AACR IO
DISCOVERY AND INNOVATION IN CANCER IMMUNOLOGY:
REVOLUTIONIZING TREATMENT THROUGH IMMUNOTHERAPY
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AACR
American Association for Cancer Research®

New Developments in Drugging the Adenosine Pathway

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Disclosure Information

Juan C. Jaen

I have the following relevant financial relationships to disclose:

- Employee of: Arcus Biosciences
- Stockholder in: Arcus Biosciences, Hexagon Biosciences, Shasqi, Breakpoint Therapeutics

The Tumor Microenvironment Continuously Produces Immunosuppressive Adenosine in Response to Cell Death

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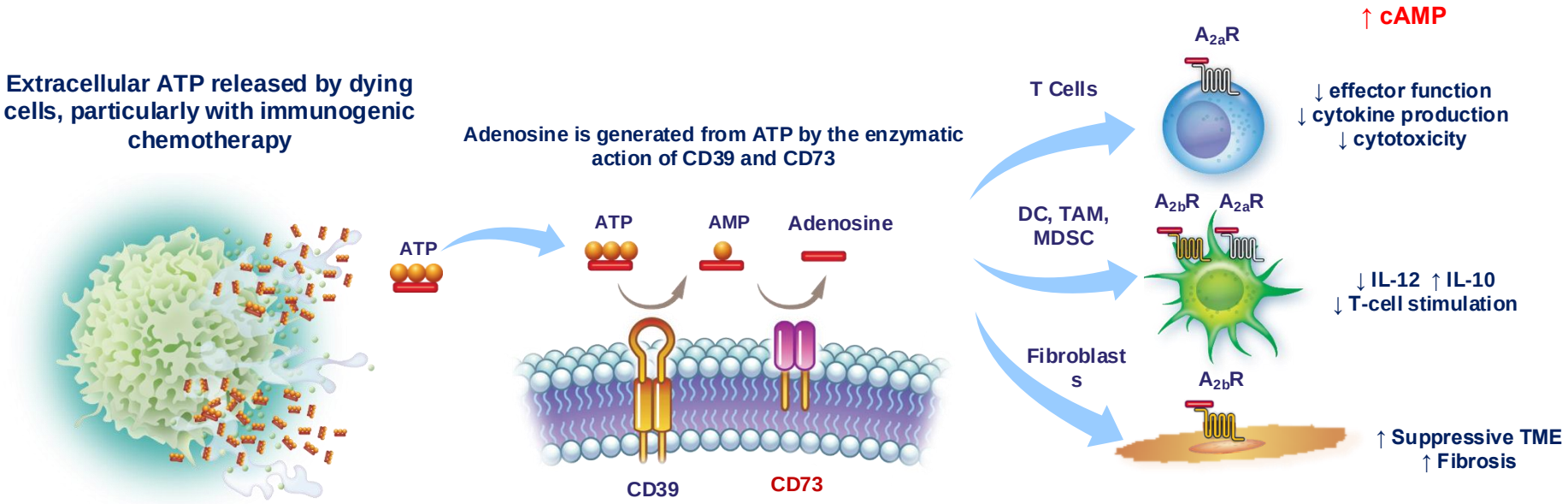

Biological Impact of Quemliclustat and Etrumadenant on the Tumor Microenvironment

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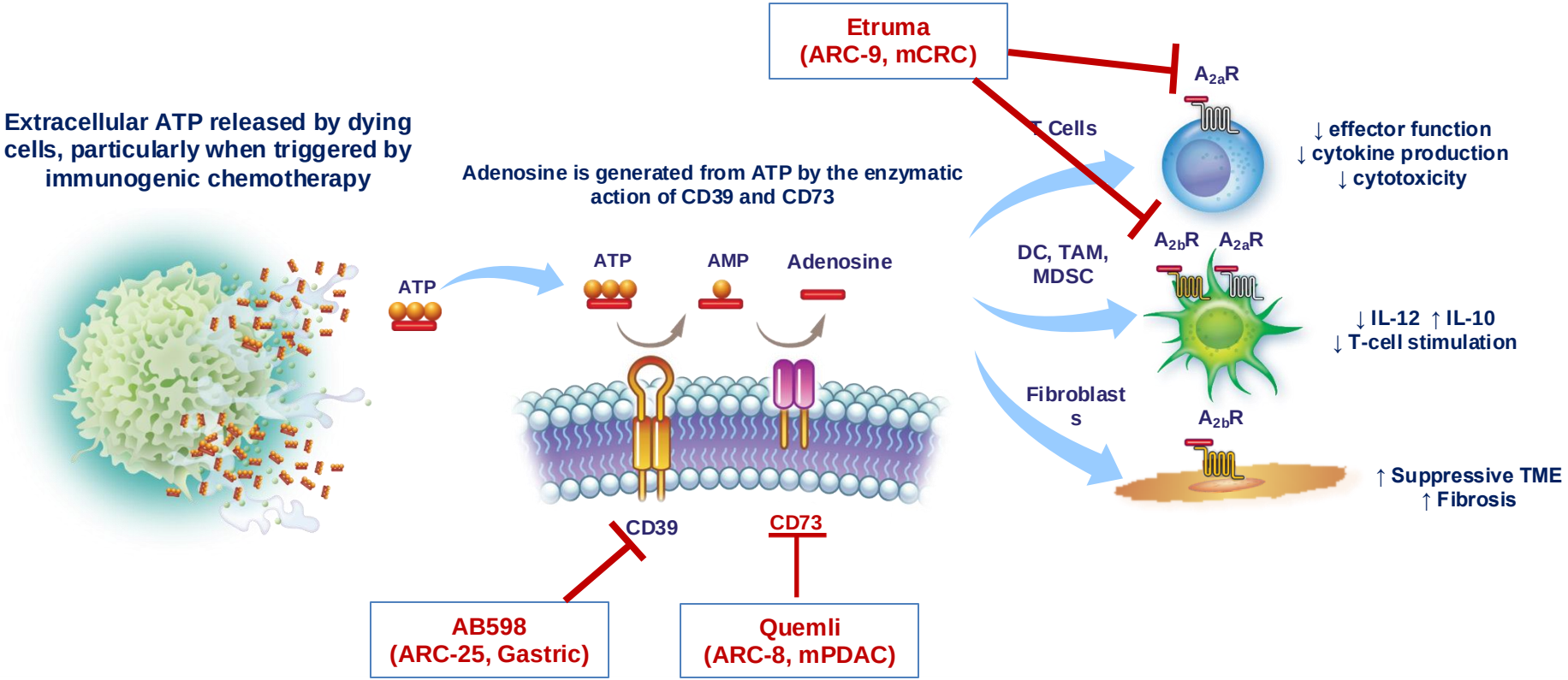

Inhibition of Adenosine Axis Enhances Multiple Steps of the Cancer Immunity Cycle

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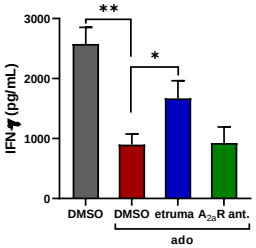
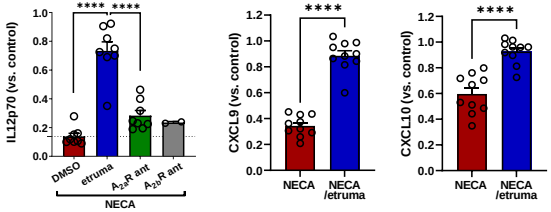
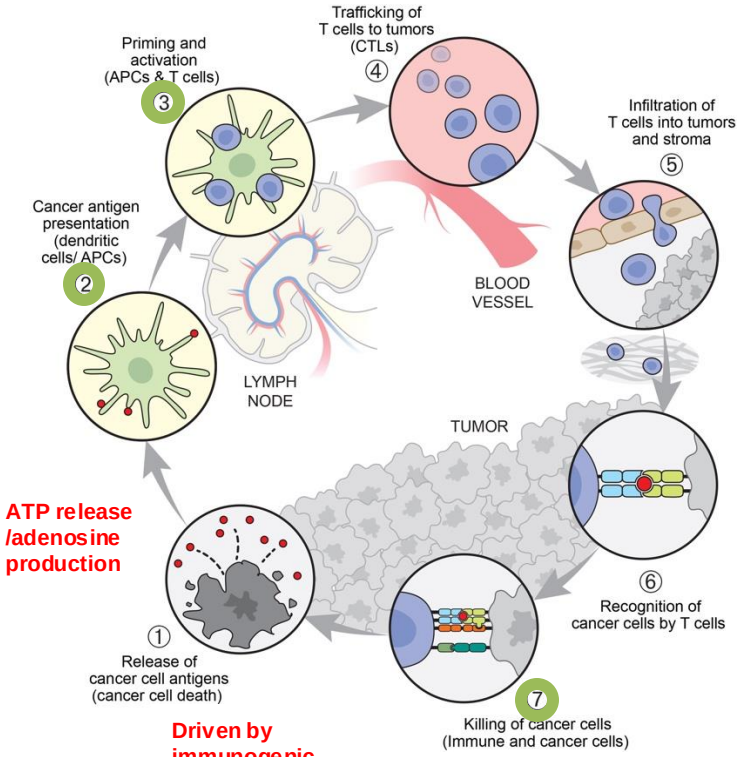
moDC/CD4 MLR



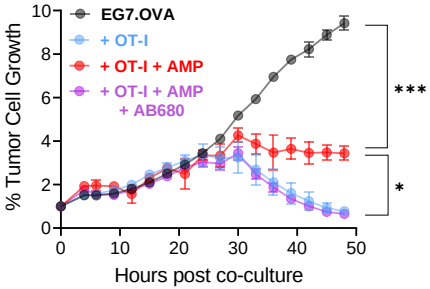
Isolated Human Dendritic Cells



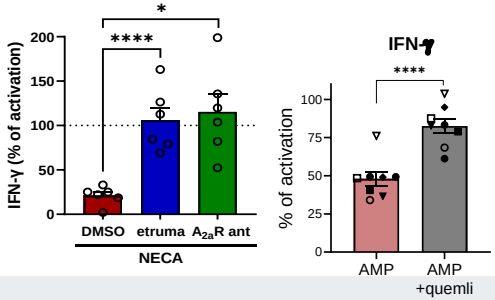
Mellman et al. *Immunity*. 2023



Antigen-Specific Killing



Isolated Human CD8+ T Cells



Enhanced AT3-OVA Tumor Control and Immune Infiltration Caused by Etrumadenant + Platinum-based Chemotherapy

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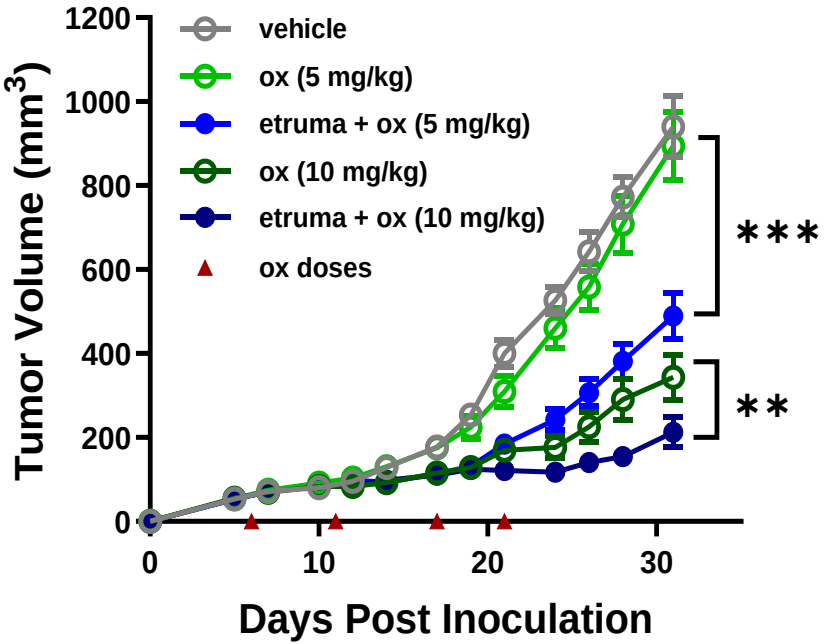
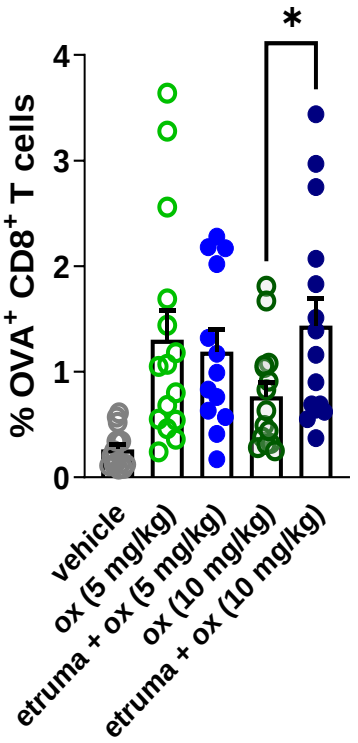
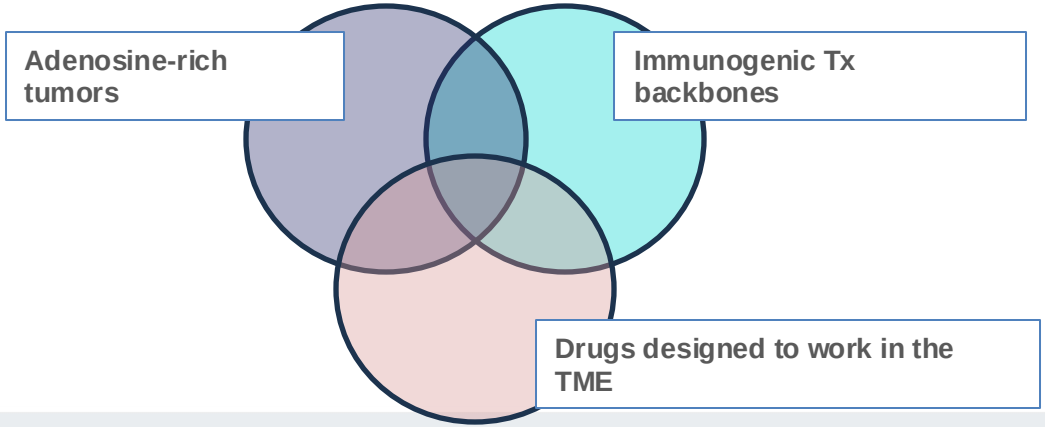




Therapeutic Hypothesis

- Tumors with high capacity to convert ATP into adenosine will not experience the full anti-tumor immune response that would otherwise result from certain SOCs (e.g., platinum-containing chemo, radiation, etc.)
- Evaluate adenosine agents…
  - in combination with immunogenic backbones
  - in tumor types that contain high levels of adenosine / adenosine-generation machinery
- Clinical benefit will, most likely, be apparent as long-term PFS/OS improvement (resulting from improved adaptive immunity, TME remodeling, etc.)



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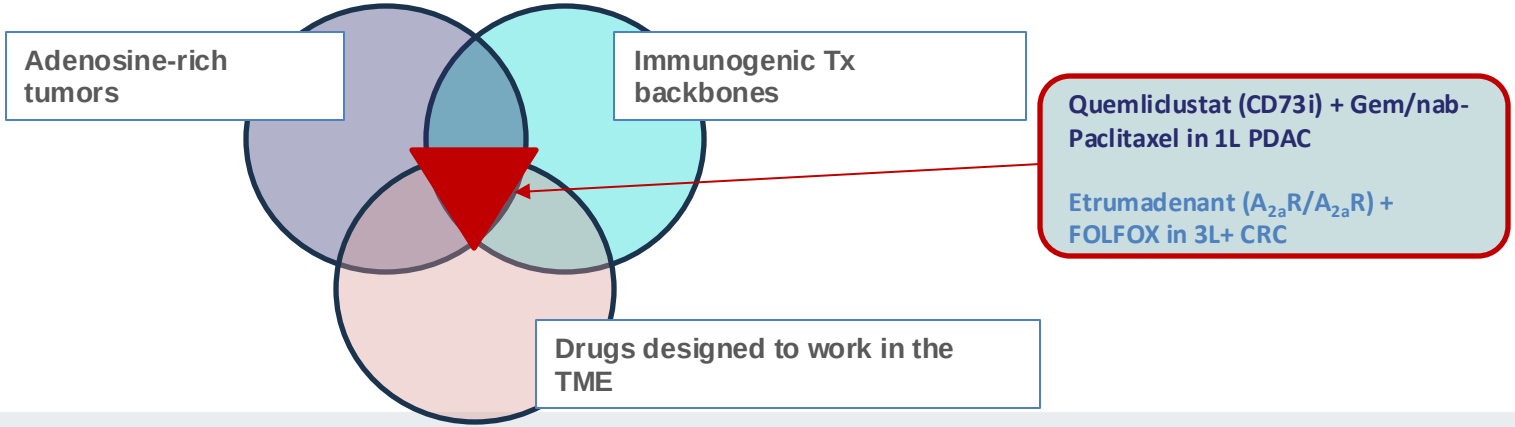
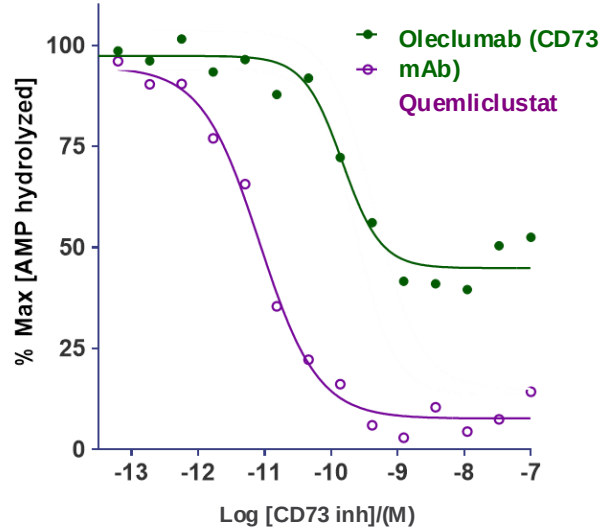


Unlike Oleclumab, Quemliclustat is a Potent Inhibitor of Both Soluble and Cell-Bound CD73

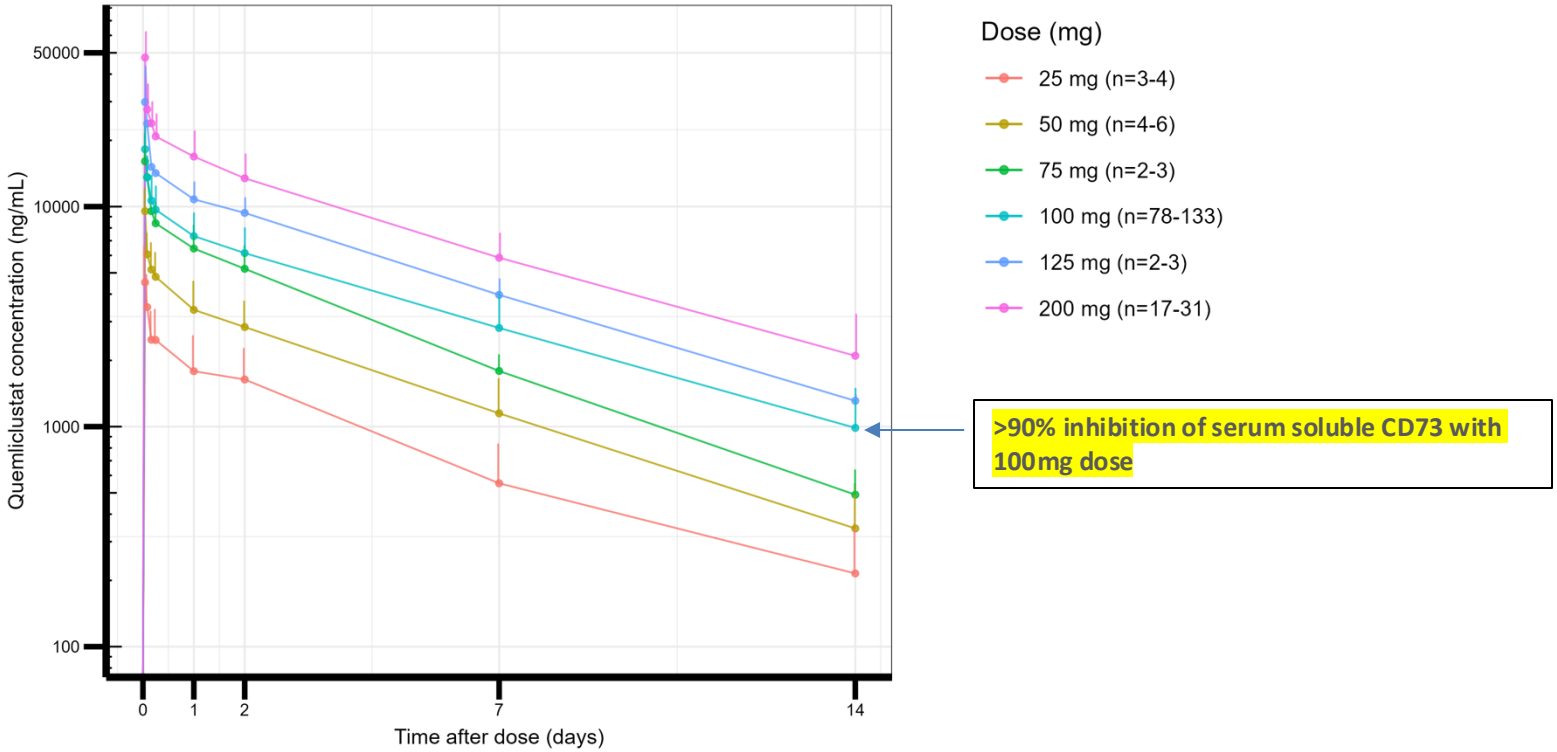
	Potency (IC_{50}, nM)		
Compound	**Soluble hCD73**	**Cell surface CD73 ($CD8^+$)**	**Cell surface CD73 (CHO)**
Quemliclustat	0.014	0.0084	0.047
Oleclumab	0.017	0.096	0.28

Quemli (AB680) potently inhibits CD73 enzymatic activity on $CD8^+$ T Cells



Oleclumab (MEDI9447) was synthesized by Arcus based on the following reports: Hay et al., OncoImmunology (2016) 5, e1208875; Patent Appl. US 2016/0129108

Human PK / PD Profile of Quemliclustat



Final Overall Survival Analysis for Quemliclustat (CD73 Inhibitor) and Zimberelimab (α-PD-1) in Pancreatic Cancer (ARC-8 Study)

Data presented by Dr. Zev Wainberg at ASCO-GI (2024)

CD73 is Abundantly Expressed on Multiple Cell Types in Pancreatic Cancer

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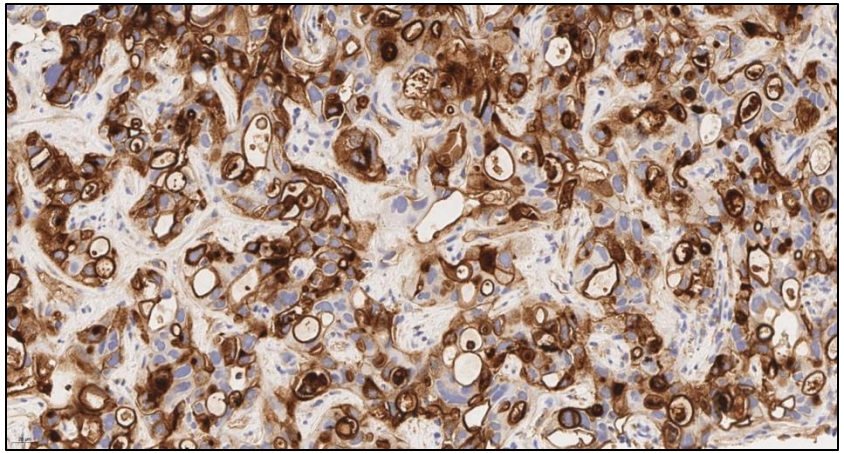
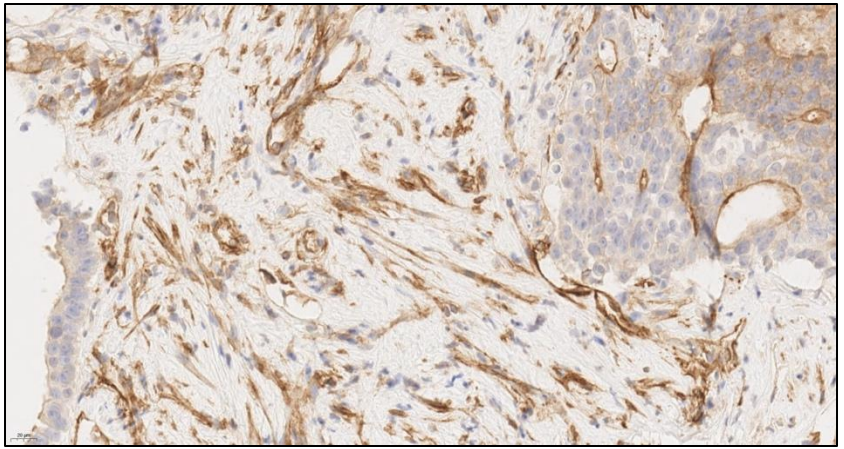
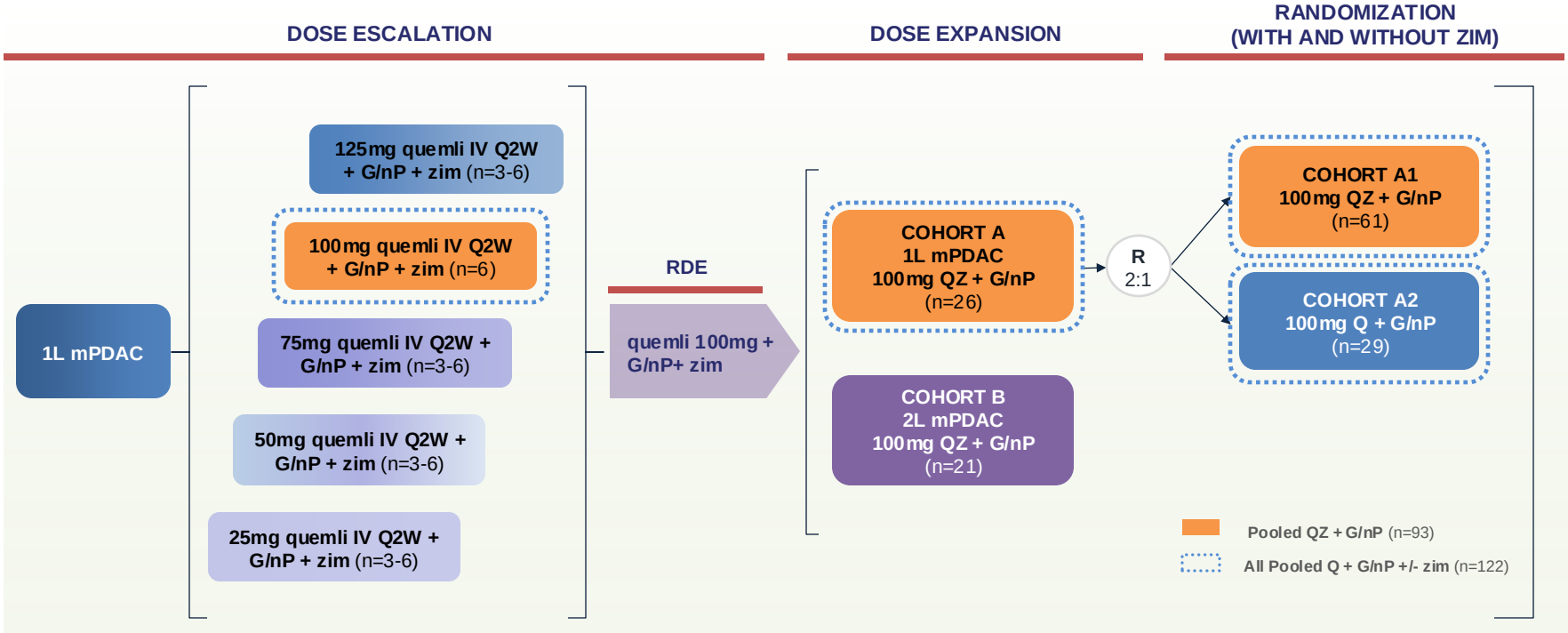
Strong Cancer Cell Staining



Strong Stromal/Fibroblast Staining



ARC-8 Study Design Included Dose Escalation, Expansion and Randomized Portions



G/nP: gemcitabine/nab-paclitaxel; Q/quemli: quemliclustat; Z/zim: zimberelimab
NCT #: NCT04104672
Wainberg ZA, et al. ASCO GI, Jan 19, 2024, data cutoff: June 19, 2023

ORR in Quemli-containing Cohorts Similar to Historical Data with Chemo Only

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- Wainberg ZA, et al. ASCO GI, Jan 19, 2024, data cut off of June 19, 2023

	A2: Q+G/nP (n=29)	A1: QZ+G/nP (n=61)	Pooled Q100 QZ+G/nP (n=93)	All pooled Q100 Q(±Z)+G/nP (n=122)
ORR, % (95% CI)	41 (24, 61)	34 (23, 48)	38 (28, 48)	39 (30, 48)
Confirmed ORR, % (95% CI)	38 (21, 58)	25 (15, 37)	26 (17, 36)	29 (21, 38)
Median DOR, months (95% CI)	5.5 (4.1, 11.2)	3.7 (2.6, 10.5)	4.7 (3.3, 9.3)	5.4 (3.7, 9.3)
Median PFS, mo (95% CI)	8.8 (6.4, 12.6)	4.9 (3.7, 6.0)	5.4 (4.9, 7.3)	6.3 (5.4, 7.7)
Median OS, mo (95% CI)	19.4 (12.1, 23.0)	14.6 (10.6, 21.5)	13.9 (11.1, 18.7)	15.7 (12.4, 20.9)
12-mo OS, %	72.3	60.9	59.6	62.7
18-mo OS, %	54.2	43.5	39.3	42.8
Median OS follow-up, mo (95% CI)	21.1 (19.8, 22.3)	17.6 (16.6, 20.3)	20.3 (17.1, 24.6)	21.0 (19.0, 22.8)
Subsequent systemic anticancer therapy, %	48.3	42.6	46.2	46.7

Based on RECIST v1.1.
DOR, duration of response; G/nP, gemcitabine/nab-paclitaxel; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q, quemliclustat; RECIST, Response Evaluation Criteria in Solid Tumors; Z, zimberelimab.

However, Promising Trends in PFS and, Particularly, OS

- Wainberg ZA, et al. ASCO GI, Jan 19, 2024, data cut off of June 19, 2023

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Favorable OS for Patients With & Without Liver Metastasis

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Liver Mets at Baseline	A2: Q + G/nP (n=17)	A1: QZ + G/nP (n=42)	Pooled Q100 QZ + G/nP (n=62)	All Pooled Q100 Q(±Z) + G/nP (n=79)	NAPOLI-3 (n=309)
Events (%)	11 (64.7)	26 (61.9)	40 (64.5)	51 (64.6)	242 (78.3)
Median OS, months	**12.1**	**12.2**	**11.1**	**12.1**	**8.6**
95% CI	10.0, 20.9	6.2, 17.9	8.1, 14.5	10.0, 15.7	

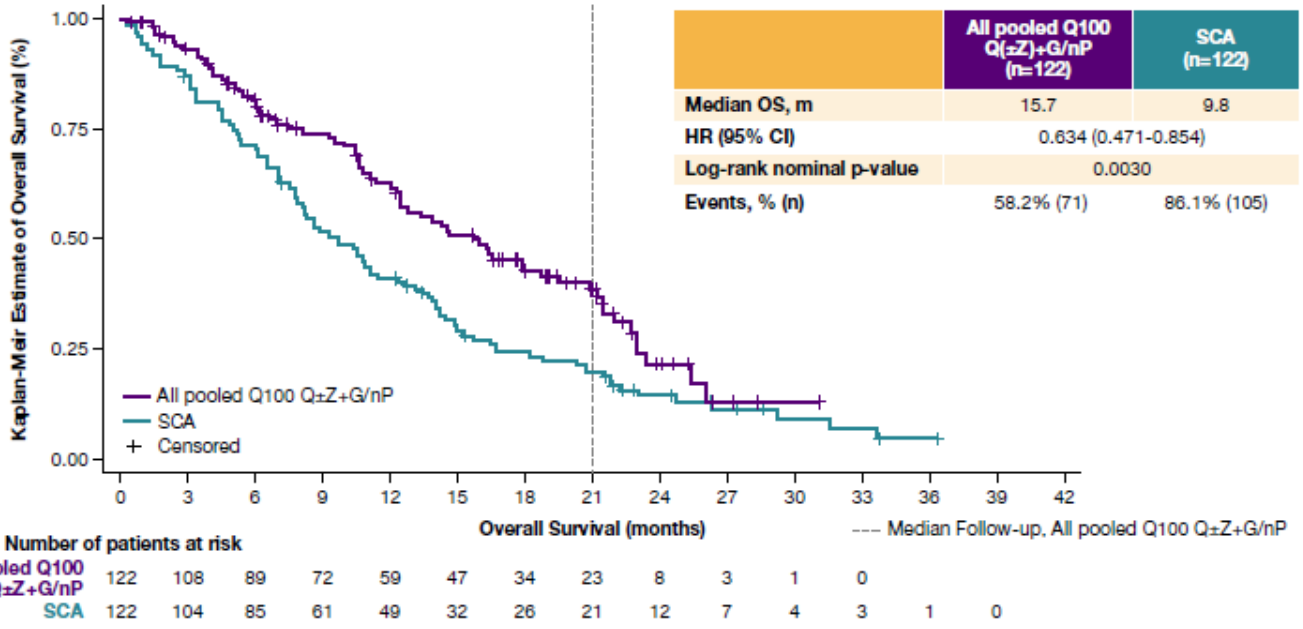
No Liver Mets at Baseline	A2: Q + G/nP (n=12)	A1: QZ + G/nP (n=19)	Pooled Q100 QZ + G/nP (n=31)	All Pooled Q100 Q(±Z) + G/nP (n=43)	NAPOLI-3 (n=78)
Events (%)	4 (33.3)	7 (36.8)	16 (51.6)	20 (46.5)	43 (55.1)
Median OS, months	**22.0**	**21.2**	**21.2**	**21.5**	**13.8**
95% CI	17.9, NE	14.6, NE	13.9, 25.4	17.9, 25.4	

BL: Baseline; CI: confidence interval; **G/nP: gemcitabine/nab-paclitaxel**; mets: metastasis; mOS: median overall survival; mos: months; NE: not estimable; OS: overall survival; Q: quemliclustat

NAPOLI-3: Wainberg, et al. *The Lancet*. Sept 2023. https://doi.org/10.1016/S0140-6736(23)01366-1. Data shown ior the G/nP arm only

Wainberg ZA, et al. ASCO GI, Jan. 19, 2024, data cut off of June 19, 2023

Quemli-based Regimen Reduced Risk of Death by 37% and increased mOS by 5.9 months Compared to SCA

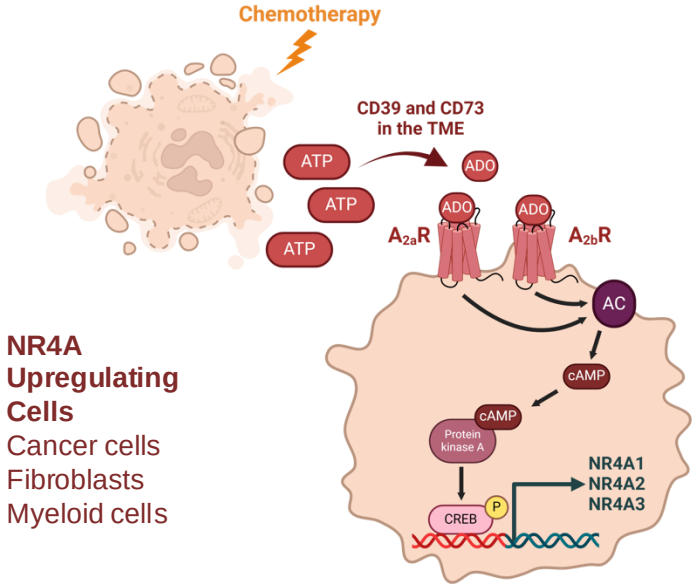


	All pooled Q100 Q(±Z)+G/nP (n=122)	SCA (n=122)
Median OS, m	15.7	9.8
HR (95% CI)	0.634 (0.471-0.854)	
Log-rank nominal p-value	0.0030	
Events, % (n)	58.2% (71)	86.1% (105)

Wainberg ZA, et al. ASCO GI, Jan. 19, 2024, data cut off of June 19, 2023

NR4A Gene Expression is a Proxy for $A_{2a}R$ / $A_{2b}R$ Adenosine Receptor Signaling

- **$A_{2a}R$ & $A_{2b}R$ receptors coupled to adenylate cyclase & drive increases in cAMP upon activation**
- **cAMP → PKA → pCREB → NR4A1-3 upregulation**



NR4A(1-3) Expression is Associated with Poor OS (and PFS) in 1L mPDAC Patients Treated with Gem/nab-Pac (GA) – PRINCE Trial

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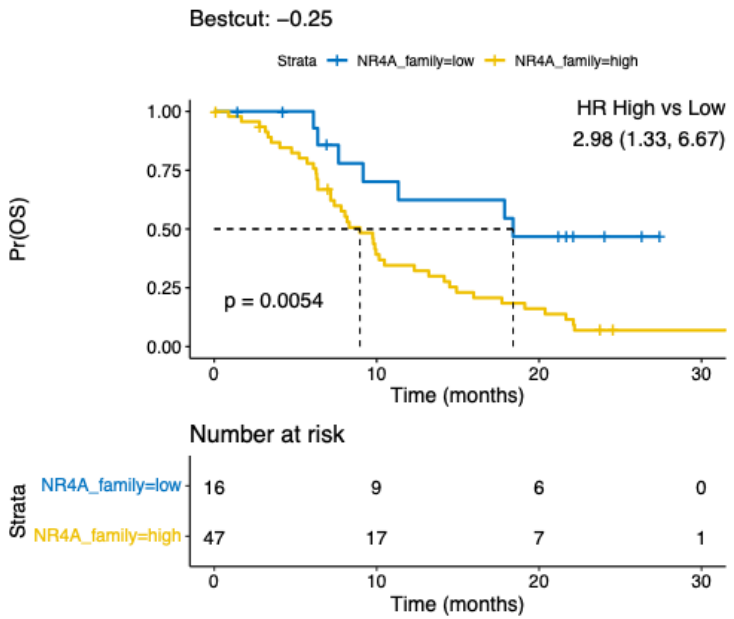
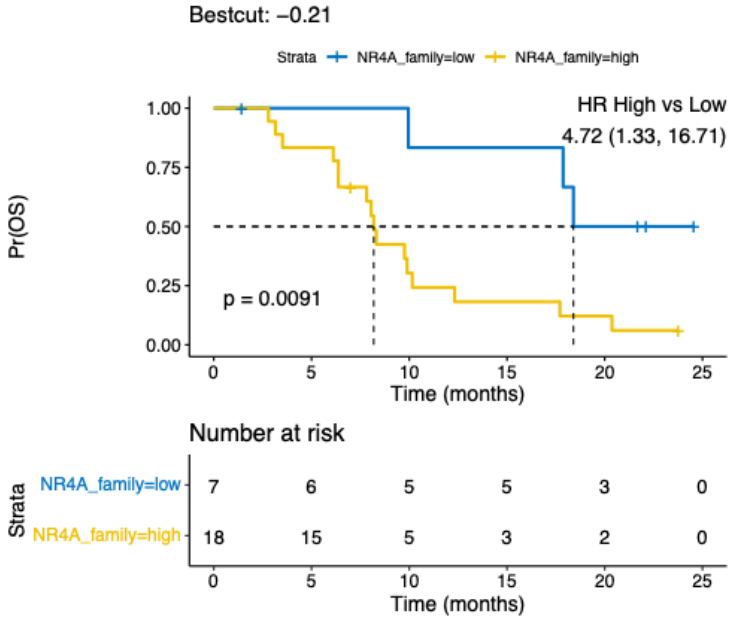
PRINCE Study (ALL PATIENTS)



PRINCE Study (GA + Nivo Cohort)



Transcriptional analysis performed by Arcus on published bulk mRNA data from the PRINCE Trial (NCT03214250); Padron et al., NATURE MEDICINE (2022)

In ARC-8 Trial, NR4A Gene Expression is Downregulated by a Quemli-containing Regimen

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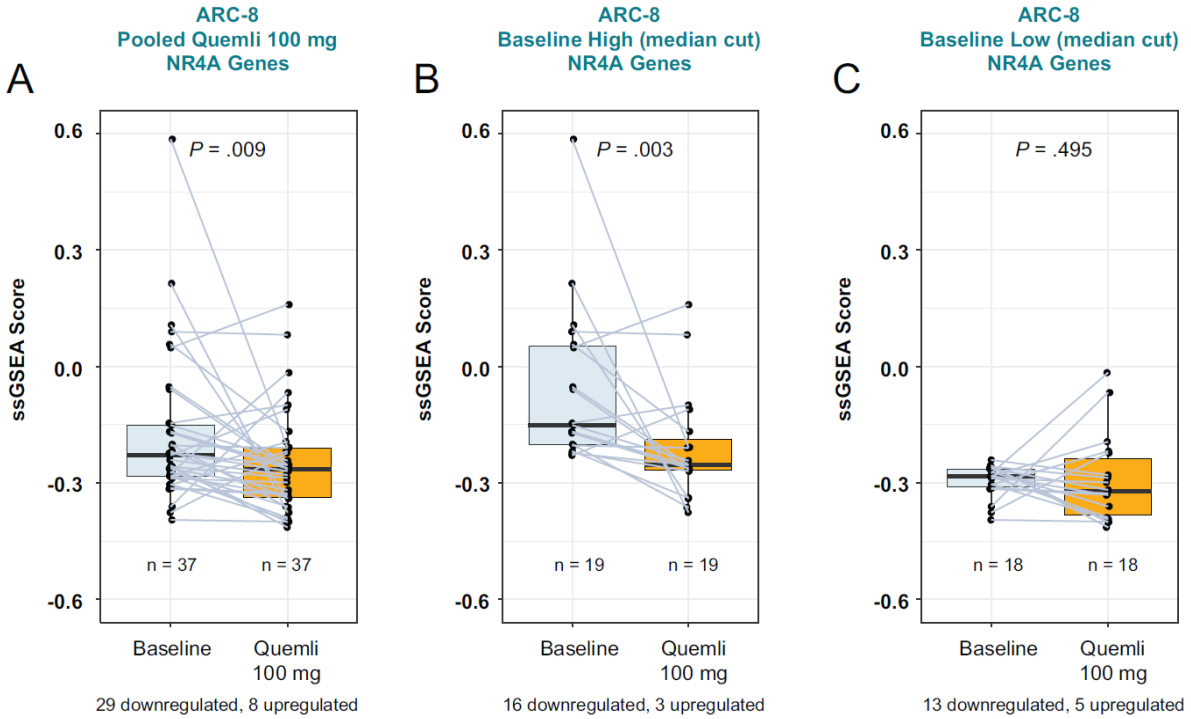

Kim et al., AACR Spec. Conf. Cancer Research (Pancreatic Cancer); Sept 15-18, 2024

In the ARC-8 Trial, Treatment with a Quemli-containing Regimen Led to Increases in Tumor Inflammation

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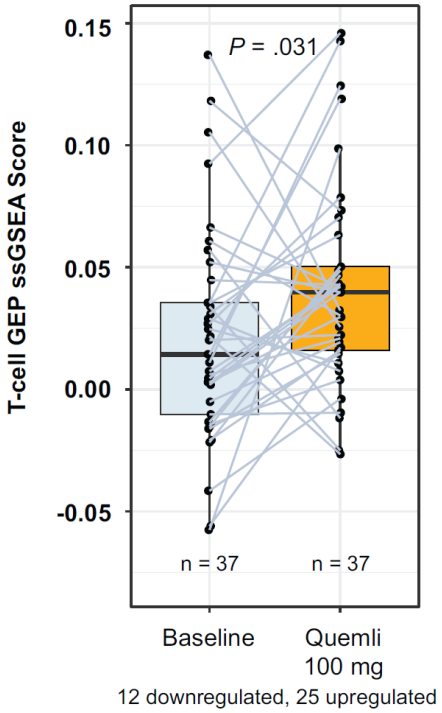
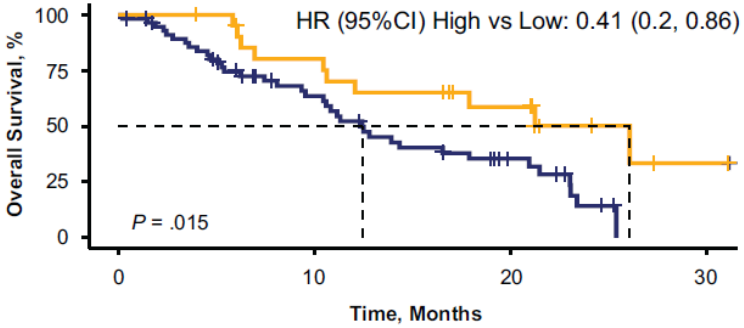
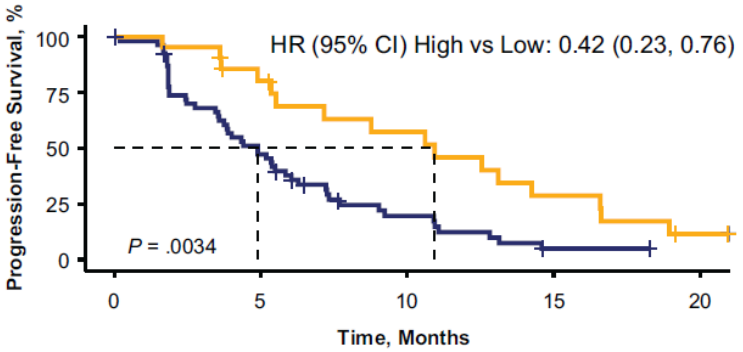


Kim et al., AACR Spec. Conf. Cancer Research (Pancreatic Cancer); Sept 15-18, 2024

Patients with the High Baseline NR4A Expression Had Greater Benefit from a Quemli-containing Regimen





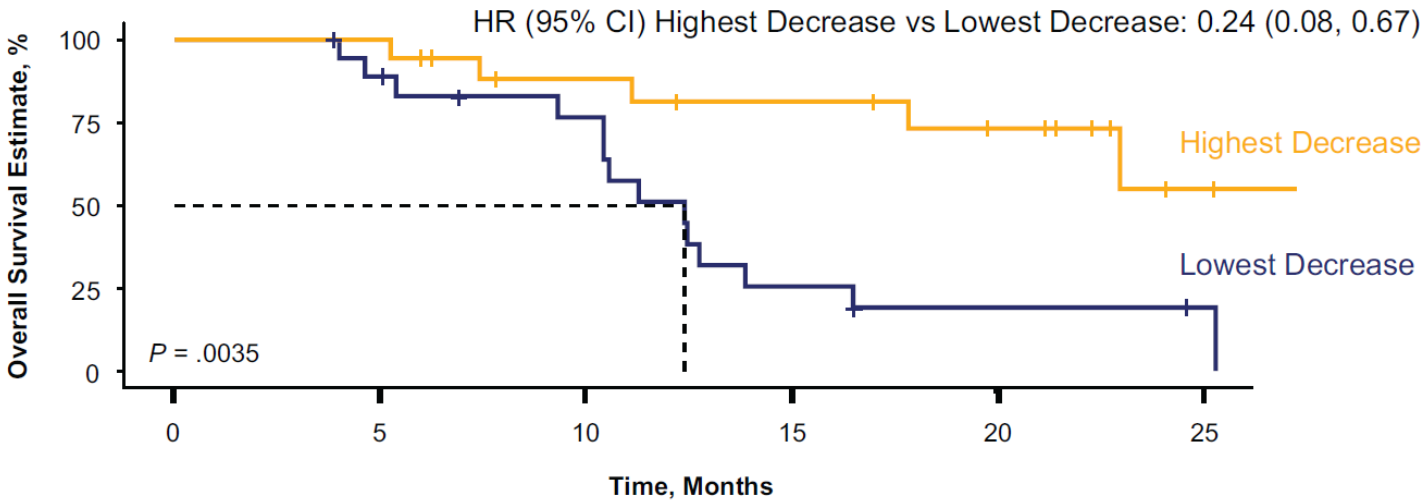
Number at Risk				
Low NR4A genes	58	28	10	0
High NR4A genes	22	16	9	1

Number at Risk					
Low NR4A genes	58	25	8	1	0
High NR4A genes	22	15	10	5	0

Lowest NR4A Expression Highest NR4A genes

Kim et al., AACR Spec. Conf. Cancer Research (Pancreatic Cancer); Sept 15-18, 2024

Patients with the Highest Decreases in Tumor NR4A Expression Experienced an OS Benefit in ARC-8 Trial



Number at Risk						
Lowest Decrease	19	16	12	4	2	1
Highest Decrease	18	18	13	11	8	2

Kim et al., AACR Spec. Conf. Cancer Research (Pancreatic Cancer); Sept 15-18, 2024

MORPHEUS-PDAC Study Design: Etruma (A2a/A2b) + Atezo + GnP vs GnP Standard of Care Control

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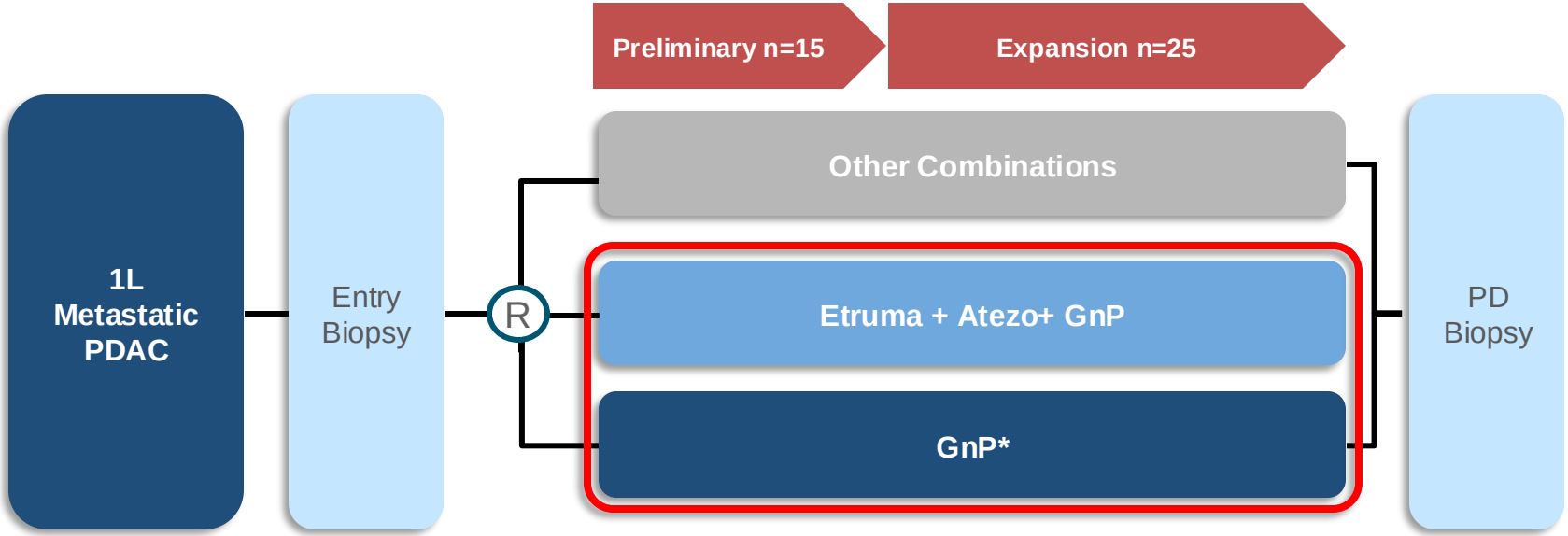
Phase Ib/II, global, open-label, randomized evaluation of atezolizumab (atezo) + etrumadenant (etruma) + chemotherapy (chemo) vs chemo alone in MORPHEUS-PDAC

Abstract CT212
Poster 12

Kyu-pyo Kim,[1] Mariano Ponz-Sarvise,[2] Teresa Macarulla,[3] Angela Alistar,[4] Eileen M. O'Reilly,[5] Mathew Boakye,[6] Hen Prizant,[7] Trista Xu,[8] Fiona Young,[9] Janet Lau,[7] Do-Youn Oh,[10] Jill Lacy[11]

[1]Asan Medical Center, Seoul, Republic of Korea; [2]Cancer Center Clínica Universidad de Navarra, Pamplona, Spain; [3]Vall d'Hebron University Hospital, Barcelona, Spain; [4]Atlantic Hematology Oncology, Atlantic Medical Group, Morristown, NJ, USA; [5]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [6]Arcus Biosciences, Hayward, CA, USA; [7]Genentech, Inc, South San Francisco, CA, USA; [8]F. Hoffmann-La Roche Ltd, Mississauga, Canada; [9]F. Hoffmann-La Roche Ltd, Welwyn Garden City, UK; [10]Seoul National University College of Medicine, Seoul, Republic of Korea; [11]Yale School of Medicine, New Haven, CT, USA

AACR April 5-10, 2024; San Diego, CA



GnP = gemcitabine plus nab-paclitaxel

MORPHEUS-PDAC: Etruma ($A_{2a}R/A_{2b}R$) + Atezo + GnP Showed Trends in Improved PFS and OS vs GnP Control

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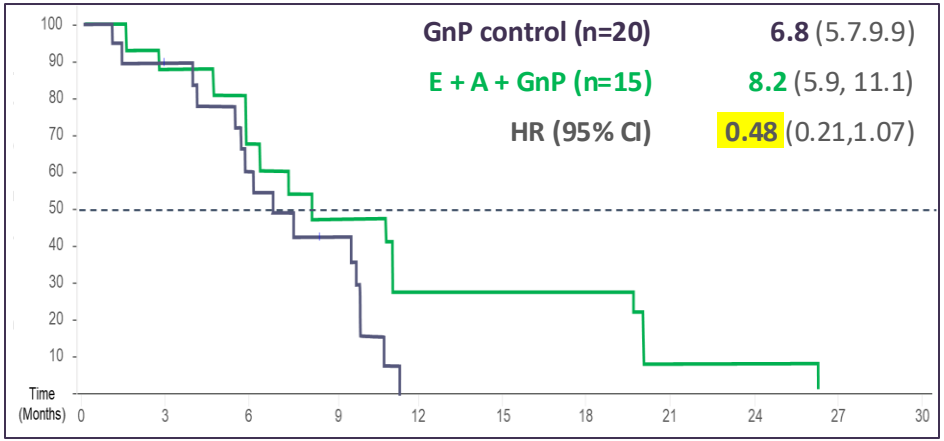
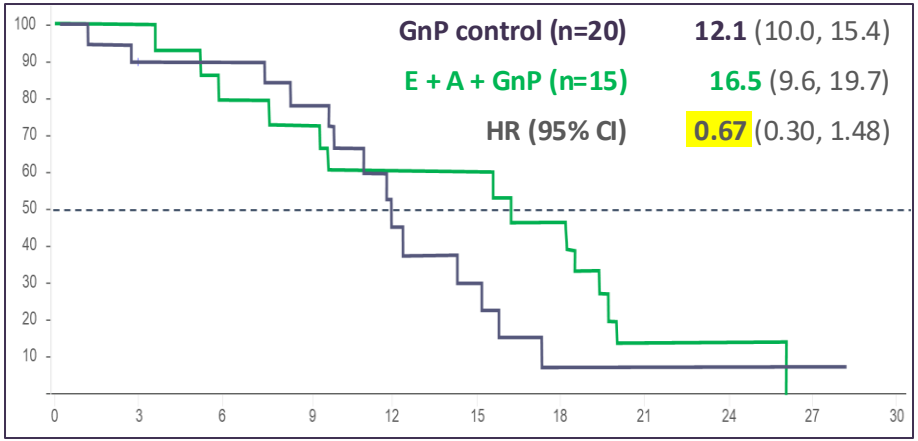
Progression-free Survival



Overall Survival



Adapted from Kim et al., AACR; April 5-10, 2024

PRISM-1: Ongoing Ph3 Randomized, Placebo Controlled, Double-Blind Study of Quemliclustat in 1L Metastatic PDAC

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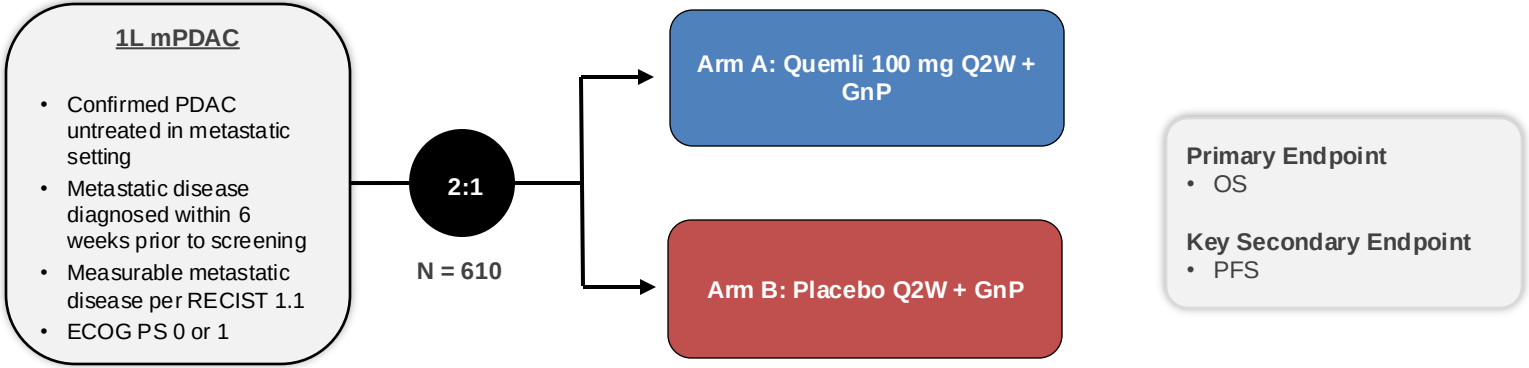
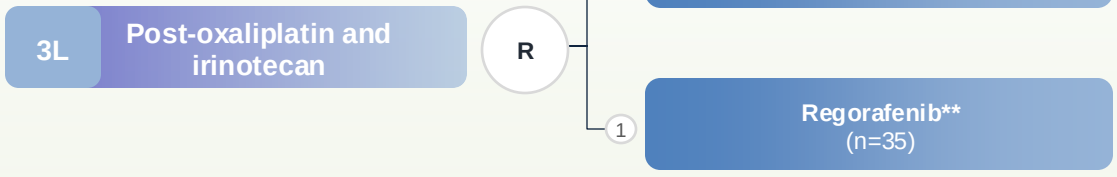
NCT06608927



GnP = gemcitabine plus nab-paclitaxel

ARC-9 Cohort B: Etruma + Zim + mFOLFOX6 + Bevacizumab (EZFB) vs Regorafenib in 3L mCRC



PRIMARY ENDPOINTS:

- PFS (investigator assessed)

KEY SECONDARY ENDPOINTS:

- OS
- ORR (investigator assessed)
- Safety

KEY INCLUSION CRITERIA

- Histologically confirmed unresectable mCRC
- Measurable disease per RECIST v1.1
- ECOG PS of 0 or 1
- Disease progression on or after treatment with oxaliplatin and irinotecan containing chemotherapy in combination with anti-VEGF(R) or anti-EGFR

KEY EXCLUSION CRITERIA

- Prior treatment with immune checkpoint blockade therapies
- Mutation in the BRAF oncogene; patients with unknown BRAF status will be required to undergo testing at a local laboratory and provide results at screening

Presented by Wainberg et al. ASCO 2024, Jun. 2, 2022; data cut-off of November 13, 2023

Two-Thirds (66%) of Patients on EZFB Experienced Tumor Reduction

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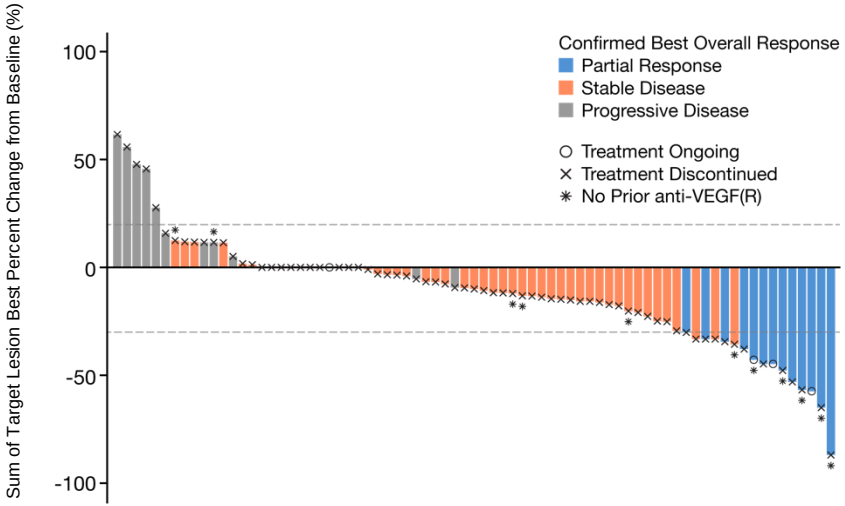
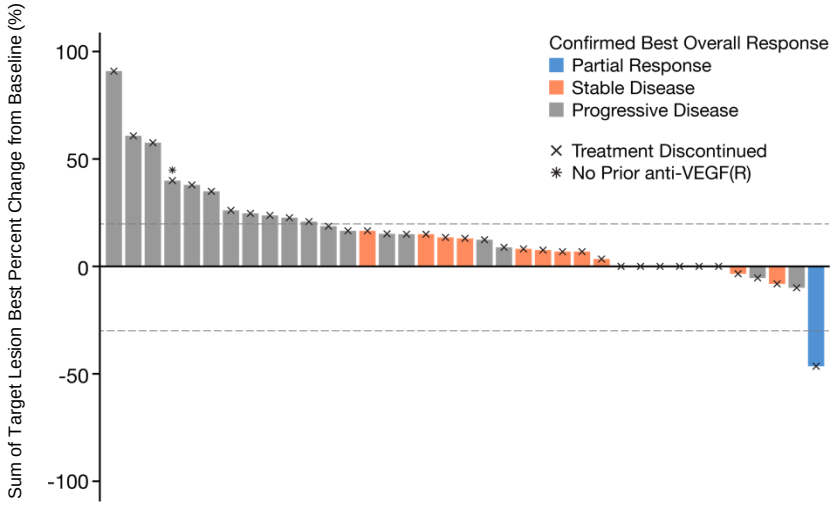
EZFB



- Confirmed ORR for EZFB: 17.3%
- Median DOR for EZFB: 11.5 months

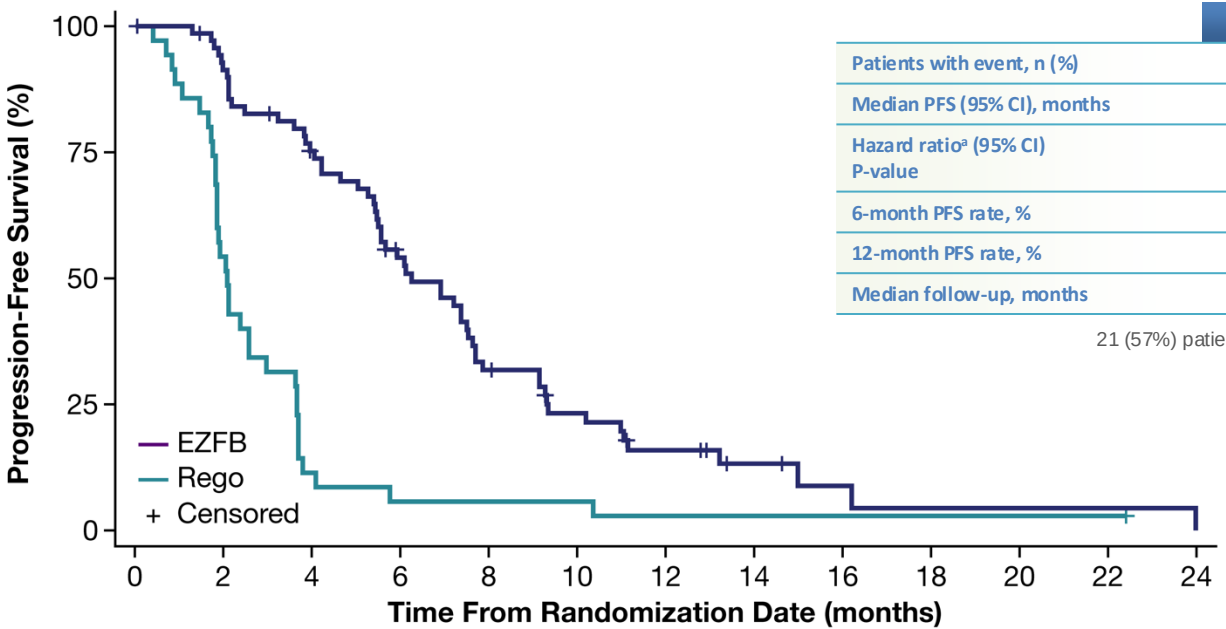
Regorafenib



- Confirmed ORR for rego: 2.7%
- Median DOR for rego: N/A

Presented by Wainberg et al. ASCO 2024, Jun. 2, 2022; data cut-off of November 13, 2023

EZFB Demonstrated Statistically Significant Improvement in PFS vs Rego



	EZFB	Rego
Patients with event, n (%)	58 (77)	34 (92)
Median PFS (95% CI), months	6.24 (5.49, 7.52)	2.07 (1.84, 2.96)
Hazard ratio[a] (95% CI) P-value	0.27 (0.17, 0.43) <0.001	
6-month PFS rate, %	54	6
12-month PFS rate, %	16	3
Median follow-up, months	20.4	

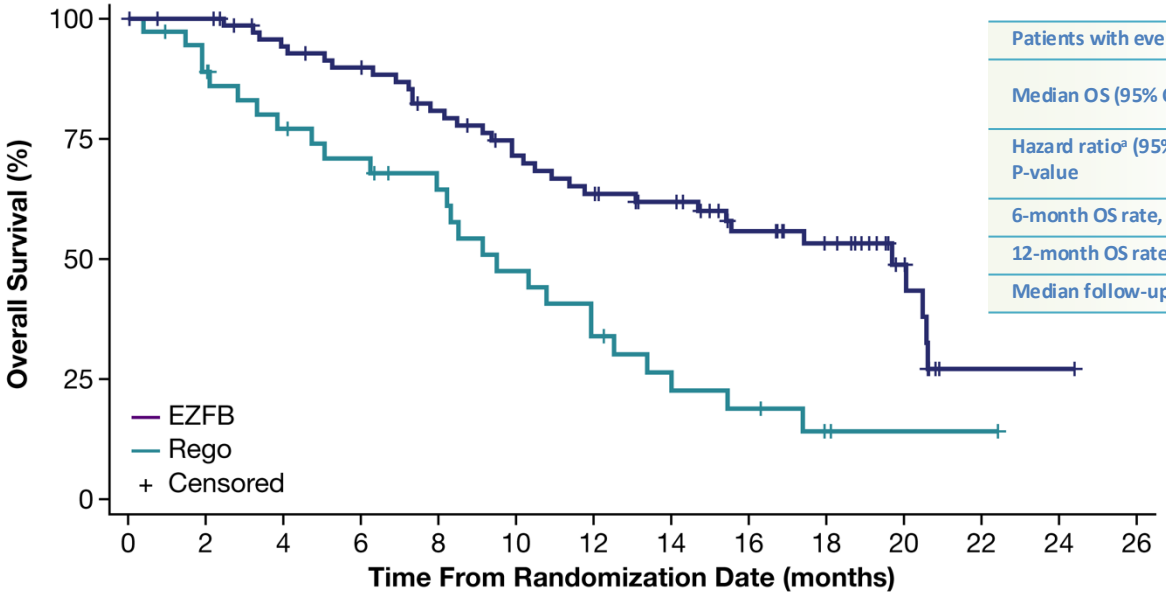
21 (57%) patients randomized to rego crossed over to EZFB

Number of patients at risk

EZFB	75	63	50	34	20	13	8	4	2	1	1	1
Rego	37	19	4	2	2	2	1	1	1	1	1	1

Presented by Wainberg et al. ASCO 2024, Jun. 2, 2022; data cut-off of November 13, 2023

EZFB Demonstrated Significant Improvement in OS vs Rego



Number of patients at risk

EZFB	75	73	65	61	53	45	40	35	26	20	10	1	1
Rego	37	32	26	23	19	14	10	6	5	2	1	1	0

	EZFB	Rego
Patients with event, n (%)	34 (45)	26 (70)
Median OS (95% CI), months	19.68 (14.69, 20.60)	9.49 (7.95, 12.52)
Hazard ratio[a] (95% CI) P-value	0.37 (0.22, 0.63) <0.001	
6-month OS rate, %	90	71
12-month OS rate, %	64	34
Median follow-up, months	20.4	

21 (57%) patients randomized to rego crossed over to EZFB

5.7 Month Median PFS and 20 Month Median OS for EZFB in Patients With Liver Metastasis

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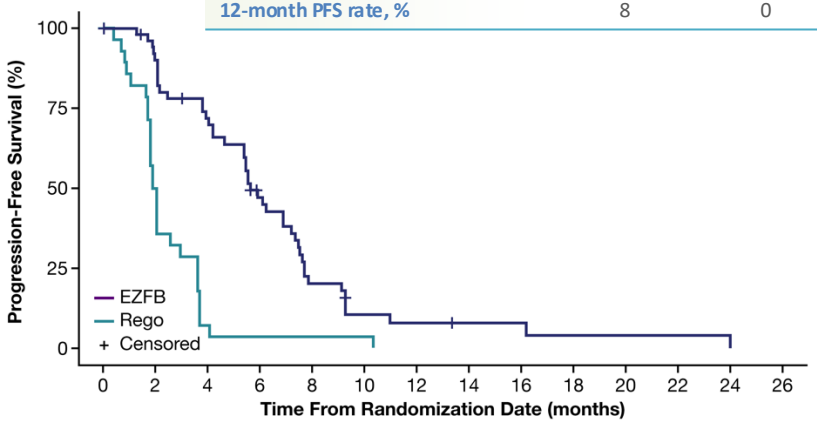
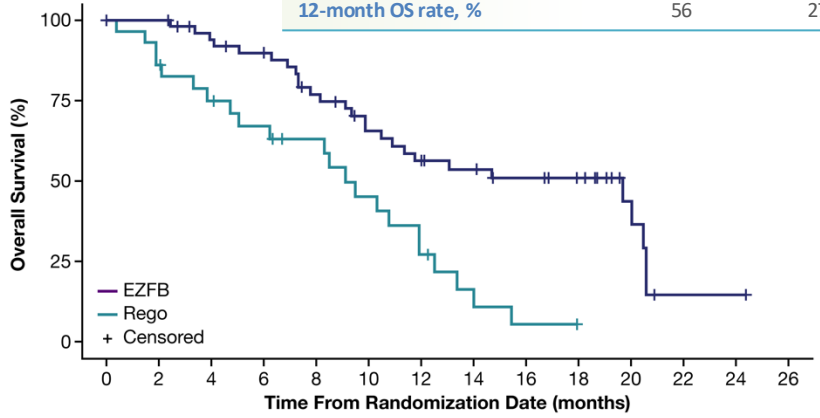
	EZFB	Rego
Patients with events , n (%)	45 (85)	28 (97)
Median PFS, months	5.65	1.97
Hazard ratio (95% CI)	0.19 (0.10, 0.35)	
6-month PFS rate, %	47	4
12-month PFS rate, %	8	0



Number of patients at risk

EZFB	53	45	35	21	9	4	3	2	2	1	1	1	0
Rego	29	14	2	1	1	1	0						

	EZFB	Rego
Patients with events , n (%)	27 (51)	22 (76)
Median OS, months	19.68	9.13
Hazard ratio (95% CI)	0.36 (0.2. 0.66)	
6-month OS rate, %	90	67
12-month OS rate, %	56	27



Number of patients at risk

EZFB	53	52	46	43	35	28	24	21	18	13	6	1	1	0
Rego	29	25	20	17	14	10	6	2	1	0				

Three Recent Clinical Datasets Demonstrate the Potential Benefits of Combining Adenosine Inhibition with Chemo

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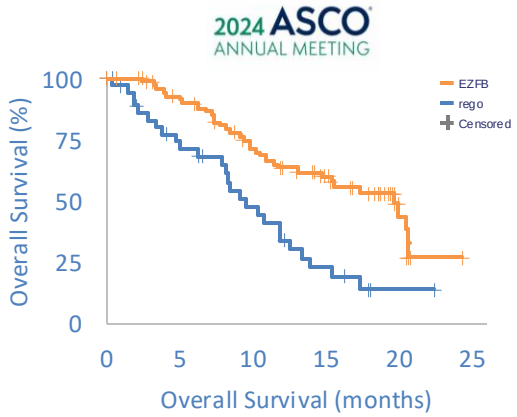
3L+ Colorectal Cancer

ARC-9

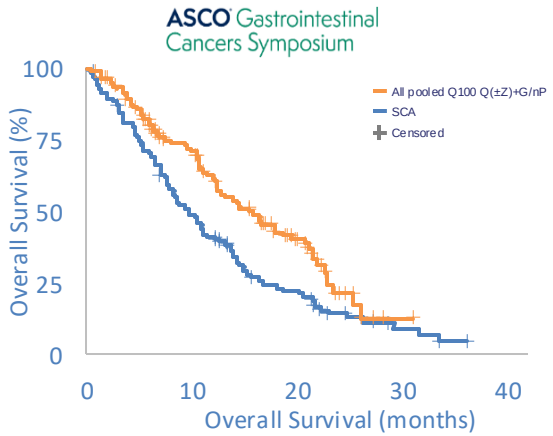
etruma + zim + FOLFOX/bev vs. rego (n=112)



1L Metastatic PDAC

ARC-8

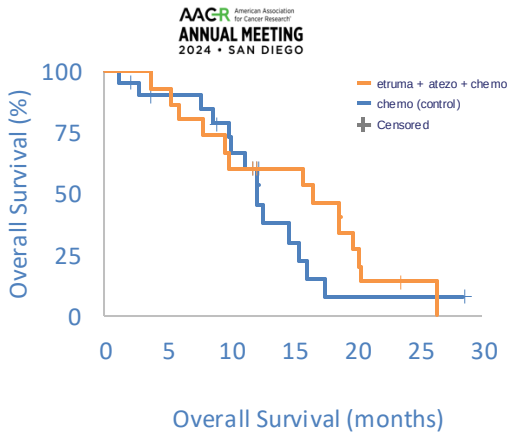
quemli ± zim + G/nP (n=122)



1L Metastatic PDAC

MORPHEUS COMBINATIONS PLATFORM

etruma + atezo + G/nP (n=35)



	EZFB	Rego	HR (95% CI)	Q(±Z)+G/nP	SCA	HR (95% CI)	etruma + atezo + chemo	Chemo	HR (95% CI)
mOS (mos)	19.68	9.13	0.36 (0.2. - 0.66)	15.7	9.8	0.63 (0.47 – 0.85)	16.5	12.1	0.67 (0.3-1.5)

63% reduction in risk of death
10.2 month increase in mOS
vs. standard of care (rego)

37% reduction in risk of death
5.9 month increase in mOS
vs. matched synthetic control arm

33% reduction in risk of death
4.4 month increase in mOS
vs. standard of care (chemo)

Conclusions – Drugging the Adenosine Pathway

- Critical considerations:
  - Clinical setting (CD73 expression) – baseline or induced (e.g., radiation)
  - Immunogenic therapeutic backbone (e.g., platinum, taxane) to release ATP
  - Optimal molecules (e.g., complete CD73 inh, $A_{2a}R$ and $A_{2b}R$ dual blockade, etc.) / doses
- Emerging biomarker data supportive of the proposed MoA:
  - Treatment with quemli- or etruma-containing regimens drives reduction in “adenosine” signaling and increased tumor inflammation
  - High tumor baseline levels of “adenosine” (as inferred by CD73 or NR4A expression) are negative predictors of response to SOC. These are in fact the ones with better clinical outcomes.
- Next steps: advancement of these agents into pivotal studies (e.g., quemli in PRISM-1 (1L PDAC); etruma in advanced mCRC)