Fifth Annual
National General Medical Oncology Summit

Saturday, April 25, 2026

Moderator

Neil Love, MD

Faculty

John N Allan, MD
Deborah K Armstrong, MD
Adam M Brufsky, MD, PhD
Terence Friedlander, MD
Mrinal Gounder, MD
Erika Hamilton, MD
Yelena Y Janjigian, MD
Kevin Kalinsky, MD, MS, FASCO
Adam Kittai, MD
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David M O'Malley, MD
Eileen M O'Reilly, MD
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Philip A Philip, MD, PhD
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Richard F Riedel, MD

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Co-Moderators

Susmitha Apuri, MD
Inverness and Lecanto, Florida

Maria Regina Flores, MD
Orlando, Florida

Maen Hussein, MD
The Villages, Florida

Mamta Choksi, MD
Trinity, Florida

Gustavo Adolf Fonseca, MD
Lecanto, Florida

Vikas Malhotra, MD
Spring Hill, Florida

Uday Dandamudi, MD
New Port Richey, Florida

Sunil Gandhi, MD
Lecanto, Florida

Shachar Peles, MD
Lake Worth, Florida

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Disclosures for Moderator Neil Love, MD

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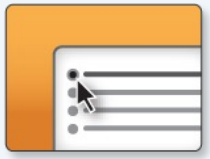
Networked iPads are available.

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



Answer Survey Questions: Complete the premeeting survey.

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

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About the Enduring Program

- The live meeting is being video and audio recorded.
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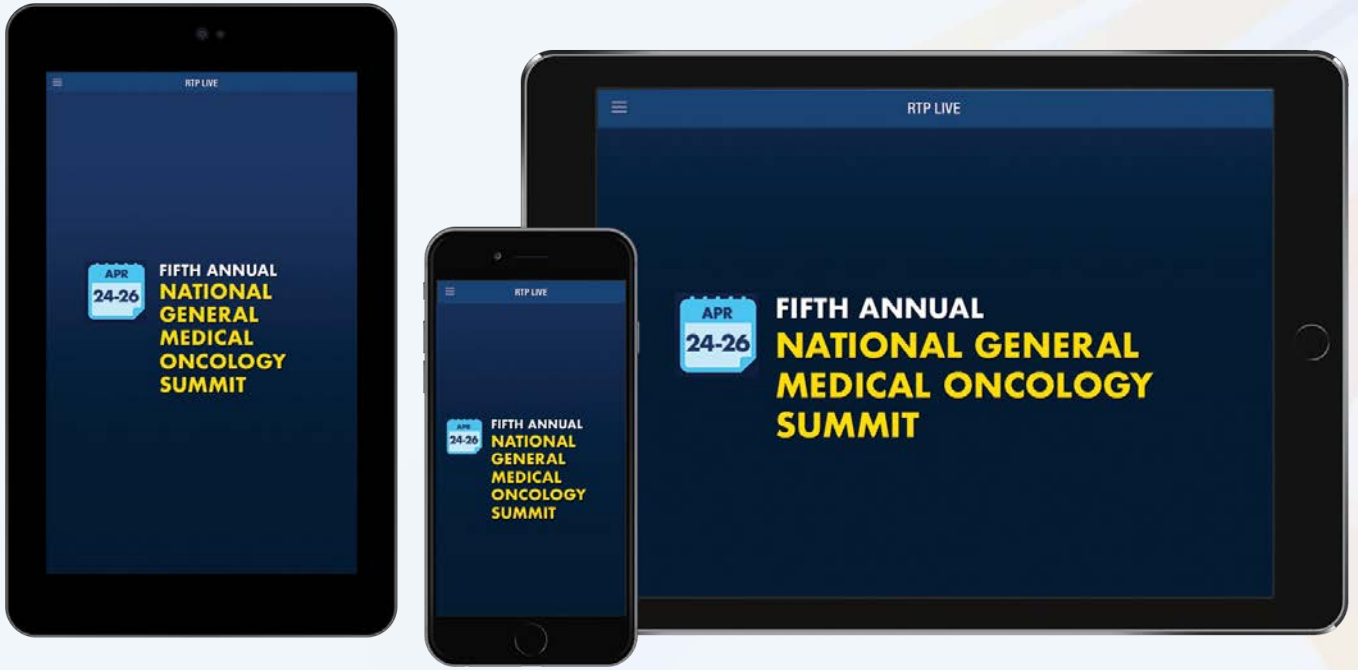

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Module 1: Chronic Lymphocytic Leukemia

Current Management of Newly Diagnosed CLL — Dr Allan

Noncovalent BTK Inhibitors and Other Novel Strategies — Dr Kittai

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Module 1: Chronic Lymphocytic Leukemia

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Module 1: Chronic Lymphocytic Leukemia

We would like to do a “best paper or presentation of the year” activity. Please suggest one “paper of the year” and 2 other worthy papers based on the value in treatment of current and future patients.

Weill Cornell Medicine

Current Management of CLL in The 1L Setting

John N. Allan
Associate Professor of Clinical Medicine
Weill Cornell

Research To Practice
Fifth Annual National General Medical Oncology (GMO) Summit
Orlando, FL, April 25, 2026

Disclosures

Advisory Committees	NeoGenomics
Consulting Agreements	AbbVie Inc, Adaptive Biotechnologies Corporation, ADC Therapeutics, AstraZeneca Pharmaceuticals LP, BeOne, Genentech, a member of the Roche Group, Janssen Biotech Inc, Lilly, Pharmacyclics LLC, an AbbVie Company
Contracted Research	Adaptive Biotechnologies Corporation, BeOne, Bristol Myers Squibb, Genentech, a member of the Roche Group
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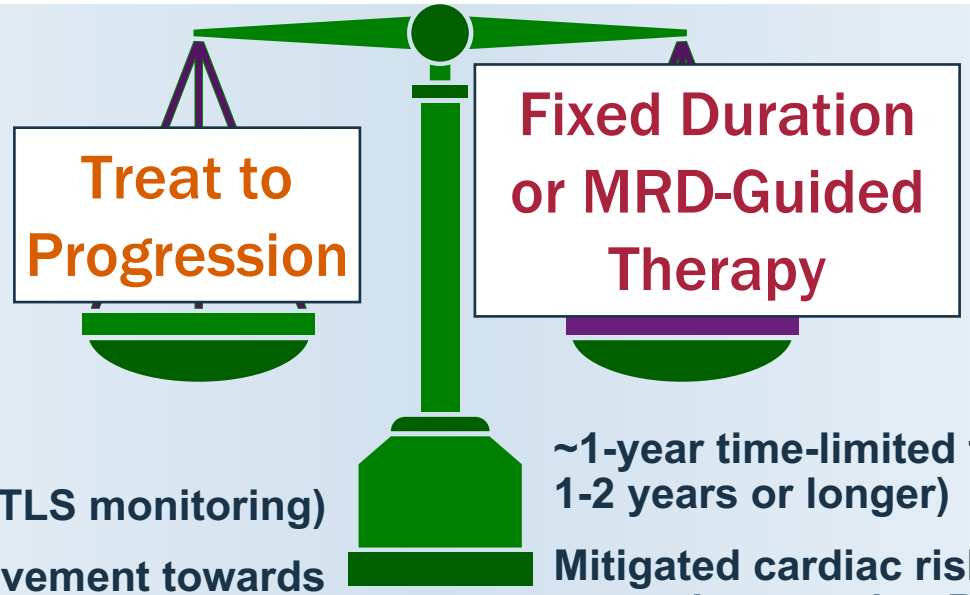
Shifting Trends in Management of Frontline CLL



Treat to Progression

- Convenience (no infusions or TLS monitoring)
- Longer-term efficacy data (movement towards second-generation selective agents)
- Survival advantage compared to chemoimmunotherapy
- Improves versus diminishes immune function
- Does not cause clonal hematopoiesis
- Indefinite treatment
- Potential for cumulative cardiac toxicity

Fixed Duration or MRD-Guided Therapy

- ~1-year time-limited therapy (MRD-guided may extend 1-2 years or longer)
- Mitigated cardiac risks by discontinuation or use of second-generation BTKi
- Less concern over long-term adherence
- Potential for cost savings
- Time intensive (infusions possible, venetoclax ramp-up monitoring)
- Ideal Patient type for Oral Doublet vs Triplet vs. Ven-G or MRD-guided therapy is not defined (possible benefit of Triplet over Doublet in *IGHV* unmutated)

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BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; *IGHV*, immunoglobulin heavy-chain variable region gene; MRD, measurable residual disease; TLS, tumor lysis syndrome; Ven-G, venetoclax, obinutuzumab; vs, versus.

Summary of BTKi Monotherapy Data

Study	Treatment	Follow-up	Longest PFS reported	Longest OS reported	AF (Gr ≥3)	Infection (Gr ≥3)	Discontinued due to AEs
RESONATE-2[1]	Ibrutinib	10.0 years	mPFS: 8.9 years	68% at 10 years	NR	NR	33%
NIH Phase 2 (TP53-aberrant / older patients)[2]	Ibrutinib	10.0 years	mPFS: 6.8 years	65.7% at 10 years	NR	NR	36.9%
ELEVATE-TN[3]	Acalabrutinib	74.5 months	Est. 72m: 61.5%	Est. 72m: 75.5%	1.7%	Pneumonia 6.1%; COVID-19 7.3%	17.9%
ELEVATE-TN[3]	Acalabrutinib + obinutuzumab	74.5 months	Est.72: 78%	Est. 72m: 83.9%	1.7%	Pneumonia 7.3%; COVID-19 9.0%	21.2%
SEQUOIA[4,5]	Zanubrutinib (Arm A)	72.8 months	Est. 72m: 74%	Est. 72m: 84%	NR	Pneumonia 8%; COVID-19 10%; URTI 2%	NR
SEQUOIA[4,5]	Zanubrutinib (Arm C del(17p))	76.7 months	Est. 72m: 64%	Est. 72m: 83%	NR	Pneumonia 6%; COVID-19 7%; URTI 3%	NR

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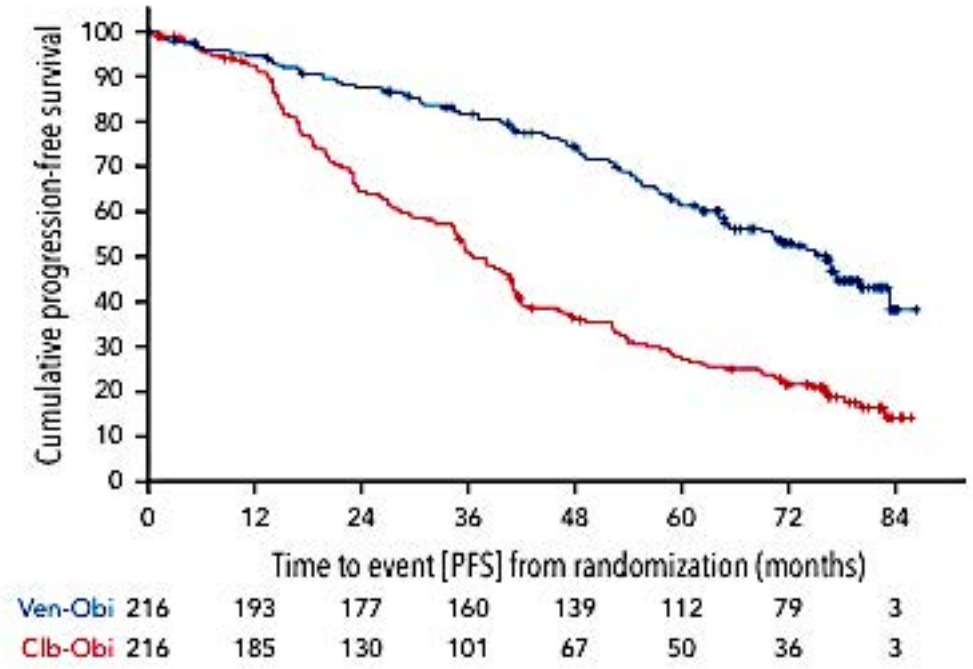
AEs, adverse events; AF, atrial fibrillation; BTKi, Bruton's tyrosine kinase inhibitor; Est, estimated; Gr, grade; m, month; mPFS, median progression-free survival; NIH, National Institutes of Health; NR, not reached; OS, overall survival; PFS, progression-free survival; TP53, tumor protein p53; URTI, upper respiratory tract infection.

1. Burger, et al. *Blood*. 2025;146(18):2168-2176. 2. Itsara, et al. *Blood*. doi:10.1182/blood.2025029971. 3. Sharman, et al. *Blood*. 2025;146(11):1276-1285. 4. Tam, et al. *Blood*. 2025;146(Suppl_1):2129. 5. Tam, et al. ASH 2025. Poster 2129.

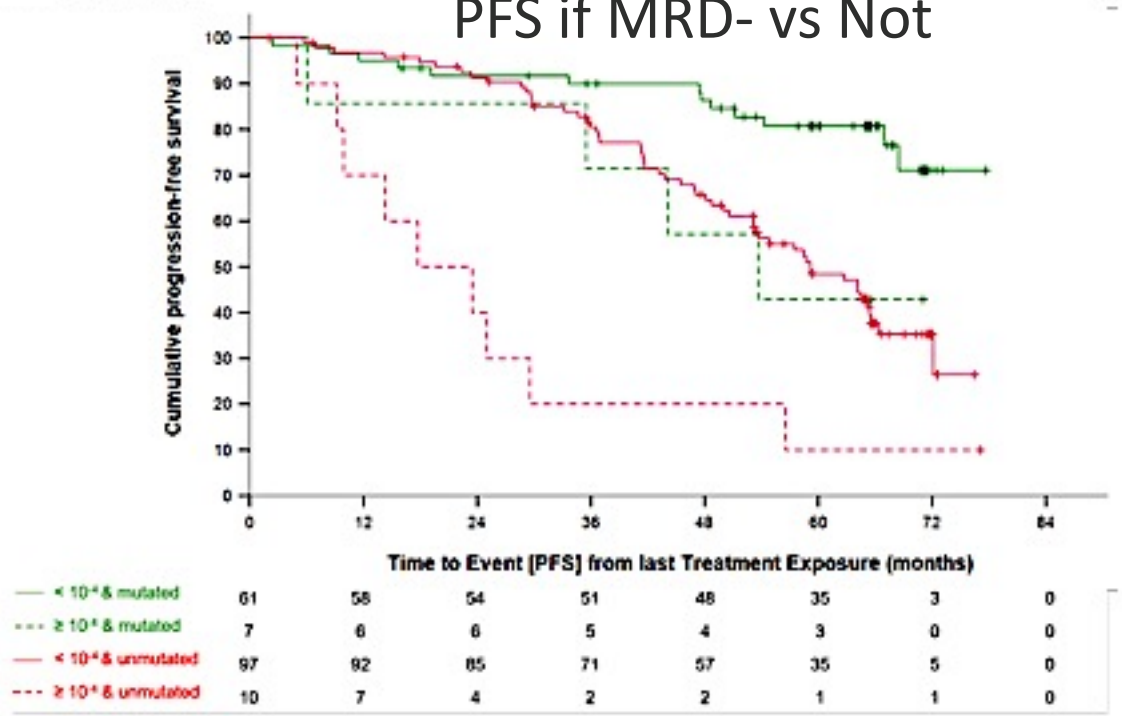
What Have We Learned from CLL14 Our Standard FD Regimen?

PFS



Ven-Obi

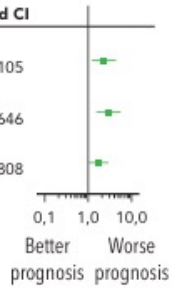
PFS if MRD- vs Not



PFS Multivariate Analysis

Ven-Obi

Cox regression PFS		Hazard ratio	95% Wald CI
IGHV mutational status			
unmutated	vs. mutated	2.310	1.300-4.105
Deletion 17p			
del(17p)	vs. no del(17p)	2.941	1.532-5.646
Lymph node size			
≥ 5 cm	vs. < 5 cm	1.768	1.114-2.808

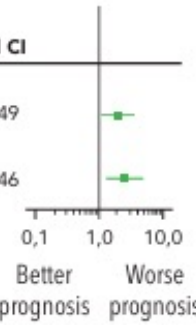


Only 8% remain uMRD at 60 months 80% had mutated IGHV

OS Multivariate Analysis

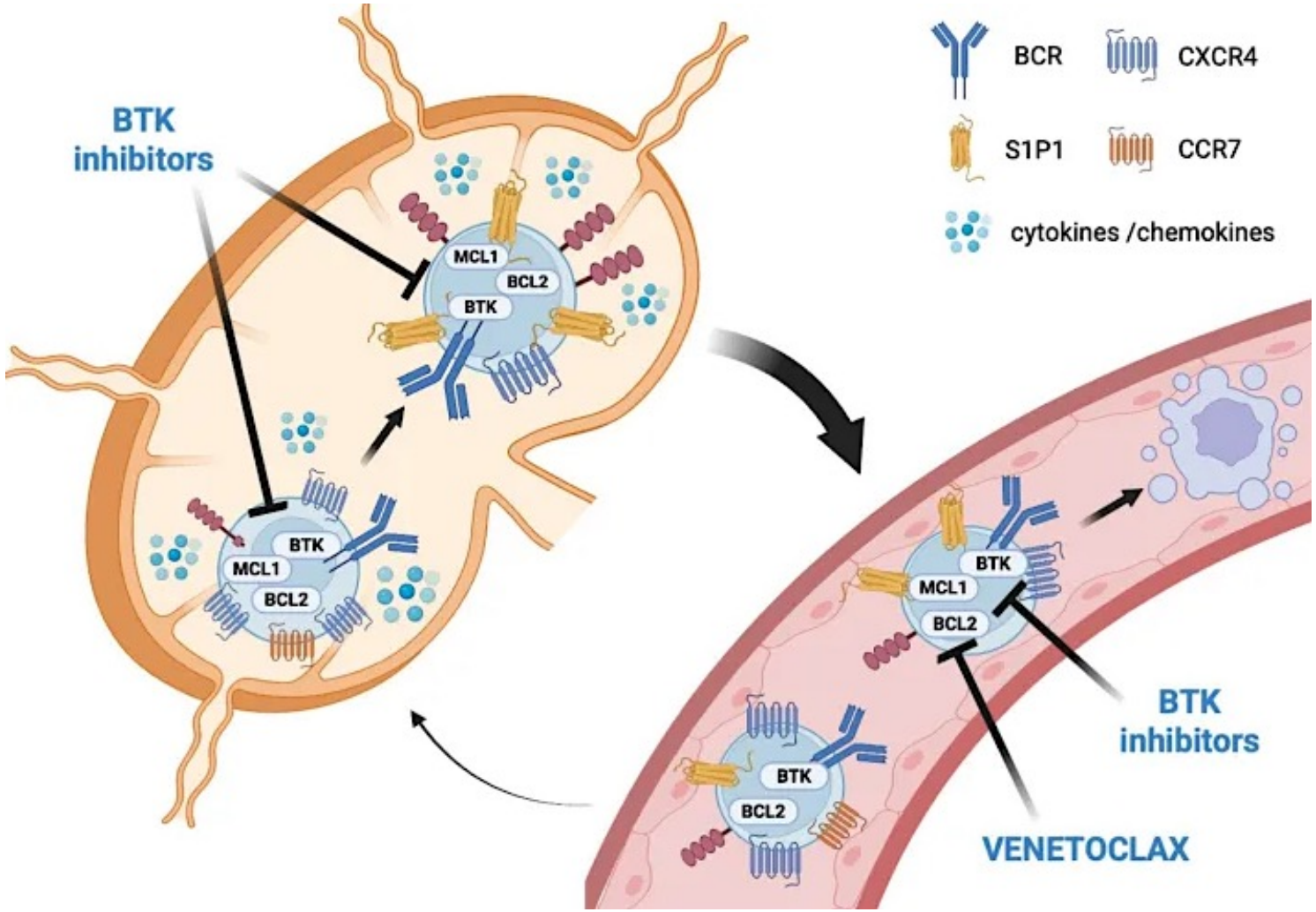
Ven-Obi

Cox regression OS		Hazard ratio	95% Wald CI
Age			
> 74 years	vs. ≤ 74 years	1.923	1.072-3.449
Complex karyotype			
complex karyotype/ highly complex karyotype	vs. noncomplex karyotype	2.474	1.317-4.646



Al Sawaf et al Blood (2024) 144 (18): 1924–1935.

Mechanistic Rationale of Potential Synergies of BTK/BCL2 Dual Inhibition



Visetin and Mauro Oncol. Rev., 17 December 2025

AMPLIFY: Firstline Treatment of CLL With Acalabrutinib + Venetoclax[1,2]

Key Inclusion Criteria
- Age ≤ 18 years
- TN CLL requiring treatment per iwCLL 2018 criteria
- Without del(17p) or *TP53*[a]
- ECOG PS ≤ 2

Key Exclusion Criteria
- CIRS geriatric > 6
- Significant cardiovascular disease

Stratification
- Age (> 65 vs ≤ 65 years)
- IGHV mutational status
- Rai stage ≥3 vs < 3
- Geographic region

AMPLIFY, randomized, multicenter, open-label, phase 3

N = 867

R 1:1:1

- **AV (14 cycles)** n = 291
- **AVO (14 cycles)** n = 286
- **FCR/BR (6 cycles)** n = 290

Crossover not built into protocol

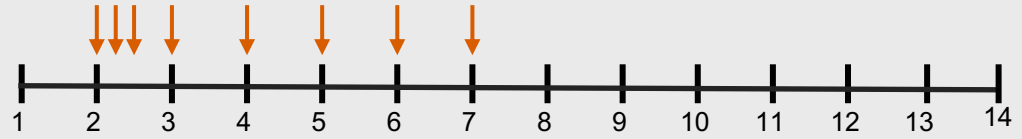
Primary endpoints
- IRC-assessed PFS (AV vs FCR/BR)
- If primary endpoint is met, secondary endpoints tested in fixed sequential hierarchy
- 1. IRC-PFS (AVO vs FCR/BR)
- 2. uMRD (AV vs FCR/BR)
- 3. uMRD (AVO vs FCR/BR)
- 4. OS (AV vs FCR/BR)
- 5. OS (AVO vs FCR/BR)

AV and AVO dosing schedule

Acalabrutinib 100 mg PO BID (cycles 1–14)

Venetoclax 400 mg PO QD (cycles 3–14)

Obinutuzumab (AVO only) 1000 mg (cycles 2–7)



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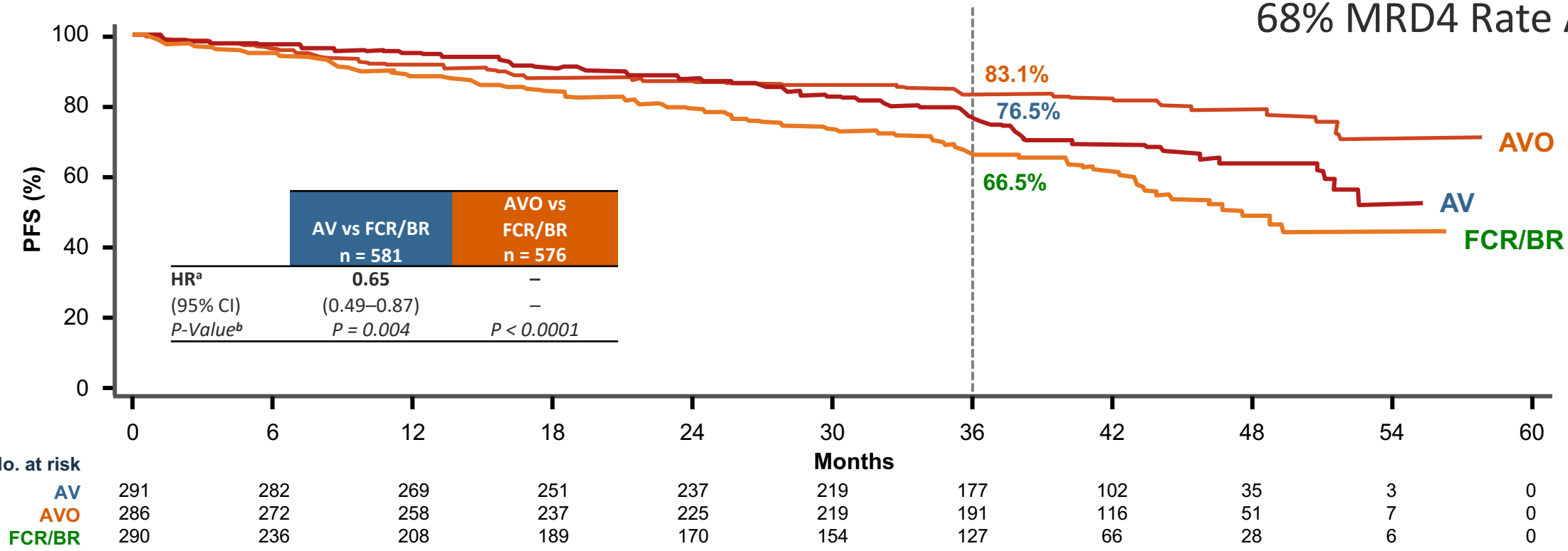
1. Brown JR, et al. *Blood.* 2024;144 (Supplement 1):1009. 2. Brown JR, et al. *N Engl J Med.* 2025 Feb 20;392(8):748-762.

AMPLIFY: IRC-Assessed PFS[1,2]

EOT
34% MRD4 Rate AV
68% MRD4 Rate AVO



Median PFS was NR for AV and AVO, and was 47.6 mo for FCR/BR

ITT population. Median follow-up from randomization: 40.8 months (range, 0-59 months).
[a]Hazard ratio (95% CI) computed using a Cox proportional-hazards model stratified by the randomization strata. *P*-value based on stratified log-rank test. A hazard ratio and corresponding 95% confidence interval is not shown for any comparison that violated the proportional-hazards assumption.

AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; CI, confidence interval; FCR, fludarabine-cyclophosphamide-rituximab; HR, hazard ratio; IRC, independent review committee; ITT, intent-to-treat; NR, not reached; PFS, progression-free survival.

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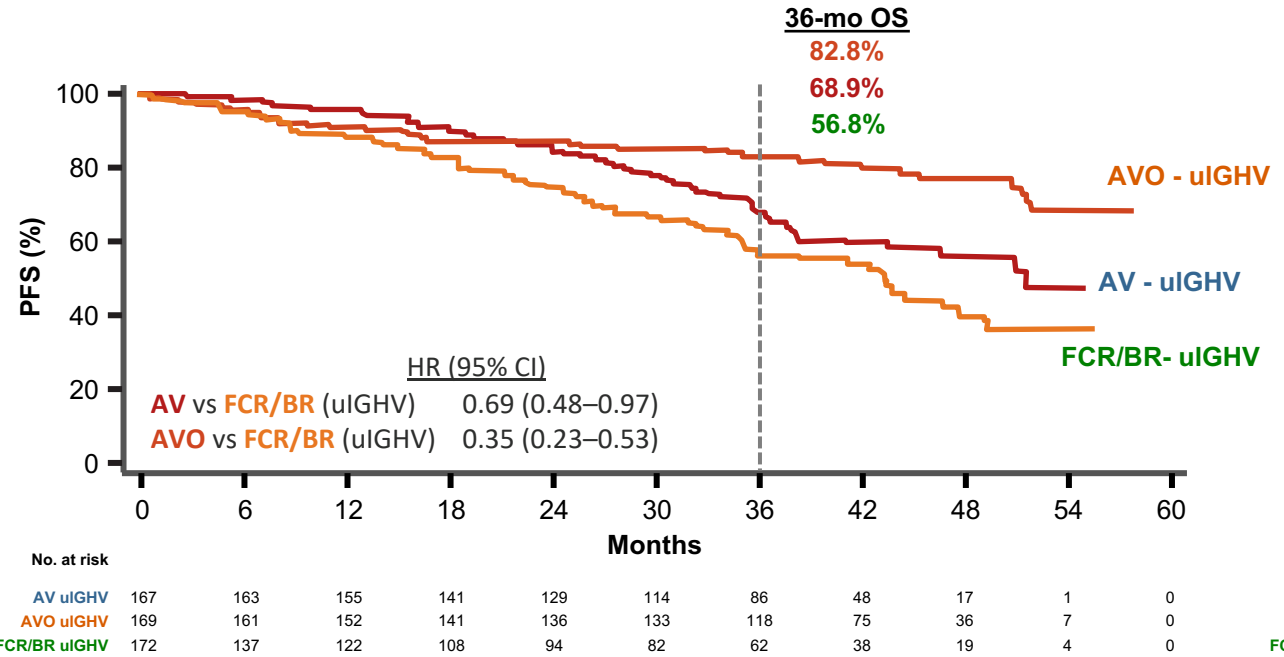
1. Brown JR. *N Engl J Med*. 2025;392(8):748-762. 2. Brown J, et al. ASH 2024. Oral session 1009.

AMPLIFY: PFS and IGHV Status[1,2]

PFS in the u*IGHV* Subgroup

	AVO - uIGHV	AV - uIGHV	FCR/BR - uIGHV
Events/N	36/169	61/167	67/172
Median (mo)	NR	51.5	43.3

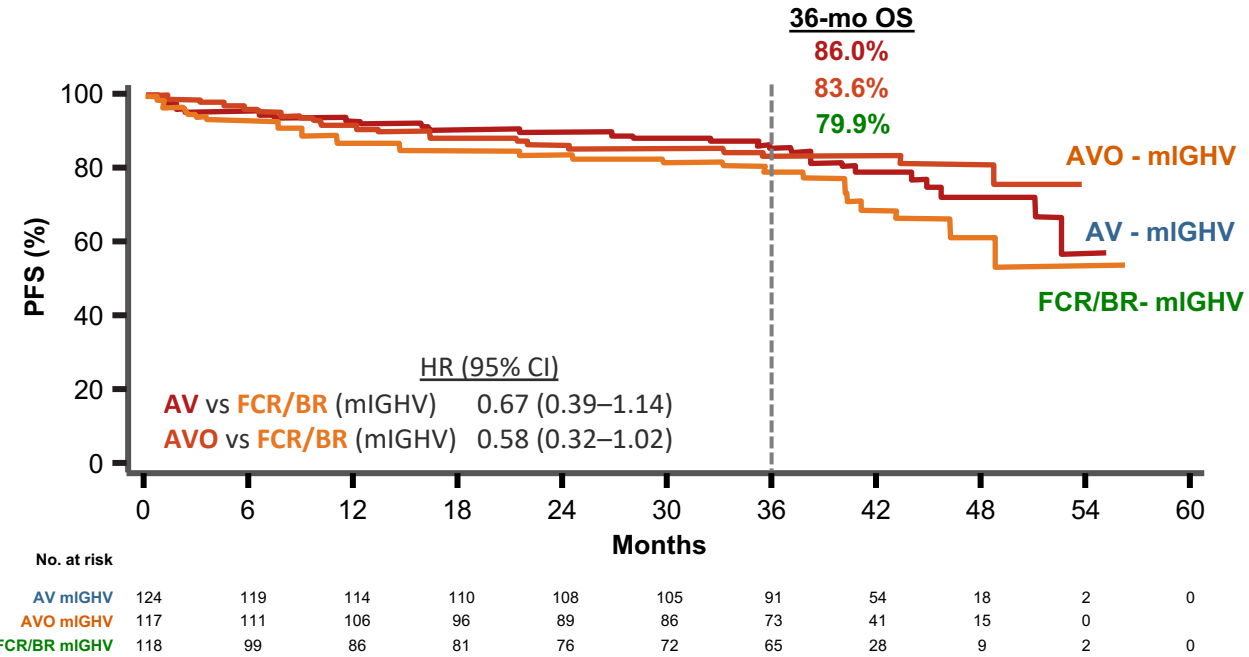


No. at risk

AV uIGHV	167	163	155	141	129	114	86	48	17	1	0
AVO uIGHV	169	161	152	141	136	133	118	75	36	7	0
FCR/BR uIGHV	172	137	122	108	94	82	62	38	19	4	0

PFS in the m*IGHV* Subgroup

	AVO - mIGHV	AV - mIGHV	FCR/BR - mIGHV
Events/N	20/117	28/124	28/118
Median (mo)	NR	NR	NR



No. at risk

AV mIGHV	124	119	114	110	108	105	91	54	18	2	0
AVO mIGHV	117	111	106	96	89	86	73	41	15	0	
FCR/BR mIGHV	118	99	86	81	76	72	65	28	9	2	0

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1. Brown JR. *N Engl J Med*. 2025;392(8):748-762. 2. Brown J, et al. ASH 2024. Oral session 1009.

AMPLIFY: AESI

	AV (n=291)		AVO (n=284)		FCR/BR (n=259)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any ECI	222 (76.3)	136 (46.7)	242 (85.2)	188 (66.2)	185 (71.4)	141 (54.4)
Cardiac events	27 (9.3)	5 (1.7)	34 (12.0)	7 (2.5)	9 (3.5)	3 (1.2)
Atrial fibrillation	2 (0.7)	1 (0.3)	6 (2.1)	2 (0.7)	2 (0.8)	2 (0.8)
Ventricular tachyarrhythmias[a]	2 (0.7)	0	3 (1.1)	0	0	0
Hypertension	12 (4.1)	8 (2.7)	11 (3.9)	6 (2.1)	7 (2.7)	2 (0.8)
Hemorrhage	94 (32.3)	3 (1.0)	86 (30.3)	6 (2.1)	11 (4.2)	1 (0.4)
Major hemorrhage	3 (1.0)	3 (1.0)	8 (2.8)	6 (2.1)	2 (0.8)	1 (0.4)
Neutropenia (any)[b]	108 (37.1)	94 (32.3)	143 (50.4)	131 (46.1)	132 (51.0)	112 (43.2)
Infections (any)	148 (50.9)	36 (12.4)	153 (53.9)	67 (23.6)	82 (31.7)	26 (10.0)
Second primary malignancies	15 (5.2)	5 (1.7)	12 (4.2)	5 (1.8)	2 (0.8)	0
Excl. non-melanoma skin	8 (2.7)	5 (1.7)	7 (2.5)	4 (1.4)	1 (0.4)	0
Tumor lysis syndrome	1 (0.3)	1 (0.3)	1 (0.4)	1 (0.4)	8 (3.1)	8 (3.1)

Data are n (%). ECIs listed by category and sub-category.
[a]Ventricular tachyarrhythmias consisted of ventricular extrasystoles (n=1 in AV arm; n=2 in AVO arm) and ventricular tachycardia (n=1 each in AV and AVO arms).
[b]Includes neutropenia, neutrophil count decreased, and febrile neutropenia.
AEs with an onset date or that worsen on or after the date of first dose and up to and including 30 days following the date of last dose of treatment or up to the day prior to start of subsequent anti-CLL therapy, whichever comes first.
AE, adverse event; AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; ECI, event of clinical interest; FCR, fludarabine-cyclophosphamide-rituximab.

COVID-19 deaths: 10 (AV), 25 (AVO), 21 (FCR/BR)

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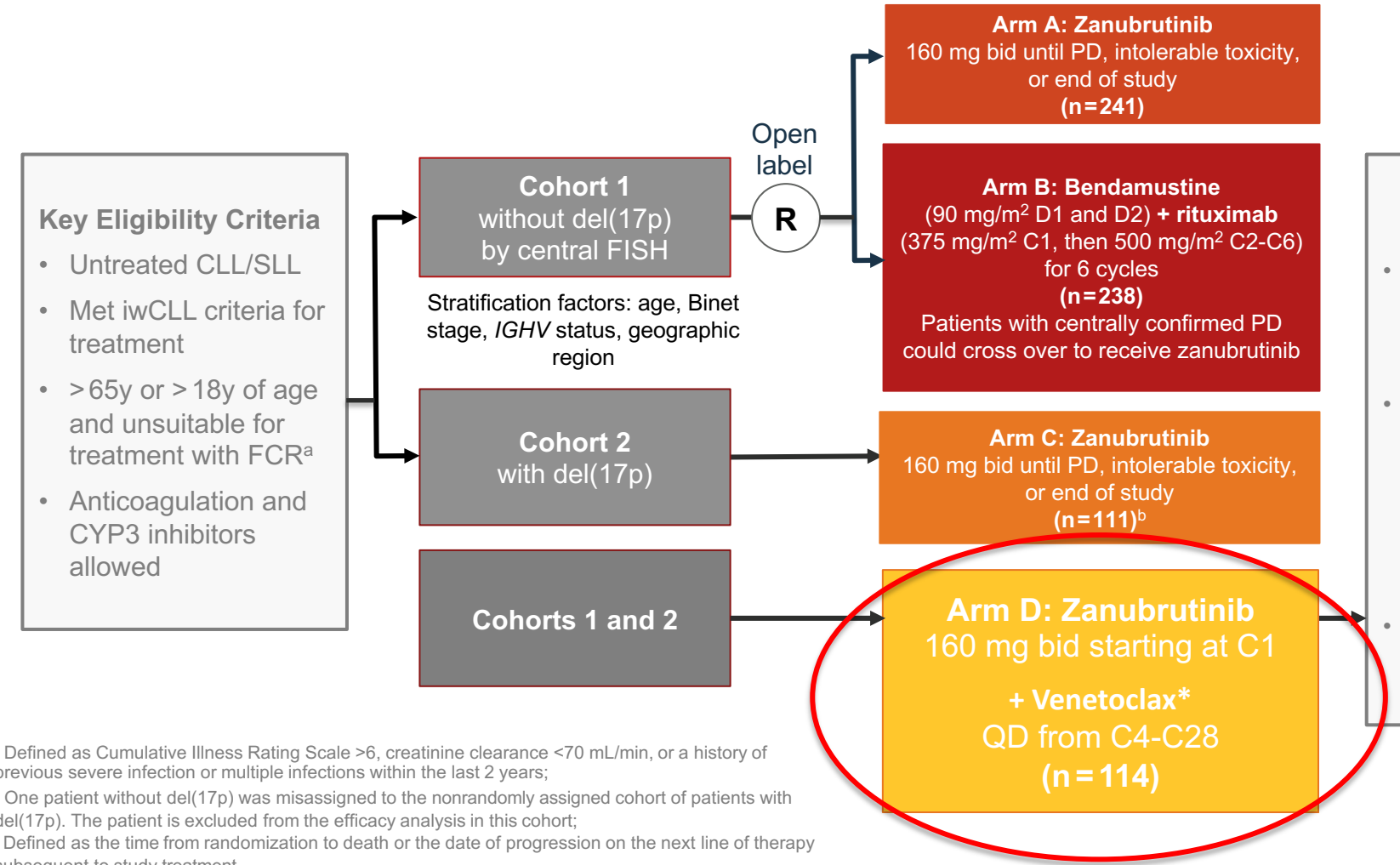
Brown et al NEJM 2025

SEQUOIA Arm D: Phase 3 Trial of Zanu/Ven Combinations as First-line Treatment for CLL/SLL



Disease Assessments

- Response assessments conducted every 3 cycles until C28 and every 6 cycles after C28 until PD
- Bone marrow MRD repeated every 12-24 weeks in pts with CR/CRi and two consecutive PB-undetectable MRDs ~12 wks apart, optional after C27 for pts with detectable MRD in BM
- TLS at baseline and pre-venetoclax initiation

Endpoints for Arm D

- PFS
- ORR
- OS
- uMRD4 rate ($<10^{-4}$ sensitivity)
- Safety

NCT03336333
Statistical analysis: Efficacy endpoints analyzed using ITT analysis and the per protocol analysis set. Safety was assessed in all patients who received >1 dose of treatment.

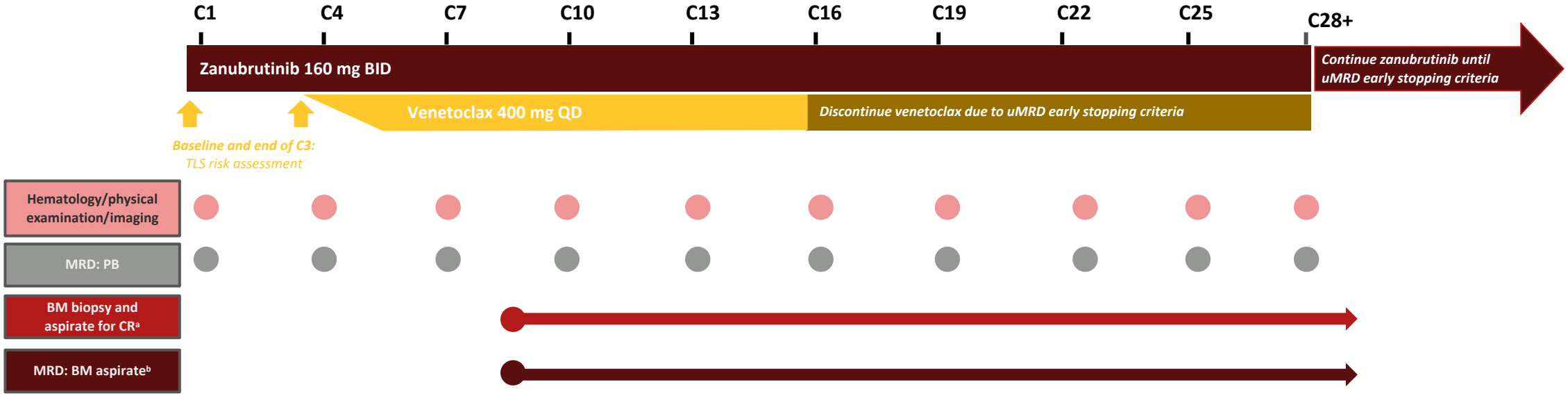
[a] Defined as Cumulative Illness Rating Scale >6, creatinine clearance <70 mL/min, or a history of previous severe infection or multiple infections within the last 2 years;
[b] One patient without del(17p) was misassigned to the nonrandomly assigned cohort of patients with del(17p). The patient is excluded from the efficacy analysis in this cohort;
[c] Defined as the time from randomization to death or the date of progression on the next line of therapy subsequent to study treatment.

BID, twice daily; BM, bone marrow; C, cycle; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CR, complete response; CRi, complete response; FCR, fludarabine, cyclophosphamide, rituximab; FISH, fluorescence in situ hybridization; *IGHV*, immunoglobulin heavy chain variable region; ITT, intention-to-treat; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PB, peripheral blood; PD, progressive disease; PFS, progression-free survival; QD, once daily; TLS, tumor lysis syndrome; uMRD4, undetectable minimal residual disease at 10^{-4} sensitivity.

1. Tam, et al. *Lancet Oncol*. 2022;23(8):1031-1043. 2. Shadman, et al. 17th ICML. June 13-17, 2023; Abstract 154. 3. Shadman, et al. ASCO 2025. May 30 – June 3, 2025. Chicago, IL. Abstract 7009.

*This regimen is not yet FDA-approved

SEQUOIA Arm D: Schedule



Median follow-up: 38.5 months

uMRD-guided stopping criteria

All conditions must be met:

1. Response assessed as CR or CRi confirmed by a BM biopsy
2. uMRD <1x10^{-4} (uMRD4) achieved in 2 consecutive peripheral blood MRD tests conducted ≥12 weeks apart
3. uMRD4 achieved in 2 consecutive BM aspirate MRD tests conducted ≥12 weeks apart
4. Received:
   - i) Minimum of 12 cycles of venetoclax (to stop venetoclax early)
   - ii) Minimum of 27 cycles of zanubrutinib (to stop zanubrutinib early)

aBM biopsy and aspirate are required to confirm a suspected CR/Cri (BM biopsy collection timepoint not defined per protocol), starting after cycle 9 and then annually if needed. bPatients with confirmed CR/CRi and 2 consecutive PB-uMRD results at least 12 weeks apart.

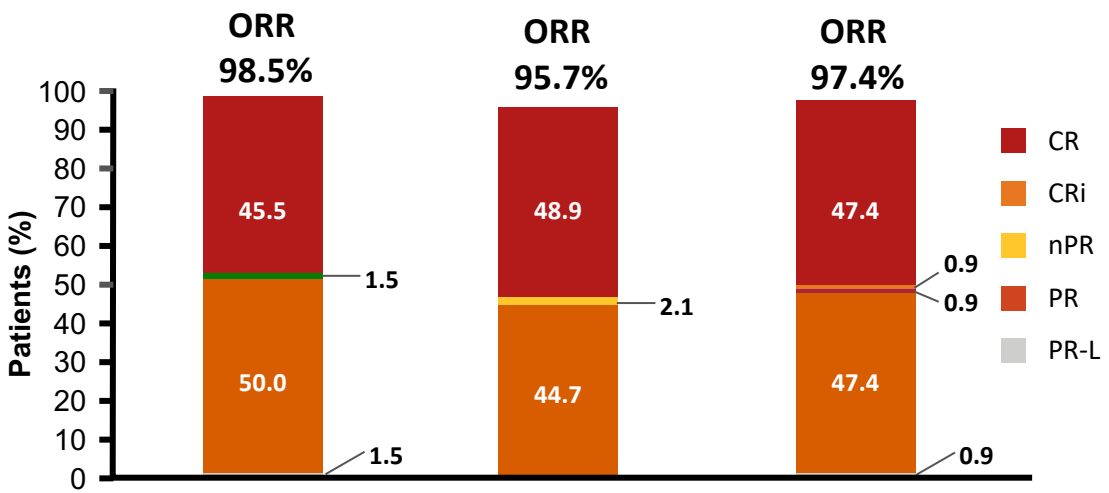
BID, twice daily; BM, bone marrow; C, cycle; CR, complete response; CRi, complete response with incomplete hematologic recovery; MRD, minimal residual disease; PB, peripheral blood; QD, once daily; TLS, tumor lysis syndrome; uMRD, undetectable minimal residual disease; uMRD4, undetectable MRD at 10^{-4} sensitivity

1. Tam, et al. *Lancet Oncol*. 2022;23(8):1031-1043. 2. Shadman, et al. 17th ICML. June 13-17, 2023; Abstract 154. 3. Shadman, et al. ASCO 2025. May 30 – June 3, 2025. Chicago, IL. Abstract 7009.

*This regimen is not yet FDA-approved

SEQUOIA Arm D: Response and MRD Rates

Response Rates



	With del(17p) and/or *TP53*mut (n = 66)	Without del(17p) and/or *TP53*mut (n = 47)	All patients (n = 114)
Median study follow-up, Months (range)	**38.7** (0.4-58.0)	**29.6** (0.6-31.9)	**31.2** (0.4-58.0)

Peripheral Blood uMRD Rates by Genomic Risk and Treatment Duration

Outcome	Overall	del(17p) and/or *TP53*mut	No del(17p)/ *TP53*mut	Unmutated *IGHV*	Mutated *IGHV*
Best peripheral blood uMRD rate	60%	59%	62%	-	-
uMRD after 15 cycles	-	15%	40%	23%	33%
uMRD after 27 cycles	-	38%	36%	40%	29%

Treatment Discontinuation and Durability

Measure	Value
Patients meeting early stopping criteria	13/114
Patients meeting criteria to stop ZV	42/114
Patients maintaining uMRD after discontinuation (18-month follow-up)	92-100%

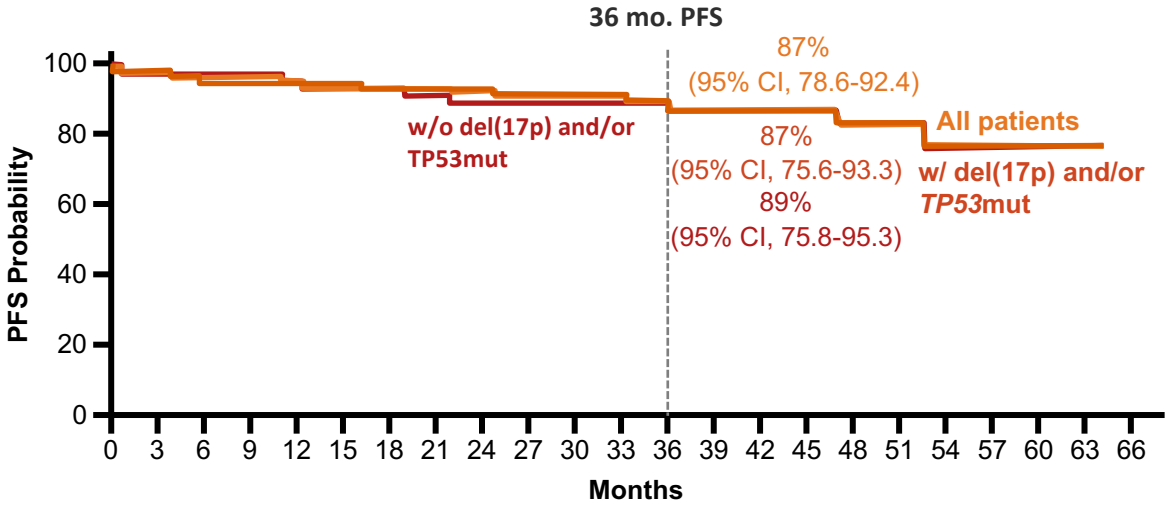
CR, complete response; CRi, complete response with incomplete hematopoietic recovery; EOS, end of study; *IGHV*, immunoglobulin heavy-chain variable region gene; MRD, minimal residual disease; mut, mutation; nPR, nodular partial response; ORR, overall response rate; PB-uMRD, peripheral blood-undetectable minimal residual disease; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; uMRD, undetectable minimal residual disease; TP53, tumor protein p53; ZV, zanubrutinib + venetoclax.

*This regimen is not yet FDA-approved

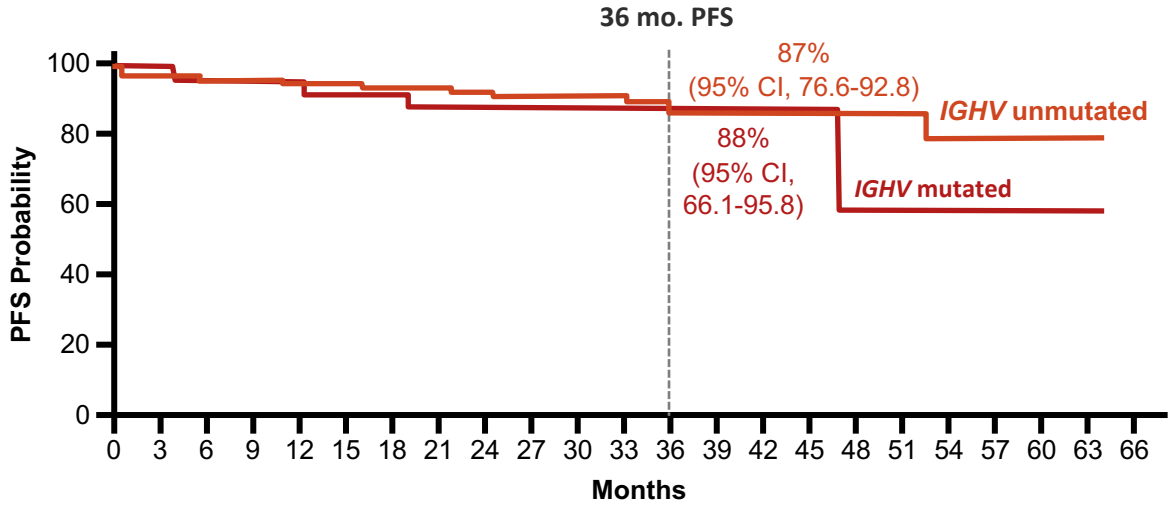
1. Tam, et al. *Lancet Oncol*. 2022;23(8):1031-1043. 2. Shadman, et al. 17th ICML. June 13-17, 2023; Abstract 154. 3. Shadman, et al. ASCO 2025. May 30 – June 3, 2025. Chicago, IL. Abstract 7009.

SEQUOIA Arm D: PFS

Overall Population and Patients with and without del(17p) and/or *TP53*mut



Unmutated and Mutated *IGHV*



- Median study follow-up
  - With del(17p) and/or *TP53*mut: 46.1months
  - Without del(17p) and *TP53*mut: 36.9 months

Zanu + ven demonstrated durable PFS, with comparable outcomes in patients harboring del(17p)/*TP53* mutations.

CI, confidence interval; *IGHV*, immunoglobulin heavy-chain variable region gene; ITT, intention-to-treat; mut, mutation; PFS, progression-free survival; *TP53*, tumor protein p53; ven, venetoclax; w/o, without; zanu, zanubrutinib.

*This regimen is not yet FDA-approved

1. Tam, et al. *Lancet Oncol*. 2022;23(8):1031-1043. 2. Shadman, et al. 17th ICML. June 13-17, 2023; Abstract 154. 3. Shadman, et al. ASCO 2025. May 30 – June 3, 2025. Chicago, IL. Abstract 7009.

SEQUOIA Arm D: Safety

TEAEs in >15% of Patients

Any TEAE	All Patients (N=114)	
	Any Grade, n (%)	Grade ≥3, n (%)[a]
COVID-19	63 (55)	2 (2)
Diarrhea	49 (43)	7 (6)
Contusion	37 (33)	0
Nausea	36 (32)	0
Neutropenia/neutrophil count decreased	30 (26)	27 (24)
Fatigue	28 (25)	0
Arthralgia	24 (21)	0
Upper respiratory tract infection	22 (19)	1 (1)
Cough	21 (18)	0
Hypertension	18 (16)	10 (9)

TEAEs of Special Interest

	All Patients (N=114)	
	Any Grade, n (%)	Grade ≥3, n (%)
Any TEAE of special interest	111 (97)	50 (44)
Infections	96 (84)	14 (12)[b]
Grade 3	-	13 (11)
Hemorrhage	61 (54)	2 (3)
Neutropenia	31 (27)	27 (24)
Second primary malignancies	22 (19)	6 (5)
Skin cancers	15 (13)	0
Hypertension	18 (16)	10 (9)
Thrombocytopenia	13 (11)	5 (4)
Anemia	10 (9)	1 (1)
Major hemorrhage	4 (4)	3 (3)
Atrial fibrillation and flutter	3 (3)	2 (2)
Opportunistic infections	3 (3)	0
Tumor lysis syndrome	1 (1)	0

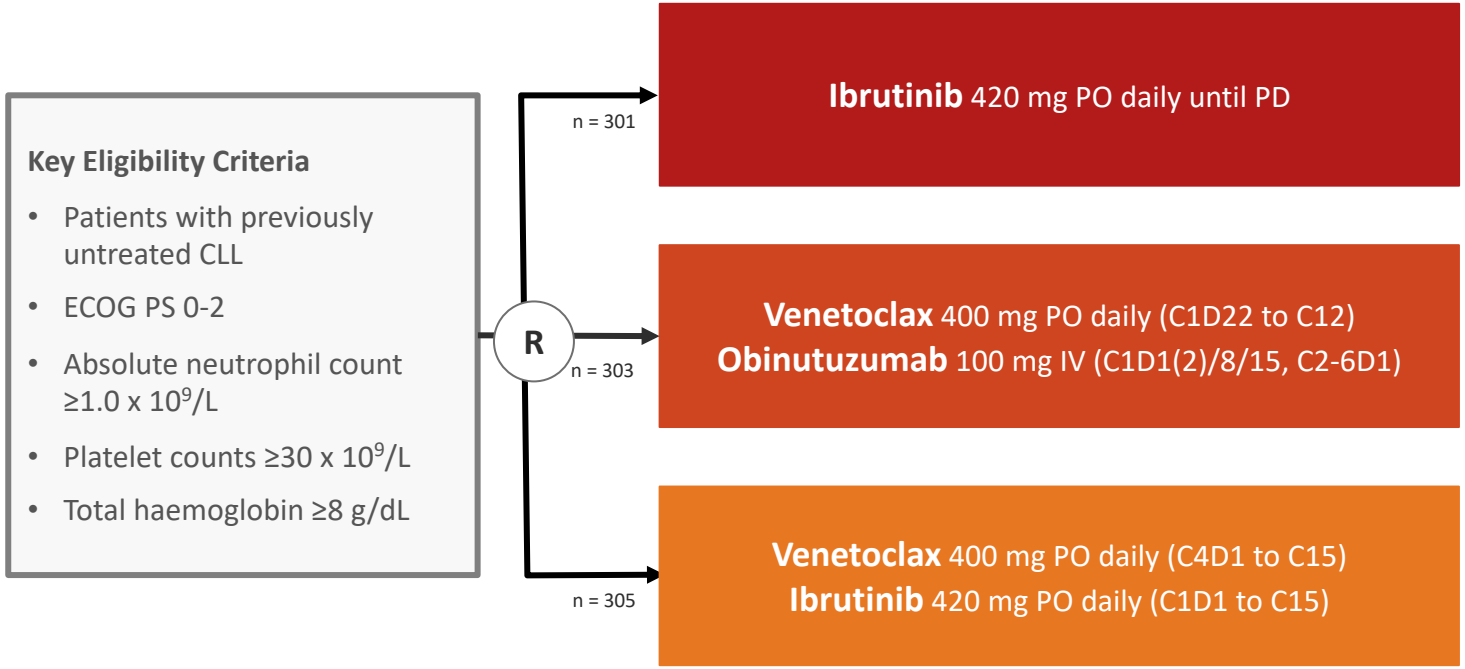
Zanubrutinib + venetoclax had a favorable safety profile. Five deaths occurred in this study due to AEs (none were treatment related); no new events were reported at this follow-up at 38.5 months.

[a]TEAEs in ≥5% of patients are reported. [b]Grade 5 infection occurred in one patient (pneumonia staphylococcal and septic shock).
AE, adverse event; TEAE, treatment-emergent adverse event.

*This regimen is not yet FDA-approved

1. Tam, et al. *Lancet Oncol*. 2022;23(8):1031-1043. 2. Shadman, et al. 17th ICML. June 13-17, 2023; Abstract 154. 3. Shadman, et al. ASCO 2025. May 30 – June 3, 2025. Chicago, IL. Abstract 7009.

CLL17: Phase 3 Trial of Continuous Ibrutinib Monotherapy vs Fixed-Duration Venetoclax-Based Regimens as First-Line Treatments for CLL



Primary Endpoints
• Investigator-assessed PFS
Key Secondary Endpoints
• Minimal residual disease • Response • OS • Safety

- 976 patients screening in 174 sites, across 13 countries
- Patient enrollment from February 2021 to November 2022
- Median observation time: 34.2 months (IQR 30.3-39.3)

Weill Cornell Medicine

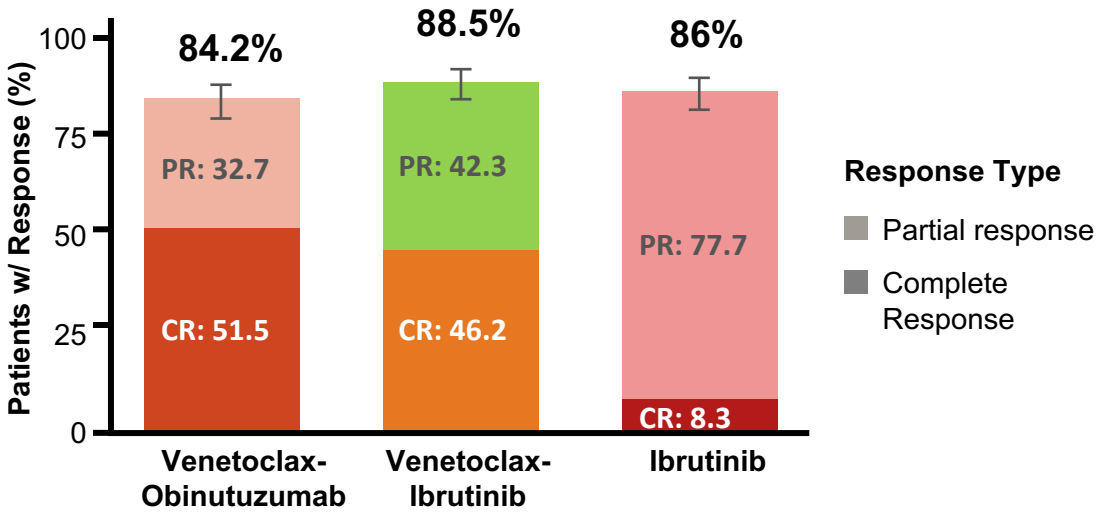
*Venetoclax + ibrutinib is not yet FDA-approved

CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IQR, interquartile range; IV, intravenous; PD, progressive disease; PFS, progression-free survival; PO, oral administration; OS, overall survival.

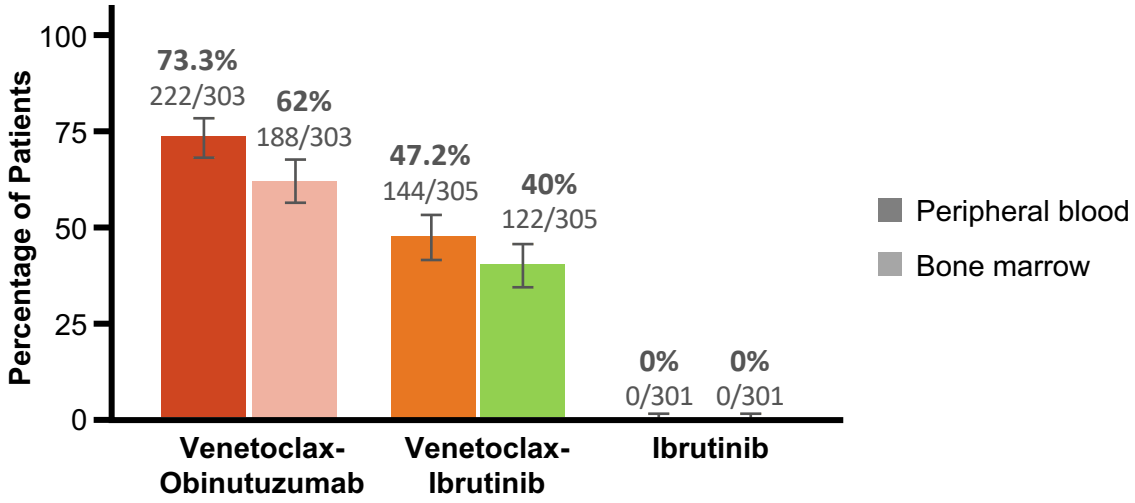
Al-Sawaf, et al. *N Engl J Med*. Published online December 6, 2025. doi:10.1056/NEJMoa2515458

CLL17: Response to Treatment

iwCLL Response at Final Restaging (C18D1)



uMRD <10^{-4} in Peripheral Blood and Bone Marrow, by Flow Cytometry, at Final Restaging



Weill Cornell Medicine

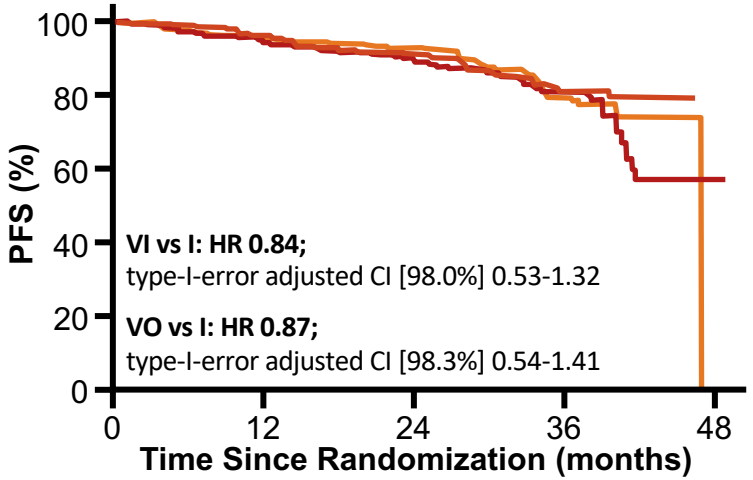
*Venetoclax + ibrutinib is not yet FDA-approved

iwCLL, international workshop on CLL; uMRD, undetectable measurable residual disease.

Al-Sawaf, et al. *N Engl J Med*. Published online December 6, 2025. doi:10.1056/NEJMoa2515458

CLL17: Survival Across Treatment Arms

PFS by Treatment Arm



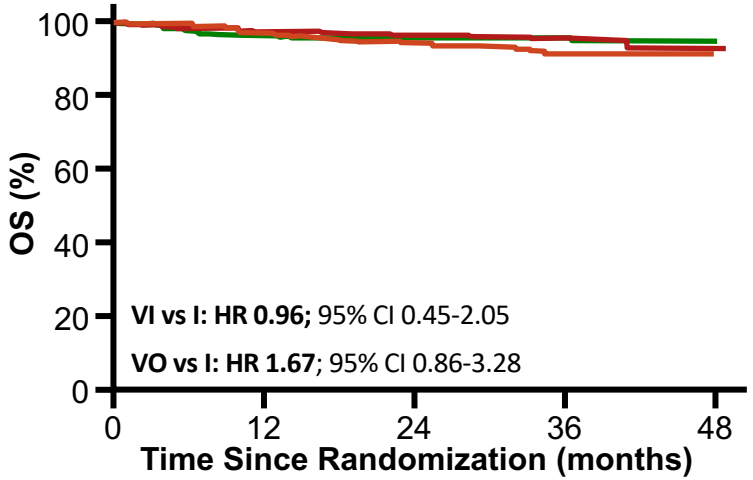
3-year PFS
VO 81.1%
I 81.0%
VI 79.4%

No. at risk

VO	303	278	256	77	0
VI	305	278	267	82	0
I	301	267	243	94	1

	VO	I	VI
PD	25	46	37
Death	21	11	13

OS by Treatment Arm



3-year OS
VO 91.5%
I 95.7%
VI 96.0%

No. at risk

VO	303	284	269	102	0
VI	305	281	279	114	1
I	301	284	276	141	2

Cause of death	VO	I	VI
Infection	12 (7 Covid)	3	7 (2 Covid)
Cardiovascular	5	5	3
PD/RT	1	0	0
SPM	4	2	2
Other	0	4	1
Total	**22**	**14**	**13**

Fixed-duration treatment with venetoclax–obinutuzumab or venetoclax–ibrutinib was noninferior to continuous ibrutinib with regards to investigator-assessed PFS.

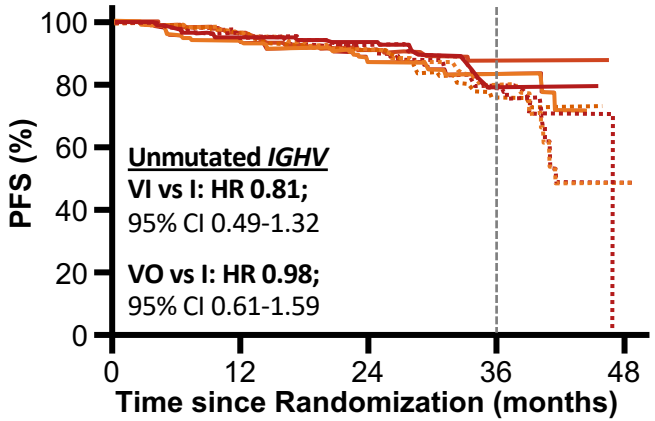
CI, confidence interval; CLL, chronic lymphocytic leukemia; HR, hazard ratio; I, ibrutinib; no. number; OS, overall survival; PD, progressive disease; PD/RT, progressive disease/Richter transformation; PFS, progression-free survival; SPM, second primary malignancies; VI, venetoclax–ibrutinib; VO, venetoclax–obinutuzumab.

Al-Sawaf, et al. *N Engl J Med*. Published online December 6, 2025. doi:10.1056/NEJMoa2515458

*Venetoclax + ibrutinib is not yet FDA-approved

CLL17: PFS According to *IGHV* and *TP53*/del17p Status

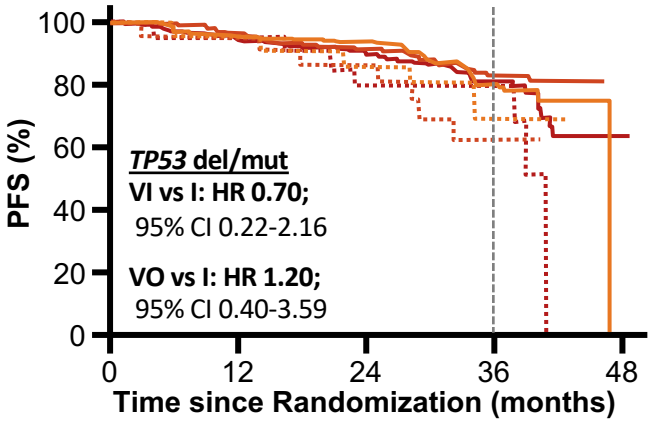
PFS According to *IGHV* status



3-year PFS	
I, u*IGHV*	79.7%
I, m*IGHV*	83.5%
VI, u*IGHV*	78.9%
VI, m*IGHV*	80.0%
VO, u*IGHV*	**75.8%**
VO, m*IGHV*	**87.6%**

No. at risk					
VO, unmutated	171	156	142	40	0
VO, mutated	129	119	111	36	0
VI, unmutated	172	157	151	50	0
VI, mutated	129	117	112	32	0
I, unmutated	171	156	145	55	1
I, mutated	126	108	95	37	0

PFS According to *TP53*/del17p status



3-year PFS	
I, *TP53*del/mut	**79.4%**
I, *TP53*-WT	**81.0%**
VI, *TP53*del/mut	69.0%
VI, *TP53*-WT	80.1%
VO, *TP53*del/mut	62.0%
VO, *TP53*-WT	82.7%

No. at risk					
VO, del/mut	23	21	16	5	0
VO, WT	280	257	240	72	0
VI, del/mut	25	20	18	4	0
VI, WT	279	257	248	78	0
I, del/mut	21	19	15	7	0
I, WT	279	247	227	87	1

CI, confidence interval; CLL, chronic lymphocytic leukemia; HR, hazard ratio; I, ibrutinib; *IGHV*, immunoglobulin heavy-chain variable region gene; m*IGHV*, mutated *IGHV;* PFS, progression-free survival; *TP53*del/mut, *TP53* deletion and/or mutation; u*IGHV*, unmutated *IGHV*; VI, venetoclax–ibrutinib; VO, venetoclax–obinutuzumab; WT, wild type.

Al-Sawaf, et al. *N Engl J Med*. Published online December 6, 2025. doi:10.1056/NEJMoa2515458

*Venetoclax + ibrutinib is not yet FDA-approved

CLL17: Selected Adverse Events of Interest

	VO	VI	I
Safety population – n (%)	295	303	298
Blood and lymphatic system disorders	174 (59.0)	130 (42.9)	85 (28.5)
Febrile neutropenia	14 (4.7)	7 (2.3)	0 (0)
Neutropenia	155 (52.5)	110 (36.3)	49 (16.4)
Cardiac disorders	41 (13.9)	72 (23.8)	103 (34.6)
Atrial fibrillation	11 (3.7)	38 (12.5)	50 (16.8)
Gastrointestinal disorders	176 (59.7)	225 (74.3)	189 (63.4)
Diarrhea	80 (27.1)	143 (47.2)	104 (34.9)
Infections and infestations	225 (76.3)	243 (80.2)	238 (79.9)
COVID-19	113 (38.3)	128 (42.2)	117 (39.3)
Pneumonia	41 (13.9)	28 (9.2)	40 (13.4)
Metabolism and nutrition disorders	90 (30.5)	75 (24.8)	72 (24.2)
Tumor lysis syndrome	12 (4.1)	4 (1.3)	1 (0.3)
Neoplasms benign, malignant and unspecified	35 (11.9)	35 (11.6)	55 (18.5)
Richter Transformation	4 (1.4)	1 (0.3)	4 (1.3)
Vascular disorders	60 (20.3)	102 (33.7)	124 (41.6)
Hypertension	34 (11.5)	51 (16.8)	72 (24.2)

I, ibrutinib; VI, venetoclax–ibrutinib; VO, venetoclax–obinutuzumab.

Al-Sawaf, et al. *N Engl J Med*. Published online December 6, 2025. doi:10.1056/NEJMoa2515458

*Venetoclax + ibrutinib is not yet FDA-approved

Section Summary

- A+V is now approved in the US as a second FD option
    - Guidelines do acknowledge Triplet or Response Adapted Approaches allowing coverage and use adding third and “fourth” FD options.
    - uIGHV appears to benefit from Triplet Approaches in terms of PFS over VenG or AV
    - mIGHV may still benefit from attaining MRD or using antiCD20 but may not require Triplet therapy to achieve the optimal outcome
        - Current evidence at short follow-up shows no differences in outcome based on MRD status with oral doublets
- CLL17 currently at 3 years of follow-up (1.5 years after cessation) no differences between groups or approaches in PFS or OS.
    - Thus at this time anything goes, still about preferences, comorbidities, philosophy

QUESTIONS?

Module 1: Chronic Lymphocytic Leukemia

Current Management of Newly Diagnosed CLL — Dr Allan

Noncovalent BTK Inhibitors and Other Novel Strategies — Dr Kittai

Noncovalent BTK Inhibitors and Other Novel Strategies

Adam S. Kittai, MD, MBA
Associate Professor
Director, CLL – NYU Perlmutter Cancer Center
Research To Practice
Orlando, Florida

Disclosures

Advisory Committees	AbbVie Inc, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Galapagos NV, Genmab US Inc, Pfizer Inc
Consulting Agreements	AbbVie Inc, Lilly
Honoraria for Unbranded Speaking Engagements	AstraZeneca Pharmaceuticals LP, Janssen Biotech Inc, Lilly

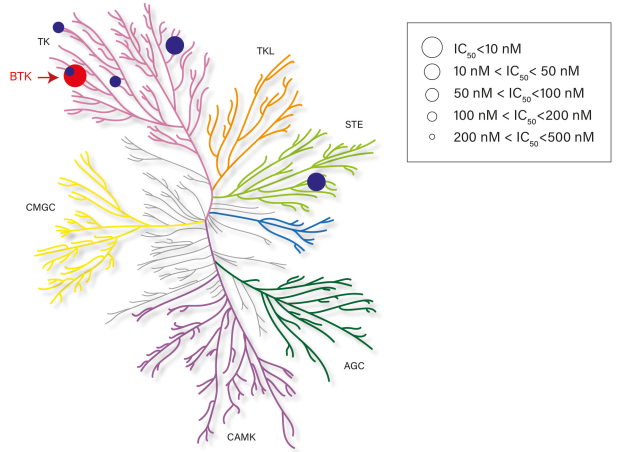
Objectives

- Pharmacologic similarities and differences between covalent and noncovalent BTK inhibitors
- Long-term efficacy and safety findings with pirtobrutinib in patients with BTK inhibitor-pretreated CLL
- Key findings from the Phase III BRUIN CLL-314 study of pirtobrutinib versus ibrutinib in patients with treatment-naïve or previously treated, BTK inhibitor-naïve CLL
- Efficacy advantage documented with pirtobrutinib versus bendamustine/rituximab for patients with treatment-naïve CLL without del(17p) in the Phase III BRUIN CLL-313 trial
- Similarities and differences between sonrotoclax and venetoclax; early data with sonrotoclax in combination with an anti-CD20 antibody in R/R and treatment-naïve CLL and ongoing Phase III evaluation
- Mechanistic similarities and differences between BTK degraders and BTK inhibitors; preliminary data with and ongoing evaluation of BTK degraders (eg, BGB-16673) in patients with heavily pretreated CLL

Non-covalent BTKi

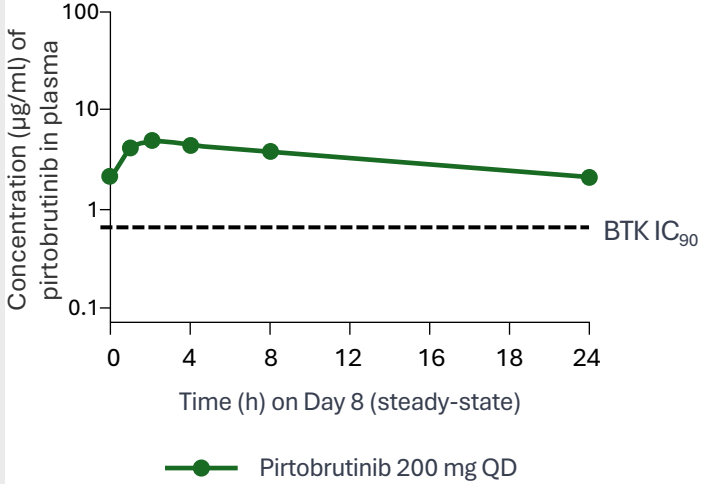
Pirtobrutinib – a non-covalent BTK inhibitor

Highly selective for BTK[2,3]



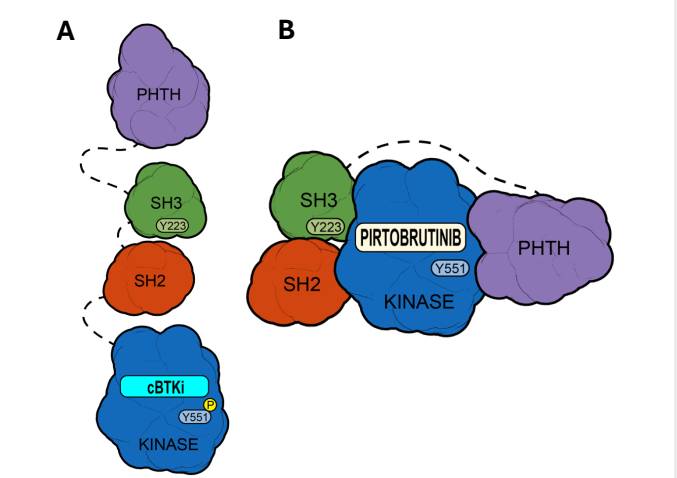
Pirtobrutinib shows high selectivity for BTK (more than 300-fold) over other kinases, which may **reduce its potential for off-target activity**.[1–3]

Plasma exposures exceeded BTK IC90 throughout the dosing interval[1,2]



Pirtobrutinib concentration in plasma exceeds the BTKi concentration of 90% **(IC90)** throughout the dosing interval at the recommended dose of 200 mg QD.[1,2]

Pirtobrutinib may stabilize/maintain BTK in a closed inactive conformation[4]

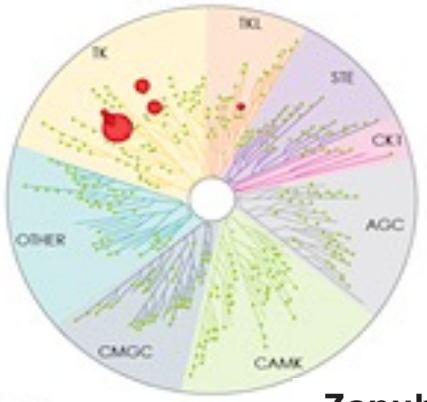


In contrast to cBTKi (A), Pirtobrutinib (B) appears to stabilize BTK in a **closed, inactive conformation**, blocking access to upstream kinases and phosphorylation of Y551, thus inhibiting scaffolding interactions that support kinase-independent BTK signaling.[3,4]

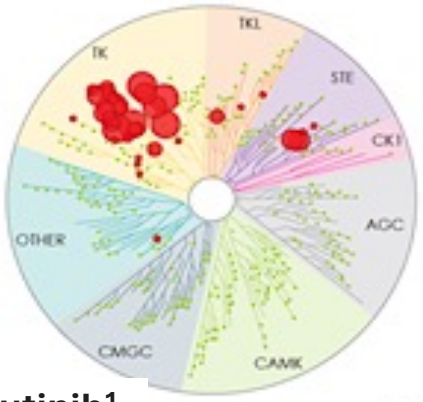
1. Pirtobrutinib. Prescribing Information. Eli Lilly and Company; 12/2025 2. Mato AR, et al. Lancet. 2021;397(10277):892-901. 3. Woyach JA, et al. Poster Presentation ASH 2023. 4. Gomez EB, et al. Blood. 2023;142(1):62-72.

Comparison of Kinome Maps – cBTKi vs. ncBTKi

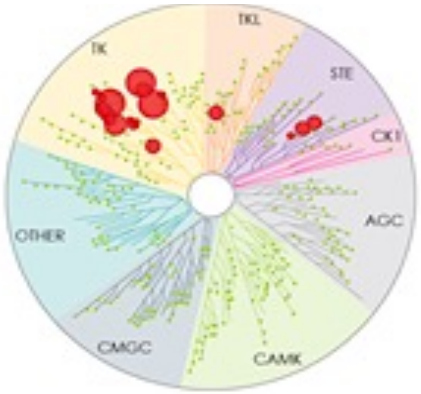
Acalabrutinib[1]

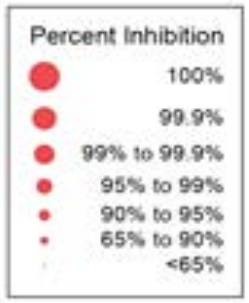


Ibrutinib[1]

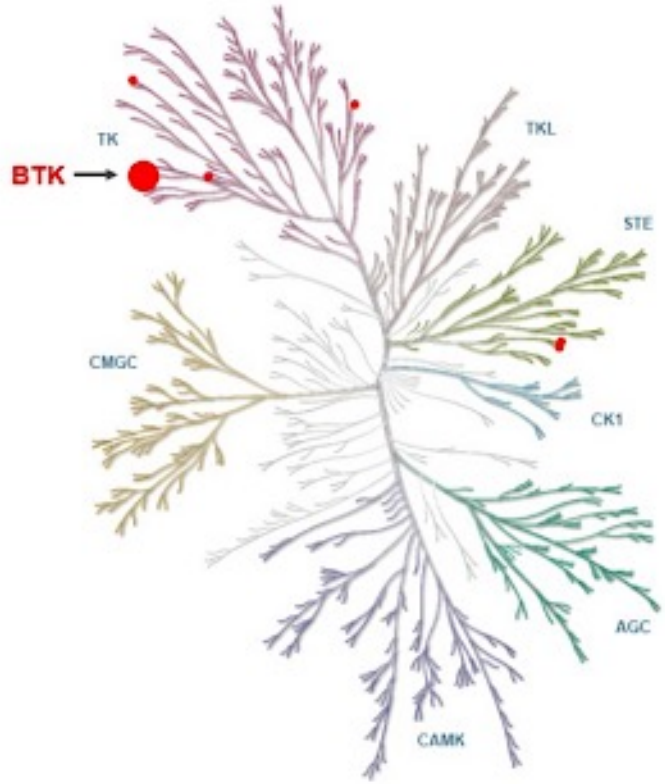


Zanubrutinib[1]





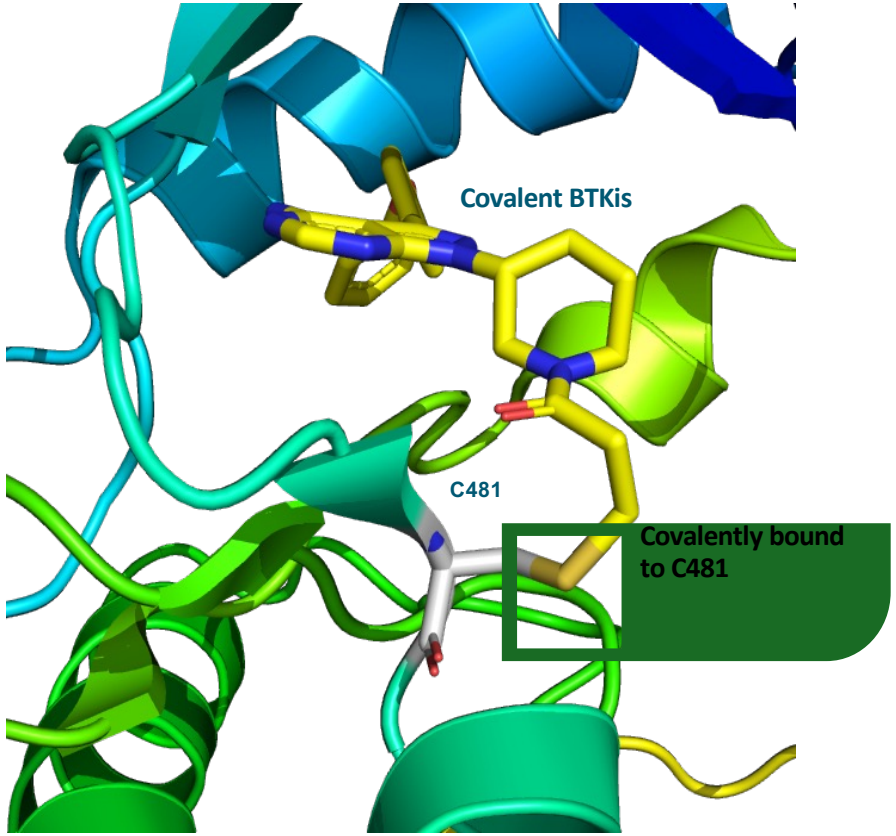
Pirtobrutinib[2]



Kaptein A, et al. *Blood*. 2018;132(Suppl 1):1871. 2, Mato AR, et al. *Lancet*. 2021;397:892-901.

Non-Covalent BTKis overcome C481S resistance

Covalent BTK Inhibitors (Ibrutinib, Acalabrutinib, Zanubrutinib) Require WT *BTK* for Activity



Gu. J Hematol Oncol. 2021;14:40.

BTK Resistance Mutations of clinical significance:

- **C481S – Most common**
  - **C481* - Not always a cysteine to serine, can be other amino acids as well**
  - **Resistance to cBTKi**
- T474I – Gatekeeper mutation
  - Resistance to cBTKi and ncBTKi
- L528W – Kinase dead mutation
  - Resistance to cBTKi and ncBTKi
- PLCG2 – Downstream of BTK

Tam CS et al. Blood. 2025

Phase 1/2 BRUIN Study: CLL Patients

Characteristic	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Median age (range), years	69 (36-88)	69 (36-87)	68 (41-88)
Male, n (%)	192 (68)	106 (69)	86 (67)
Rai staging			
0-II	147 (52)	94 (61)	53 (41)
III-IV	120 (43)	58 (38)	62 (48)
Missing	15 (5)	2 (1)	13 (10)
Bulky lymphadenopathy ≥5 cm, n (%)	88 (31)	42 (27)	46 (36)
ECOG PS, n (%)			
0	144 (51)	89 (58)	55 (43)
1	118 (42)	56 (36)	62 (48)
2	20 (7)	9 (6)	11 (9)
Median number of prior lines of systemic therapy (range)	4 (1-11)	3 (1-9)	5 (1-11)
Prior therapy, n (%)			
BTKi	282 (100)	154 (100)	128 (100)
Anti-CD20 antibody	251 (89)	127 (83)	124 (97)
Chemotherapy	228 (81)	114 (74)	114 (89)
BCL2i	128 (45)	0	128 (100)
PI3K inhibitor	71 (25)	17 (11)	54 (42)
CAR-T	17 (6)	2 (1)	15 (12)
Allogeneic stem cell transplant	7 (3)	1 (1)	6 (5)

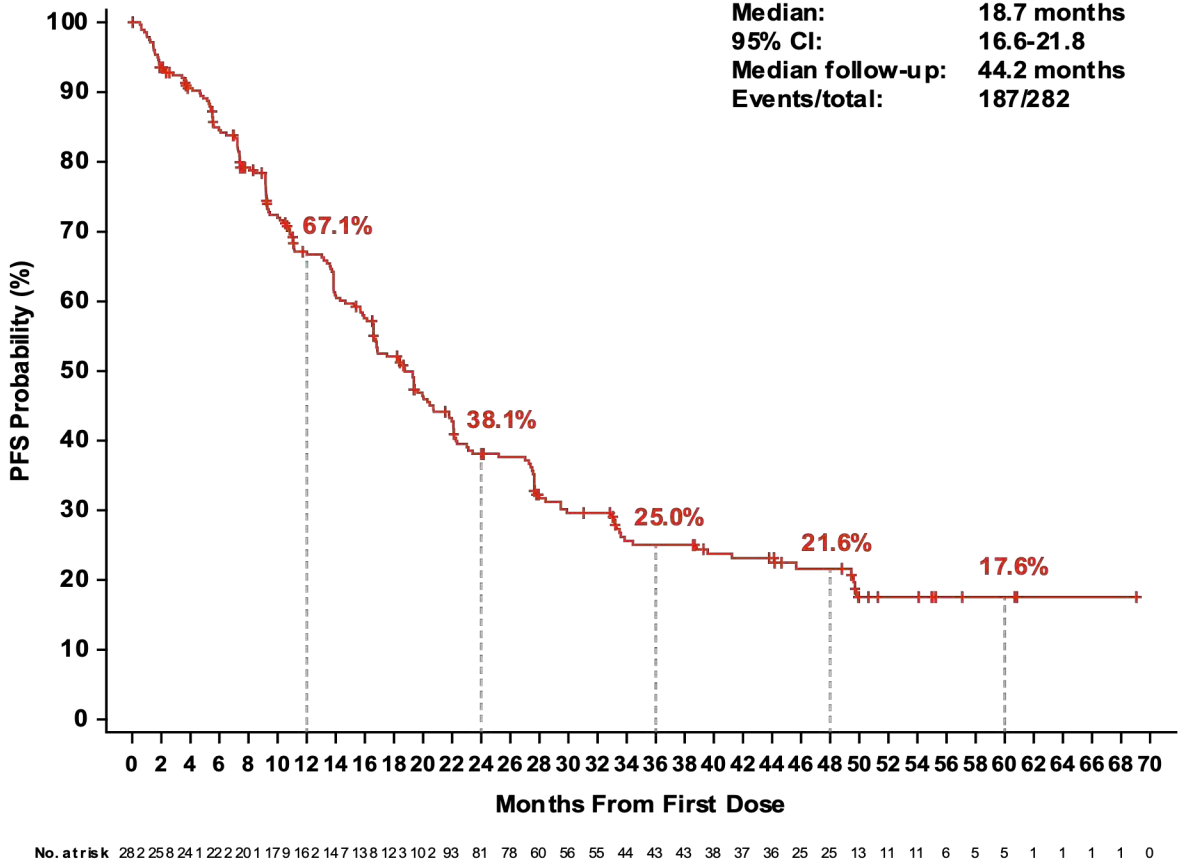
Characteristic	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Median time from diagnosis to first dose (IQR), years	11 (8-15)	11 (7-15)	12 (8-15)
Reason for any prior BTKi discontinuation,[a] n (%)			
Progressive disease	217 (77)	110 (71)	107 (84)
Toxicity/Other	64 (23)	43 (28)	21 (16)

Baseline Molecular Characteristic[b]	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Mutation status, n/N available (%)			
BCL2 mutated	19/246 (8)	0/133 (0)	19/113 (17)
BTK C481 mutated	96/245 (39)	57/138 (41)	39/107 (36)
PLCg2 mutated	18/245 (7)	10/138 (7)	8/107 (8)
High-risk molecular features, n/N available (%)			
17p deletion and/or *TP53* mutation	104/217 (48)	57/123 (46)	47/94 (50)
IGHV unmutated	193/225 (86)	100/125 (80)	93/100 (93)
Complex karyotype	33/73 (45)	17/41 (42)	16/32 (50)
11q deletion	47/202 (23)	28/115 (24)	19/87 (22)

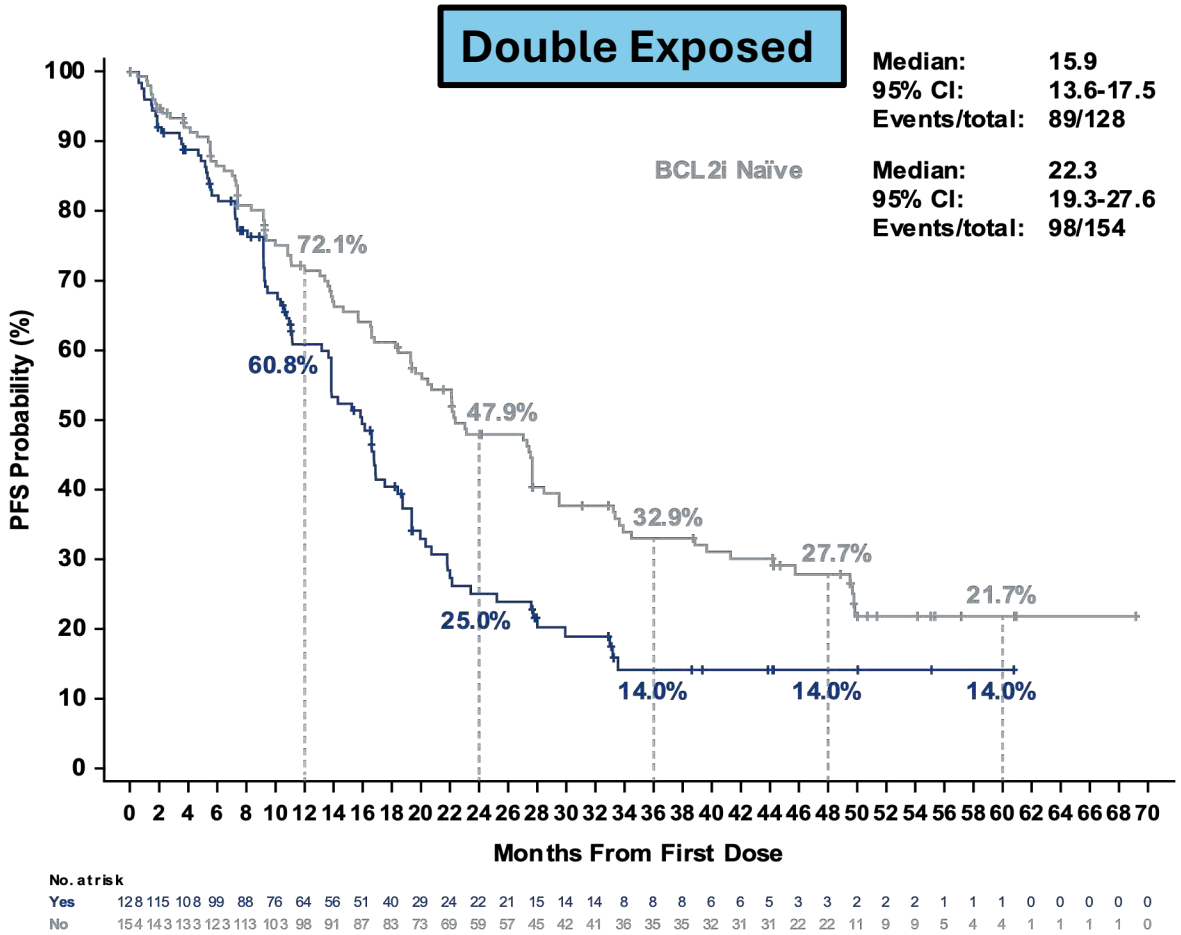
Wierda, et al; ASH 2025

Phase 1/2 BRUIN Study: PFS

Pirtobrutinib PFS in Patients With CLL/SLL Who Received Prior cBTKi

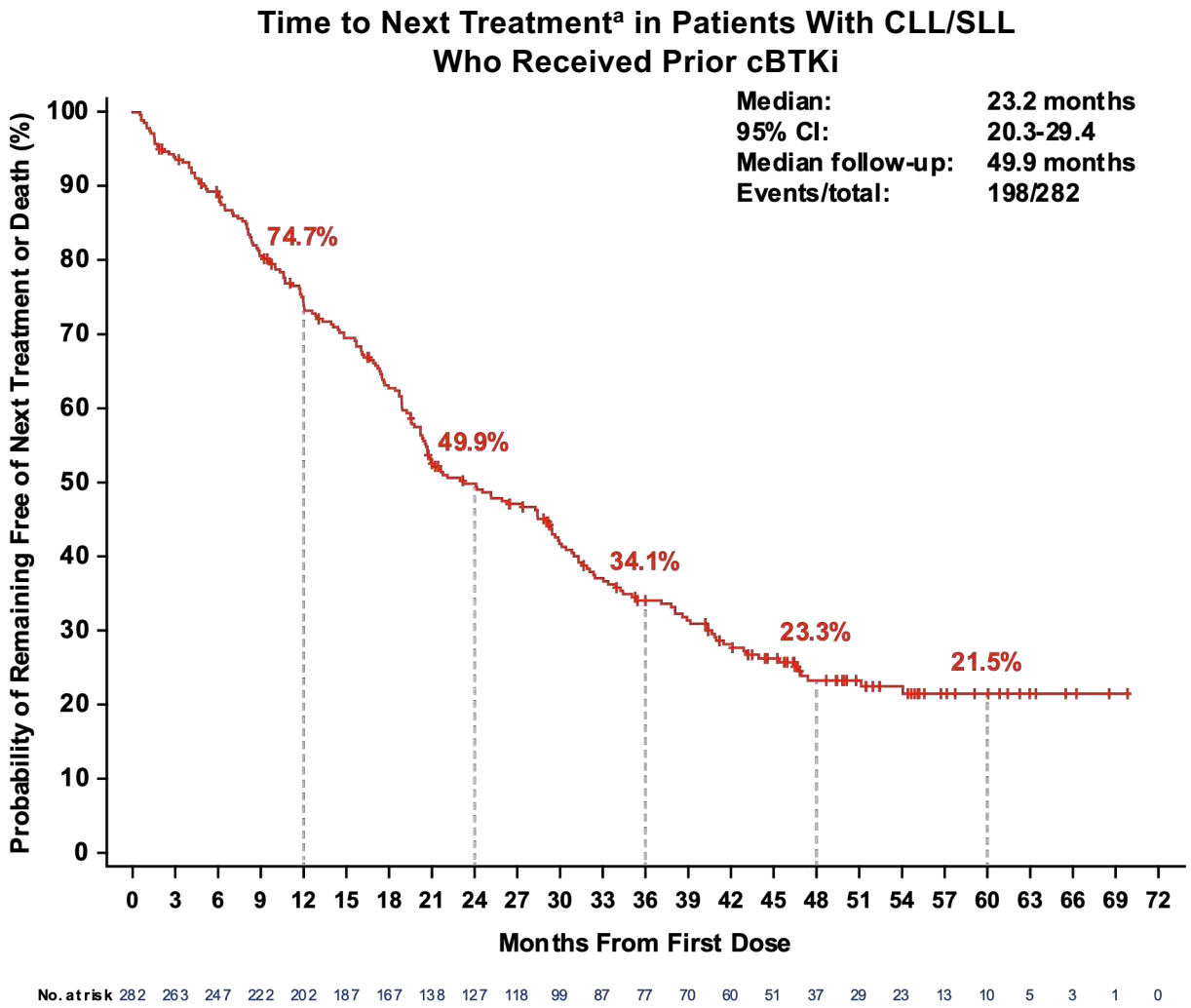


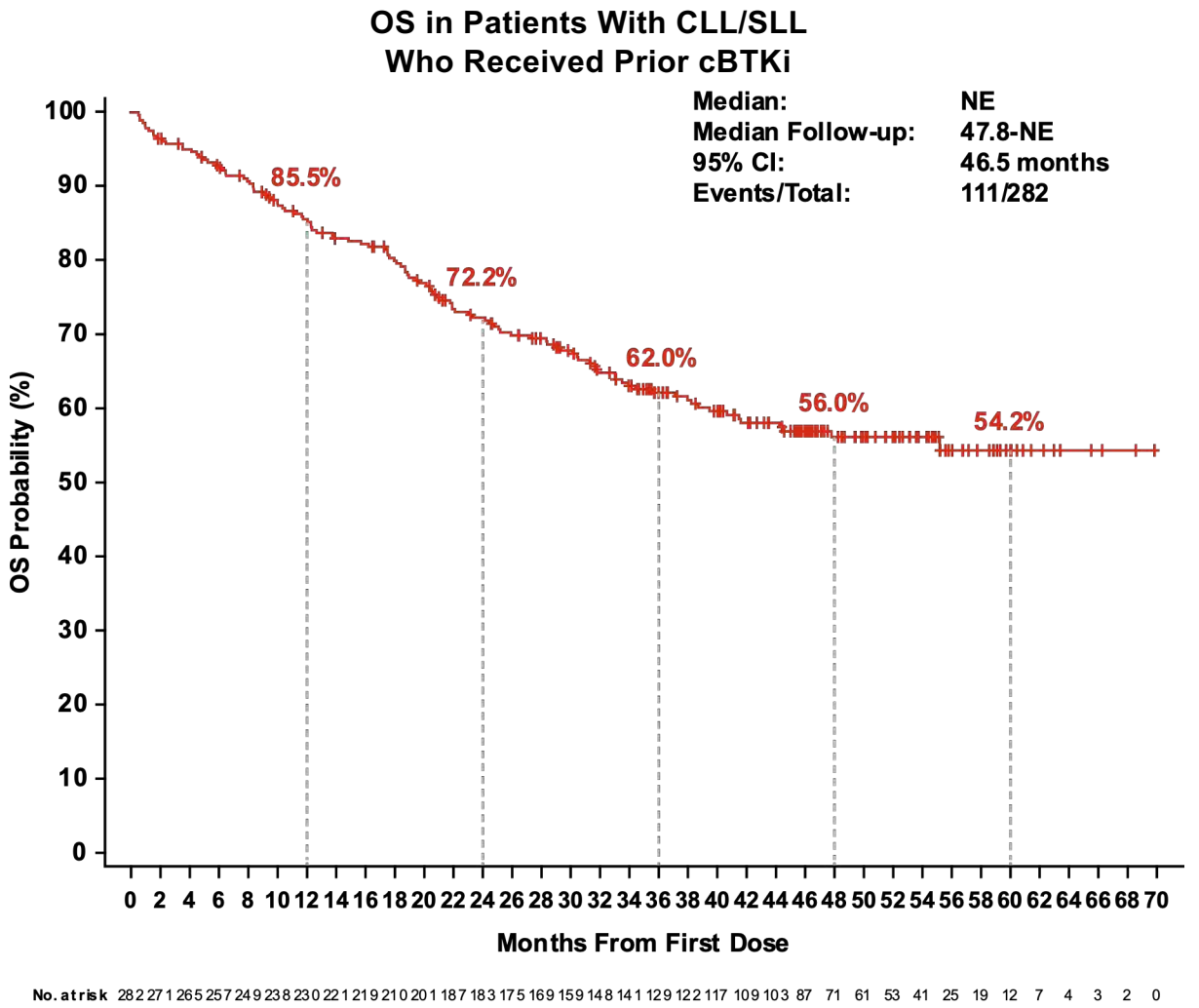
Pirtobrutinib PFS in Patients With CLL/SLL Who Received Prior cBTKi, by BCL2i Exposure



Wierda, et al; ASH 2025

Phase 1/2 BRUIN Study: CLL Patients TTNT + OS





Wierda, et al; ASH 2025

Phase 1/2 BRUIN Study: CLL Patients Safety Profile

AE, ≥20%	TEAEs in Patients With CLL/SLL (n=282)			
	All-Cause AEs		Treatment-Related AEs, %	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Fatigue	38.7	1.8	3.9	0.0
Neutropenia[a,b]	35.8	29.8	20.6	16.3
Diarrhea	30.5	0.4	8.9	0.0
Cough	29.8	0.0	2.1	0.0
Contusion	27.7	0.0	18.8	0.0
COVID-19	28.4	6.0	0.7	0.0
Dyspnea	23.4	2.5	0.7	0.4
Nausea	23.4	0.0	3.9	0.0
Abdominal pain	21.6	2.1	2.1	0.4
AEs of Interest[c]	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Infections[d]	76.2	36.5	14.9	5.7
Bruising[e]	31.2	0.0	20.2	0.0
Rash[f]	25.2	1.1	5.7	0.4
Arthralgia	23.0	1.4	4.6	0.0
Hemorrhage[g]	25.2	3.2	8.2	1.4
Hypertension	16.0	5.3	3.9	0.7
Atrial fibrillation/flutter[h,i]	5.0	2.1	1.4	0.7

Median (IQR) time on treatment was 20.0 (9.6-37.7) months

11 (3.9%) patients had treatment-related AE leading to pirtobrutinib dose reduction

9 (3.2%) patients had treatment-related AE leading to pirtobrutinib discontinuation

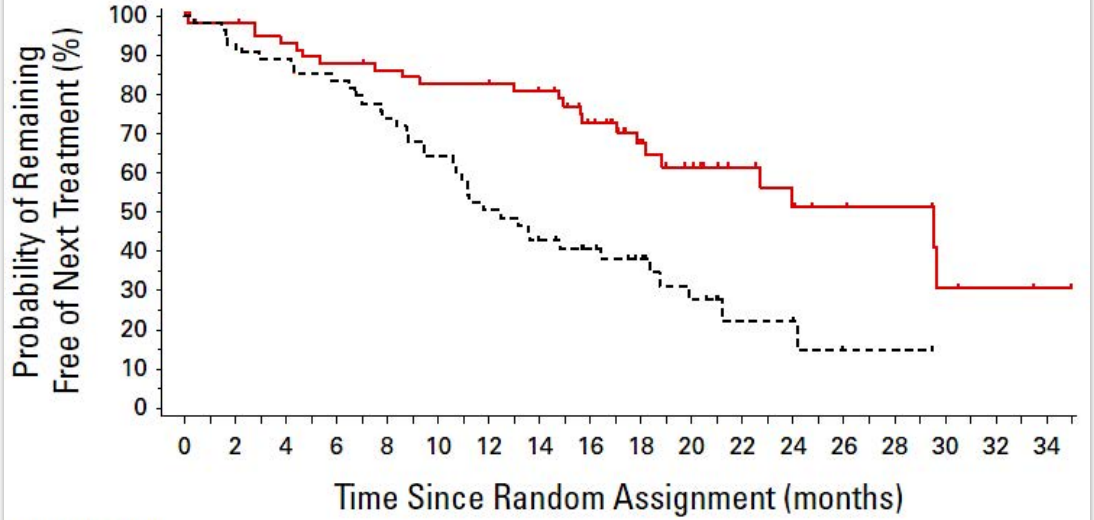
Wierda, et al; ASH 2025

BRUIN CLL-321—Pirto vs IdelaR/BR in BTKi

Prior Venetoclax Exposure Makes an Impact—TTNT

Venetoclax-naive Patients

	No. of Patients	No. of Events	Median, Months (95% CI)	HR (95% CI)	P*
Pirtobrutinib	59	23	29.5 (18.2-NE)	0.36 (0.21-0.61)	.0001
IdelaR/BR	59	37	12.5 (9.5-18.4)		

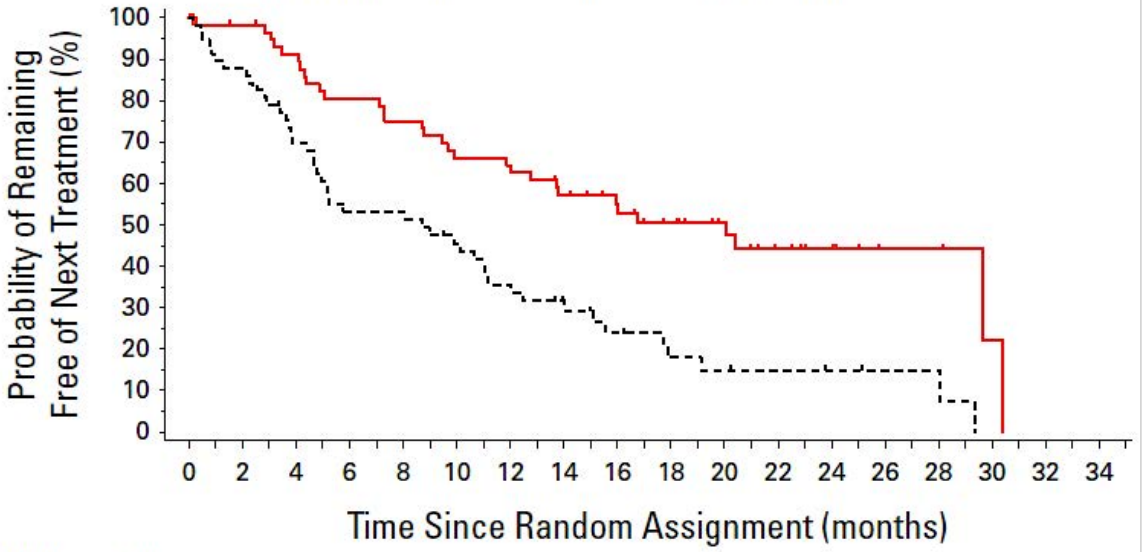


Number at risk:

Pirtobrutinib	59	58	54	51	49	47	46	43	34	24	18	13	10	7	6	3	2	1
IdelaR/BR	59	51	48	44	38	33	26	21	17	13	8	4	4	1	1	0	0	0

Venetoclax-Treated Patients

	No. of Patients	No. of Events	Median, Months (95% CI)	HR (95% CI)	P*
Pirtobrutinib	60	31	20.0 (12.0-NE)	0.37 (0.23-0.60)	< .0001
IdelaR/BR	60	45	8.7 (4.8-11.1)		



Number at risk:

Pirtobrutinib	60	56	51	45	42	37	35	31	26	21	16	10	7	3	3	1	0
IdelaR/BR	60	50	38	28	28	23	18	12	9	6	5	4	3	2	2	0	0

Sharman JP, et al. *J Clin Oncol*. 2025; 43:2538-2549.

Ph I/II BRUIN & Ph III BRUIN CLL-321 (Pooled Analysis)

Safety and efficacy of pirtobrutinib for patients with 2L CLL/SLL previously treated with 1L cBTKi therapy and no prior exposure to a BCL2i, using pooled data from the BRUIN and CLL-321

Study Population

- **37 eligible pts**
  - (BRUIN, n=17; CLL-321, n=20)
- Median age: 69 years (range 42-87)

Baseline Characteristics (evaluable samples)

- IGHV unmutated: 85% (22/26)
- Complex karyotype (≥3 abnmlts): 65% (11/17)
- TP53 mutated: 43% (13/30)
- Del(17p): 48% (15/31)

Key Efficacy Findings

- mF/U: 30.3 months
- **mPFS: 19.5 months (95% CI 11.7-44.7)**
- **mTTNT: 32.5 months (95% CI 16.6-47.4)**
- mOS: Not reached
- 24-month OS rate: 81.1% (95% CI 61.9-91.3)

Adverse Events

- Most Common TEAEs (any grade): Anemia: 27%; Neutropenia/neutrophil count decreased: 24%; Hemorrhage/hematoma: 22%; Pneumonia: 22%
- Grade ≥3 TEAEs: 68%
- TEAEs of Special Interest: Atrial fibrillation/flutter: 1 pt (Grade 3-4); Hypertension: 5 pts total, Grade 3-4: 4 pts; Hemorrhage: 8 pts total; Grade 3: 1 pt, Grade 4: 1 pt

BRUIN CLL-314—Pirto vs Ibr in RR and TN CLL

- Global, multicenter, open-label, randomized Phase III study (N = 662)
- BTKi-naive disease (relapsed/refractory or treatment-naive)
- Primary endpoint: ORR
- Key secondary endpoint: PFS

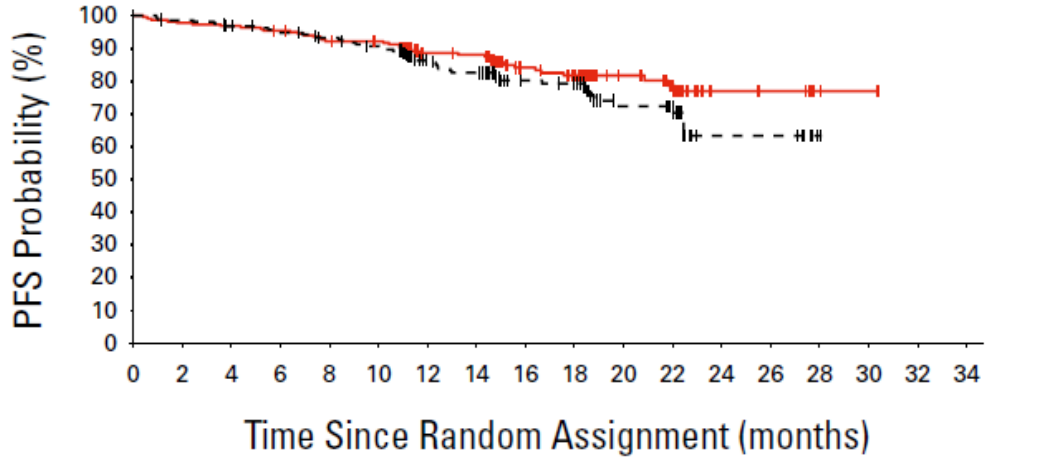
	ITT, n (%)		Relapsed/Refractory, n (%)		Treatment-naive, n (%)	
BOR	**Pirtobrutinib (n = 331)**	**Ibrutinib (n = 331)**	**Pirtobrutinib (n = 219)**	**Ibrutinib (n = 218)**	**Pirtobrutinib (n = 112)**	**Ibrutinib (n = 113)**
ORR (PR or better) ratio	1.1080		1.1233		1.0797	
95% CI	1.034 to 1.187		1.020 to 1.237		0.989 to 1.179	
***P*-value for noninferiority**	<.0001		<.0001		—	

Woyach JA, et al. *J Clin Oncol*. 2025 Dec 7:JCO2502477. doi: 10.1200/JCO-25-02477.

BRUIN CLL-314—PFS

Relapsed/Refractory

	No. of Patients	No. of Events	18-Month PFS Rates (95% CI)	HR (95% CI)	P*
Pirtobrutinib	219	37	81.7 (75.1 to 86.7)	0.729 (0.471 to 1.128)	.1563
Ibrutinib	218	45	79.2 (72.3 to 84.6)		

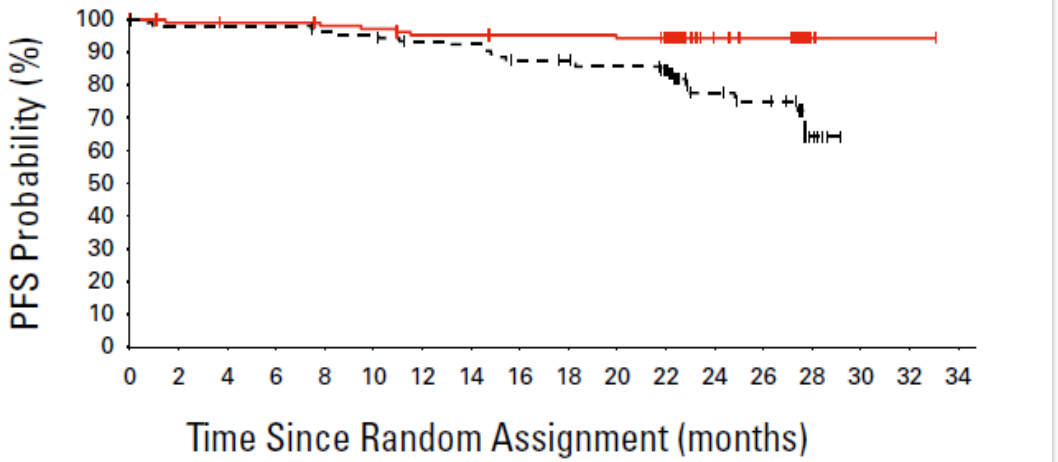


Number at risk
(number censored)

Pirtobrutinib	219 (0)	212 (2)	209 (3)	205 (4)	197 (5)	195 (7)	157 (38)	155 (39)	106 (82)	99 (86)	56 (129)	46 (137)	13 (169)	12 (170)	3 (179)	2 (180)	0 (182)	0 (182)
Ibrutinib	218 (0)	205 (10)	198 (13)	192 (15)	186 (18)	179 (20)	138 (53)	131 (54)	87 (95)	84 (97)	43 (133)	37 (139)	12 (161)	12 (161)	1 (172)	0 (173)	0 (173)	0 (173)

Treatment Naive

	No. of Patients	No. of Events	18-Month PFS Rates (95% CI)	HR (95% CI)	P*
Pirtobrutinib	112	6	95.3 (89.1 to 98.0)	0.239 (0.098 to 0.586)	.0007
Ibrutinib	113	24	87.6 (79.7 to 92.6)		



Number at risk
(number censored)

Pirtobrutinib	112 (0)	107 (4)	106 (5)	106 (5)	104 (6)	103 (6)	100 (7)	100 (7)	99 (8)	99 (8)	98 (8)	94 (12)	35 (71)	33 (73)	4 (102)	1 (105)	1 (105)	0 (106)
Ibrutinib	113 (0)	105 (6)	105 (6)	105 (6)	102 (7)	101 (7)	97 (9)	96 (9)	90 (10)	89 (11)	86 (12)	81 (16)	32 (61)	29 (63)	5 (84)	0 (89)	0 (89)	0 (89)

Woyach JA, et al. *J Clin Oncol*. 2025 Dec 7.

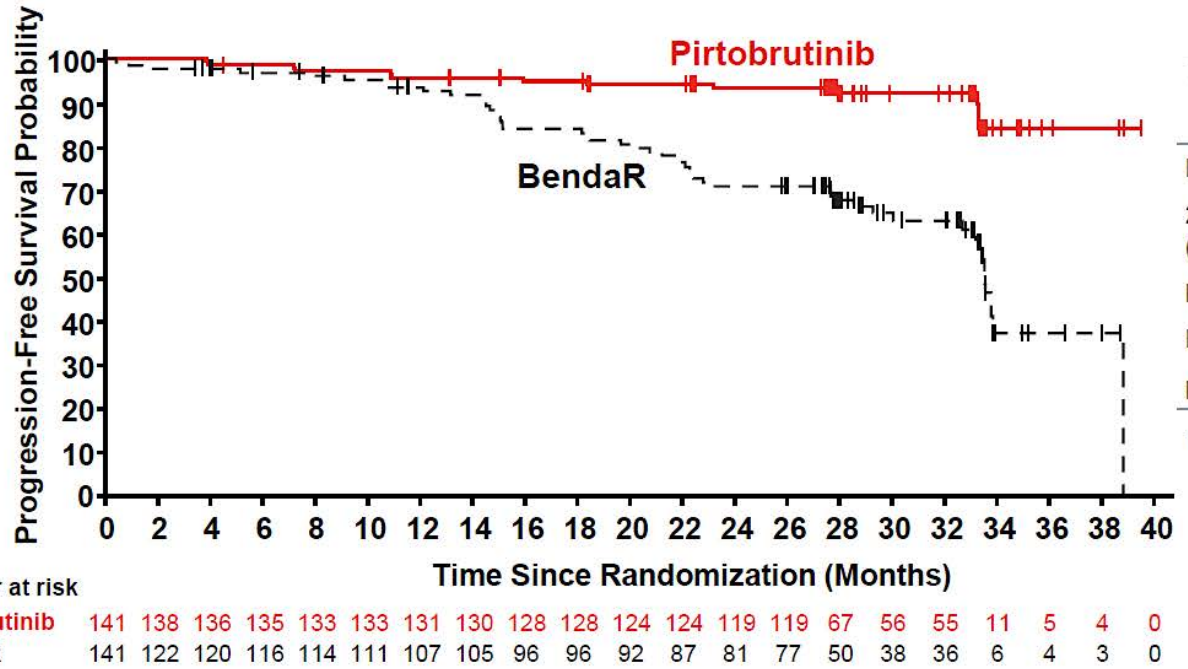
BRUIN CLL-314 — Safety

	Pirtobrutinib (n = 330)		Ibrutinib (n = 325)	
AE, n (%)	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Any TEAE	320 (97.0)	181 (54.8)	318 (97.8)	174 (53.5)
AE of Interest				
Anemia	51 (15.5)	20 (6.1)	51 (15.7)	12 (3.7)
Atrial fibrillation and atrial flutter	8 (2.4)	3 (0.9)	44 (13.5)	13 (4.0)
Bleeding	115 (34.8)	11 (3.3)	118 (36.3)	9 (2.8)
Hypertension	35 (10.6)	11 (3.3)	49 (15.1)	16 (4.9)
Infections	226 (68.5)	56 (17.0)	241 (74.2)	54 (16.6)
Neutropenia	103 (31.2)	83 (25.3)	76 (23.4)	57 (17.5)
Thrombocytopenia	39 (11.8)	12 (3.6)	57 (17.5)	13 (4.0)

Woyach JA, et al. *J Clin Oncol*. 2025 Dec 7. [Epub ahead of print]

BRUIN CLL-313: Pirto vs BR in TN CLL/SLL

Primary Endpoint: Progression-Free Survival



	Pirtobrutinib (n=141)	BendaR (n=141)
Number of events, n (%)	13 (9.2)	48 (34.0)
24-month PFS rate, (95% CI)	**93.4** (87.6, 96.5)	**70.7** (61.5, 78.1)
Median follow-up, months	28.1	28.3
Hazard ratio (95% CI)	**0.20 (0.11, 0.37)**	
p-value[a]	<0.0001[a]	

The PFS results presented are IRC assessed

Pirtobrutinib demonstrated a statistically significant and clinically meaningful PFS improvement, with an 80% reduction in risk of PD or death compared with BendaR

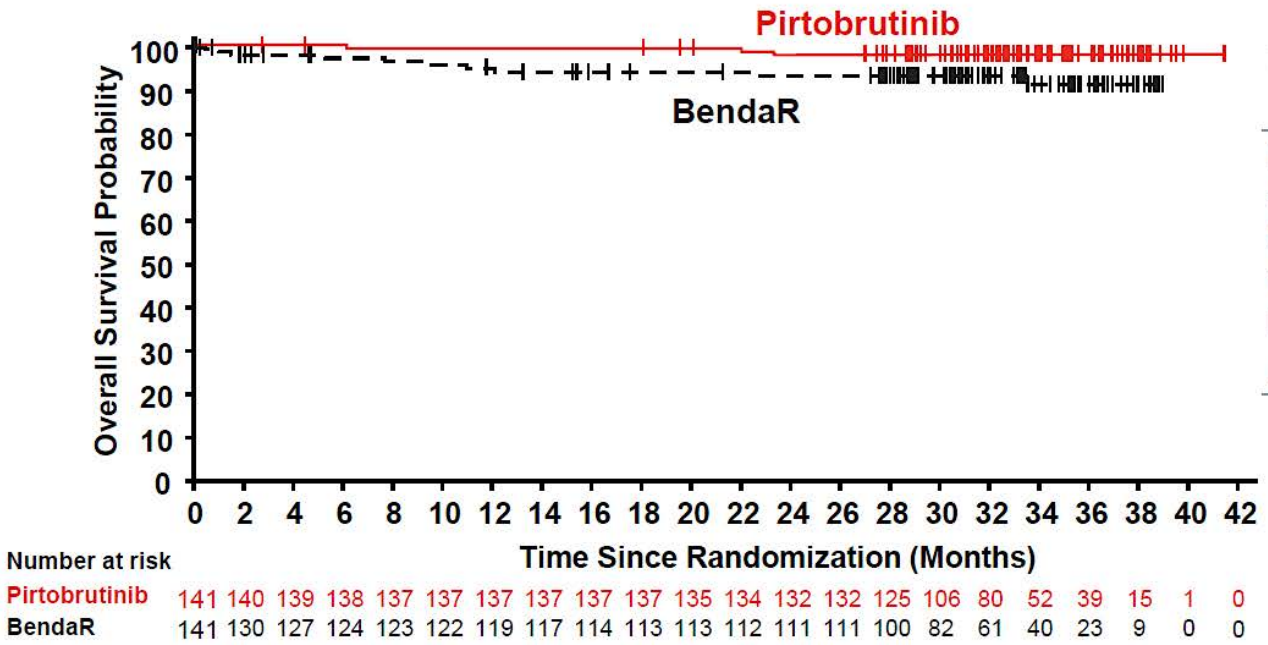
[a]Stratified log-rank 2-sided p-value.

Abbreviations: BendaR, bendamustine plus rituximab; CI, confidence interval; IRC, independent review committee; PD, progressive disease; PFS, progression-free survival.

Jurczak W et al. ASH 2025; LBA3

BRUIN CLL-313: Pirto vs BR in TN CLL/SLL

Overall Survival



	Pirtobrutinib n=141	BendaR n=141
Number of events, n (%)	3 (2.1)	10 (7.1)
24-month OS rate, (95% CI)	**97.8** (93.3, 99.3)	**93.0** (87.0, 96.3)
Median follow-up, months	32.7	31.7
Hazard ratio (95% CI)	**0.26 (0.07, 0.93)**	
p-value	0.0261[a]	

Effective crossover rate[b]:

52.9% (18/34)

OS data were immature, but trended in favor of pirtobrutinib, despite a high effective crossover rate

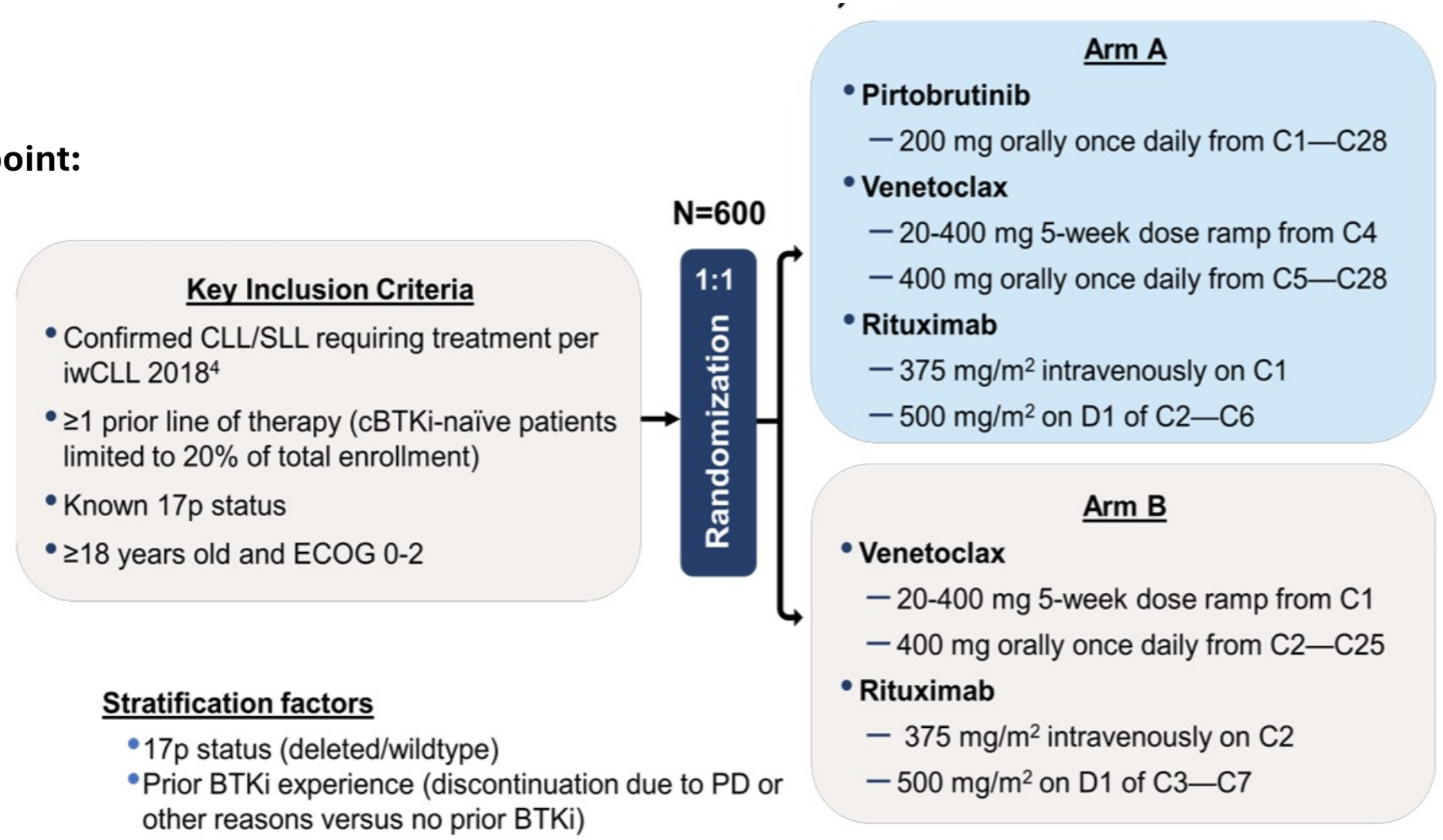
[a]Stratified log-rank 2-sided p-value; the 2-sided alpha level was 0.000001 at this interim OS analysis. [b]Uses the number of patients with investigator-assessed PD as the denominator; eligible patients receiving BendaR could crossover to receive pirtobrutinib monotherapy upon confirmation of PD by IRC per protocol.

Abbreviations: BendaR, bendamustine plus rituximab; CI, confidence interval; IRC, independent review committee; OS, overall survival; PD, progressive disease.

Jurczak W et al. ASH 2025; LBA3

BRUIN CLL-322: An Ongoing Phase III Trial

Primary Endpoint:
PFS by IRC



Eyre TAA et al. ASCO 2023; Leow CC et al. iwCLL 2023

Pirtobrutinib added to venetoclax time-limited regimen significantly increased progression-free survival in patients with previously treated CLL/SLL

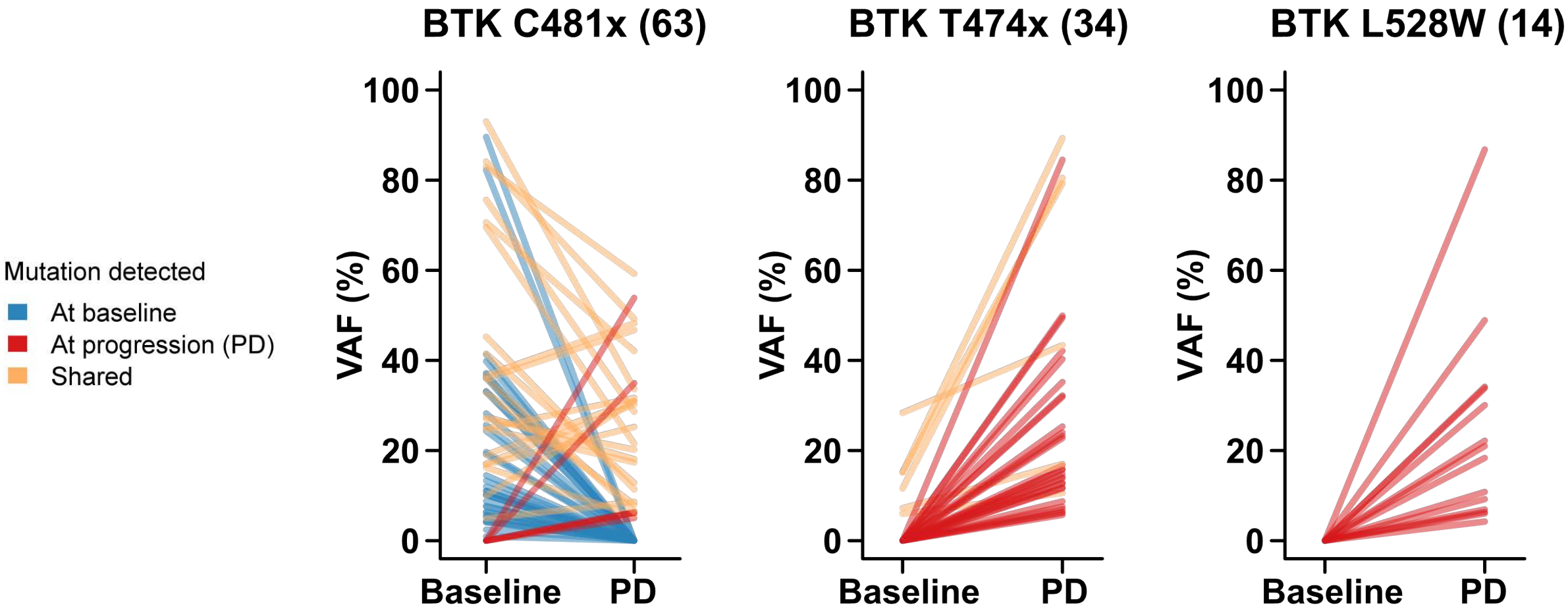
On April 13, 2026, positive topline results were announced from the Phase 3 BRUIN CLL-322 trial of pirtobrutinib plus venetoclax and rituximab versus venetoclax and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL).

“Treatment in both study arms was administered for up to two years, after which patients do not take any CLL therapy until their disease progresses. The study met its primary endpoint, demonstrating that the addition of pirtobrutinib to venetoclax plus rituximab led to a statistically significant and clinically meaningful improvement in progression-free survival (PFS), as assessed by an independent review committee (IRC). Results were consistent across clinically relevant subgroups and regardless of whether patients were previously treated with a covalent BTK inhibitor.

Overall survival (OS), a key secondary endpoint, was not yet mature at this analysis, but was trending in favor of the pirtobrutinib combination regimen. The overall safety profile of this regimen was consistent with the known safety profile of each medicine. Rates of adverse events were similar across the study arms, with low rates of treatment regimen discontinuations, also similar between arms.”

https://investor.lilly.com/news-releases/news-release-details/lillys-jaypirca-pirtobrutinib-significantly-extended-progression

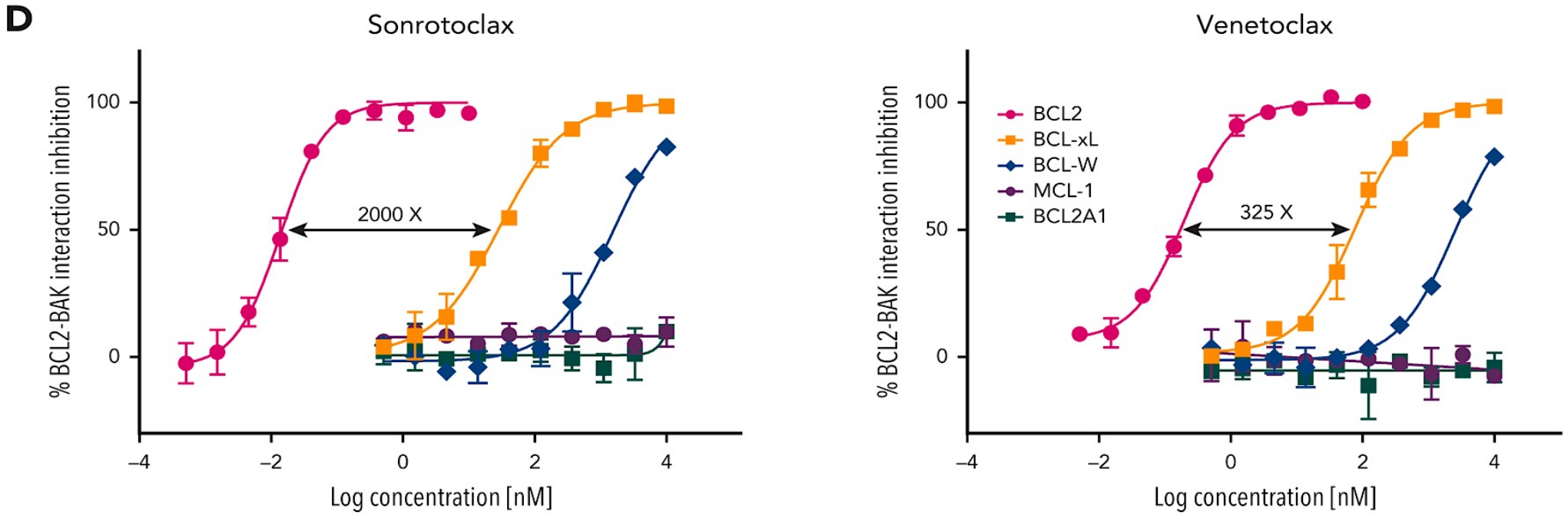
Pirtobrutinib leads to non-C481S mutations



Brown et al ASH 2023

Emerging Therapies – Sonrotoclax + Degraders

Next Generation BCL2i - Sonrotoclax



IC_{50} of sonrotoclax and venetoclax for different Bcl-2 members

Protein	BCL2	BCL-xL	BCL-W	MCL1	BCL2A1
IC_{50} (nM) of sonrotoclax	0.014 ± 0.0021	28 ± 3.6	1803 ± 83	>10000	>10000
IC_{50} (nM) of venetoclax	0.20 ± 0.015	65 ± 9.1	2730 ± 250	>10000	>10000

Liu et al Blood 2024

Sonrotoclax + Zanu TN CLL

- N = 137
- 60% IGHV unmutated
- 22% TP53 aberration
- 78% stopped therapy per protocol after 24 cycles
- Most common TEAE – Neutropenia 42%, 27% Grade ≥3
- ORR 100% - CR 47%
- Median time to response – 2.6 months
- uMRD4 – 94%

Sonrotoclax + Obin TN CLL

- N = 55
- 58% IGHV unmutated
- 17 patients stopped due to uMRD4
- Median follow-up was 8.9 months
- Most common TEAE – Thrombocytopenia (56%) then infusion reaction (56%) then neutropenia (49%), 38% Grade ≥3 neutropenia
- ORR was 89 – CR 46%
- Best uMRD4 rate per was 87%

Hoffman et al ASH 2025 Abstract 793, Soumerai et al ASH 2024 Abstract 1012

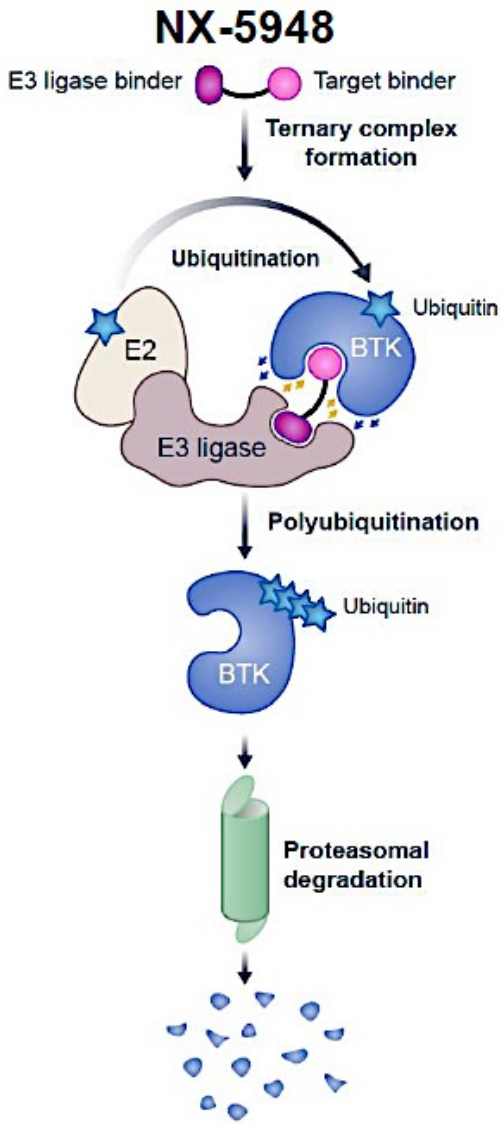
2 Randomized Studies – Celestial

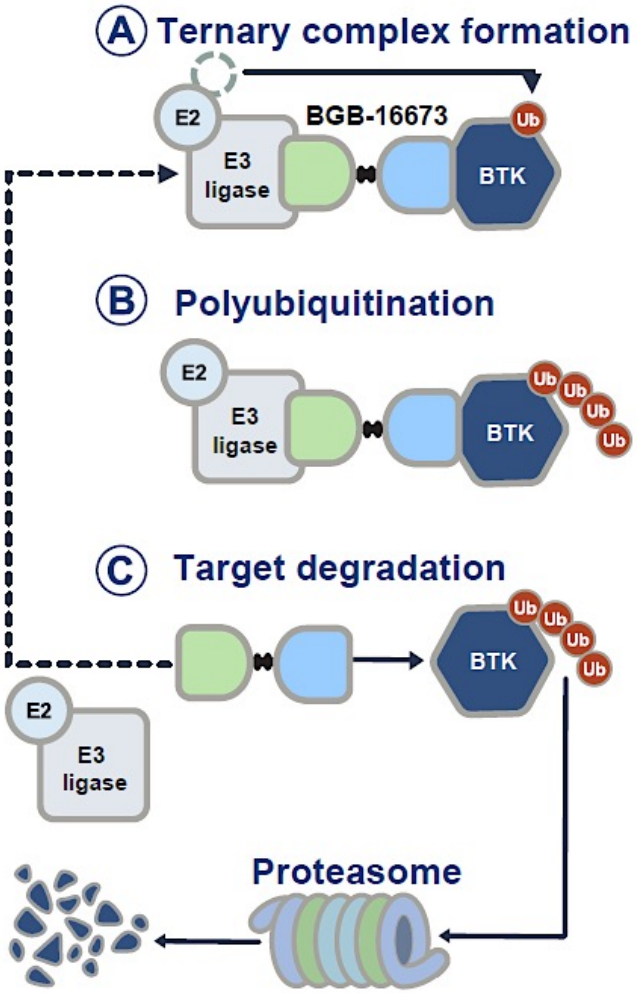
CELESTIAL-TNCLL: An Ongoing, Open-Label, Multiregional, Phase 3 Study of Sonrotoclax (BGB-11417) + Zanubrutinib vs Venetoclax + Obinutuzumab for Treatment-Naive CLL

A phase 3, randomized, open-label, multicenter study of sonrotoclax (BGB-11417) plus anti-CD20 antibody therapies vs venetoclax plus rituximab in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL-RR1/CELESTIAL-RRCLL)

Al-Sawaf O et al. ASH 2025; Patten PEM et al. ASH 2024

BTK degraders: NX-5948 & BGB-16673





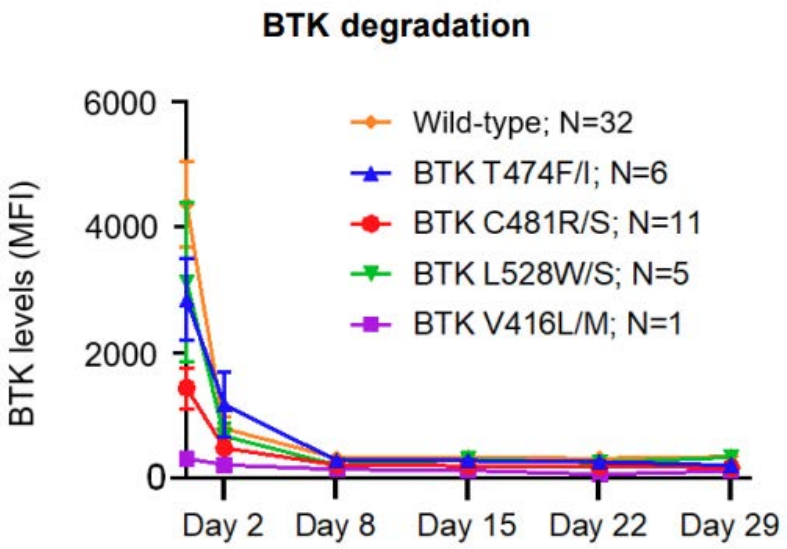
Shah N, et al. ASH 2024. Oral 884. 2. El-Sharkwai D, et al. BSH ASM. 2024. 3. Thompson MC, et al. ASH 2024.Oral 885.

NX-5948

CLL response-evaluable patients	Primary ORR analysis[b] ≥1 response assessment(s) at 8 weeks (n=49)[c]	Exploratory ORR analysis[b] ≥2 response assessments at 16 weeks (n=38)[c]
Objective response rate (ORR),[a] % (95% CI)	75.5 (61.1–86.7)	84.2 (68.7–94.0)
Best response, n (%)		
CR	0 (0.0)	0 (0.0)
PR	36 (73.5)	32 (84.2)
PR-L	1 (2.0)	0 (0.0)
SD	10 (20.4)	4 (10.5)
PD	2 (4.1)	2 (5.3)

	Patients with CLL/SLL (n=57)[c]
Baseline mutation status, n (%)	
BTK mutations[1,a,b]	22 (38.6)
C481S	12 (21.1)
C481R	2 (3.5)
L528W	4 (7.0)
L528S	1 (1.8)
T474I	5 (8.8)
T474F	1 (1.8)
V416M	1 (1.8)
V416L	1 (1.8)
G541V	1 (1.8)

[a]Patients could have multiple prior treatments and BTK mutations; BTK mutations were tested at baseline by next-generation sequencing centrally. ≥5% allelic frequency is reported
[b]Patients can have more than one resistance mutation
[c]Patients with available mutation status



Note: Some patients have multiple BTK mutations

Shah N, et al. ASH 2024. Oral 884.

BGB-16673

	50 mg (n=1)	100 mg (n=22)	200 mg (n=16)	350 mg (n=15)	500 mg (n=12)	Total (N=66)
Best overall response, n (%)						
CR/CRi	0	1 (4.5)	1 (6.3)	0	1 (8.3)	**3 (4.5)**
PR[a]	1 (100)	11 (50.0)	12 (75.0)	11 (73.3)	9 (75.0)	44 (66.7)
PR-L	0	6 (27.3)	2 (12.5)	0	1 (8.3)	9 (13.6)
SD	0	4 (18.2)	0	0	1 (8.3)	5 (7.6)
PD	0	0	1 (6.3)	1 (6.7)	0	2 (3.0)
Discontinued prior to first assessment	0	0	0	3 (20.0)	0	3 (4.5)
Overall response rate, n (%)[b]	1 (100)	18 (81.8)	**15 (93.8)**	11 (73.3)	11 (91.7)	**56 (84.8)**
Time to first response, median (range), months[c]	2.9 (2.9-2.9)	2.8 (2.0-6.2)	2.9 (2.6-8.3)	2.8 (2.6-19.4)	2.8 (2.6-13.8)	2.8 (2.0-19.4)
Time to best response, median (range), months	2.9 (2.9-2.9)	2.8 (2.0-11.1)	3.4 (2.6-13.8)	5.6 (2.6-19.4)	8.3 (2.7-13.8)	3.4 (2.0-19.4)
Duration of exposure, median (range), months	29.6 (29.6-9.6)	7.1 (3.7-23.7)	16.2 (2.9-24.6)	15.6 (0.2-22.8)	15.3 (6.8-21.4)	12.9 (0.2-29.6)

Subgroup	ORR, n/N with known status (%)
Double exposure (previously received cBTKi + BCL2i)	38/42 (90.5)
Triple exposure (previously received cBTKi + ncBTKi + BCL2i)	9/12 (75.0)
del(17p) and/or *TP53* mutation	35/43 (81.4)
Complex karyotype (≥3 abnormalities)	16/22 (72.7)
***BTK* mutations**	18/24 (75.0)
***PLCG2* mutations**	9/10 (90.0)

Scarfò, L, et al. EHA 2025. S158.

QUESTIONS?

Module 2: Pancreatic Cancer

Optimal Incorporation of Chemotherapy into the Management of Advanced Pancreatic Cancer — Dr Philip

Other Available and Emerging Novel Approaches for Pancreatic Cancer — Dr O'Reilly

Faculty

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Module 2: Pancreatic Cancer

Optimal Incorporation of Chemotherapy into the Management of Advanced Pancreatic Cancer — Dr Philip

Other Available and Emerging Novel Approaches for Pancreatic Cancer — Dr O'Reilly

Module 2: Pancreatic Cancer

We would like to do a “best paper or presentation of the year” activity. Please suggest one “paper of the year” and 2 other worthy papers based on the value in treatment of current and future patients.

Pancreatic Cancer

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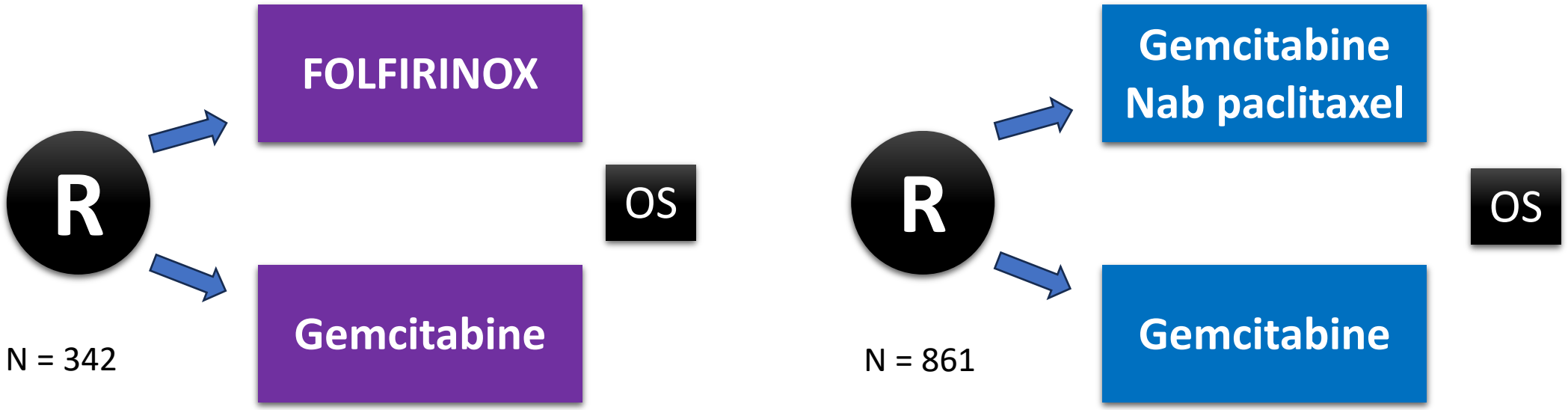
Disclosures

Advisory Committees	Corcept Therapeutics Inc, Ipsen Biopharmaceuticals Inc, Jazz Pharmaceuticals Inc, Novocure Inc, Revolution Medicines Inc
Consulting Agreements	Novocure Inc
Contracted Research	Bristol Myers Squibb, Novartis, Revolution Medicines Inc, Taiho Oncology Inc
Data and Safety Monitoring Boards/Committees	J-Pharma Co Ltd, Oncolytics Biotech Inc

Clinical and biologic factors affecting choice of up-front and later-line therapy in metastatic PDAC

- Performance status
- Age
- Organ function
  - Liver
  - Neuropathy
- Genetics (germline)
  - BRCA/PALB2
  - DYPD
  - UGT1A1
- Genomics (somatic)
  - KRAS, NRG-1, MSI, NTRK,
- Clinical trial availability
- Patient preference!

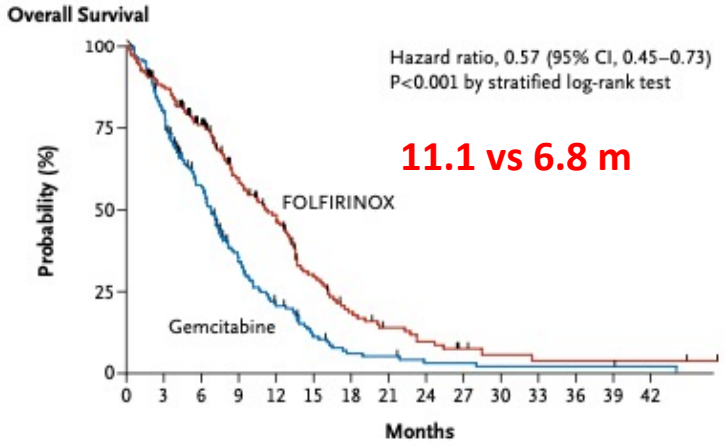
Phase 3 trials establishing FOLFIRINOX and gemcitabine nab-paclitaxel as standards of care in frontline metastatic PDAC

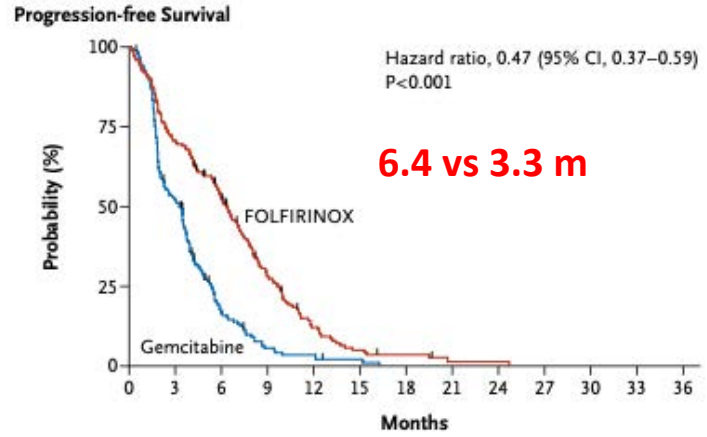


Conroy et al, NEJM, 2011; Von Hoff et al, NEJM, 2013

Data establishing efficacy and safety of FOLFIRINOX and gemcitabine/nab paclitaxel for untreated advanced PADC

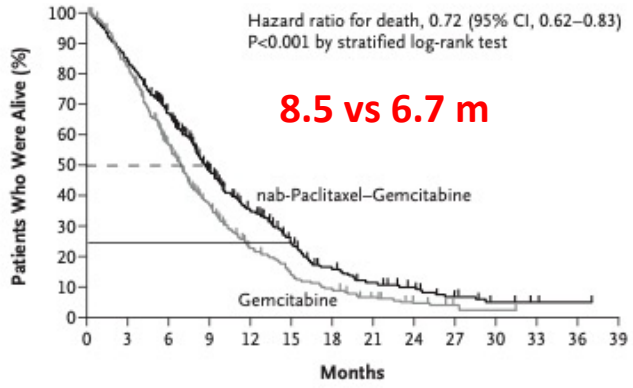
FOLFIRINOX

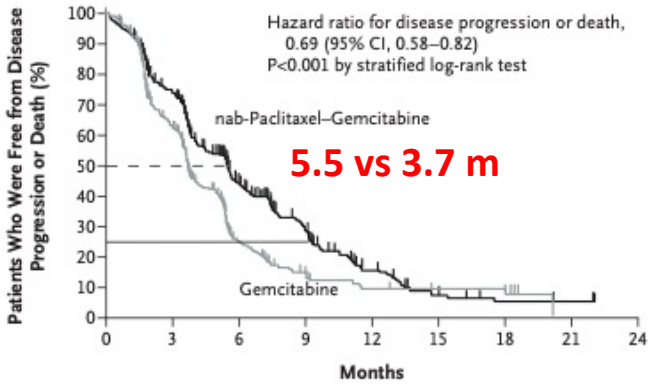




Conroy et al, NEJM, 2011;

Gem-Nab paclitaxel



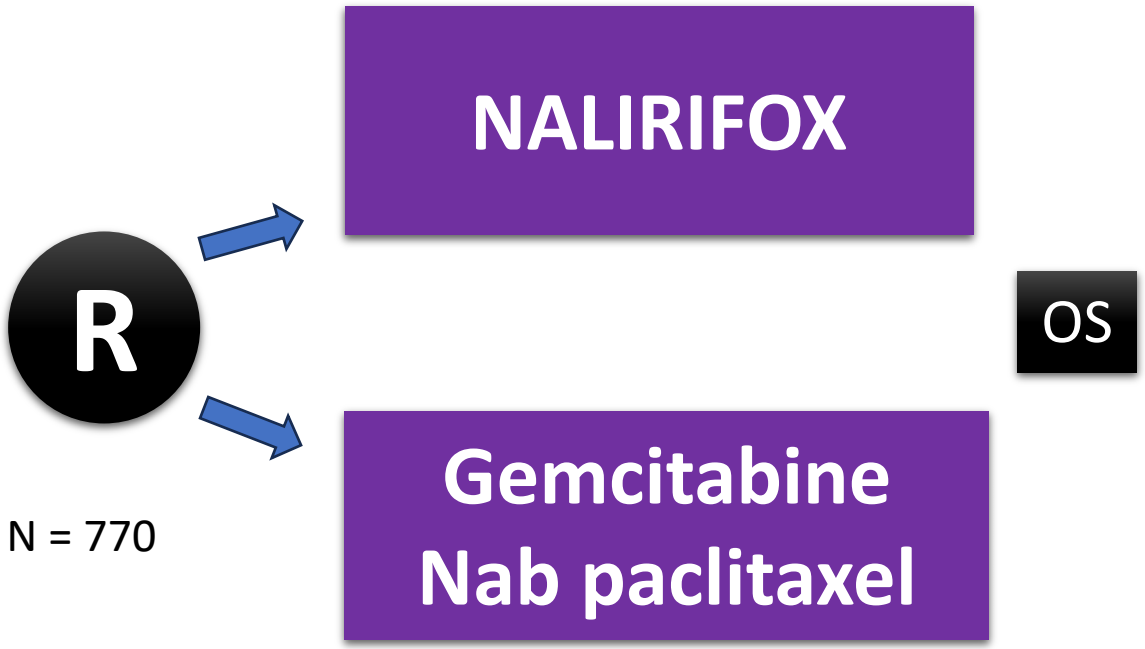


Von Hoff et al, NEJM, 2013

Grade 3 or 4 toxicities %

	FFX	GemNab
Neutrop	45.7	38.0
FN	5.4	3.0
Thromb	9.1	13.0
Diarrhea	12.7	6.0
Neuropa	9.0	17.0
Fatigue	23.6	17.0

NAPOLI-3: randomised phase 3 trial of NALIRIFOX versus nab-paclitaxel/gemcitabine in treatment-naive pts with metastatic PDAC

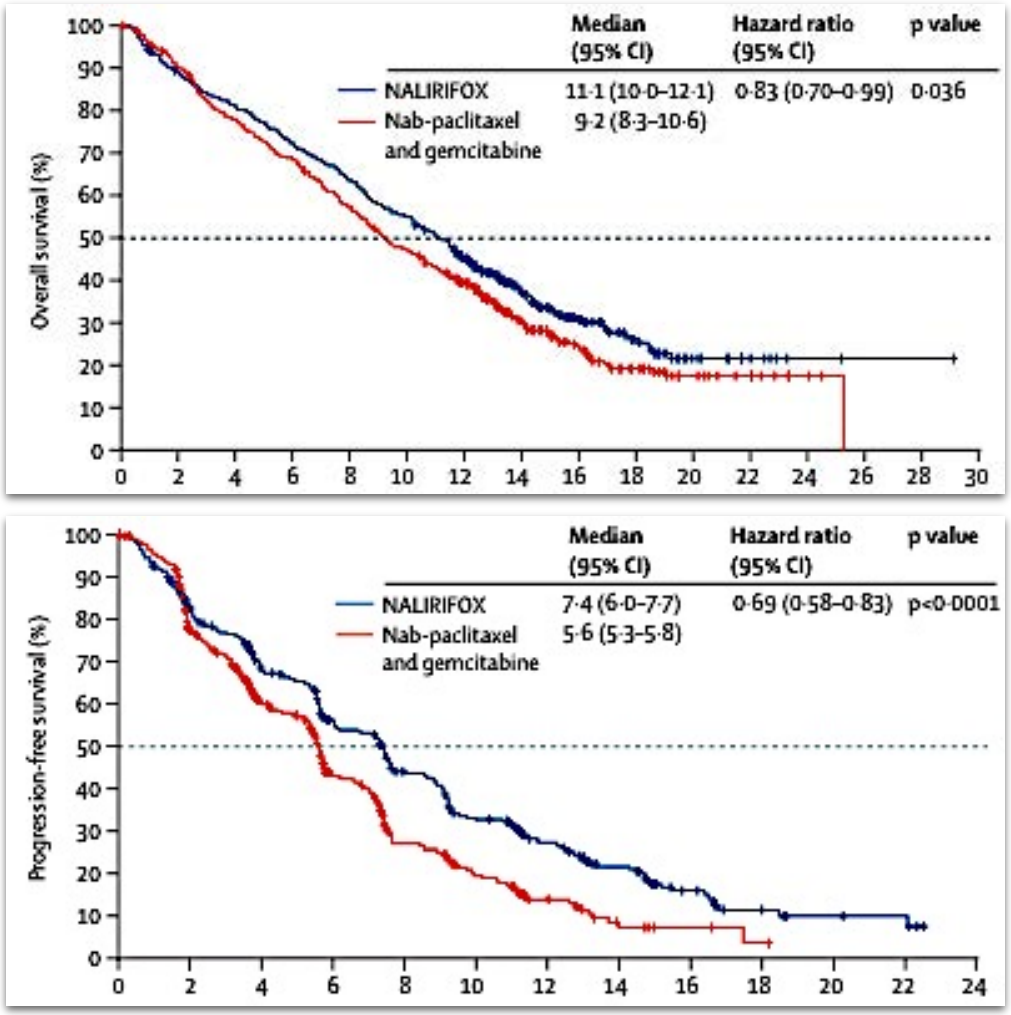


NALIRIFOX dosing compared to FOLFIRINOX mg/m^2

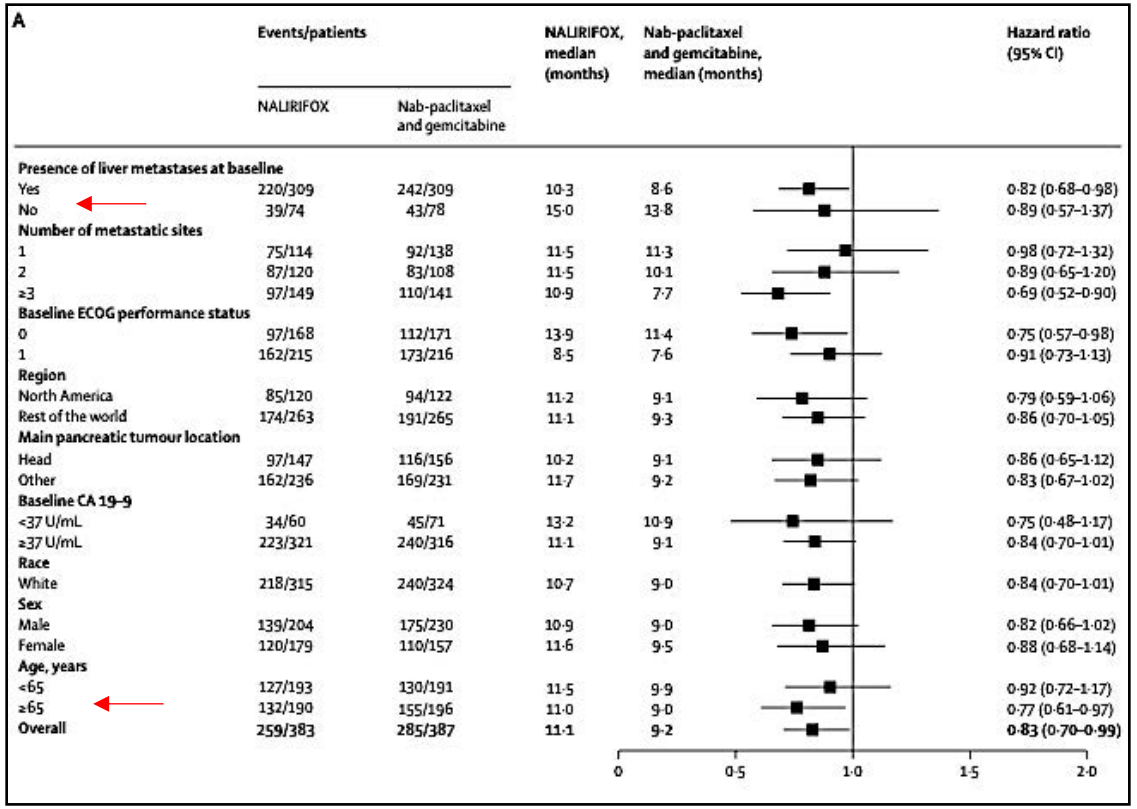
	FOLFIRINOX	NALIRIFOX
5-FU	2,400	2,400
LCV	400	400
IVB 5-FU	400 (0)	0
Oxaliplatin	85	60
irinotecan	180 (150)	50

Wainberg et al, Lancet, 2023

NAPOLI-3: Efficacy



Overall Survival

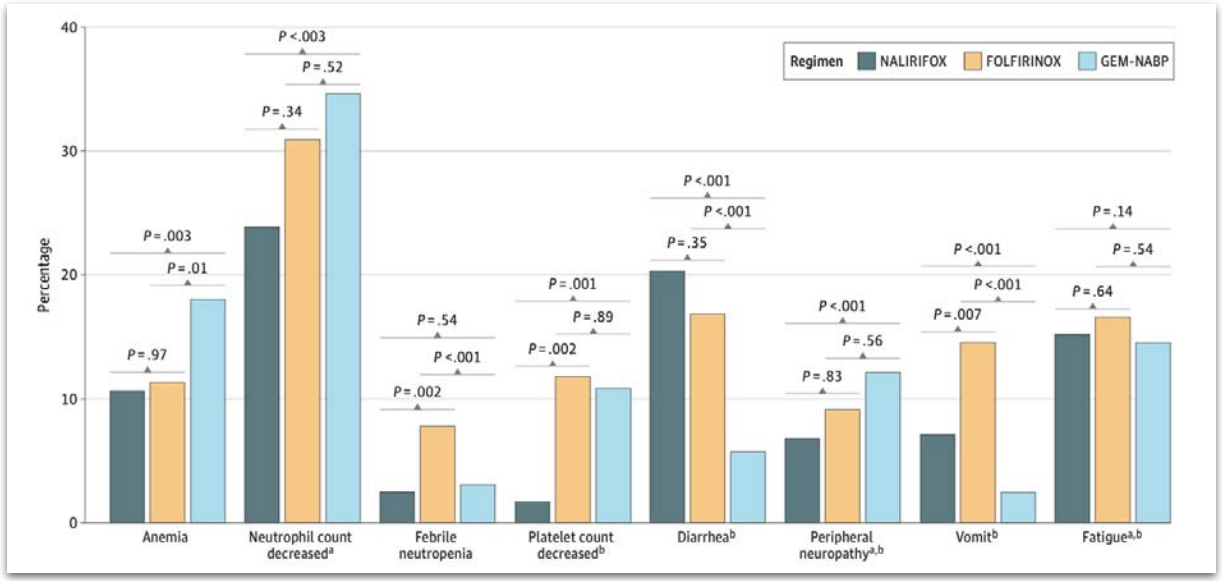


A	Events/patients		NALIRIFOX, median (months)	Nab-paclitaxel and gemcitabine, median (months)	Hazard ratio (95% CI)
	NALIRIFOX	Nab-paclitaxel and gemcitabine			
Presence of liver metastases at baseline					
Yes	220/309	242/309	10·3	8·6	0·82 (0·68–0·98)
No	39/74	43/78	15·0	13·8	0·89 (0·57–1·37)
Number of metastatic sites					
1	75/114	92/138	11·5	11·3	0·98 (0·72–1·32)
2	87/120	83/108	11·5	10·1	0·89 (0·65–1·20)
≥3	97/149	110/141	10·9	7·7	0·69 (0·52–0·90)
Baseline ECOG performance status					
0	97/168	112/171	13·9	11·4	0·75 (0·57–0·98)
1	162/215	173/216	8·5	7·6	0·91 (0·73–1·13)
Region					
North America	85/120	94/122	11·2	9·1	0·79 (0·59–1·06)
Rest of the world	174/263	191/265	11·1	9·3	0·86 (0·70–1·05)
Main pancreatic tumour location					
Head	97/147	116/156	10·2	9·1	0·86 (0·65–1·12)
Other	162/236	169/231	11·7	9·2	0·83 (0·67–1·02)
Baseline CA 19-9					
<37 U/mL	34/60	45/71	13·2	10·9	0·75 (0·48–1·17)
≥37 U/mL	223/321	240/316	11·1	9·1	0·84 (0·70–1·01)
Race					
White	218/315	240/324	10·7	9·0	0·84 (0·70–1·01)
Sex					
Male	139/204	175/230	10·9	9·0	0·82 (0·66–1·02)
Female	120/179	110/157	11·6	9·5	0·88 (0·68–1·14)
Age, years					
<65	127/193	130/191	11·5	9·9	0·92 (0·72–1·17)
≥65	132/190	155/196	11·0	9·0	0·77 (0·61–0·97)
Overall	**259/383**	**285/387**	**11·1**	**9·2**	**0·83 (0·70–0·99)**

Wainberg et al, Lancet, 2023

Comparative toxicity profile of NALIRIFOX vs. FOLFIRINOX vs. gemcitabine/nab paclitaxel: % grade 3 or 4 toxicities

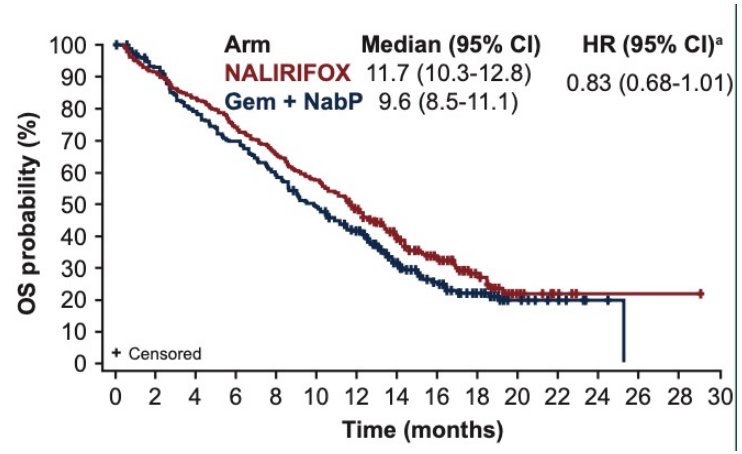
	FOLFIRINOX	NALIRIFOX	Gem/Nab Paclitaxel
Neutropenia	45.7	14	25
Anemia	7.8	11	17
Fatigue	23.6	6	5
Vomiting	14.5	7	2
Diarrhea	12.7	20	5
Neuropathy	9	3	6
Appetite	-	9	3
Hypokalemia	-	15	4

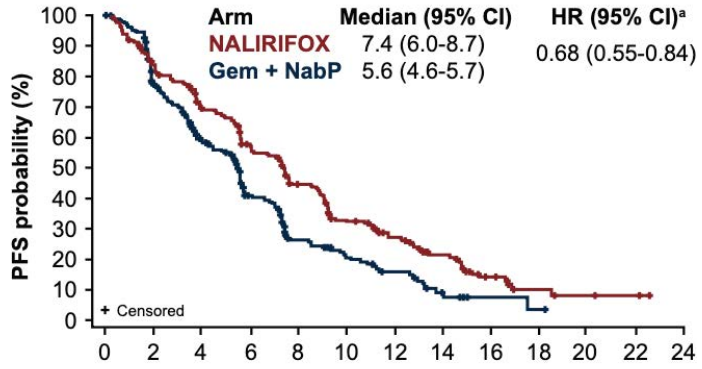


Conroy et al, NEJM, 2011; Wainberg et al, Lancet, 2023; Nichetti et al, JAMA Network Open, 2024

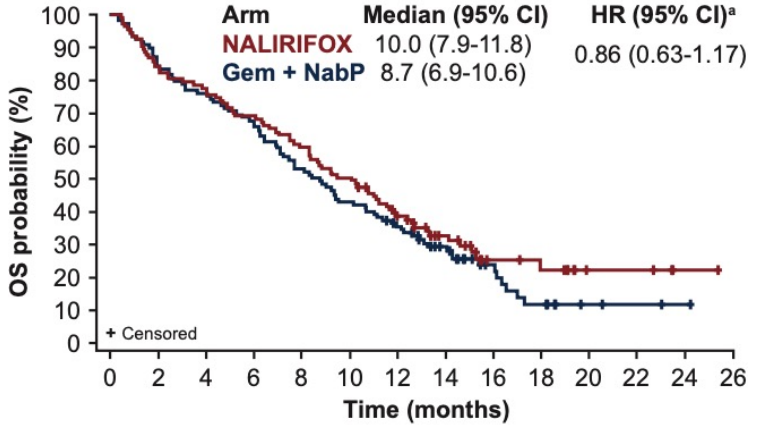
NALIRIFOX is as efficacious and tolerable in PDAC patients over 70 years

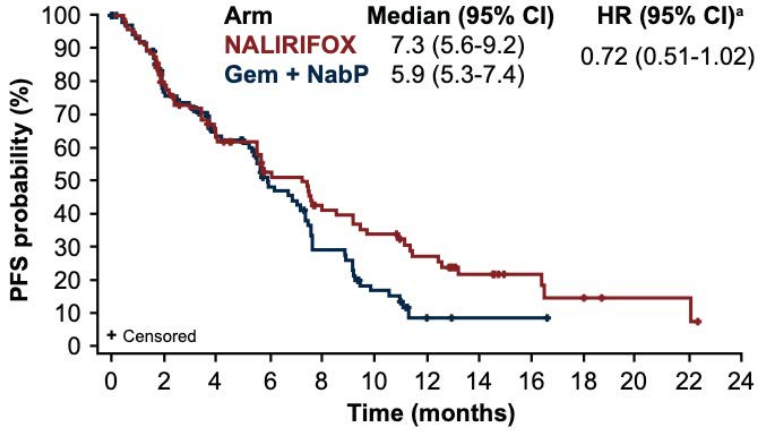
< 70 years





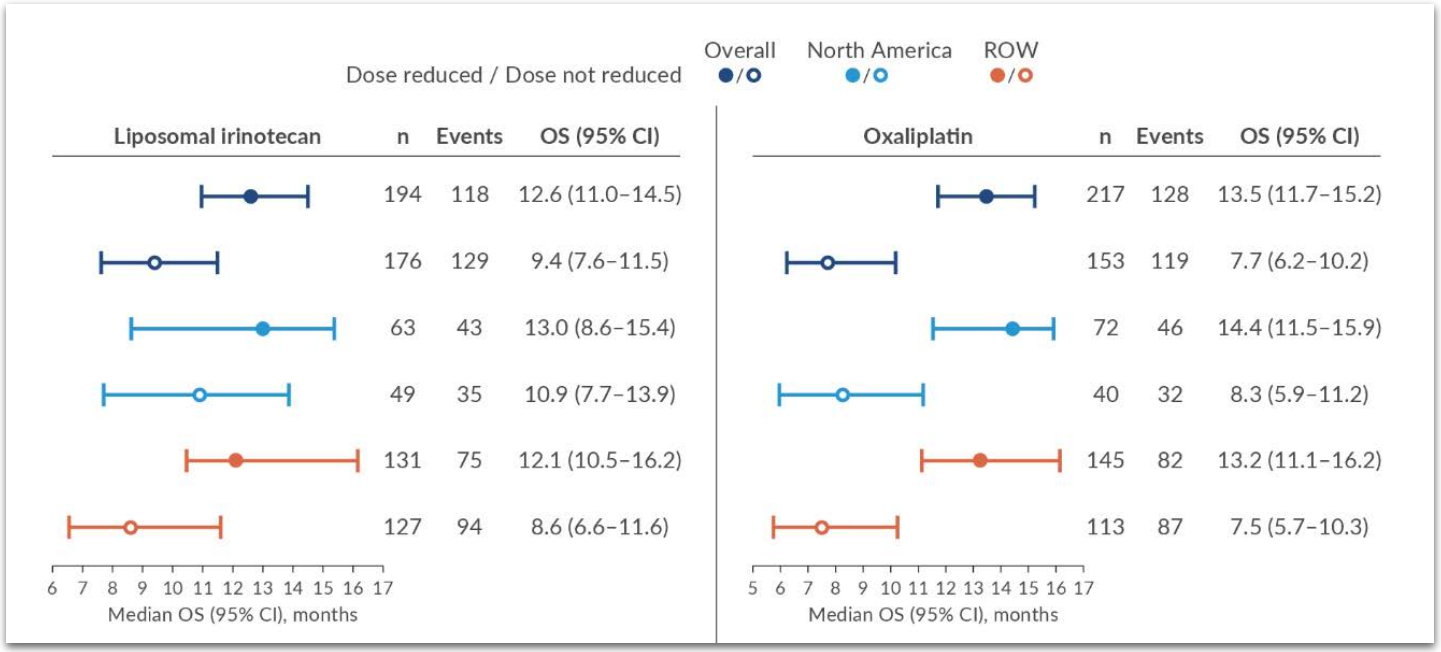
≥ 70 years





Macarulla et al, ESMO Open 2026

Patients who received NALIRIFOX in NAPOLI-3 and had dose reductions of liposomal irinotecan and/or oxaliplatin did not impact OS



	N	Median OS months
Liposomal IRI		
50 mg/m^2	173	9.1
40 mg/m^2	118	11.8
32.5 mg/m^2	56	16.9
25 mg/m^2	23	13.5
Oxaliplatin		
60 mg/m^2	150	7.9
48 mg/m^2	116	11.7
39 mg/m^2	73	17.1
30 mg/m^2	30	14.4

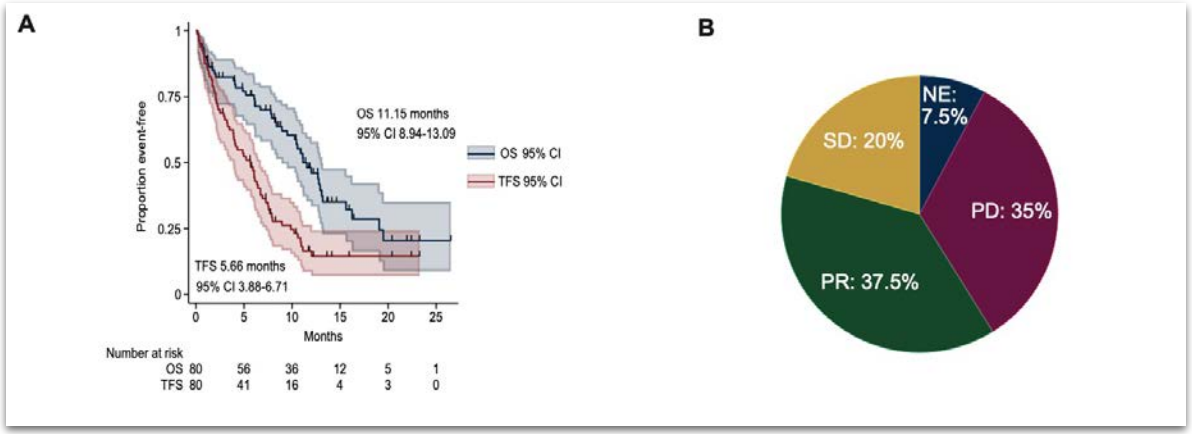
Patel A et al, ASCO GI 2026, Abs 716

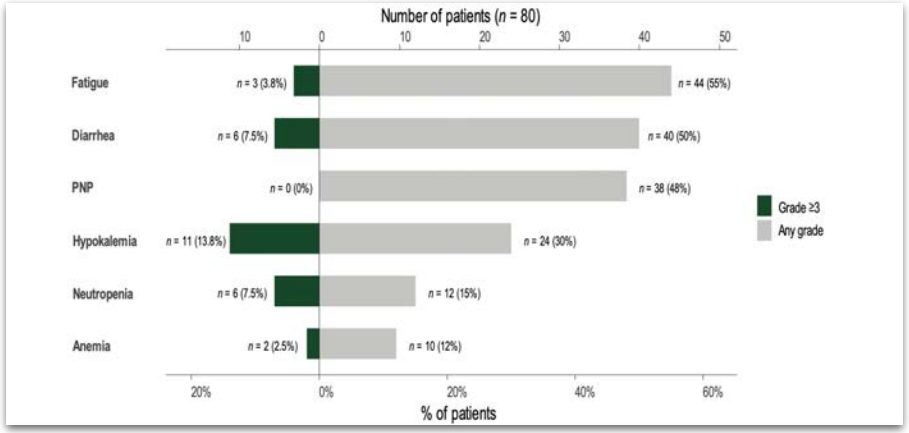
Dose reductions resulted in longer duration of drug exposure and higher cumulative doses

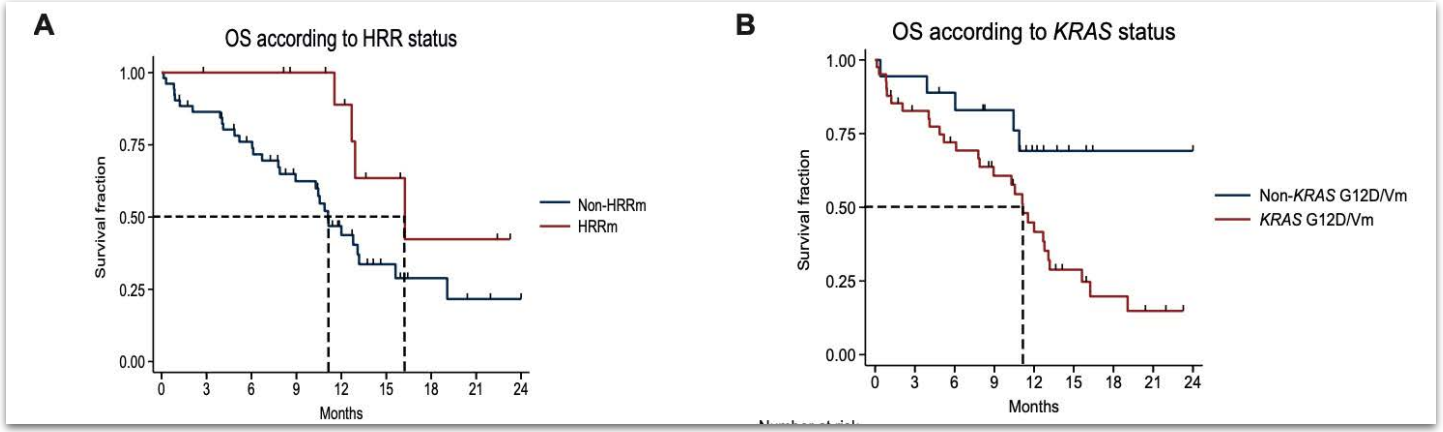
	Overall		North America		Rest of the world	
	Dose not reduced	Dose reduced	Dose not reduced	Dose reduced	Dose not reduced	Dose reduced
Liposomal irinotecan	**n = 176**	**n = 194**	**n = 49**	**n = 63**	**n = 127**	**n = 131**
Cumulative dose, median (IQR), mg/m^2	248.9 (100.0–760.0)	536.0 (295.6–870.1)	403.5 (102.1–809.4)	460.1 (245.9–966.9)	200.9 (99.7–755.0)	544.9 (320.0–824.4)
Duration of exposure at any dose, median (IQR), weeks	10.6 (3.9–35.6)	31.7 (17.1–51.7)	18.1 (4.1–35.0)	25.3 (15.1–53.7)	8.3 (3.0–36.3)	32.1 (18.0–50.1)
Oxaliplatin	**n = 153**	**n = 217**	**n = 40**	**n = 72**	**n = 113**	**n = 145**
Cumulative dose, median (IQR), mg/m^2	239.9 (119.1–595.5)	635.6 (360.5–907.3)	327.6 (121.6–628.5)	653.8 (304.9–974.8)	238.1 (60.3–595.4)	635.6 (410.7–860.3)
Duration of exposure at any dose, median (IQR), weeks	8.1 (2.9–23.0)	30.0 (17.3–40.1)	12.1 (3.6–24.7)	25.2 (15.1–43.8)	8.0 (2.1–21.3)	30.1 (18.0–39.7)

Anjan et al, ASCO GI 2026, Abs 716

NALIRIFOX: Real world data on efficacy, toxicity and impact of *KRAS*^{mut}

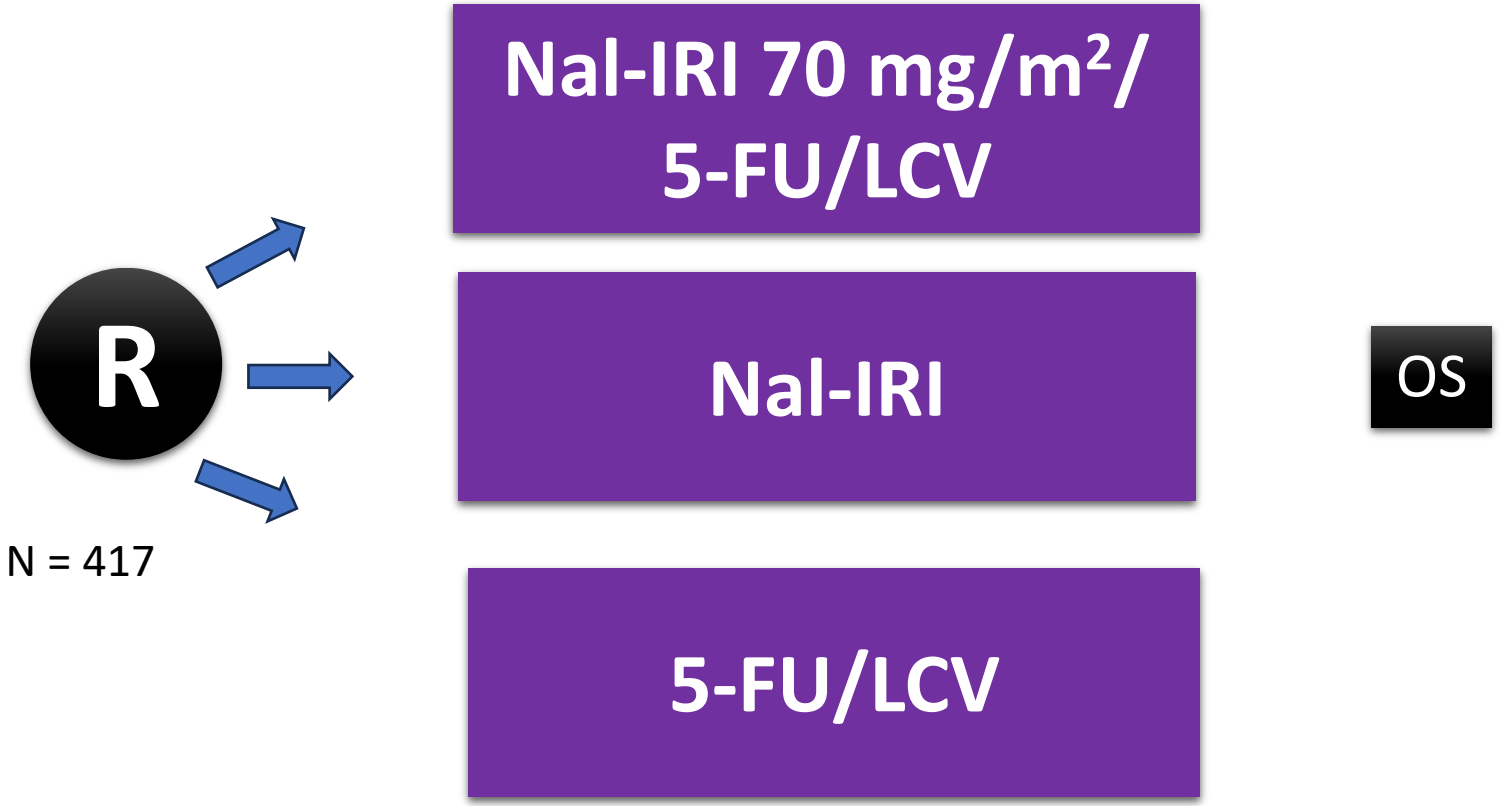






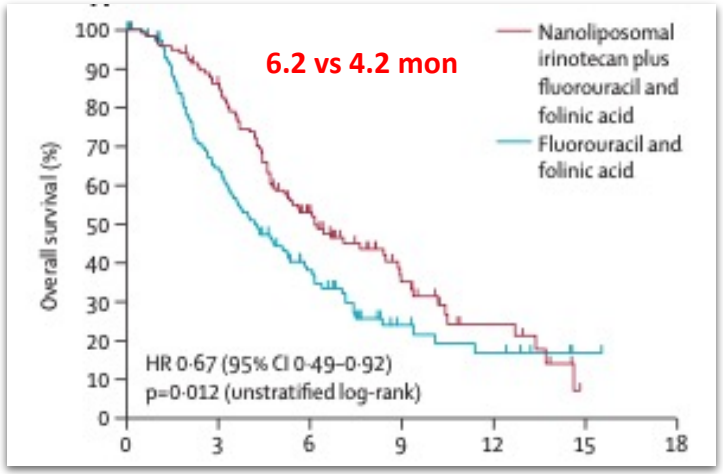
Reichinger et al, ESMO Open, 2025

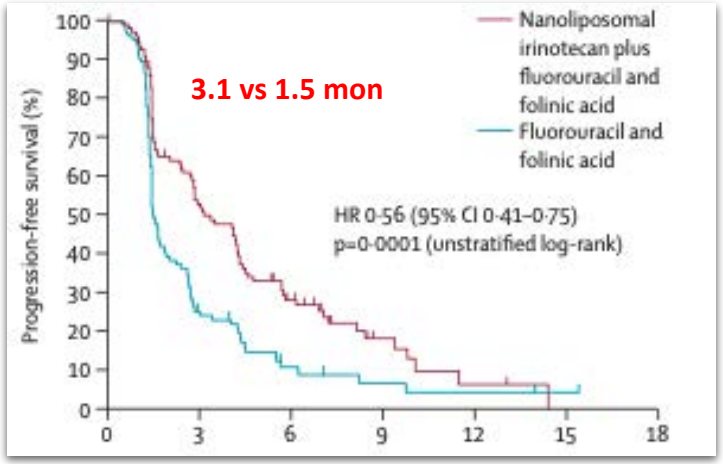
NAPOLI-1: Phase 3 trial of Nal-IRI plus 5-FU/LV in metastatic PDAC progressing on gem-based therapy



Wang-Gillam et al, Lancet, 2015

NAPOLI-1: Nal-IRI/5FU/LCV significantly improved overall survival compared to 5FU/LCV





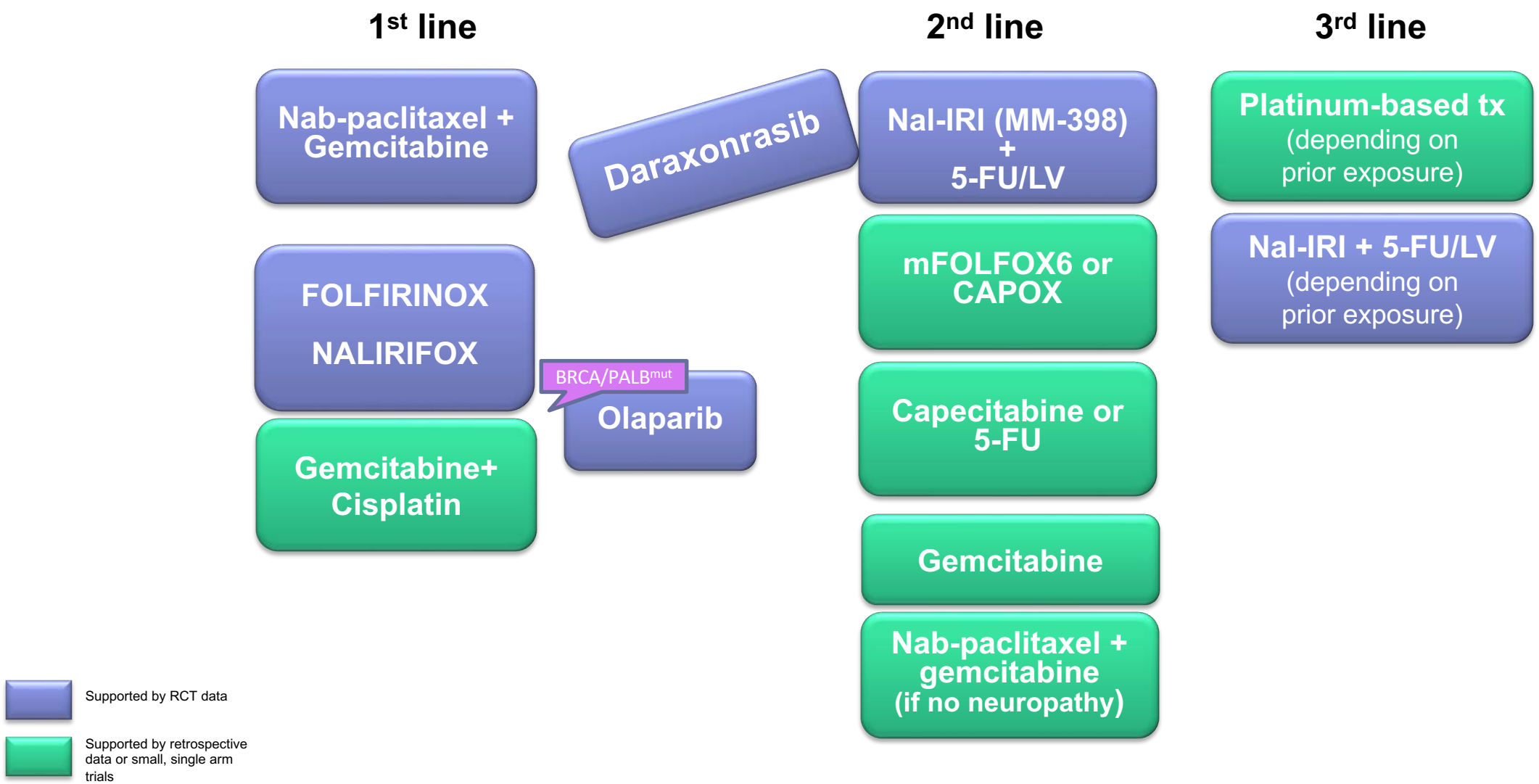
Grade 3 or 4 toxicities %

	Nal/5FU/LCV	5FU/LCV
Diarhea	13	4
Vomiting	11	3
Nausea	8	3
Appetite	4	2
Fatigue	14	4
Neutropenia	27	1
Anemia	9	7
Hypokalemia	3	2

Wang-Gillam et al, Lancet, 2015; Wang-Gillam et al, ASCO, 2016

Treatment Sequencing Approach For mPDAC In 2026:

A Clinical Trial Must Always Be Considered Before Starting Therapy



QUESTIONS?

Module 2: Pancreatic Cancer

Optimal Incorporation of Chemotherapy into the Management of Advanced Pancreatic Cancer — Dr Philip

Other Available and Emerging Novel Approaches for Pancreatic Cancer — Dr O'Reilly

Research To Practice

Pancreas Adenocarcinoma The Coming Future!

Eileen M. O’Reilly, MD, FASCO

Winthrop Rockefeller Endowed Chair, Memorial Sloan Kettering Cancer Center

Chair, Human Research Protection Program and IRB

Professor of Medicine, Weill Cornell Medicine

April 25th, 2026

Memorial Sloan Kettering Cancer Center

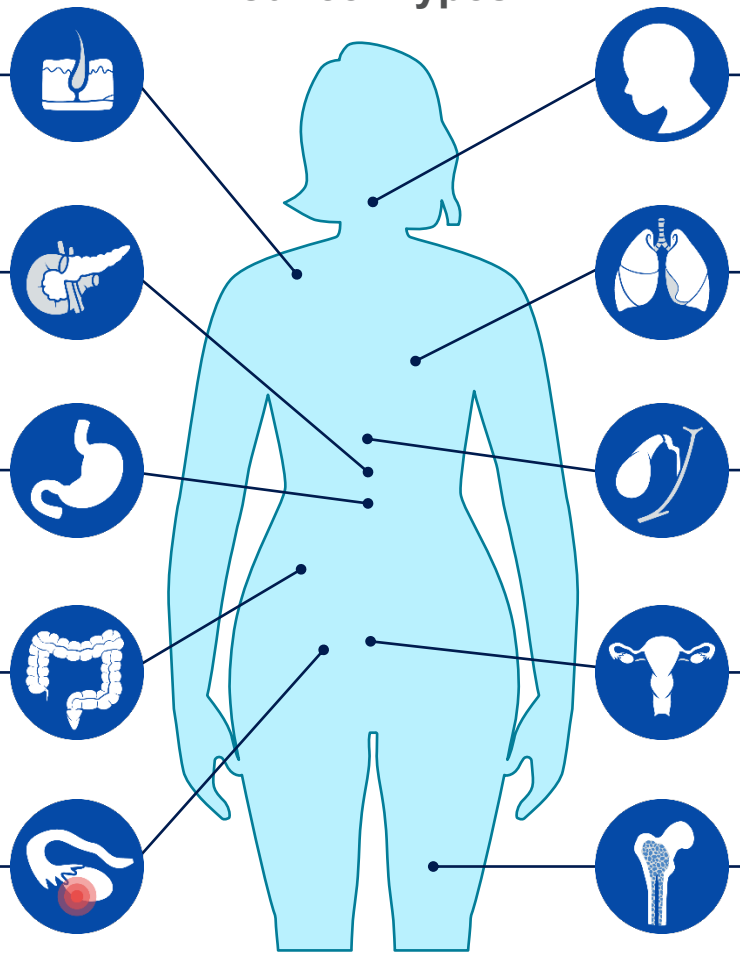
Disclosures

Advisory Committees and Consulting Agreements (Uncompensated)	Agenus Inc, Alligator Bioscience, Amgen Inc, Arcus Biosciences, Astellas, AstraZeneca Pharmaceuticals LP, BioNTech SE, Bristol Myers Squibb, Ikena Oncology, Immuneering Corporation, Ipsen Biopharmaceuticals Inc, Merck, MOMA Therapeutics, Novartis, Pfizer Inc, Regeneron Pharmaceuticals Inc, Revolution Medicines Inc, Tango Therapeutics
Contracted Research	Agenus Inc, Amgen Inc, Arcus Biosciences,AstraZeneca Pharmaceuticals LP, BioNTech SE, Digestive Care Inc, Elicio Therapeutics, Genentech, a member of the Roche Group, Incyte Corporation, Revolution Medicines Inc, Tango Therapeutics
Nonrelevant Financial Relationships	American Association of Cancer Research (Editor), American Society of Clinical Oncology (Editor), Break Through Cancer, Imedex, National Cancer Institute (Cancer Center Support Grant/Core Grant), National Institutes of Health (research grant), Stand Up 2 Cancer

KRAS Genomics

RAS Mutations in ~20% of All Cancers

RAS Mutations Across Cancer Types



Melanoma
KRAS 1%, *HRAS* 2%, *NRAS* 17%

Pancreas
***KRAS* 88%**

Esophagogastric
KRAS 3%, *KRAS*-amp 6%

Colorectal
KRAS 42%, *NRAS* 4%

Ovarian
KRAS 9%, *NRAS* 2%

Head and neck
KRAS 2%, *HRAS* 5%, *NRAS* 2%

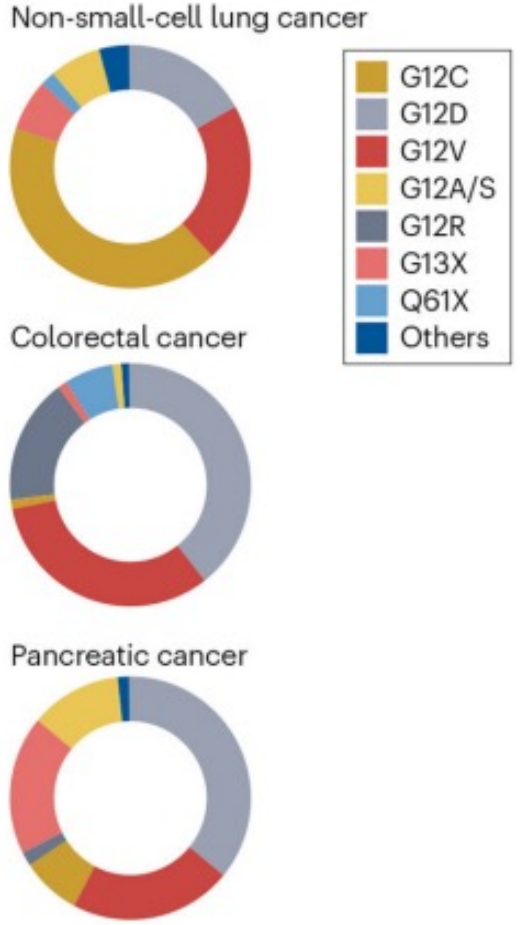
Non-small cell lung cancer
KRAS 32%

Gallbladder, cholangiocarcinoma
KRAS 21%, *NRAS* 2%

Endometrial
KRAS 17%, *NRAS* 3%

Leukemia
KRAS 5%, *NRAS* 14%

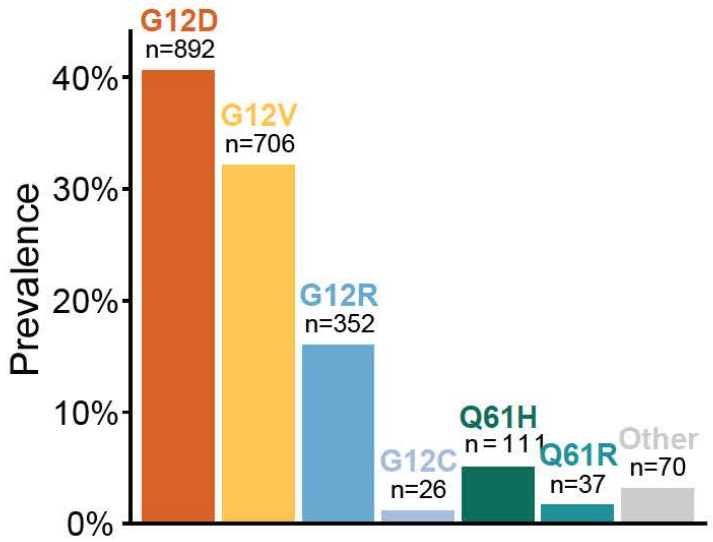
KRAS Alleles in NSCLC, CRC, and Pancreatic Cancers



Yang, X. J Haematol Oncol, 2024
Singhal, A… O'Reilly, EM. Nat Med, 2024

Differential Genomic, Prognostic Features of *KRAS* Variants

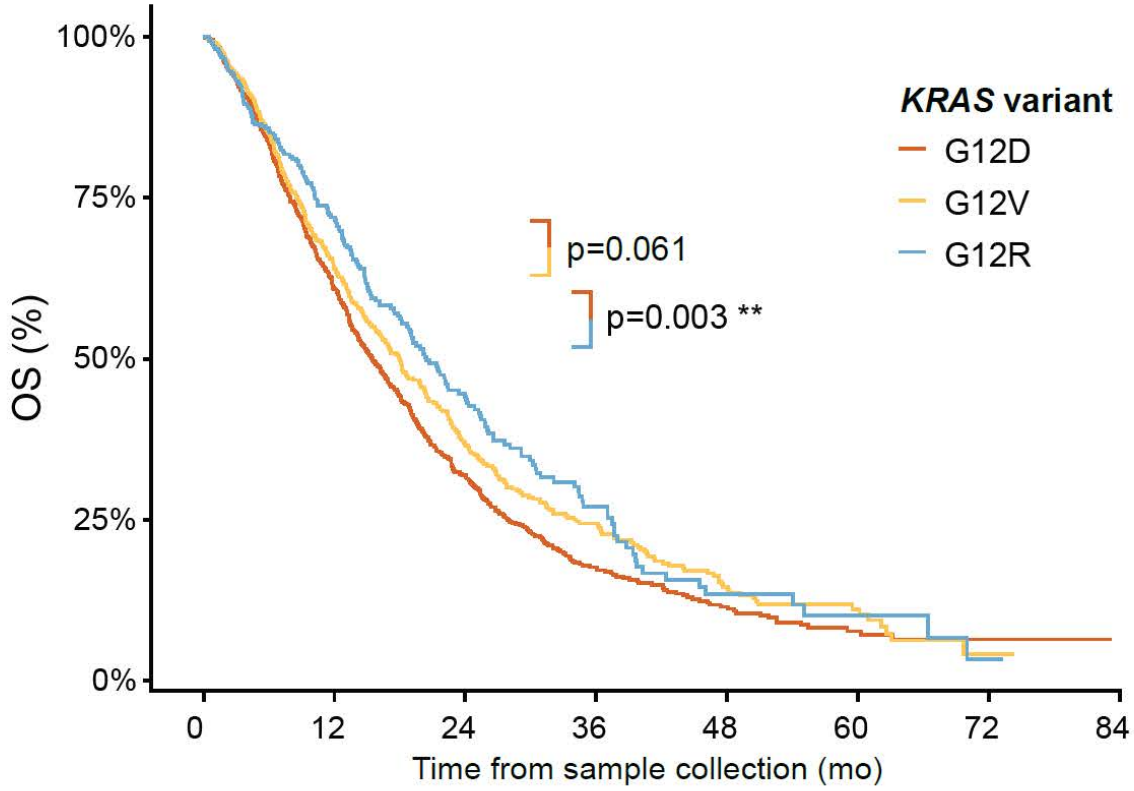
KRAS G12R and *KRAS* Wild-Type Prognostic



Prevalence *KRAS* variants

98% *KRAS* substitutions G12 (91%), Q61 (7%)

N= 14 (0.6%) multiple hotspot mutations



Kaplan-Meier of OS among *KRAS* variants

Varghese, A, Perry, M…Schultz, N, Berger, MF, Iacobuzio-Donahue, C, Bandlamudi, C, O'Reilly, EM. Nat Med, 2025

RAS Therapeutics

Therapeutic Agents in Development (Incomplete….)

Truly a Feast… and in Pancreas Cancer!

G12C Inhibitors

Sotorasib (Amgen)
Adagrasib (Mirati/BMS)
Divarasib (Genentech/Roche)
Olomorasib (Lilly)
Fulzerasib/IBI351 (GenFleet)
Glecirasib (Jacobio)
Calderasib/MK-1084 (Merck)
Opnurasib (Novartis)
Garsorasib/D-1553 (InventisBio)
FMC-376 (Frontier Medicines)
RMC-6291 (Rev Medicines)
BBO-8520 (BridgeBio)
D3S-001 (D3Bio)

G12D Inhibitors

ASP3082 (Astellas)
ASP4326 (Astellas)
RMC-9805 (Rev Medicines)
HRS-4642 (Hengrui)
TSN1611 (Taison Biopharma)
QTX3046 (Quanta)
GDC-7035 (Genentech)
AZD0022 (AstraZeneca)
INCB161734 (Incyte)
GFH375/VS-7375 (Genfleet/Verastem)
D3S-003 (D3Bio)
LY3962673 (Lilly)
KQB548 (Kumquat Biosciences)
siG12D-LODER SIL-204 (Silexion)
VRTX153 (Vrise)
ABSK141 (Abbisko Therapeutics)
AZD0240 (AstraZeneca) TCR
RNK08954 (Ranok Ther; Hangzhou)

Pan (K)RAS Inhibitors

RMC-6236/daraxonrasib (Rev Medicines)
BI-2492 (BI)
QTX3034, QTX3544 (Quanta)
PF-07934040 (Pfizer)
PF-07985045 (Pfizer)
BGB-53038 (Beigene)
BBO-11818 (BridgeBio Oncology)
ALTA-3263 (Alterome)
LUNA18 (Chugai)
LY406634 (Lilly)
JAB-23425 (Jacobio)
ABREV001 (Agastiya)
AUBE00 (Chugai)
TRN-372 (Treeline)
AMG410 (Amgen)
ADT-1004
ERAS-0015 (Erasca)
AN9025 (Adlai Nortye)
ASP5834 (Astellas)

KRAS Biology

Mechanisms of Action Differ between Therapeutics

Mutant/Allele Selective On/Off; Tri-Complex Multi(ON); Degraders

Mutant-selective off-state inhibitors

Adagrasib, sotorasib

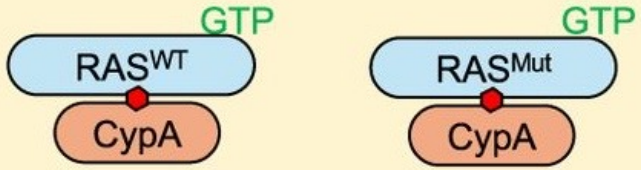
MRTX1133

Mutant-selective on-state inhibitor

BBO-8520, FMC-376

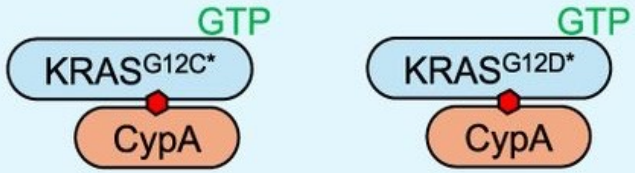
Tri-complex RAS-multi on-state inhibitor

RMC-7977, RMC-6236



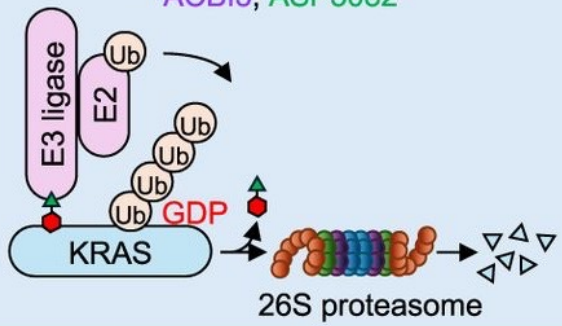
Tri-complex mutant-selective on-state inhibitors

RMC-4998 RMC-9805



KRAS-targeted proteolysis targeting chimera (PROTAC)

ACBI3, ASP3082



*Covalent modification; Approved; Clinical development; Preclinical

Cox AD, Der CJ. Genes Dev. 2025

Pancreas Cancer: G12C Inhibitor RAS Therapeutics

KRAS G12C (G→C) Allele Inhibitors: Promising Signal

1-2% of Pancreas Cancers

	N	Response Rate	Disease Control	Median PFS	Median OS
Sotorasib (CodeBreaK 100)	38	21% (8/38)	84% (32/38)	4 m	6.9 m
Adagrasib (KRYSTAL-1)	21	33% (7/21)	81% (17/21)	5.4 m	8 m
Divarasib	7	43% (3/7)	100% (7/7)	-	-
Olomorasib (LY3537982)	24	42% (10/24)	92% (22/24)	6.9 m	-
Glecirasib (JAB-21822)	31	42% (13/31)	93.5% (29/31)	5.5 m	10.8 m
HRS-7058	9	75% (6/8)	100% (8/8)	-	-
Garorasib	22	45.5%		7.6 m	

NCCN guidelines: ECOG 0-3

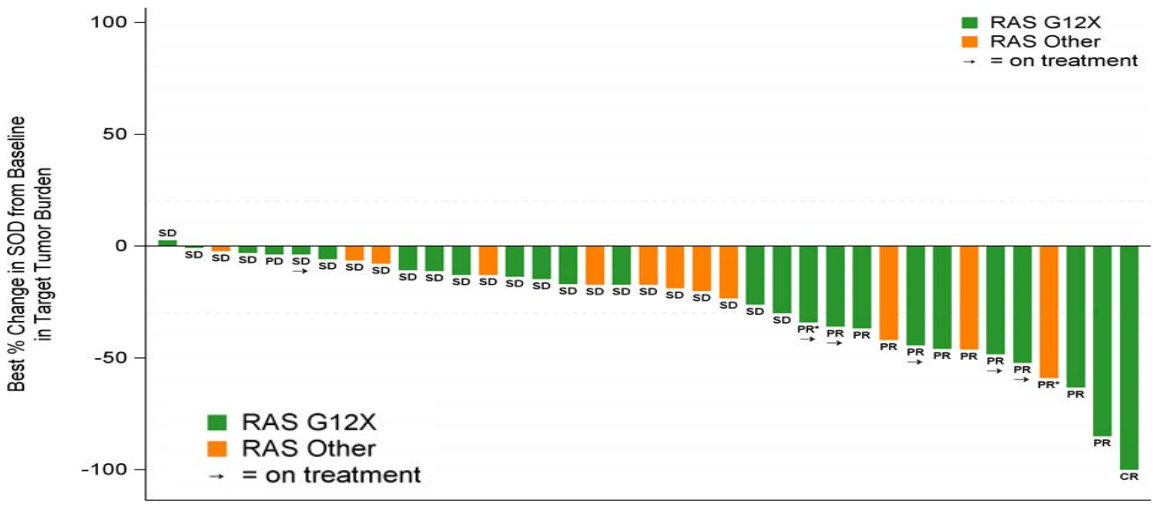
Stickler, J. New Engl J Med, 2023
Bekaii-Saab, T…Pant, S. J Clin Oncol, 2023
Sacher, A. New Engl J Med, 2023
Murciano-Goroff, Y. AACR, 2023
Hollebecque, A. Gastrointestinal Cancers Symposium, 2024
Li, J. Gastrointestinal Cancers Symposium, 2024
Huang, D. Abstract 9140, ESMO, 2025
Yamamoto, N. BJC, 2025
Li, J. Cancer Communications, 2025

RAS Therapeutics: PanRas Inhibitor

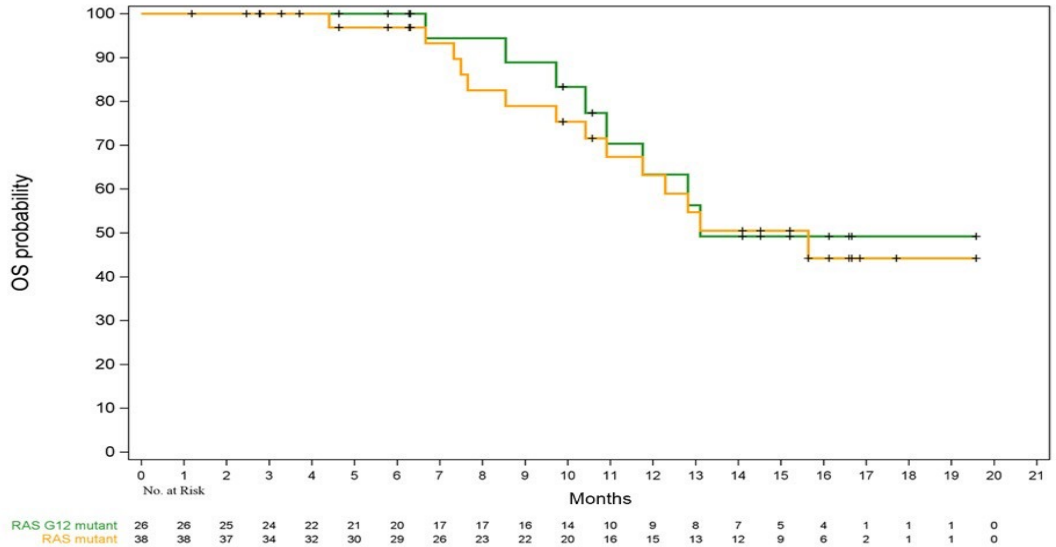
Daraxonrasib: Early Outcomes in 2L PDAC 300 mg PO

Multi-RAS(ON) Tri-Complex Inhibitor (*KRAS* H, N, Wild-Type)

Response Rate (N= 38)



Overall Survival (N= 38)



	Overall RR	DCR Rate	PFS (m)	OS (m)
RAS G12X (N= 26)	35%	92%	8.5 (6.7- 10.5)	13.1 (10.9- NE)
RAS mutant (N= 38)	29%	29%	8.1 (5.9- 10.1)	15.6 (10.9- NE)

**RAS* mutant: G12X, G13X, Q61X; Median f/up > 16 m

Data cut off 06-30-2025
Courtesy Revolution Medicine website 09 2025

Daraxonrasib 300 mg: Safety, Adjustments 2L+ (N= 83)

Toxicity: Primarily Cutaneous/GI

Toxicity	Any Grade	Grade > 3
Rash	75 (90%)	6 (7%)
Mucositis	45 (54%)	3 (4%)
Diarrhea	43 (52%)	3 (4%)
Nausea/Vomiting	~39%/ 26%	-
Paronychia	15 (18%)	--
Fatigue	14 (17%)	1 (1%)
Platelets	8 (10%)	3 (4%)
Anemia	7 (8%)	6 (7%)
AST/ALT	10%/ 7%	4%/ 2%

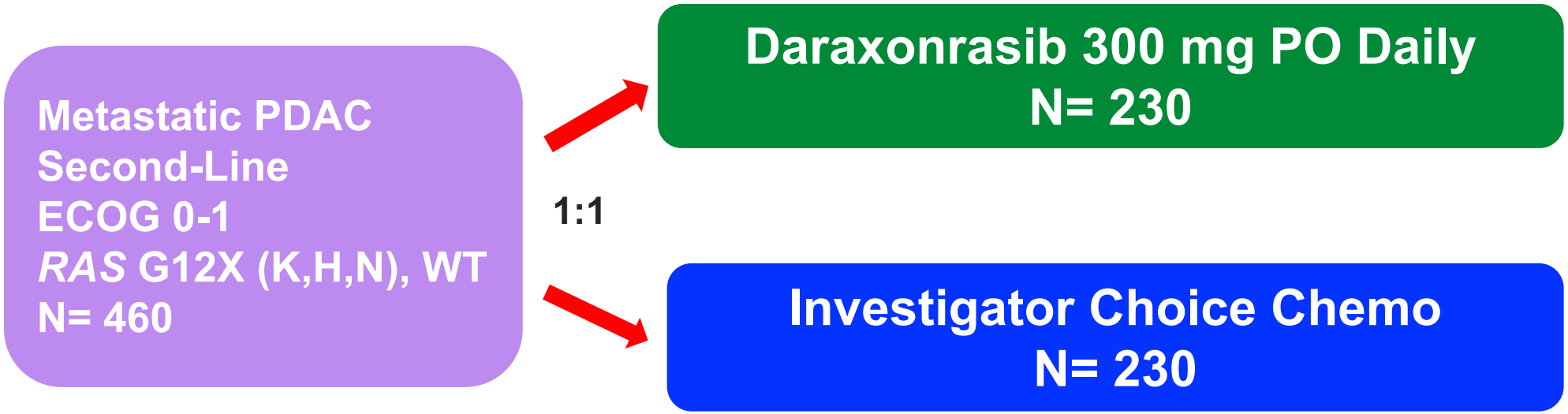
Dose Adjustments	N= 83
Dose modifications	40 (48%)
Dose interruption	36 (43%)
Dose reduction	25 (30%)
Discontinuation AE	-

Data cut off 06-30-2025
Courtesy Revolution Medicine website 09 2025

Pancreas Cancer: PanRAS Inhibitor

RASolute 302: Phase III PDAC 2L Daraxonrasib vs Chemo

Accrual Complete



Co-primary endpoints: Progression-free survival; OS (G12X)
Secondary endpoints: PFS, OS (all), Overall response rate, duration of response, safety, QoL

HR 0.7 OS (G12X 7.1 → 10.1 m)
HR 0.54 PFS (G12X 3.5 → 6.5 m)

NCT06625320

Pancreas Cancer: PanRAS Inhibitor

RASolute 302: Phase III PDAC 2L Daraxonrasib vs Chemo

- Trial met all primary and key secondary endpoints

- In the overall (intent-to-treat) study population:

  Daraxonrasib demonstrated median OS 13.2 vs 6.7 months for chemotherapy
  Hazard ratio of 0.40, p < 0.0001

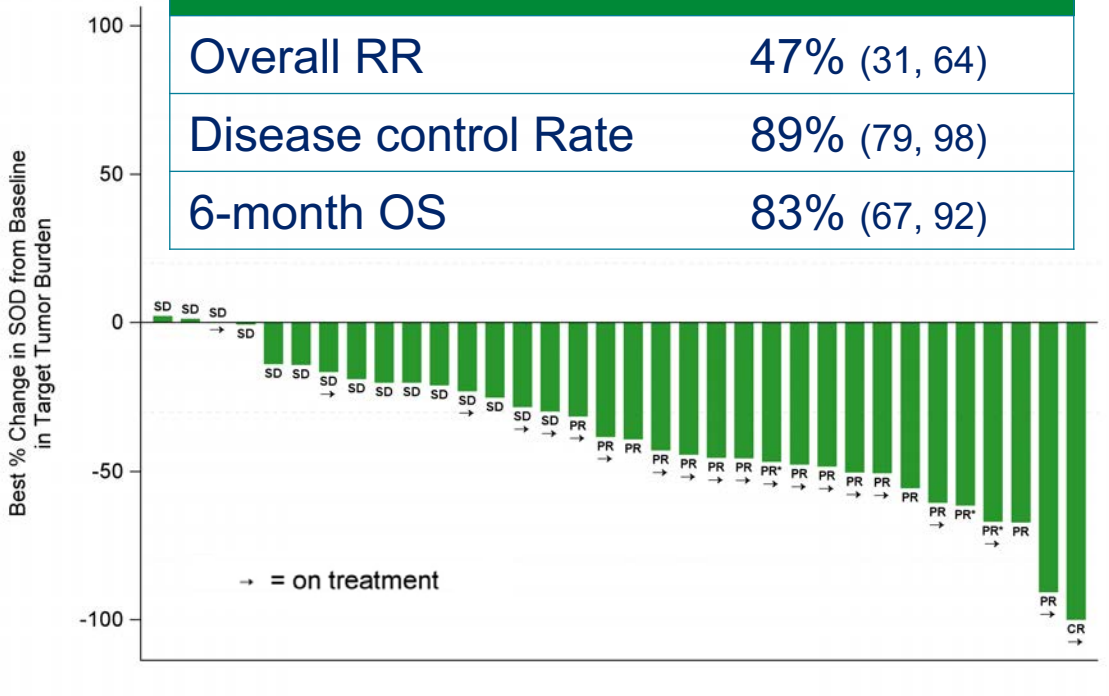
https://ir.revmed.com/news-releases/news-release-details/daraxonrasib-demonstrates-unprecedented-overall-survival-benefit

RAS Therapeutics: PanRAS Inhibitor

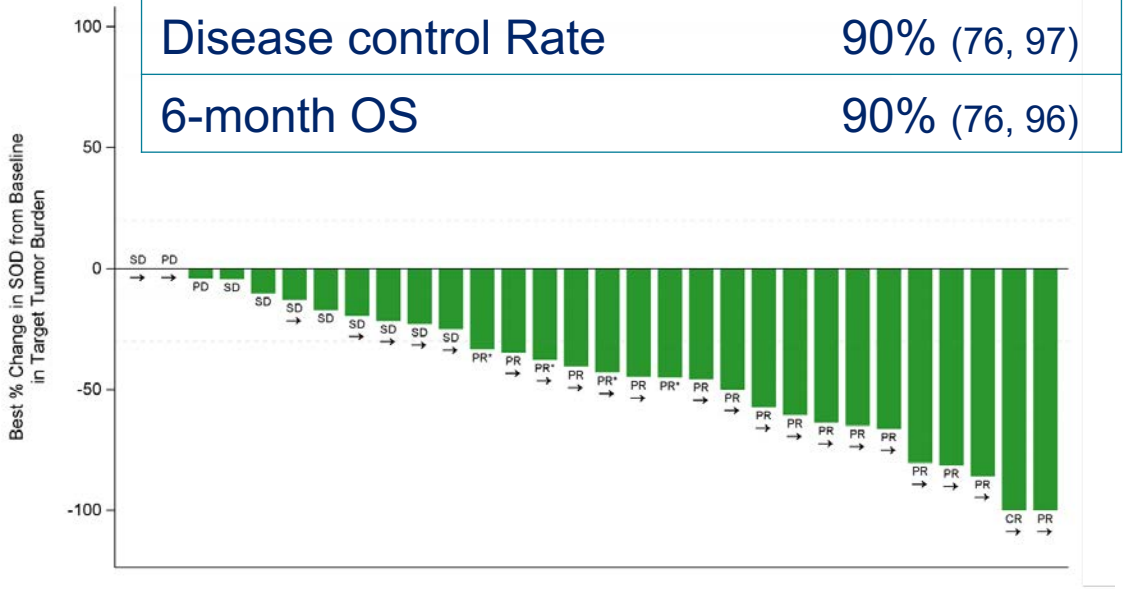
Daraxonrasib +/- Gem/nab-Paclitaxel: 1L Pancreas Cancer

Promising Single Agent, Combination Signals in First Line PDAC (AACR 2026)

Daraxonrasib	N= 38
Overall RR	47% (31, 64)
Disease control Rate	89% (79, 98)
6-month OS	83% (67, 92)



Daraxonrasib+Gem/nab-P	N= 40
Overall RR	58% (41, 73)
Disease control Rate	90% (76, 97)
6-month OS	90% (76, 96)

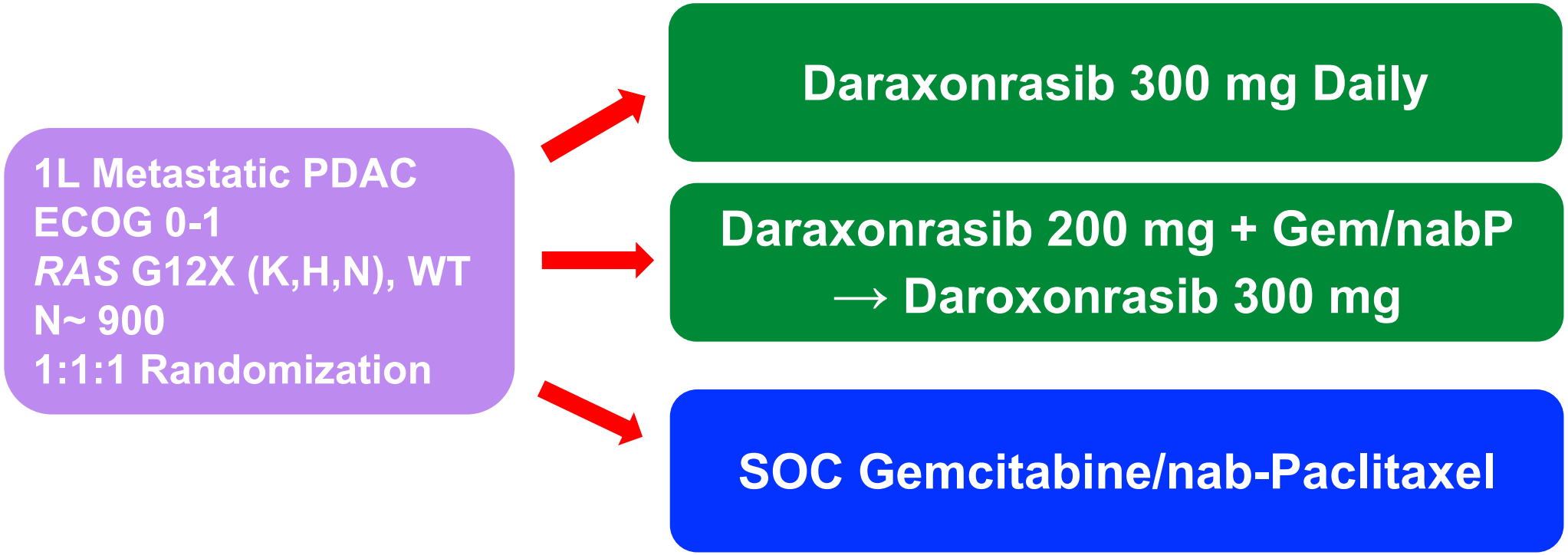


O'Reilly, EM…Garrido-Laguna, I. AACR, 2026
Wolpin, B….Sohal, D. AACR, 2026

Pancreas Cancer: PanRAS Inhibitor

RASolute 303: Phase III 1L Metastatic PDAC

Activated Q1 2026



Co-primary endpoints: Progression-free survival; OS

Secondary endpoints: PFS, OS, Overall response rate, duration of response, safety, QoL

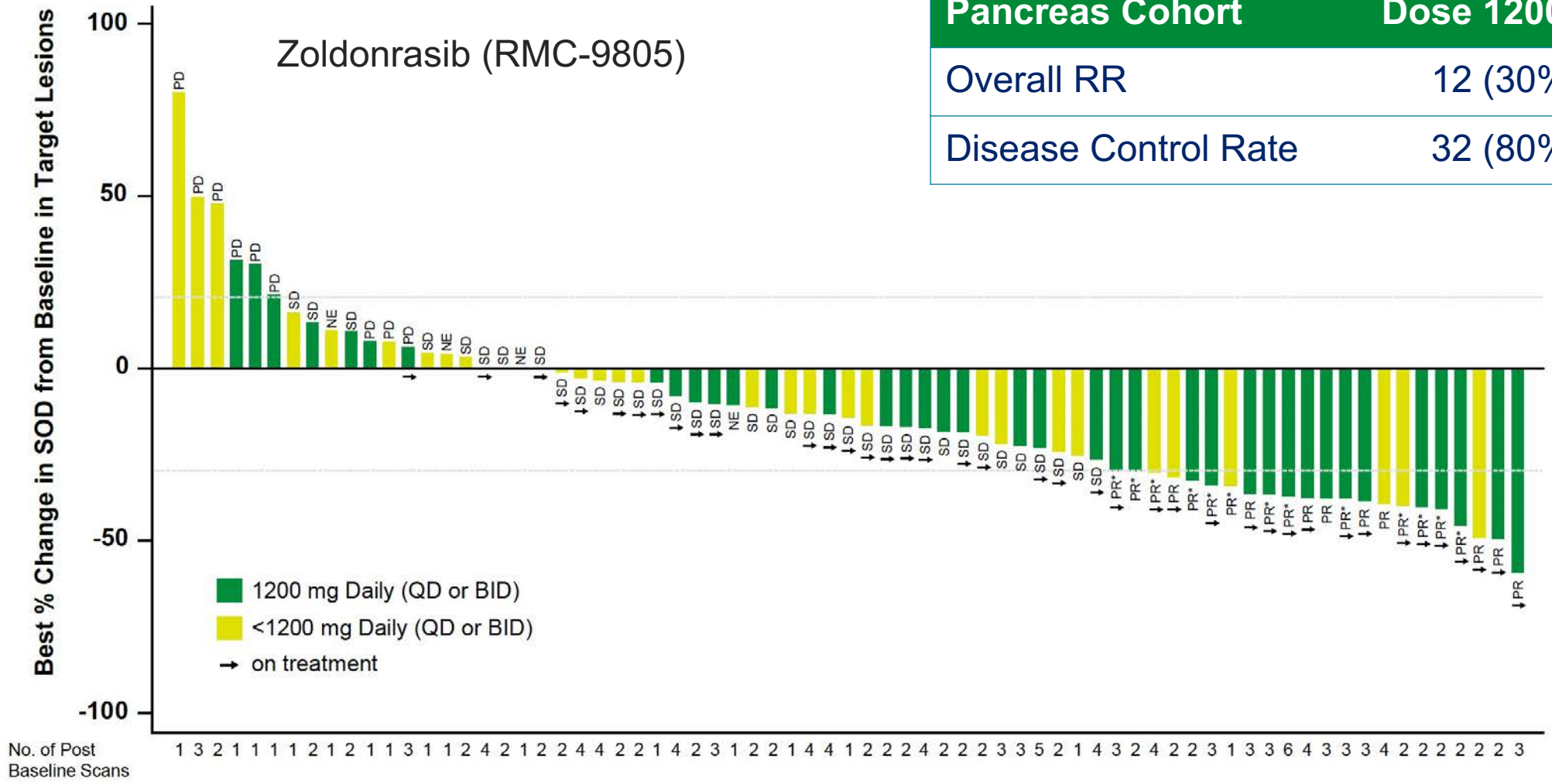
NCT07491445

RAS Therapeutics: Allele Specific

Zoldonrasib: Phase I G12D RAS-On Allele Specific Inhibitor

Multiple G12D Inhibitors in Development

Pancreas Cohort	Dose 1200 mg
Overall RR	12 (30%)
Disease Control Rate	32 (80%)

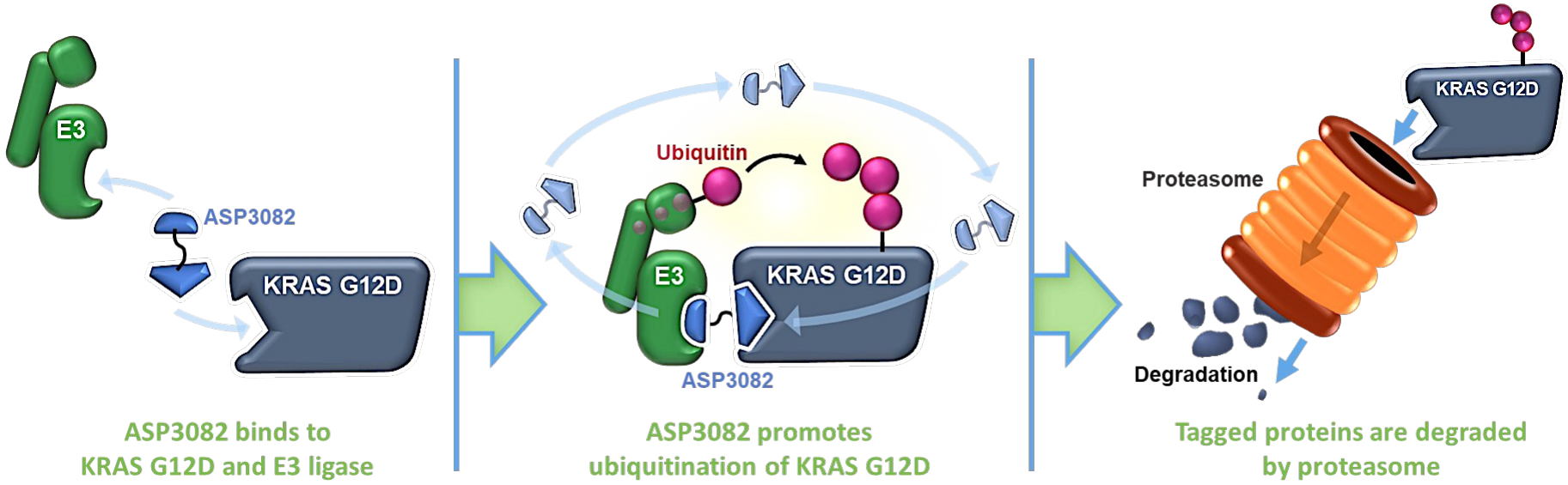


Hong, D. EORTC-NCI-AACR, 2024
Spira, A. Gastrointestinal Cancers Symposium, 2025

RAS Therapeutics: Degrader

ASP-3082: Protein-Selective Degradation KRAS G12D

PROTAC: Proteolysis Targeting Chimera (E3 Ubiquitin Ligase and Ligand)



KRAS G12D Mutation: PDAC (35-40%); CRC (15%); NSCLC (5%)

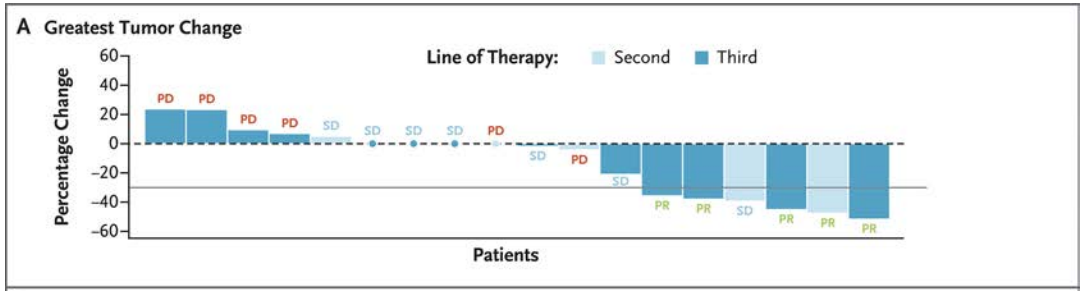
Targeted drug development strategy for intra-cellular proteins

Park, W..Tolcher, A. ESMO, 2024
Lee, JK, NPJ Precision Oncol, 2022
Stickler, S. Oncol, Res, 2024
Yang, J. Cell Discovery, 2024
NCT05382559

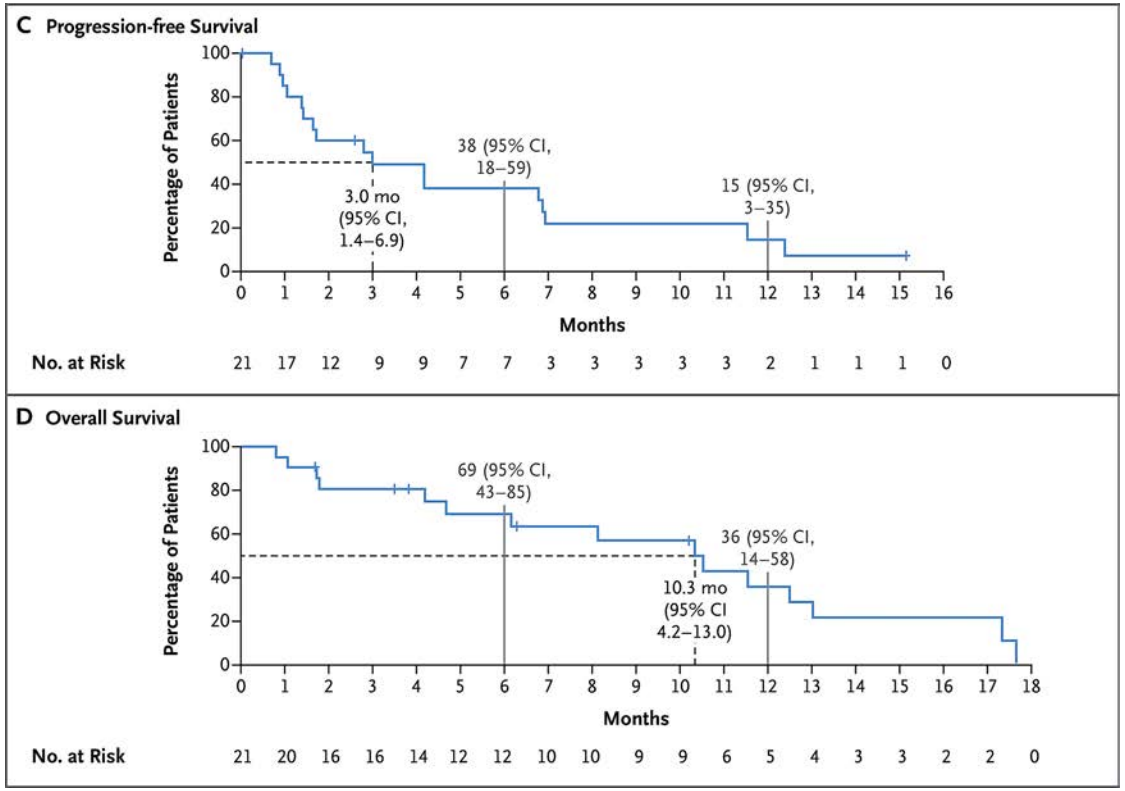
RAS Therapeutics: Degrader

ASP-3082/Setidegrasib KRAS G12D Protein Degrader

First in Class: Destruction of Mutant KRAS Alleles



PDAC 2L (N= 7); 3L (N= 14)	N= 21 600 mg IV
Overall RR	5 (24%)
Median PFS	3 m (1.14- 6.9)
Median OS	10.3 (4.2- 13)



Park, W.…Tolcher, A. Abst 608O. ESMO, 2024
Park, W. New Eng J Med, 2026

RAS Therapeutics: G12D Allele Specific Inhibitors

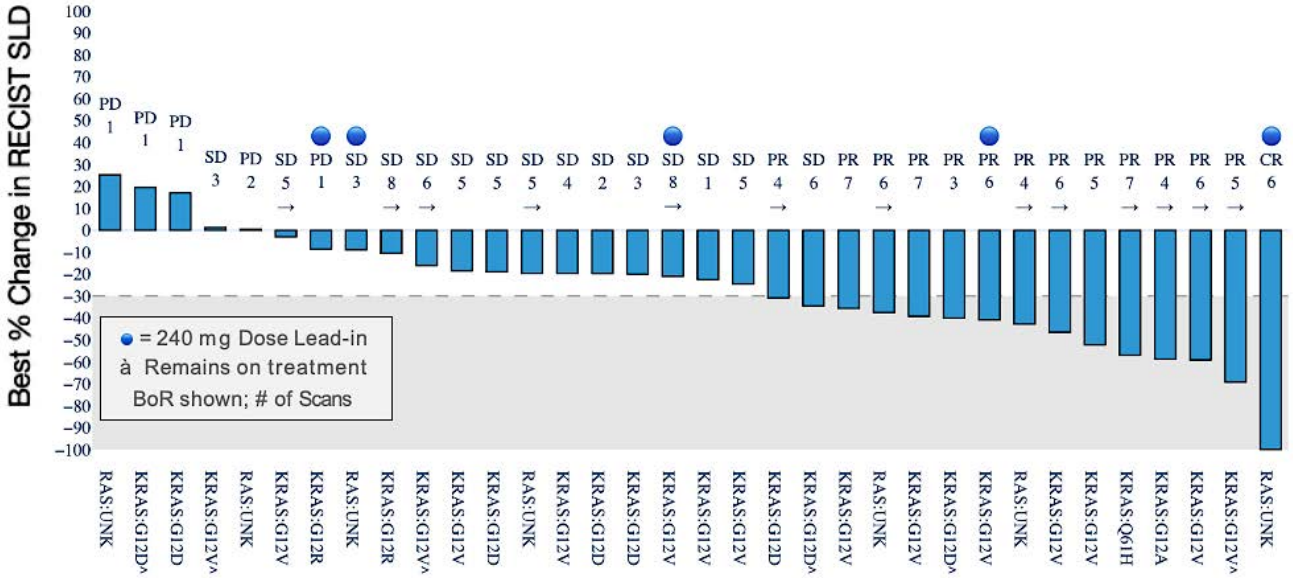
PDAC Selected Other G12Di Monotherapy/ Combination

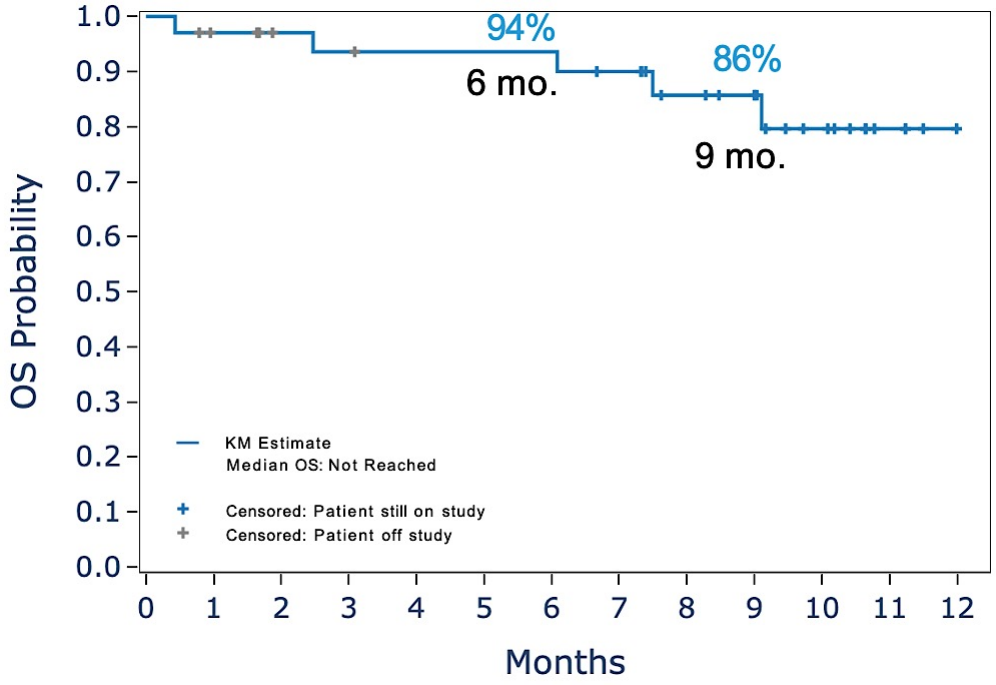
Drug	Mechanism	N	Outcome
GFH375 600 mg P0 VS-7373 Median 2L	G12D 'on/off' state	66	ORR 40.7%, DCR 96.7% Median PFS 5.2 m Median OS NR
INCB161734	G12D non-covalent 'on/off' state	25 29	ORR 20% 600 mg; DCR 64% **ORR 34% 1200 mg; DCR 86%**
HRS-4642 500/ 1200 mg Gem, nab-P d1,8 q 3w 1L	G12D non-covalent	30	ORR 63%, DCR 93% Median PFS NR (est > 1 yr)
Setigrasib (ASP-3082) + mFOLFIRINOX	G12D degrader	14	Responses observed
RNK08954	G12D non-covalent	13	ORR 33% PDAC (small N)

Wang, L, LBA84, ESMO, 2025
Desai, J, Abstract 916O, ESMO, 2025
Zhou, A, Abstract 915O, ESMO, 2025
Xie, L. Can Disc, 2026

Phase IIa Atebimetinib, Gem/nab-Paclitaxel 1L (N= 36)

Encouraging Early Signal – Novel MEK Inhibitor





	Statistics
Overall RR	39% (14/36)
Disease control rate	81% (29/36)
OS (preliminary)	86% @ 9m

Unpublished; Courtesy Immuneering website, 2025

RAS/MAPK Inhibitors: Pancreas Cancer

Selected Phase III Trials Activated / Announced in PDAC

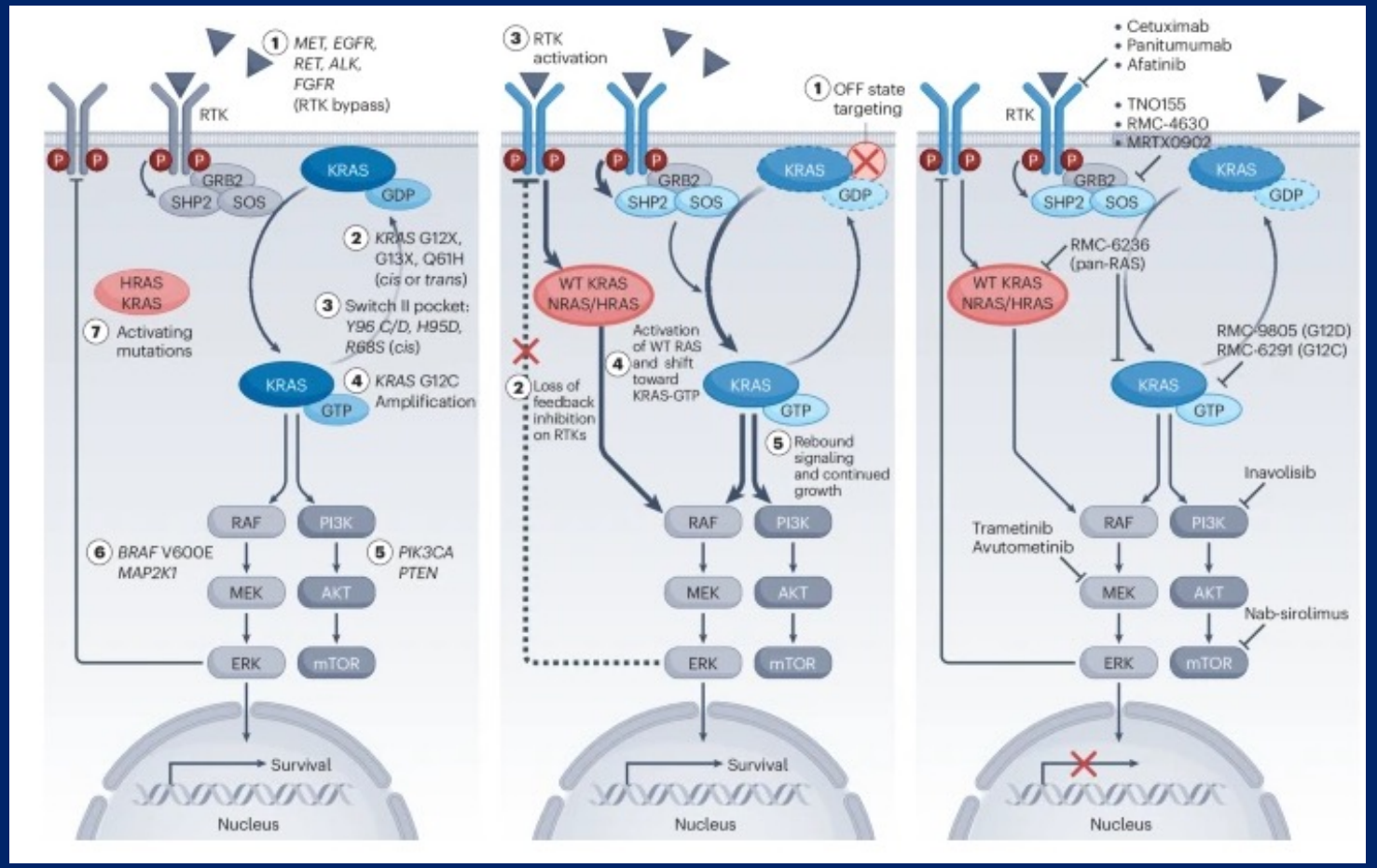
Trial Name	Therapeutic	Target	N	Disease Setting	Status
RASolute 302	Daraxonrasib vs Chemo	PanRAS	460	2nd line metastatic	**Enrolled/ Awaited**
RASolute 303	Gem/nabP +/- Daraxonrasib, D	PanRAS	~900	1st line metastatic	Activated Q1 2026
RASolute 304	Daraxonrasib	PanRAS	500	Adjuvant	Activated Q4 2025
RASolute 305	Zoldonrasib + chemo/Z	KRAS G12D		1st line metastatic	Pending 2026
RASolute 309	Zoldonrasib + Daraxonrasib	KRAS G12D, panRAS		1st line metastatic	Pending 2026
Pending	mFOLFIRINOX +/- Setigrasib	KRAS G12D		1st line metastatic	Pending 2026
DAWN 303	Chemo +/- INCB161734	KRAS G12D		1st line metastatic	Pending 2026
MAPKeeper 301	Gem/nabP +/- Atebimetinib	MEK		1st line metastatic	Pending 2026
HRS-4642-302 China	Chemo +/- HRS-4642	KRAS G12D		1st line metastatic	Activated Q4 2025
GFH375-X1301 China	VS-7375 vs Chemo	KRAS G12D		2nd line metastatic	Activated Q4 2025

KRAS Therapy

RAS Resistance Targeting

Combination approaches:
Allele specific, panRAS
+Upstream receptor TKI signaling
+MAPK pathway targeting
+Immunotherapy
+Chemotherapy
+Classical state targeting

Genetic Resistance to G12C | Adaptive Resistance | Addressing Resistance with Combinations



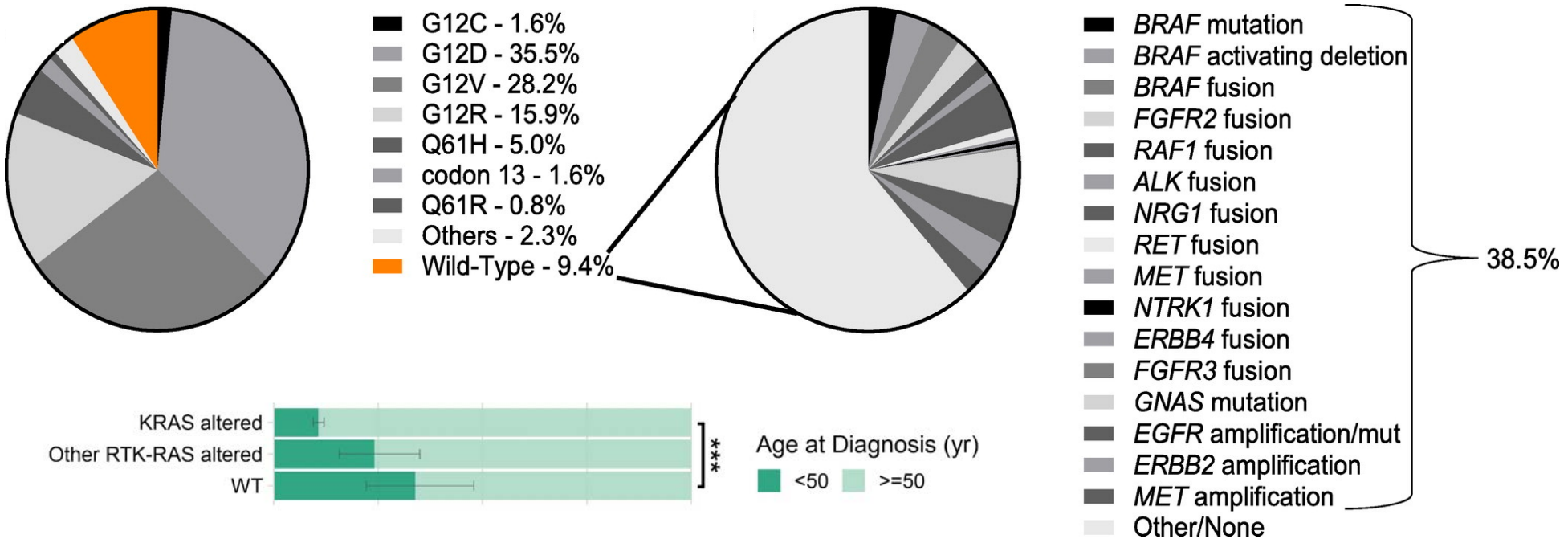
Singhal, A, Li, B, O'Reilly, EM. Nat Med, 2024

KRAS Wild-Type PDAC

Pancreas Cancer: *KRAS* Wild-Type

Early Onset PDAC: *KRAS*^{WT} PDAC (~5-8%)

Rare but Important Oncogenic Drivers beyond *RAS*



Early onset PDAC (< 55 years)

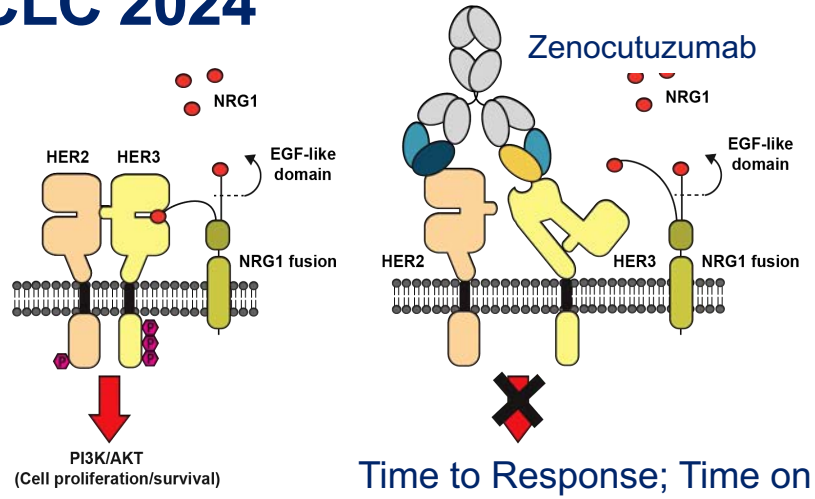
- More likely to be *KRAS*^{WT} (15-20%)
- More likely to have germline alteration
- More likely to have fusion

Lee, MS, Pant, S. ASCO Educational Book, 2021
Philip, P. Clin Can Res, 2022
Singh, H. Clin Can Res, 2023
Varghese, A..O'Reilly, EM. JNCI, 2021
Singhi, AD. Gastroenterology, 2019
Varghese, A…O'Reilly, EM. Nat Med, 2025

Pancreas *KRAS* Wild-Type: Bispecific Antibodies

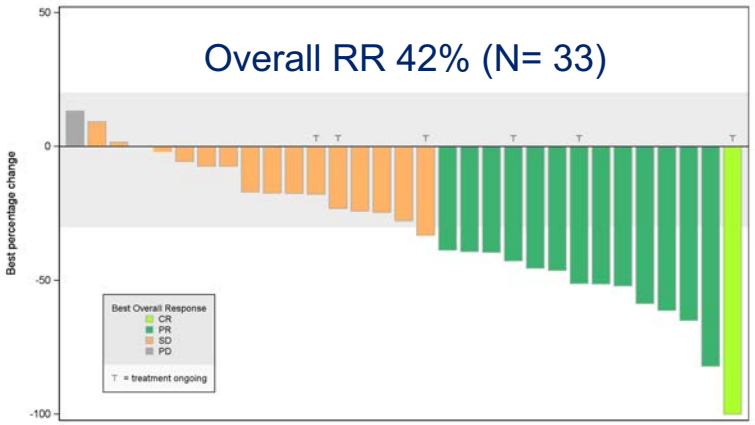
Zenocutuzumab: Bispecific Ab Targets HER2/HER3
NRG1 Fusion(+) PDAC; Approved PDAC, NSCLC 2024

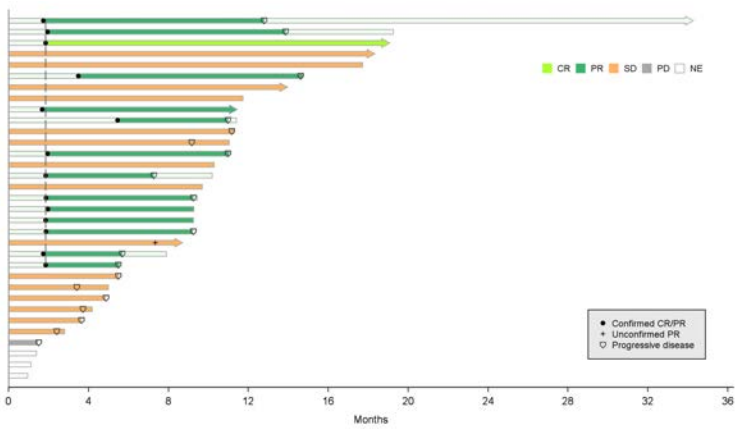
- Neuregulin 1 (*NRG1*) ligand binds HER3 → HER2/HER3 heterodimerization, oncogenesis
- Zenocutuzumab binds extracellular domains HER2, HER3, blocks anti-tumor activity; ADCC



- *NRG1*(+) PDAC (N= 33)
  - ORR 42% (39% PR; 3% CR)
  - Tumor reduction 82%
  - Med duration response 9.1 m

Time to Response; Time on Therapy



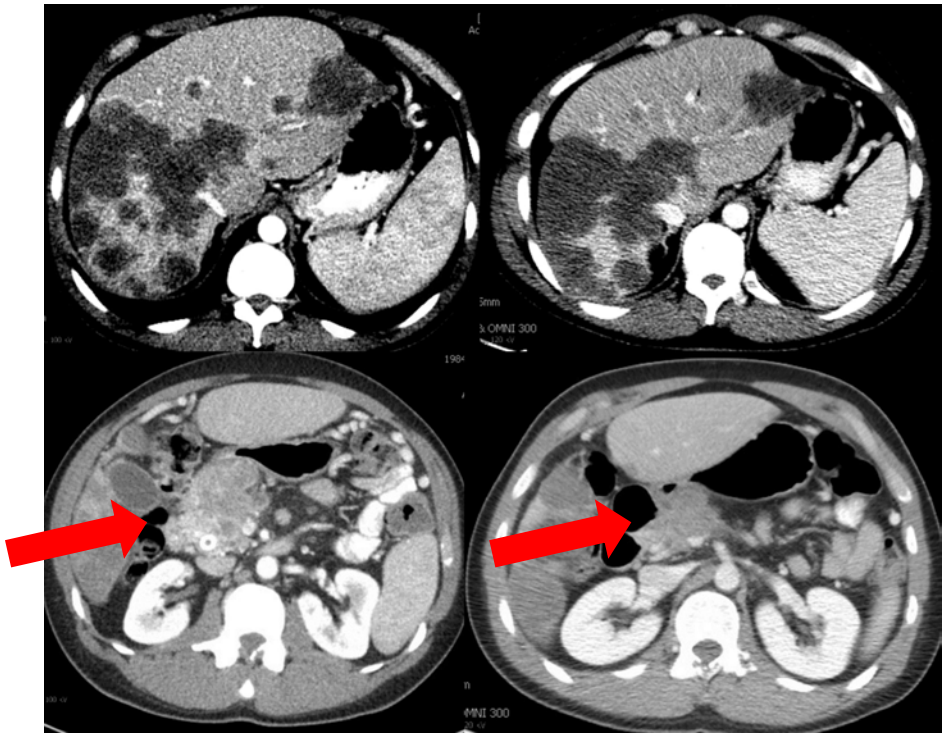


Schram, A……O'Reilly, EM. ESMO, 2023
Schram, A…Drilon, A. New Eng J Med, 2025

Pancreas *KRAS* Wild-Type: Bispecific Antibodies

Young Man; KRAS Wild-Type: *NRG1* Fusion

Zenocutuzumab



Baseline
Ca 19-9 ~450

T+ 2 m
Ca 19-9 <50

Features *NRG*1(+) PDAC Tumors

Younger patients/ early onset PDAC
KRAS wild-type
Low Ca 19-9, disease bulk

Can respond well to chemotherapy

Testing methodology key:
DNA, RNA

Schram, A. ASCO, 2021
Varghese, A. JNCI, 2021
Singhi, AD. Gastroenterology, 2019
Schram, A. Cancer Discovery, 2022
Schram, A…Drilon A. NEJM, 2025

Other Targets, Claudin, *MTAP* deletion, PRMT5i and IO in PDAC

Claudin 18.2: Promising Target in PDAC

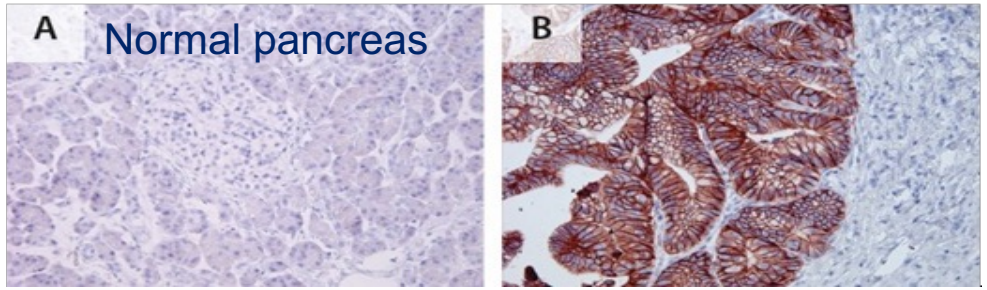
GLEAM: Randomized Phase II Gemcitabine/nab-Paclitaxel +/- Zolbetuximab

Metastatic PDAC
CLDN 18.2(+) 75%
ECOG 0-1
N= 357

2: 1

Gemcitabine/nab-Paclitaxel + Zolbetuximab N= 238
1000 mg/m^2 d1 (load); 600 mg/m^2 IV d1,15

Gemcitabine/nab-Paclitaxel N= 119



Zolbetuximab: mAb IgG1 CLDN 18.2: ADCC, CDC
Primary endpoint: OS
10.5 m → 15.0; 80% power, 2-sided 0.05, HR 0.776

Press release 10 2025: Primary endpoint not met

Eligibility: CLDN 18.2 mod/strong ≥ 75% tumor cells (IHC)

Park W…Kunieda F et al. ASCO 2022. Abstract TPS4186
https://newsroom.astellas.com/2025-10-13-Astellas-Confirms-Phase-2-GLEAM-Trial-Did-Not-Meet-Primary-Endpoint-of-Overall-Survival-in-Patients-with-Metastatic-Pancreatic-Cancer

Claudin-Based Therapy: ADC

IBI343: Fully Human anti-Claudin 18.2 mAb, Exatecan

Innovent; Arcotatug Tavatecan

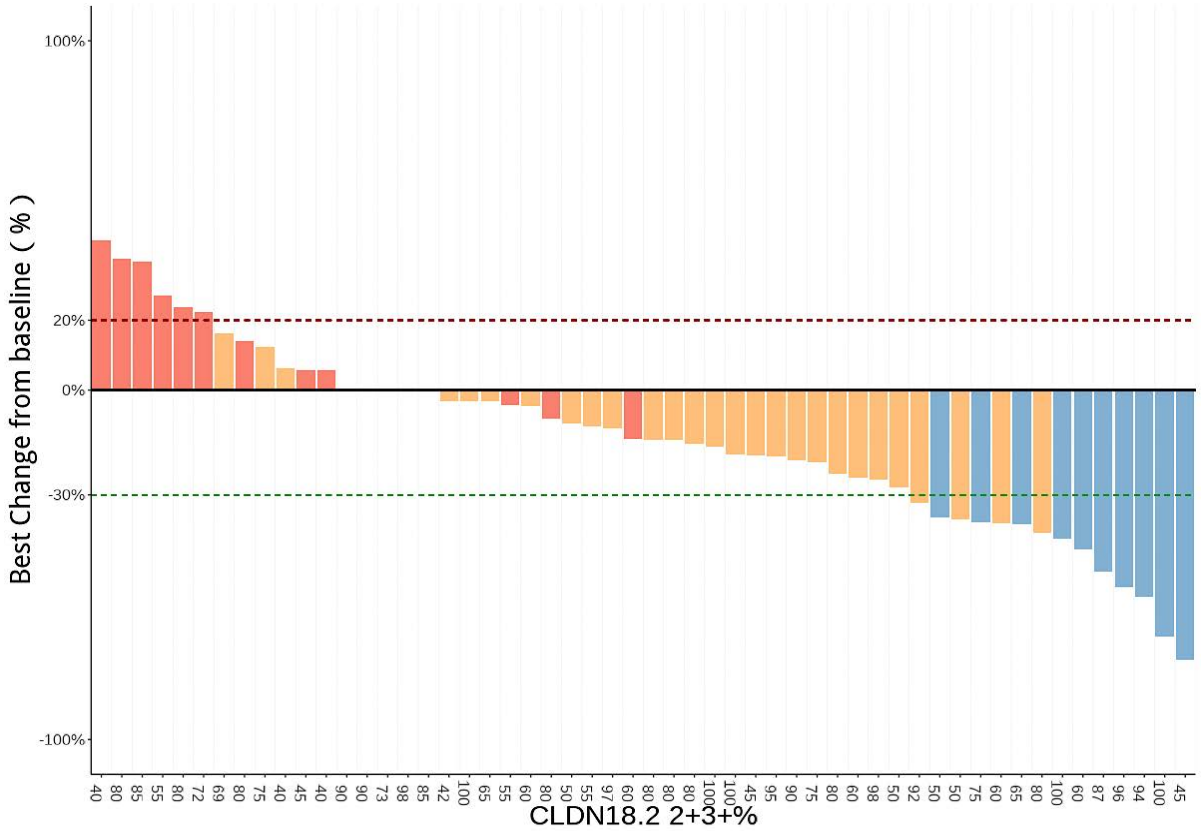
Dose escalation IBI343, dose expansion **6mg/kg IV Q3W** (China) CLDN18.2 2+- 3+ ≥40%

Median age 62, 66% 2L+ therapy

cORR 17.9%, DCR 73.2% (N= 56)

mPFS 4.2 m, mOS 8.8 m

ORR 35% mOS 12.1 m irinotecan naïve (N= 20)



N= 62

Grade 3: Anemia 8%, neutrophils 23%, platelets 7%, nausea 3%

NCT05458219

Claudin-Based Therapy: ADC

IBI343: G-Hope-002 Phase III

Innovent; Arcotatug Tavatecan: Recruiting Fudan, China

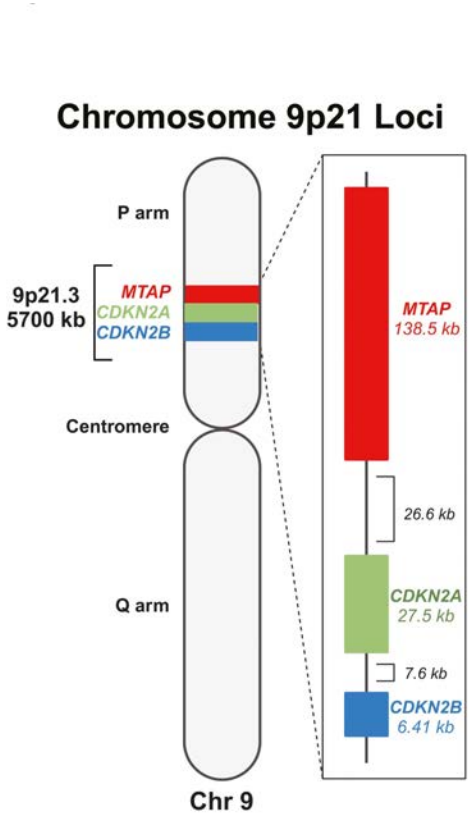
Primary endpoint: OS
Claudin threshold: not defined

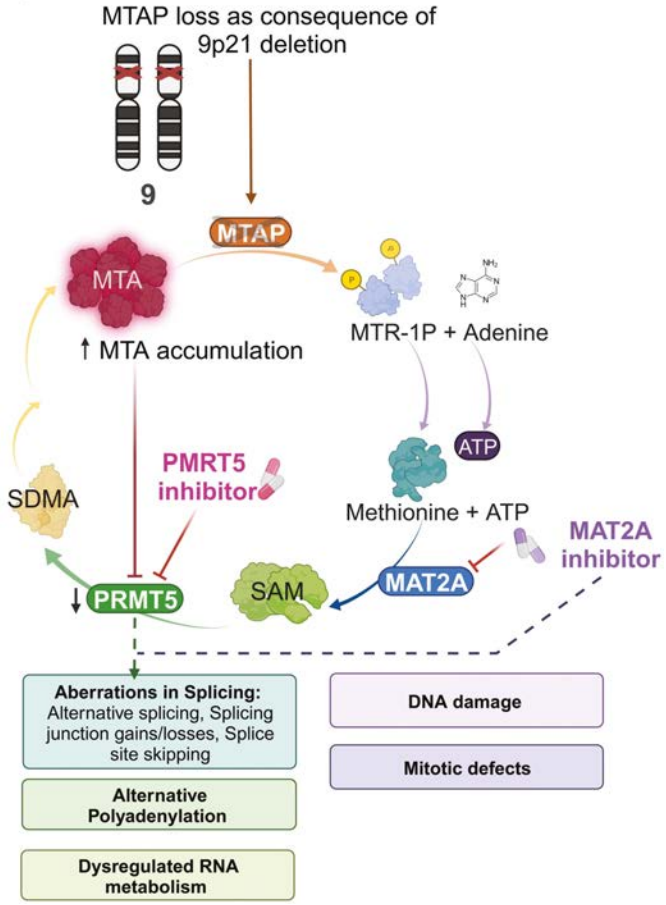
NCT07066098

MTAP Targeting Biology

Synthetic Lethality: New Approach – PRMT5, MTA Inhibition

- Methylthioadenosine phosphorylase (*MTAP*)
- *MTAP* deletion/loss ~15% multiple solid tumors; 8% GI cancers; PDAC 15- 25%
- *MTAP* adjacent, often co-deleted *CDKN2A* (9p21)
- *MTAP, CDKN2A* associated with resistance to IO therapies ('cold' TME)
- *MTAP*-loss novel biomarker for agents inhibiting MAT2A and PRMT5
- *MTAP* associated with resistance to ICB



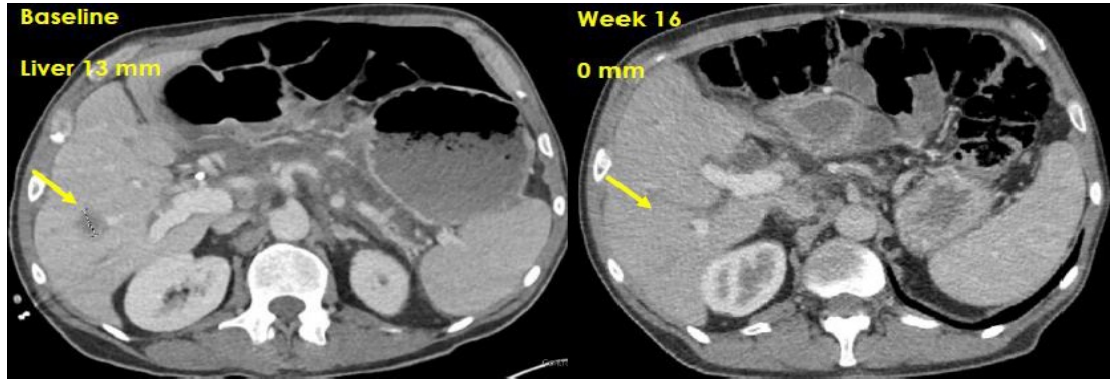


Ngoi, NYL…Rodon Ahnet. Oncologist, 2024
Stopa, N. Cell Reports, 2016
Rodon, J. AACR-EORTC-NCI, 2023

MTAP Targeting: PRMT5 Inhibitors

MTAP-Deleted Solid Tumors: Phase I AMG 193 (2nd Gen)

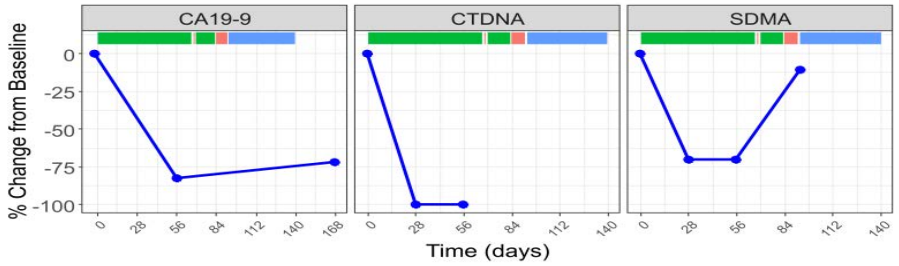
MTD 1200 mg PO; Efficacy in Multiple Solid Tumors

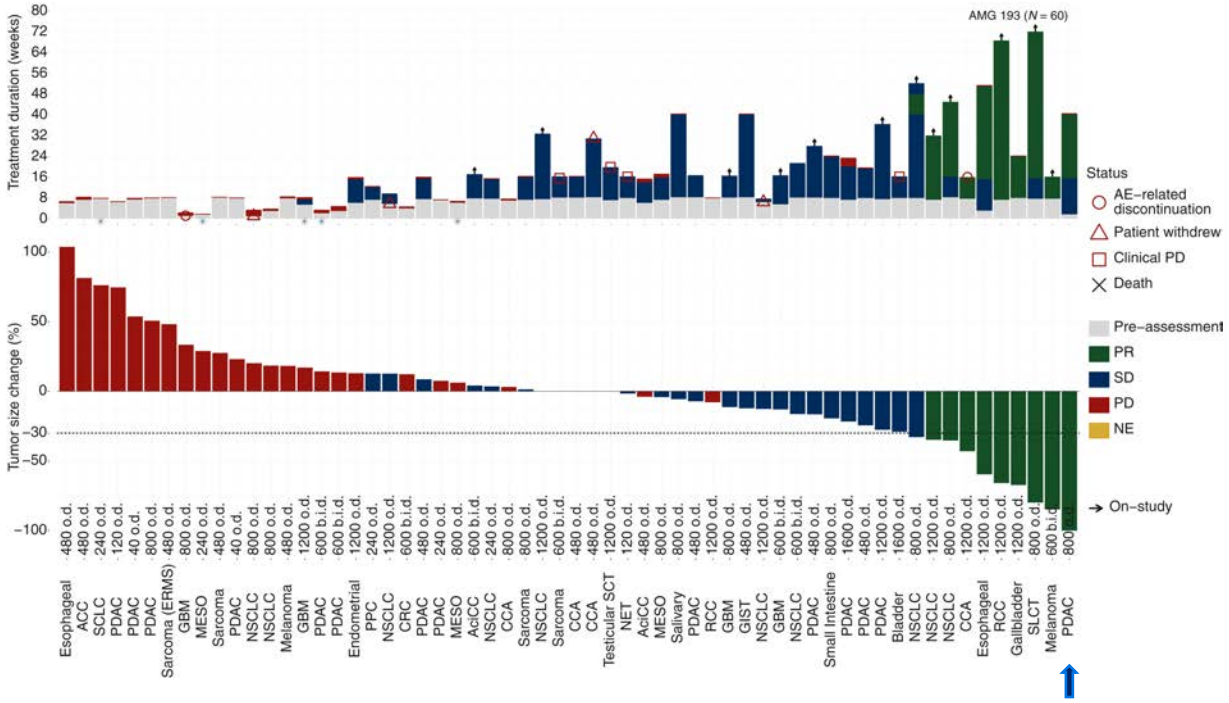


PDAC

65 y/o male
2 prior lines

- *TP53m*
- *CDKN2A/2B*-loss, *MTAP*-loss
- *KRAS*





- ESMO 2024 PDAC sub-cohort N= 23: 5 PR's (2 confirmed); 4 SD
- Multiple PRMT5, MAT2A agents/combinations in development

Rodon J et al. AACR-EORTC-NCI 2023.Abstract PR006
Sacher A et al. ESMO 2024.Abstract 604O
Rodon J…O'Neil B et al. *Ann Oncol.* 2024

Pancreas Cancer: *MTAP* Targeting

Ongoing/Planned: PRMT5 Inhibitors Solid Tumors/PDAC

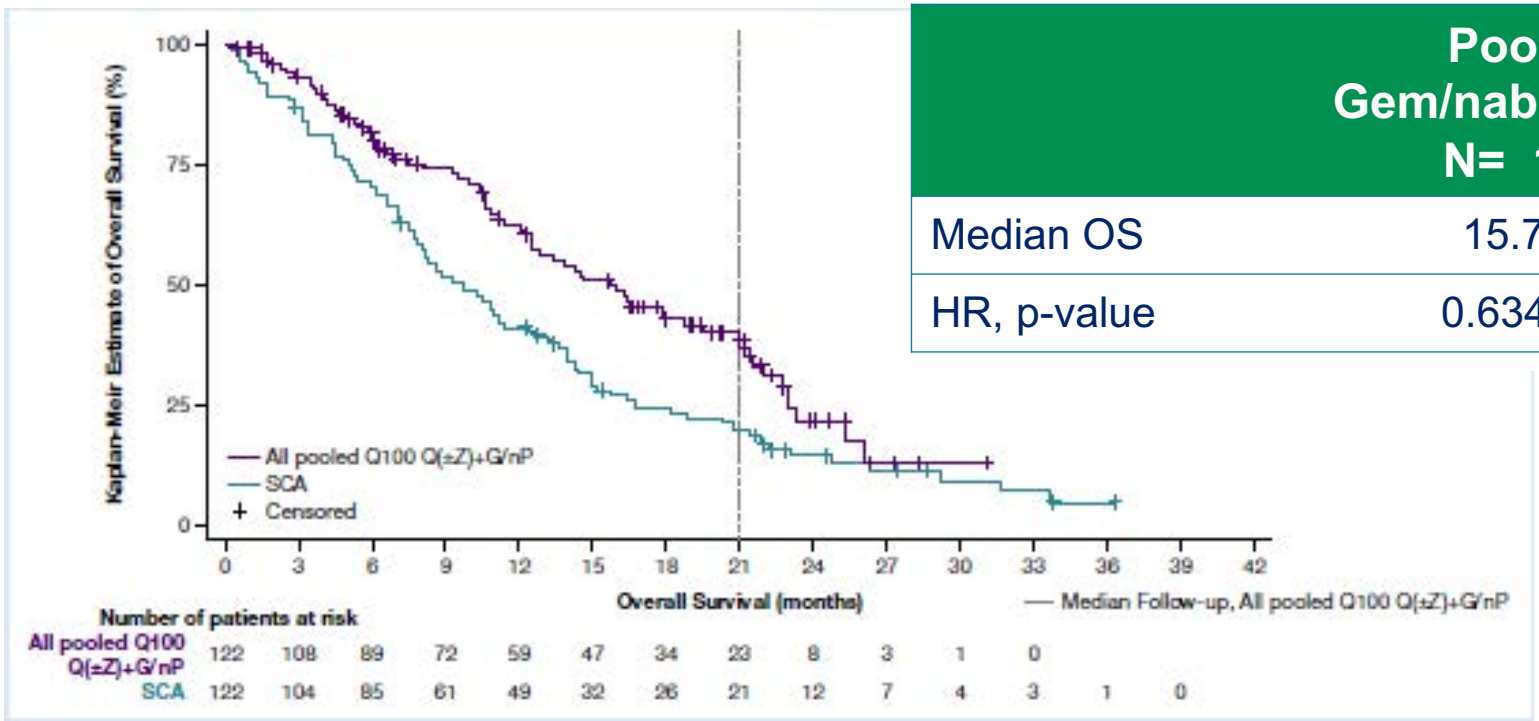
Drug/Target	Trial/Population	Design	NCT
AMG 193	*MTAP*ESTRY	Phase Ib + mFOLFIRINOX or Gemcitabine/nab-Paclitaxel + RAS therapies	NCT06360354
BMS-986504 (MRTX1719)	Mountain-TAP 30	1L Rand Phase II/III Gem/nab-P +/- BMS-986504	NCT07076121
TNG462 (vopimetostat)		Advanced solid tumors PDAC 2L ORR 25%; DCR 79%*	NCT05732831
TNG462		2L Rand Phase III TNG-462 vs chemo	NCT pending
TNG462 + Daraxonrasib or Zoldonrasib	*MTAP*del + *RAS*^{MUT} or *KRAS* G12D	Phase I Novel, novel targeting	NCT0692259
AZD3470	PRIMROSE	Phase I/IIa	NCT06130553

*Press release 10/23/2025

Pancreas Cancer: Adenosine Immune Targeting

ARC-8: Phase I/IB: Gem/Nab-P + Quemliclustat (anti-CD73)

Promising Early Signal – Phase III PRISM 1 Enrollment Completed



	Pooled Gem/nabP+Q+/-Z N= 122	SOC Control N= 122
Median OS	15.7 m	9.8 m
HR, p-value	0.634 (0.471, 0.854); p= 0.0030	

PRISM 1: Randomized phase III gemcitabine/nab-paclitaxel +/- quemliclustat/placebo (N= 610; 2:1)

Wainberg ZA…O'Reilly EM et al. ASCO GI 2024. Abstract 665
Wainberg, Z…O'Reilly, EM. Nat Med, 2026
NCT06608927

Pancreas Cancer & Therapy 2026 – Changing….

Pancreas Cancer Current 2026	• Cytotoxic-based 3 or 2 drug combinations for most • Targeted: *BRCA*/HRD, *RAS*-wild-type – fusions
RAS Therapies	• RAS inhibitors – new 2L standard 2026? • Rapidly moving to 1L, Adjuvant • Multiple agents, multiple mechanisms in development
Other Targets	• *MTAP*-loss: PRMT5 inhibitors, Claudin • Immunotherapy: Adenosine modulation, CD40 • Vaccines: Personalized neoantigen, RAS immunotherapy

QUESTIONS?

We are taking a short break!

The program will resume at 10:00 AM ET

Up Next…

Drs Deborah K Armstrong and David M O'Malley discuss the management of ovarian cancer

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