what would be your preferred first-line therapy for a 65-year-old asymptomatic patient with metastatic nonsquamous NSCLC (PD-L1 TPS 50%) and a MET exon 14 skipping mutation?

Stanford MEDICINE

Non-Small Cell Lung Cancer – Immunotherapeutic and Other Novel Strategies

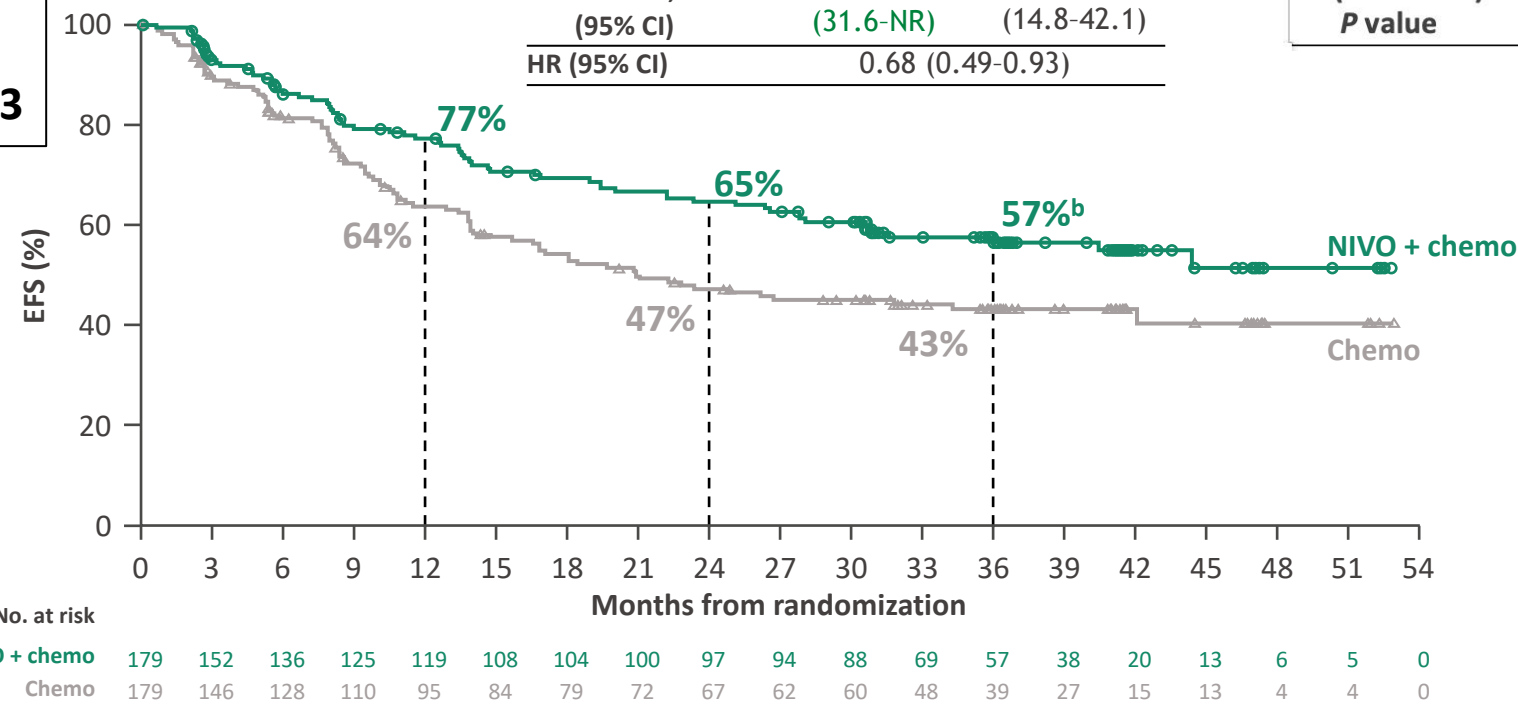
Heather Wakelee, MD, FASCO
Deputy Director, Stanford Cancer Institute
Professor of Medicine–Oncology
Chief, Division of Oncology

Early Stage NSCLC and IO

CM816- EFS with neoadjuvant NIVO + chemo vs chemo: 3-year update[a]

Stage IB- Stage IIIA (63%)
50% PD-L1 >1%
No EGFR/ALK
IO + Chemo VS Chemo x 3

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median EFS, mo (95% CI)	NR (31.6-NR)	21.1 (14.8-42.1)
HR (95% CI)	0.68 (0.49-0.93)	



	NIVO + chemo (n = 179)	Chemo (n = 179)
Median OS, mo (95% CI)	NR (NR–NR)	NR (46.8–NR)
HR (99.34% CI)	0.62 (0.36–1.05)	
P value	0.0124[a]	

Minimum/median follow-up: 32.9/41.4 months.

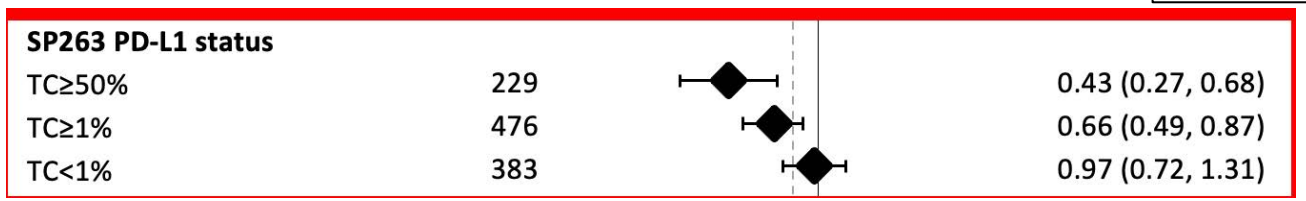
[a]Exploratory analysis. Time from randomization to any disease progression precluding surgery, disease progression/recurrence after surgery, progression in patients without surgery, or death due to any cause per BICR. Patients who received subsequent therapy were censored at the last evaluable tumor assessment on or prior to the date of subsequent therapy. [b,c]95% CIs for 3-year EFS rates: [b]48–64; [c]35–51.

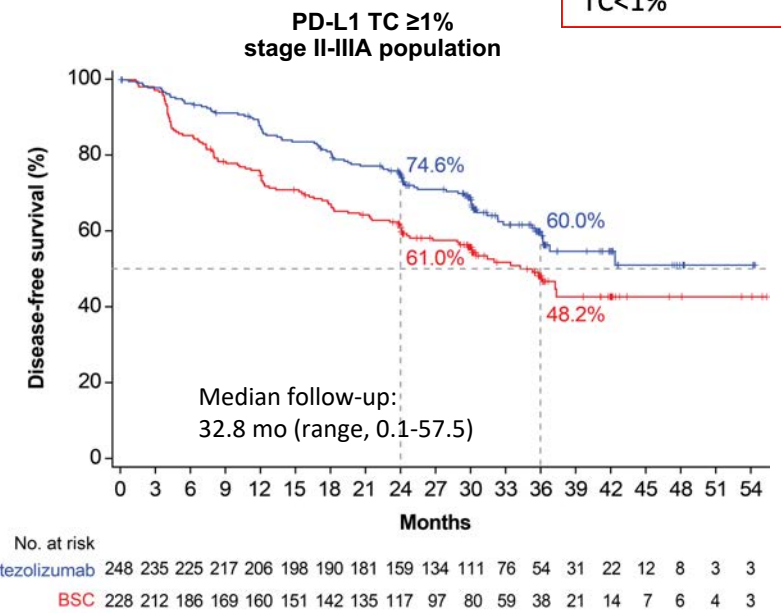
PD-L1 expression level				
<1%	155	25.1 (14.6–NR)	18.4 (13.9–26.2)	0.85 (0.54–1.32)
≥1%	178	NR (NR–NR)	21.1 (11.5–NR)	0.41 (0.24–0.70)
1–49%	98	NR (27.8–NR)	26.7 (11.5–NR)	0.58 (0.30–1.12)
≥50%	80	NR (NR–NR)	19.6 (8.2–NR)	0.24 (0.10–0.61)

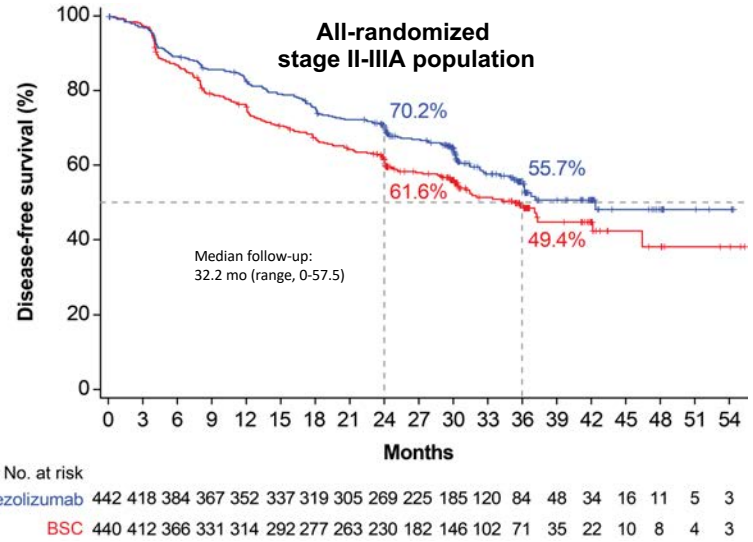
Forde, Spicer, Girard, et al. ELCC2023

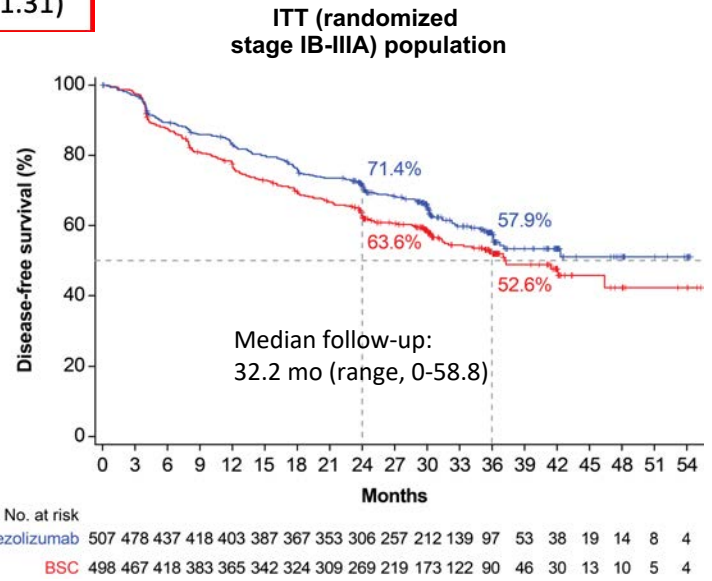
IMpower010: DFS in the PD-L1 TC ≥1%[a] stage II-IIIA, all-randomized stage II-IIIA and ITT pop (primary endpoint)

12% stage 1B, ~50% stage II, 40% stage IIIA
55% PD-L1+; ~15% known driver mutation









	Atezolizumab (n=248)	BSC (n=228)
Median DFS (95% CI), mo	NE (36.1, NE)	35.3 (29.0, NE)
Stratified HR (95% CI)	0.66 (0.50, 0.88)	
P value[b]	0.004[c]	

	Atezolizumab (n=442)	BSC (n=440)
Median DFS (95% CI), mo	42.3 (36.0, NE)	35.3 (30.4, 46.4)
Stratified HR (95% CI)	0.79 (0.64, 0.96)	
P value[b]	0.02[c]	

	Atezolizumab (n=507)	BSC (n=498)
Median DFS (95% CI), mo	NE (36.1, NE)	37.2 (31.6, NE)
Stratified HR (95% CI)	0.81 (0.67, 0.99)	
P value[b]	0.04[d]	

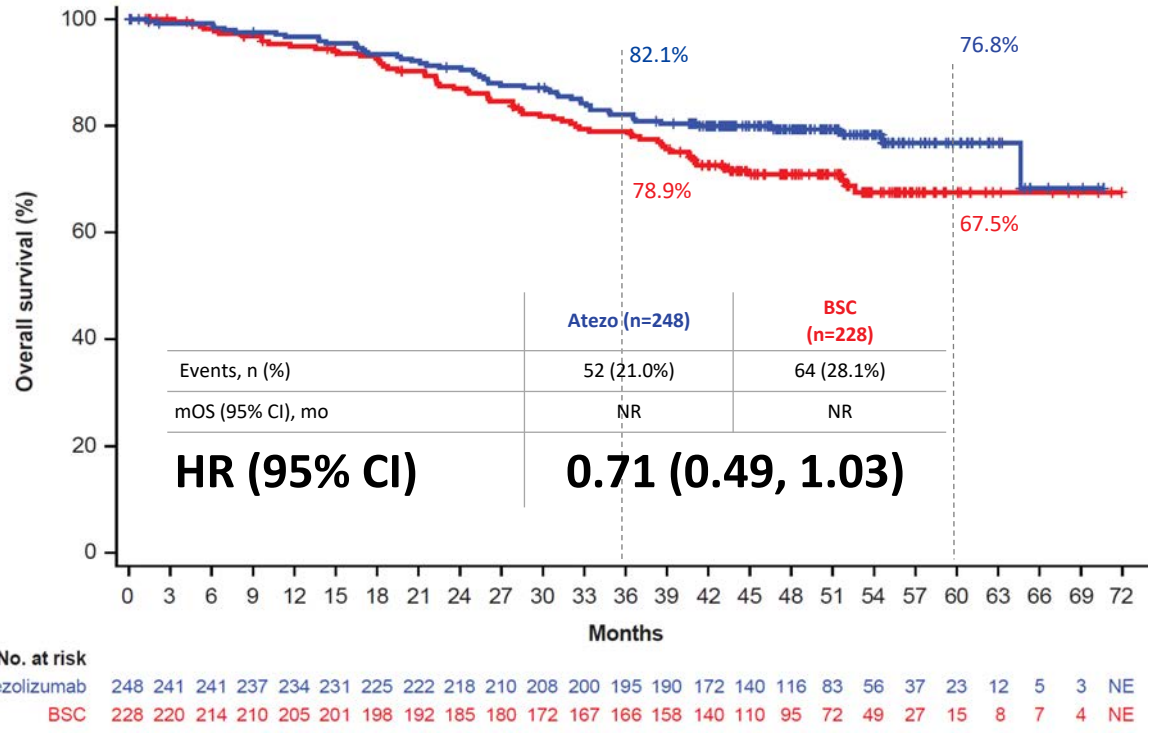
Clinical cutoff: January 21, 2021. [a] Per SP263 assay. [b] Stratified log-rank. [c] Crossed the significance boundary for DFS. [d] The statistical significance boundary for DFS was not crossed.

US FDA approval Oct 15, 2021

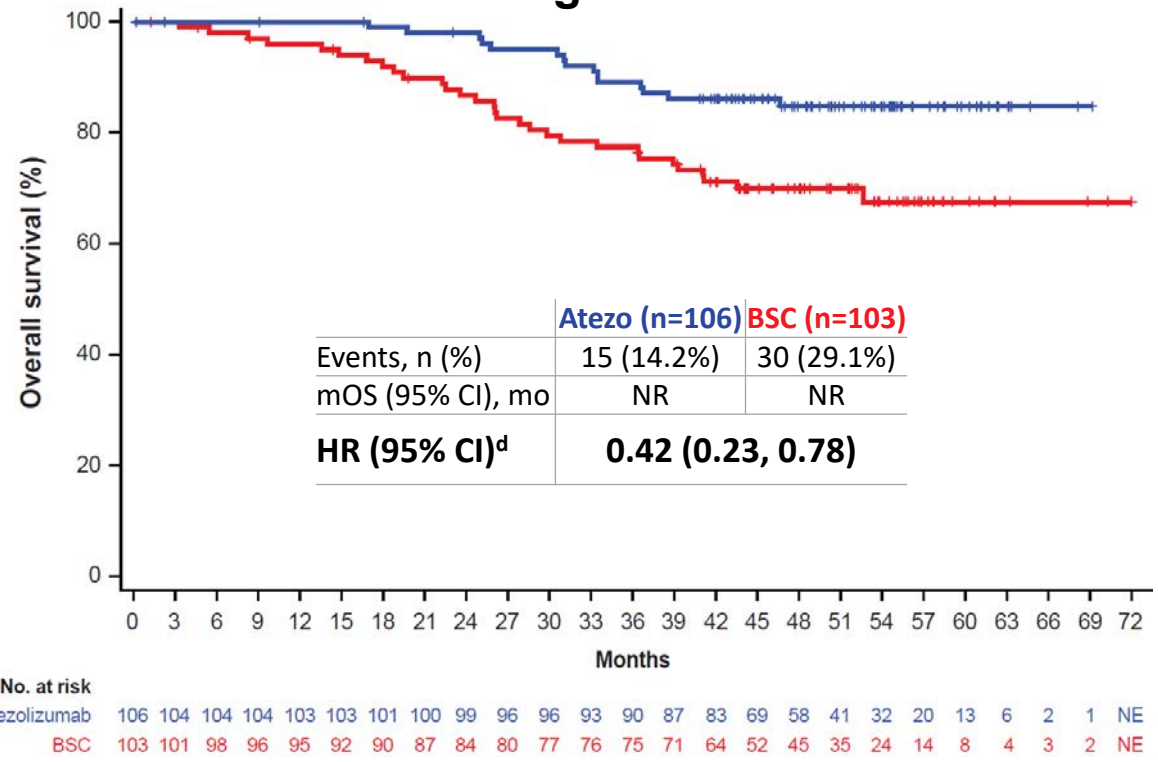
Wakelee ASCO 2021 abstr 8500; Felip Lancet 2021

IMpower010: Overall Survival – Selected Subsets

OS: PD-L1 TC ≥1%[a] (stage II-IIIA)



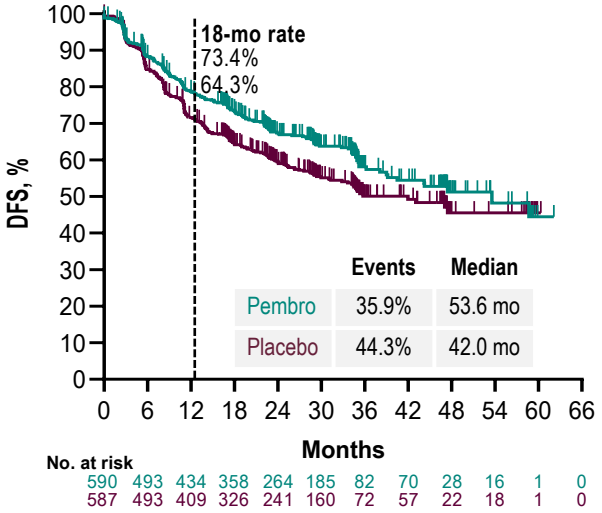
OS: PD-L1 TC ≥50% (stage II-IIIA) excluding *EGFR/ALK*+



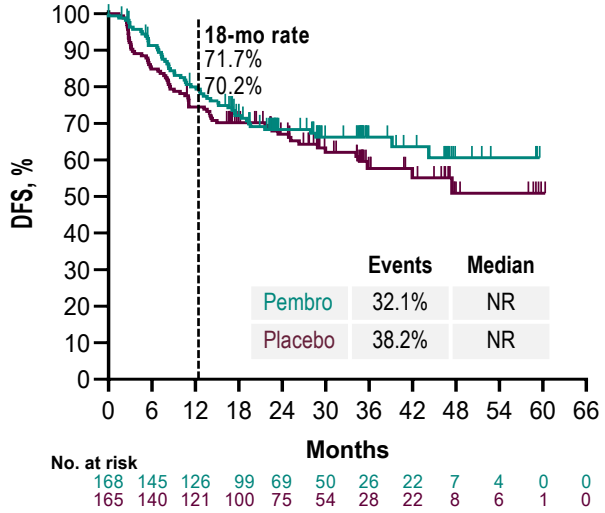
PEARLS/KN-091:
Results Second Interim Analysis

14% stage 1B, ~56% stage II, 30% stage IIIA
60% PD-L1+; ~8% known driver mutation

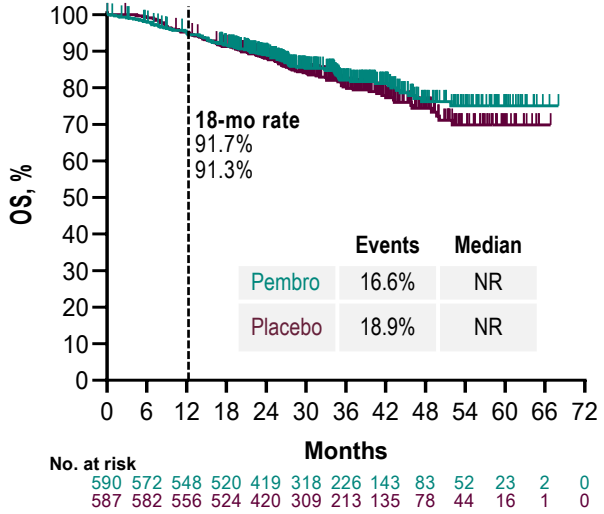
DFS, Overall Population
HR 0.76 (95% CI 0.63-0.91)
***P* = 0.0014**



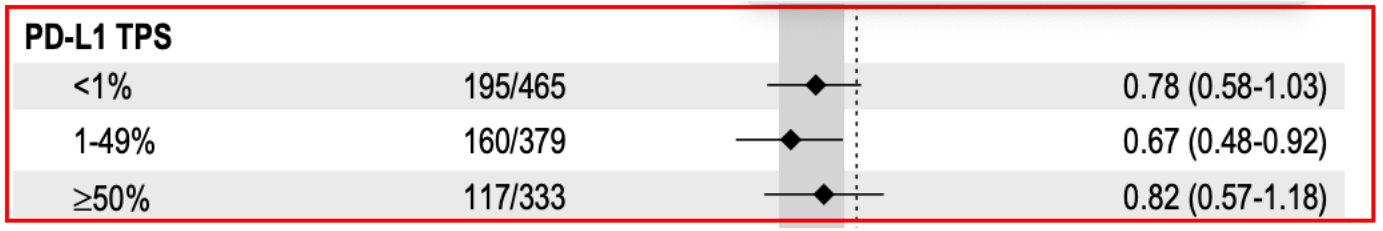
DFS, PD-L1 TPS ≥50% Population
HR 0.82 (95% CI 0.57-1.18)
***P* = 0.14**



OS, Overall Population
HR 0.87 (95% CI 0.67-1.15)
***P* = 0.170**



Impower010 DFS HR: all comer 0.81, PD-L1 ≥50% 0.43

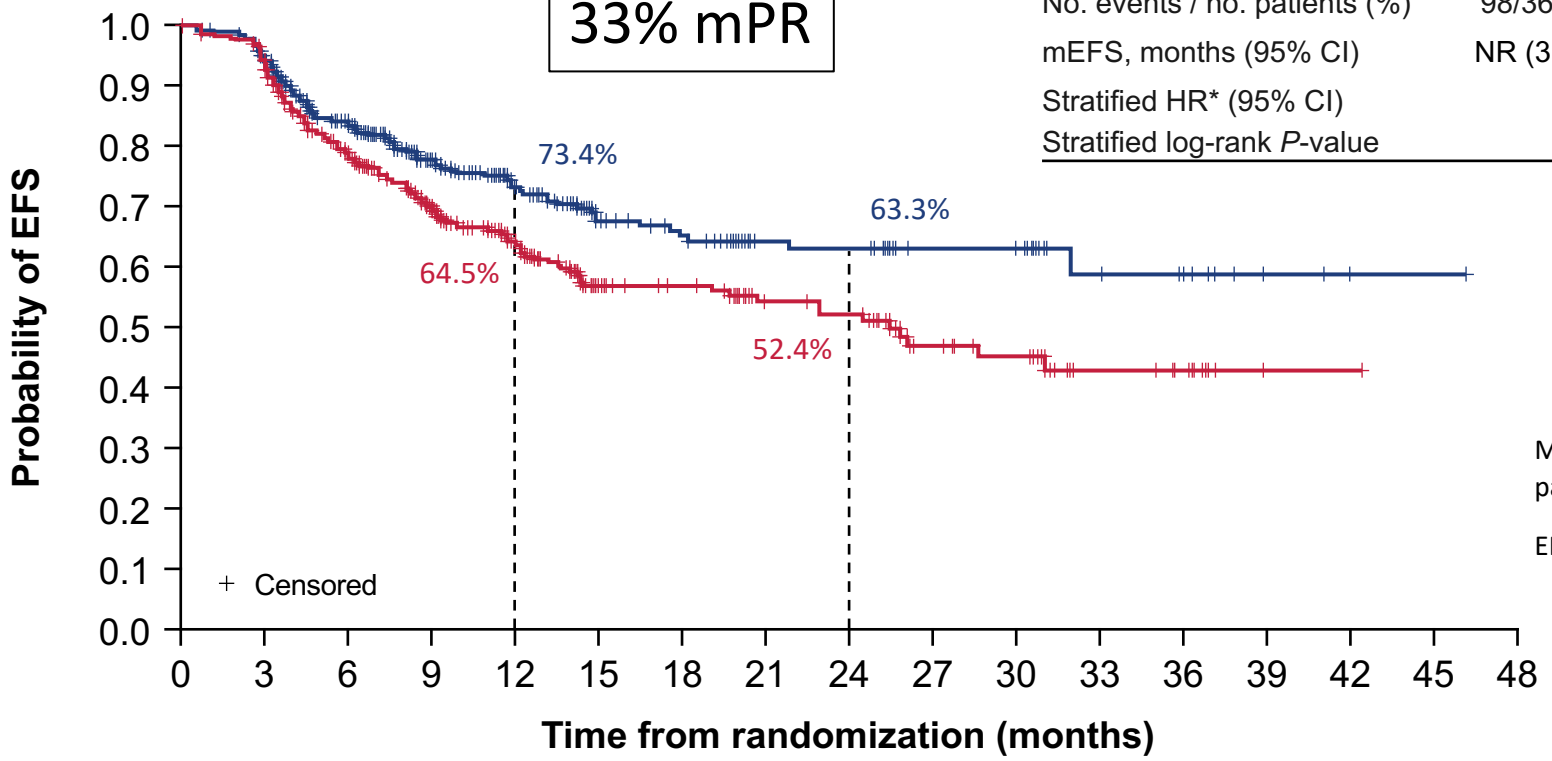


AEGEAN: EFS using RECIST v1.1 (BICR) (mITT)

First planned interim analysis of EFS

4 cycles pre-op, FEW EGFR/ALK
~30% stage II;
~ 1/3 each PD-L1 group (0, 1-49, 50+%)

17% pCR
33% mPR



	D arm	PBO arm
No. events / no. patients (%)	98/366 (26.8)	138/374 (36.9)
mEFS, months (95% CI)	NR (31.9–NR)	25.9 (18.9–NR)
Stratified HR* (95% CI)	0.68 (0.53–0.88)	
Stratified log-rank *P*-value	0.003902	

Median follow-up (range) in censored patients: 11.7 months (0.0–46.1)

EFS maturity: 31.9%

Heymach AACR 2023

No. at risk:

D arm	366	336	271	194	140	90	78	50	49	31	30	14	11	3	1	1	0
PBO arm	374	339	257	184	136	82	74	53	50	30	25	16	13	1	1	0	0

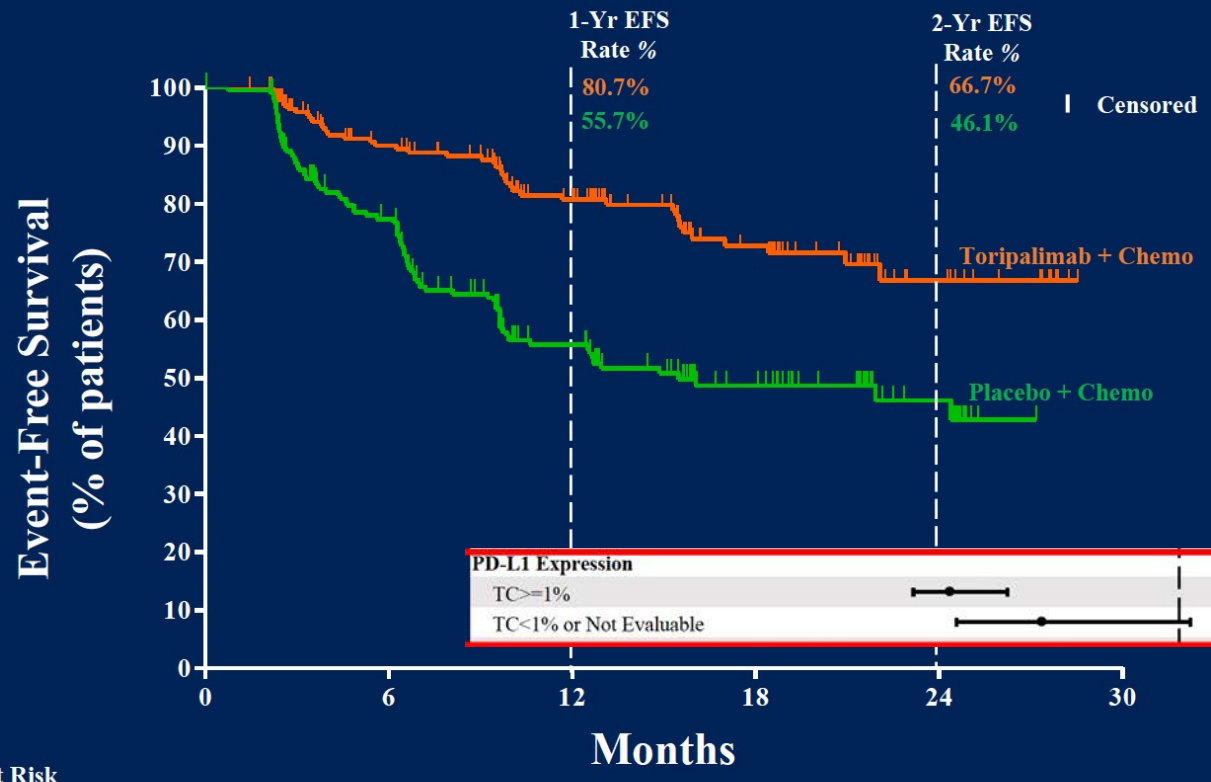
PD-L1 expression at baseline†	TC <1%	247	NR (14.9–NR)	20.6 (13.9–NR)	0.76 (0.49–1.17)
	TC 1–49%	277	NR (31.9–NR)	25.4 (12.2–NR)	0.70 (0.46–1.05)
	TC ≥50%	216	NR (NR–NR)	26.2 (14.3–NR)	0.60 (0.35–1.01)

NEOTORCH

~25% pCR
3 cycle pre, 1 post
NO EGFR/ALK66% PD-L1 >1; 78% squamous

Event-Free Survival Analysis by IRC

Intent-to-treat Stage III patients assessed by IRC per RECIST v1.1



	No. of Events/ No. of Patients	Median EFS *mo* (95% CI)
Toripalimab + Chemo	43/202	NE (NE, NE)
Placebo + Chemo	87/202	15.5 (9.9, NE)

Median follow-up: 18.25 months

HR 0.40 (95%CI 0.271, 0.572)

nominal P<0.0001

PD-L1 Expression			
TC>=1%	28/133	65/132	0.31 (0.197, 0.481)
TC<1% or Not Evaluable	19/69	32/70	0.59 (0.327, 1.034)

No. at Risk

Toripalimab + Chemo	202	150	107	60	17	0
Placebo + Chemo	202	134	74	38	14	0

Data cutoff date: Nov. 30, 2022
NE: not evaluable
HR; Hazard ratio
CI: confidence interval

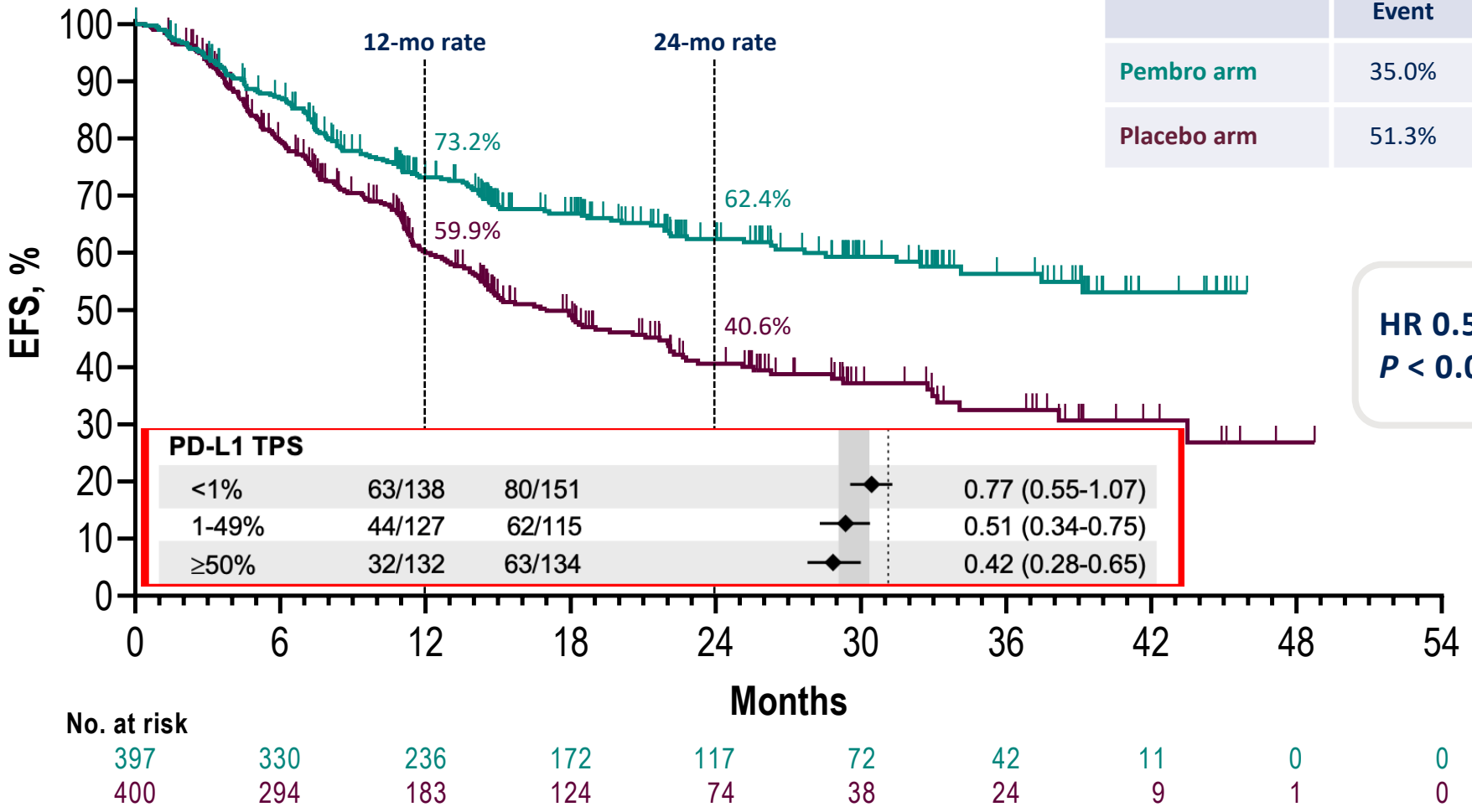
Lu, S ASCO Virtual Plenary April 20, 2023

KN671 - EFS

4 cycles pre-op chemo +/- IO
~30% stage II; ~1/3 each PD-L1 group (<1, 1-49, 50+)
Limited EGFR/ALK

18% pCR
30% mPR

	Pts w/ Event	Median (95% CI), mo
Pembro arm	35.0%	NR (34.1-NR)
Placebo arm	51.3%	17.0 (14.3-22.0)



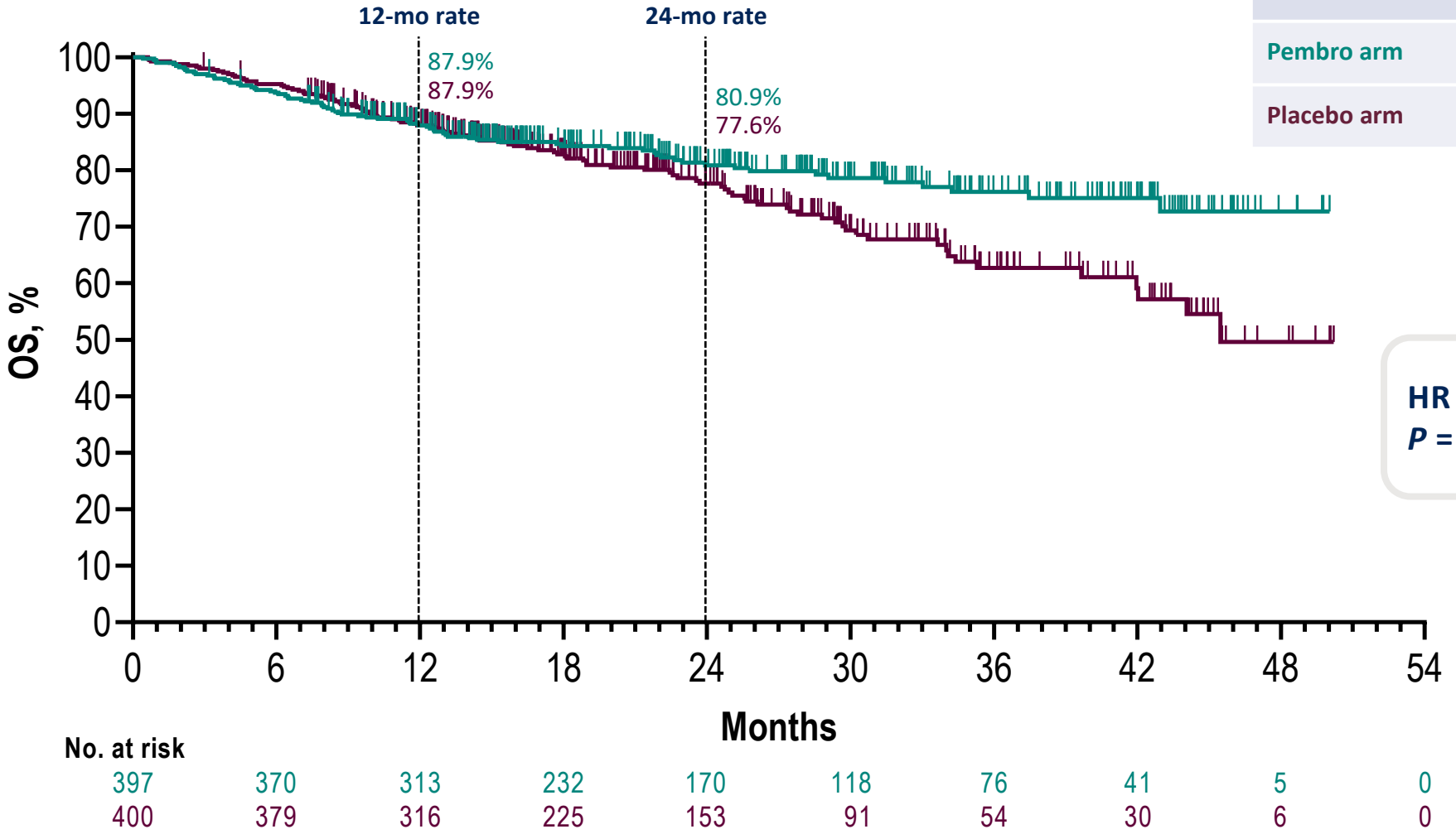
HR 0.58 (95% CI, 0.46-0.72)
***P* < 0.00001**

EFS defined as time from randomization to first occurrence of local progression precluding planned surgery, unresectable tumor, progression or recurrence per RECIST v1.1 by investigator assessment, or death from any cause. Data cutoff date for IA1: July 29, 2022 (median follow-up, 25.2 mo [range, 7.5-50.6]).

Dr. Heather Wakelee

KN671- Overall Survival

	Pts w/ Event	Median (95% CI), mo
Pembro arm	19.1%	NR (NR-NR)
Placebo arm	25.3%	45.5 (42.0-NR)



HR 0.73 (95% CI, 0.54-0.99)
***P* = 0.02124[a]**

OS defined as time from randomization to death from any cause. [a] Significance boundary not met at IA1; OS will continue to be tested according to the analysis plan. Data cutoff date for IA1: July 29, 2022 (median follow-up, 25.2 mo [range, 7.5-50.6]).

Dr. Heather Wakelee

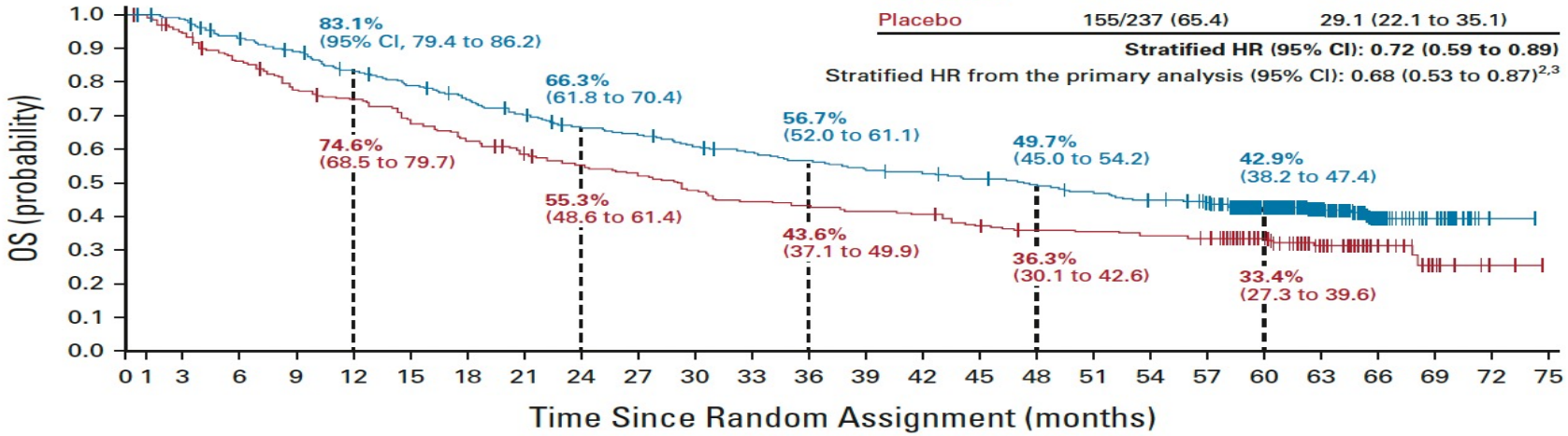
PACIFIC Updated Overall Survival Results Durva vs PCB x 1 yr post chemoXRT

A

Arm	No. of Events/ Total No. of Patients (%)	Median OS (95% CI), Months
Durvalumab	264/476 (55.5)	47.5 (38.1 to 52.9)
Placebo	155/237 (65.4)	29.1 (22.1 to 35.1)

Stratified HR (95% CI): 0.72 (0.59 to 0.89)

Stratified HR from the primary analysis (95% CI): 0.68 (0.53 to 0.87)[2,3]



No. at risk:

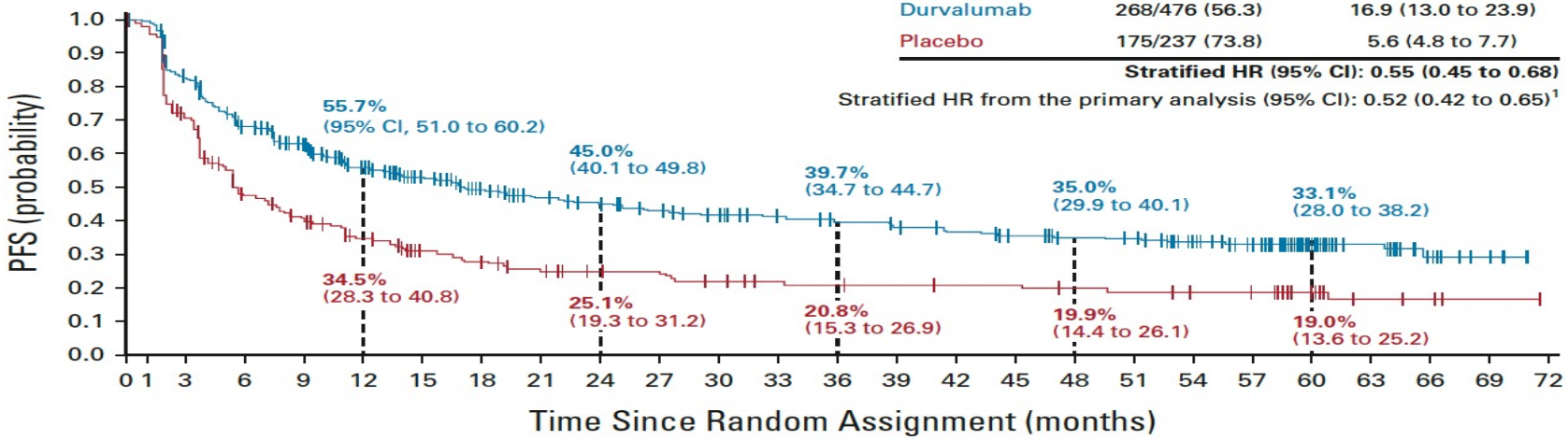
Durvalumab	476	464	431	414	385	364	343	319	298	289	273	264	252	241	236	227	218	207	196	183	134	91	40	18	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	78	77	74	72	56	33	16	7	2	0

B

Arm	No. of Events/ Total No. of Patients (%)	Median PFS (95% CI), Months
Durvalumab	268/476 (56.3)	16.9 (13.0 to 23.9)
Placebo	175/237 (73.8)	5.6 (4.8 to 7.7)

Stratified HR (95% CI): 0.55 (0.45 to 0.68)

Stratified HR from the primary analysis (95% CI): 0.52 (0.42 to 0.65)[1]



No. at risk:

Durvalumab	476	377	301	267	215	190	165	147	137	128	119	110	103	97	92	85	81	78	67	57	34	22	11	5	0
Placebo	237	164	105	87	68	56	48	41	37	36	30	27	26	25	24	24	22	21	19	19	14	6	4	1	0

Antonio NEJM 2017
Spigel, JCO 2023

Metastatic 1st line and Long Term Outcomes IO (+/-IO) +/- Chemo

Five-year outcomes with pembrolizumab KEYNOTE-042 >1%

TABLE 2. Key Efficacy Outcomes

Outcome	ITT Population						Completed 35 Cycles of Pembrolizumab[a] (PD-L1 TPS ≥ 1%) (n = 102)
	PD-L1 TPS ≥ 50%		PD-L1 TPS ≥ 20%		PD-L1 TPS ≥ 1%		
	Pembrolizumab (n = 299)	Chemotherapy (n = 300)	Pembrolizumab (n = 413)	Chemotherapy (n = 405)	Pembrolizumab (n = 637)	Chemotherapy (n = 637)	
OS							
Median, months (95% CI)	20.0 (15.9 to 24.2)	12.2 (10.4 to 14.6)	18.0 (15.5 to 21.5)	13.0 (11.6 to 15.3)	16.4 (14.0 to 19.6)	12.1 (11.3 to 13.3)	NR
HR (95% CI)	0.68 (0.57 to 0.81)		0.75 (0.64 to 0.87)		0.79 (0.70 to 0.89)		—
5-year rate,[b] % (95% CI)	21.9 (17.3 to 26.9)	9.8 (6.6 to 13.7)	19.4 (15.6 to 23.4)	10.1 (7.2 to 13.5)	16.6 (13.7 to 19.6)	8.5 (6.4 to 11.0)	61.8 (50.1 to 71.5)[e]
PFS[c]							
Median, months (95% CI)	6.5 (5.9 to 8.6)	6.5 (6.2 to 7.6)	6.2 (5.4 to 7.8)	6.9 (6.3 to 8.2)	5.6 (4.3 to 6.2)	6.8 (6.4 to 7.9)	31.9[d] (25.6 to NR)
HR (95% CI)	0.86 (0.72 to 1.02)		0.94 (0.81 to 1.09)		1.03 (0.91 to 1.16)		—
5-year rate,[b] % (95% CI)	9.2 (5.9 to 13.4)	2.1 (0.7 to 5.0)	7.8 (5.2 to 11.1)	1.6 (0.5 to 3.9)	6.9 (4.9 to 9.4)	1.2 (0.5 to 2.7)	NR[e]
Tumor response							
ORR,[c] % (95% CI)	39.1 (33.6 to 44.9)	32.3 (27.1 to 37.9)	33.2 (28.6 to 37.9)	29.1 (24.8 to 33.8)	27.3 (23.9 to 31.0)	26.7 (23.3 to 30.3)	84.3 (75.8 to 90.8)
Best overall response, No. (%)							
CR	3 (1.0)	1 (0.3)	3 (0.7)	1 (0.2)	4 (0.6)	3 (0.5)	3 (2.9)
PR	114 (38.1)	96 (32.0)	134 (32.4)	117 (28.9)	170 (26.7)	167 (26.2)	83 (81.4)
SD	89 (29.8)	132 (44.0)	145 (35.1)	195 (48.1)	246 (38.6)	332 (52.1)	15 (14.7)
PD	55 (18.4)	26 (8.7)	77 (18.6)	31 (7.7)	133 (20.9)	48 (7.5)	1 (1.0)
NE[f]	5 (1.7)	3 (1.0)	7 (1.7)	5 (1.2)	11 (1.7)	9 (1.4)	0
NA[g]	33 (11.0)	42 (14.0)	47 (11.4)	56 (13.8)	73 (11.5)	78 (12.2)	0
DOR, months, median (range)	28.1 (2.1+ to 70.0+)	10.8 (1.8+ to 63.5+)	27.7 (2.1+ to 70.0+)	10.8 (1.8+ to 63.5+)	26.5 (2.1+ to 70.0+)	8.4 (1.8+ to 63.5+)	47.4 (4.4 to 70.0+)
DOR ≥ 60 months,[b] %	28.4	16.0	26.0	16.6	27.0	13.4	—
Time to response, months, median (range)	2.1 (1.3-18.5)	2.1 (1.3-32.4)	2.1 (1.3-18.5)	2.1 (1.3-32.4)	2.1 (1.3-26.7)	2.1 (1.3-32.4)	2.1 (1.4-26.7)

Long term benefit (~20% survival at 5 years),
Most benefit seen in pts with tumors with high PD-L1

de Castro G Jr et al. KEYNOTE-042. J Clin Oncol 2022

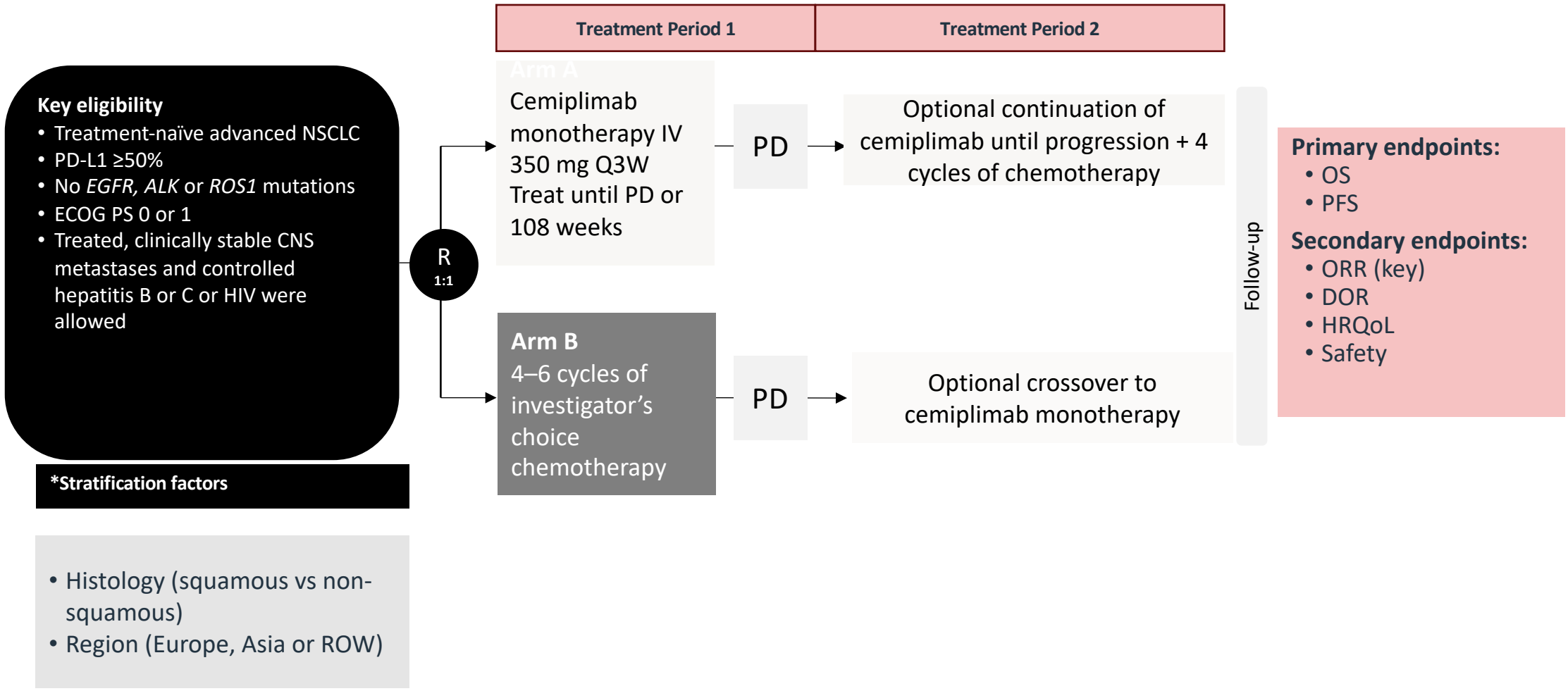
KN042 5 yr Outcomes

TABLE 1. Patient Demographics and Baseline Characteristics

Characteristic	ITT Population: Pembrolizumab TPS ≥ 1% (n = 637)	ITT Population: Chemotherapy TPS ≥ 1% (n = 637)	Completed 35 Cycles of Pembrolizumab (n = 102)
Age, years, median (range)	63.0 (25-89)	63.0 (31-90)	62.0 (33-81)
Men	450 (70.6)	452 (71.0)	73 (71.6)
Brain metastasis	35 (5.5)	35 (5.5)	14 (13.7)
PD-L1 tumor proportion score			
≥ 50%	299 (46.9)	300 (47.1)	66 (64.7)
20%-49%	114 (17.9)	105 (16.5)	14 (13.7)
1%-19%	224 (35.2)	232 (36.4)	22 (21.6)

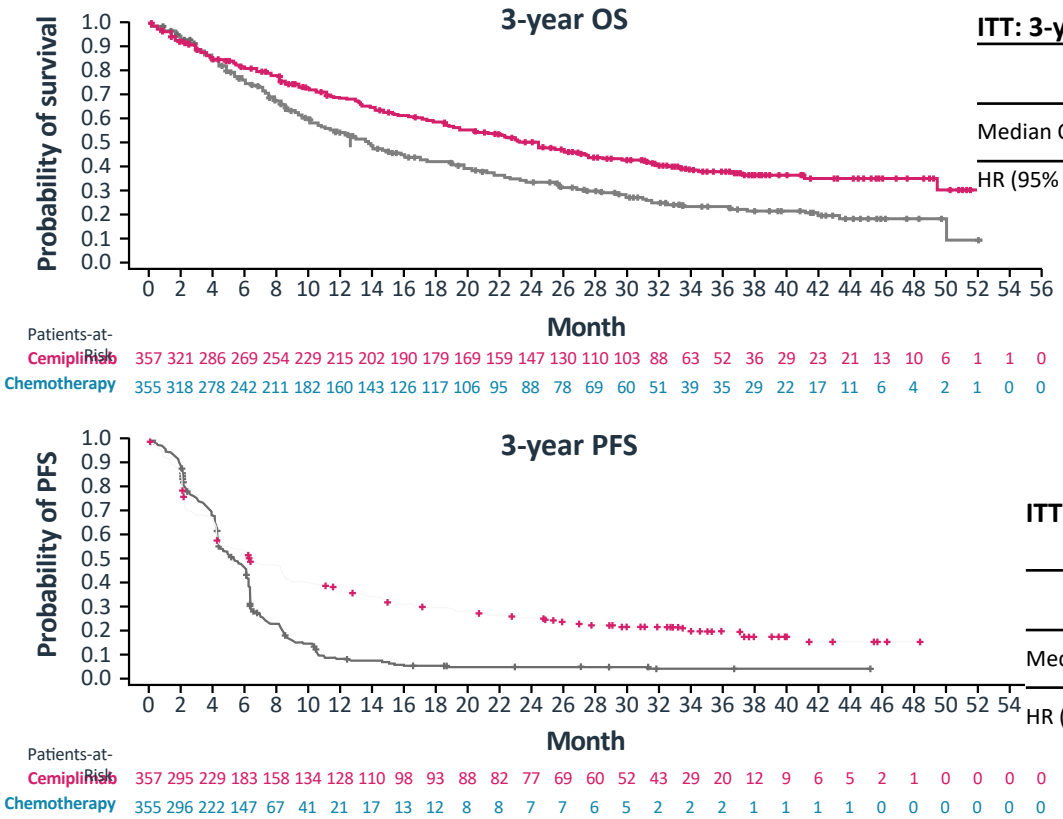
deCastro JCO 2022 5 yr KN042 outcomes

EMPOWER-Lung 1: Continued cemiplimab beyond progression



Özgüroğlu M et al. 3yr EMPOWER-Lung 1 trial. ESMO 2022;Abstract LBA54.

EMPOWER-Lung 1: Continued cemiplimab beyond progression



ITT: 3-year OS

	Cemiplimab (n=357)	Chemotherapy (n=355)
Median OS, months (95% CI)	23.4 (19.4, 27.4)	13.7 (11.2, 16.2)
HR (95% CI)	**0.63 (0.52, 0.77); P=0.0001**	

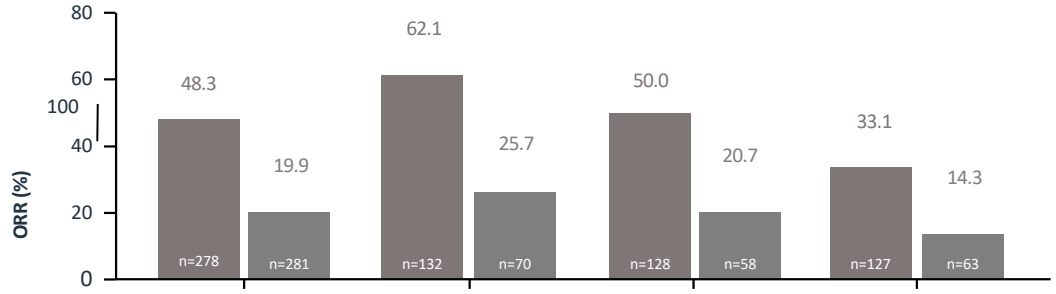
ITT: 3-year PFS

	Cemiplimab (n=357)	Chemotherapy (n=355)
Median PFS, months (95% CI)	6.3 (4.6, 8.3)	5.3 (4.3, 6.0)
HR (95% CI)	**0.56 (95% CI, 0.47-0.67); P=0.0001**	

Özgüroğlu M et al. 3yr EMPOWER-Lung 1 trial. ESMO 2022;Abstract LBA54

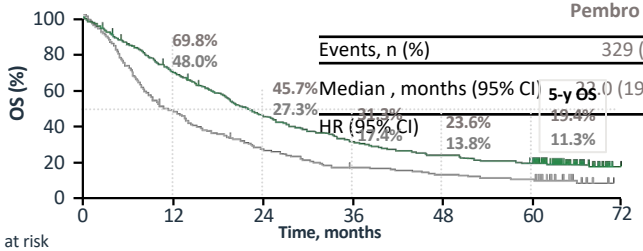
5-year outcomes from KEYNOTE-189 study

Tumor response



	ITT		PD-L1 TPS ≥50%		PD-L1 TPS 1% - 49%		PD-L1 TPS <1%	
	Pembro + chemo	Placebo + chemo	Pembro + chemo	Placebo + chemo	Pembro + chemo	Placebo + chemo	Pembro + chemo	Placebo + chemo
DOR[b] Median (range),[b] months	12.7 (1.1+ to 68.3+)	7.1 (2.4 to 31.5)	15.3 (1.2+ to 68.3+)	7.1 (3.4 to 31.5)	13.6 (2.1+ to 67.6+)	7.6 (2.4 to 31.0+)	10.8 (1.1 to 59.4+)	7.8 (4.1 to 28.3+)

OS (ITT population)

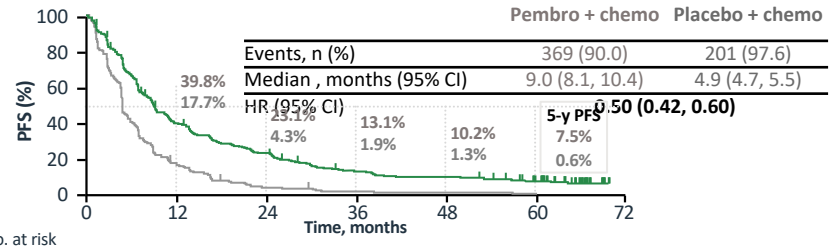


	Pembro + chemo	Placebo + chemo
Events, n (%)	329 (80.2)	183 (88.8)
Median , months (95% CI)	23.0 (19.5, 24.5)	10.6 (8.7, 13.6)
HR (95% CI)	0.60 (0.50, 0.72)	

No. at risk							
Pembro + chemo	410	283	184	126	95	77	0
Placebo + chemo	206	96	55	34	27	22	0

	PD-L1 TPS ≥50%		PD-L1 TPS 1% - 49%		PD-L1 TPS <1%	
	Pembro + chemo (n=132)	Placebo + chemo (n=70)	Pembro + chemo (n=128)	Placebo + chemo (n=58)	Pembro + chemo (n=127)	Placebo + chemo (n=63)
OS HR (95% CI)	0.68 (0.49, 0.96)		0.65 (0.46, 0.90)		0.55 (0.39, 0.76)	
5-y OS rate[b], %	29.6	21.4	19.8	7.7	9.6	5.3

PFS (ITT population)



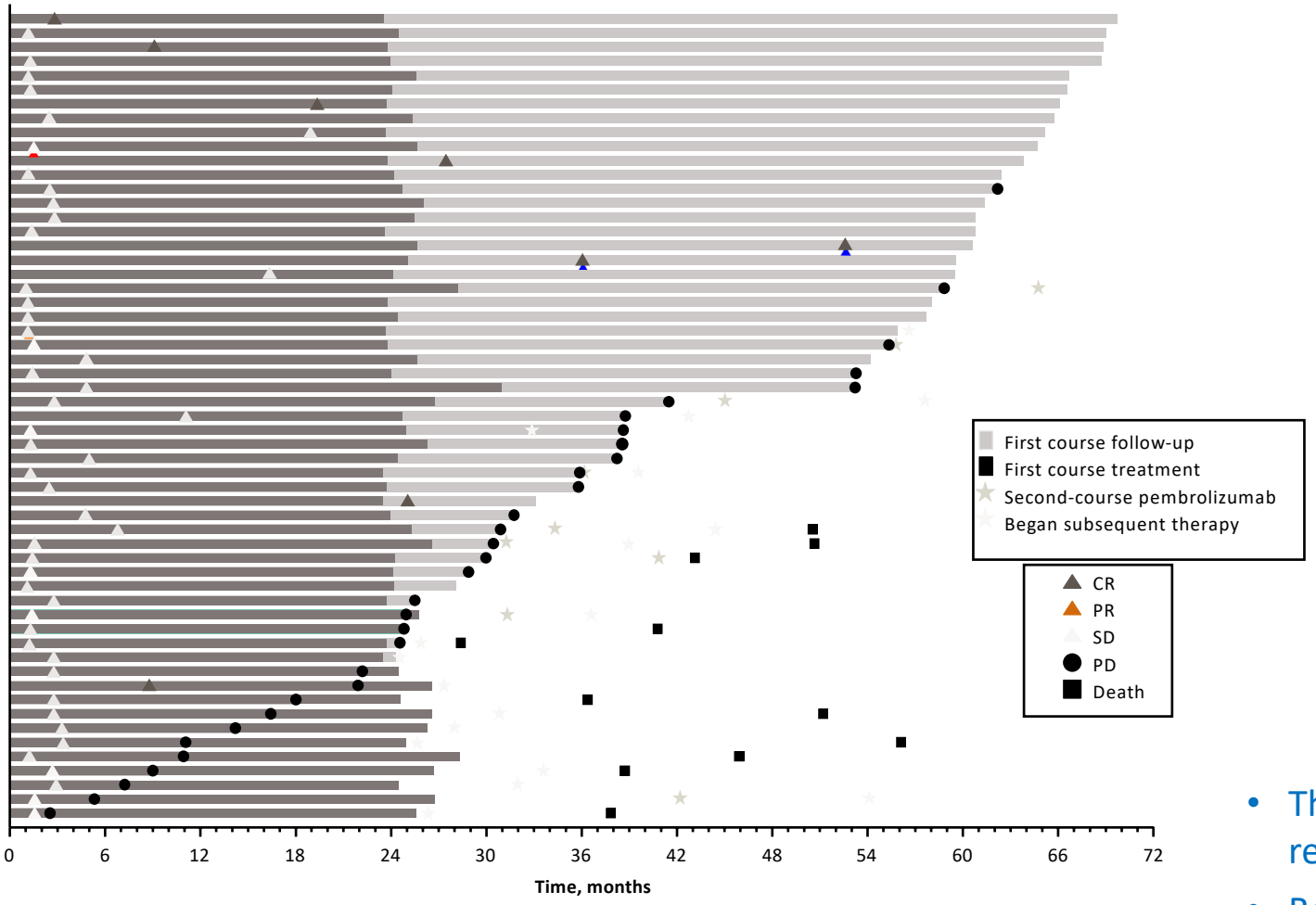
	Pembro + chemo	Placebo + chemo
Events, n (%)	369 (90.0)	201 (97.6)
Median , months (95% CI)	9.0 (8.1, 10.4)	4.9 (4.7, 5.5)
HR (95% CI)	0.50 (0.42, 0.60)	

No. at risk							
Pembro + chemo	410	158	91	49	37	21	0
Placebo + chemo	208	35	8	3	2	1	0

	PD-L1 TPS ≥50%		PD-L1 TPS 1% - 49%		PD-L1 TPS <1%	
	Pembro + chemo (n=132)	Placebo + chemo (n=70)	Pembro + chemo (n=128)	Placebo + chemo (n=58)	Pembro + chemo (n=127)	Placebo + chemo (n=63)
PFS HR (95% CI)	0.35 (0.25, 0.49)		0.57 (0.41, 0.80)		0.67 (0.49, 0.92)	
5-y PFS rate[b], %	12.8	0	6.5	1.9	2.4	0

Garassino MC 5-year outcomes KEYNOTE-189 study. J Clin Oncol 2023

5-year outcomes from KEYNOTE-189 study



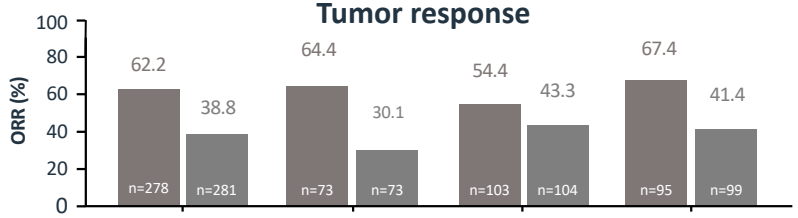
	N=57
ORR (95% CI),[a] %	86.0 (74.2, 93.7)
Best overall response, n (%)	
CR	8 (14.0)
PR	41 (71.9)
Median DOR (range),[b] months	57.7 (4.2–68.3)
3-year OS rate after completing 35 cycles[c]	71.9%
Alive without PD or subsequent therapy, n (%)	23 (40.4)

- This update confirms long-term benefit of the KN189 regimen including OS, despite crossover
- Benefit is seen regardless of PD-L1 level, but best survival in those with high PD-L1

Garassino MC 5-year outcomes KEYNOTE-189 study. J Clin Oncol 2023

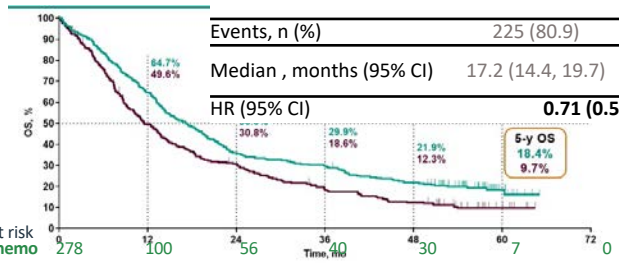
5-year update of KEYNOTE-407

Tumor response



	ITT		PD-L1 TPS ≥50%		PD-L1 TPS 1% - 49%		PD-L1 TPS <1%	
DOR[b] Median (range),[b] months	Pembro + chemo	Placebo + chemo	Pembro + chemo	Placebo + chemo	Pembro + chemo	Placebo + chemo	Pembro + chemo	Placebo + chemo
	9.0 (1.3–61.5)	4.9 (1.3–58.6)	10.4 (2.7–59.4)	4.6 (1.3–58.6)	11.1 (1.3– 61.5)	4.8 (2.0–58.6)	6.9 (1.4– 58.9)	5.7 (1.4–55.8)

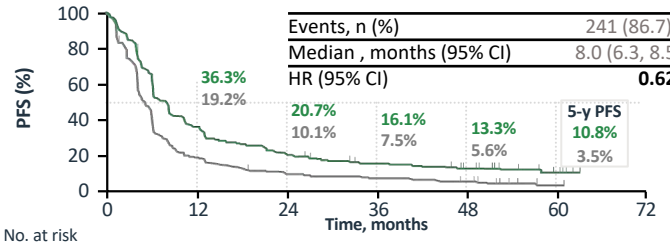
OS (ITT population)



	Pembro + chemo	Placebo + chemo
Events, n (%)	225 (80.9)	265 (94.3)
Median , months (95% CI)	17.2 (14.4, 19.7)	11.6 (10.1, 13.7)
HR (95% CI)	**0.71 (0.59, 0.85)**	

	PD-L1 TPS ≥50%		PD-L1 TPS 1% - 49%		PD-L1 TPS <1%	
	Pembro + chemo (n = 73)	Placebo + chemo (n = 73)	Pembro + chemo (n = 103)	Placebo + chemo (n = 104)	Pembro + chemo (n = 95)	Placebo + chemo (n = 99)
OS HR (95% CI)	0.48 (0.33-0.69		0.60 (0.45-0.81)		0.70 (0.52-0.95)	
5-y OS rate[b], %	15.0	NR	11.8	NR	7.1	6.7

PFS (ITT population)

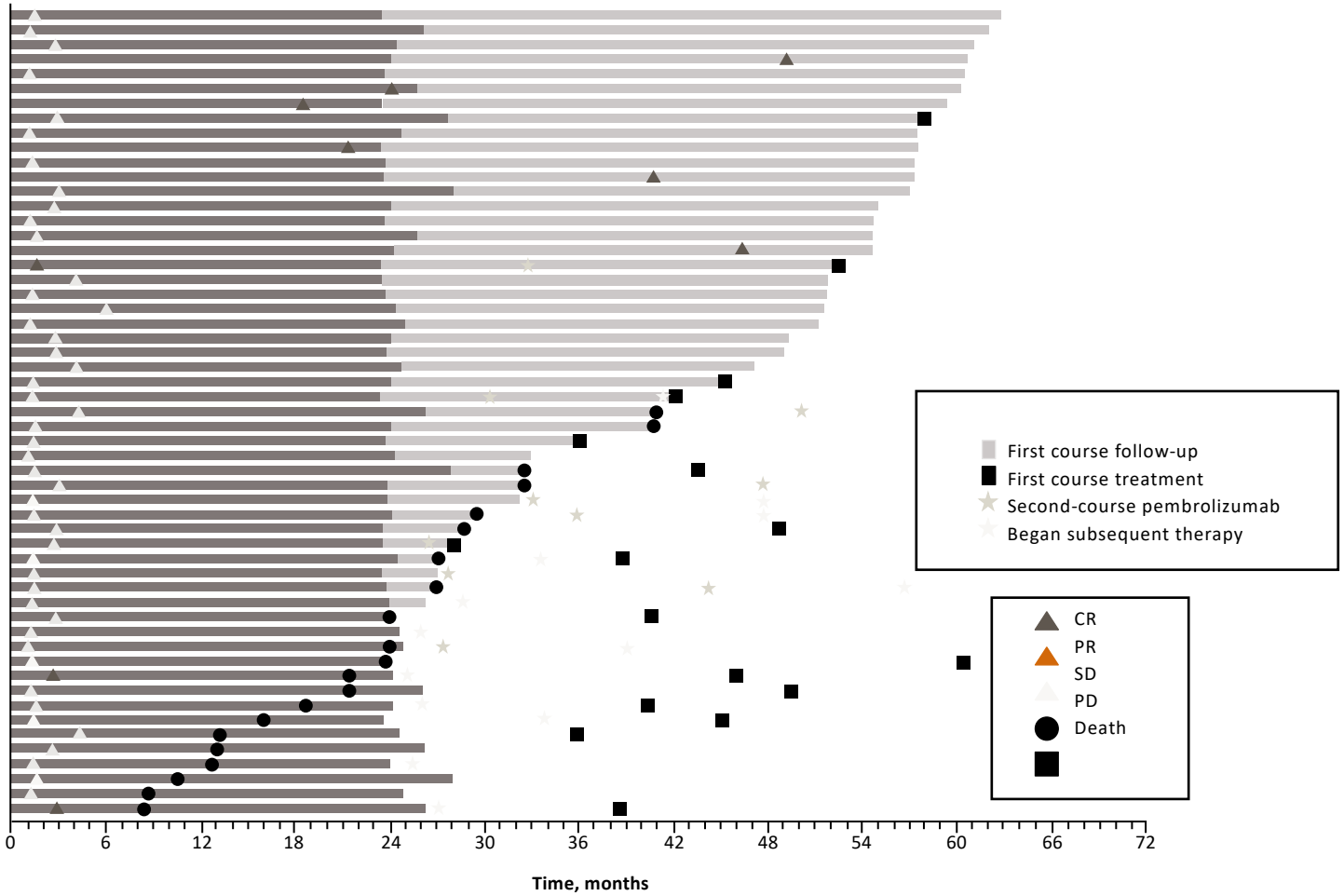


	Pembro + chemo	Placebo + chemo
Events, n (%)	241 (86.7)	265 (94.3)
Median , months (95% CI)	8.0 (6.3, 8.5)	5.1 (4.3, 6.0)
HR (95% CI)	**0.62 (0.52, 0.74)**	

	PD-L1 TPS ≥50%		PD-L1 TPS 1% - 49%		PD-L1 TPS <1%	
	Pembro + chemo (n = 73)	Placebo + chemo (n = 73)	Pembro + chemo (n = 103)	Placebo + chemo (n = 104)	Pembro + chemo (n = 95)	Placebo + chemo (n = 99)
PFS HR (95% CI)	0.48 (0.33-0.69		0.60 (0.45-0.81)		0.70 (0.52-0.95)	
5-y PFS rate[b], %	15.0	NR	11.8	NR	7.1	6.7

Novello S et al. 5-year KEYNOTE-407 study. J Clin Oncol 2023

5-year update of KEYNOTE-407

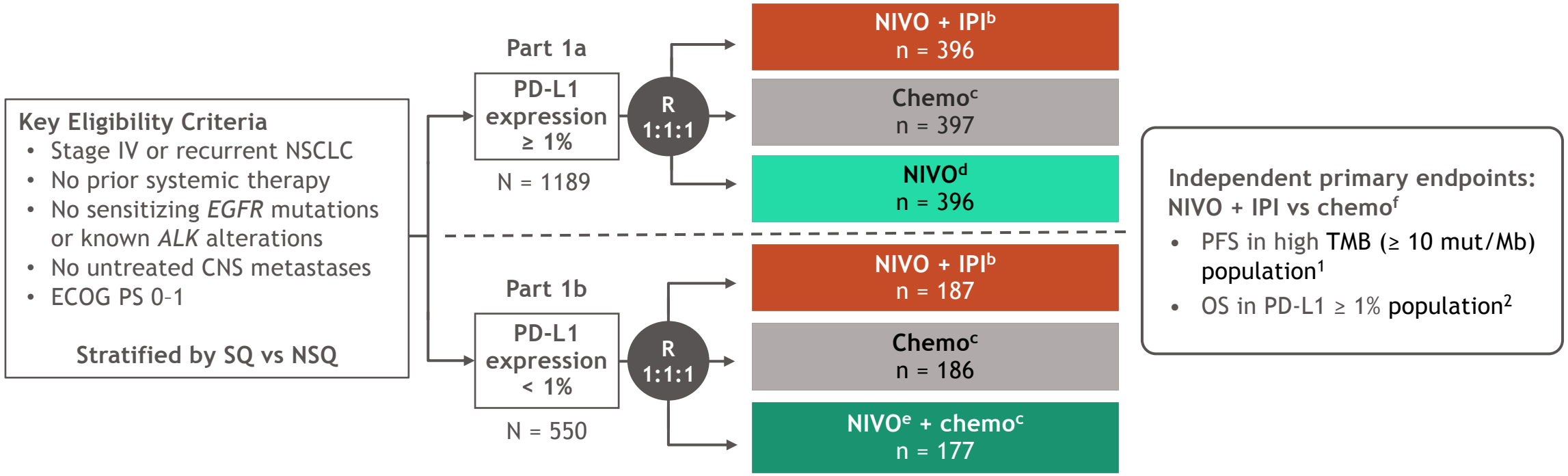


	n = 55
ORR (95% CI),[a] %	90.9 (80.0, 97.0)
Best overall response, n (%)	
CR	9 (16.4)
PR	41 (74.5)
Median DOR (range),[b] months	NR (7.1–61.5)
3-year OS rate after completing 35 cycles[c]	69.5%
Alive without PD or subsequent therapy, n (%)	24 (43.6)

- This update confirms long-term benefit of the KN407 regimen including OS, despite crossover

Novello S et al. 5-year KEYNOTE-407 study. J Clin Oncol 2023

CheckMate 227 Part 1 study design



Database lock: February 28, 2020; minimum / median follow-up for OS: 37.7 months / 43.1 months.

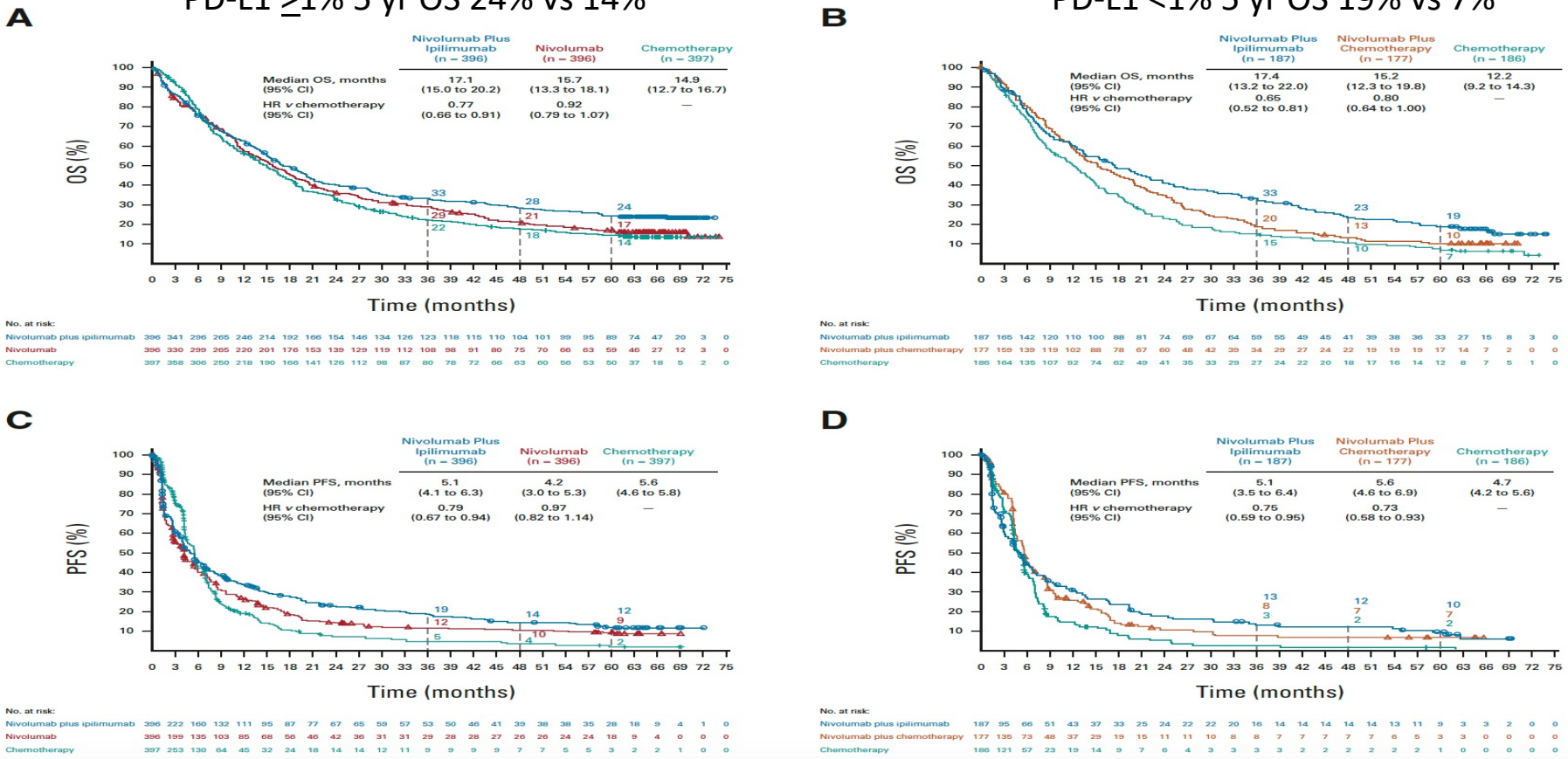
Treatment was continued until disease progression, unacceptable toxicity, or for 2 years for immunotherapy; [a]NCT02477826; [b]NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W); [c]**NSQ:** pemetrexed + cisplatin or carboplatin, Q3W for ≤ 4 cycles, with optional pemetrexed maintenance following chemo or NIVO + pemetrexed maintenance following NIVO + chemo; **SQ:** gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤ 4 cycles; [d]NIVO (240 mg Q2W); [e]NIVO (360 mg Q3W); [f]Both endpoints were met; results were previously reported.

1. Hellmann MD, et al. *N Engl J Med* 2018;378(22):2093–2104; 2. Hellmann MD, et al. *N Engl J Med* 2019;381(21):2020–2031.

Five-year survival outcomes CheckMate 227

PD-L1 ≥1% 5 yr OS 24% vs 14%

PD-L1 <1% 5 yr OS 19% vs 7%



OS, PFS, and ORR/DOR in randomly assigned patients by tumor PD-L1 expression level. OS in patients with (A) tumor PD-L1 expression ≥1% or (B) tumor PD-L1 expression,<1%; PFS in randomly assigned patients with (C) tumor PD-L1 expression ≥1%or (D) tumor PD-L1 expression <1%

2/3 of long-term survivors were off therapy

Long term benefit (~20% survival at 5 years),
Benefit seen in pts regardless of tumor PD-L1 levels

Brahmer JR et al. Five-year CheckMate 227. J Clin Oncol 2023;41(6):1200-12

3-year update - CheckMate 9LA

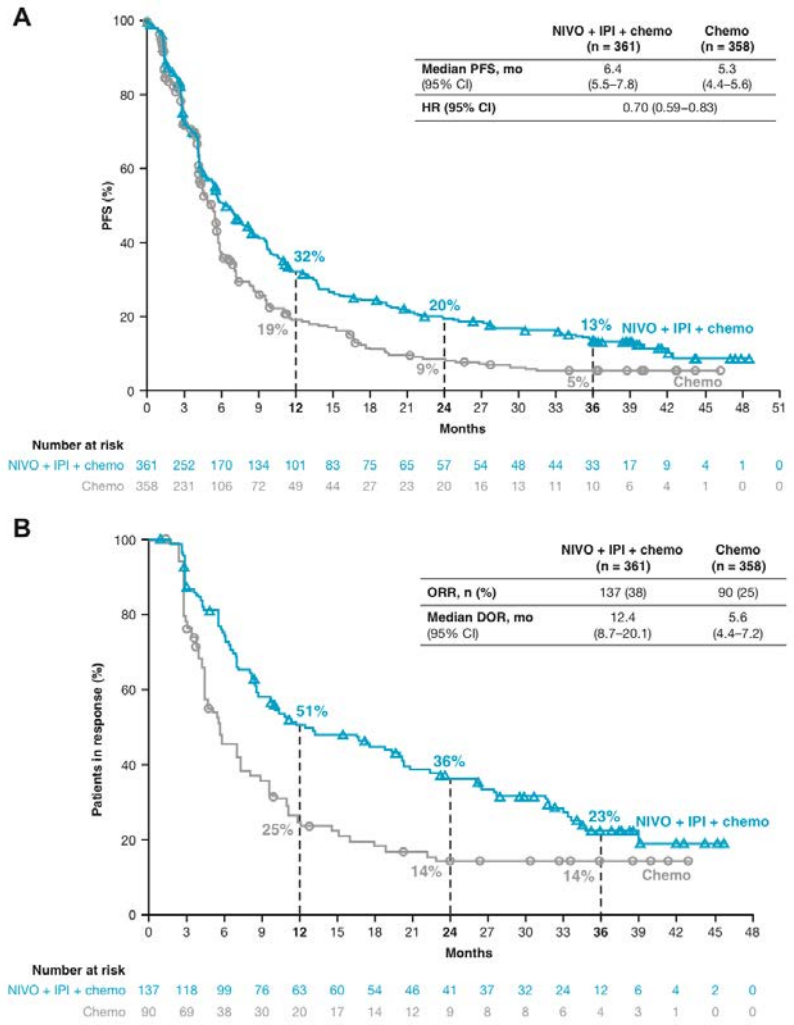


Figure 3. (*A*) PFS and (*B*) DOR in all randomized patients. Minimum follow-up of 35.2 months. The 95% CIs for 3-year PFS rates with NIVO plus IPI plus chemo and chemo were (*A*) 9.7 to 17.4 and 3.0 to 8.7 and (*B*) 15.0 to 31.0 and 8.0 to 23.0, respectively. Chemo, chemotherapy; CI, confidence interval; DOR, duration of response; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; ORR, objective response rate; PFS, progression-free survival.

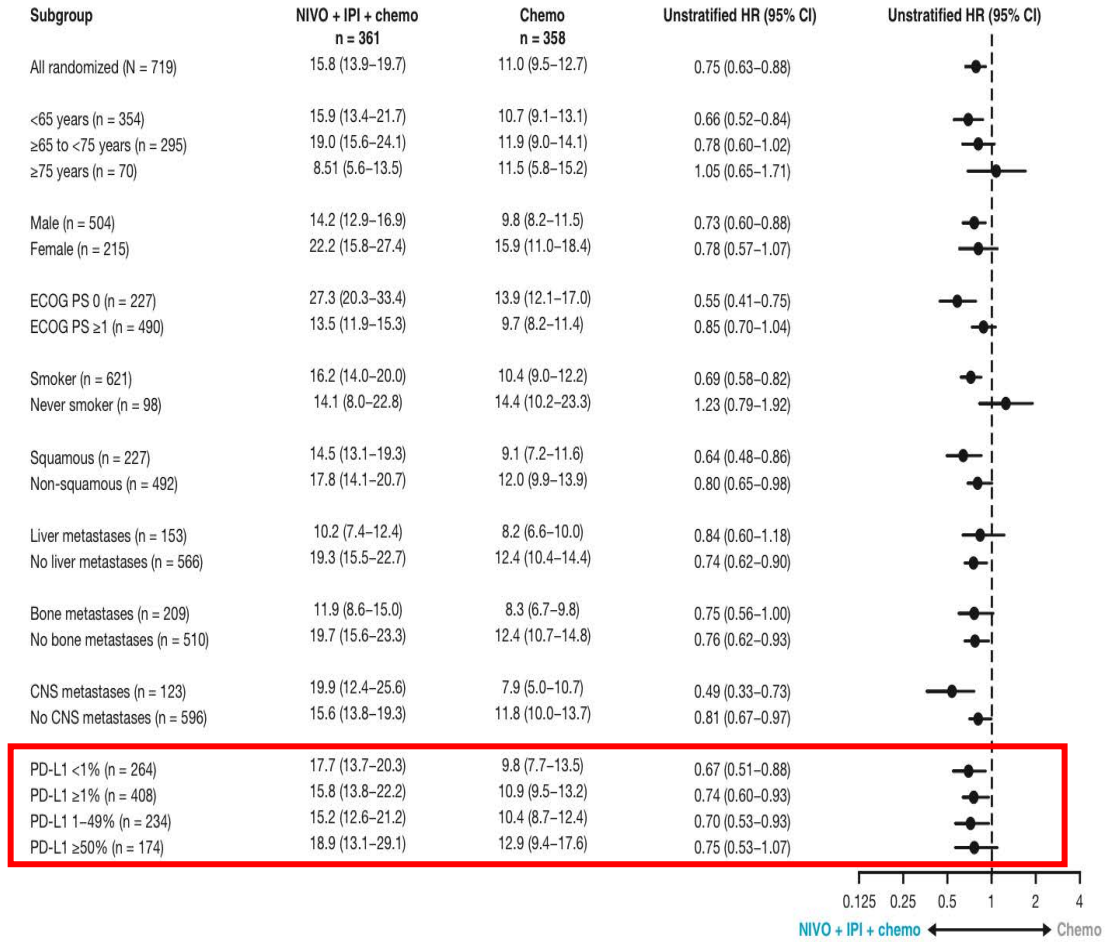


Figure 2. OS by prespecified subgroups. Chemo, chemotherapy; CI, confidence interval; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; PD-L1, programmed death-ligand 1.

OS: 15.8 versus 11.0 mo [0.74; 0.62–0.87]; 3-y OS: 27% versus 19%

Long term benefit seen with 3yr OS 27%
Benefit seen in pts regardless of tumor PD-L1 levels

Paz-Ares LG 3-year update - CheckMate 9LA ASCO 2022;Abstract LBA9026; JTO 18(2), 2023

4 yr Survival Update POSEIDON study

N=1013

Key eligibility

- Stage IV NSCLC
- No *EGFR* or *ALK* alterations
- Treatment naïve for metastatic disease
- ECOG PS 0–1

R 1:1:1

- **Durvalumab** 1500 mg + CT Q3W (4 cycles) followed by maintenance
- **Durvalumab** 1500 mg + **tremelimumab** 75 mg +CT* Q3W (4 cycles) followed by maintenance
- **Platinum-based CT** Q3W (up to 6 cycles) followed by maintenance

Stratification factors

- PD-L1 expression
- Disease stage
- Histology

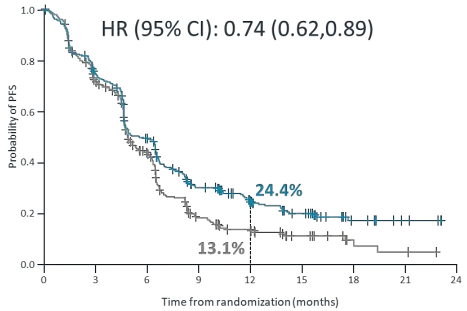
Primary endpoints:

- PFS (BICR)
- OS

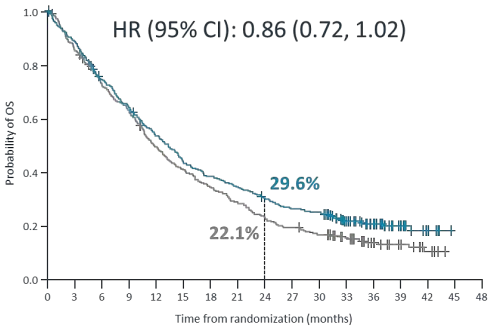
Key secondary endpoints:

- ORR, DoR, BOR
- HRQoL Safety

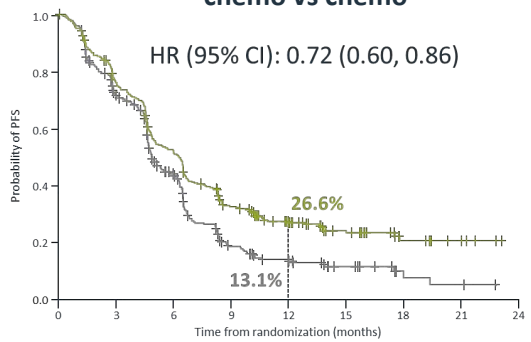
PFS: Durvalumab +chemo vs chemo[1]



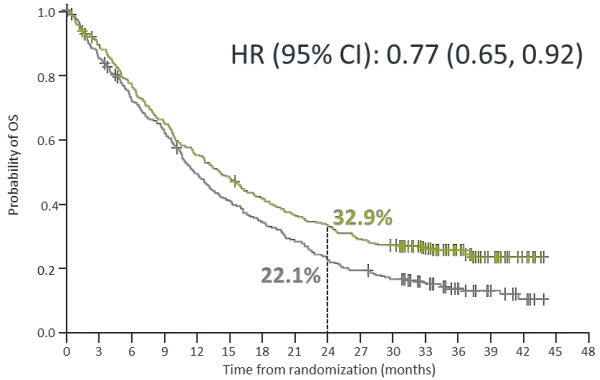
OS: Durvalumab + chemo vs chemo[1]



PFS: Durvalumab + tremelimumab/ chemo vs chemo[1]



OS: Durvalumab + tremelimumab/ chemo vs chemo[1]

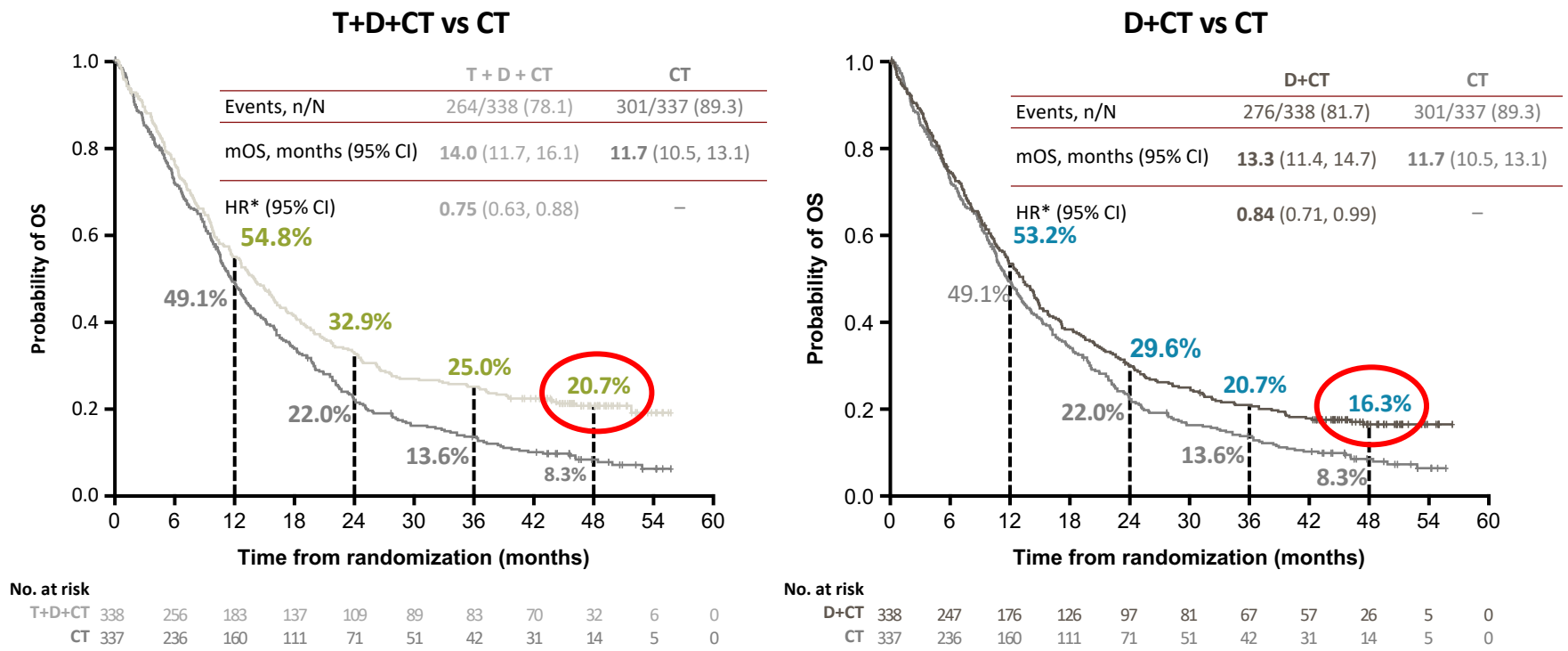


	D+C	C	HR
Tumor PD-L1 expression			
TC ≥ 50%	64/94	80/97	0.63 (0.45 to 0.88)
TC < 50%	200/243	205/240	0.94 (0.77 to 1.14)
TC ≥ 1%	165/224	170/207	0.79 (0.64 to 0.98)
TC < 1%	99/113	115/130	0.99 (0.76 to 1.30)

	T+D+C	C	HR
Tumor PD-L1 expression			
TC ≥ 50%	69/101	80/97	0.65 (0.47 to 0.89)
TC < 50%	182/237	205/240	0.82 (0.67 to 1.00)
TC ≥ 1%	151/213	170/207	0.76 (0.61 to 0.95)
TC < 1%	100/125	115/130	0.77 (0.58 to 1.00)

Johnson ML 4 yr update . POSEIDON study. J Clin Oncol 2023;41(6):1213-27;

4 yr Survival Update POSEIDON study



Long term benefit (~20% survival at 4 years) with T+D+CT,
Benefit regardless of PD-L1 with T+D, but PD-L1 dependent for D alone

Johnson ML 4 yr update . POSEIDON study. J Clin Oncol 2023;41(6):1213-27

Dato-DXd

TROPION-Lung02: Datopotamab deruxtecan + pembrolizumab ± platinum chemotherapy for advanced NSCLC

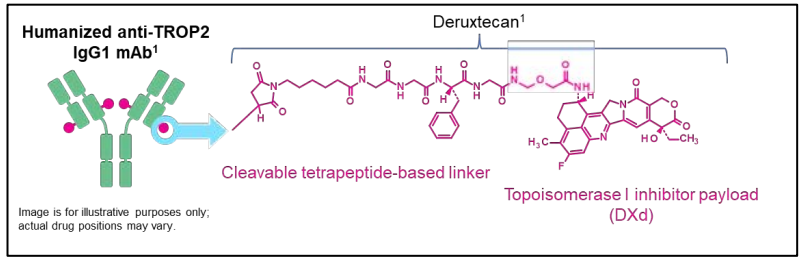
Key eligibility
- Advanced/metastatic NSCLC
- **Dose escalation:** ≤2 lines of prior therapy
- **Dose expansion:**
  - ≤1 line of platinum-based chemo (cohorts 1 and 2)
  - Treatment naive (cohort 2, enrollment after Jun 30, 2022)
  - Treatment naive (cohorts 3–6)

	Dato-DXd IV Q3W	+	Pembro IV Q3W	+	Platinum CT IV Q3W	
Cohort 1 (n=20):	4 mg/kg	+	200 mg			Doublet
Cohort 2 (n=44):	6 mg/kg	+	200 mg			
Cohort 3 (n=20):	4 mg/kg	+	200 mg	+	carboplatin AUC 5	Triplet
Cohort 4 (n=30):	6 mg/kg	+	200 mg	+	carboplatin AUC 5	
Cohort 5 (n=12):	4 mg/kg	+	200 mg	+	cisplatin 75 mg/m^2	
Cohort 6 (n=10):	6 mg/kg	+	200 mg	+	cisplatin 75 mg/mp^2	

Primary endpoints
- Safety, tolerability

Secondary endpoints
- Efficacy
- Pharmacokinetics
- Anti-drug antibodies

- Of patients receiving doublet or triplet therapy, 48% and 74% were treated in the 1L setting, respectively
- Immunotherapy was previously given in 23% of patients receiving doublet therapy and 27% receiving triplet therapy



Dato-DXd, datopotamab deruxtecan.
Goto Y, et al. ASCO 2023. Abstract 9004.

Baseline characteristics

		Doublet (n=64)	Triplet (n=72)
Age, median (range), years		65 (44–83)	64 (33–84)
Male, n (%)		48 (75)	48 (67)
Histology, n (%)	Adenocarcinoma	45 (70)	46 (68)
	Squamous	16 (25)	15 (21)
History of brain metastases, n (%)		11 (17)	14 (19)
PD-L1 expression, n (%)	<1%	23 (36)	29 (40)
	1–49%	28 (44)	24 (33)
	≥50%	13 (20)	18 (25)
Prior lines of therapy, median (range)		1 (0–4)	0 (0–3)
Previous systemic treatment, n (%)	Immunotherapy	12 (19)	18 (25)
	Platinum chemotherapy	24 (38)	17 (24)
Dato-DXd combination line of therapy, n (%)	1L	37 (58)	54 (75)
	2L+	27 (42)	18 (255)

TROPION-Lung02: Efficacy of Dato-DXd + pembrolizumab ± chemo

Antitumor response

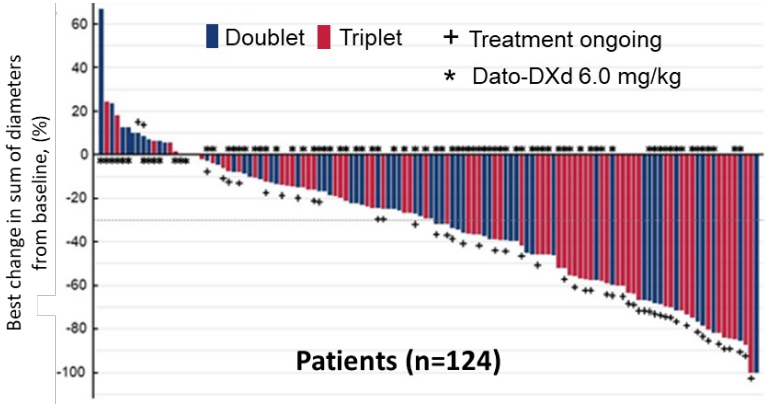
	All patients		Patients treated 1L	
	Doublet (n=61)	Triplet (n=71)	Doublet (n=34)	Triplet (n=53)
ORR, confirmed/pending, n (%) [95% CI]	23 (38) [26, 51]	35 (49) [37, 61]	17 (50) [32, 68]	30 (57) [42, 70]
BOR, confirmed/ pending, n (%)				
CR, confirmed	0	1 (1)	0	1 (2)
CR, pending	0	0	0	0
PR, confirmed	21 (34)	34 (48)	15 (44)	29 (55)
PR, pending	2 (3)	0	2 (6)	0
SD, n (%)	30 (49)	27 (38)	16 (47)	18 (34)
DCR, n (%)	51 (84)	62 (87)	31 (91)	48 (91)
Median DOR, months (95% CI)	NE (8.8, NE)	NE (5.8, NE)	NE (5.5, NE)	NE (5.7, NE)

BOR, best overall response; CR, complete response; Dato-DXd, datopotamab deruxtecan DCR, disease control rate; DOR, duration of response; ORR, objective response rate; PR, pathological response; SD, stable disease.

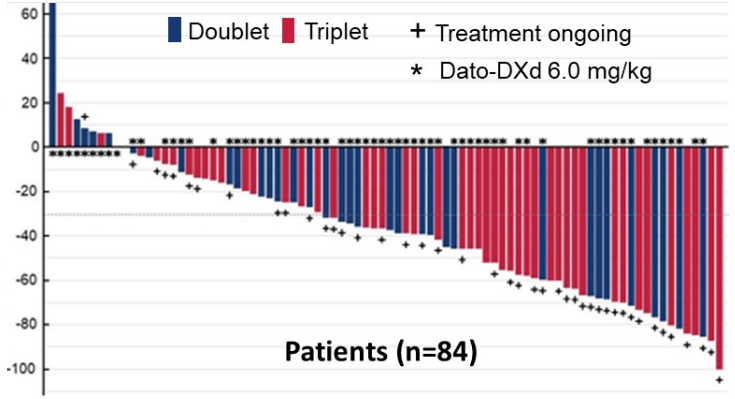
Goto Y, et al. ASCO 2023. Abstract 9004.

Tumor shrinkage

All patients

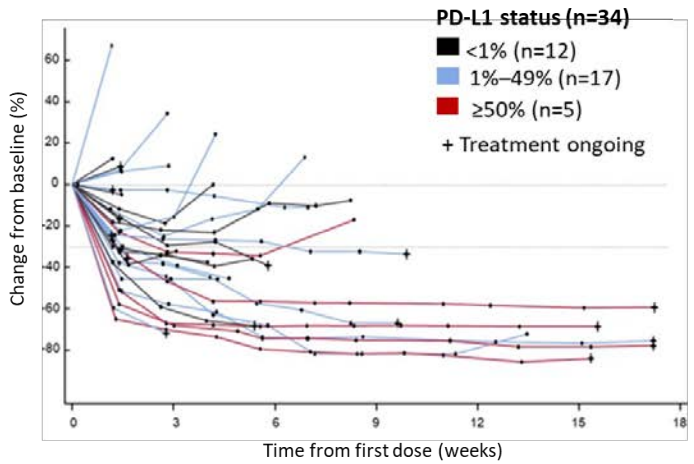


Patients in the 1L setting

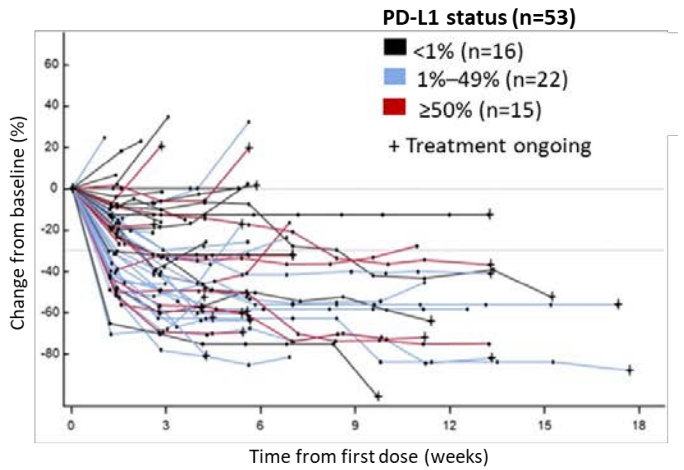


Durability of response in the 1L setting

Doublet therapy, 1L subgroup



Triplet therapy, 1L subgroup



- In patients receiving doublet or triplet therapy in the 1L setting, median DOR was NE (95% CI: 5.5, NE) and NE (95% CI: 5.7, NE), respectively

TROPION-Lung02: Safety of Dato-DXd + pembrolizumab ± chemo

Safety summary

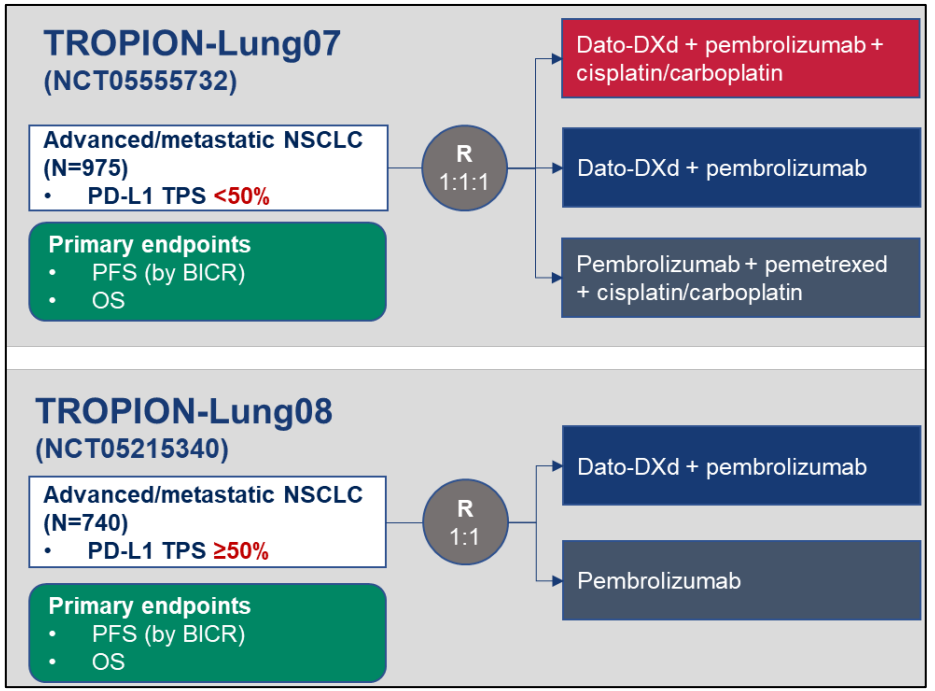
Event, n (%)	Doublet (n=64)	Triplet (n=72)
TEAEs	62 (97)	72 (100)
Study treatment related	58 (91)	72 (100)
Grade ≥3 TEAEs	34 (53)	55 (76)
Study treatment related	20 (31)	42 (58)
Serious TEAEs	20 (31)	29 (40)
Study treatment related	6 (9)	16 (22)
TEAEs associated with:		
Death	3 (5)	5 (7)
Discontinuation due to any drug	14 (22)	14 (19)
Discontinuation due to Dato-DXd	14 (22)	11 (15)

- Most frequent TEAEs of any grade were stomatitis, nausea, anemia, and fatigue
- Hematologic TEAEs of Grade ≥3 were more frequent with triplet therapy than with doublet therapy

7/10/2023:
Datopotamab deruxtecan (Dato-DXd) led to a statistically significant improvement of progression-free survival (PFS) vs docetaxel for the treatment of patients with locally advanced or metastatic non–small cell lung cancer (NSCLC) who received at least 1 prior therapy, according to findings from the TROPION-Lung01 phase 3 trial (NCT04656652).

AEs of special interest

n (%)	Doublet (n=64)		Triplet (n=68)	
	All grades	Grade ≥3	All grades	Grade ≥3
IRR	15 (23)	0	10 (14)	0
Oral mucositis/stomatitis	37 (58)	5 (8)	31 (43)	4 (6)
Ocular surface toxicity	10 (16)	1 (2)	17 (24)	2 (3)
ILD/pneumonitis adjudicated as drug related	11 (17)	2 (3)	16 (22)	2 (3)



BICR, blinded independent central review; Dato-DXd, datopotamab deruxtecan; ILD, interstitial lung disease: IRR, infusion related reaction.
Goto Y, et al. ASCO 2023. Abstract 9004.

Datopotamab Deruxtecan Met the Dual Primary Endpoint of Progression-Free Survival for Patients with Advanced NSCLC in the TROPION-Lung01 Phase III Trial

Press Release – July 3, 2023

"Positive high-level results from the TROPION-Lung01 Phase III trial showed datopotamab deruxtecan (Dato-DXd) demonstrated a statistically significant improvement for the dual primary endpoint of progression-free survival (PFS) compared to docetaxel, the current standard of care chemotherapy, in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) treated with at least one prior therapy.

For the dual primary endpoint of overall survival (OS), the data were not mature and an early trend was observed in favour of datopotamab deruxtecan versus docetaxel that did not meet the prespecified threshold for statistical significance at this interim analysis. The trial will continue as planned to assess OS with greater maturity. The investigators and participants will remain blinded to the results.

The safety profile of datopotamab deruxtecan was consistent with previous clinical trials with no new safety signals identified. All grade interstitial lung disease was generally consistent with prior clinical trials, with the majority being low grade. Some Grade 5 events were observed."

https://www.astrazeneca.com/media-centre/press-releases/2023/datopotamab-deruxtecan-met-dual-primary-endpoint-of-progression-free-survival-in-patients-with-advanced-non-small-cell-lung-cancer.html

RTP RESEARCH TO PRACTICE

Tumor Treating Fields - TTFields

LUNAR (Phase 3): Randomized study of TTFields therapy with SOC for metastatic NSCLC following platinum failure

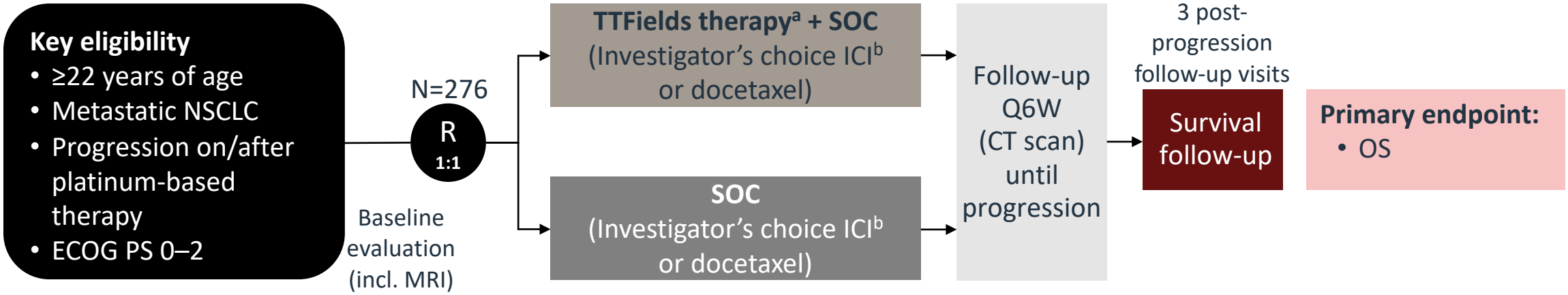
- Non-invasive, locoregional, anticancer treatment modality
- Delivered by a portable, wearable medical device and two pairs of arrays (adhesive bandages with biocompatible insulated ceramic discs covered by hydrogel)[1]
- FDA-approved for glioblastoma and malignant pleural mesothelioma[2,3]
- TTFields exert physical forces on electrically charged cellular components in dividing cancer cells, disrupting cell function[1,2]
- Cell stress following TTFields application induces ICD and cancer cell ICD triggers a systemic anti-tumor immune response

TTFields, tumor treating fields.

1. Novocure. NovoTTF™-100L system: instructions for use for unresectable pleural malignant mesothelioma; 2. Stupp R et al. Eur J Cancer. 2012;48:2192–2202;
3. Stupp R et al. JAMA. 2017;318:2306–2316.
Leal T, et al. ASCO 2023. LBA9005.

LUNAR (Phase 3): Study Design

Objective: To evaluate safety and efficacy of TTFields therapy with SOC compared to SOC alone in metastatic NSCLC progressing on or after platinum-based therapy



Stratification factors

- Region
- SOC treatment
- Histology

Data cut-off: November 26, 2022
Study sites: 124 in 17 countries (N USA, Europe, Asia)

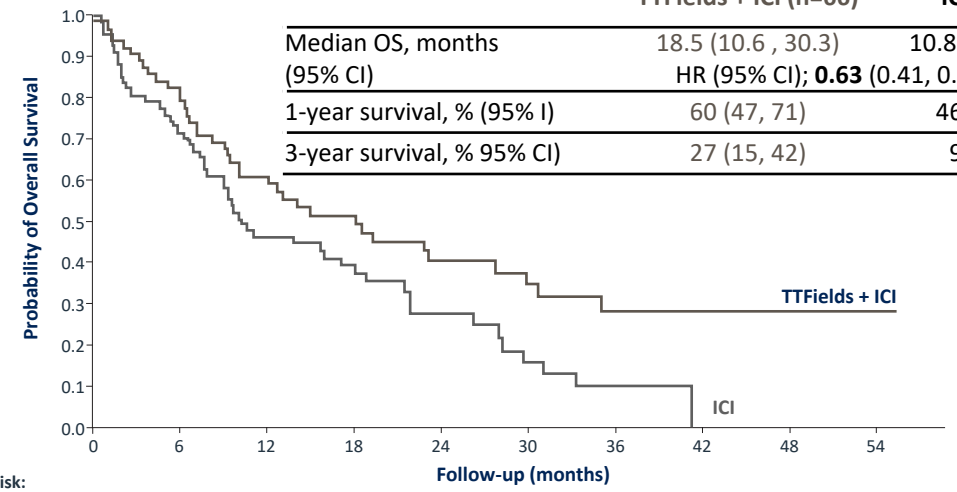
Following a planned interim analysis (March 2021), DMC recommended reducing patient accrual from 534 to 276 patients and follow-up from 18 to 12 months

[a]150 kHz; ≥18 h/day; [b]Pembrolizumab, nivolumab, or atezolizumab.
ECOG PS, Eastern Cooperative Oncology Group performance status; ICI, immune checkpoint inhibitor; TTFields, Tumor Treating Fields.
Leal T, et al. ASCO 2023. LBA 9005.

LUNAR: Efficacy of TTFields therapy by previous treatment

OS in ICI-Treated Patients

	TTFields + ICI (n=66)	ICI (n=68)
Median OS, months (95% CI)	18.5 (10.6 , 30.3)	10.8 (8.2 , 18.4)
	HR (95% CI); **0.63** (0.41, 0.96); P=0.03	
1-year survival, % (95% I)	60 (47, 71)	46 (33, 57)
3-year survival, % 95% CI)	27 (15, 42)	9 (3, 22)

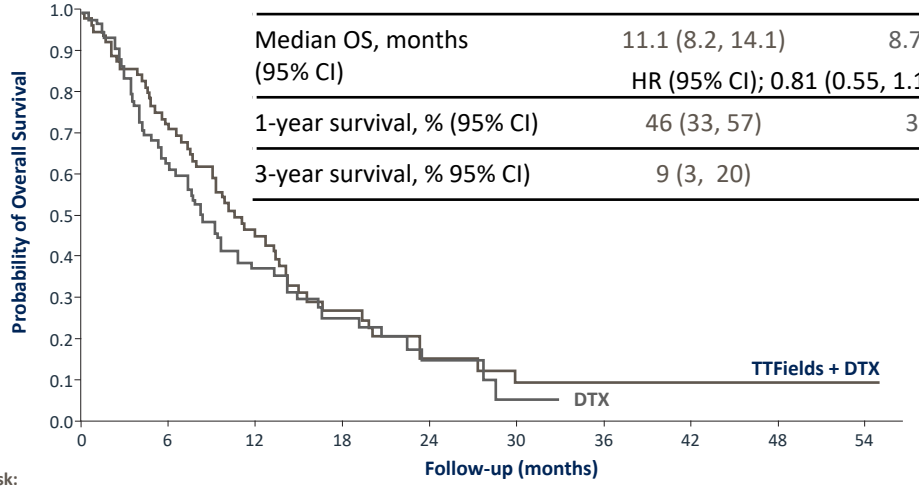


Number at risk:

TTFields + ICI	66	50	35	24	16	12	8	6	2	1
ICI	68	48	28	20	11	6	3	0	0	0

OS in DTX-Treated Patients

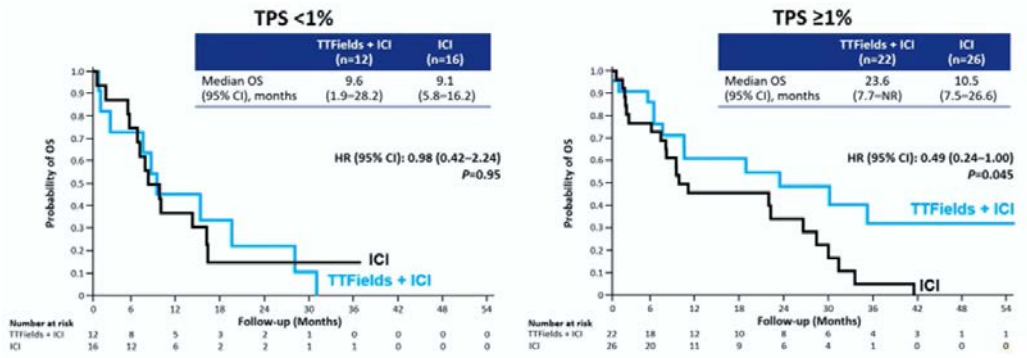
	TTFields + DTX (n=71)	DTX (n=71)
Median OS, months (95% CI)	11.1 (8.2, 14.1)	8.7 (6.3, 11.3)
	HR (95% CI); 0.81 (0.55, 1.19); P=0.28	
1-year survival, % (95% CI)	46 (33, 57)	38 (27, 49)
3-year survival, % 95% CI)	9 (3, 20)	5 (0, 18)



Number at risk:

TTFields + DTX	71	50	27	12	6	4	3	3	3	2
DTX	71	48	26	11	5	1	0	0	0	0

OS in the ICI subgroup with TPS <1% vs TPS ≥1%



- ITT:
  - ORR 20% (vs 17% SOC)
  - PFS HR: 0.85 (95% CI: 0.67, 1.11)
- Most frequent TTFields TRAE was Grade 1–2 dermatitis, no Grade 4

Leal T, et al. ASCO 2023. LBA 9005; Leal T, et al. WCLC 2023. Abstract OA22.05.

Clinical Questions and Cases

Case Presentation: 56-year-old man with locally advanced unresectable adenocarcinoma of the lung receives RT with weekly carboplatin/paclitaxel → consolidation durvalumab (skin rash)

Dr Mamta Choksi (New Port Richey, Florida; 10-5-2021)

RTP RESEARCH TO PRACTICE

Non-Small Cell Lung Cancer
Immunotherapy for Localized/Locally Advanced Disease

- Neoadjuvant/adjuvant immunotherapy; key trials/current algorithm
- Recent chemotherapy shortage
- Immunotherapy consolidation (durvalumab) for unresectable locally advanced disease

Discussion Question

Regulatory and reimbursement issues aside, what would you most likely recommend as consolidation treatment for a patient with locally advanced NSCLC who has completed chemoradiation therapy and is found to have an EGFR-activating mutation?

Discussion Question

Regulatory and reimbursement issues aside, what would you most likely recommend as consolidation treatment for a patient with locally advanced NSCLC who has completed chemoradiation therapy and is found to have a MET exon 14 skipping mutation?

Case Presentation: 94-year-old woman with metastatic adenocarcinoma of the lung (ECOG PS 3) and PD-L1 TPS 75% responds dramatically to pembrolizumab

Dr Zanetta Lamar (Naples, Florida; 8-17-2020)

RTP
RESEARCH
TO PRACTICE

Non-Small Cell Lung Cancer
Immunotherapy and Other Issues in Metastatic Disease

- Tislelizumab, cemiplimab: Are IOs interchangeable?
- Combination immunotherapy: Ipilimumab/nivolumab; durvalumab/tremelimumab
- New antibody-drug conjugates: Dato-DXd
- Tumor treating fields

Discussion Question

Do you have a preferred anti-PD-1/PD-L1 antibody when administered as monotherapy for patients with metastatic squamous cell carcinoma of the lung with high PD-L1 (TPS ≥50%)?

Discussion Question

Regulatory and reimbursement issues aside, what first-line treatment regimen would you recommend for a 65-year-old patient with metastatic nonsquamous NSCLC, no identified targetable mutations and a PD-L1 TPS of 0%?

Discussion Question

A recent press release stated that data from a Phase III trial that will be presented at an upcoming conference demonstrated a significant improvement in progression-free survival with which therapy compared to docetaxel for patients with previously treated NSCLC?

Discussion Question

Which patients with metastatic NSCLC derived the greatest benefit from tumor treating field therapy in the Phase III LUNAR trial?

Current Approaches and Future Strategies in Oncology: A Multitumor Educational Symposium in Partnership with Florida Cancer Specialists and Research Institute

A CME/MOC- and NCPD-Accredited Event

Saturday, October 7, 2023
7:15 AM – 12:30 PM ET

RTP
RESEARCH
TO PRACTICE

Agenda

Module 1 — ER-Positive Breast Cancer: *Drs Burstein and Jhaveri*

Module 2 — Prostate Cancer: *Drs Morgans and Smith*

Module 3 — Non-Small Cell Lung Cancer: *Drs Riely and Wakelee*

Module 4 — Colorectal and Gastroesophageal Cancers:
Drs Bekaii-Saab and Philip

Module 5 — Chronic Lymphocytic Leukemia: *Drs Chanan-Khan and Kahl*

RTP
RESEARCH
TO PRACTICE

Colorectal and Gastroesophageal Cancers Faculty

Tanios Bekaii-Saab, MD
Professor
Mayo Clinic College of Medicine and Science
Program Leader, Gastrointestinal Cancer
Mayo Clinic Cancer Center
Consultant, Mayo Clinic in Arizona
Chair, ACCRU Research Consortium
Phoenix, Arizona

Philip A Philip, MD, PhD, FRCP
Professor of Oncology and Pharmacology
Leader, GI and Neuroendocrine Oncology
Henry Ford Cancer Institute
Wayne State University
Detroit, Michigan

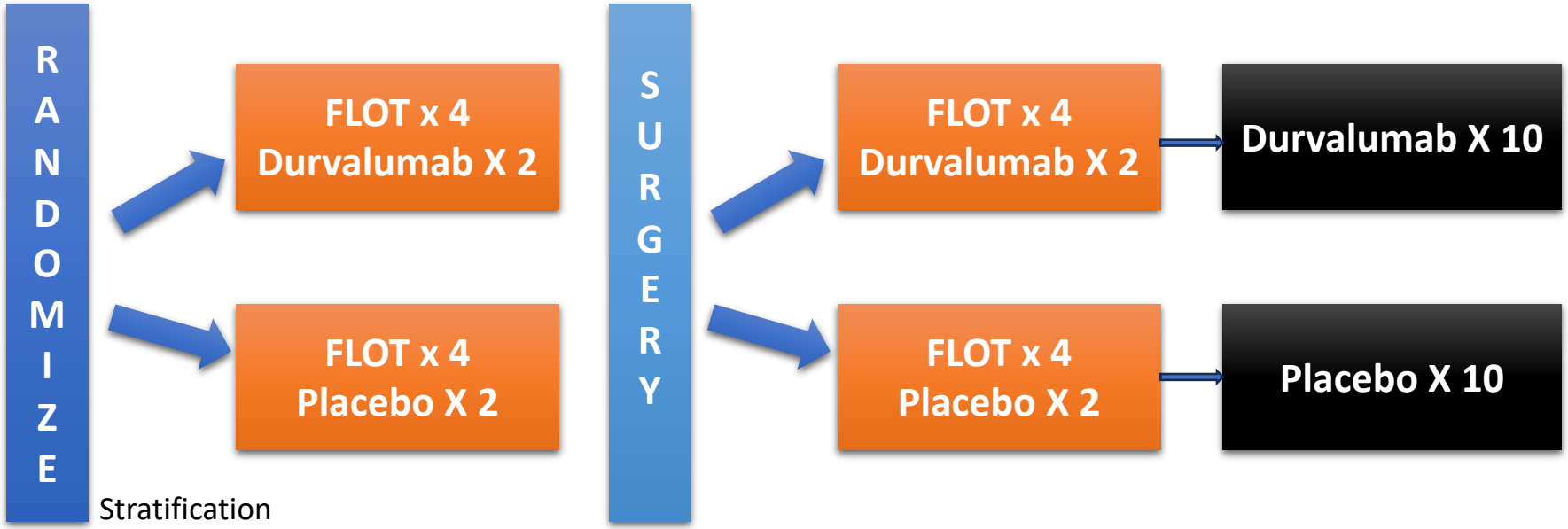
RTP
RESEARCH
TO PRACTICE

Gastroesophageal Cancers

Philip Agop Philip, MD, PhD, FRCP
Henry Ford Cancer Center
Wayne State University
Detroit, MI

MATTERHORN Phase III Trial: role of IO in neoadjuvant and adjuvant treatment of resected gastric and GEJ cancers

- Eligible patients
  - Gastric/GEJ
  - Stage II or higher
  - Any PDL1
- Primary endpoint
  - Event-free survival
  - Tolerability
- N = 900
- Started Nov 2020



Stratification
1. Geography
2. cLN
3. PDL1

Janjigian et al, Future Oncology, 2022

NCT04592913

Durvalumab with Chemotherapy Significantly Improved Pathologic Complete Response for Patients with Gastric and Gastroesophageal Junction Cancers in the MATTERHORN Phase III Trial

Press Release – June 2, 2023

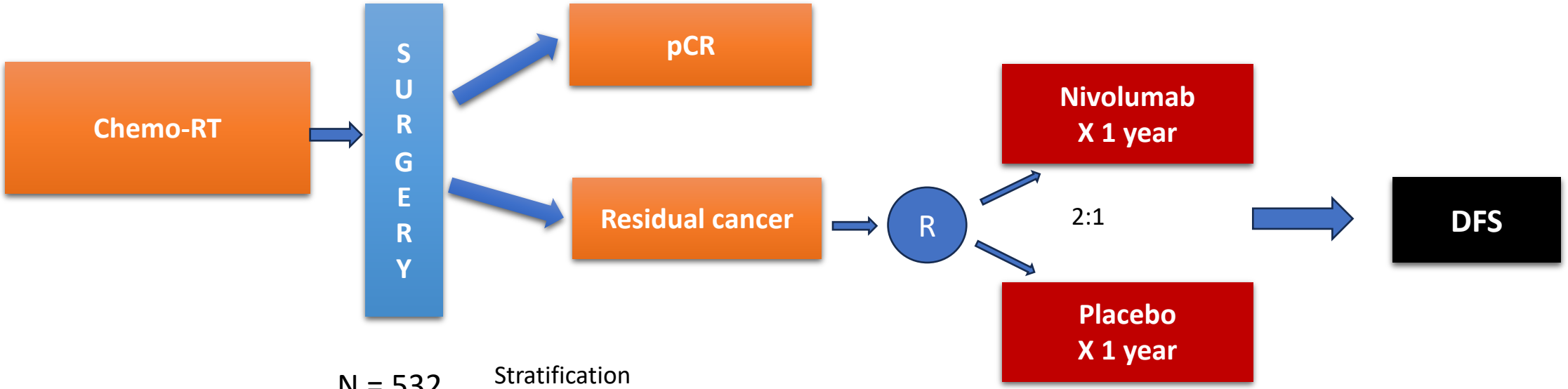
"Positive high-level results from a planned interim analysis of the MATTERHORN Phase III trial showed treatment with durvalumab added to standard-of-care FLOT (fluorouracil, leucovorin, oxaliplatin, and docetaxel) neoadjuvant (before surgery) chemotherapy demonstrated a statistically significant and clinically meaningful improvement in the key secondary endpoint of pathologic complete response (pCR) versus neoadjuvant chemotherapy alone for patients with resectable, early-stage and locally advanced (Stages II, III, IVA) gastric and gastroesophageal junction (GEJ) cancers.

The trial will continue as planned to assess EFS and overall survival to which the trial team, investigators and participants remain blinded.

The safety and tolerability of adding durvalumab to neoadjuvant FLOT chemotherapy was consistent with the known profile of this combination and did not decrease the number of patients able to undergo surgery versus chemotherapy alone."

https://www.astrazeneca.com/media-centre/press-releases/2023/imfinzi-plus-chemotherapy-significantly-improved-pathologic-complete-response-in-gastric-and-gastroesophageal-junction-cancers-in-matterhorn-phase-iii-trial.html

CheckMate 577: Adjuvant nivolumab in resected esophageal or GEJ cancer

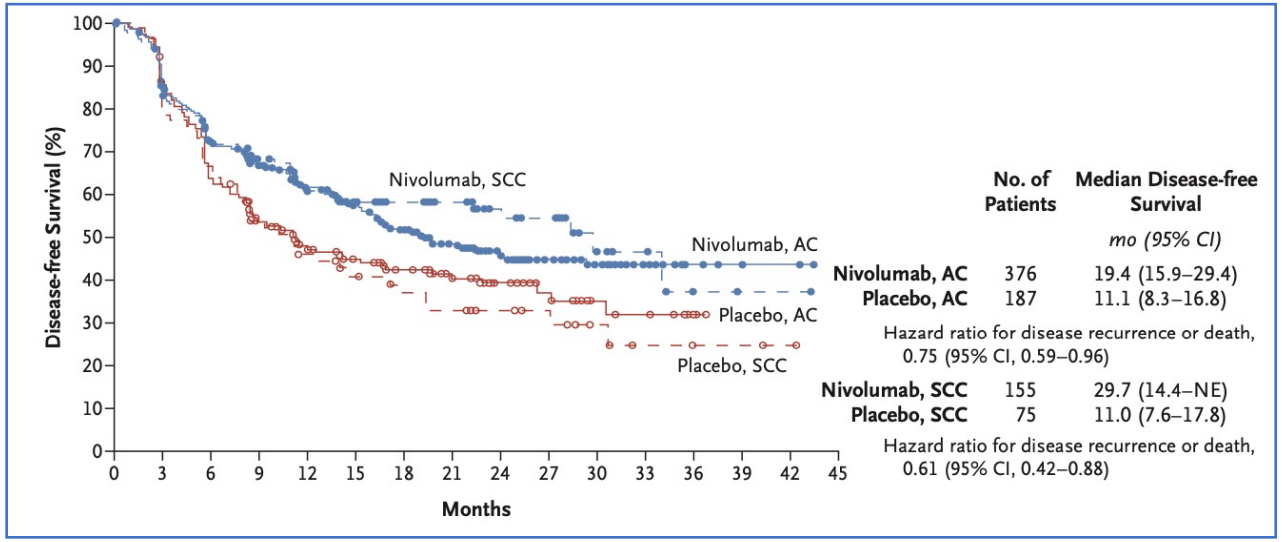


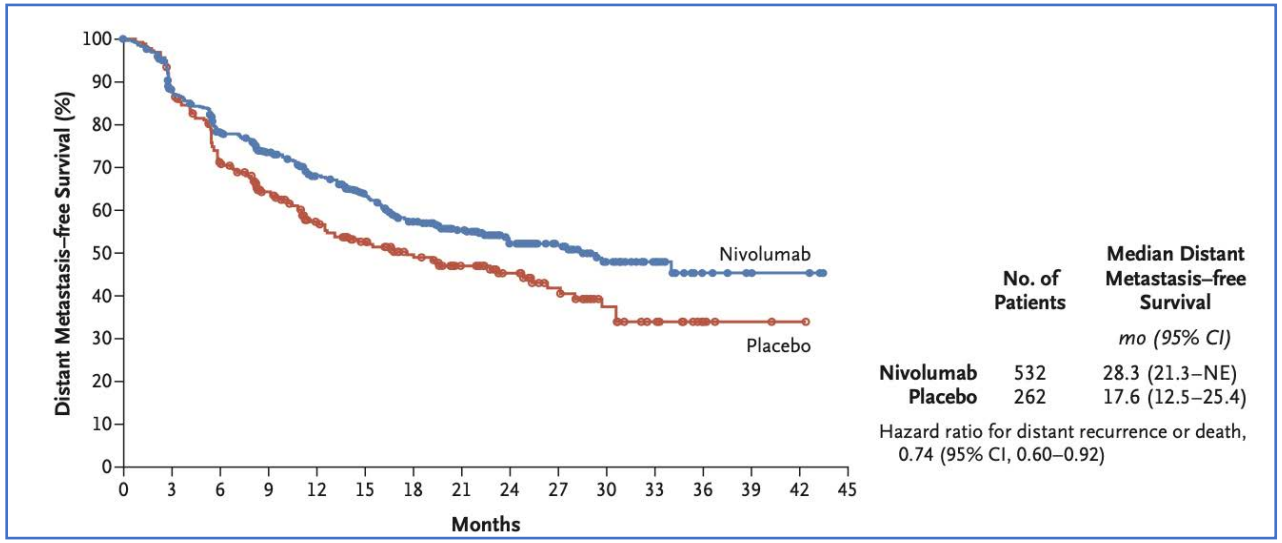
N = 532

Stratification
1. Geography
2. cLN
3. PDL1

Kelly et al, NEJM, 2021

CheckMate 577: Adjuvant nivolumab doubled median disease-free survival in resected esophageal or GEJ cancer





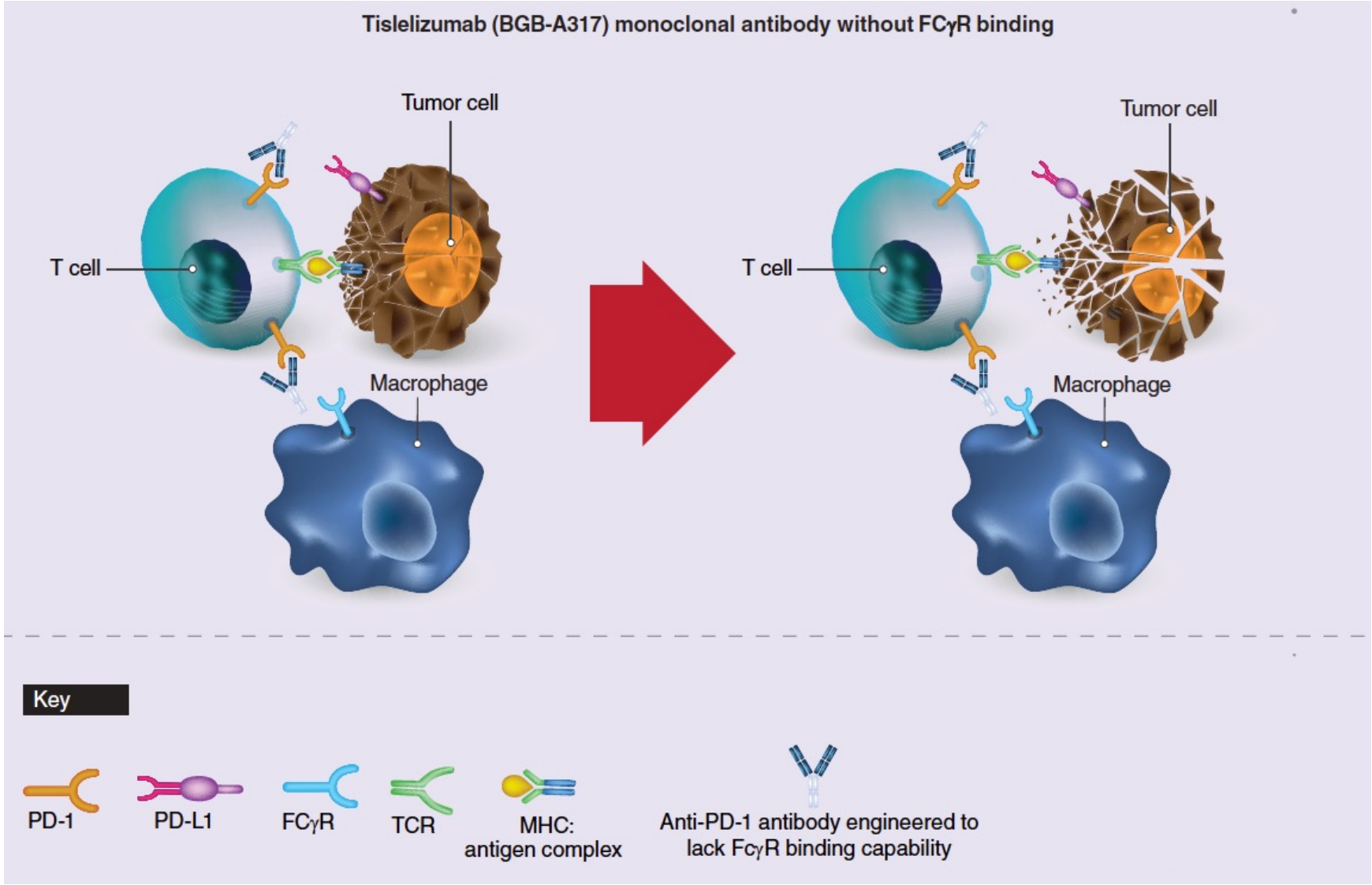
Kelly et al, NEJM, 2021

First-line studies of pembrolizumab and nivolumab in gastric, esophageal and GEJ cancers

Study	Setting	Randomization	Primary endpoints	Hazard ratio (*p*-value)
KN-062	Metastatic gastric/ GEJ ADC	Pembro vs Pembro/chemo vs Placebo/chemo	OS (CPS ≥1)	Pembro vs chemo: 0.91 (NR) Pembro + chemo vs chemo: 0.85 (0.046)
KN-590	Metastatic gastric/GEJ/esophageal	Pembro + chemo vs Placebo + chemo	OS in ESCC CPS ≥10 OS in ESCC OS in CPS ≥10 OS in all patients	0.57 (<0.0001) 0.72 (0.0006) 0.62 (<0.0001) 0.73 (<0.0001)
CM-649	Metastatic gastric/GEJ/esophageal	Nivo + chemo vs Chemo	OS (CPS ≥5)	0.71 (<0.0001)
ATTRACTION-4	Metastatic gastric/GEJ	Nivo + chemo vs Placebo + chemo	PFS (all comers) OS (all comers)	0.68 (0.0007) 0.90 (0.257)

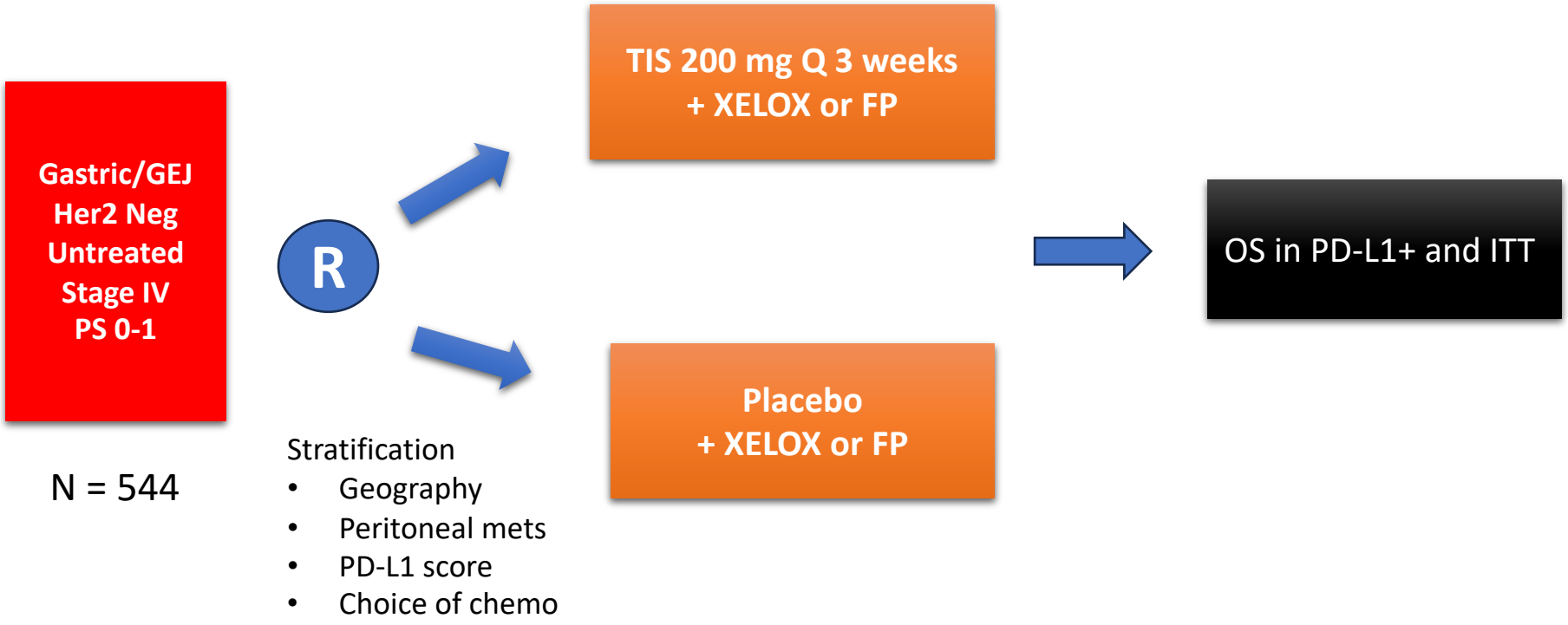
Shitara et al, JAMA Oncol, 2020; Sun et al, Lancet, 2021; Janjigian et al, Lancet, 2021; Kang et al, Lancet Oncology, 2022

Tislelizumab: Mechanism of Action



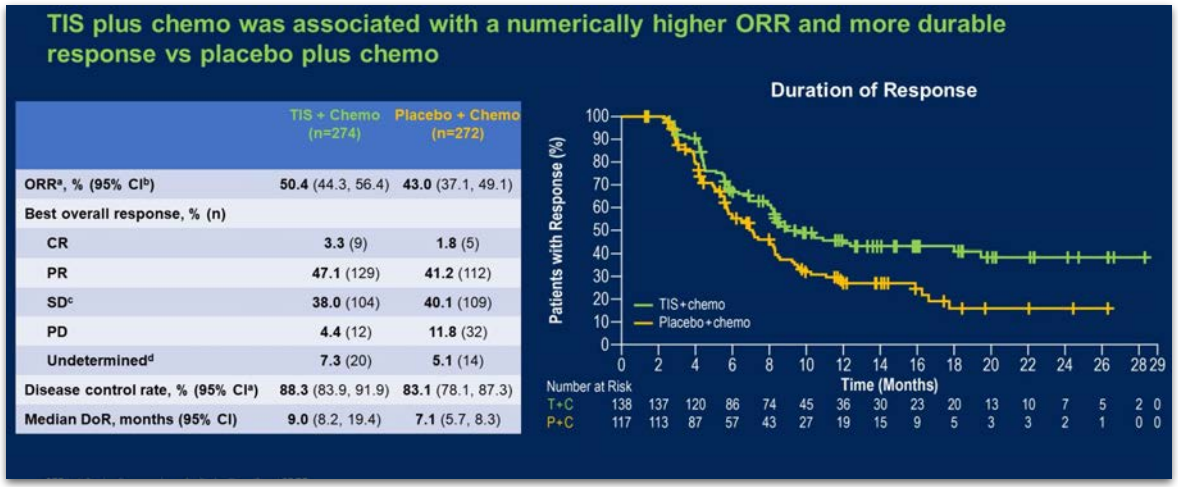
Qin S et al. *Future Oncol* 2019;15(16):1811-22.

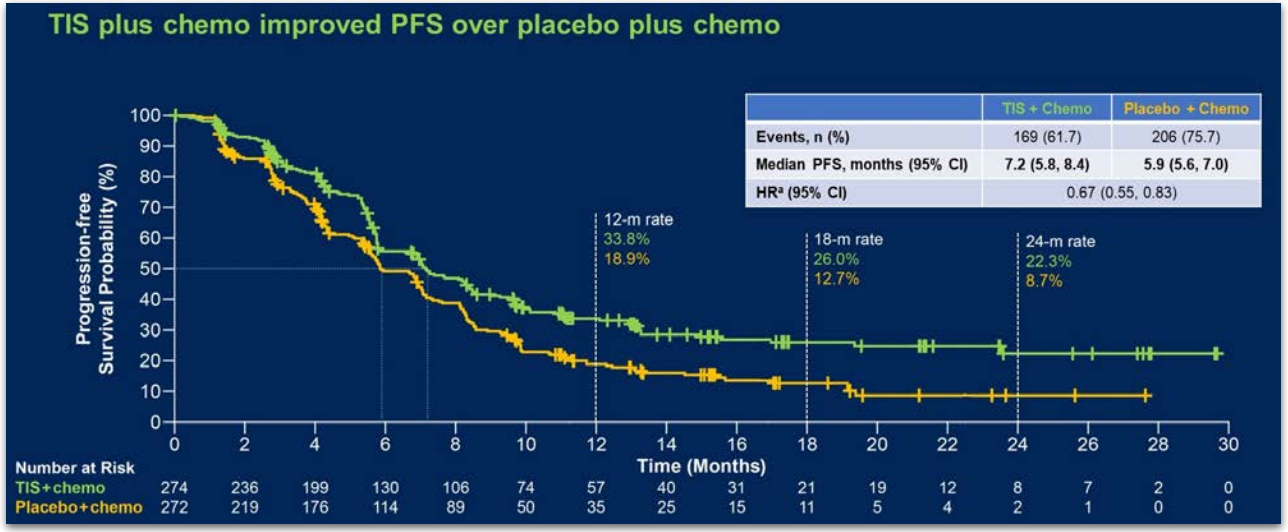
RATIONALE-305: Phase 3 study of tislelizumab (anti-PD-1) plus chemo vs placebo plus chemo in 1st line gastric/GEJ ca

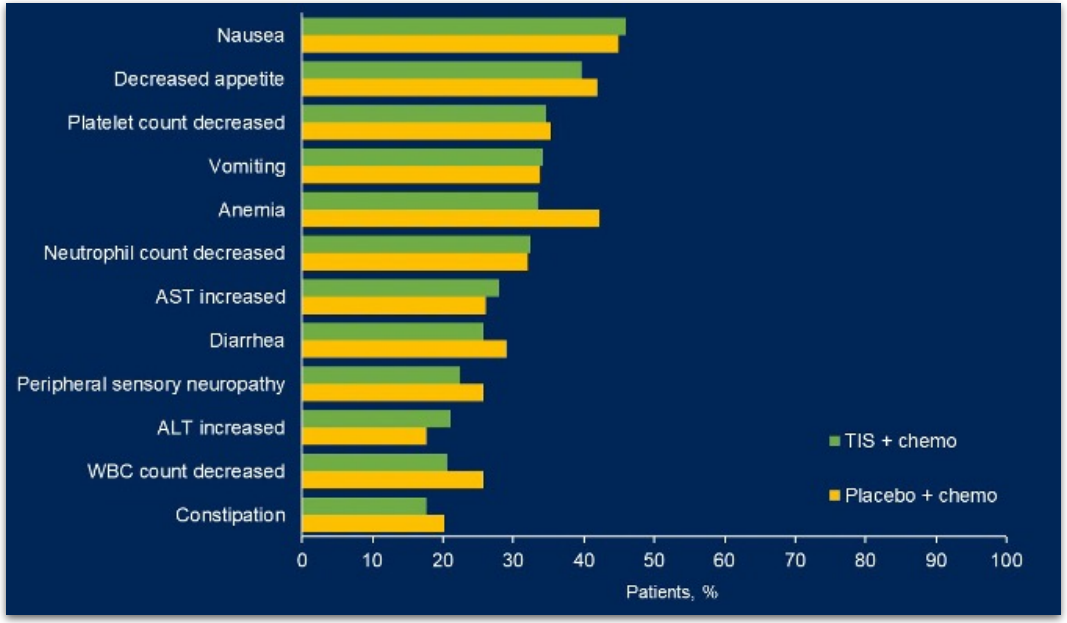


Moehler et al, ASCO GI, 2023

RATIONALE-305: Phase 3 study of tislelizumab (anti-PD-1) plus chemo vs placebo plus chemo in 1st line gastric/GEJ ca

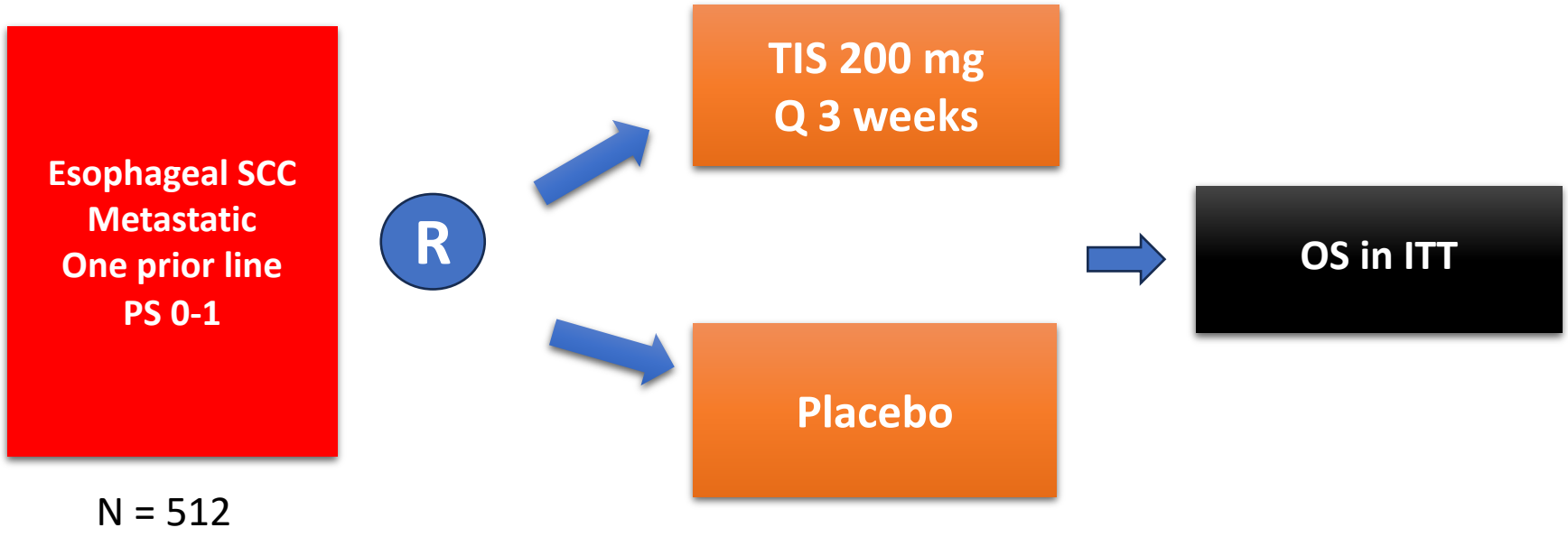






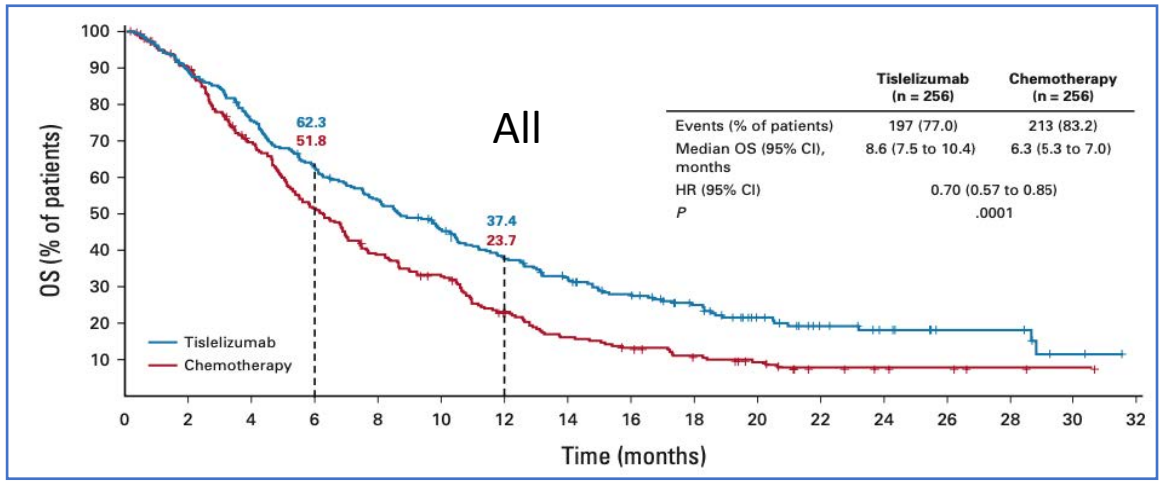
Moehler et al, ASCO GI, 2023

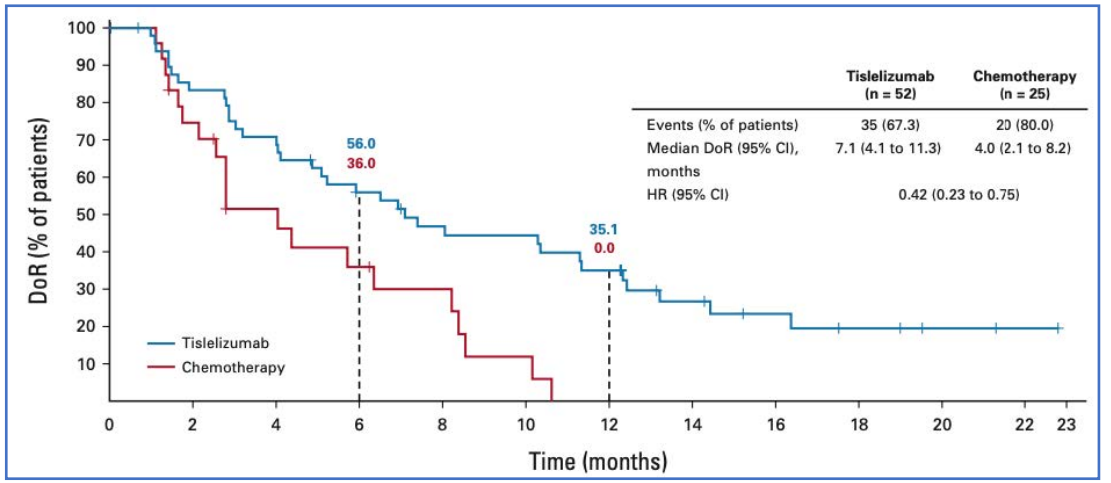
RATIONALE-302: Phase 3 study of tislelizumab (anti-PD-1) vs. chemo in 2nd line metastatic esophageal SCC

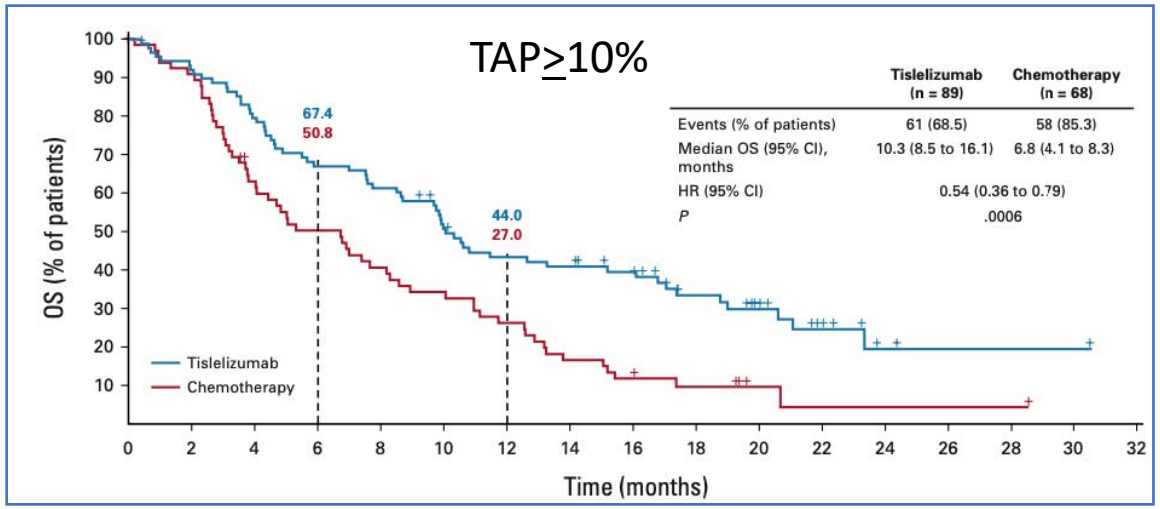


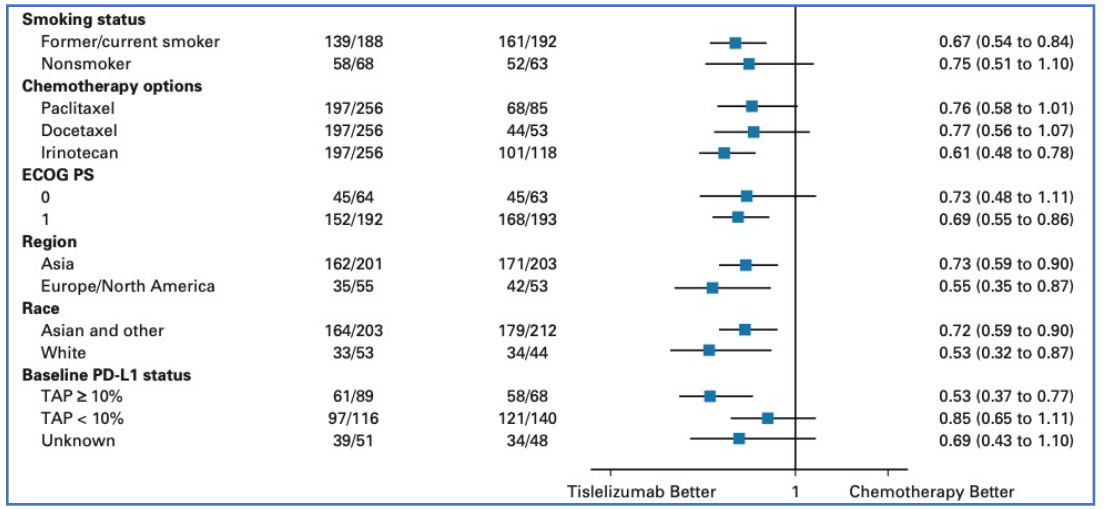
Shen et al, JCO, 2022

RATIONALE-302: Phase 3 study of tislelizumab (anti-PD-1) vs. chemo in 2nd line metastatic esophageal SCC



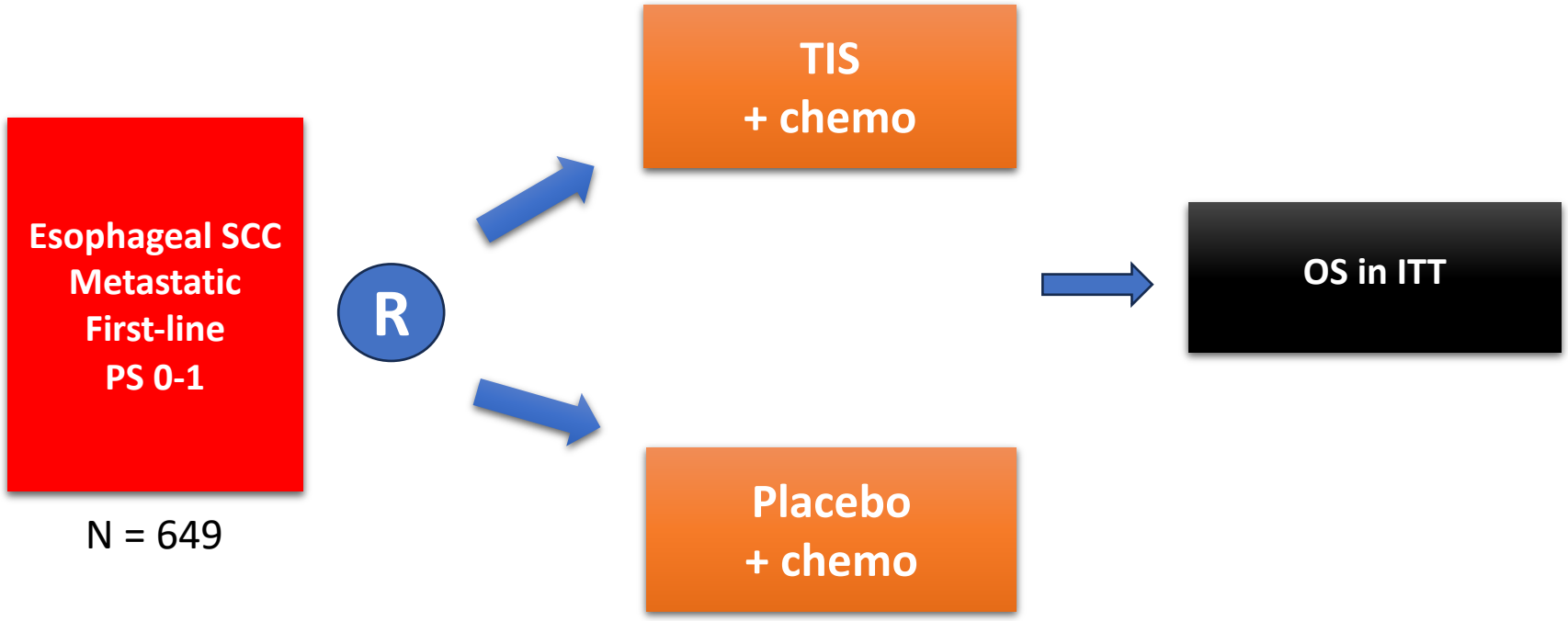






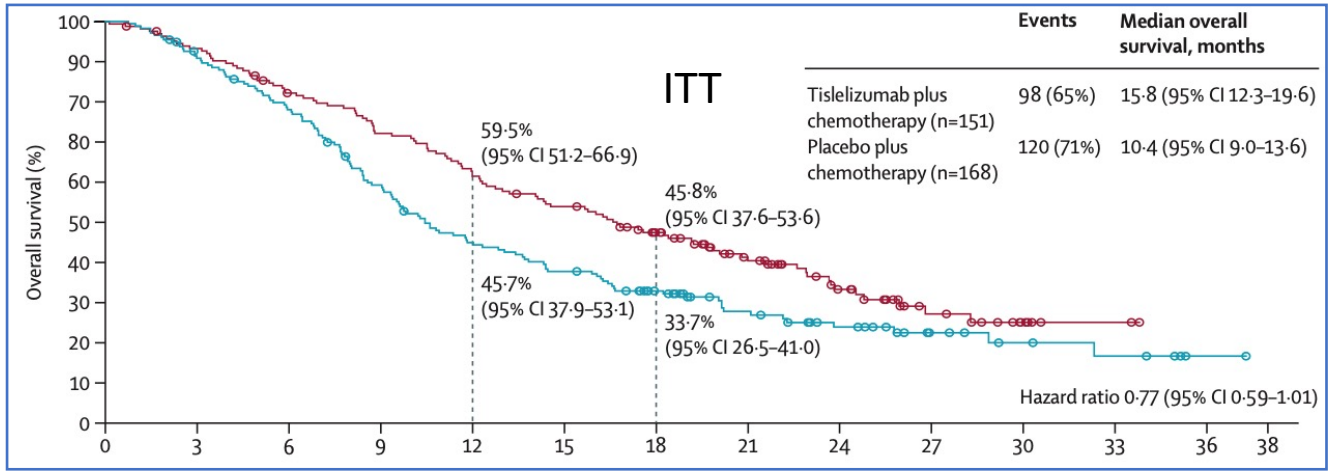
Shen et al, JCO, 2022

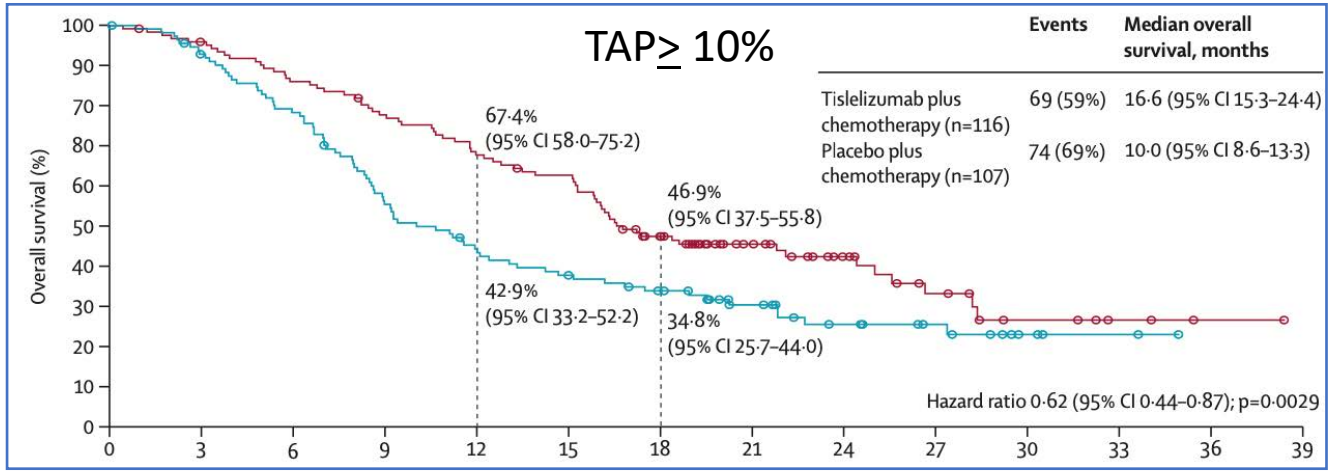
RATIONALE-306: Phase 3 study of tislelizumab (anti-PD-1) plus chemo vs. placebo plus chemo in 1st line metastatic esophageal SCC

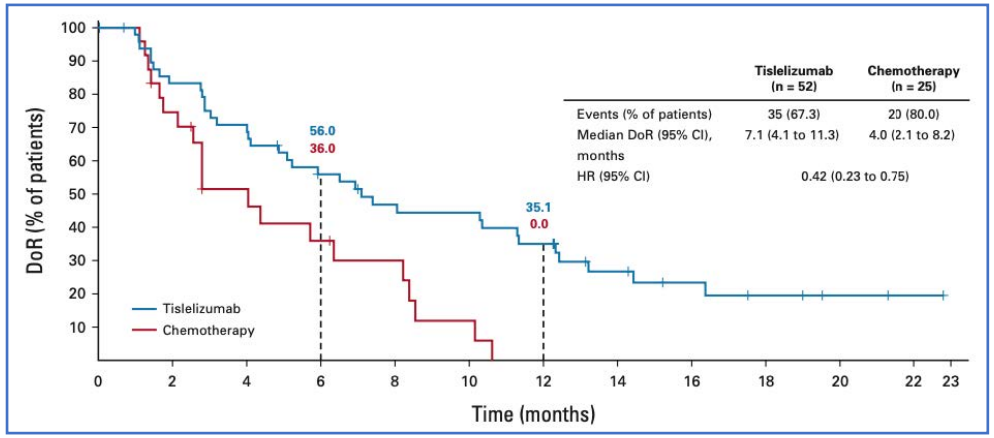


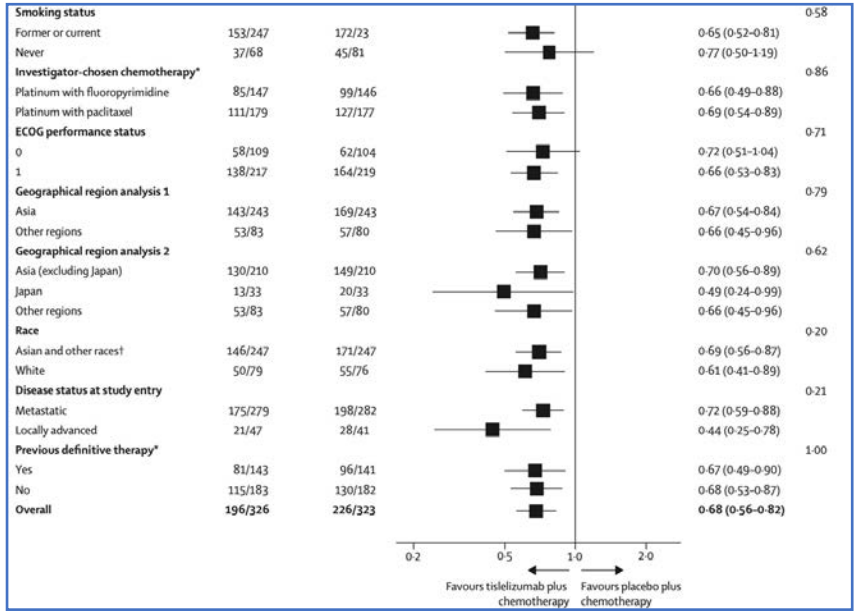
Xu et al, Lancet Oncology, 2023

RATIONALE-306: Phase 3 study of tislelizumab (anti-PD-1) plus chemo vs. placebo plus chemo in 1st line metastatic esophageal SCC





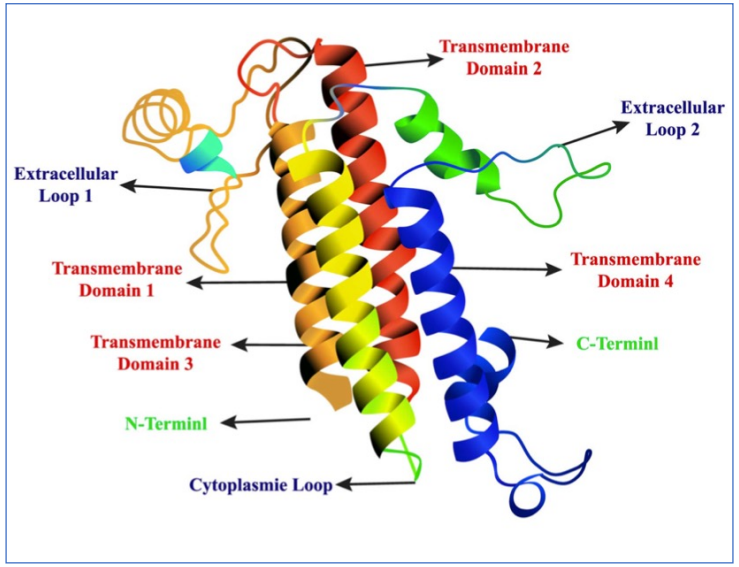


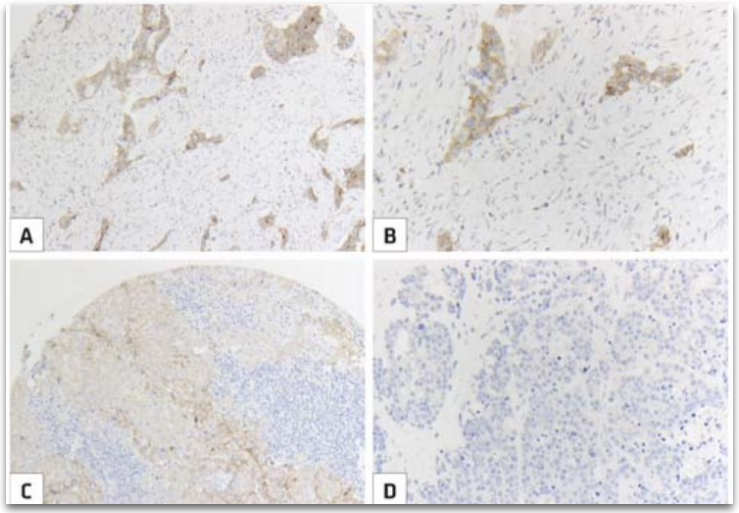


Smoking status			0·58
Former or current	153/247	172/23	0·65 (0·52–0·81)
Never	37/68	45/81	0·77 (0·50–1·19)
Investigator-chosen chemotherapy*			0·86
Platinum with fluoropyrimidine	85/147	99/146	0·66 (0·49–0·88)
Platinum with paclitaxel	111/179	127/177	0·69 (0·54–0·89)
ECOG performance status			0·71
0	58/109	62/104	0·72 (0·51–1·04)
1	138/217	164/219	0·66 (0·53–0·83)
Geographical region analysis 1			0·79
Asia	143/243	169/243	0·67 (0·54–0·84)
Other regions	53/83	57/80	0·66 (0·45–0·96)
Geographical region analysis 2			0·62
Asia (excluding Japan)	130/210	149/210	0·70 (0·56–0·89)
Japan	13/33	20/33	0·49 (0·24–0·99)
Other regions	53/83	57/80	0·66 (0·45–0·96)
Race			0·20
Asian and other races†	146/247	171/247	0·69 (0·56–0·87)
White	50/79	55/76	0·61 (0·41–0·89)
Disease status at study entry			0·21
Metastatic	175/279	198/282	0·72 (0·59–0·88)
Locally advanced	21/47	28/41	0·44 (0·25–0·78)
Previous definitive therapy*			1·00
Yes	81/143	96/141	0·67 (0·49–0·90)
No	115/183	130/182	0·68 (0·53–0·87)
Overall	**196/326**	**226/323**	**0·68 (0·56–0·82)**

Xu et al, Lancet Oncology, 2023

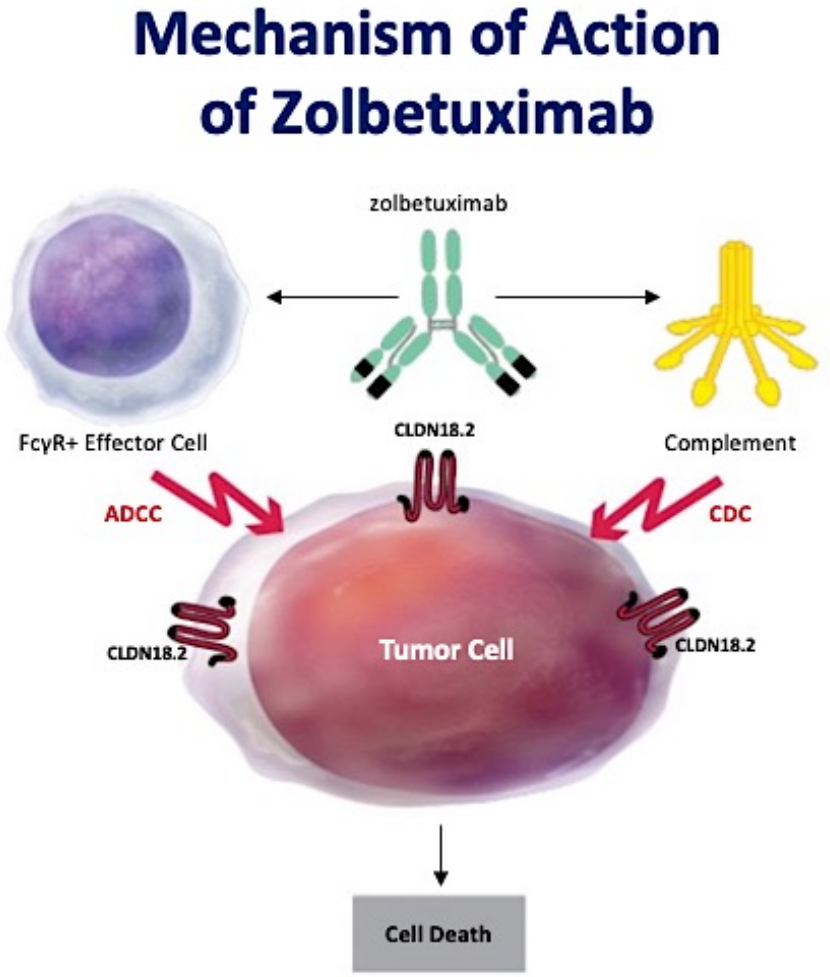
Zolbetuximab in Claudin 18.2 positive gastric adenocarcinoma





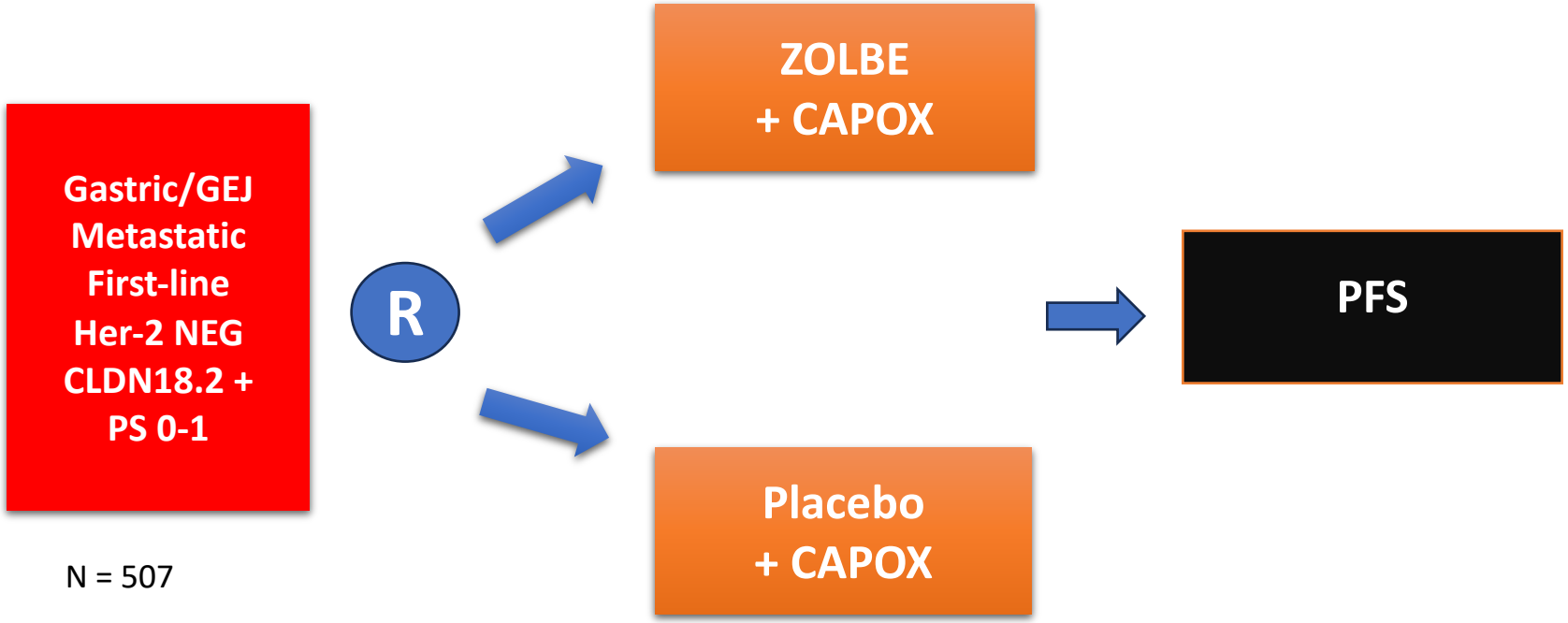
Claudin 18.2

- Family of tight junction molecules involved in the regulation of permeability, barrier function
- With malignant transformation, epitopes of CLDN18.2 become exposed and available for binding
- CLDN18.2 appears altered in approximately 30-40% of gastric/GEJ cancers



Sahin et al, Annals of Oncology DOI: 10.1016/j2021.02.005; Singh et al, J Hem Onc, 2017; Moentenich et al, Oncol Lett, 2020

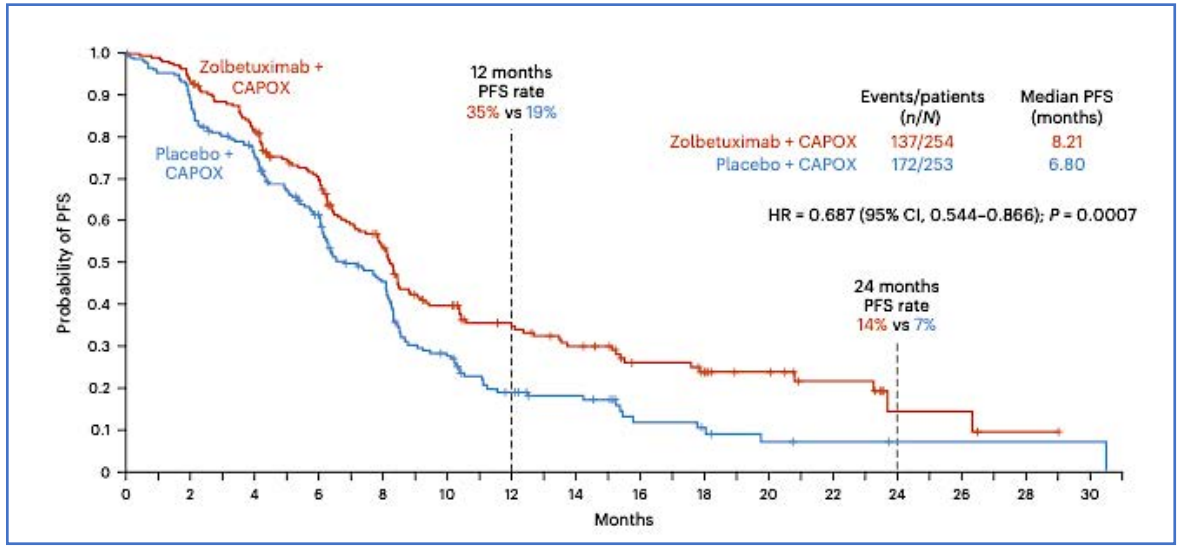
GLOW: Phase 3 trial of zolbetuximab (anti-CLDN18.2) plus CAPOX in 1st line metastatic gastric or GEJ cancer

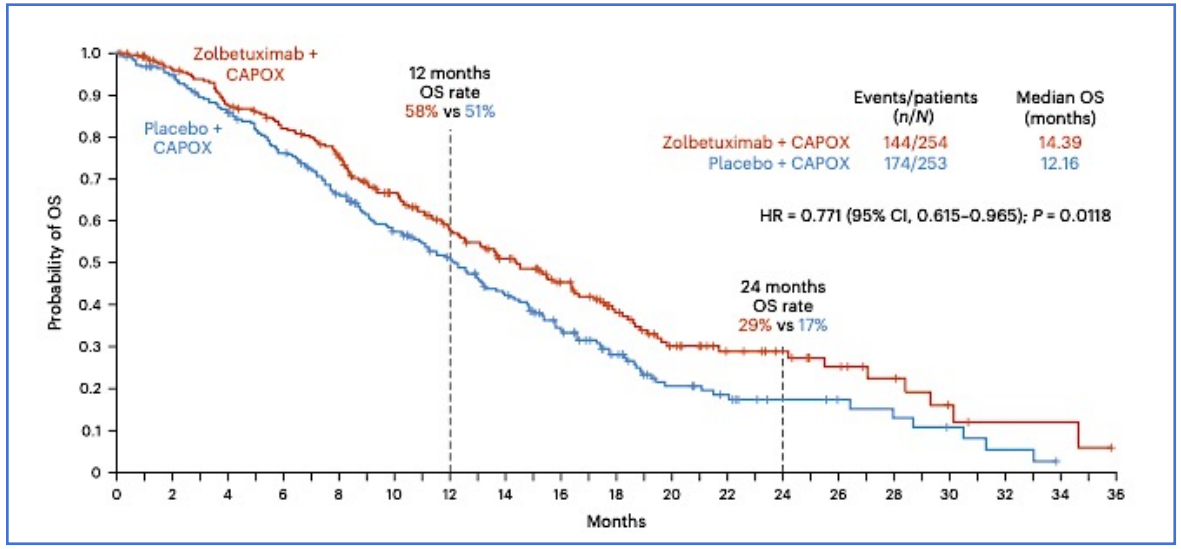


N = 507

Shah et al, Nature Medicine, 2023

GLOW: Phase 3 trial of zolbetuximab (anti-CLDN18.2) plus CAPOX in 1st line metastatic gastric or GEJ cancer

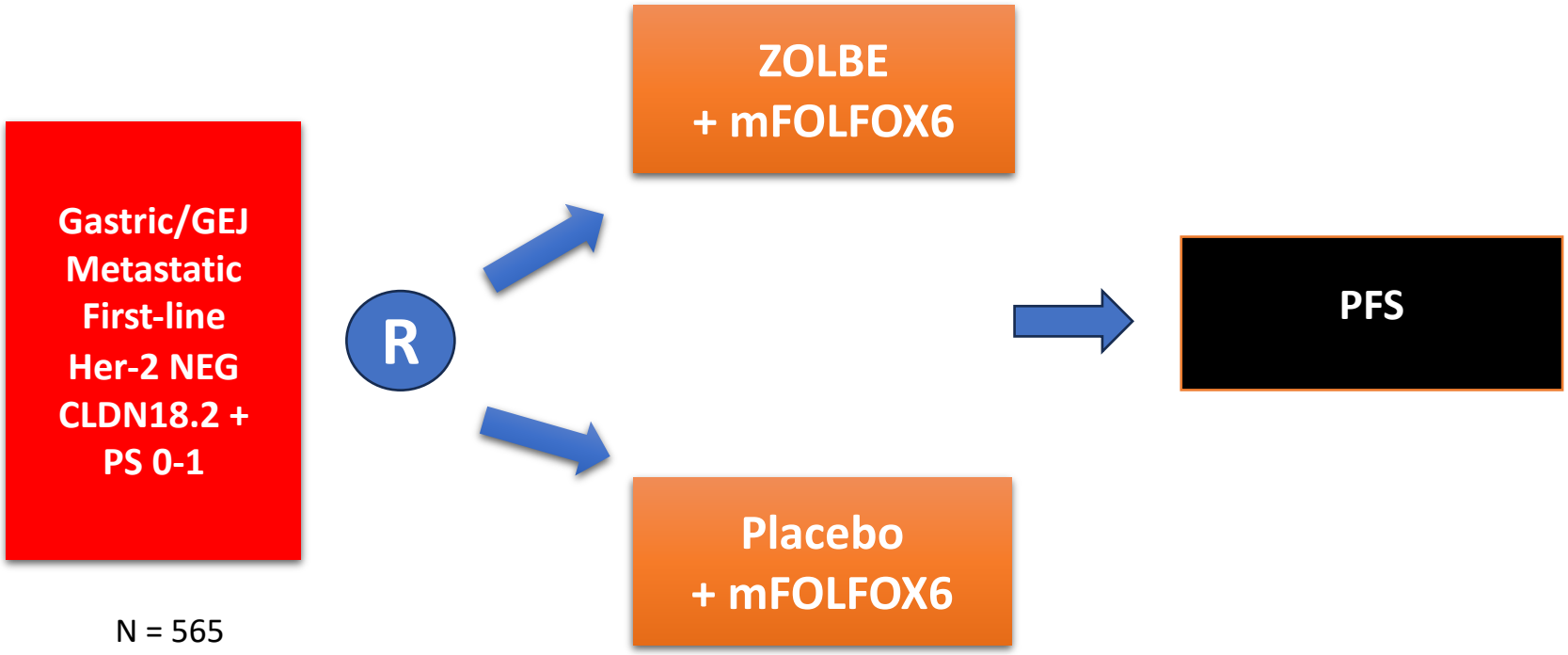




	ZOLBE/C	P/C
PR %	39	38.3
CR %	3.5	2.0
SD %	18.1	22.5
PD %	4.3	11.1

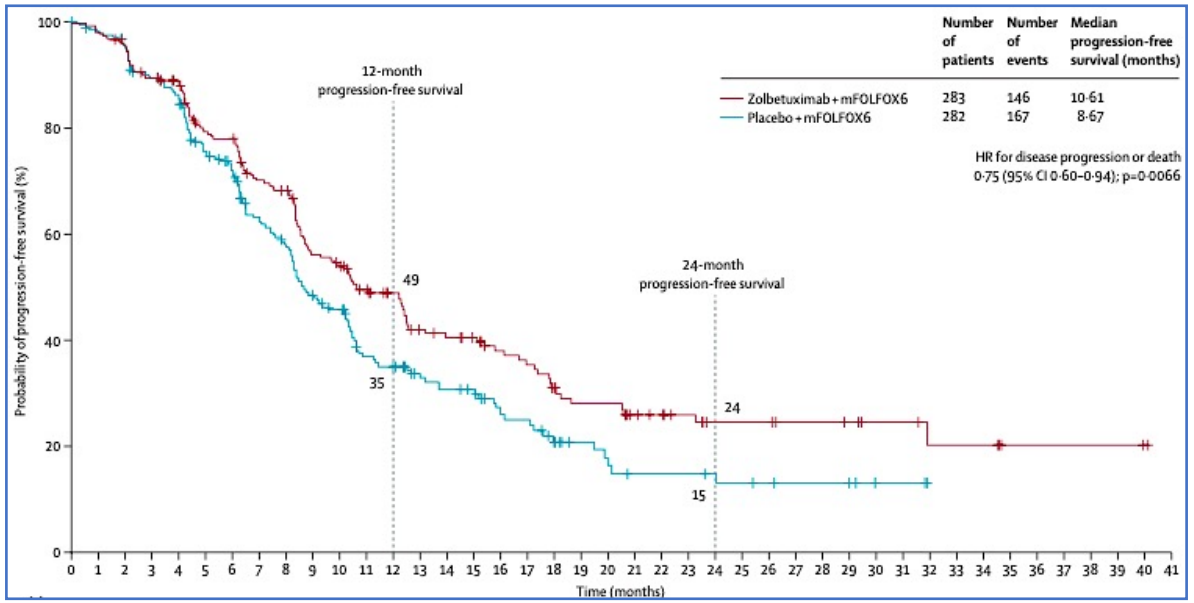
Shah et al, Nature Medicine, 2023

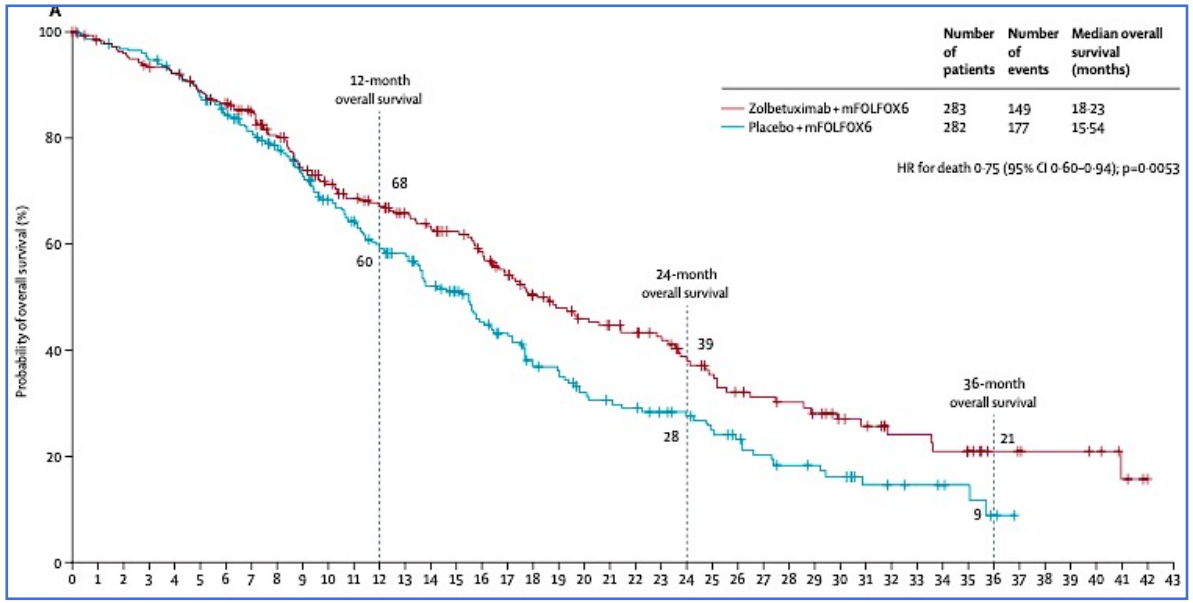
SPOTLIGHT: Phase 3 trial of zolbetuximab (anti-CLDN18.2) plus mFOLFOX6 in 1st line metastatic gastric or GEJ cancer



Shitara et al, Lancet Oncology, 2023

SPOTLIGHT: Phase 3 trial of zolbetuximab (anti-CLDN18.2) plus mFOLFOX6 in 1st line metastatic gastric or GEJ cancer





Shitara et al, Lancet Oncology, 2023

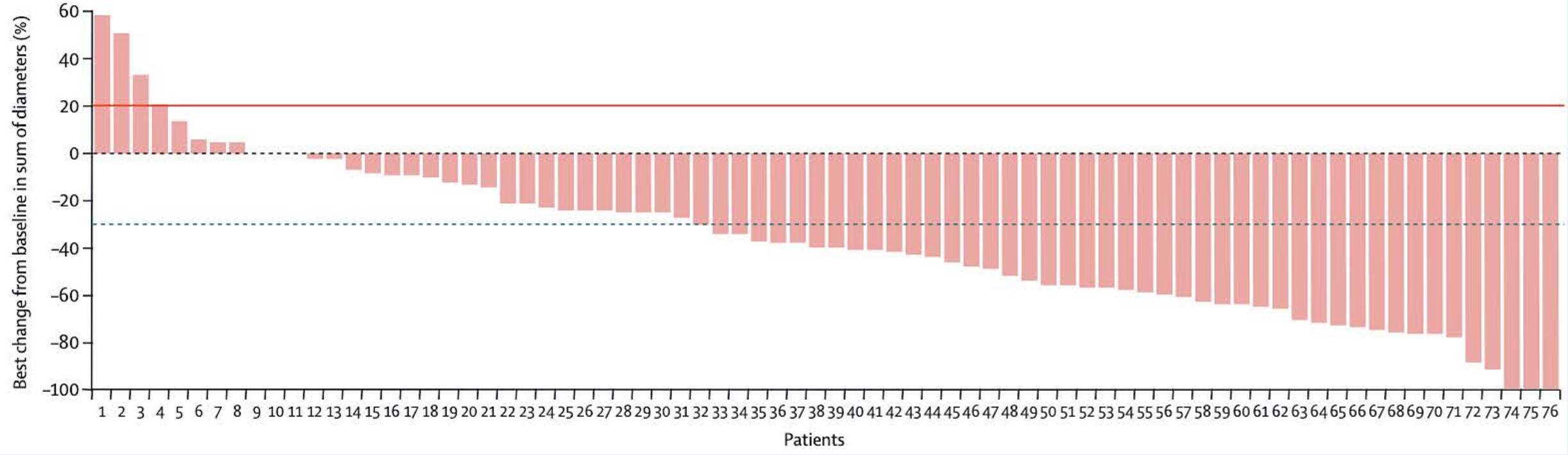
Select grade 3 toxicities of zolbetuximab plus chemotherapy (%)

	SPOTLIGHT		GLOW	
	Zolbe/FFX	Pl/FFX	Zolbe/CAPOX	Pl/CAPOX
Vomiting	16	6	12.2	3.6
Neutropenia	28	23	7.1	2.8
Neuropathy	4	5	0.4	2.4
Asthenia	7	3	2.8	1.2
platelets	1	2	2.8	2.8
Death	2	1	2.4	2.8

Trastuzumab deruxtecan in patients in the USA and Europe with HER2-positive advanced gastric or gastroesophageal junction cancer with disease progression on or after a trastuzumab-containing regimen (DESTINY-Gastric02): primary and updated analyses from a single-arm, phase 2 study

Eric Van Cutsem, Maria di Bartolomeo, Elizabeth Smyth, Ian Chau, Haeseong Park, Salvatore Siena, Sara Lonardi, Zev A Wainberg, Jaffer Ajani, Joseph Chao, Yelena Janjigian, Amy Qin, Jasmeet Singh, Ferdous Barlaskar, Yoshinori Kawaguchi, Geoffrey Ku

DESTINY-Gastric02: Best Percentage Change of Tumor Size and Objective Response Rate (Full Analysis Set)



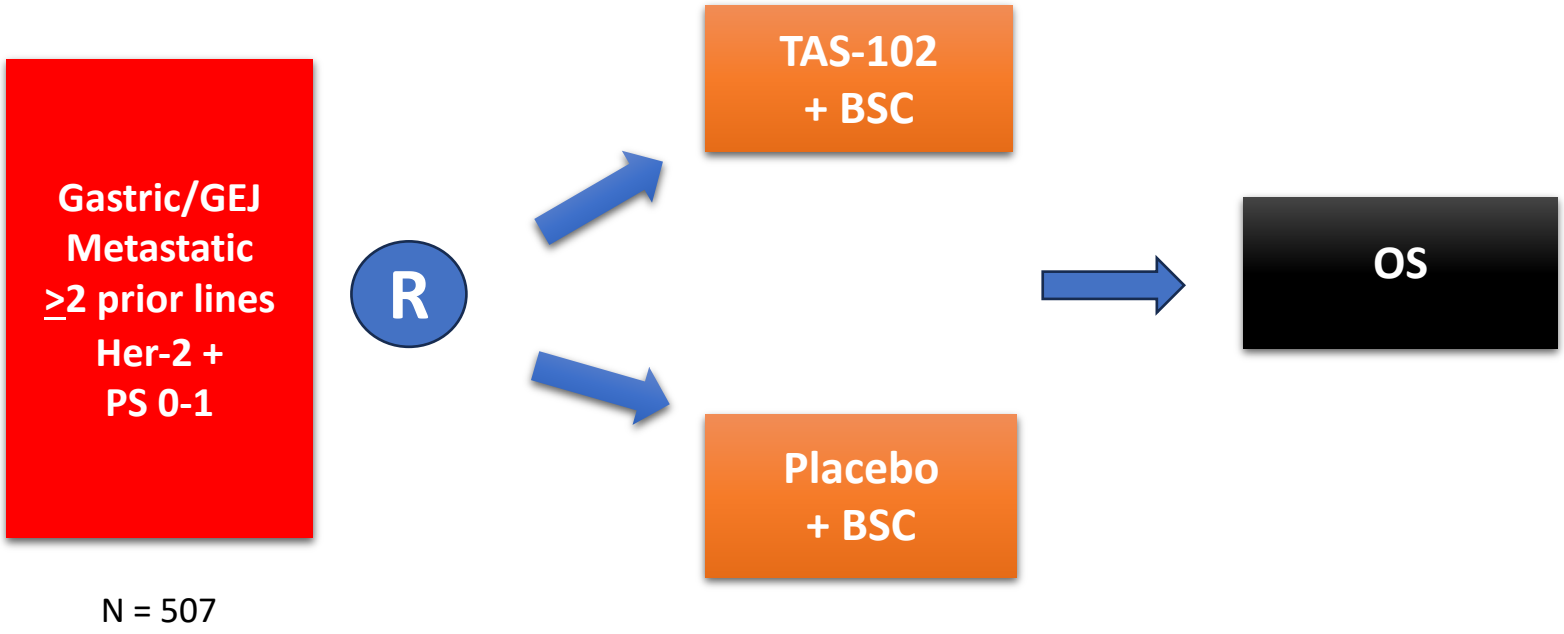
Van Cutsem E et al. *Lancet Oncol* 2023;24(7):744-56.

DESTINY-Gastric02: Summary of Response Assessment by Independent Central Review (Full Analysis Set)

	April 9, 2021, data cutoff; patients (N=79)	Nov 8, 2021, data cutoff; patients (N=79)
Confirmed objective response	30 (38%; 27·3–49·6)	33 (42%; 30·8–53·4)
Confirmed best overall response		
Complete response	3 (4%)	4 (5%)
Partial response	27 (34%)	29 (37%)
Stable disease	34 (43%)	31 (39%)
Progressive disease	13 (16%)	13 (16%)
Not evaluable	2 (3%)	2 (3%)
Median progression-free survival, months	5·5 (4·2–7·2)*	5·6 (4·2–8·3)†
Patients with events	44 (56%)	51 (65%)
Progressive disease	37 (47%)	44 (56%)
Death	7 (9%)	7 (9%)
Median overall survival, months	12·1 (8·6–NE)‡	12·1 (9·4–15·4)§
Patients with events	26 (33%)	46 (58%)
Patients without events (censored)	53 (67%)	33 (42%)
Alive	46 (58%)	26 (33%)
Lost to follow-up	7 (9%)	7 (9%)
Confirmed disease control	64 (81%; 70·6-89·0)	64 (81%; 70·6–89·0)
Median time to response, months	1·4 (1·4–2·6)	1·4 (1·4–2·7)
Median duration of response, months	8·1 (4·1–NE)¶	8·1 (5·9–NE)‖

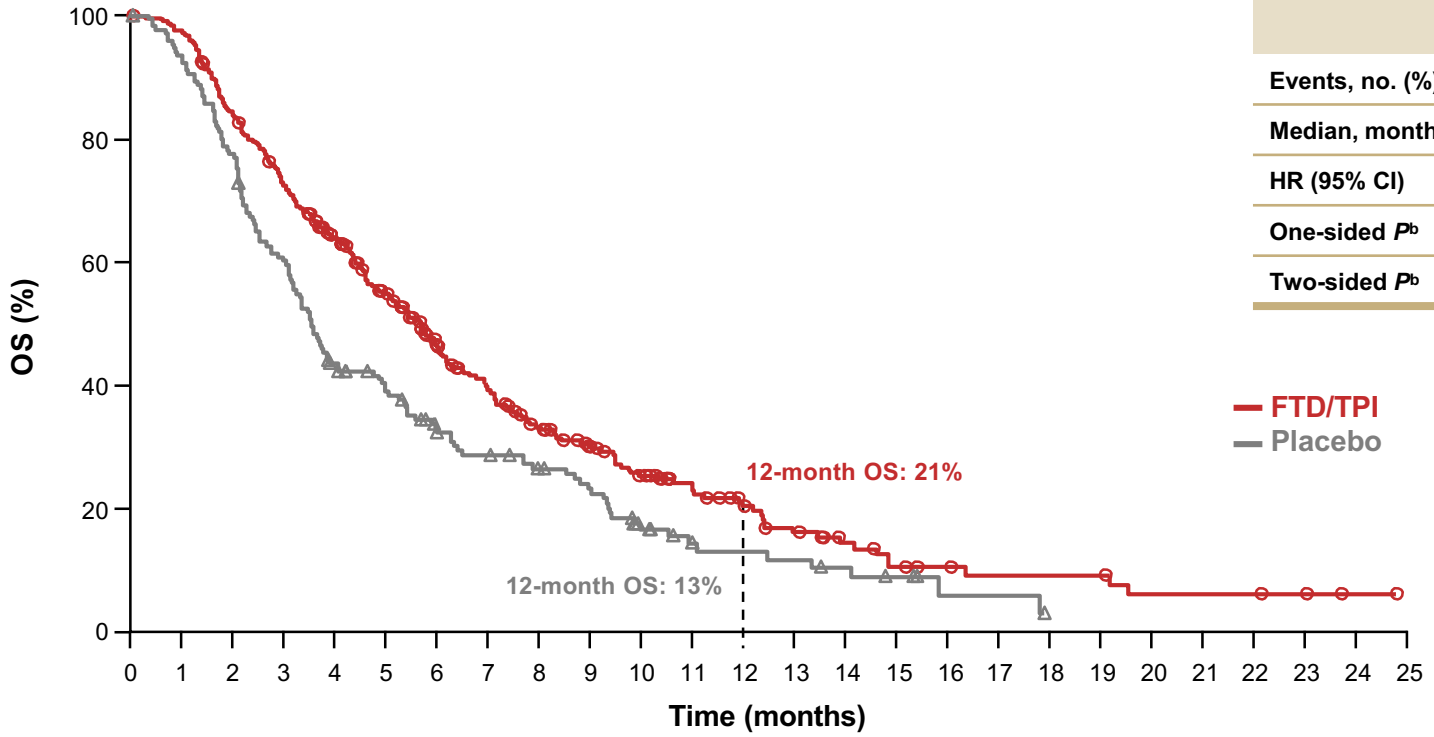
Van Cutsem E et al. *Lancet Oncol* 2023;24(7):744-56.

TAGS: Phase 3 trial of trifluridine/tipiracil (TAS-102) in heavily pre-treated metastatic gastric or GEJ cancer



Shitara et al, Lancet Oncology, 2018

TAGS: Phase 3 trial of trifluridine/tipiracil (TAS-102) in heavily pre-treated metastatic gastric or GEJ cancer



	FTD/TPI (n=337)[a]	Placebo (n=170)[a]
Events, no. (%)	244 (72)	140 (82)
Median, months	5.7	3.6
HR (95% CI)	0.69 (0.56–0.85)	
One-sided *P*[b]	0.0003	
Two-sided *P*[b]	0.0006	

Shitara et al, Lancet Oncology, 2018

Clinical Questions and Cases

Gastroesophageal Cancers
Localized Disease

- **Neoadjuvant/postneoadjuvant immunotherapy**
- **MATTERHORN trial (press release and upcoming ESMO presentation)**

Discussion Question

Regulatory and reimbursement issues aside, would you recommend neoadjuvant immunotherapy (alone or with chemotherapy) for a patient with locally advanced mismatch repair (MMR)-deficient/microsatellite instability (MSI)-high gastric adenocarcinoma?

Discussion Question

Regulatory and reimbursement issues aside, which adjuvant systemic therapy would you currently recommend to a patient with HER2-negative, MSS squamous cell carcinoma of the esophagus who receives neoadjuvant carboplatin/paclitaxel and concurrent radiation therapy and has residual disease at surgery with a PD-L1 CPS of 0?

Discussion Question

A recent press release stated that interim data from a Phase III trial that will be presented at an upcoming conference demonstrated a significant improvement in pathologic complete response (pCR) rate when which of the following was added to neoadjuvant FLOT chemotherapy?

Case Presentation: 60-year-old man with metastatic squamous cell carcinoma of the esophagus (PD-L1 70%) receives mFOLFOX + nivolumab with response

Dr KS Kumar (Trinity, Florida; 3-31-2022)

RTP
RESEARCH
TO PRACTICE

Case Presentation: A 74-year-old man with multiple comorbidities and HER2-negative, MSS, PD-L1-positive metastatic GEJ adenocarcinoma responds to FOLFOX + nivolumab

Dr Shaachi Gupta (Lake Worth, Florida; 5-28-2022)

RTP RESEARCH TO PRACTICE

Gastroesophageal Cancers
Metastatic Disease

- **First-line treatment**
  - **Zolbetuximab and claudin 18.2**
  - **Alternative anti-PD-1/PD-L1 antibodies (tislelizumab)**

Discussion Question

Two Phase III trials of zolbetuximab in combination with chemotherapy versus chemotherapy alone as first-line therapy for patients with claudin 18.2-positive, HER2-negative advanced gastric/GEJ adenocarcinoma demonstrated which outcome?

Discussion Question

Which of the following toxicities was most commonly observed with the addition of zolbetuximab to chemotherapy for patients with previously untreated claudin 18.2-positive, HER2-negative advanced gastric/GEJ adenocarcinoma in Phase III studies?

Discussion Question

The anti-PD-1 antibody tislelizumab was engineered to minimize binding to which of the following receptors?

Case Presentation: 61-year-old man with metastatic HER2-positive esophageal adenocarcinoma (PD-L1 CPS 11-20) responds to mFOLFOX + nivolumab + trastuzumab

Dr KS Kumar (Trinity, Florida; 3-31-2022)

RTP
RESEARCH
TO PRACTICE

Gastroesophageal Cancers
Metastatic Disease

- **HER2-positive disease**
  - **First-line chemotherapy/trastuzumab +/- pembrolizumab**
  - **Second-line T-DXd**

Discussion Question

Emerging data from a Phase III trial investigating the addition of pembrolizumab to trastuzumab and chemotherapy as first-line treatment for HER2-positive advanced gastric or GEJ adenocarcinoma indicate which of the following?

Discussion Question

Regulatory and reimbursement issues aside, what would you currently recommend as second-line therapy for a patient with metastatic HER2-positive, MSS gastric adenocarcinoma (PD-L1 CPS 10) whose disease has progressed on FOLFOX/trastuzumab/pembrolizumab?

Colorectal Cancer (CRC)

Tanios Bekaii-Saab, MD

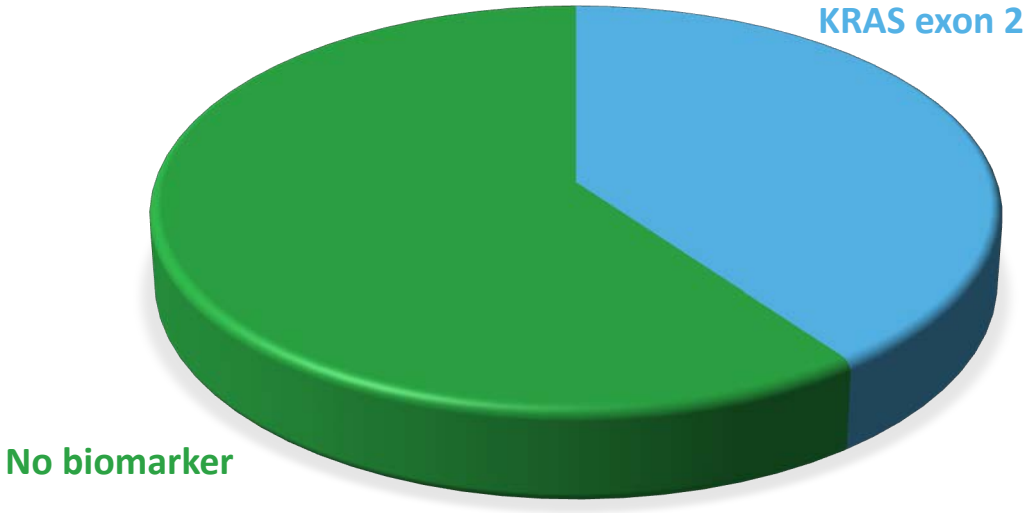
Professor, Mayo Clinic College of Medicine and Science

Consultant, Mayo Clinic AZ

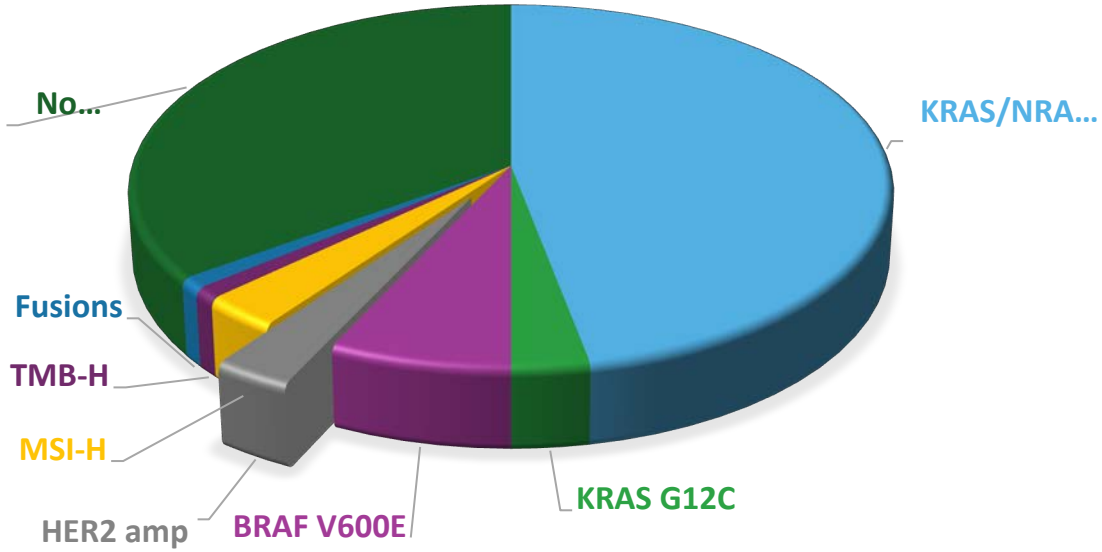
Chair, ACCRU Consortium

Actionable colorectal cancer targets

2012



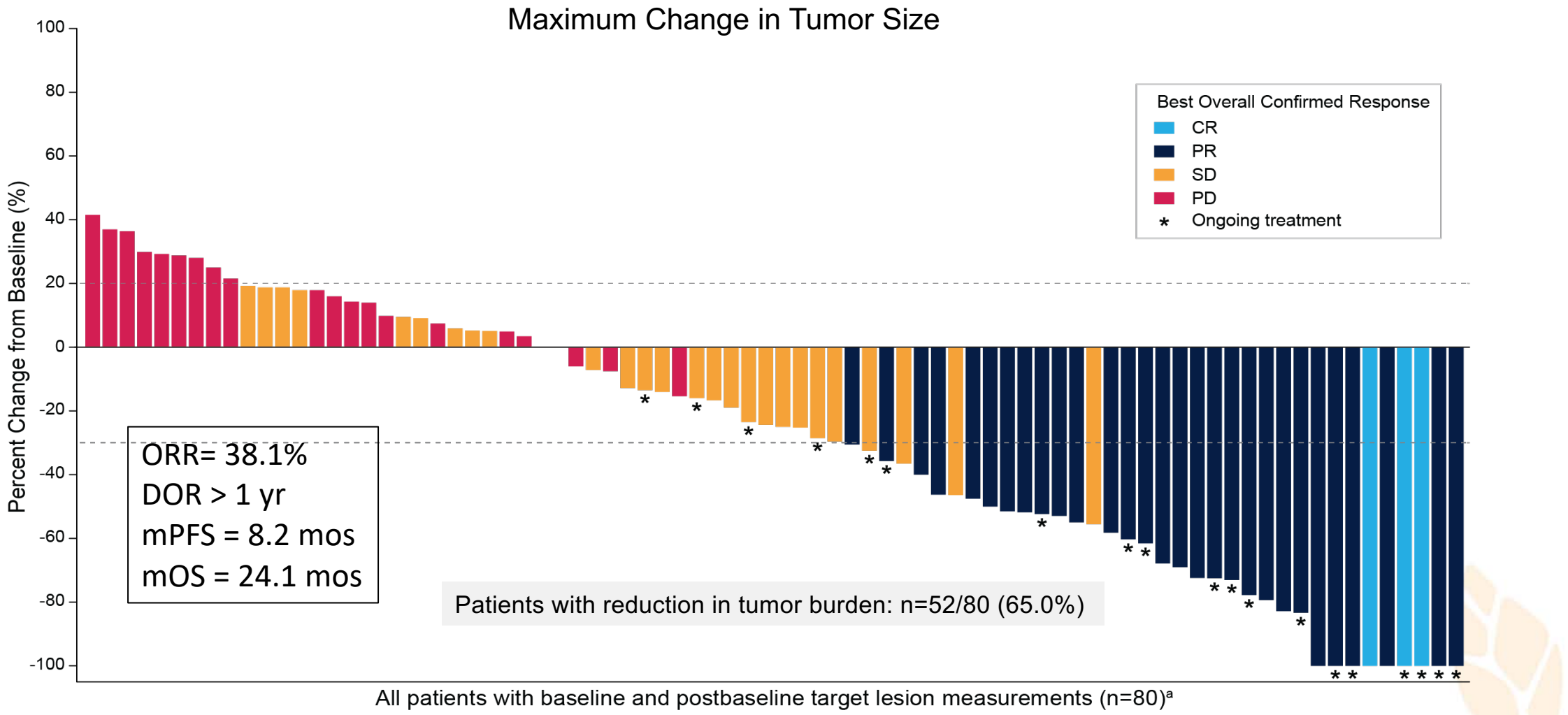
2023



DESTINY CRC-02 in HER2+ mCRC : T-DXd @ Lower Dose = Winner !

	T-DXd 5.4 mg/kg Q3W	T-DXd 6.4 mg/kg Q3W
	Total N = 82	Total N = 40
cORR, n (%) [95% CI]	**31 (37.8) [27.3-49.2]**	**11 (27.5) [14.6-43.9]**
Confirmed DCR, n (%) [95% CI]	71 (86.6) [77.3-93.1]	34 (85.0) [70.2-94.3]
Median DoR, mo (95% CI)	5.5 (4.2-8.1)	5.5 (3.7-NE)
Median PFS, mo [95% CI]	5.8 (4.6-7.0)	5.5 (4.2-7.0)
Median OS, mo [95% CI]	13.4 (12.5-16.8)	NE (9.9-NE)
G3/4/5 Toxicities (%)	49	59
ILD/Pneumonitis (%) / G5 (%)	8.4 (0)	12.8 (2.6)

MOUNTAINEER : Tucatinib + Trastuzumab in HER2+ mCRC



a Four patients who did not have baseline and/or post-baseline target lesion measurements are excluded

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Data cutoff: 28 Mar 2022

Data of HER2-targeted therapies in patients with advanced or metastatic colorectal cancer

Regimen									on Grade 3+ AEs
Trastuzumab deruxtecar									ia 17% %
Tucatinib + trastuzumab									on 7% 5%

ctDNA, circulating tumor DNA; n/a, not available; NE, not evaluable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; WT, wildtype.
1. Meric-Bernstam et al … Oncol 39, 2021 (suppl 15; abstr 3004); 3. Nakamura et al., Nature Medicine 27, 2021; 4. Raghav et al., J Clin On … O Precision Oncology 2022.

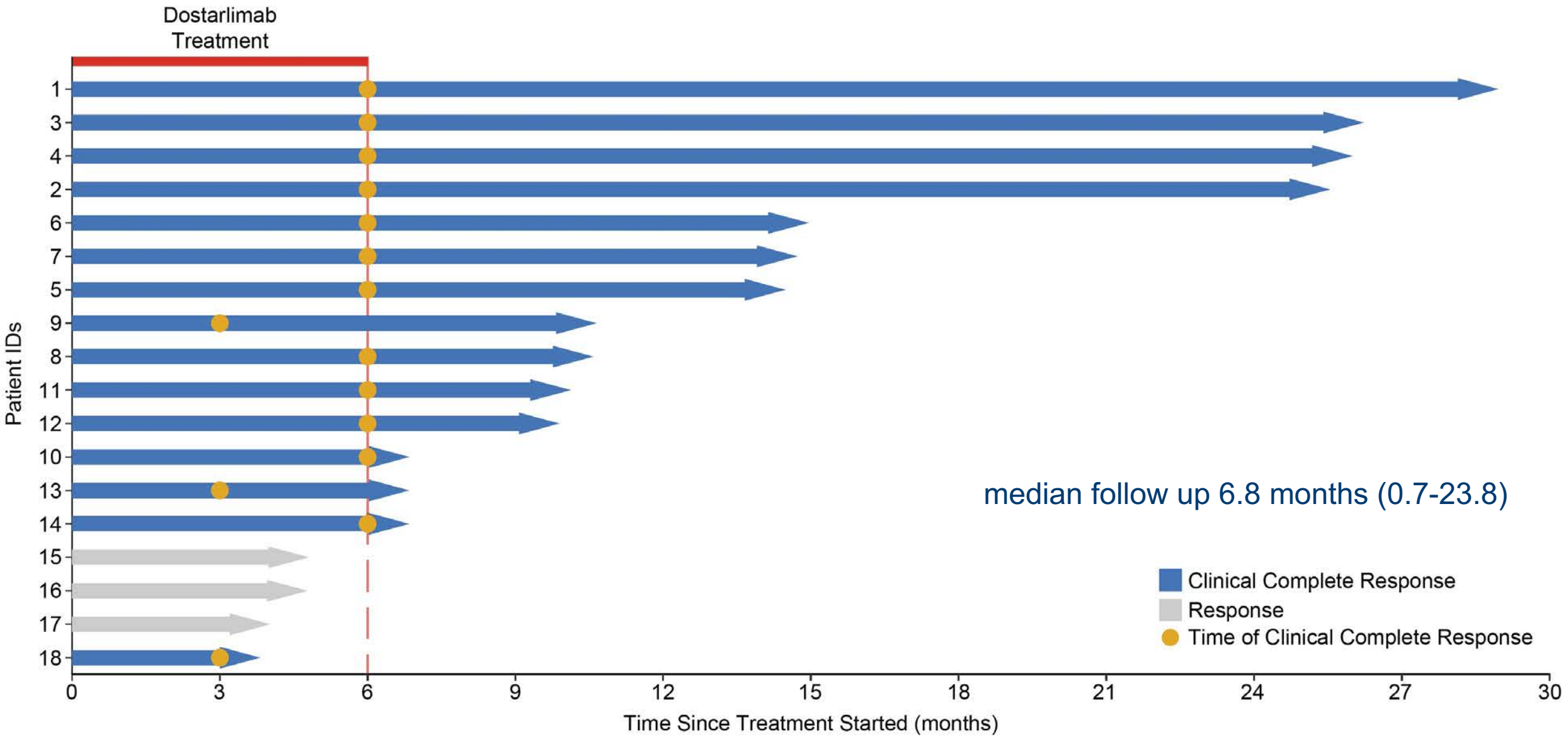
FDA Approval Jan 19 2023

Tosi F, Sartore-Bianchi A, et al. Clin Colorectal Cancer. 2020 Dec;19(4):256-262.e2. doi: 10.1016/j.clcc.2020.06.009. Epub 2020 Jun 27.
Meric-Bernstam F, et al. Lancet Oncol. 2019 Apr;20(4):518-530. doi: 10.1016/S1470-2045(18)30904-5. Epub 2019 Mar 8.
Sartore-Bianchi A, et al. ESMO Open. 2020 Sep;5(5):e000911.
Siena S, et al; Lancet Oncol. 2021 Jun;22(6):779-789. doi: 10.1016/S1470-2045(21)00086-3. Epub 2021 May 4.
Strickler J et al ; *Lancet Oncology* , 2023.

Her-2 Directed Therapy in patients with HER2 expressing mCRC

- ✓ Patient who fail at least 1L of chemotherapy with Her2+ mCRC should be considered for Her2 directed therapy
- ✓ Tucatinib + Trastuzumab (TT) 1st FDA approved treatment for patients with HER2+ mCRC (1/19/2023)
  - Well Tolerated with most toxicities as G1
- ✓ Consideration for Trastuzumab Deruxtecan post TT
  - Toxicity concerns including ILD (6%)

Dostarlimab in Stage II and III mismatch repair deficient rectal cancer



Cercek, ASCO 2022

Nivo (3) + Ipi (1) in Early-Stage Colon Cancer

Major pathologic response in 95% of patients; 67% pCR

Pathologic response (RVT)		Patients *n*= 107
Yes	**(≤ 50%)**	**106 (99%)**
Major	(≤10%)	**102 (95%)**
Complete	(0%)	**72 (67%)**
Partial	(10% - 50%)	4 (4%)
No	**(≥50%)**	**1 (1%)**

RVT = residual viable tumor

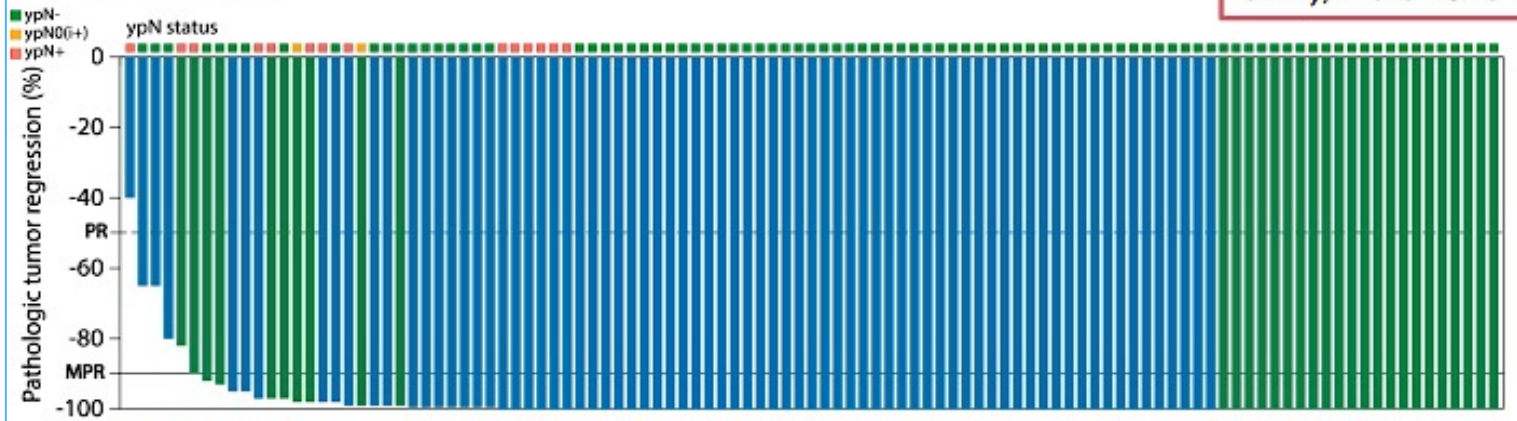
Adjuvant chemotherapy (CTx)

14 patients with ypN+ disease
- 3 patients received adjuvant CTx*
- 5 patients >70 years
- 6 patients refused

* 1 non-responder, 1 partial responder and 1 MPR

Disease recurrence

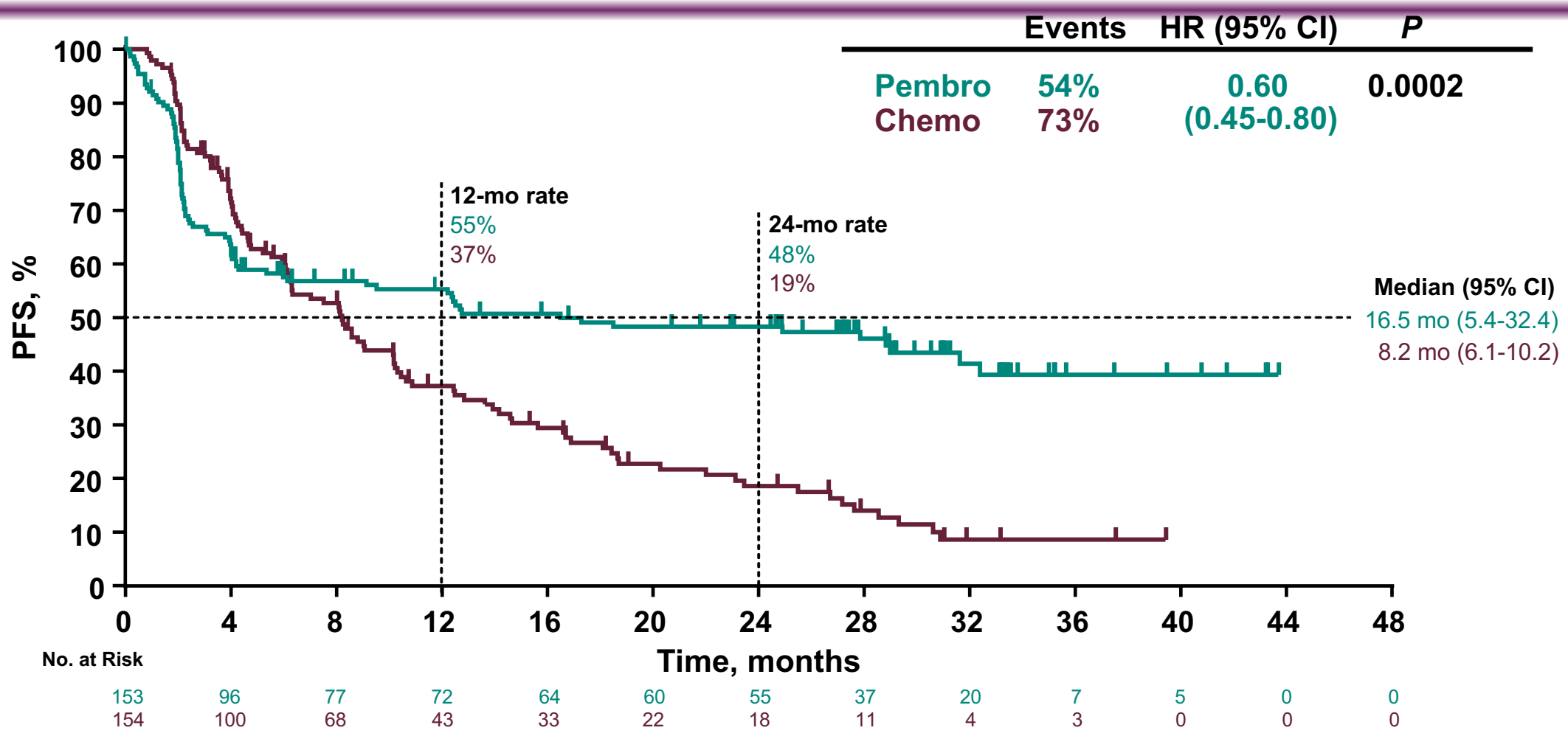
With a median follow-up of 13.1 months (1.4 - 57.4), there have been no disease recurrences



Green bars = NICHE-1 cohort
Blue bars = NICHE-2 cohort

ypN- = tumor-free lymph nodes; ypN+ = lymph nodes with tumor, including micrometastases; ypN(i+) = lymph nodes with isolated tumor cells

KEYNOTE-177 : 1L in MSI-H mCRC and PFS



Median study follow-up: 32.4 months (range, 24.0 – 48.3); PFS (time from randomization to first documented disease progression or death) assessed per RECIST v1.1 by BICR; Superiority of pembrolizumab vs chemotherapy for PFS was demonstrated at the pre-specified one-sided α = 0.0117; Data cut-off: 19Feb2020.

Table 1. Immune checkpoint inhibitors in MSI/dMMR metastatic colorectal cancer.

Clinical Trials	Prior Systemic Treatment	*n*	CR (%)	PR (%)	SD (%)	PD (%)	NE (%)	1-Year PFS Rate (%)	1-Year OS Rate (%)	2-Year PFS Rate (%)	2-Year OS Rate (%)	Median Follow-Up (Months)
Keynote-016 [11]												
Pembrolizumab	≥1	28	11	46	32	4	7	-	-	-	-	8.7
Keynote-164 [12–14]												
Pembrolizumab, cohort A	≥2	61	3	30	18	46	3	34	72	31	55	31
Pembrolizumab, cohort B	≥1	63	8	25	24	40	3	41	76	37	63	24
CheckMate-142 [15–18]												
Nivolumab	≥1	74	9	24	31	31	5	44	-	-	-	21
Nivolumab + Ipilimumab	≥1	119	6	52	28	12	3	71	85	60	74	25.4
Nivolumab + Ipilimumab	0	45	13	56	16	13	2	77	83	74	79	29.0
NIPICOL [19]												
Nivolumab + Ipilimumab	≥2	57	19	40	30	5	3	73	84	-	-	18.1
CD-ON-MEDI4736-1108 [20]												
Durvalumab	≥1	36	22		-	-	-	38			54	29
NCT02227667 [20]												
Durvalumab	≥1	11	27		-	-	-	36				30
GARNET [21]												
Dostarlimab	≥1	69	36		-	-	-	-	-	-	-	-

- dMMR = mismatch repair-deficient; MSI-H = microsatellite instability-high

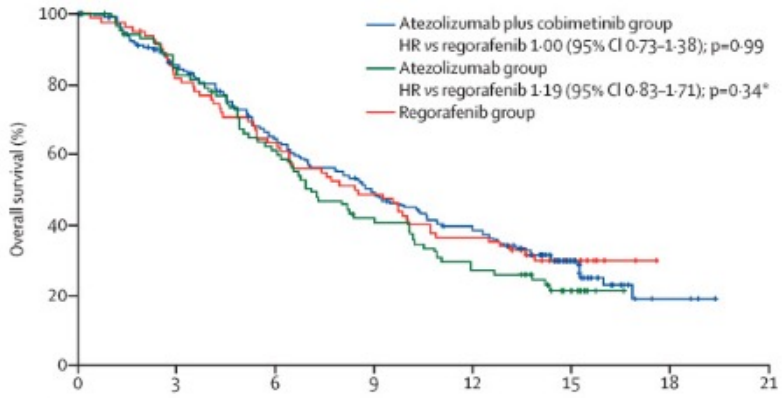
Cohen R, et al. *Cancers (Basel).* 2021;13(5):1149.

• The role of Immunotherapy in MSI-H CRC

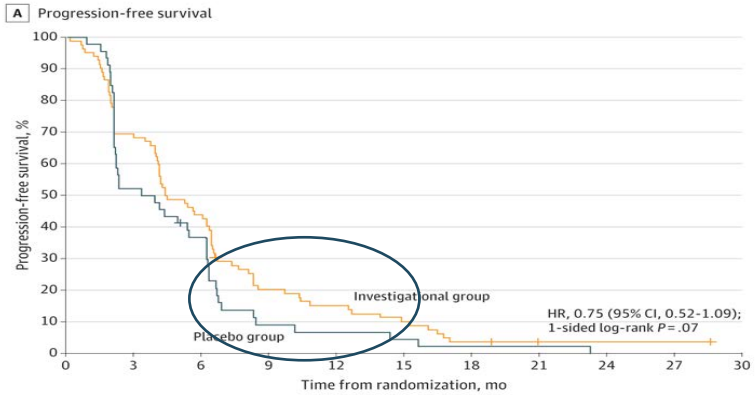
- ✓ Early Stage Rectal Cancer? Neoadjuvant -- May be
- ✓ Early Stage Colon Cancer? Neoadjuvant --Not Yet
- ✓ Metastatic Colorectal Cancer? Yes in 1L

Randomized PII/III studies with IO+ for MSS mCRC: From Negative to Borderline Positive

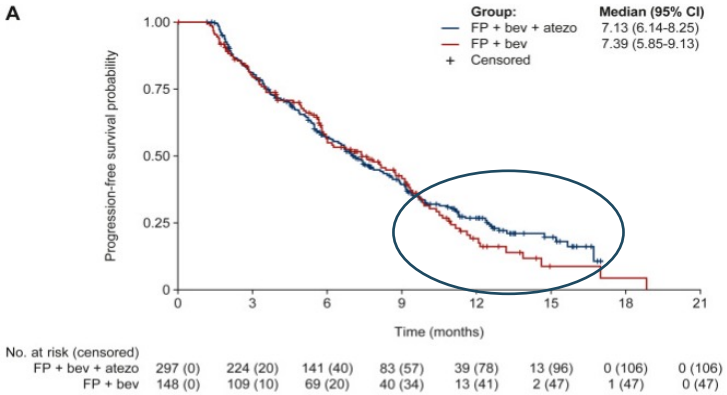
IMblaze370: Ref L Atezo +/- cobi vs. Rego



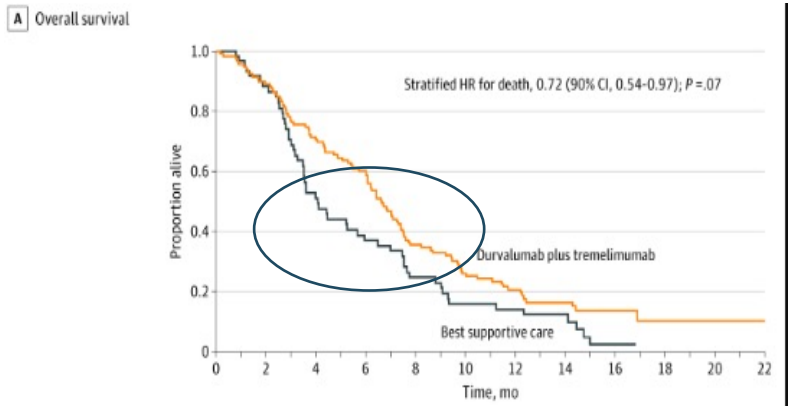
BACCI: Ref L Cape/Bev +/- Atezo/PBO



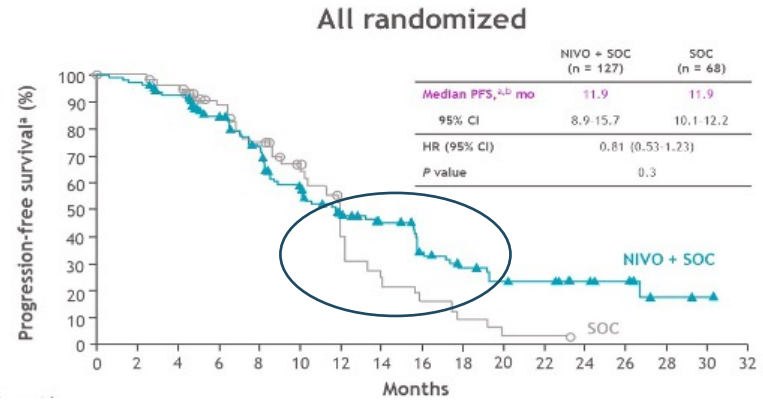
MODUL: Maint FP/Bev +/- Atezo



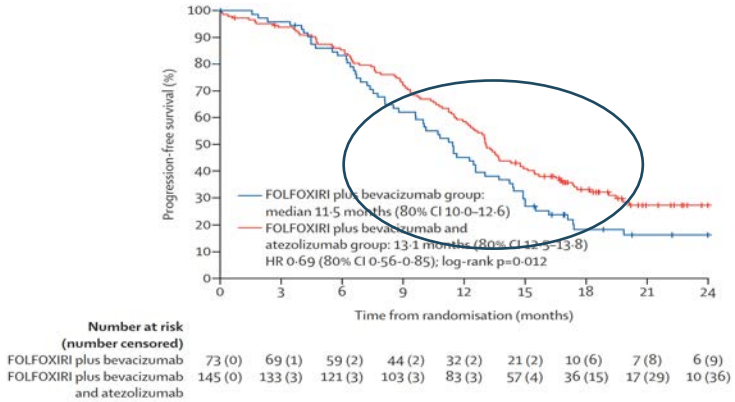
CO.26: Ref L Tremi/Durva vs. BSC



CM 9X8: 1L mFOLFOX6 + Bev +/- Nivo



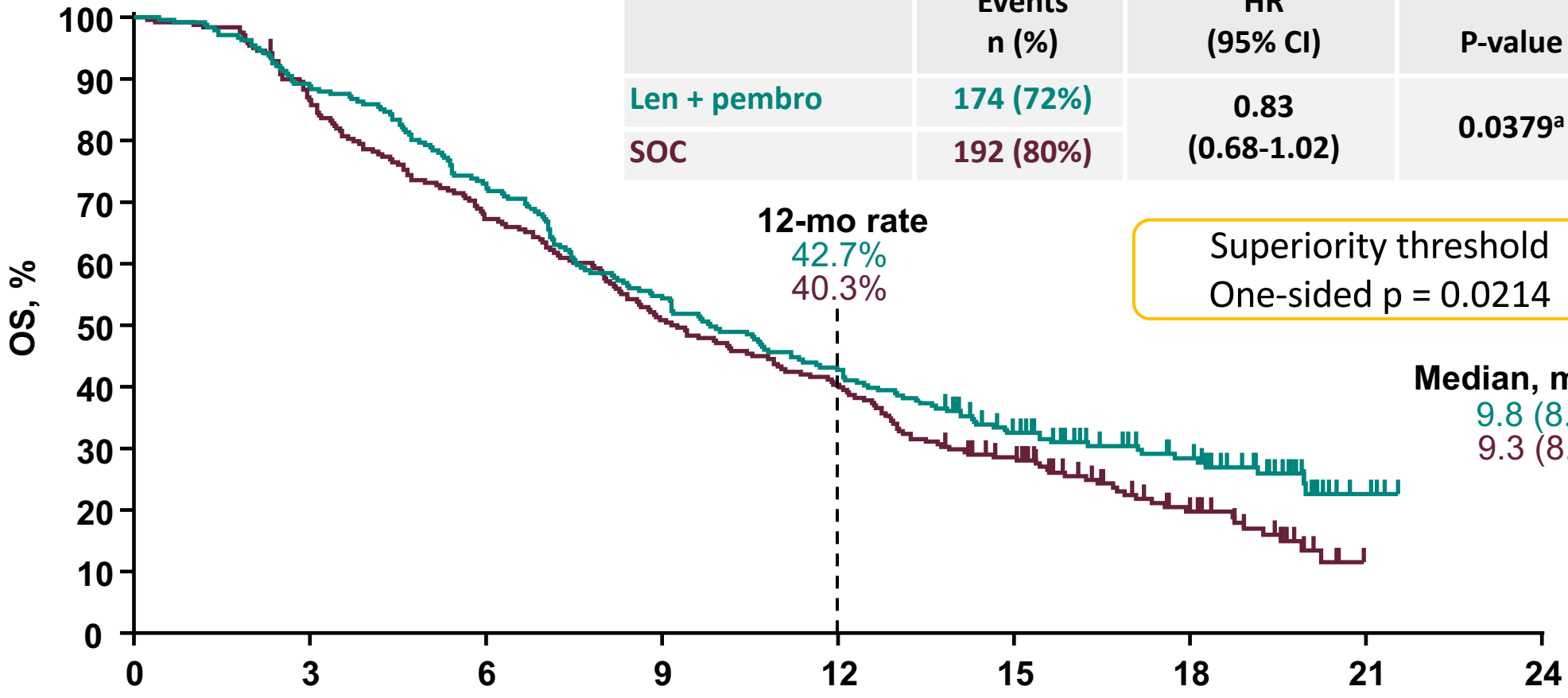
AtezoTRIBE: 1L FOLFOXIRI/Bev +/- Atezo



Eng C et al . *Lancet Oncol* 2019; Mettu N et al . *JAMA NO*, 2022; Tabernero J et al . *ESMO Open* 2022; Chen E et al , *JAMA Oncol*, 2020; Lenz HJ. ASCO GI 2022; Antoniotti C et al . *Lancet Oncol* 2022

LEAP-017 Lenva + Pembro vs. Rego/TAS102

	Events n (%)	HR (95% CI)	P-value
Len + pembro	174 (72%)	0.83 (0.68-1.02)	0.0379[a]
SOC	192 (80%)		

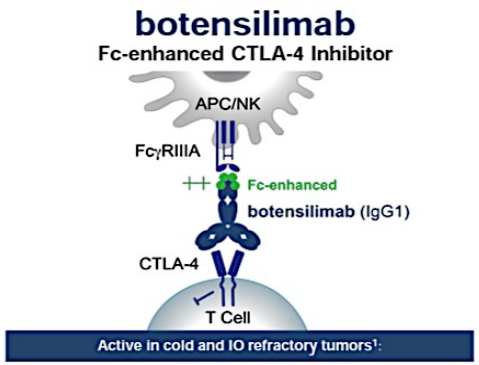


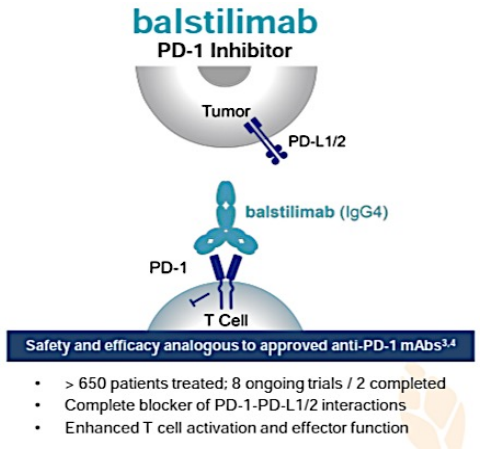
No. at Risk

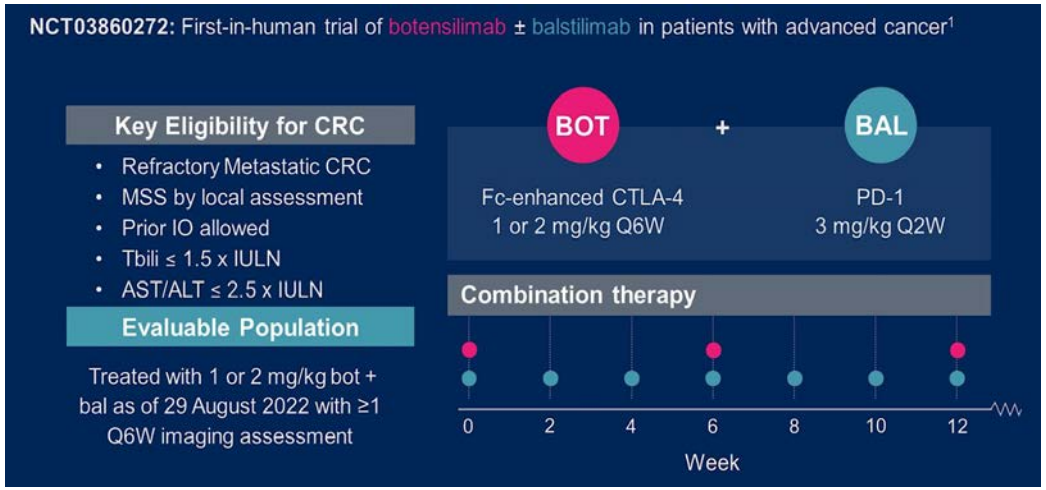
Len + pembro	241	214	176	132	103	70	41	5	0
SOC	239	206	160	121	96	63	28	0	0

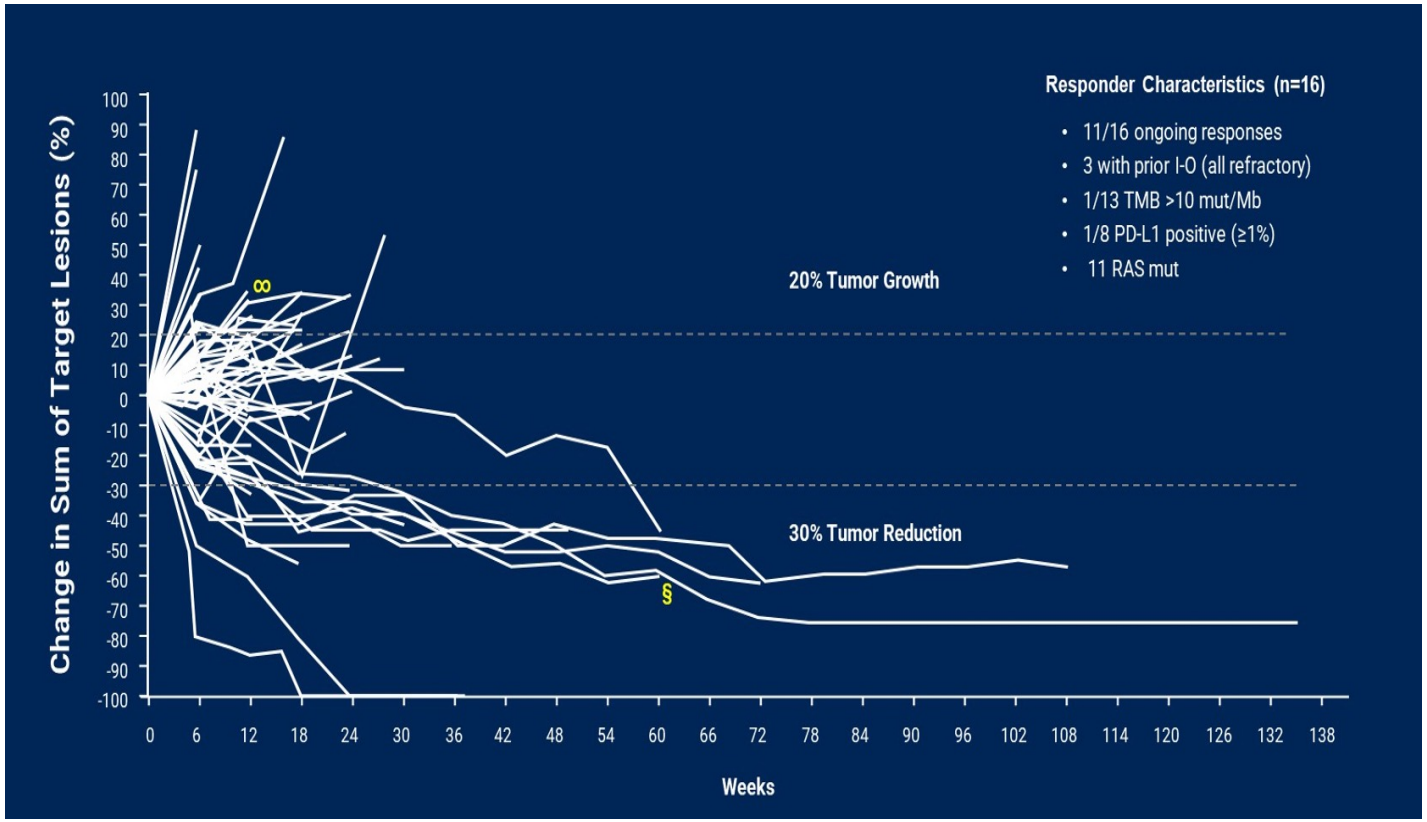
[a]OS did not meet pre-specified superiority threshold of one-sided p = 0.0214; Data cut-off February 20, 2023.

A phase 1a/1b study of Botensilimab plus Balstilimab in MSS CRC





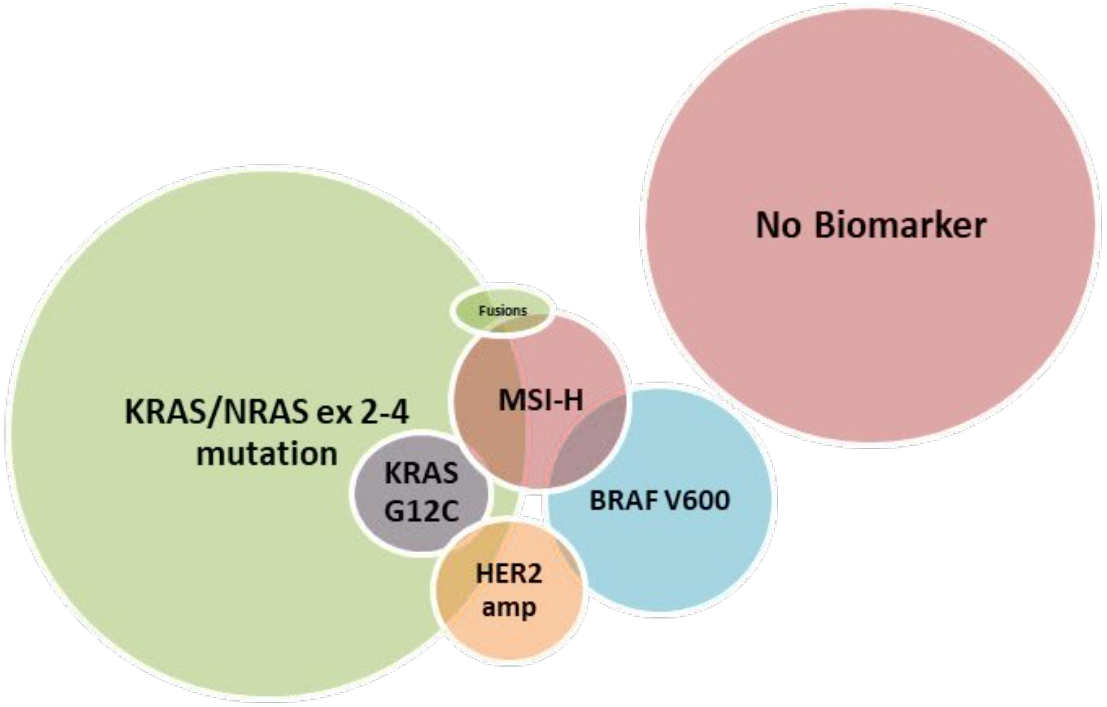




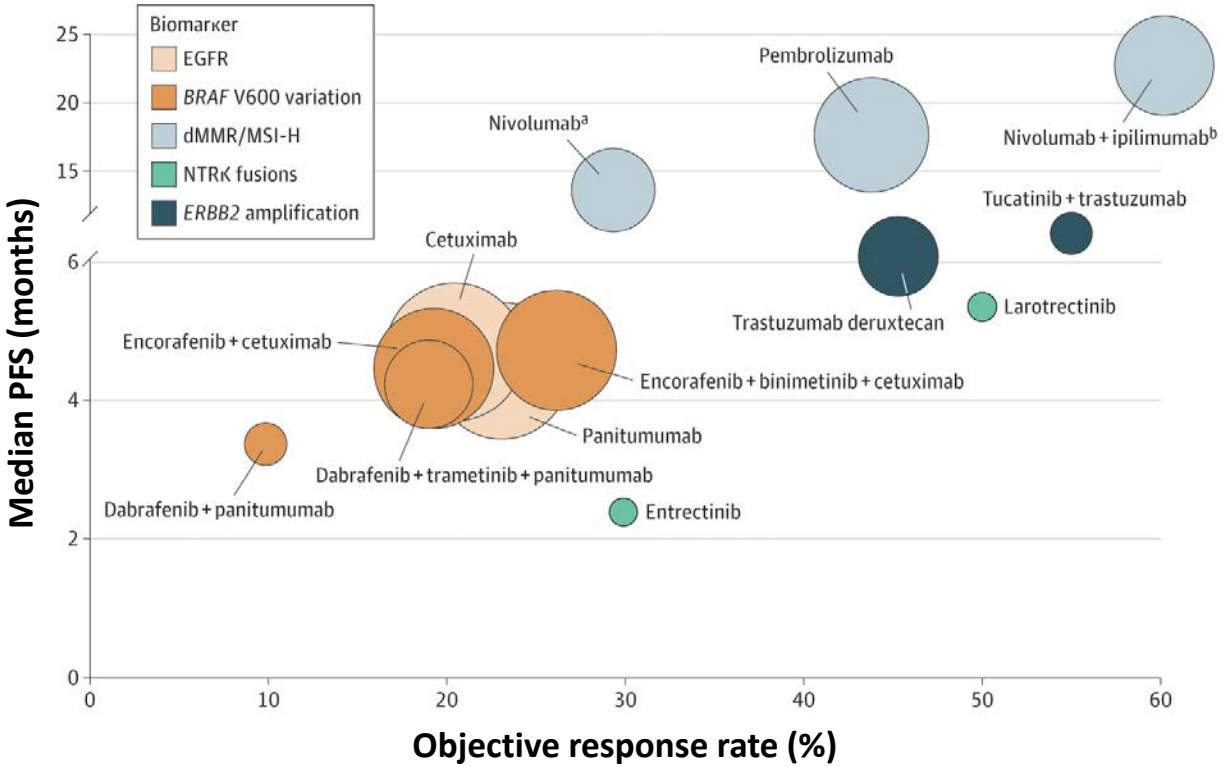
El-Khoueiry, GI ASCO 2023

Precision cancer medicine guides the modern management of metastatic CRC

Actionable targets in metastatic CRC



Clinical outcomes with select targeted therapies



Strickler … Bekaii-Saab et al., *JAMA Oncol.* 2022;8(5):760-769.

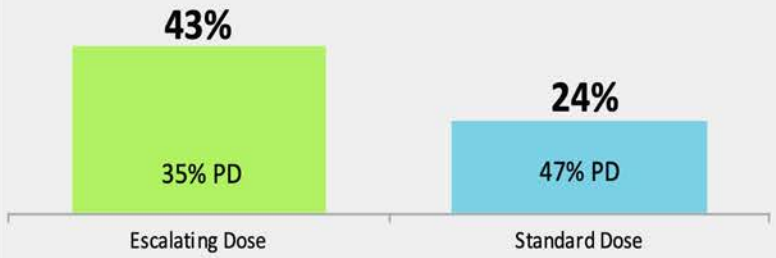
ReDOS: Regorafenib Dose-Optimization Study Investigating Escalating Dosing in Patients With Refractory mCRC – a Randomized Phase II Trial

ReDOS[1] Dose Escalation Schedule

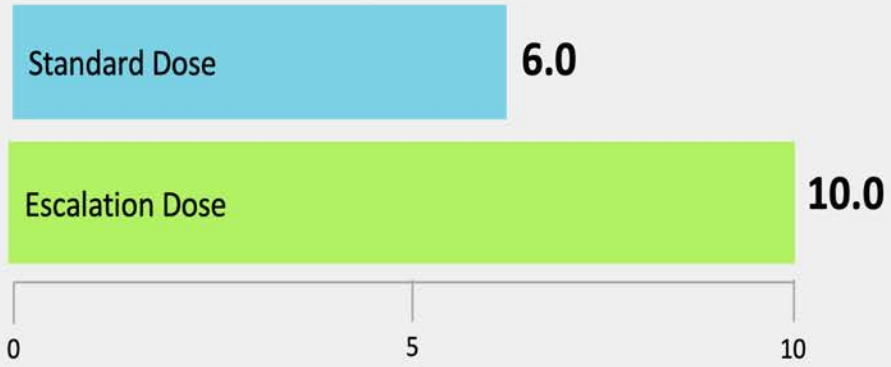
	Cycle 1				Cycle 2
Week	1	2	3	4	1
Once-daily dose	80 mg	120 mg	160 mg	Dosing-free interval	Last dose from cycle 1

ReDOS Dose Optimization Study[1] Results

Percentage Patients Starting Treatment at Cycle 3
(primary endpoint)
P = .0281



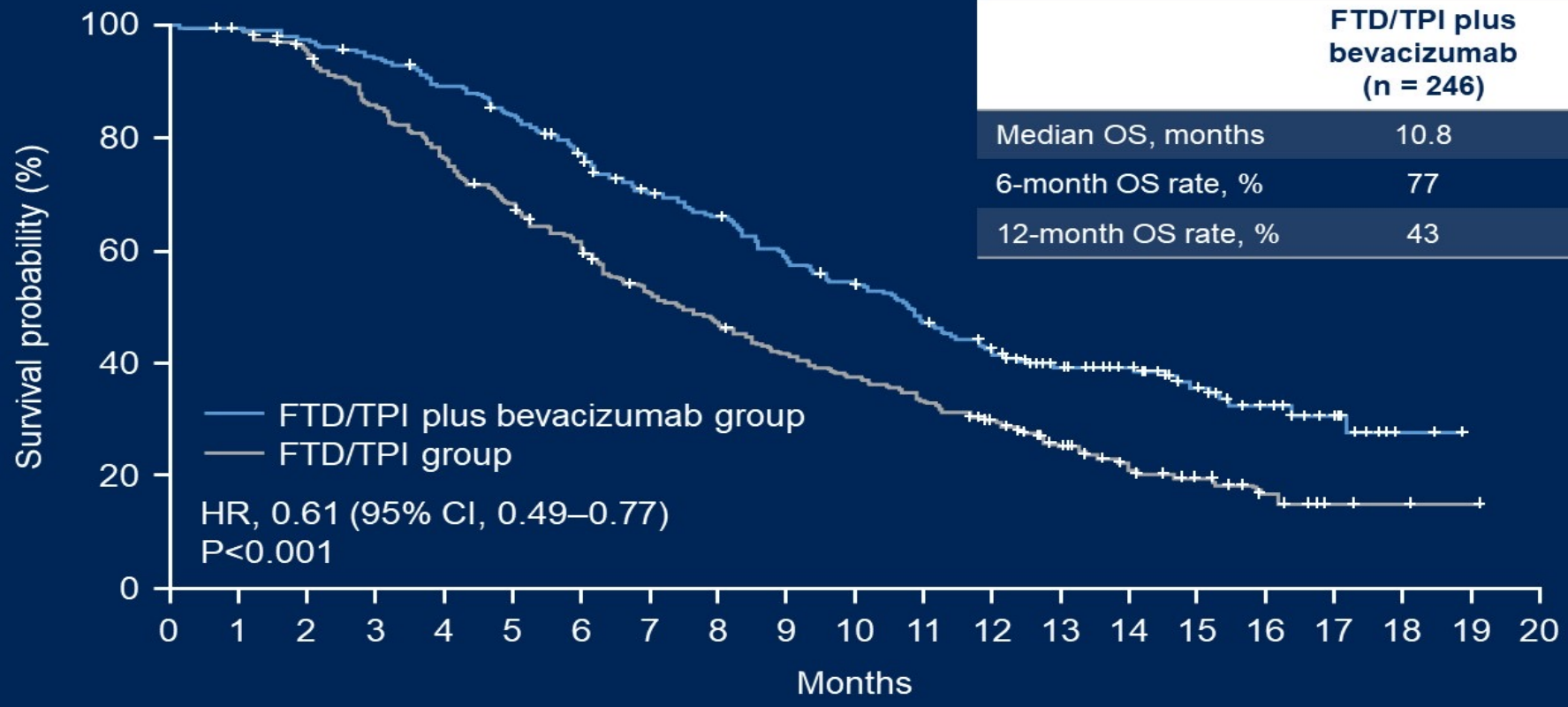
Median OS (months)



1 Bekaii-Saab TS, et al. Lancet Oncology , 2019

SUNLIGHT study: TAS 102 +/- Bevacizumab

OS in full analysis set (primary endpoint)



	FTD/TPI plus bevacizumab (n = 246)	FTD/TPI (n = 246)
Median OS, months	10.8	7.5
6-month OS rate, %	77	61
12-month OS rate, %	43	30

No. at risk

FTD/TPI plus bevacizumab group	246	244	239	230	217	203	183	160	149	131	119	104	88	69	52	37	24	13	2	0	0
FTD/TPI group	246	242	230	205	184	163	143	120	108	95	85	76	63	44	24	16	10	5	2	1	0

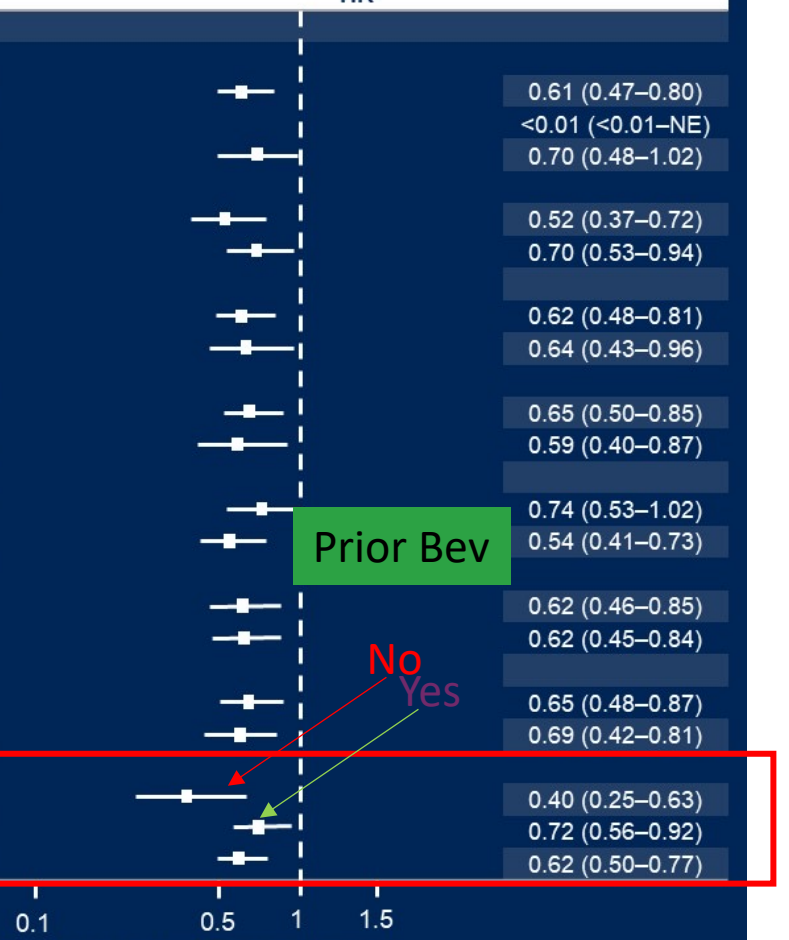
CI, confidence interval; FTD/TPI, trifluridine/tipiracil; HR, hazard ratio; OS, overall survival.

Josep Tabernero et al, presented at ASCO GI 2023, 21st Jan 2023, Prager GW, et al. *N Engl J Med*. 2023;388(18):1657-1667.

SUNLIGHT study: OS by prespecified subgroup

OS by prespecified subgroup

Subgroup	FTD/TPI plus bevacizumab group	FTD/TPI group	FTD/TPI plus bevacizumab group	FTD/TPI group	HR
	No. of events/total no.		*Median OS (95% CI)*		
Region					
European Union	97/158	121/157	10.6 (9.0–11.8)	7.0 (6.0–8.5)	0.61 (0.47–0.80)
North America	0/8	4/8	NE	6.0 (4.2–NE)	<0.01 (<0.01–NE)
Rest of the world	51/80	58/81	10.7 (8.5–14.2)	8.5 (6.3–10.7)	0.70 (0.48–1.02)
Time from diagnosis of first metastasis, months					
<18	65/104	82/105	10.8 (8.8–12.5)	6.1 (5.1–7.4)	0.52 (0.37–0.72)
≥18	83/142	101/141	10.8 (9.0–12.1)	8.6 (7.2–10.6)	0.70 (0.53–0.94)
RAS status					
Mutant	103/171	128/170	10.6 (9.0–11.3)	7.5 (6.3–8.6)	0.62 (0.48–0.81)
Wild-type	45/75	55/76	11.9 (9.0–14.9)	7.1 (5.9–10.9)	0.64 (0.43–0.96)
Location of primary disease					
Left	108/184	120/169	10.7 (9.3–12.2)	8.2 (6.7–9.3)	0.65 (0.50–0.85)
Right	40/62	63/77	10.8 (8.5–11.9)	6.2 (5.2–8.0)	0.59 (0.40–0.87)
ECOG PS					
0	70/119	74/106	10.8 (8.8–14.5)	9.3 (7.7–11.6)	0.74 (0.53–1.02)
≥1	78/127	109/140	10.8 (9.0–11.9)	6.3 (5.4–7.5)	0.54 (0.41–0.73)
Sex					
Female	79/124	85/112	10.7 (9.0–11.4)	6.9 (6.0–9.0)	0.62 (0.46–0.85)
Male	69/122	98/134	10.8 (9.0–14.6)	7.8 (6.5–9.4)	0.62 (0.45–0.84)
Age, years					
<65	89/146	94/129	10.7 (8.5–12.1)	7.5 (6.3–9.3)	0.65 (0.48–0.87)
≥65	59/100	89/117	11.0 (9.4–12.9)	7.2 (6.0–8.8)	0.69 (0.42–0.81)
Prior bevacizumab					
No	30/68	48/69	15.1 (12.1–NE)	8.1 (6.3–9.7)	0.40 (0.25–0.63)
Yes	118/178	135/177	9.0 (8.3–10.8)	7.1 (6.0–8.5)	0.72 (0.56–0.92)
Overall	148/246	183/246	10.8 (9.4–11.8)	7.5 (6.3–8.6)	0.62 (0.50–0.77)

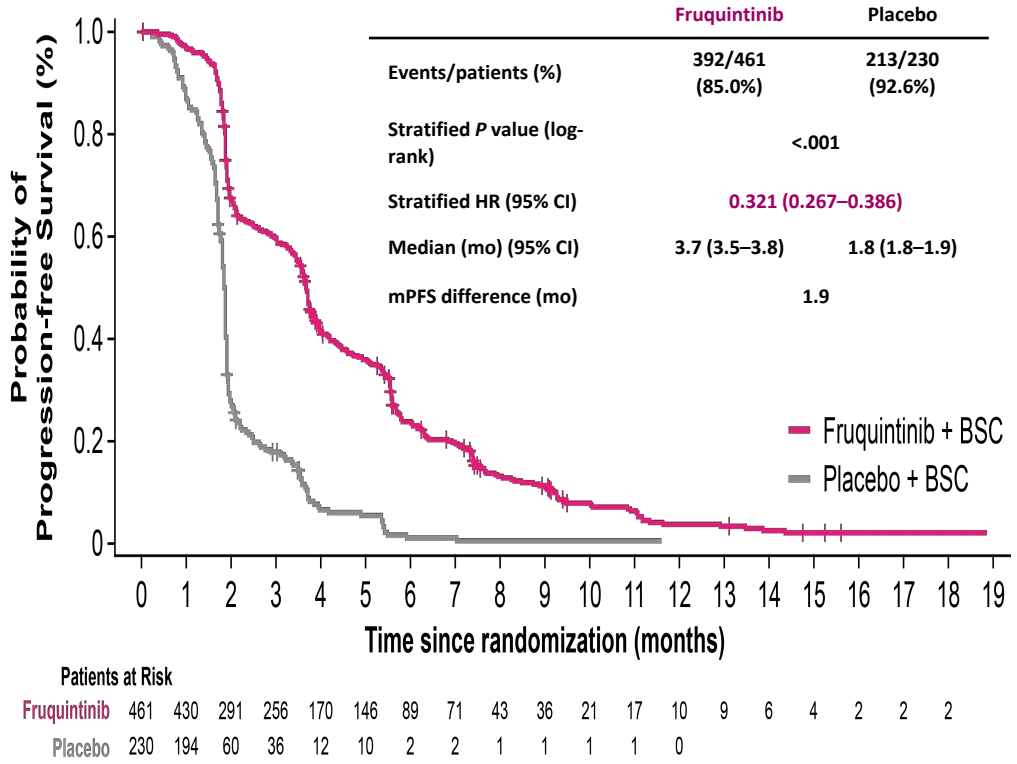


CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; FTD/TPI, trifluridine/tipiracil; HR, hazard ratio; NE, not evaluable; OS, overall survival.

Josep Tabernero et al, presented at ASCO GI 2023, 21st Jan 2023,

FRESCO-2: Phase III Study of Fruquintinib in Patients With mCRC

Progression-free survival

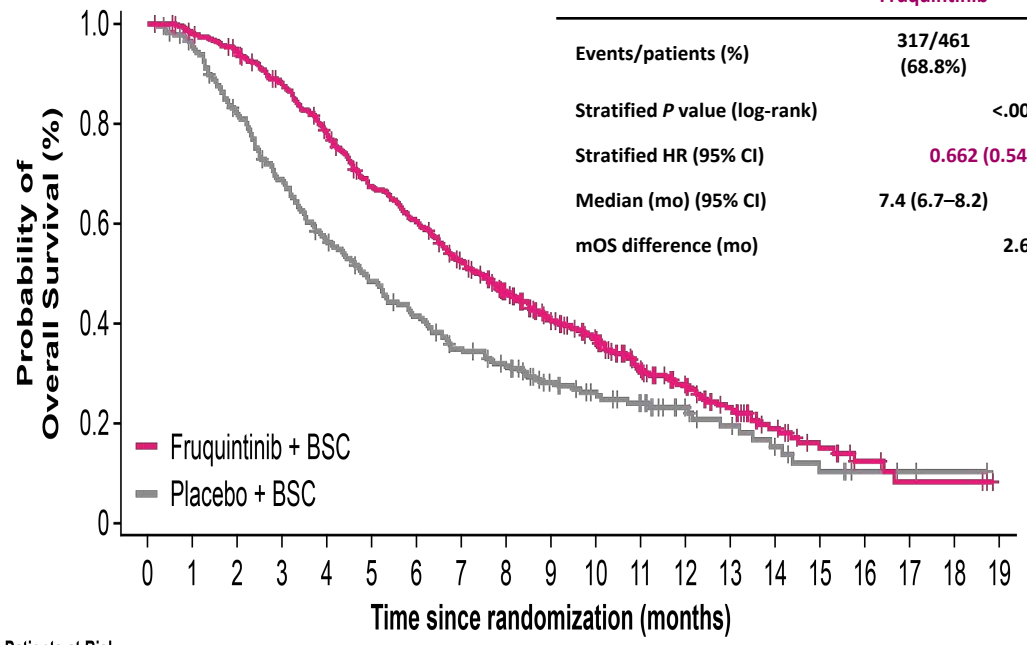


	Fruquintinib	Placebo
Events/patients (%)	392/461 (85.0%)	213/230 (92.6%)
Stratified *P* value (log-rank)	<.001	
Stratified HR (95% CI)	0.321 (0.267–0.386)	
Median (mo) (95% CI)	3.7 (3.5–3.8)	1.8 (1.8–1.9)
mPFS difference (mo)	1.9	

Patients at Risk

Fruquintinib	461	430	291	256	170	146	89	71	43	36	21	17	10	9	6	4	2	2	2
Placebo	230	194	60	36	12	10	2	2	1	1	1	1	0						

Overall survival



	Fruquintinib	Placebo
Events/patients (%)	317/461 (68.8%)	173/230 (75.2%)
Stratified *P* value (log-rank)	<.001	
Stratified HR (95% CI)	0.662 (0.549–0.800)	
Median (mo) (95% CI)	7.4 (6.7–8.2)	4.8 (4.0–5.8)
mOS difference (mo)	2.6	

Patients at Risk

Fruquintinib	461	449	429	395	349	297	266	224	184	143	113	79	58	41	23	14	7	4	4	0
Placebo	230	216	184	153	125	105	89	73	63	45	37	31	20	15	10	6	3	2	1	0

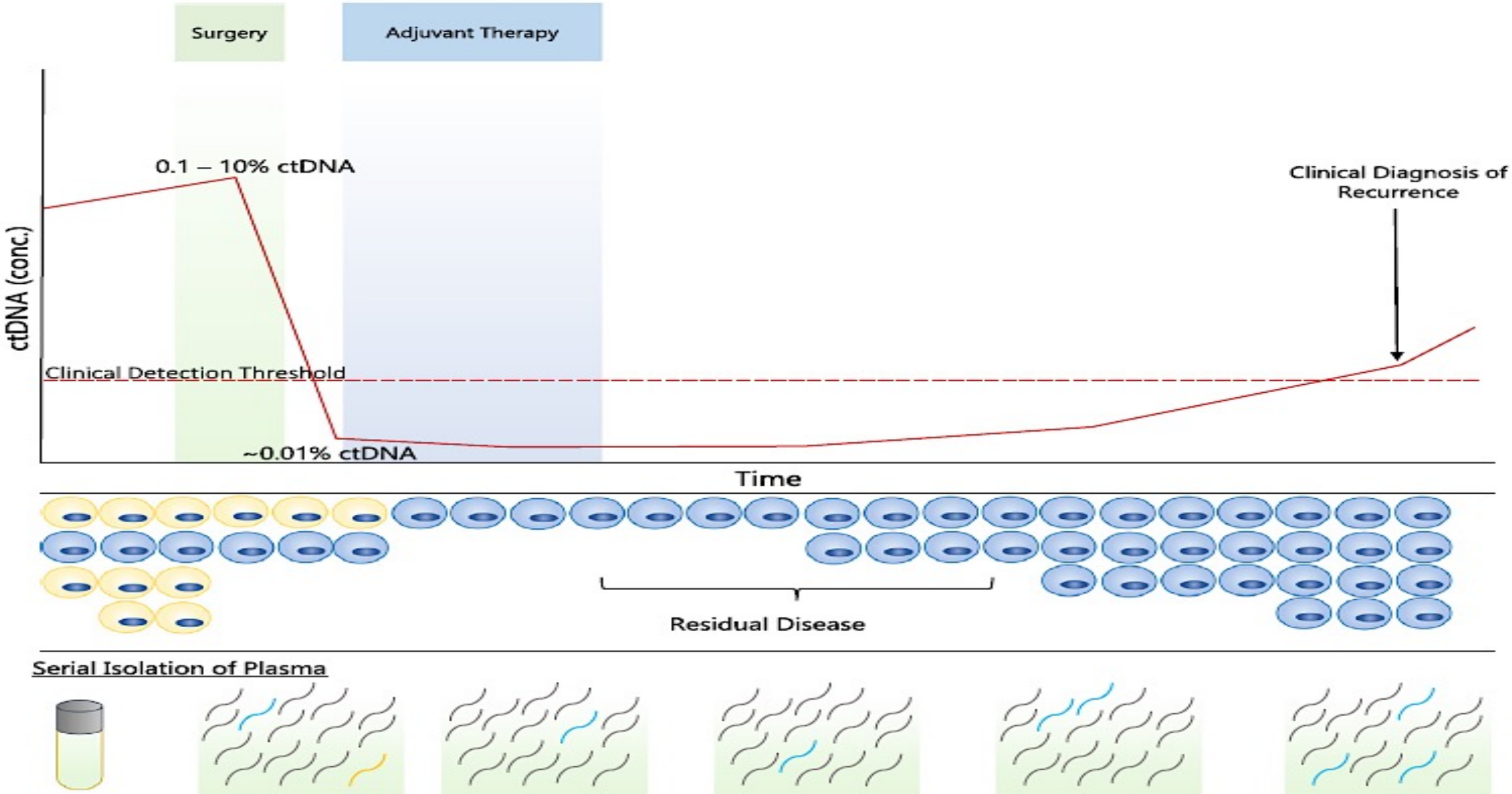
Prior TAS-102 and/or regorafenib	TAS-102	240 (52.1)	121 (52.6)
	Regorafenib	40 (8.7)	18 (7.8)
	Both	181 (39.3)	91 (39.6)

Dasari A, et al. ESMO 2022. Abstract LBA25.

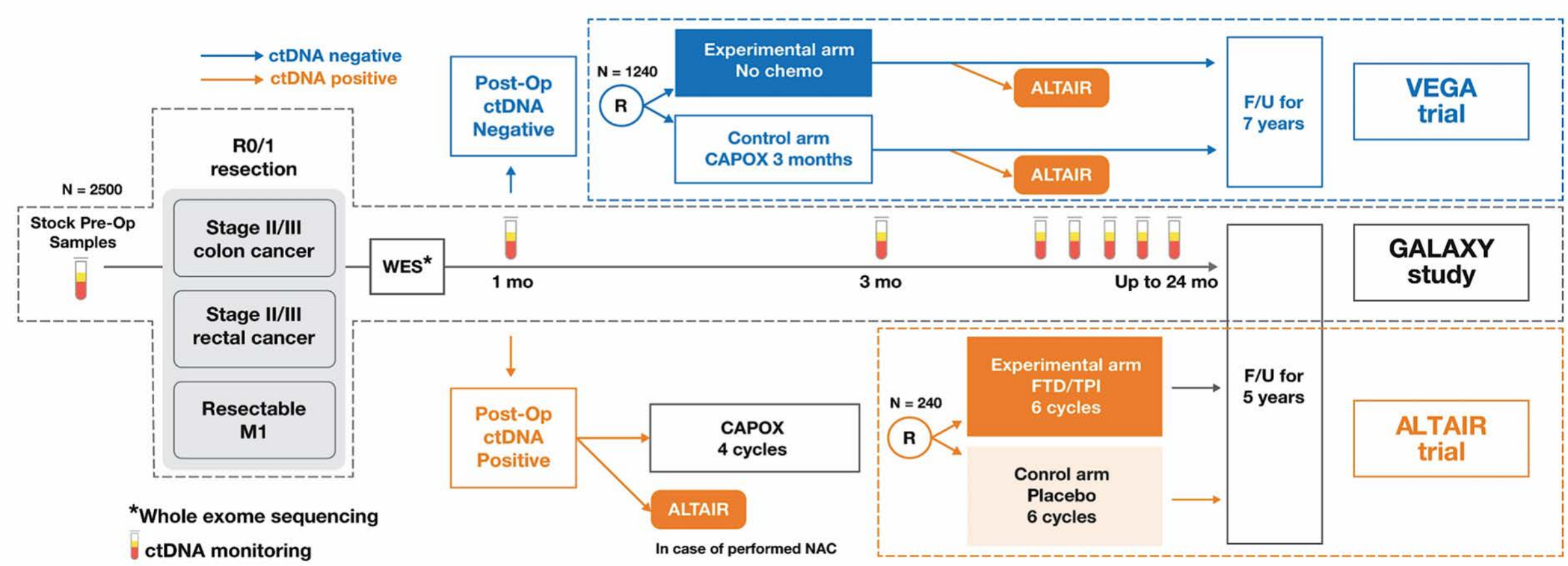
Comparison of Modern Studies With Regorafenib, Fruquintinib, and TAS-102 ± Bevacizumab in mCRC

Agent	Regorafenib		Fruquintinib		TAS-102 ± Bevacizumab			
Trial	**ReDOS**		**FRESCO-2**		**SUNLIGHT**			
Prior biologics	100% bevacizumab 100% EGFR mAbs		100% bevacizumab 100% EGFR mAbs 100% regorafenib or TAS-102		Prior bevacizumab (72%) ?? EGFR		No prior bevacizumab (28%) ?? EGFR	
	Regorafenib (n = 54)	Regorafenib 160 (n = 62)	Fruquintinib (n = 136)	BSC + PL (n = 68)	TAS-102 + bevacizumab n = 178	TAS-102 n = 177	TAS-102 + bevacizumab n = 68	TAS-102 n = 69
Prior lines ≤2 >3	 0% 100%	 0% 100%	 0% 100%	 0% 100%	100% 0%			
Median OS, mo	10	6	7.4	4.8	9.0	7.1	15.1	8.1

Minimal Residual Disease (MRD)



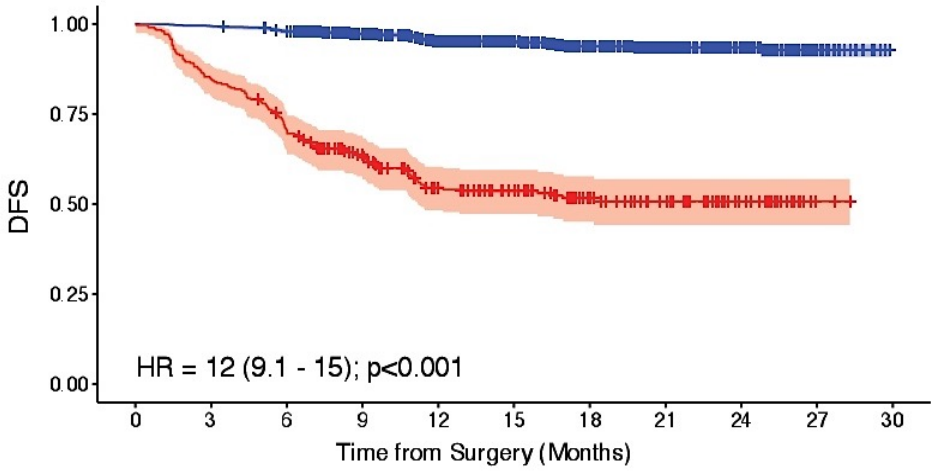
CIRCULATE-Japan Study: Flowchart



- Detect MRD
- Measure treatment responsiveness in resectable CRC
- The blood samples will be collected before surgery and at 4, 12, 24, 36, 48, 72, and 96 weeks after surgery
- Computed tomography (CT) will be performed every 6 months after surgery for 7 years

CIRCULATE-Japan GALAXY Study: Updated Results

ctDNA status at 4-weeks MRD time point

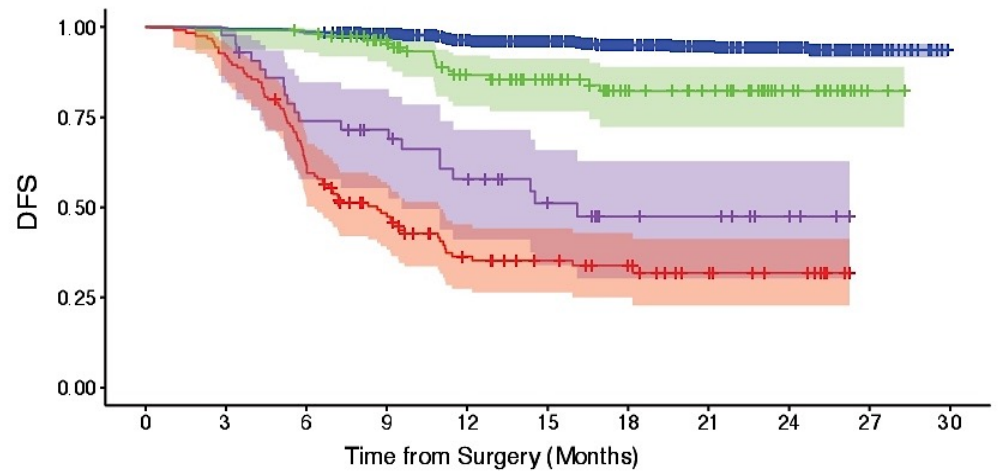


Number at risk

ctDNA (-)	1797	1786	1756	1568	1323	1054	731	502	231	37	0
ctDNA (+)	286	242	200	158	113	93	62	49	27	2	0

Dynamics	ctDNA Negative	ctDNA Positive
Events (n)	96/1797 (5.3%)	130/286 (45.5%)
18M - DFS	93.9 (92.5 - 95)	51.6 (45.2 - 57.6)
HR	Reference	12
95% CI	Not applicable	9.1 - 15
P	Not applicable	<0.001

ctDNA Dynamics between weeks 4 and 12 post surgery



Number at risk

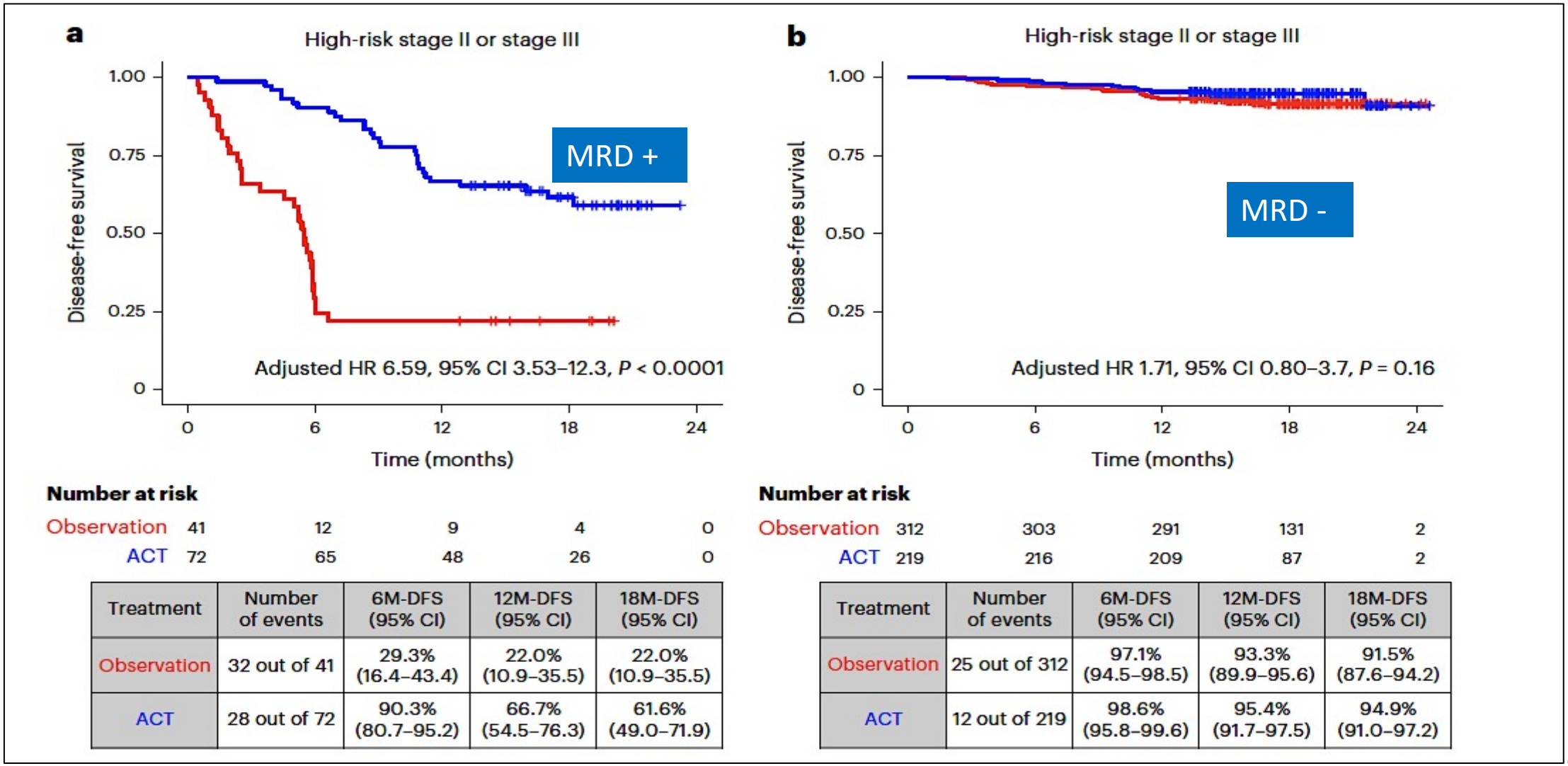
Persistently Negative	1529	1524	1508	1391	1176	938	648	439	204	35	0
Converted Negative	112	111	109	95	74	60	42	36	19	2	0
Converted Positive	43	42	31	27	21	14	9	8	4	0	0
Persistently Positive	124	114	76	52	33	27	18	11	7	0	0

Dynamics	Persistently Negative	Converted Negative	Converted Positive	Persistently Positive
Events (n)	69/1529 (4.5%)	16/112 (14.3%)	20/43 (46.5%)	78/124 (62.9%)
18M - DFS	94.9 (93.5 - 96)	82.2 (72.3 - 88.9)	47.4 (30.4 - 62.7)	33.8 (25 - 42.8)
HR	Reference	3.5	14.5	25.4
95% CI	Not applicable	1.9 - 5.8	8.8 - 23.8	18.3 - 35.3
P	Not applicable	<0.001	<0.001	<0.001

Oki E et al. ASCO 2023;Abstract 3521.

RTP RESEARCH TO PRACTICE

ctDNA-based MRD testing is predictive of response to ACT in postsurgical patients with CRC



Number at risk

Observation	41	12	9	4	0
ACT	72	65	48	26	0

Treatment	Number of events	6M-DFS (95% CI)	12M-DFS (95% CI)	18M-DFS (95% CI)
Observation	32 out of 41	29.3% (16.4–43.4)	22.0% (10.9–35.5)	22.0% (10.9–35.5)
ACT	28 out of 72	90.3% (80.7–95.2)	66.7% (54.5–76.3)	61.6% (49.0–71.9)

Number at risk

Observation	312	303	291	131	2
ACT	219	216	209	87	2

Treatment	Number of events	6M-DFS (95% CI)	12M-DFS (95% CI)	18M-DFS (95% CI)
Observation	25 out of 312	97.1% (94.5–98.5)	93.3% (89.9–95.6)	91.5% (87.6–94.2)
ACT	12 out of 219	98.6% (95.8–99.6)	95.4% (91.7–97.5)	94.9% (91.0–97.2)

Nature Medicine 2023

DYNAMIC Study Design

ACTRN12615000381583

Stage II Colon Cancer

- R0 resection
- ECOG 0 – 2
- Staging CT within 8 weeks
- Provision of adequate tumor tissue within 4 weeks post-op
- No synchronous colorectal cancer

Plasma Collections
Week 4 + 7 post-op

R
2:1

ctDNA-Guided Management

- **ctDNA-Positive → Adjuvant Chemo**
  (oxaliplatin-based or single agent FP)
- **ctDNA-Negative → Observation**

ctDNA-Positive = Positive result at week 4 and/or 7

Standard Management

Adjuvant treatment decisions based on conventional clinico-pathologic criteria

Endpoints

Primary
- RFS rate at 2 years

Key Secondary
- Proportion receiving adjuvant chemo

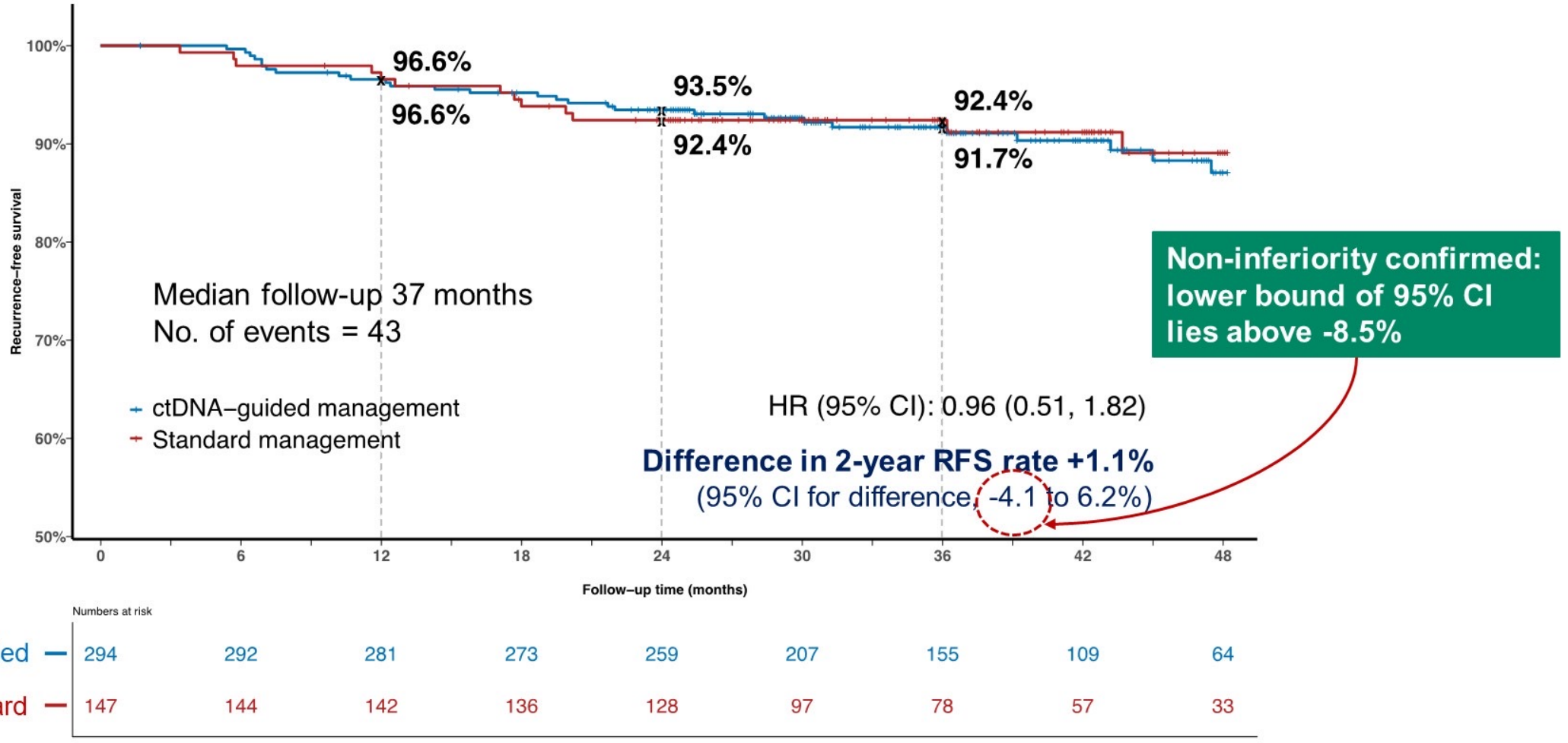
Secondary
- RFS by ctDNA status for ctDNA-guided arm
- TTR
- OS

Stratification Factors
- T stage (T3 vs T4)
- Type of participating center (metropolitan vs regional)

Surveillance:
- CEA → 3-monthly for 24M, then 6-monthly for 36M
- CT C/A/P → 6-monthly for 24M, then at 36M

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Recurrence-Free Survival



Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Adjuvant Treatment Delivery

Treatment Information	ctDNA-Guided N = 294	Standard Management N = 147	P-value
Adjuvant Chemotherapy received, n	45 **(15%)**	41 **(28%)**	0.0017
Chemotherapy regimen received, n			
Oxaliplatin-based doublet	28/45 **(62%)**	4/41 **(10%)**	
Single agent fluoropyrimidine	17/45 **(38%)**	37/41 **(90%)**	<.0001
Time from surgery to commencing chemotherapy, median (IQR), days	83 (76, 89)	53 (49, 61)	<.0001
Treatment duration, median (IQR), weeks	24 (19, 24)	24 (21, 24)	0.9318
Completed planned treatment, n	38 (85%)	32 (78%)	0.7036
Percentage of full dose delivered, median (IQR)	78 (56, 100)	84 (64, 100)	0.6194

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

MRD assessment in early stage CRC

- cfDNA detection and quantification methods have the potential to transform clinical practice through determining the risk for relapse (MRD assessment/prognosis)
  - ✓ Tumor-informed vs. tumor-naïve platforms
  - ✓ Residual disease detection at earlier timepoints than standard clinical and/or imaging surveillance
- Will this allow for improved patient selection for ?
  - ✓ Adjuvant chemotherapy (ACT) ? ACT Duration?
  - ✓ Whether ctDNA-based early detection of colon cancer recurrence improved overall survival in patients is unclear and is a subject of future studies.

Clinical Questions and Cases

Case Presentation: 34-year-old woman and single mother is diagnosed with MSS, TMB-low mCRC with no targetable mutations and undergoes resection

Dr Mamta Choksi (New Port Richey, Florida; 10-5-2021)

RTP RESEARCH TO PRACTICE

Case Presentation: 66-year-old woman with multiregimen-recurrent RAS WT, HER2-positive metastatic rectal cancer s/p response to T-DxD is now receiving trastuzumab/tucatinib

Dr Sunil Gandhi (Lecanto, Florida; 2-7-2023)

RTP
RESEARCH
TO PRACTICE

Case Presentation: 59-year-old man with multiregimen-recurrent mCRC receives TAS-102

Dr Lowell Hart (Fort Myers, Florida; 10-12-2020)

RTP RESEARCH TO PRACTICE

Colorectal Cancer

- **Adjuvant: Circulating tumor DNA (Signatera™, others)**
- **Metastatic disease**
  - **HER2 overexpressing**
    - **T-DXd**
    - **Tucatinib/trastuzumab (MOUNTAINEER)**
  - **MSI high**
  - **KRAS G12C: Sotorasib/panitumumab (press release and upcoming ESMO presentation)**
  - **TAS-102 with bevacizumab, fruquintinib**

Discussion Question

A patient undergoes R0 resection for low-risk Stage II colorectal cancer (CRC). What would be your approach to adjuvant therapy?

A patient undergoes R0 resection for high-risk Stage II CRC. What would be your approach to adjuvant therapy?

A patient undergoes R0 resection for Stage III (T2N1) CRC (1 positive node). What would be your approach to adjuvant therapy?

Have you or would you order a ctDNA assay for a patient with CRC who has undergone surgical resection of an isolated oligometastasis?

Discussion Question

Regulatory and reimbursement issues aside, what would be your likely second-line anti-HER2 treatment for a patient with pan-RAS wild-type, MSS, HER2-positive mCRC who receives FOLFOX/ bevacizumab and experiences low-volume, asymptomatic disease progression with no visceral metastases after 9 months of maintenance bevacizumab?

Regulatory and reimbursement issues aside, what would be your likely second-line anti-HER2 treatment for a patient with pan-RAS wild-type, MSS, HER2-positive mCRC who receives FOLFOX/ bevacizumab and experiences high-volume, symptomatic disease progression with visceral metastases after 9 months of maintenance bevacizumab?

RTP RESEARCH TO PRACTICE

Discussion Question

What is your usual first-line treatment for a patient with left-sided, pan-RAS wild-type, MSI-high mCRC?

RTP
RESEARCH
TO PRACTICE

Discussion Question

Regulatory and reimbursement issues aside, for a patient with mCRC with a KRAS G12C mutation, would you generally administer KRAS-targeted therapy (eg, sotorasib, adagrasib) at some point in the treatment course?

Discussion Question

A 65-year-old patient with MSS, RAS-mutant mCRC receives first-line FOLFOX/bevacizumab and second-line FOLFIRI/bevacizumab and is now experiencing low-volume, asymptomatic disease progression with no visceral metastases. Regulatory and reimbursement issues aside and assuming you could access all of these, what would you most likely recommend as third-line treatment?

A 75-year-old patient with MSS, RAS-mutant mCRC receives first-line FOLFOX/bevacizumab and second-line FOLFIRI/bevacizumab and is now experiencing low-volume, asymptomatic disease progression with no visceral metastases. Regulatory and reimbursement issues aside and assuming you could access all of these, what would you most likely recommend as third-line treatment?

RTP
RESEARCH
TO PRACTICE

Current Approaches and Future Strategies in Oncology: A Multitumor Educational Symposium in Partnership with Florida Cancer Specialists and Research Institute

A CME/MOC- and NCPD-Accredited Event

Saturday, October 7, 2023
7:15 AM – 12:30 PM ET

RTP
RESEARCH
TO PRACTICE

Agenda

Module 1 — ER-Positive Breast Cancer: *Drs Burstein and Jhaveri*

Module 2 — Prostate Cancer: *Drs Morgans and Smith*

Module 3 — Non-Small Cell Lung Cancer: *Drs Riely and Wakelee*

Module 4 — Colorectal and Gastroesophageal Cancers:
Drs Bekaii-Saab and Philip

Module 5 — Chronic Lymphocytic Leukemia: *Drs Chanan-Khan and Kahl*

RTP
RESEARCH
TO PRACTICE

Chronic Lymphocytic Leukemia Faculty

Asher Chanan-Khan, MD
Professor of Medicine and Oncology
Mayo Clinic
Jacksonville, Florida

Brad S Kahl, MD
Professor of Medicine
Washington University School of Medicine
Director, Lymphoma Program
Siteman Cancer Center
St Louis, Missouri

Chronic Lymphocytic Leukemia: Considerations for Frontline Treatment

Brad Kahl, MD

SITEMAN CANCER CENTER
A NATIONAL CANCER INSTITUTE COMPREHENSIVE CANCER CENTER
BARNES-JEWISH Hospital BJC HealthCare
Washington University in St. Louis SCHOOL OF MEDICINE
SITEMAN Kids AT ST. LOUIS Children's HOSPITAL Washington University Physicians
NCI Designated Comprehensive Cancer Center
NCCN National Comprehensive Cancer Network®

Options for 1st line CLL

- BTK inhibitors
  - Ibrutinib (FDA approved 2016)
  - Acalabrutinib (FDA approved 2019)
  - Zanubrutinib (FDA approved 2023)
- BCL-2 inhibitors
  - Venetoclax (FDA approved 2019)
- New anti-CD20 MoAbs
  - Obinutuzumab (FDA approved 2019)
    - Combination with Venetoclax (yes)
    - Combination with Ibrutinib or Acalabrutinib (optional)

Factors guiding therapy

- Does your patient prefer time limited therapy
  - If yes, then Venetoclax-Obinutuzumab is done in 12 months
- Does your patient wish to avoid infusions and frequent monitoring
  - BTKi is simpler than VO
- Does your patient have an underlying bleeding risk or significant cardiac disease
  - Perhaps wish to avoid BTKi
- Does your patient have significant underlying renal impairment
  - Increases risk for TLS, may wish to avoid VO and opt for BTKi
- Does your patient have a 17p del or p53 mutation
  - BTKi appears to control disease better than time limited options

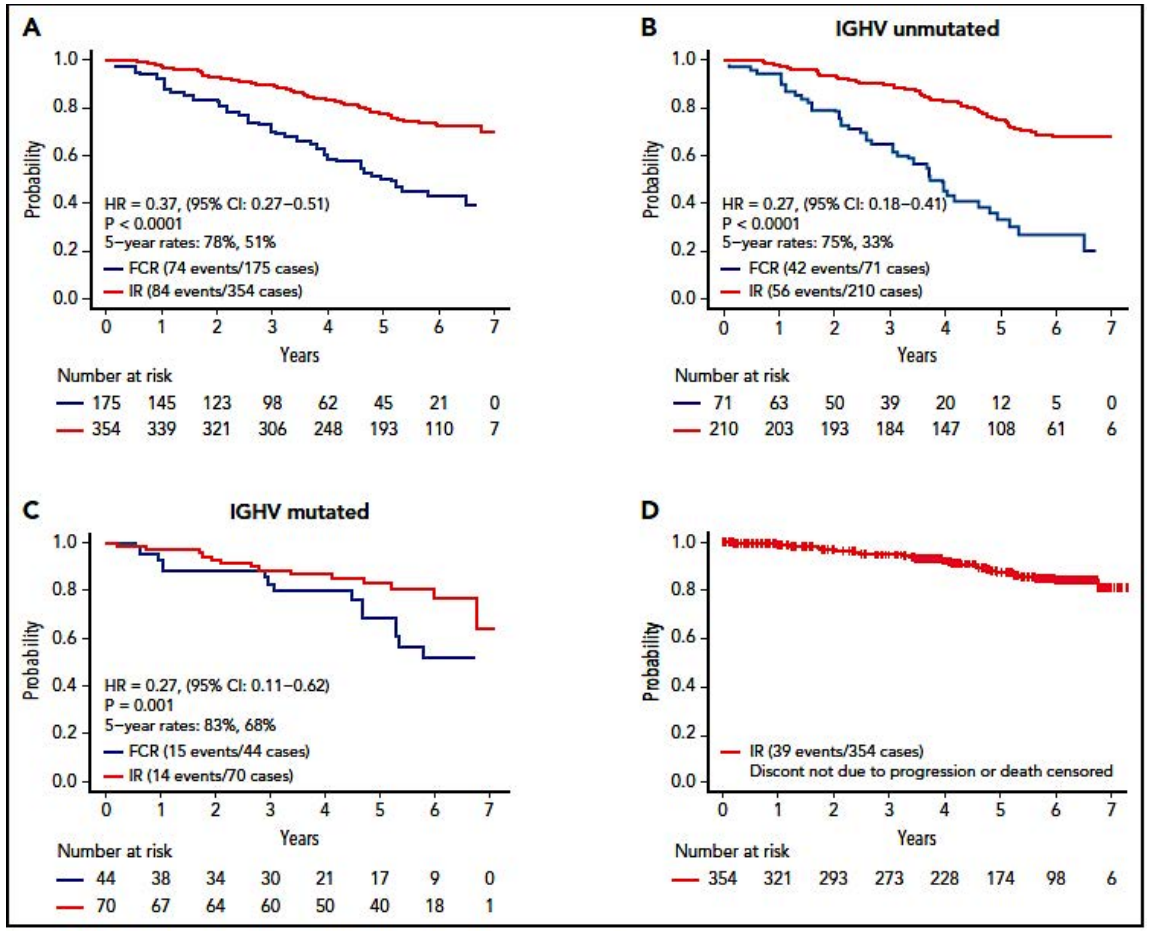
Ibrutinib

- 1st generation BTK inhibitor
  - Associated with lymphocytosis (due to lymphocyte redistribution)
- Highly effective
  - Response rate ~ 90%, 75% still in remission at 5 years
  - 420 mg/day
  - Remissions shallow – need for indefinite therapy
- Generally well tolerated
  - Arthralgias/myalgias tend to improve with time
  - Rash/skin issues can be nagging
  - Hypertension (can be hard to manage)
  - Atrial fibrillation 10-15%
  - Bleeding (need to hold for surgery)
    - No warfarin. Careful with other agents.

Long-term outcomes for ibrutinib–rituximab and chemoimmunotherapy in CLL: updated results of the E1912 trial

Tait D. Shanafelt,[1] Xin Victoria Wang,[2] Curtis A. Hanson,[3] Elisabeth M. Paietta,[4] Susan O'Brien,[5] Jacqueline Barrientos,[6] Diane F. Jelinek,[3] Esteban Braggio,[3] Jose F. Leis,[3] Cong Christine Zhang,[7] Steven E. Coutre,[1] Paul M. Barr,[8] Amanda F. Cashen,[9] Anthony R. Mato,[10] Avina K. Singh,[11] Michael P. Mullane,[12] Richard F. Little,[13] Harry Erba,[14] Richard M. Stone,[2] Mark Litzow,[3] Martin Tallman,[10] and Neil E. Kay[3]

Progression-Free Survival

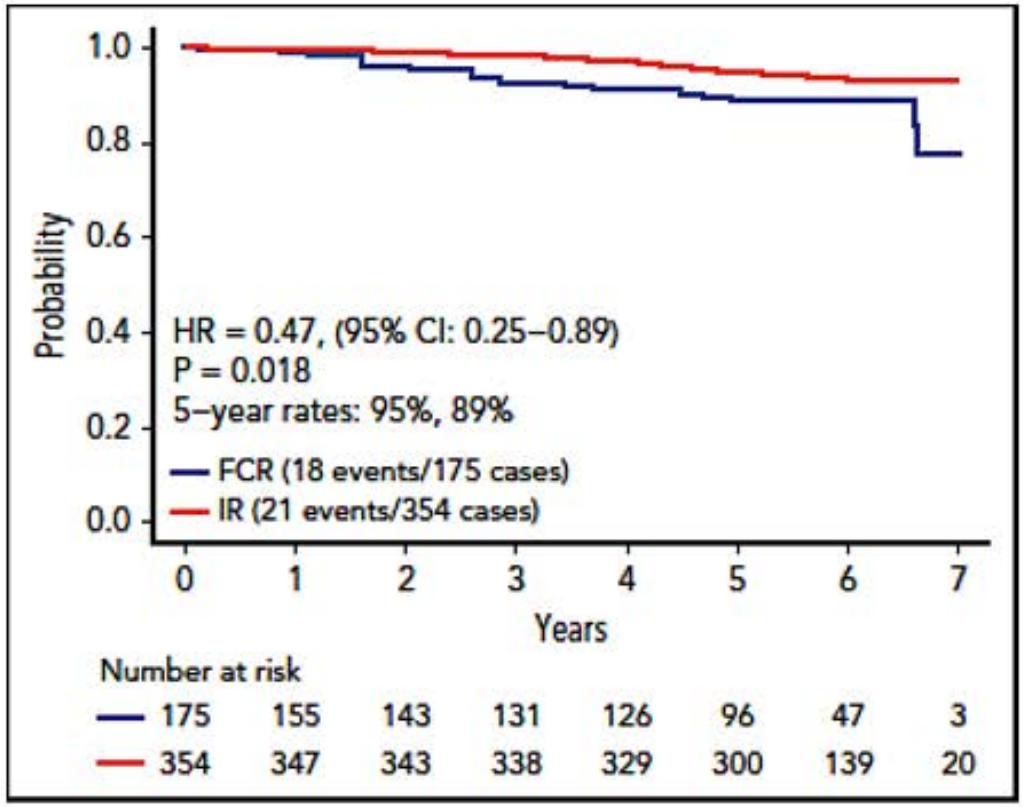


(A) PFS among all patients; (B) PFS among patients with unmutated IGHV; (C) PFS among patients with mutated IGHV; (D) PFS for patients remaining on ibrutinib. Patients who went off ibrutinib for AEs or reasons other than progression are censored at the time of ibrutinib discontinuation.

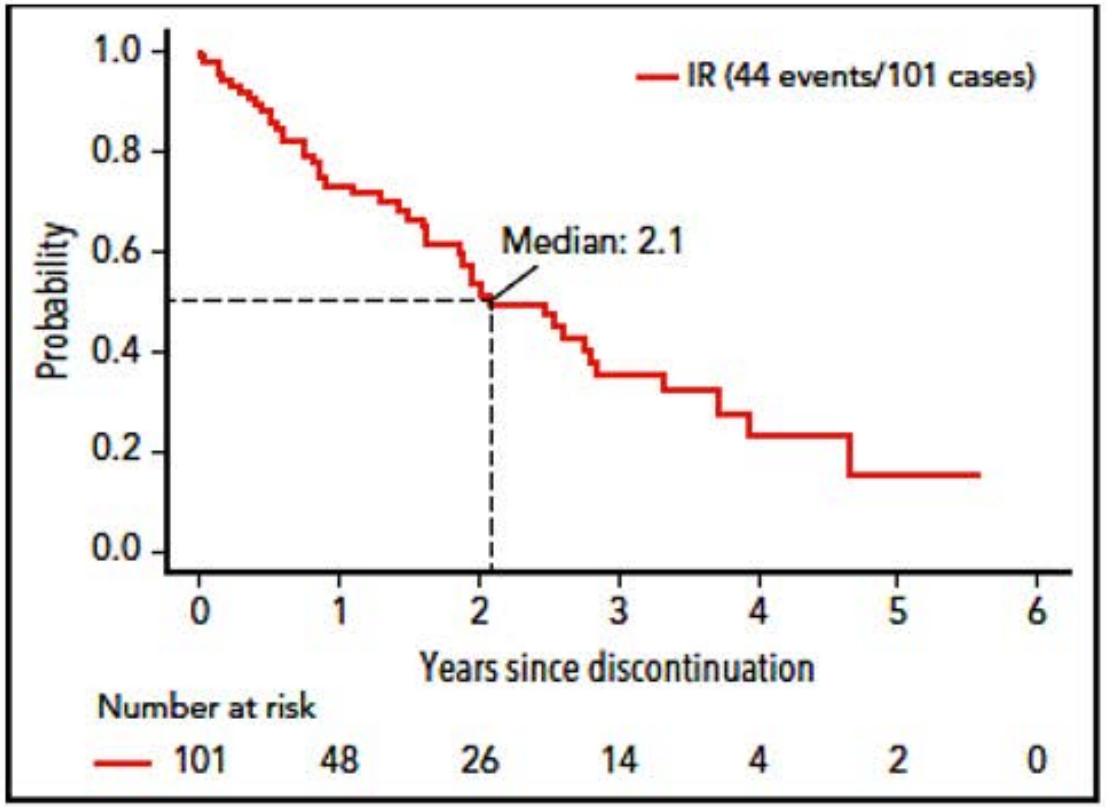
Blood 2022

E1912 Long Term Follow Up

OS Comparison for IR versus FCR



PFS from Discontinuation of Ibrutinib



Includes patients who discontinued ibrutinib for reasons other than progression or death and known to be progression-free at the time of discontinuation.

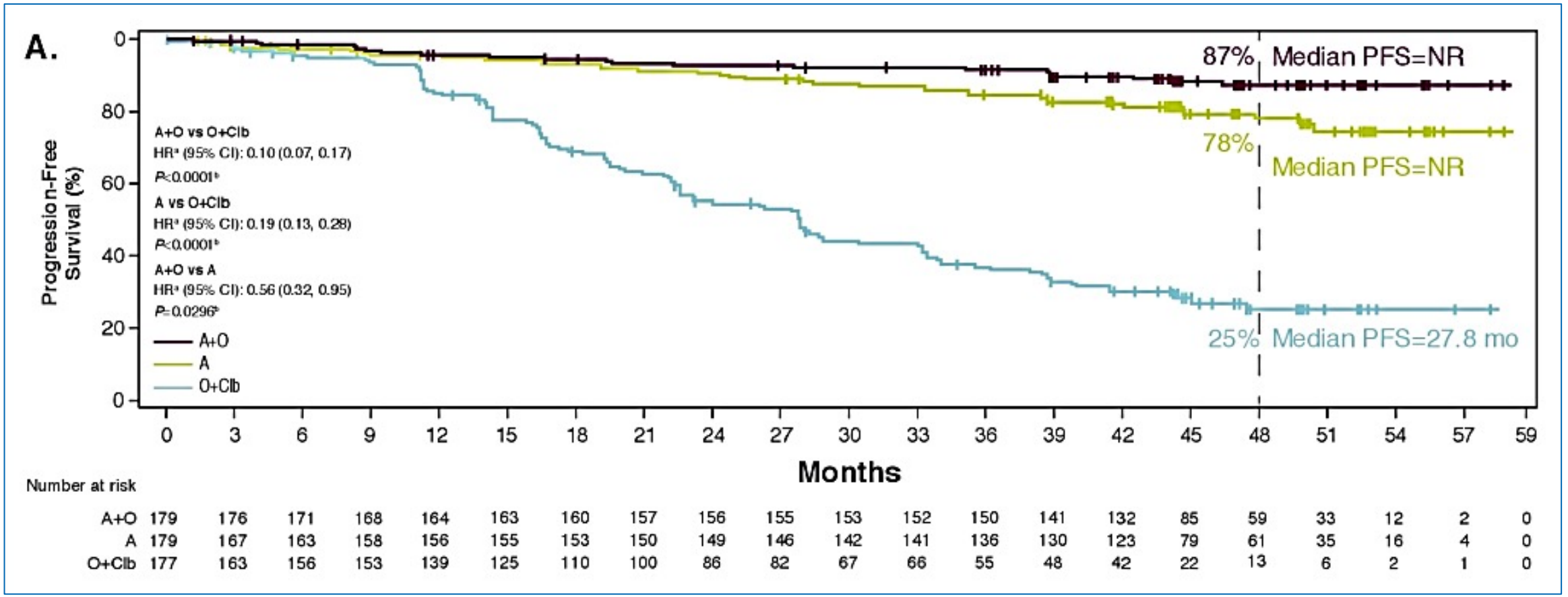
Shanafelt TD et al. *Blood* 2022;140(2):112-20.

Acalabrutinib

- 2nd Generation BTK inhibitor
  - More selective kinase inhibitor = less AE's
- Highly effective
  - Activity appears comparable to ibrutinib
- Better tolerated (ELEVATE RR TRIAL)
  - Less arthralgia, myalgia, HTN, Afib, Bleeding
  - Does cause headache – caffeine helps
- Other issues
  - 100 mg po BID
  - PPI interaction no longer an issue

Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in TN CLL: ELEVATE 4-Year Follow-Up

ELEVATE-TN: Investigator-Assessed PFS (Overall Population)



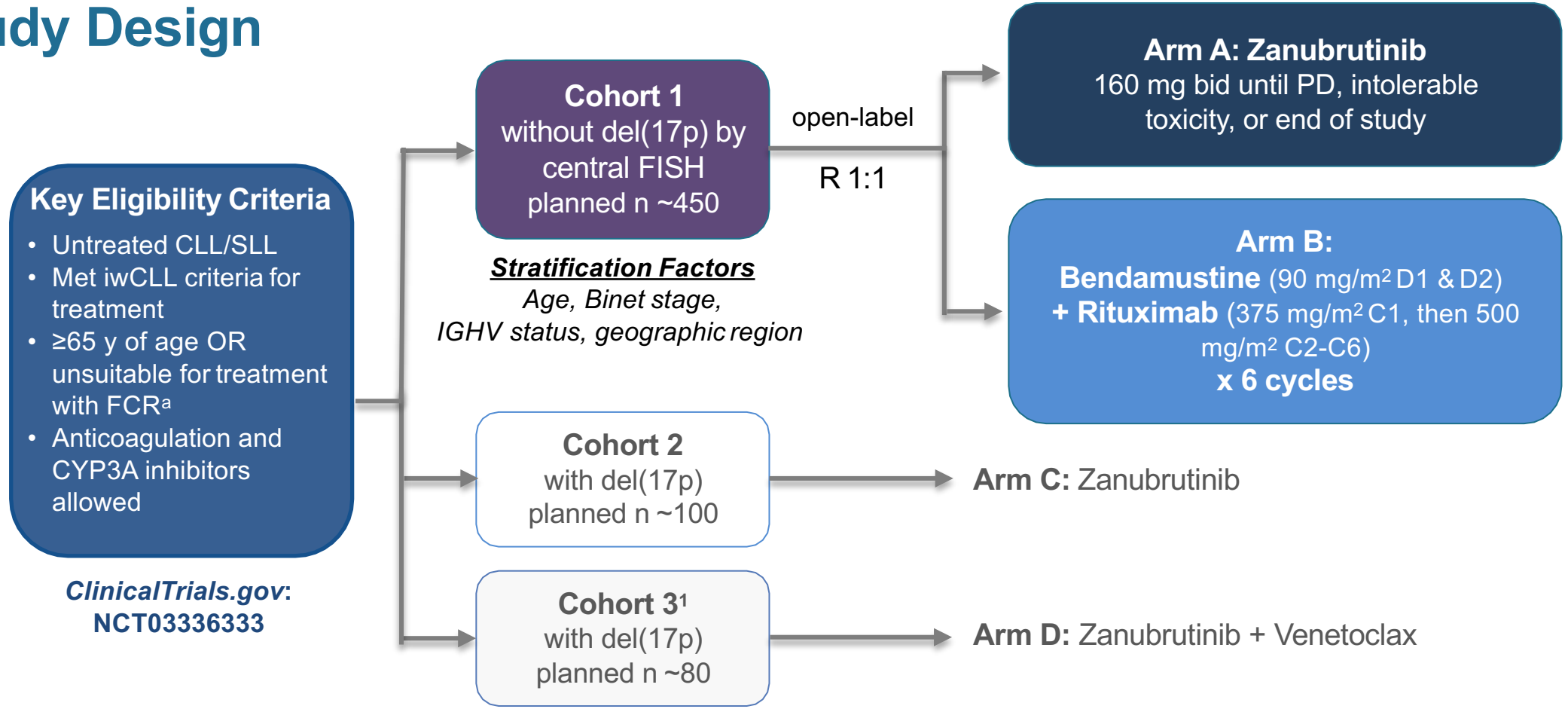
Sharman et al, Leukemia 2022

Zanubrutinib

- 2nd Generation BTK inhibitor
  - More selective kinase inhibitor = less AE's
- Highly effective
  - Superior to BR in 1st line CLL (SEQUOIA)
  - Recent study suggests more active than ibrutinib R/R CLL (ALPINE)
  - No 5 year follow up at this point
- Better tolerated than Ibrutinib (ALPINE)
  - Less Atrial fibrillation, Bleeding, Diarrhea
- FDA approved in Jan 2023
  - 160 mg po BID

SEQUOIA (BGB-3111-304)

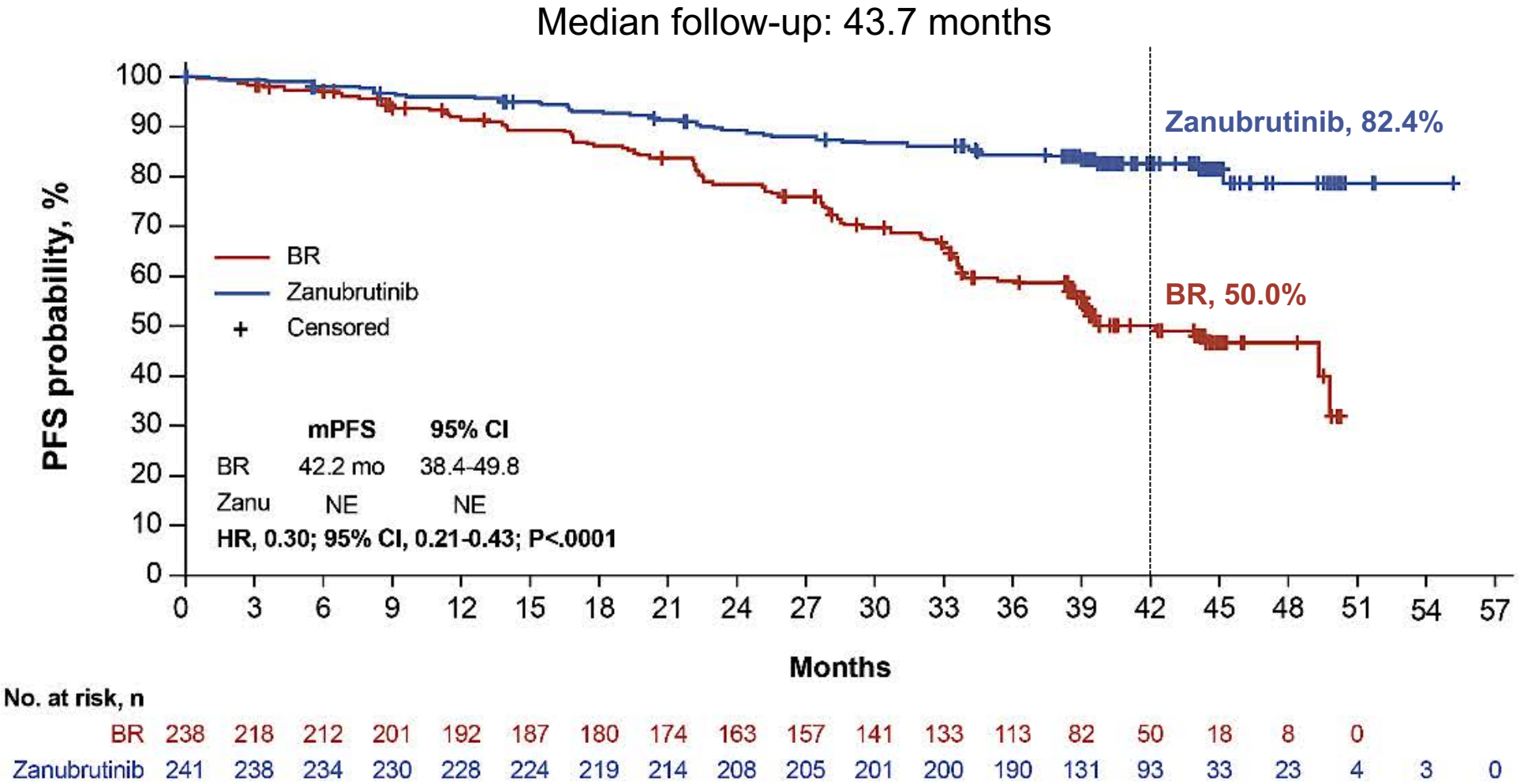
Study Design



Tam et al, 2022

THE LANCET Oncology

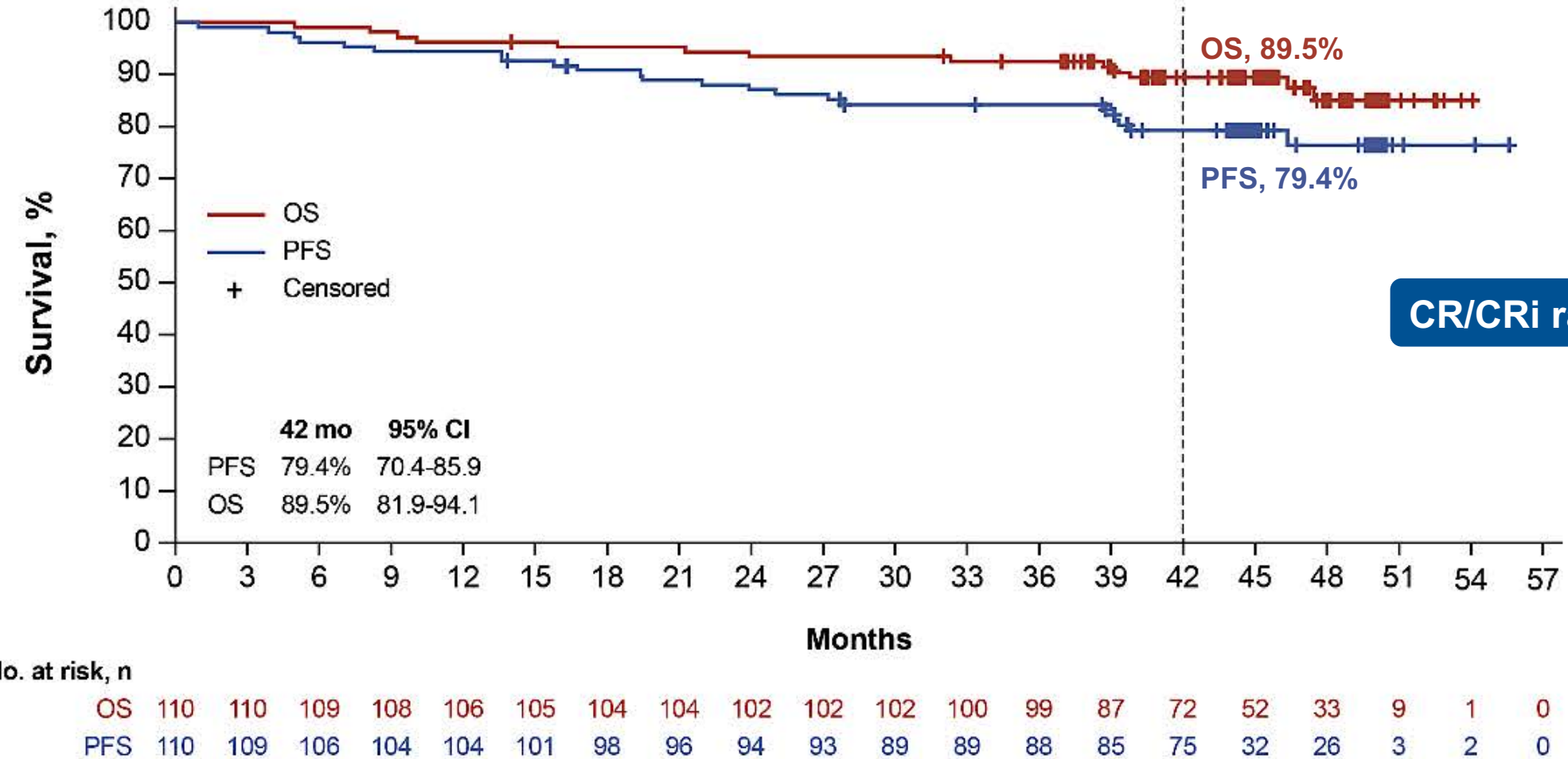
Cohort 1: PFS in Patients Without del(17p)



Tam CS et al. *Lancet Oncol* 2022;23(8):1031-43.

Cohort 2: PFS and OS in Patients With del(17p)

Median follow-up: 47.9 months



CR/CRi rate, 14.5%

Tam CS et al. *Lancet Oncol* 2022;23(8):1031-43.

So which BTKi should you choose?

BTKi Comparisons

- Acalabrutinib and Zanubrutinib better tolerated than Ibrutinib in CLL and WM
  - ELEVATE R/R trial
  - ALPINE Trial
  - ASPEN Trial

- Acalabrutinib same efficacy as Ibrutinib in ELEVATE R/R
- Zanubrutinib more active than Ibrutinib in ALPINE

- If A = I, and if Z > I, is Z > A?

- Zanubrutinib vs. Acalabrutinib never tested

Venetoclax

- BCL-2 inhibitor
  - No lymphocytosis
- Highly effective
  - Remission “deeper” than with BTKi’s
    - More complete responses. More MRD negativity.
  - Developed as a 12-month “time limited therapy” when used with obinutuzumab in 1st line
  - Responses in ~90%. No 5-year data yet.
- Generally very well tolerated
  - GI side effects, cytopenias
- Tumor Lysis Syndrome

Venetoclax

- Toxicity profile different from other targeted agents: TLS risks

Figure 1. **Intrapatient dose ramp-up scheme for CLL patients initiating venetoclax**

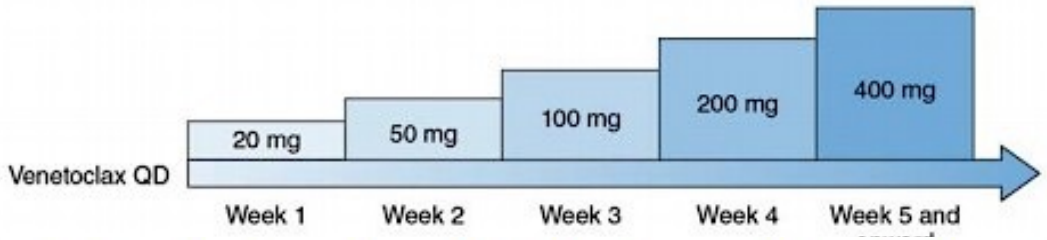


Figure 2. **Tumor lysis syndrome risk stratification, prophylaxis, and monitoring for CLL patients initiating venetoclax**

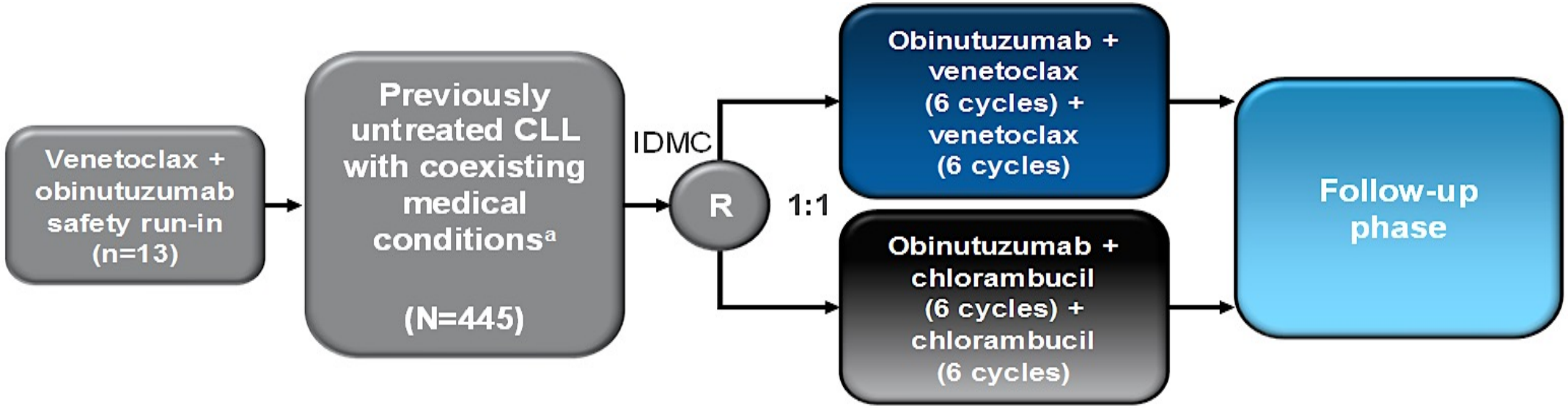
LOW RISK Nodal mass <5 cm and ALC <25,000 K/μL	**MEDIUM RISK** Nodal mass ≥5 cm and <10 cm or ALC ≥25,000 K/μL	**HIGH RISK** Nodal mass ≥10 cm or Nodal mass ≥5 cm but <10 cm and ALC ≥25,000 K/μL
Oral hydration (1.5-2L), allopurinol	Oral hydration (1.5-2L), consider IV hydration, allopurinol	Oral hydration (1.5-2L) and IV hydration (150-200 mL/hr as tolerated), allopurinol, consider rasburicase if elevated baseline uric acid
Outpatient administration	–Outpatient administration –Consider inpatient if CrCl <80 mL/min	–Inpatient administration for initial dose of 20 mg and 50 mg –Outpatient administration for subsequent dose escalations
Labs pre-dose, then 6-8 and 24 hours post-dose after initial dose of 20 mg and 50 mg	Labs pre-dose, then 6-8 and 24 hours post-dose after initial dose of 20 mg and 50 mg	**Inpatient:** Labs pre-dose, then 4, 8, 12, and 24 hours post-dose **Outpatient:** Labs pre-dose, then 6-8 and 24 hours post-dose

Blood. 2017;130(9):1081

Obinutuzumab

- Anti-CD20 MoAb
  - Designed to be a new and improved rituximab
  - Better than rituximab for CLL
- Dosing: 1000 mg flat dose
  - Cycle 1: Day 1 (100mg), 2 (900mg), 8, 15
  - Cycle 2-6 Day 1
- When to use it
  - If using venetoclax 12-month time limited therapy, combine with obinutuzumab
  - If using BTKi, obinutuzumab use is optional
    - Improves outcomes marginally
    - Adds some toxicity (mostly infections)

Venetoclax + G vs CHL + G: (CLL-14)



Primary endpoint:

- PFS as assessed by investigator[3]

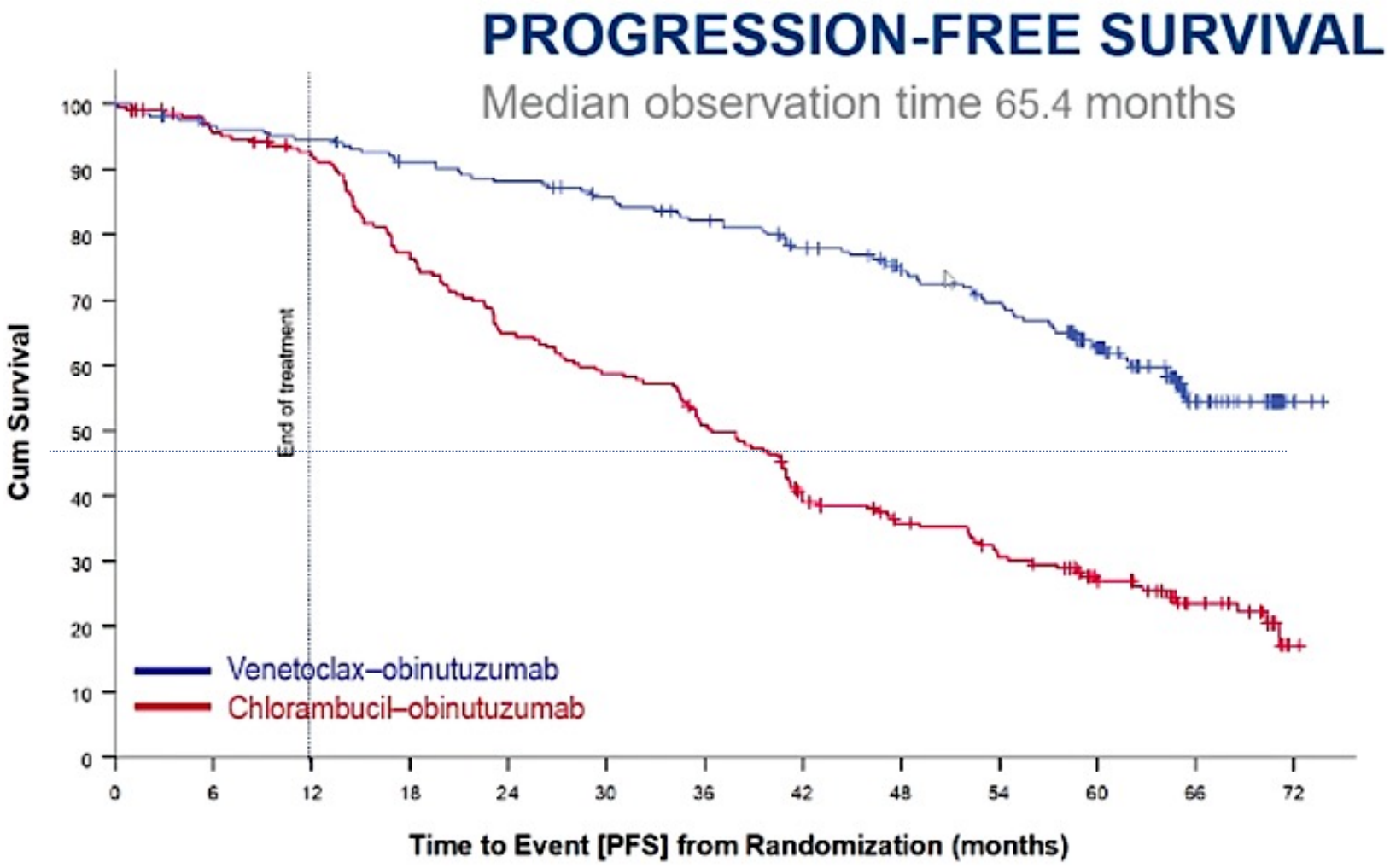
Secondary endpoints[3]:

- PFS as assessed by IRC
- MRD
- ORR
- CR rate
- DOR
- EFS
- OS
- TTNT
- Safety

[a]CIRS >6 and/or CrCl <70 mL/min

Fischer, NEJM,2019

Venetoclax + G vs CHL + G (CLL-14)



Median PFS
Ven-Obi: not reached
Clb-Obi: 36.4 months

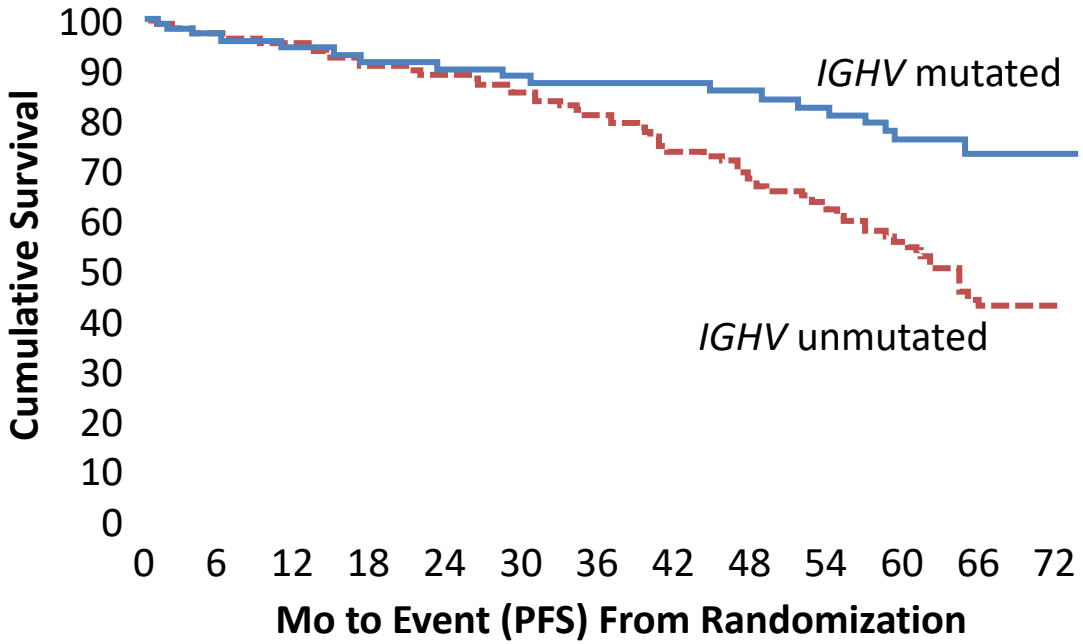
5-year PFS rate
Ven-Obi: 62.6%
Clb-Obi: 27.0%

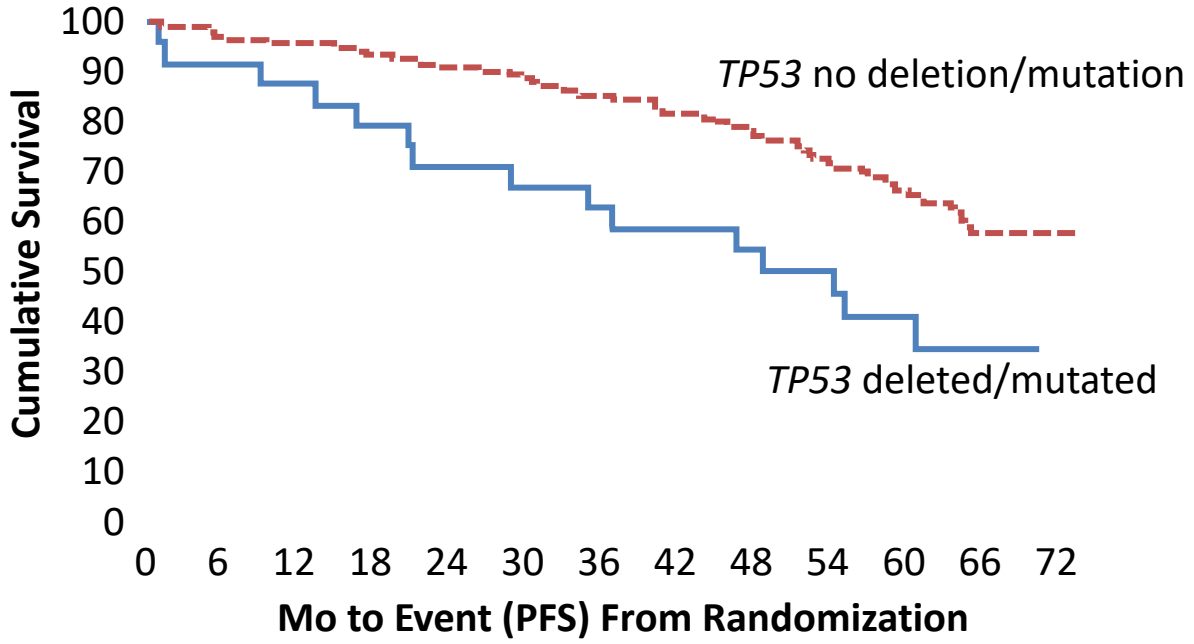
HR 0.35, 95% CI [0.26-0.46]
P<0.0001

Al-Sawaf, EHA, 2022

CLL14 (Venetoclax + Obinutuzumab Arm): PFS by *IGHV* and *TP53* Mutation Status

- Median observation time: 65.4 mo





PFS by *IGHV* Status on Ven + Obin Arm	*IGHV* Mutated (n = 76)	*IGHV* Unmutated (n = 121)
Median PFS, mo	NR	64.2 mo

PFS by *TP53* Status on Ven + Obin Arm	*TP53* Del and/or Mut (n = 25)	*TP53* No Del and/or Mut (n = 184)
Median PFS, mo	49.0	NR

Al-Sawaf. EHA 2022. Abstr S148.

Which Therapy Is the Best Initial Therapy in CLL?

Targeted Therapies	PFS Outcomes
RESONATE-2: ibrutinib[1]	70% at 5 yr
ELEVATE-TN: acalabrutinib[2]	72% at 5 yr
ELEVATE-TN: acalabrutinib + obinutuzumab[2]	84% at 5 yr
SEQUOIA: zanubrutinib[4]	80% at 4 yr
CLL 14: venetoclax + obinutuzumab[3] (IGHV mutated)	75% at 5 yr
CLL 14: venetoclax + obinutuzumab[3] (IGHV unmutated)	50% at 5 yr

*Note: All 4 trials conducted in older CLL patients.

1. Burger. Leukemia. 2020. 2. Sharman. ASCO 2022. Abstr 7539.
3. Al-Sawaf. EHA 2021. Abstr S146. 4. Tam. Lancet Oncol. 2022;23:1031.

Updated NCCN Guidelines: 1st line therapy

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2023
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

NCCN Guidelines Index
Table of Contents
Discussion

SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL without del(17p)/*TP53* mutation
(alphabetical by category)

FIRST-LINE THERAPY[e]		
Preferred regimens	**Other recommended regimens**	**Useful in certain circumstances**
• Acalabrutinib[f,*] ± obinutuzumab (category 1) • Venetoclax[f,g] + obinutuzumab (category 1) • Zanubrutinib[f,*] (category 1)	• Ibrutinib (category 1)[f,h,*] • Bendamustine[i] + anti-CD20 mAb[d,j,k] • Chlorambucil + obinutuzumab[l] • Obinutuzumab[l] • High-dose methylprednisolone (HDMP) + rituximab or obinutuzumab (category 2B; category 3 for patients <65 y without significant comorbidities) • Ibrutinib[f,*] + obinutuzumab[l] (category 2B) • Ibrutinib[f,*] + rituximab[p] (category 2B) • Ibrutinib[*] + venetoclax[f,g] (category 2B)	(consider for IGHV-mutated CLL in patients age <65 y without significant comorbidities) • FCR (fludarabine, cyclophosphamide, rituximab)[m,n,o]

[*] Covalent (irreversible) BTK inhibitors.

Note: Ibrutinib approval in MCL and MZL voluntarily withdrawn in 2023

Ongoing questions

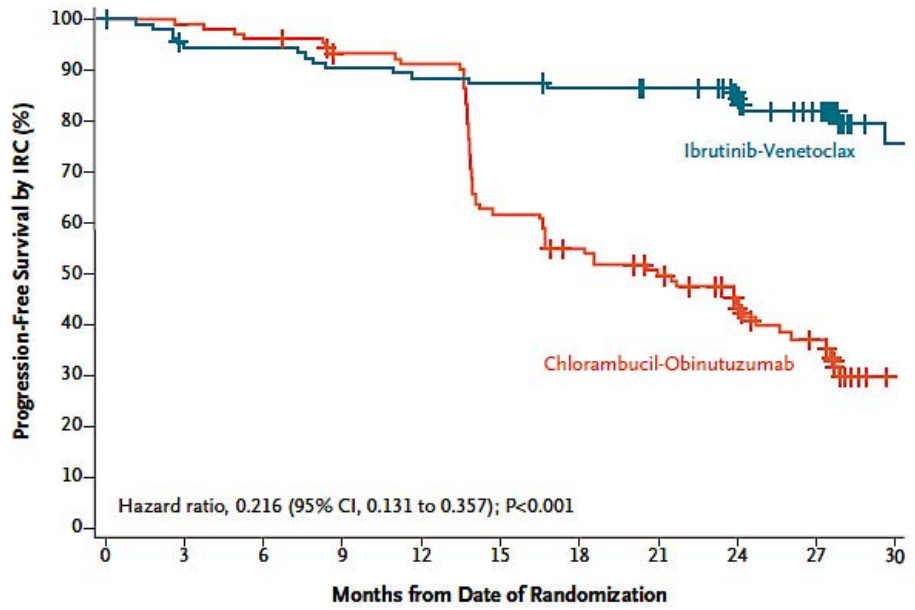
1. What about novel-novel combinations?
   - Ibrutinib plus Venetoclax x 1 year (GLOW trial)
2. Could MRD assessments guide therapy duration in a rational way?
   - CAPTIVATE and MAJIC may inform on this question
3. Are there newer "better" targeted agents on the horizon?
   - 3rd generation BTK inhibitors looking very promising

ORIGINAL ARTICLE

Fixed-Duration Ibrutinib-Venetoclax in Patients with Chronic Lymphocytic Leukemia and Comorbidities

Arnon P. Kater, M.D., Ph.D.,[1] Carolyn Owen, M.D.,[2] Carol Moreno, M.D.,[3] George Follows, B.M.Bch., Ph.D.,[4] Talha Munir, M.B.B.S.,[5] Mark-David Levin, M.D.,[6] Ohad Benjamini, M.D.,[7] Ann Janssens, M.D., Ph.D.,[8] Anders Osterborg, M.D., Ph.D.,[9] Tadeusz Robak, M.D., Ph.D.,[10] Martin Simkovic, M.D., Ph.D.,[11] Don Stevens, M.D.,[12] Sergey Voloshin, M.D., Ph.D.,[13] Vladimir Vorobyev, Ph.D.,[14] Loic Ysebaert, M.D., Ph.D.,[15] Rui Qin, Ph.D.,[16] Andrew J. Steele, Ph.D.,[17] Natasha Schuier, M.D.,[18] Kurt Baeten, Ph.D.,[19] Donne Bennett Caces, M.D., Ph.D.,[16] and Carsten U. Niemann, M.D., Ph.D.,[20] for the GLOW Investigators*

A



No. at Risk											
Ibrutinib-Venetoclax	106	98	98	94	92	91	89	87	71	59	20
Chlorambucil-Obinutuzumab	105	104	101	95	93	63	54	47	36	25	6

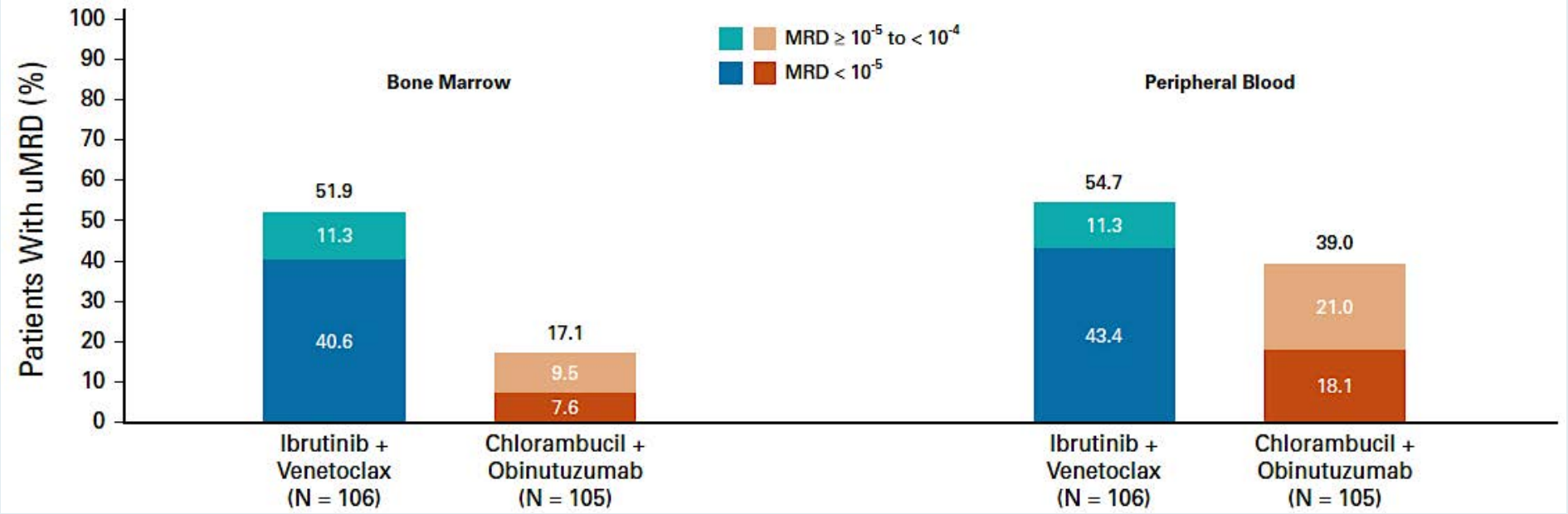
Kater AP et al. *N Engl J Med Evidence* 2022 May 13

Impact of Minimal Residual Disease on Progression-Free Survival Outcomes After Fixed-Duration Ibrutinib-Venetoclax Versus Chlorambucil-Obinutuzumab in the GLOW Study

Talha Munir, MBBS[1]; Carol Moreno, MD[2]; Carolyn Owen, MD[3]; George Follows, PhD[4]; Ohad Benjamini, MD[5]; Ann Janssens, MD, PhD[6]; Mark-David Levin, MD[7]; Anders Osterborg, MD, PhD[8]; Tadeusz Robak, MD, PhD[9]; Martin Simkovic, MD, PhD[10]; Don Stevens, MD[11]; Sergey Voloshin, MD, PhD[12]; Vladimir Vorobyev, PhD[13]; Munci Yagci, MD[14]; Loic Ysebaert, MD, PhD[15]; Keqin Qi, PhD[16]; Qianya Qi, PhD[17]; Lori Parisi, MPH[17]; Srimathi Srinivasan, PhD[18]; Natasha Schuier, MD[19]; Kurt Baeten, PhD[20]; Angela Howes, PhD[21]; Donne Bennett Caces, MD, PhD[17]; Carsten U. Niemann, MD, PhD[22]; and Arnon P. Kater, MD, PhD[23]

J Clin Oncol 2023 July 20;41(21):3689-99

GLOW: Minimal Residual Disease (MRD) Outcomes

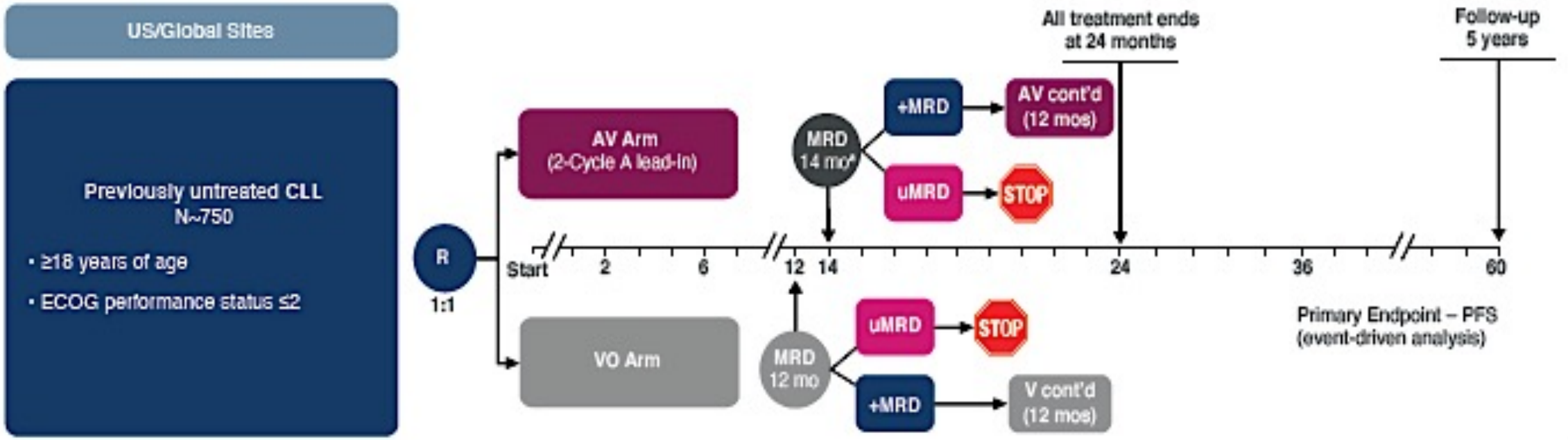


uMRD = undetectable MRD

RTP RESEARCH TO PRACTICE

MAJIC: Ven-Obin vs. Ven-Acala

Figure 1. MAJIC Study Design



Patients eligible for randomization will be stratified by the following factors:

- Age
- del(17p) and/or *TP53* mutation status
- IGHV mutation status

Clinical Questions and Cases

Chronic Lymphocytic Leukemia
Up-Front Management

- Biomarker evaluation (17p, TP53, IGVH, other)
- Indications to treat
- First-line treatment: Standard risk
  - BTK inhibitors: Second-generation covalent inhibitors — acalabrutinib, zanubrutinib
  - Venetoclax combinations
- First-line treatment: Higher risk (17p, TP53, other)
- Trials of venetoclax + BTK inhibitor +/- anti-CD20 antibody

Case Presentation: 45-year-old man with night sweats, weight loss and adenopathy, massive splenomegaly, IGHV-mutated CLL

Dr Shachar Peles (Lake Worth, Florida; 10-13-2020)

Discussion Question

Regulatory and reimbursement issues aside, what would be your most likely initial regimen for a 45-year-old man with CLL, B symptoms, lymphadenopathy and a massive 32-cm spleen extending to the pelvis?

Case Presentation: 69-year-old man with recurrent DVT who is receiving warfarin, is diagnosed with IGHV-mutated del(13q) CLL and receives obinutuzumab/venetoclax

Dr Shaachi Gupta (Lake Worth, Florida; 5-28-2022)

RTP
RESEARCH
TO PRACTICE

Discussion Question

Regulatory and reimbursement issues aside, what would be your preferred initial regimen for a 69-year-old patient with IGHV-mutated CLL with extensive adenopathy who is receiving warfarin for recurrent deep vein thromboses?

Case Presentation: 70-year-old man with multiple musculoskeletal comorbidities and transportation limitations who develops symptomatic IGHV-mutated CLL with cytopenias

Dr Syed Zafar (Fort Myers, Florida; 10-28-22)

RTP
RESEARCH
TO PRACTICE

Discussion Question

Does a history of migraine headache or the use of a proton pump inhibitor affect your choice of acalabrutinib versus zanubrutinib?

Discussion Question

Does anti-CD20 therapy provide additional benefit to patients receiving acalabrutinib as first-line treatment for CLL?

MAYO CLINIC | School of Continuous Professional Development

TREATMENT OF RELAPSED/REFRACTORY CLL; NOVEL AND INVESTIGATIONAL STRATEGIES

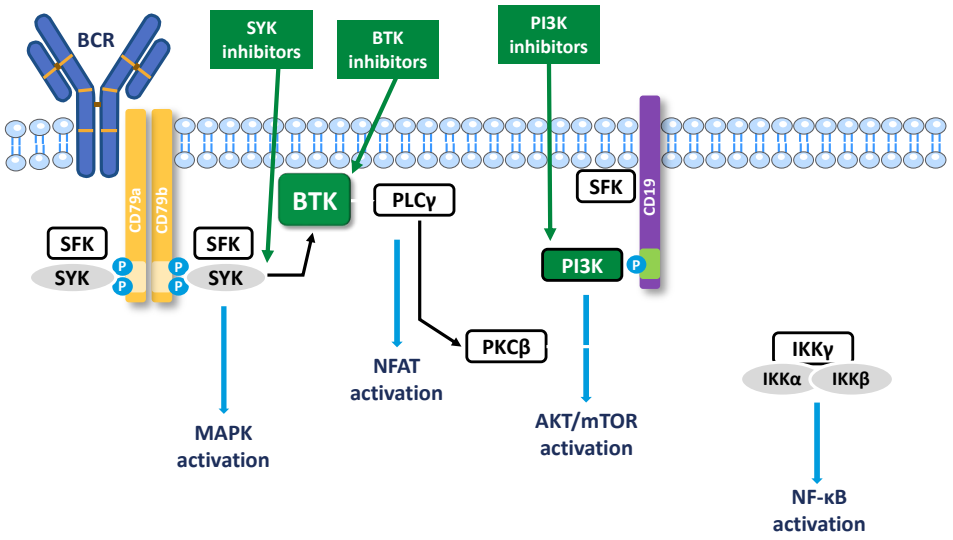
Asher Chanan-Khan, MD
Professor of Medicine

LEARNING OBJECTIVES

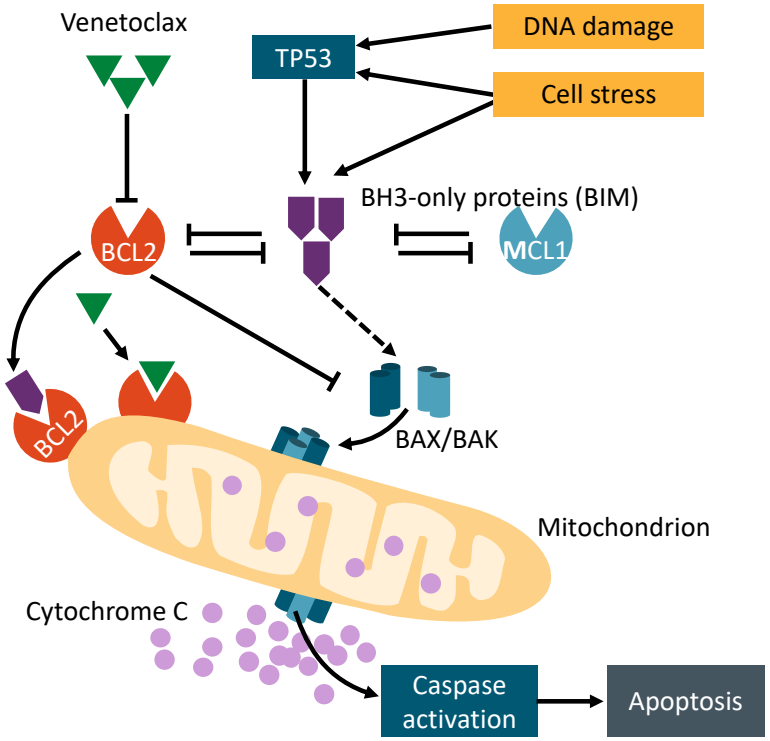
- Update on Phase III in relapse/refractory CLL
- Double dipping with BTKi!
- What's new in the toolbox
- Establishing an approach for your Practice Needs

HIGH TUMOR CELL PROLIFERATION PROMPTS MITOCHONDRIAL STABILIZATION

Progressive Cell Proliferation

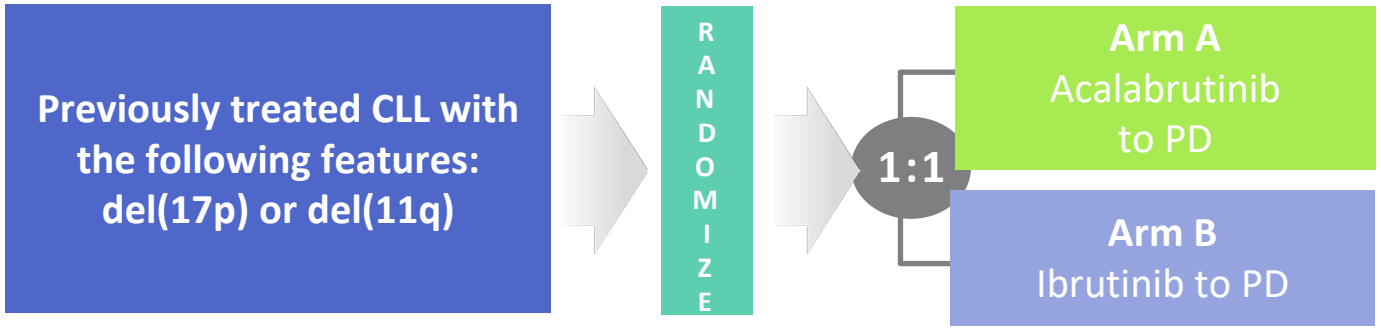


Progressive Cell Preservation



BTK Inhibitors

ELEVATE-RR: Phase 3 Study of Acalabrutinib vs Ibrutinib in R/R CLL



N=500 planned; 533 randomized

Stratification by

- Presence of del(17p)
- ECOG PS (2 vs ≤1)
- Number of prior therapies (1-3 vs ≥4)

Primary endpoint:
PFS by IRC

- Noninferiority[a]; tested after 250 events

Secondary endpoints[b]

- Incidence of atrial fibrillation
- Incidence of Grade ≥3 infections
- Incidence of Richter's transformation
- OS

FPI Oct 2015-LPI Nov 2017 (25 months)

Final analysis

- 279 IRC-assessed PFS events (DCO Sept 2020; DBL Nov 2020)

Final analysis population

- **ITT:** acalabrutinib, n=268; ibrutinib, n=265
- **Safety:** acalabrutinib, n=266; ibrutinib, n=263

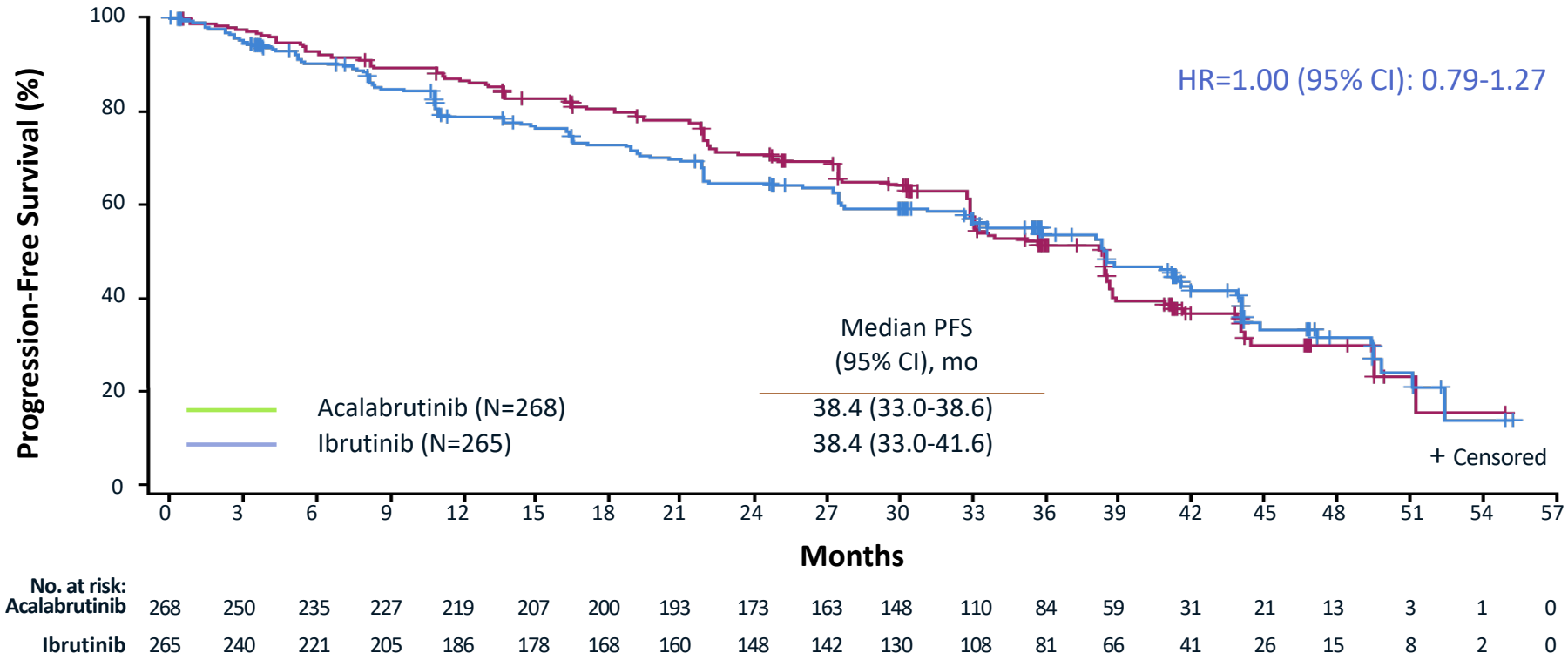
[a]NI achieved if the upper bound of the 95% CI of HR is less than the prespecified NI margin of 1.429.
[b]If noninferior PFS achieved, the secondary endpoints will be tested in a manner that maintains the type I error rate at ≤5%.
DBL, database lock; DCO, data cutoff; FPI, first patient in; LPI, last patient in; PD, progressive disease.
Byrd JC, et al. *J Clin Oncol.* 2021 Nov 1;39(31):3441-3452

ELEVATE-RR: Phase 3 Study of Acalabrutinib vs Ibrutinib in R/R CLL – Primary Endpoint Results

Patient Population

- Previously treated CLL with del(17p) or del(11q) (N=500 planned; N=533 randomized)

PRIMARY ENDPOINT: IRC-Assessed PFS at Median Follow-up of 41 Months



Primary Endpoint: Noninferiority met on IRC-assessed PFS

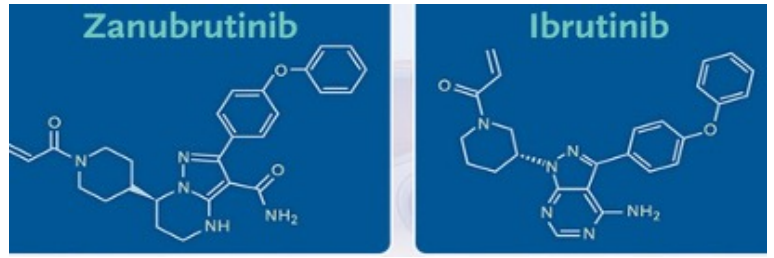
Noninferiority achieved if the upper bound of the 95% CI of HR is less than the prespecified NI margin of 1.429

NI, noninferiority

Byrd JC, et al. *J Clin Oncol.* 2021;39(31):3441-52.

ALPINE: Zanubrutinib vs Ibrutinib in R/R CLL/SLL

- International, open-label, randomized phase III trial
- 113 sites



Patients with R/R CLL/SLL; ≥1 prior systemic tx for CLL/SLL; measurable lymphadenopathy; no Richter transformation, prior BTKi, warfarin, other vitamin K antagonists; ECOG PS 0-2
(N = 652; interim analysis: n = 415)

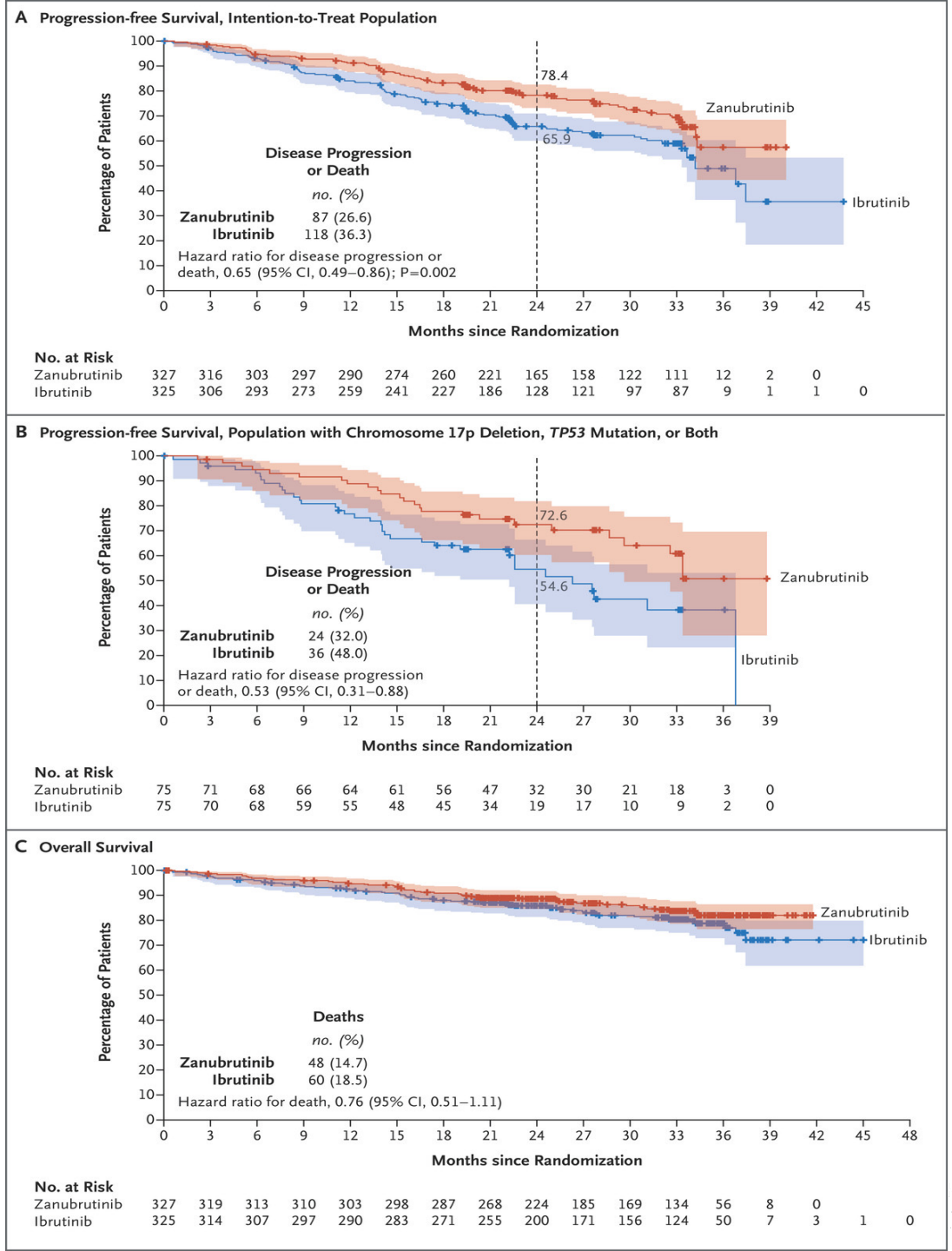
Zanubrutinib 160 mg PO BID
(n = 227)

Ibrutinib 420 mg PO QD
(n = 225)

Until PD or unacceptable toxicity

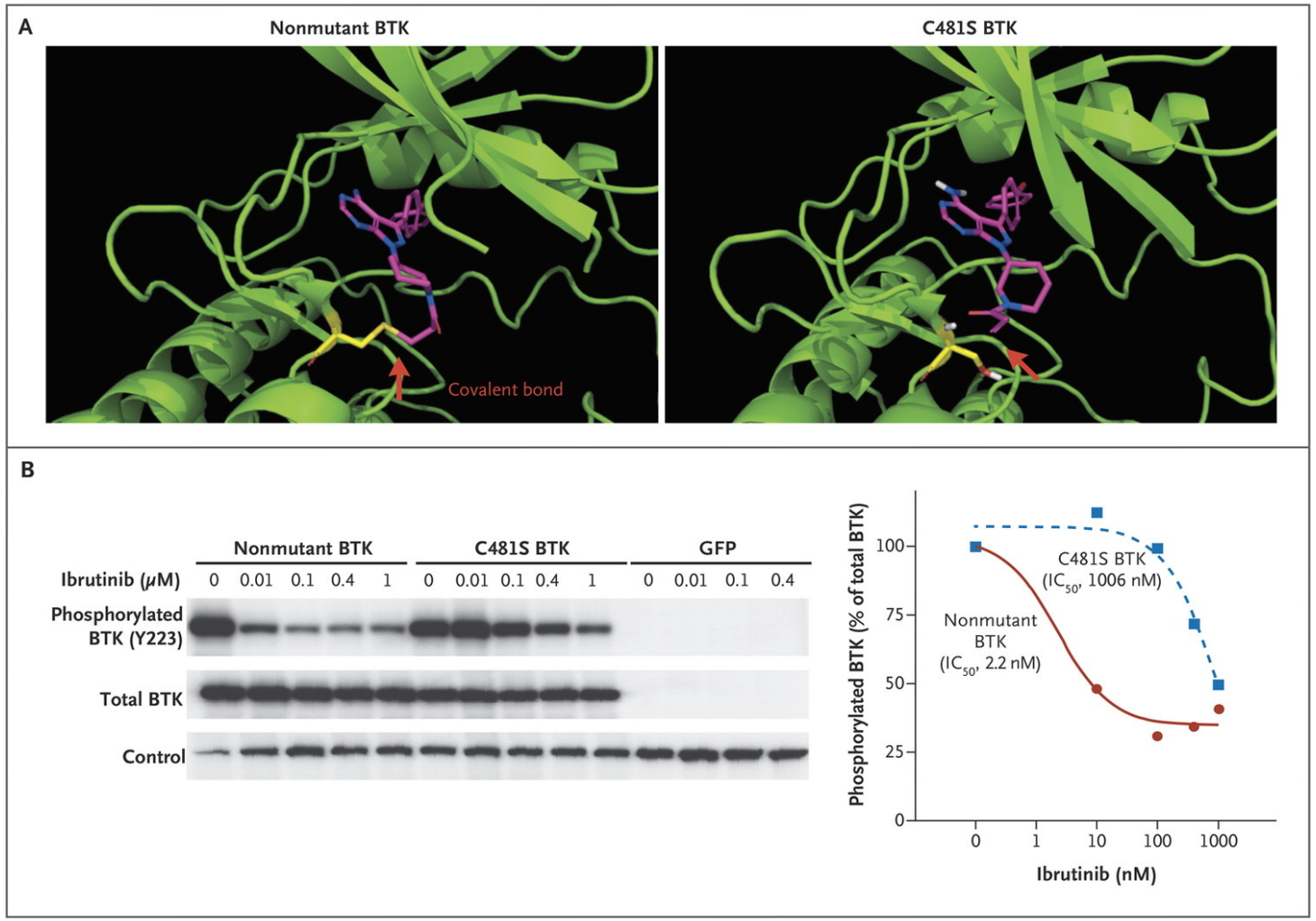
- Primary endpoint: noninferiority and superiority of investigator-assessed ORR
- Secondary endpoints: DoR, PFS, OS, TTF, rate of PR-L or higher, PROs, atrial fibrillation, safety

JR Brown et al. N Engl J Med 2023;388:319-332.



JR Brown et al. N Engl J Med 2023;388:319-332.

Effect of C481S Mutation of BTK on BTKi Binding



Furman RR et al. N Engl J Med 2014;370:2352-2354.

BTK Leu528Trp Mutations in Patients with CLL on Zanubrutinib

- Consecutive samples at Peter MacCallum (AUS); N=37
- BTK **Leu528Trp** mutations were significantly enriched at time of PD for zanubrutinib versus ibrutinib:
  - **54%** [7/13] vs **4%** [1/24] (p=0.001)
- Other studies have shown that Leu528Trp mutations are rarely seen with ibrutinib

BTKi mutations detected in a cohort of patients with disease progression during BTKi treatment

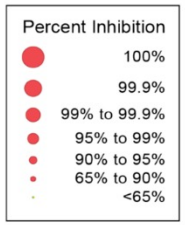
	Number of patients carrying the mutations			
	Ibrutinib-treated patients (n = 24)	Zanubrutinib-treated patients (n =13)	Total	*P*
Cys481 codon mutations	24	10	34	.03
Leu528Trp	1	7	8	.001

Both patients with Leu528Trp mutations treated with pirtobrutinib had poor responses

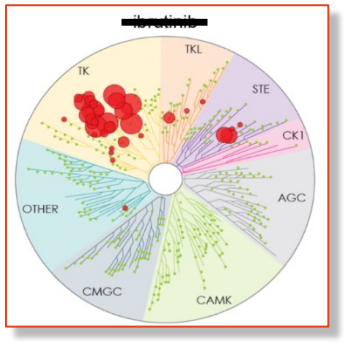
Kinase-dead BTK Leu528Trp mutation is enriched in patients with CLL progressing on zanubrutinib versus ibrutinib, which has potential implications for choice of BTK inhibitor and subsequent therapies, like pirtobrutinib, where this mutation is suspected to confer resistance

More BTKi options on the way with reversible inhibitors.

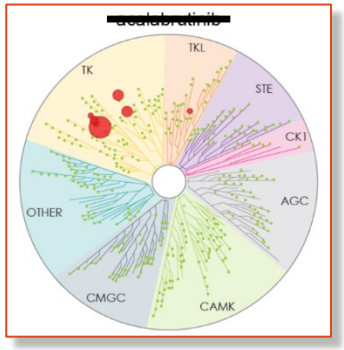
Irreversible



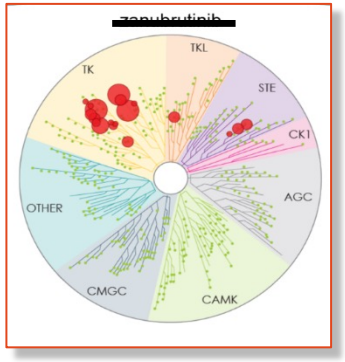
Ibrutinib



Acalabrutinib

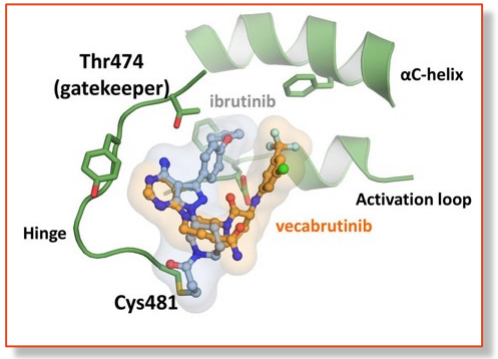


Zanubrutinib

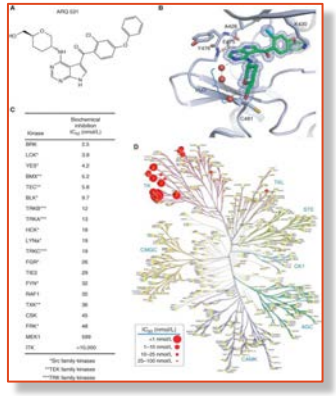


Reversible

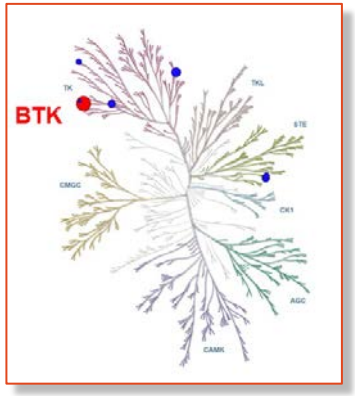
Vecabrutinib



Nemtabrutinib

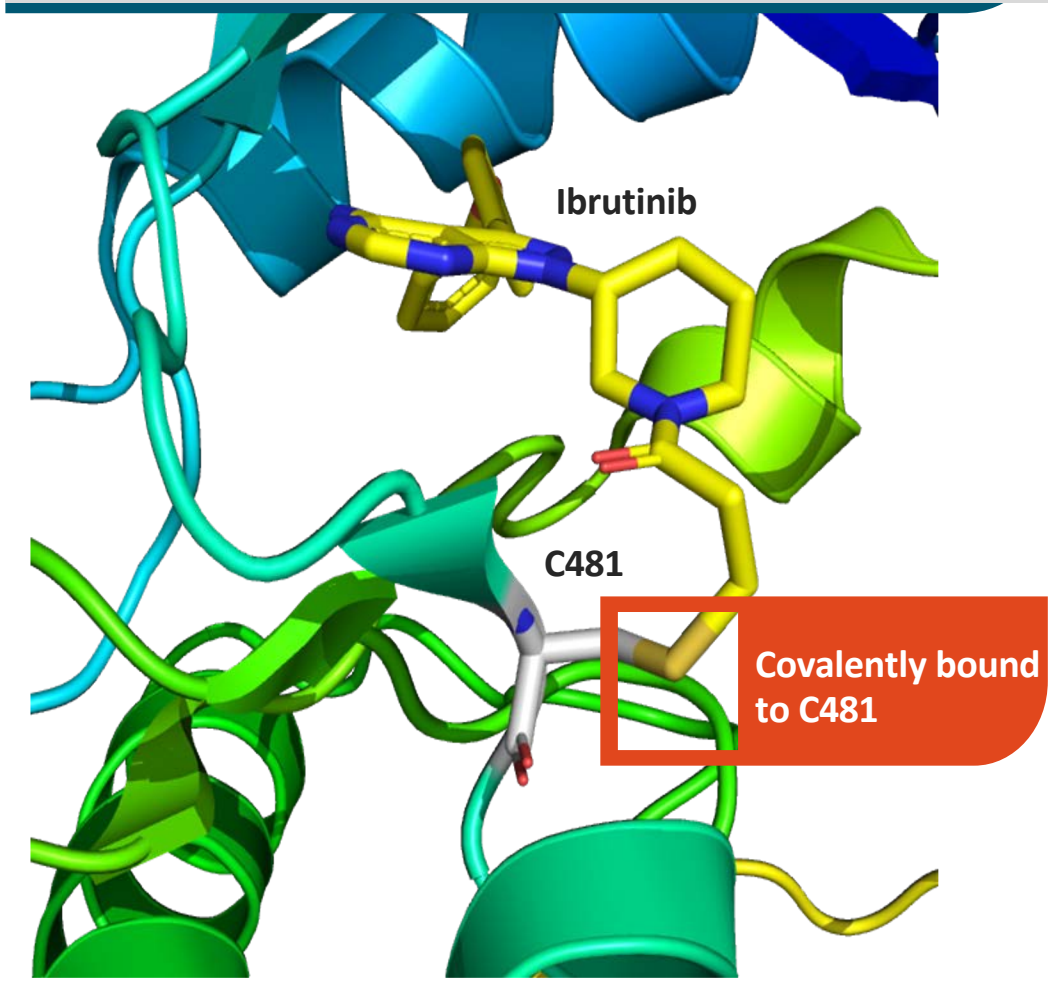


Pirtobrutinib

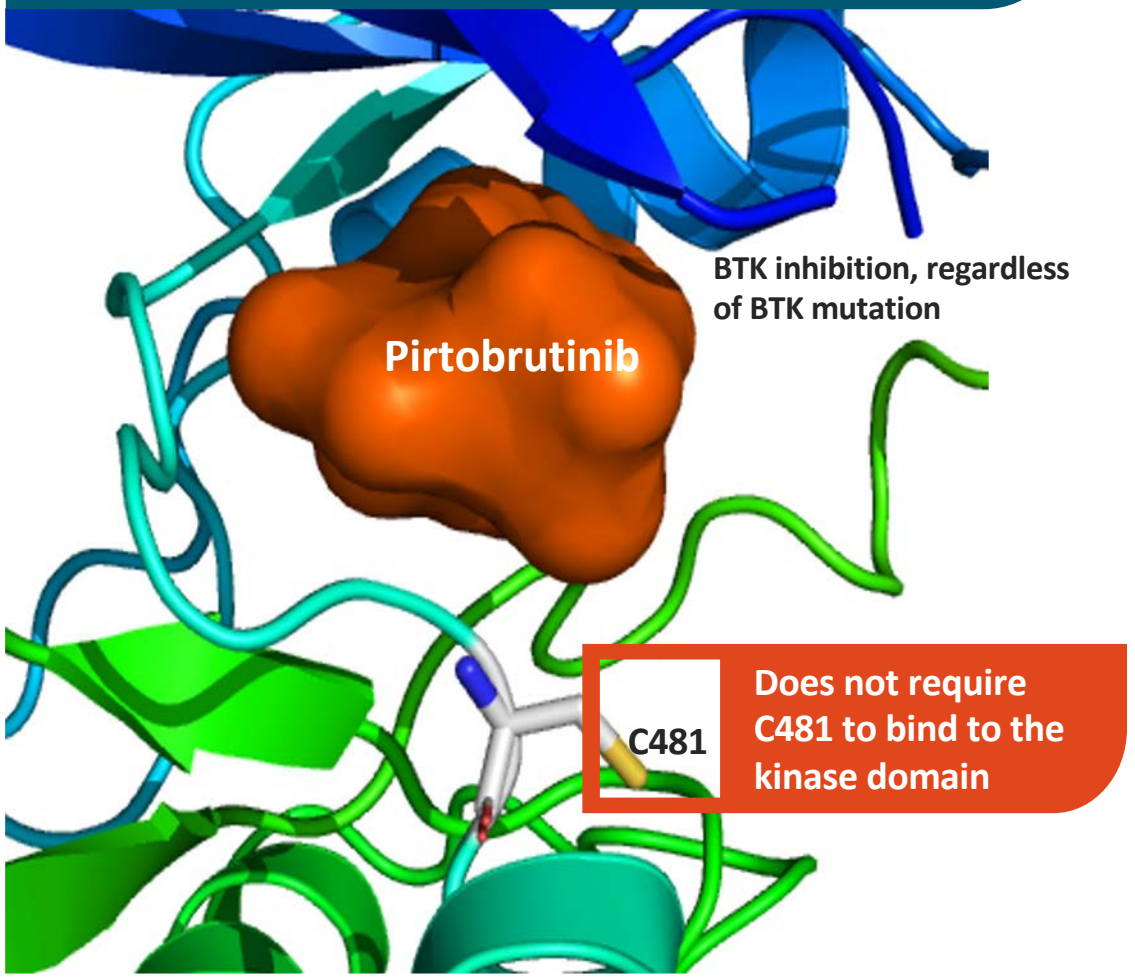


Kaptein A, et al. *Blood.* 2018;132(Supplement 1):1871.

Covalent BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib) require WT BTK for activity

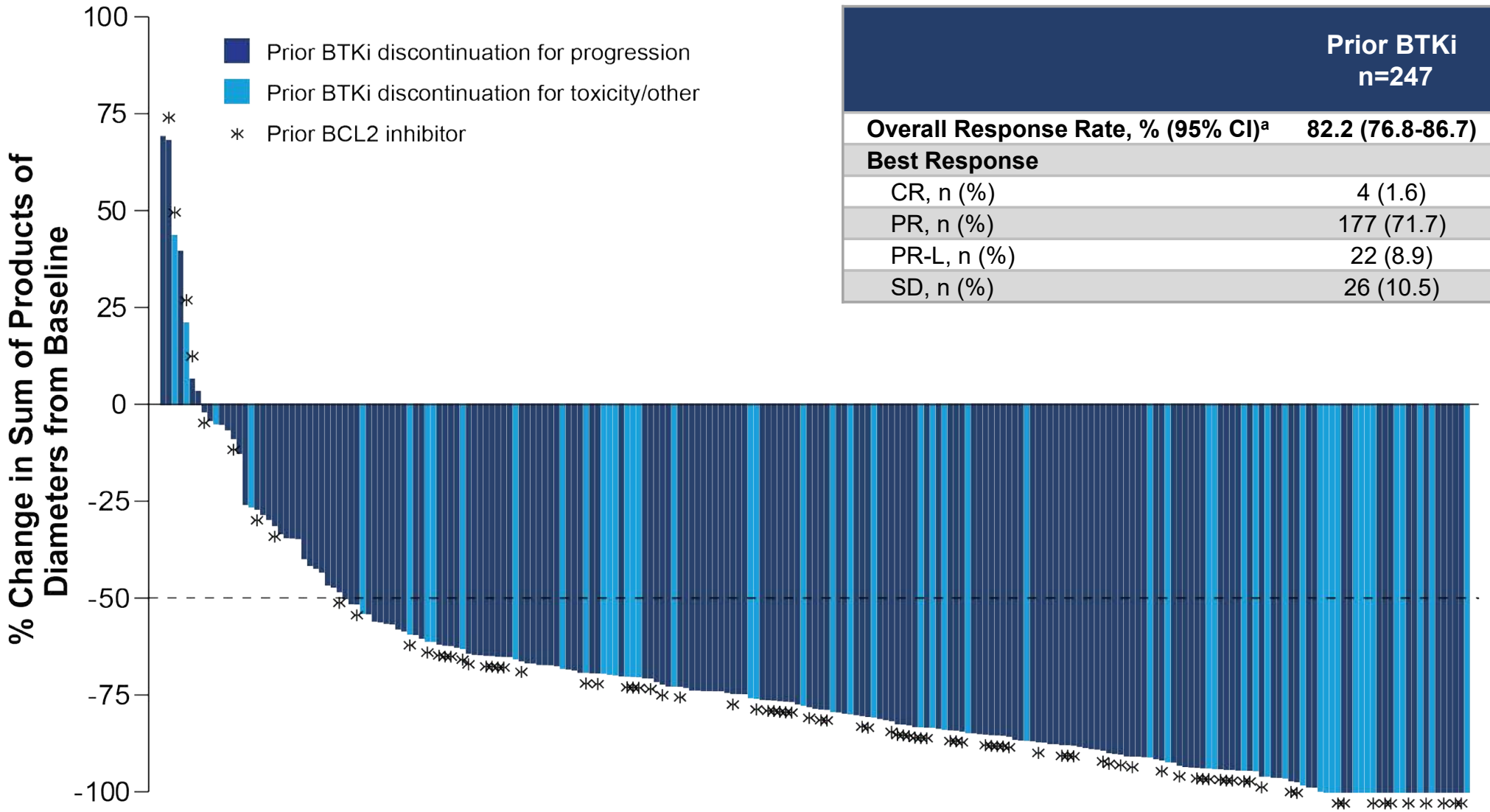


Pirtobrutinib is a non-covalent BTK inhibitor that is potent against both WT and C481-mutant BTK



Mato et al ASH 2022

BRUIN: Efficacy of Pirtobrutinib in Patients with CLL/SLL who Received Prior BTKi Treatment

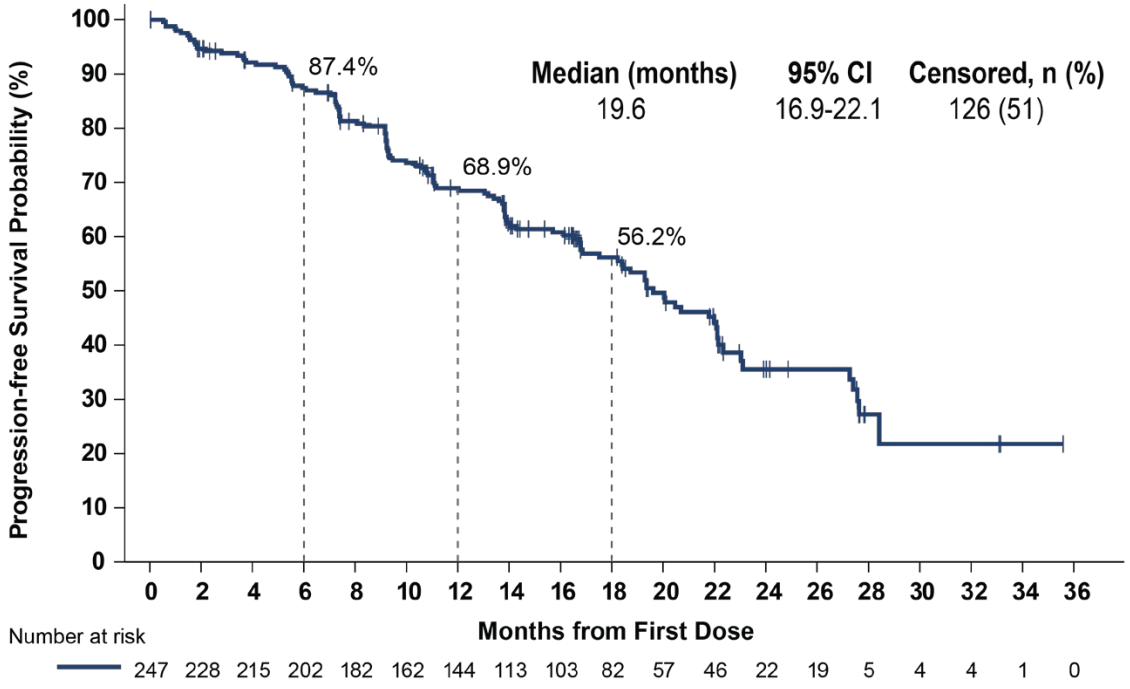


	Prior BTKi n=247	Prior BTKi+BCL2i n=100
Overall Response Rate, % (95% CI)[a]	**82.2 (76.8-86.7)**	**79.0 (69.7-86.5)**
Best Response		
CR, n (%)	4 (1.6)	0 (0.0)
PR, n (%)	177 (71.7)	70 (70.0)
PR-L, n (%)	22 (8.9)	9 (9.0)
SD, n (%)	26 (10.5)	11 (11.0)

Mato et al ASH 2022 / Mato et al N Engl J Med 2023; 389:33-44

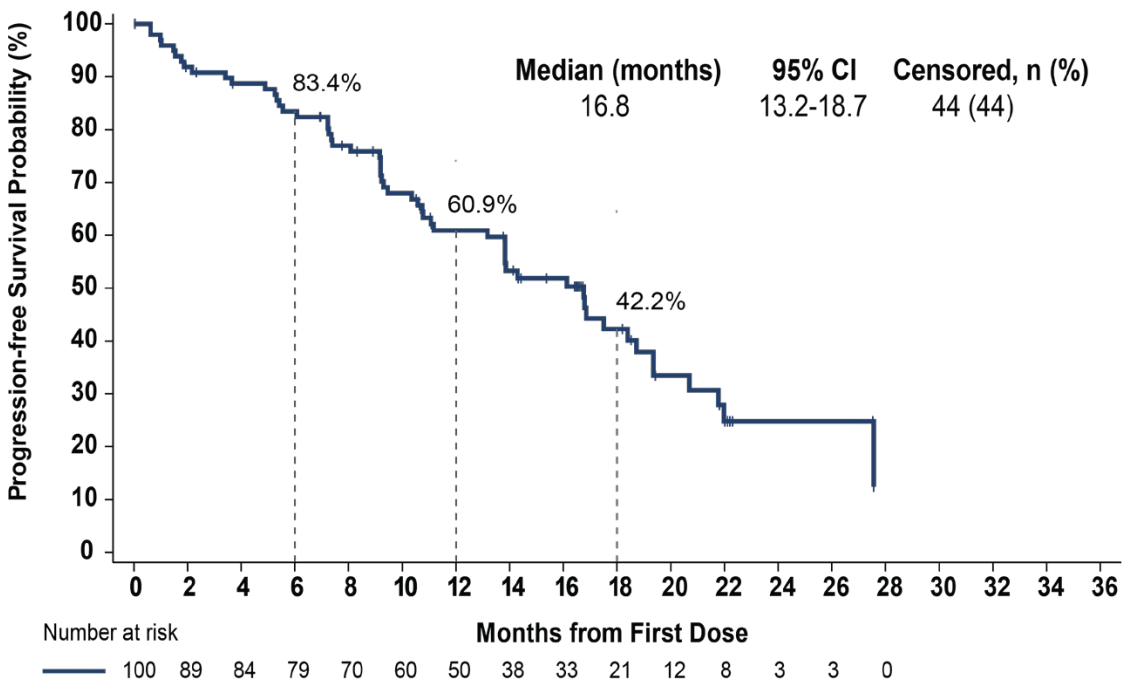
BRUIN: PFS in Patients with CLL/SLL who Received Prior BTKi Treatment

All prior BTKi patients
Median prior lines = 3



- Median follow-up of 19.4 months for patients who received prior BTKi

Prior BTKi and BCL2i patients
Median prior lines = 5



- Median follow-up of 18.2 months for patients who received prior BTKi and BCL2i

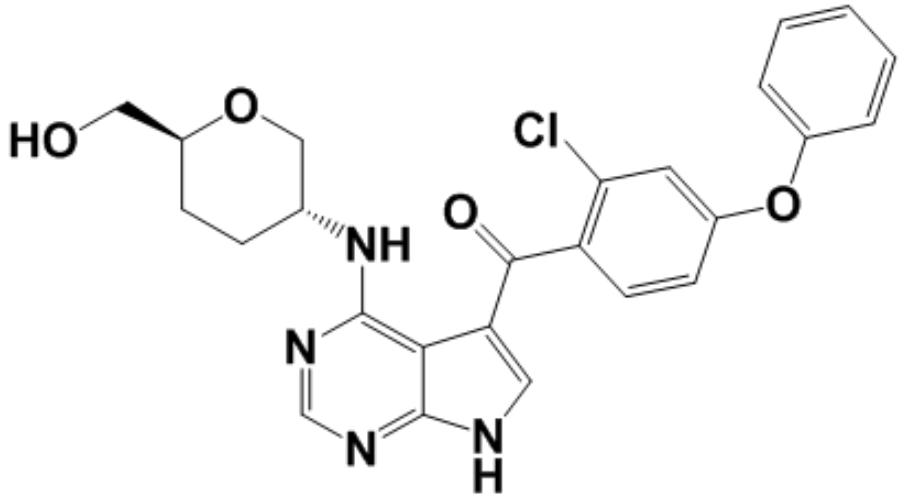
Mato et al ASH 2022 / Mato et al N Engl J Med 2023; 389:33-44

Table 2. Efficacy of Pirtobrutinib in Patients with CLL or SLL Who Had Previously Received a BTK Inhibitor.*

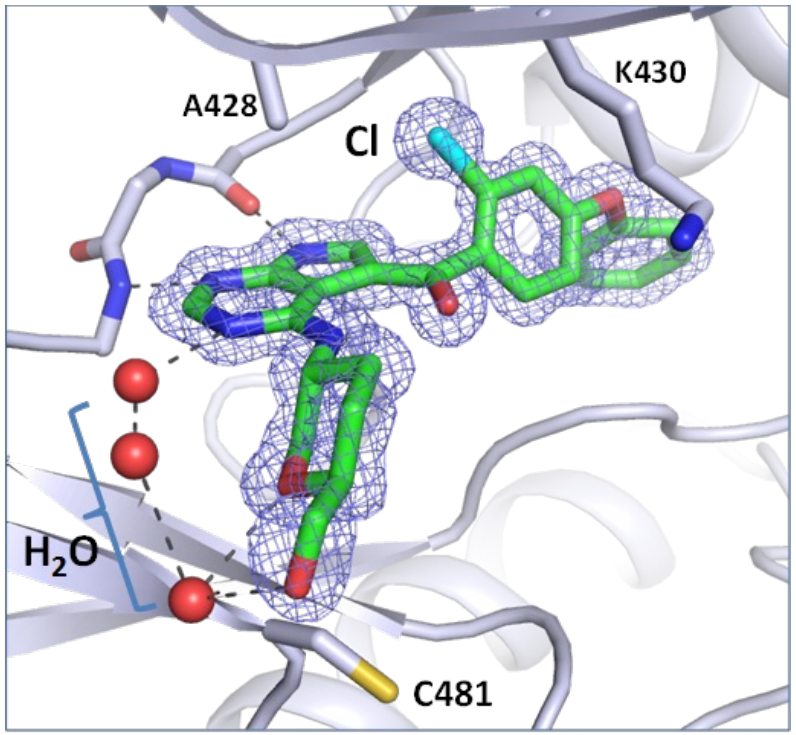
Variable	Previous BTK Inhibitor (N=247)	Previous BTK Inhibitor + BCL2 Inhibitor (N=100)
Overall response — % (95% CI)		
Including complete response, nodular partial response, or partial response	73.3 (67.3–78.7)	70.0 (60.0–78.8)
Including complete response, nodular partial response, partial response, or partial response with lymphocytosis	82.2 (76.8–86.7)	79.0 (69.7–86.5)
Best response — no. (%)		
Complete response	4 (1.6)	0
Nodular partial response	1 (0.4)	0
Partial response	176 (71.3)	70 (70.0)
Partial response with lymphocytosis	22 (8.9)	9 (9.0)
Stable disease	26 (10.5)	11 (11.0)
Progression-free survival		
Median (95% CI) — mo	19.6 (16.9–22.1)	16.8 (13.2–18.7)
Patients with censored data — no. (%)	126 (51.0)	44 (44.0)
Median follow-up — mo	19.4	18.2

* Response status was assessed by an independent review committee in accordance with the criteria from the 2018 International Workshop on Chronic Lymphocytic Leukemia.

Nemtabrutinib - ARQ 531/MK1026



ARQ 531

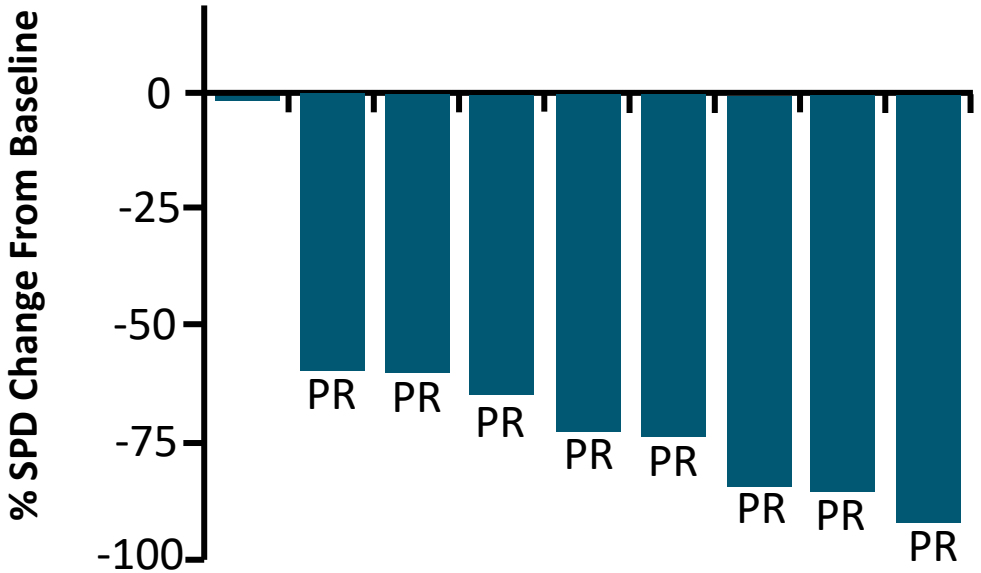


- Reversible inhibition of BTK
- Occupies the ATP binding pocket – non C481
- Orally bioavailable

Reiff et al, Cancer Discovery, 2019

Phase I Dose Escalation Study of Nemtabrutinib in Patients With R/R B-Cell Lymphoid Malignancies

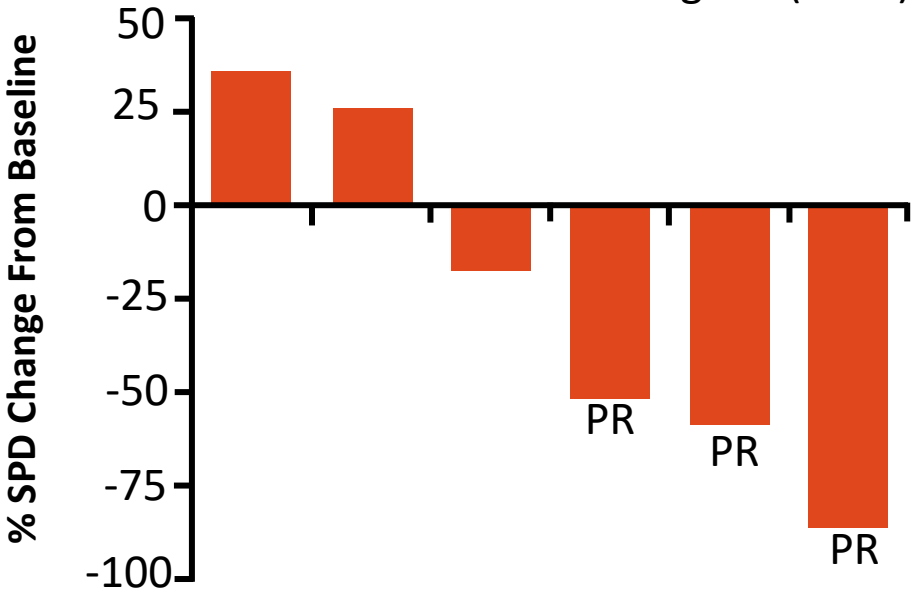
Best Responses in BTK C481S-Mutated, High-Risk R/R CLL Evaluable Patients at 65 mg QD (n = 9)



Patient No.	36†	30†	48	33	40*	32	35	43‡	27
Weeks on Therapy	12	42	9	39	27	40	38	20	54
IGHV Unmutated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Complex Karyotype	Yes	Yes	No	Yes	Yes	No	No	No	Yes

*Positive to del17p. †BTK mutation unknown. ‡Positive to del11q.

Best Responses in Richter's Transformation Evaluable Patients Treated at ≥ 65 mg QD (n = 6)



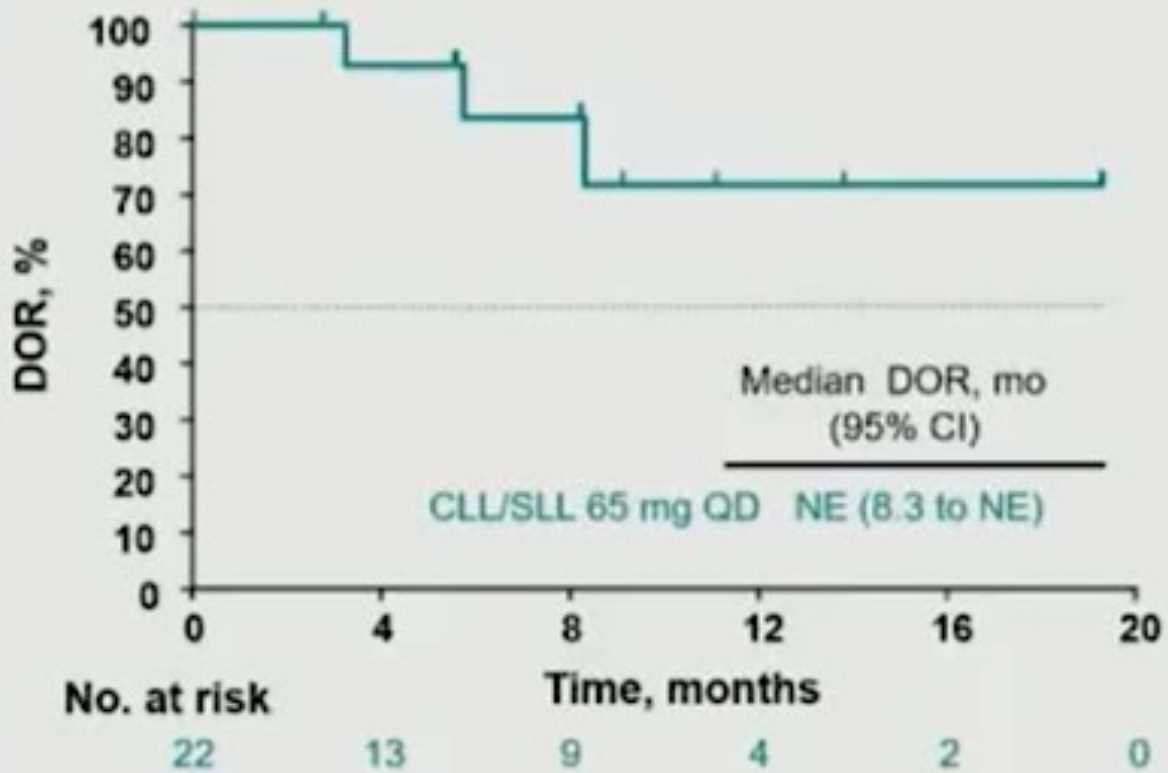
Patient No.	41	45*†	122-36†	42	34*†‡§	47*§
Wks on therapy	10	13	12	19	26	12
IGHV unmutated	Yes	Yes	Yes	Yes	No	Yes

*Positive to del17p. †Positive to del11q. ‡MYC(+)/BLC6(+)positive.
§ Positive to complex karyotype.

Woyach. ASH 2019. Abstr 4298.

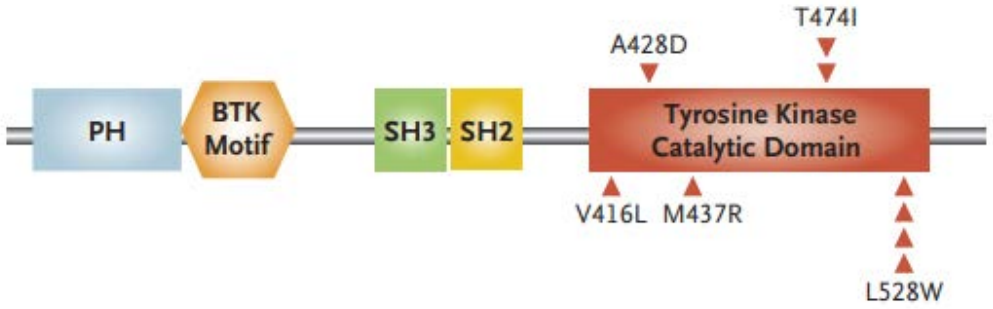
Summary of Response (CLL/SLL), Efficacy Evaluable Population

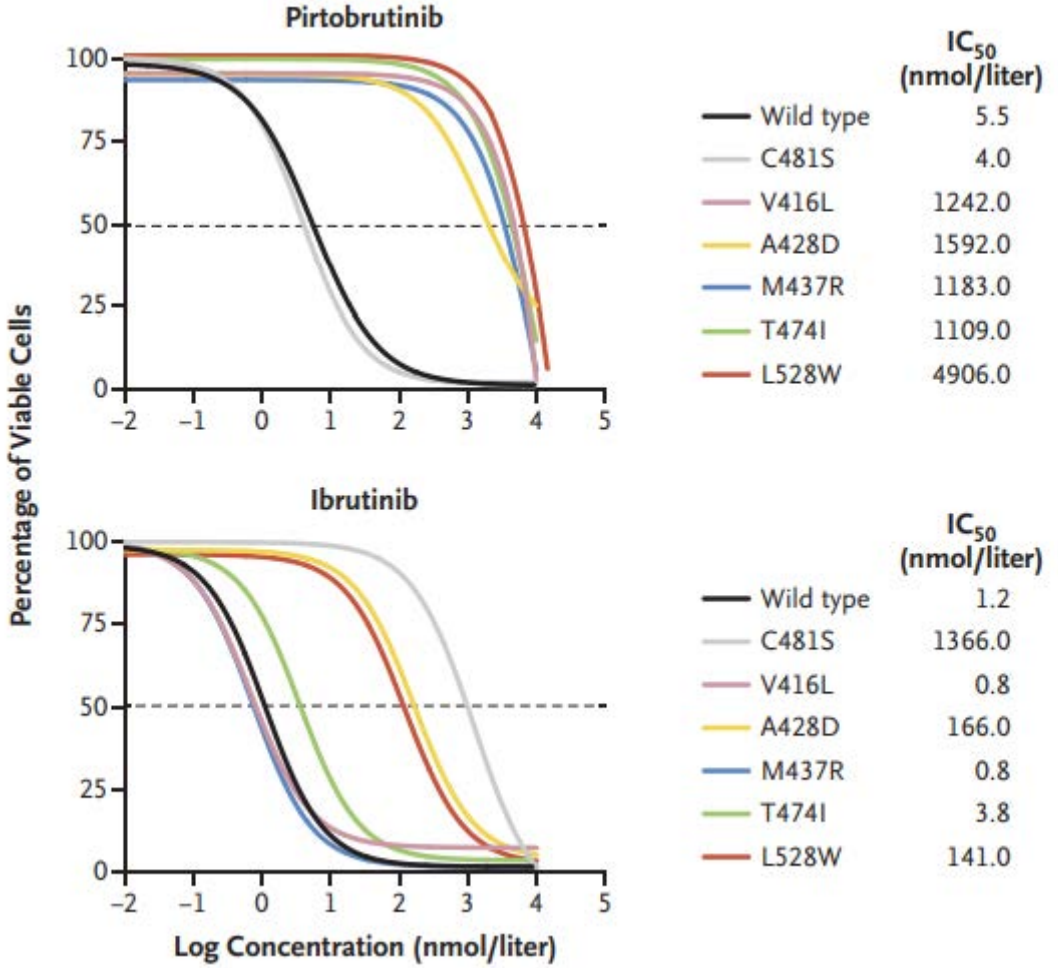
n (%) [95% CI]	CLL/SLL 65 mg QD N = 38[a]
ORR	**22 (57.9%) [40.8-73.6]**
CR	1 (2.6%) [0.0-13.8]
PR	12 (31.6%) [17.5-48.6]
PR-L	9 (23.7%) [11.4-40.2]
SD	15 (39.5%) [24.0-5.6]



Resistance to non-covalent BTK inhibitors presents a new and growing challenge to treatment

BTK mutations identified from patients progressing on the non-covalent inhibitor pirtobrutinib

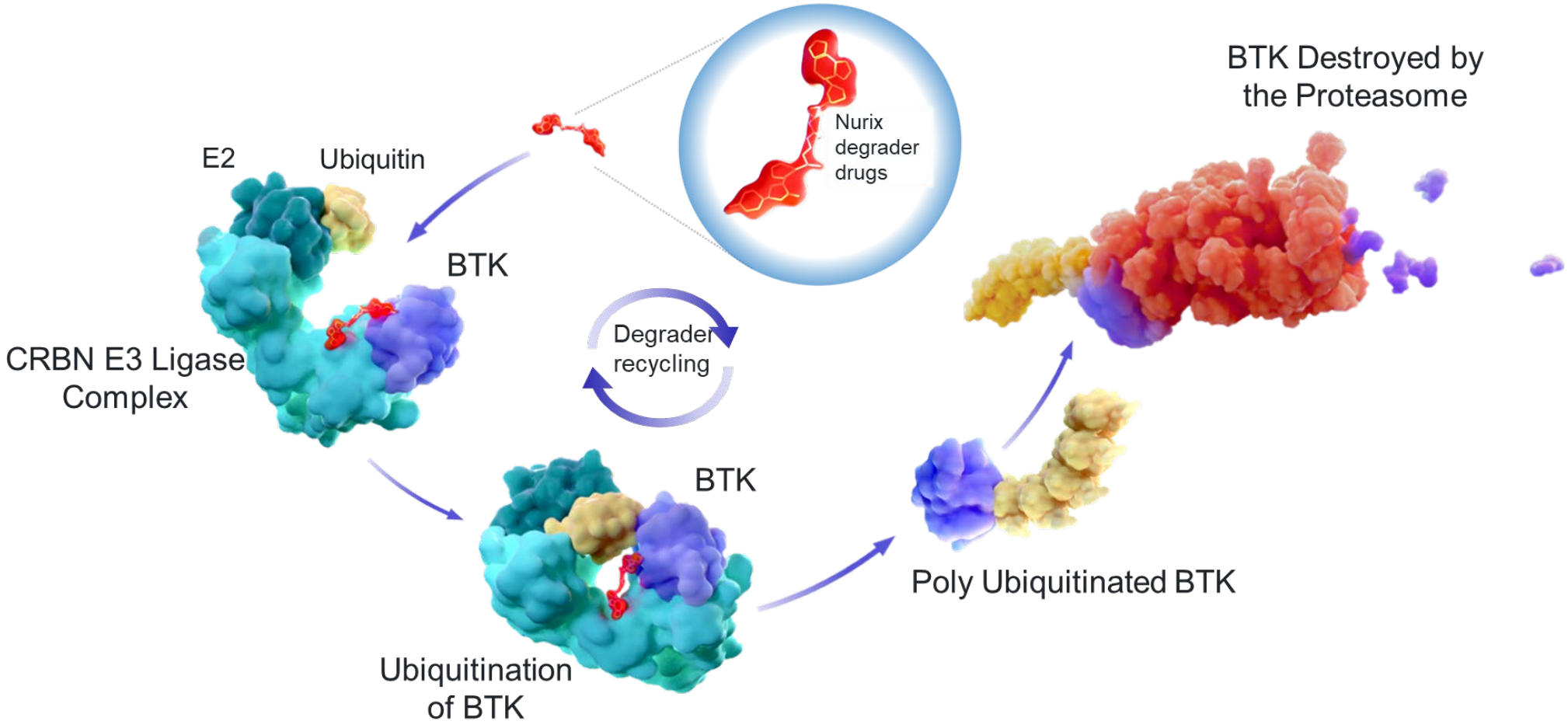




Wang et al. N Engl J Med 2022;386:735–43

NX-2127: first-in-class targeted protein degrader of BTK

Utilizing the ubiquitin-proteasome pathway to degrade BTK, a well-validated target in B-cell malignancies

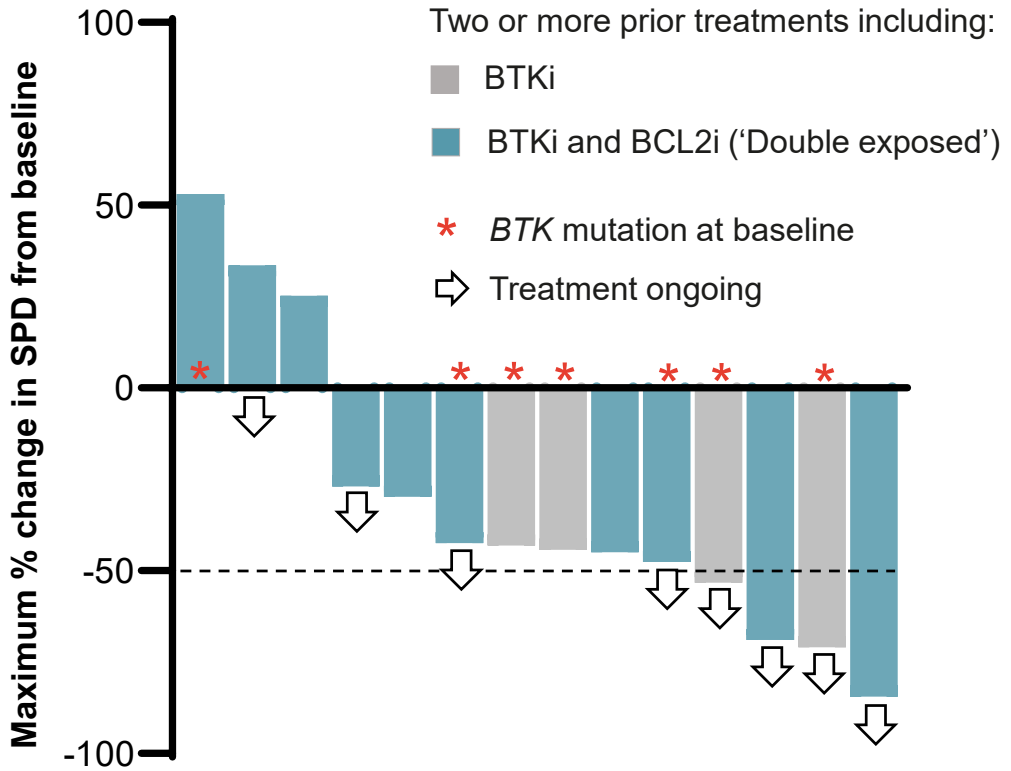


Montoya et al ASH 2022

NX-2127 preliminary efficacy (patients with CLL)

Disease-evaluable patients	n=15
Objective response rate,[a] % (95% CI)	33 (12–62)
Best response, n (%)	
CR	0 (0)
PR	5 (33.3)
SD	5 (33.3)
PD	2 (13.3)
NE[b]	3 (20)

[a]Objective response rate includes CR + CRi + nPR + PR-L + PR
[b]Patients who discontinued after a single assessment of SD are considered as NE

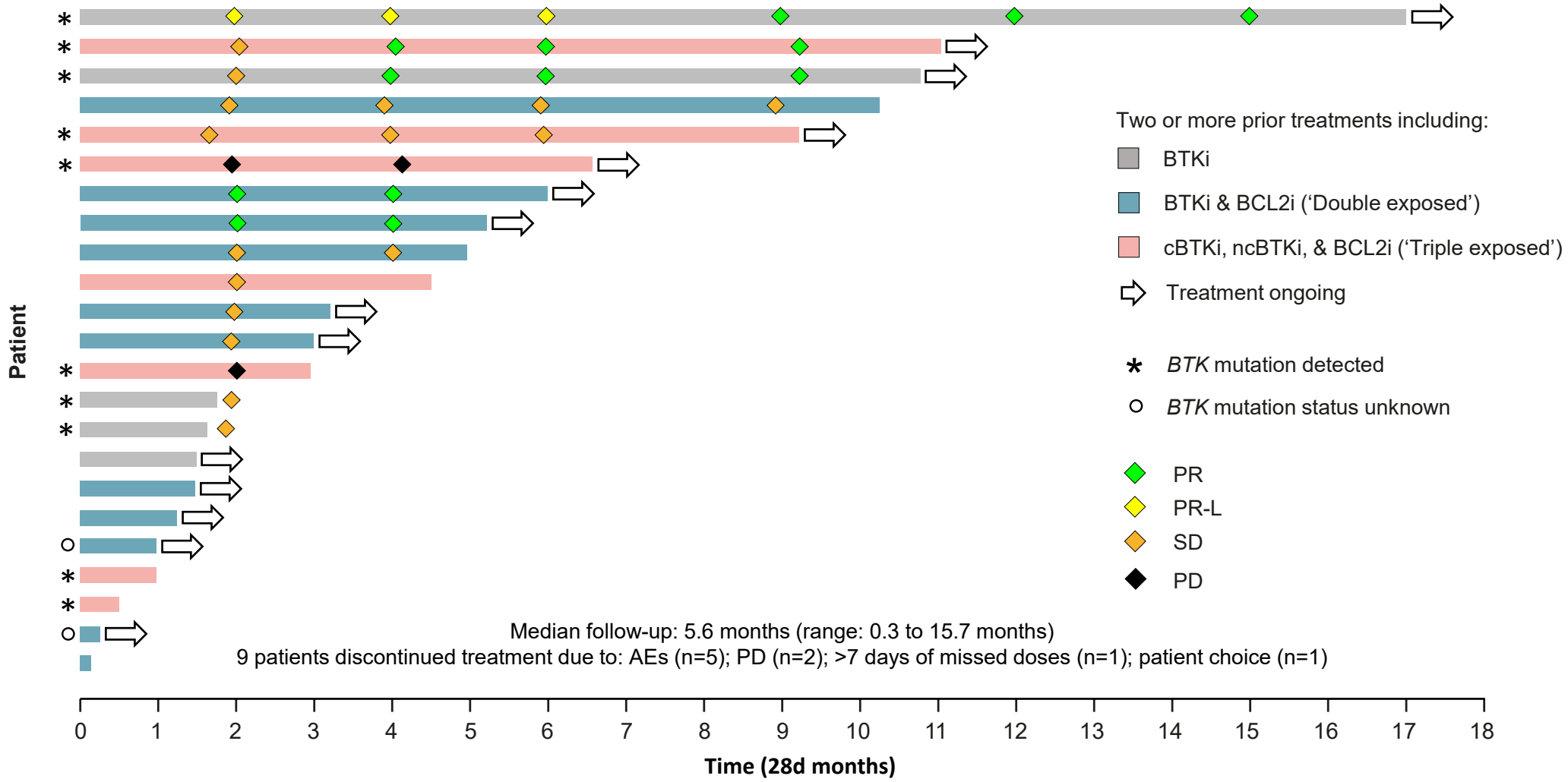


***One patient, not shown above, with prior BTKi and BCL2i treatment and with a *BTK* mutation detected at baseline, had no nodal disease at baseline. Their treatment is ongoing with a PR**

Mato et al, ASH 2022

Outcomes and time on therapy with NX-2127 (patients with CLL)

Responses seen in double and triple exposed patients



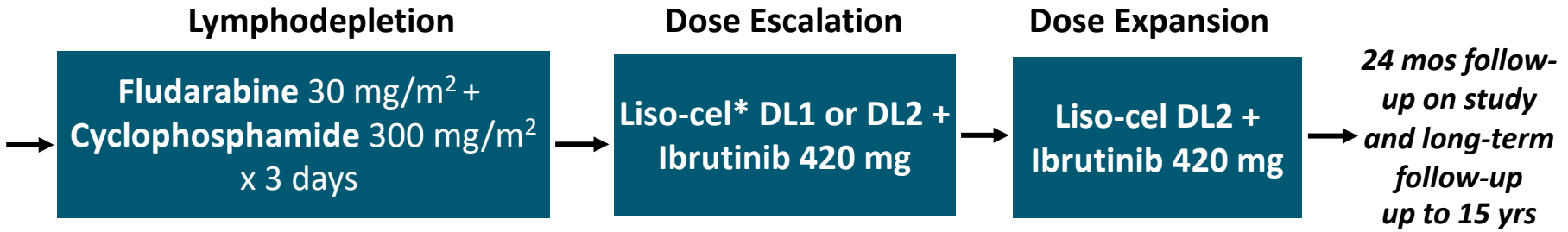
TRANSCEND CLL 004 Combination Cohort: Study Design

- Analysis of phase I combination cohort of multicenter, open-label, multicohort phase I/II study

Patients with R/R CLL/SLL who:

- Progressed on ibrutinib *OR*
- Had high-risk features[†] and received ibrutinib for ≥ 6 mos with < CR *OR*
- Had *BTK* or *PLCγ2* mutations *OR*
- Had prior ibrutinib and no contraindication to restarting ibrutinib

(N = 19)



Leukapheresis performed at enrollment to manufacture liso-cel and bridging therapy allowed between enrollment and lymphodepletion; liso-cel manufacturing success rate was 100%.

*DL1: 50 x 10^6 CAR T-cells; DL2: 100 x 10^6 CAR T-cells. [†]Complex cytogenetic abnormalities, del (17p), *TP53* mutated, or unmutated *IGHV*.

- Primary endpoints: safety and recommended dose determination
- Exploratory endpoints: antitumor activity and cellular kinetic profile

Wierda. ASH 2020. Abstr 544. NCT03331198.

TRANSCEND CLL 004 Combination Cohort: Efficacy

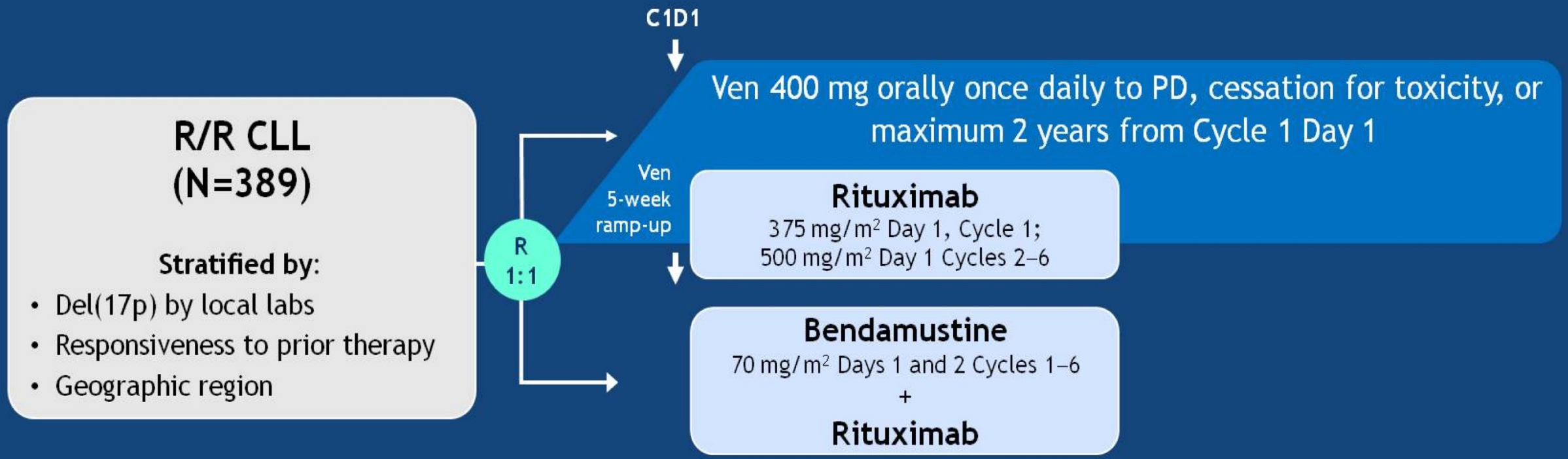
Efficacy Outcome	Total Patients (n = 19)	Liso-cel DL1 + Ibrutinib (n = 4)	Liso-cel DL2 + Ibrutinib (n = 15)
ORR, n (%)	18 (95)	3 (75)	15 (100)
▪ CR/CRi	12 (63)	2 (50)	10 (67)
▪ PR	6 (32)	1 (25)	5 (33)
Undetectable MRD ≤ 10^{-4}, n (%)			
▪ PB by flow cytometry	17 (89)	3 (75)	14 (93)
▪ BM by NGS	15 (79)	3 (75)	12 (80)

- Median follow-up: 10 mos
- All 18 responders achieved a response by day 30 after liso-cel; all 17 patients who achieved undetectable MRD in PB did so by Day 30
- Among 18 patients with ≥ 6 mos of follow-up, 16 maintained or improved response from Day 30

Wierda. ASH 2020. Abstr 544.

Bcl-2 Inhibitors

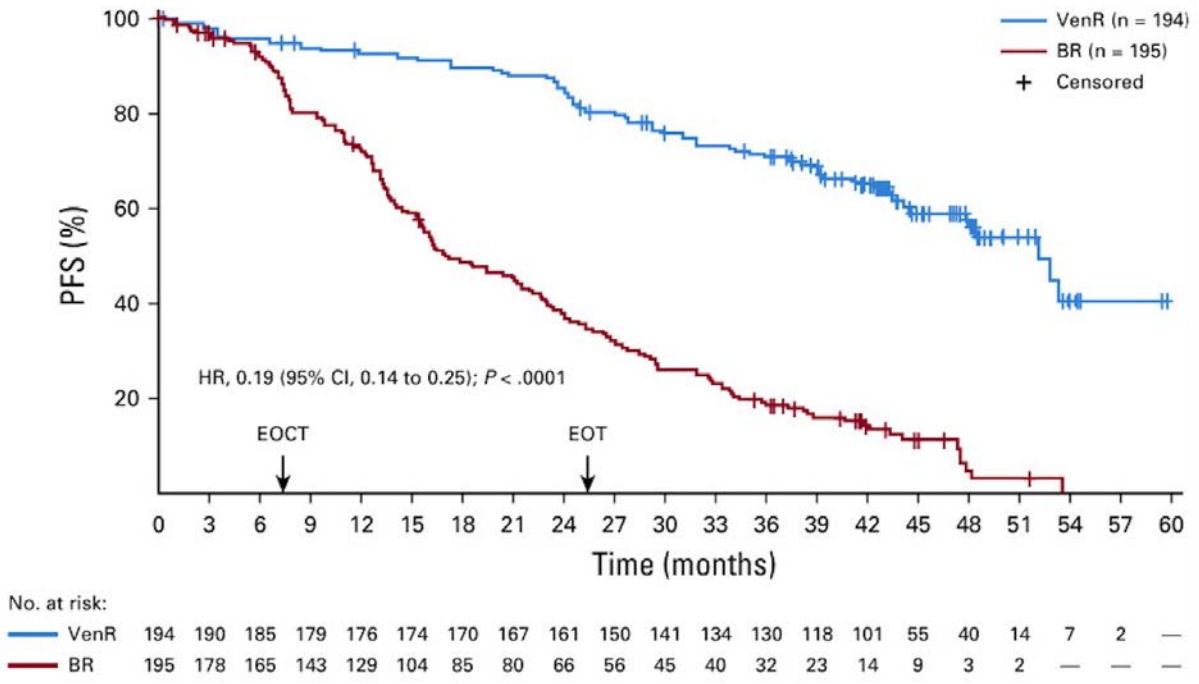
MURANO Study Design and Endpoints

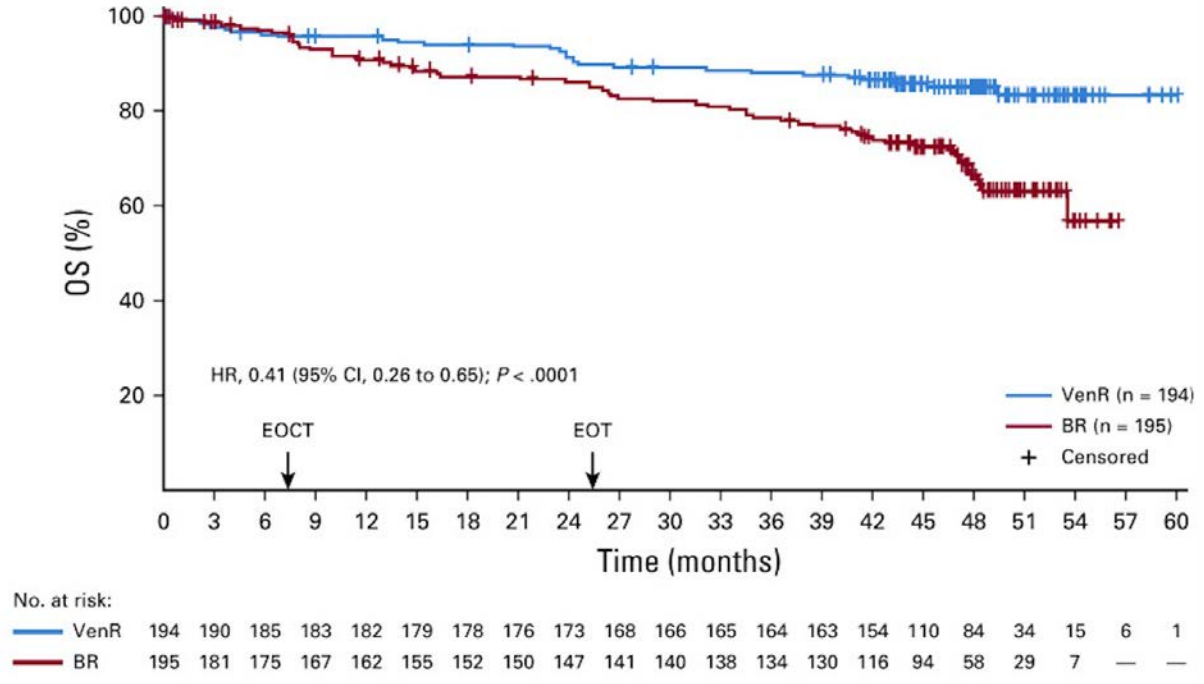


Primary Endpoint	Investigator-assessed PFS
Secondary MRD Endpoint	MRD– in peripheral blood (PB) at the end of combination treatment (EOCT) visit
Exploratory MRD Endpoints	MRD– in bone marrow (BM) at the EOCT visit MRD– in PB over time

C1D1, Cycle 1 Day 1; PD, progressive disease

Seymour JF, et al. New Engl J Med 2018;378:1107-20.



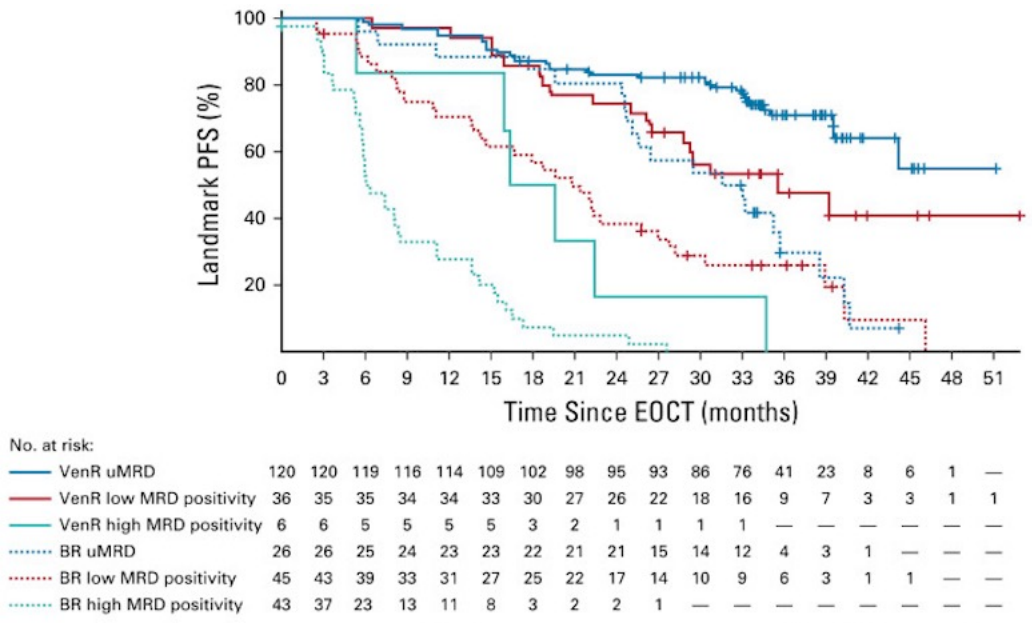


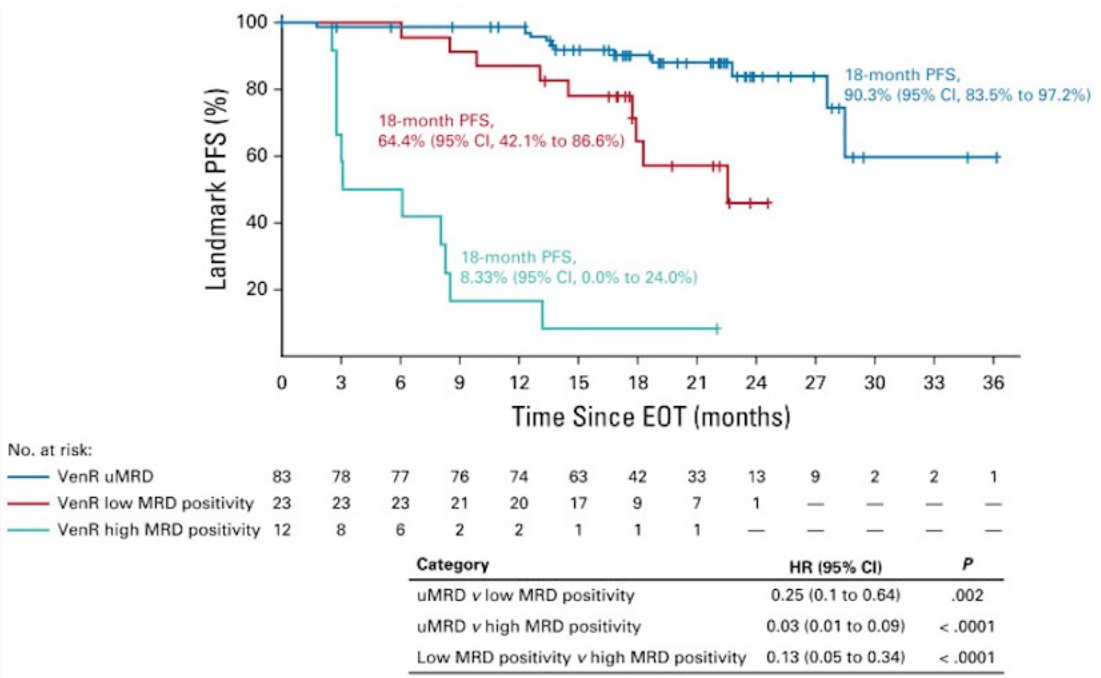
7-yrs PFS 23%(VenR) 0 (BR) OS 69.6% 51% (BR) HR (0.53)

Median time to next Rx 63 (VenR) vs. 24 (BR) mon (HR 0.03)

37.1% VenR patient – still no Rx

Seymour JCO 2020. Kater Update Hemasphere Aug 2023 7(supp)





Category	HR (95% CI)	P
uMRD *v* low MRD positivity	0.25 (0.1 to 0.64)	.002
uMRD *v* high MRD positivity	0.03 (0.01 to 0.09)	< .0001
Low MRD positivity *v* high MRD positivity	0.13 (0.05 to 0.34)	< .0001

7-yrs Among VenR - uMRD (at EOT, n=83 / 118, 70.3%) mPFS= 52.4 vs 18 months in MRD+

MRD conversion (n=63)- median time to conversion 19.4 mon and

median time from conversion to PD was 28.3 mon

7-yrs VenR-reRX (n=25) , 95% had some high-risk feature,

Median time from last Ven dose to Ven ramp-up in re-Rx = 2.3 ys (1.2-3.1)

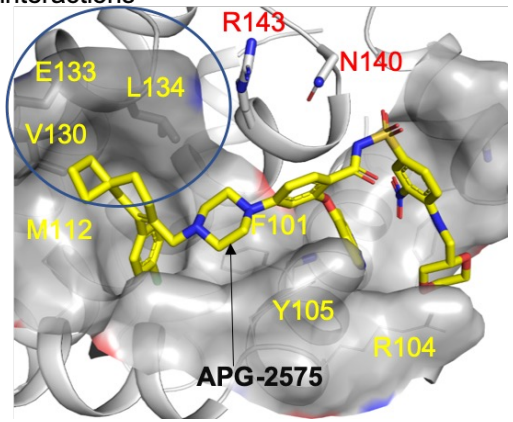
ORR to Rx = 72%, Median PFS = 23.3 m , 14 (56%) achieved uMRD at main study with 32% (n=8) again at re-Rx

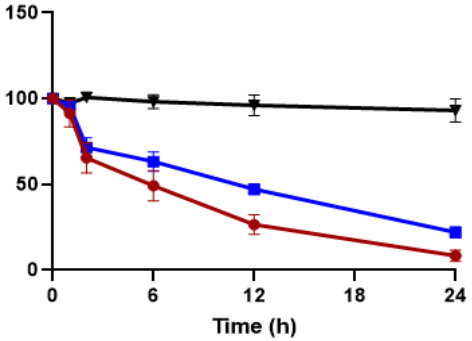
Seymour JCO 2020. Kater Update Hemasphere Aug 2023 7(supp)

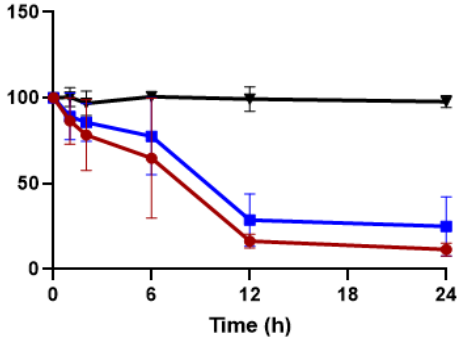
Next-gen Bcl-2 inhibitor: APG-2575 (Lisaftoclax)

APG-2575

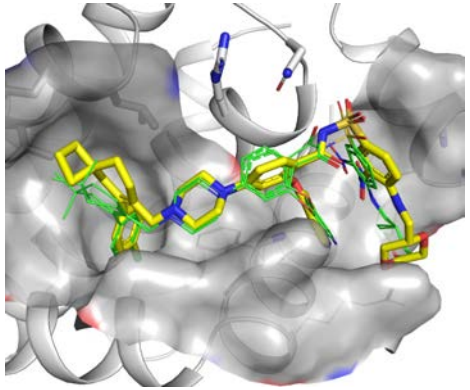
Additional Hydrophobic interactions

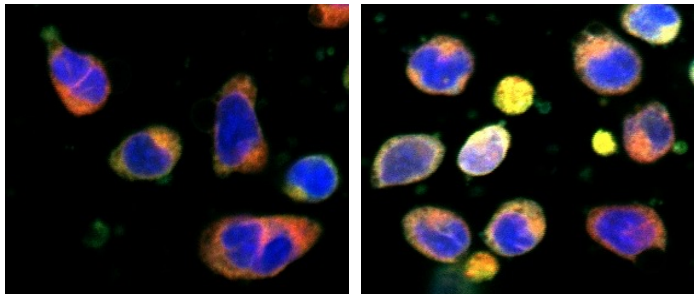






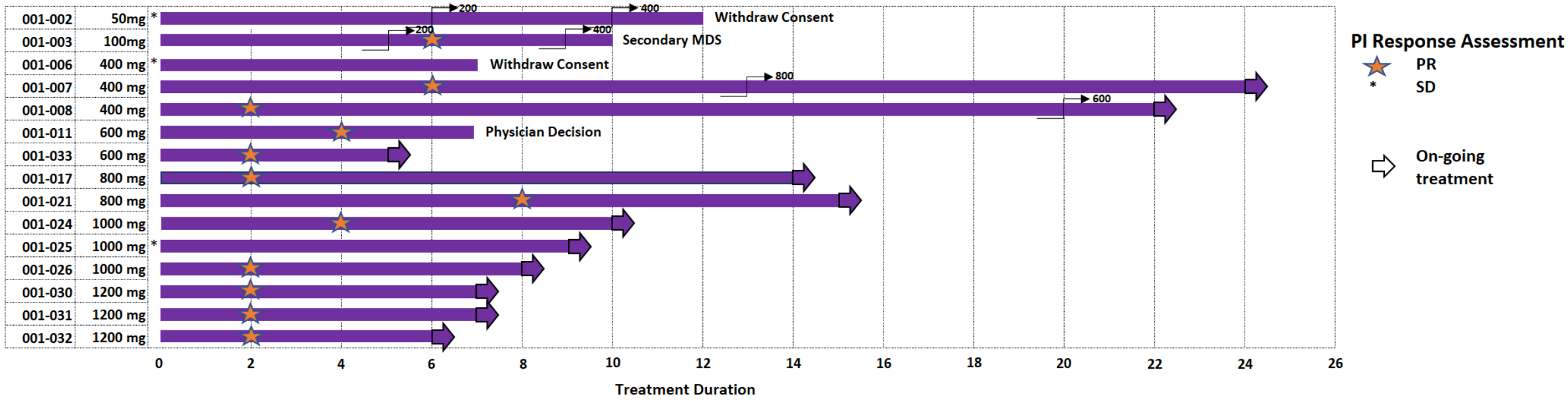
ABT-199





Red: Mitotracker Green: BIM. Blue: DAPI

Swimmer plot: efficacy of APG-2575 in patients with CLL/SLL (ORR = 80%)



001-003: The nodal size reduction reached by 48% after 4 cycles of treatment at 100mg. The patient dose escalated to 200mg and achieved PR after 1 cycle of treatment at 200mg.

- Median (range) treatment of 9 cycles (Range 5-24 cycles)
- 12 of 15 evaluable R/R CLL/SLL patients achieved partial response (PR) by 2008 iwCLL definition, for an objective response rate of 80%
- Median time to response of 2 cycles (Range 2-8 cycles)

MOLTO Study: Ven/Atezolizumab/Obinutuzumab in Richter's transformation

- N=28.
- ORR = 67.9% (95% CI, 47.6% -84.1%)
- CR = 28.6%. PR = 39.3%
- Median TTP = 16.2 m
- Median EFS = 9.9 m.
- Event free survival at 12 m = 43.9%

Median age 70

Median time to RT diag = 48.1 mon

57.% Bulky 78.6% Ann Arbor III/IV

Del 17p =42.9%

Obinutuzumab

100 mg D1C1, 900 mg D2 C1, then 1000 mg D8, D15 of C1, then D1 of C2-C8.

Atezolizumab

1200 mg on D2 C1 and D1 of C2-18.

Venetoclax

ramped-up dosing (D 15-D21 C 1, then 50 mgD1-7 C2, then 100 mg D8-14 C2, then 200 mg D15- 21 of cycle, then 400 mg per day in C3-35.

Frustaci et al 2023. 17th Annual International Conference on Malignant Lymphoma

Epcoritamab: **Results from the EPCORE CLL-1 Trial**

- Epcoritamab (GEN3013) – CD3×CD20 bispecific antibody
- Induce potent activation and cytotoxic activity of CD4+ and CD8+ T cells against CD20-expressing cells
- Most common treatment-emergent AEs (>30%) were:
  - CRS (100%), fatigue (71%), injection-site reaction (43%), nausea (43%)
  - All pts experienced CRS in the first cycle, but no CRS events were higher than grade 2. No cases of ICANS were observed. TLS was not observed

Kater et al *Blood* (2021) 138 (Supplement 1): 2627.

SUMMARY

- BTK and Bcl-2 are two prime targets in CLL
- Phase III data continues to confirm superior PFS with BTKi
- Phase III data favors 2nd Gen BTKi
- High uMRD is an important clinical endpoint
- BTK mutation challenging but new BTKi bring hope
- CART therapy is another emerging approach to CLL therapy

Clinical Questions and Cases

Chronic Lymphocytic Leukemia
Relapsed Disease

- **Noncovalent BTK inhibitors: Pirtobrutinib**
  - **Efficacy after covalent BTK inhibitors, activity in specific mutations**
  - **Comparative toxicity**
  - **Richter transformation**
- **CAR T-cell therapy**
- **Bispecific antibodies**

Case Presentation: 81-year-old asymptomatic man with IGHV-mutated newly diagnosed CLL

Dr Zanetta Lamar (Naples, Florida; 10-2-2020)

RTP
RESEARCH
TO PRACTICE

Case Presentation: 88-year-old man with CLL and PD after ibrutinib and single-agent rituximab who receives acalabrutinib on a dose-reduced schedule

Dr KS (Trinity, Florida; 10-17-2022)

RTP
RESEARCH
TO PRACTICE

Discussion Question

What is the lowest dose of acalabrutinib you would consider for an 88-year-old patient with progressive CLL after rituximab monotherapy followed by ibrutinib?

Case Presentation: 79-year-old man with IGHV-unmutated CLL and trisomy 12 who receives acalabrutinib with good disease control

Dr Vikas Malhotra (Spring Hill, Florida; 9-30-2020)

RTP RESEARCH TO PRACTICE

Discussion Question

Based on your clinical experience and knowledge of available data, how would you compare the cardiac safety profile of pirtobrutinib to that of second-generation covalent BTK inhibitors?

Discussion Question

Based on your clinical experience and knowledge of available data, how would you compare quality of life-related side effects of pirtobrutinib to those of second-generation covalent BTK inhibitors?

Discussion Question

Based on your clinical experience and knowledge of available data, how would you compare the need for dose reductions/treatment discontinuation with pirtobrutinib to that with second-generation covalent BTK inhibitors?

Discussion Question

Regulatory and reimbursement issues aside, are there situations in which you would like to use pirtobrutinib for the management of Richter syndrome?

Discussion Question

The Phase I/II BRUIN study evaluating pirtobrutinib for patients with CLL demonstrated efficacy in patients with disease progression on covalent BTK inhibitors.

What Clinicians Want to Know About the Management of Relapsed/Refractory Mantle Cell Lymphoma

A CME/MOC-Accredited Virtual Event

Tuesday, September 26, 2023
5:00 PM – 6:00 PM ET

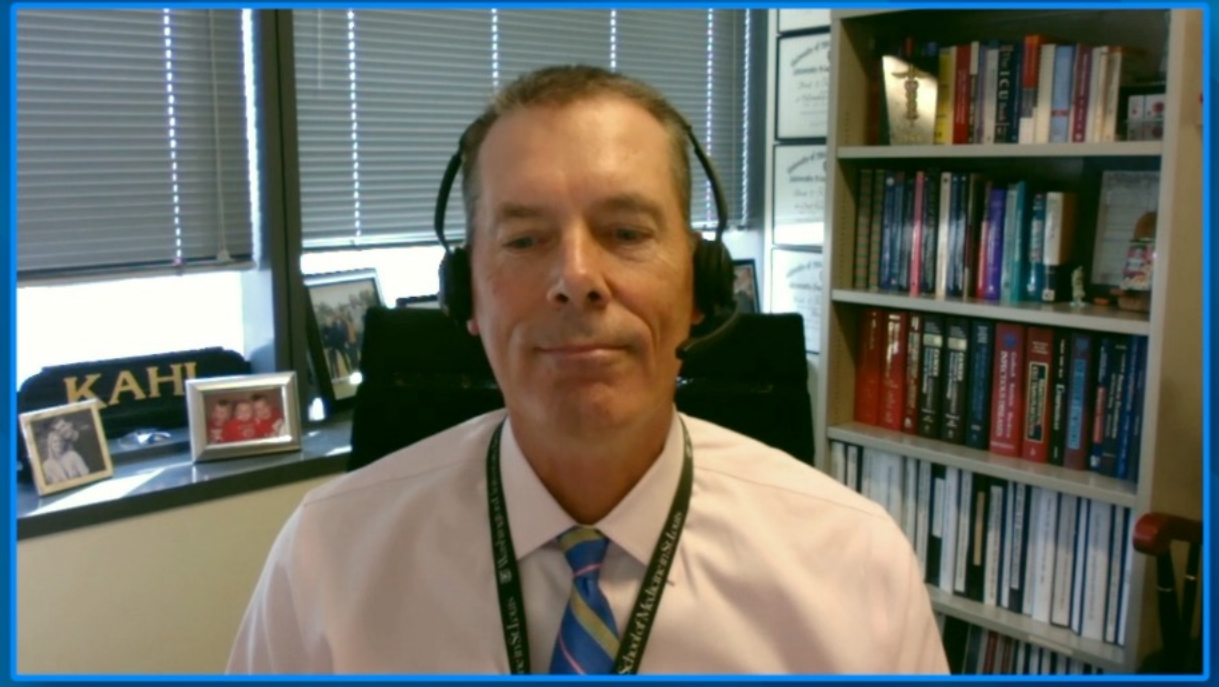
Faculty

Toby A Eyre, MBChB, DipMedEd, MRCP, MD
Brad S Kahl, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE


KAHI

Questions and Comments: Front-line treatment without chemotherapy

Dr Michael Wang (Houston, Texas)

RTP
RESEARCH
TO PRACTICE

Case Presentation: An uninsured 58-year-old man with symptomatic MCL

Dr Zanetta Lamar (Naples, Florida)

RTP RESEARCH TO PRACTICE

Current Approaches and Future Strategies in Oncology: A Multitumor Educational Symposium in Partnership with Florida Cancer Specialists and Research Institute

A CME/MOC- and NCPD-Accredited Event

Saturday, October 7, 2023
7:15 AM – 12:30 PM ET

RTP
RESEARCH
TO PRACTICE

Contributing General Medical Oncologists from FCS

Susmitha Apuri, MD
Inverness, Florida

Sunil Gandhi, MD
Lecanto, Florida

Mamta Choksi, MD
New Port Richey, Florida

Shaachi Gupta, MD, MPH
Lake Worth, Florida

Uday Dandamudi, MD
New Port Richey, Florida

Lowell L Hart, MD
Fort Myers, Florida

RTP
RESEARCH
TO PRACTICE

Contributing General Medical Oncologists from FCS

Maen Hussein, MD
The Villages, Florida

Vikas Malhotra, MD
Spring Hill, Florida

Kapisthalam (KS) Kumar, MD
Trinity, Florida

Shachar Peles, MD
Lake Worth, Florida

Zanetta S Lamar, MD
Naples, Florida

Syed F Zafar, MD
Fort Myers, Florida

RTP
RESEARCH
TO PRACTICE

Join Us In Person or Virtually

Oncology in the Real World

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

Saturday, October 14, 2023

Lymphoma

9:30 AM – 10:30 AM PT
(12:30 PM – 1:30 PM ET)

Faculty

Christopher R Flowers, MD, MS
Ann S LaCasce, MD, MMSc

Urothelial Bladder Cancer and Renal Cell Carcinoma

10:30 AM – 11:30 AM PT
(1:30 PM – 2:30 PM ET)

Faculty

Thomas E Hutson, DO, PharmD
Guru P Sonpavde, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Join Us In Person or Virtually

Oncology in the Real World

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

Saturday, October 14, 2023

Hepatobiliary and Pancreatic Cancers

11:50 AM – 12:50 PM PT
(2:50 PM – 3:50 PM ET)

Faculty

Mitesh J Borad, MD
Anthony El-Khoueiry, MD

Gynecologic Cancers

1:30 PM – 2:30 PM PT
(4:30 PM – 5:30 PM ET)

Faculty

Bradley J Monk, MD
Kathleen N Moore, MD, MS

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Join Us In Person or Virtually

Oncology in the Real World

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

Saturday, October 14, 2023

Multiple Myeloma

2:30 PM – 3:30 PM PT
(5:30 PM – 6:30 PM ET)

Faculty

Amrita Krishnan, MD
Robert Z Orlowski, MD, PhD

HER2-Positive and Triple-Negative Breast Cancer

3:50 PM – 4:50 PM PT
(6:50 PM – 7:50 PM ET)

Faculty

Sara A Hurvitz, MD, FACP
Heather McArthur, MD, MPH

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

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

Thank you for joining us!
Your feedback is very important to us.

Clinicians in the Meeting Room:

Please complete the postevent survey now available on the meeting iPads.

Attendees on Zoom:

The survey will remain open for 5 minutes after the meeting ends.

How to Obtain CME/MOC and NCPD Credit

In-person attendees: Please refer to the program syllabus for the CME/MOC and NCPD credit link or QR code.

Online/Zoom attendees: The CME/MOC and NCPD credit link is posted in the chat room.

RTP
RESEARCH TO PRACTICE