RACE ONCOLOGY

ASX Announcement

Race Announces New Clinical Programs in Acute Myeloid Leukemia and Non-Small Cell Lung Cancer

- Clinical activities expanded to capture significant value for RC220 across two major cancer markets and the established orphan indication of Acute Myeloid Leukaemia
- Pivotal Phase 3 Acute Myeloid Leukemia trial to commence, bridging RC110 to RC220 and providing a rapid, low-cost pathway to regulatory approval of RC220
- Non-Small Cell Lung Cancer trial in advanced planning using the recently discovered G4-binding mechanism of action of (E,E)-bisantrene to potentially delay or prevent resistance to established tyrosine kinase inhibitors
- Continued clinical focus on the cardioprotection/anticancer opportunity of RC220 in combination with doxorubicin, with no change to the current trial
- Webinar to discuss the expanded clinical trial program will be held on Tuesday, 18 November at 1 pm AEDT.

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17 November 2025 – Race Oncology Limited ("Race") is pleased to announce two new clinical trials for RC220 in Acute Myeloid Leukemia (AML) and Non-Small Cell Lung Cancer (NSCLC).

EGFRm Non-Small Cell Lung Cancer

The discovery that (E,E)-bisantrene, the active drug in RC220, is a DNA/RNA G-quadruplex (G4) binder (ASX Announcement: 2 Oct 2025) has identified a major clinical and commercial opportunity for RC220 in mutated epidermal growth factor receptor (EGFRm) driven NSCLC. Supported by extensive preclinical research and commercial assessment, Race has initiated a new clinical program in NSCLC to leverage the unique molecular mechanism of action of (E,E)-bisantrene to potentially address the urgent unmet patient need for better treatment options for acquired EGFR tyrosine kinase inhibitor (TKI) resistance.

Third generation EGFRm TKIs are highly effective in the treatment of EGFR-driven NSCLC, but their benefit is time limited by the inevitable emergence of treatment resistance. Once TKI resistance develops, there are limited options for patients who often experience rapid disease progression. There is significant clinical and commercial interest in new therapies that can prolong the effectiveness of TKIs by delaying or preventing resistance. The market for EGFRm TKI is large and growing with the sales leader, Tagrisso® (osimertinib, AstraZeneca), reaching US$6.6 billion in 2024.[1]

Planning for the RC220 lung cancer trial is advanced. Preclinical studies identifying the ability of RC220 to delay and prevent EGRFm TKI resistance are complete, as is the clinical trial design, protocol, and all associated documentation. Key opinion leaders, principal investigators, and five major clinical sites in Sydney, Melbourne and Brisbane have been engaged and recruited. All Clinical Research Organisations (CROs) required to support the trial have been identified and contracted. The trial protocol and required supporting documentation was submitted to the Bellberry Human Research Ethics Committee (HREC) on 29 September 2025. Written responses to minor trial related queries from the committee were returned to Bellberry on 10 November 2025.

Acute Myeloid Leukemia

In addition to the EGFRm NSCLC trial program, Race Oncology has identified a rapid and cost-effective clinical pathway to potential regulatory approval of RC220 in relapsed/refractory AML. This Phase 3 program includes a bridging and dose optimisation stage to establish the pharmacokinetic (PK) and pharmacodynamic (PD) equivalence of RC220 with the original RC110 formulation, and to identify the optimal dosage regime required to satisfy US FDA Project Optimus.[2] This bridging stage will also allow *in vivo* biomarker data to be generated assessing MYC gene silencing by (E,E)-bisantrene in patient cancer cells. As part of this program, Race will support a future low-cost, investigator sponsored Phase 1b/2 trial to identify the optimal combination of RC220 with current standard-of-care AML treatments.

Cardioprotection & Anticancer in Solid Tumours

Race Oncology's clinical focus on the cardioprotective and anticancer activity of RC220 in combination with doxorubicin remains a clear priority, with the ongoing Phase 1a/b trial of significant value for both patients and shareholders.

Commentary

Race Oncology CEO and Managing Director, Dr Daniel Tillett comments, *"It is an exciting milestone for Race Oncology to translate the mechanism of action of (E,E)-bisantrene into tangible clinical programs. The opportunity to use RC220 to delay, or even prevent, TKI resistance across a range of cancers is a compelling opportunity. The scale of the opportunity is enormous, with more than US$10 billion of EGFRm TKIs sold every year for lung cancer alone.*

I want to especially thank the Race Oncology preclinical and clinical teams for their extraordinary effort in moving from the initial discovery of the mechanism of action of (E,E)-bisantrene to a full clinical trial program in lung cancer in under 9 months."

A presentation detailing the significance and background of these new clinical programs is attached to this announcement.

Program Funding

While planning and preparation is advanced, significant expenditure on these new programs will only commence once sufficient funds are available. Shareholder exercise of the piggyback options issued in June 2024 ($1.25 strike price; expiry 29 May 2026) (ASX Announcement: 6 June 2024) will enable all announced clinical activities to be funded. As of 14 November 2025, 18% of the piggyback options have been converted with a further 12% held by Race Oncology's CEO, Dr Daniel Tillett.

Race remains well financed with cash and cash equivalents of $11.3m at 30 September 2025 (ASX Announcement: 31 October 2025). Importantly, Race is fully funded to undertake all existing trials and other programs until mid 2027 from current funds. The Board continues to evaluate all capital management and partnership options with a view to maximising shareholder value.

References

1. https://www.sec.gov/Archives/edgar/data/901832/000110465925014750/azn-20241231x20f.htm
2. https://www.fda.gov/about-fda/oncology-center-excellence/project-optimus

RACE ONCOLOGY

Webinar

Race Oncology CEO, Dr Daniel Tillett, and Principal Scientist, Dr Rodney Cusack will host an online webinar to discuss these clinical programs and answer questions from investors on Tuesday, 18 November 2025 at 1 pm AEDT.

To register for this webinar please use the following link:

https://us02web.zoom.us/webinar/register/WN_9iQ7Ukn_Q0i1Gi9p67JjSQ

A video recording of this presentation will be made available later for those investors unable to attend.

-ENDS-

About Race Oncology (ASX: RAC)

Race Oncology (ASX: RAC) is an ASX-listed Phase 3 clinical biopharmaceutical company with a dedicated mission to be at the heart of cancer care.

Race's lead asset, RCDS1 (E,E-bisantrene), is a small molecule anticancer agent that primarily functions via G4-DNA & RNA binding, leading to potent inhibition of the important cancer growth regulator MYC. RCDS1 has demonstrated therapeutic activity in cancer patients with a well characterised safety profile. Recent discoveries made by Race have enabled composition of matter IP filings that provide for 20 years of patent protection over RCDS1.

Race is advancing a proprietary formulation of RCDS1 (RC220) to address the high unmet needs of patients across multiple oncology indications, with Phase 3 clinical programs in acute myeloid leukaemia (AML), Phase 1a/b program in mutant epidermal growth factor receptor non-small cell lung cancer (EGFRm NSCLC), and a Phase 1a/b program in combination with the anthracycline doxorubicin, where we aim to deliver both cardioprotection and enhanced anticancer activity for solid tumour patients.

Race Oncology has collaborated with Astex, MD Anderson, Sheba City of Health, UNC School of Medicine, University of Wollongong and University of Newcastle, and is actively exploring partnerships, licence agreements or a commercial merger and acquisition to accelerate access to RC220 for patients with cancer across the world.

Learn more at www.raceoncology.com.

If you have any questions on this announcement or any past Race Oncology announcements, please go to the Interactive Announcements page in our Investor Hub announcements.raceoncology.com

Race encourages all investors to go paperless by registering their details with the Company's share registry, Automic Registry Services, at www.automicgroup.com.au.

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November 2025

RACE ONCOLOGY

AT THE HEART OF CANCER CARE

Dr Daniel Tillett – CEO & MD
Dr Rodney Cusack – Principal Scientist

Clinical Strategy Update

ASX: RAC | RACE ONCOLOGY LIMITED | ABN 61 149 318 749

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Continued Evolution of Race Oncology

Summary of recent positive events and evolved strategy for bisantrene

1970s – 1990s

Development by Lederle Laboratories

>50 studies & >1,500 patients in solid and liquid cancers

Approved in France for AML, but not sold due to formulation issues

2020-2024

Phase 2 AML studies with promising data

Reformulated to solve delivery issues (RC220)

GMP manufacture & non-clinical data

Discovery of cardioprotection

2025

Success treated patients with RC220 formulation

Filed composition of matter patent over (E,E)-isoform

Mechanism of action identified to silences key cancer gene expression including MYC

Building on our history and progress

Current: Phase 1a/b cardioprotection + anticancer trial of RC220 in combination with doxorubicin

New: Phase 1a/b trial of RC220 in EGFR mutated non-small cell lung cancer aimed at delaying resistance to market-leading EGFRm TKI drugs with >$10B p.a. sales

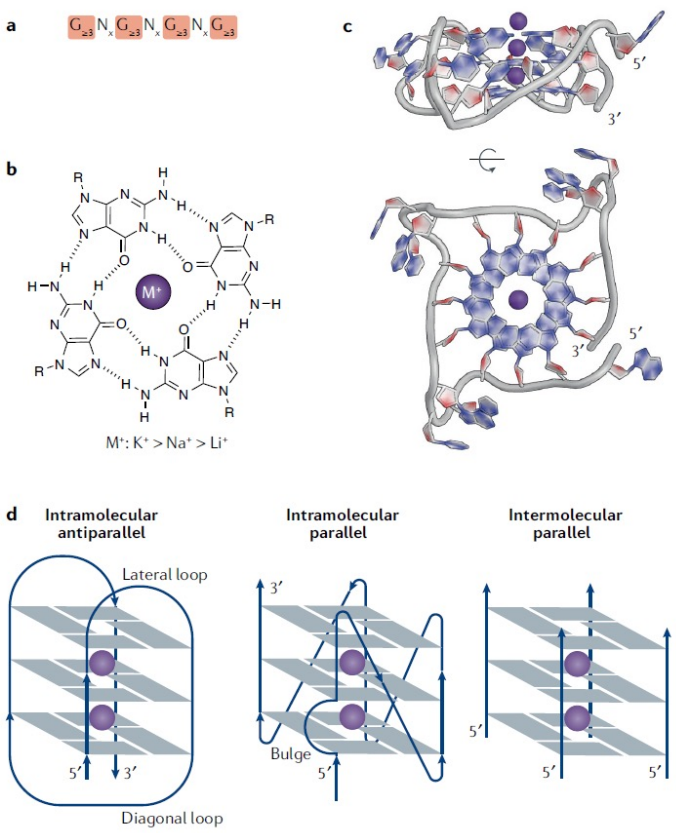
New: Phase 3 AML trial bridging RC110 to RC220

New: Preclinical & clinical exploration of the potential of MYC silencing in cancer unlocking use of RC220 in multiple major cancer indication

Background

How does (E,E)-bisantrene work?

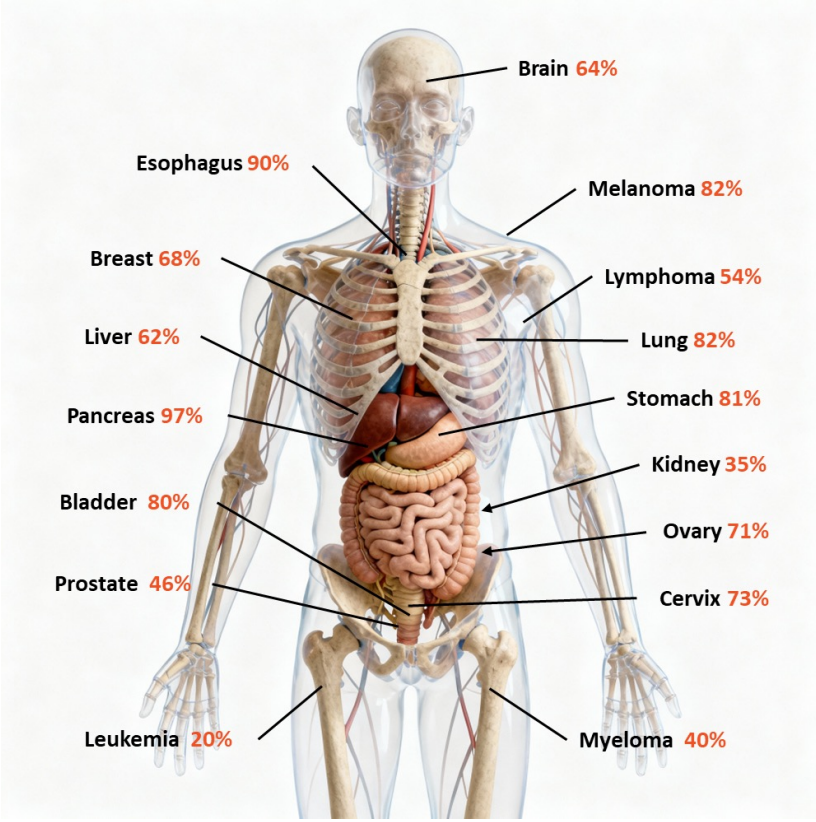
- In DNA & RNA there exists special folded structures called **G-quadruplexes (G4)**
- G4 structures act like switches that control many of the important genes that cause or allow cancer to grow
- (E,E)-bisantrene binds to and stabilizes these G4 structures, which then:
  - **Turns down cancer genes** – especially important is **MYC**, a master "on/off switch" that drives the growth of up to 70% of all cancers
  - **Blocks the activity of other enzymes** that help cancer cells grow and divide such as **telomerase** and **topoisomerase II**
  - **Increases m⁶A levels in RNA** which makes cancer cells less aggressive and less resistant to treatment
- **(E,E)-bisantrene** more than just kills cells (like traditional chemo drug), it **interferes with the controls systems of cancer making the cancer more sensitive to other cancer drugs**



MYC & Cancer

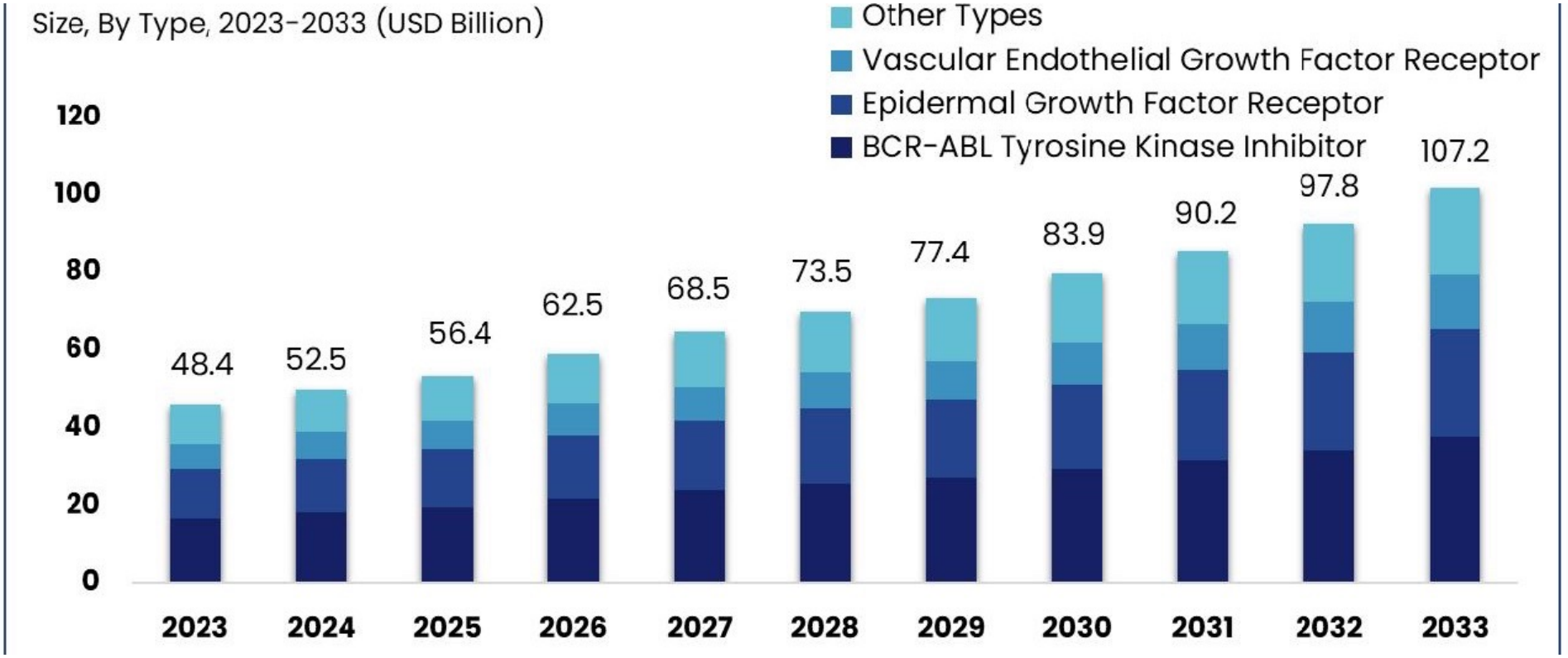
- Discovered in 1982 and quickly found to be one of the most important targets in cancer research
- Despite significant pharma industry effort, MYC is still considered to be 'undruggable'. Why?
  - No direct inhibitors in any pharma pipelines
  - Much of protein is unstructured and difficult to target
- **Function of MYC**
  - A transcription factor that regulates the expression of 2,000-4,000 genes (10-15% of all genes)
  - Acts as a **potent accelerator** of malignancy by enhancing the expression of important genes required for cell growth
- **~70% of all cancers have increased MYC activity**
  - More than 1 million new cancers in the USA alone
  - Potential market for a MYC inhibitor in the $10s billions

Major cancers with elevated MYC activity



Data from TCGA and Schaub et al., 2018, Cell Systems 6, 282–300.

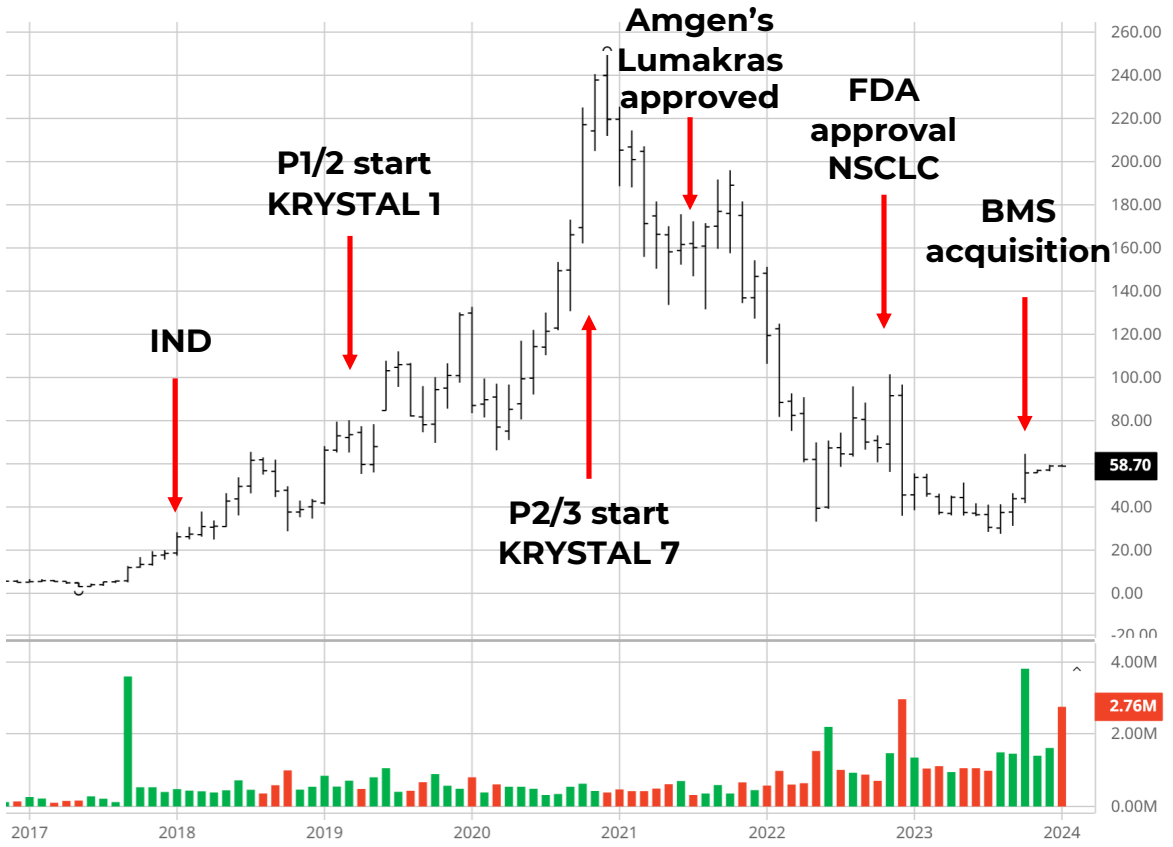
Tyrosine Kinase Inhibitor (TKI) Market



https://marketresearch.biz/report/tyrosine-kinase-inhibitors-market/

TKI Case Study – Mirati Therapeutics

- Mirati developed Krazati® (adagrasib) targeting the previously 'undruggable' KRAS G12C mutation
  - G12C accounts for only 15% of KRAS activating mutations
  - Most common in lung cancer
- Mirati's market capitalisation peaked at US$12B due to Amgen's Lumakras® (sotorasib) being approved first
- Acquired by Bristol Myers Squibb for US$4.8B + US$1B CVR in October 2023
- BMS reported US$123m of sales of Krazati® in 2024[1]

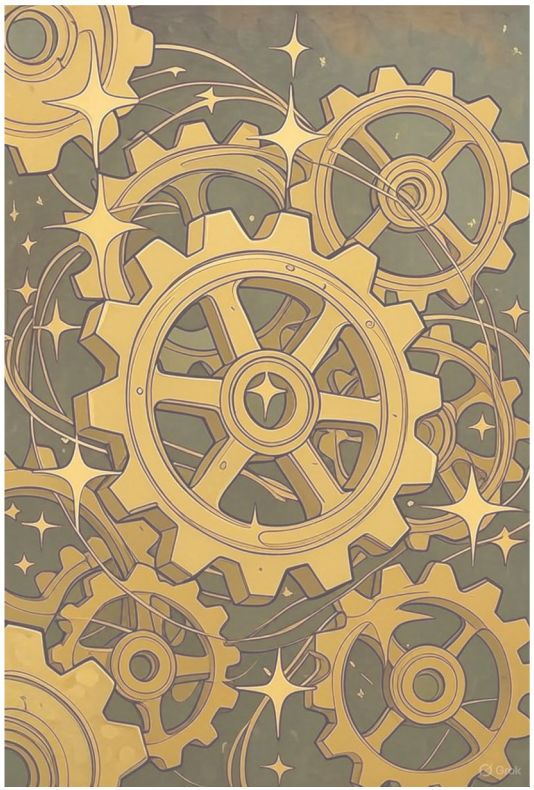


1. https://www.bms.com/assets/bms/us/en-us/pdf/investor-info/doc_presentations/2024/BMY-2024-Q4-Results-Investor-Presentation-with-Appendix.pdf

Optimal RC220 MOA Clinical Program

- Mechanism of action discovery opens an enormous range of possibilities for using RC220 in the clinic
- **We undertook a systematic process to identify new clinical program(s) based on commercial potential**
  - ✓ Large existing market – more than $10 billion p.a.
  - ✓ Excellent supportive preclinical and clinical data
  - ✓ Pressing unmet clinical need
  - ✓ Many pharma players and potential partners
  - ✓ Combination with a proprietary drug
  - ✓ Potential for rapid & low-cost, proof-of-concept trial
  - ✓ Large effect size - limited patients needed
  - ✓ Significant opportunity for FDA accelerated approval
  - ✓ Act as a template for other trials (label extension)

Outcome: EGRFm Non-Small Cell Lung Cancer



EGFRm Non-Small Cell Lung Cancer

Lung Cancer Statistics

Lung cancer is the most frequently diagnosed cancer (12.4%)

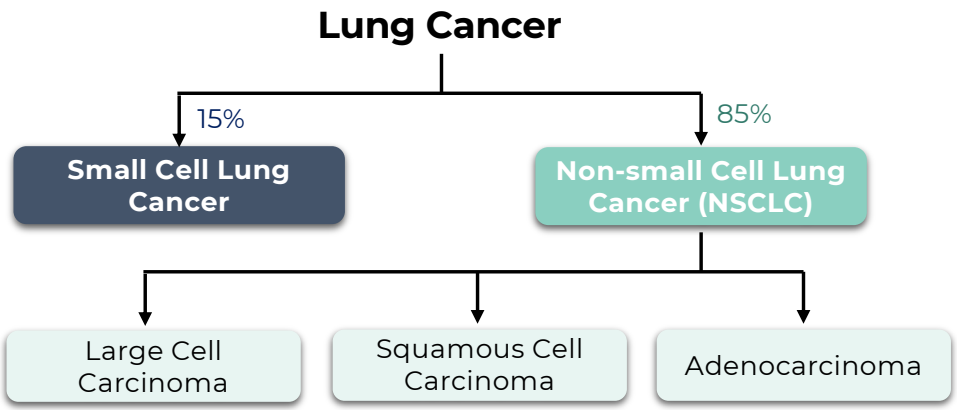
Globally 2.5M new cases pa[1]
US >200K new cases pa[2]
China >1M new cases pa[3]

Lung cancer is the leading cause (18.7%) of cancer deaths – 1.8M deaths annually[1]

Smoking is the primary risk factor.
~25% of cases are attributed to causes other than smoking, such as environmental exposures
(e.g. air pollution, exposure to asbestos or radon).[1]

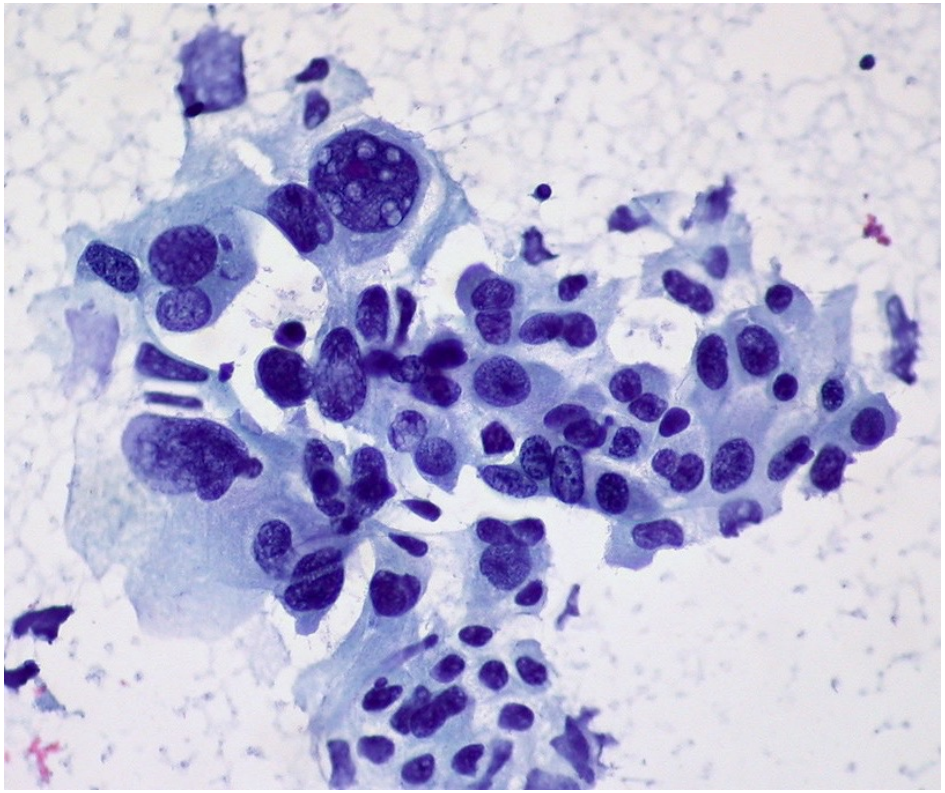
The number of new cancer cases is estimated to almost double by 2050,[1] increasing new lung cancer cases globally to ~4M per year (~3.4 M NSCLC).

~85% of lung cancers are NSCLC



1. 2022 Global cancer statistics Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries
2. U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. https://www.cdc.gov/cancer/dataviz. Accessed June 16, 2025.
3. Han B, Zheng R, Zeng H, et al. Cancer incidence and mortality in China, 2022. J of the Nat Cancer Center. 2024;4(1):47-53

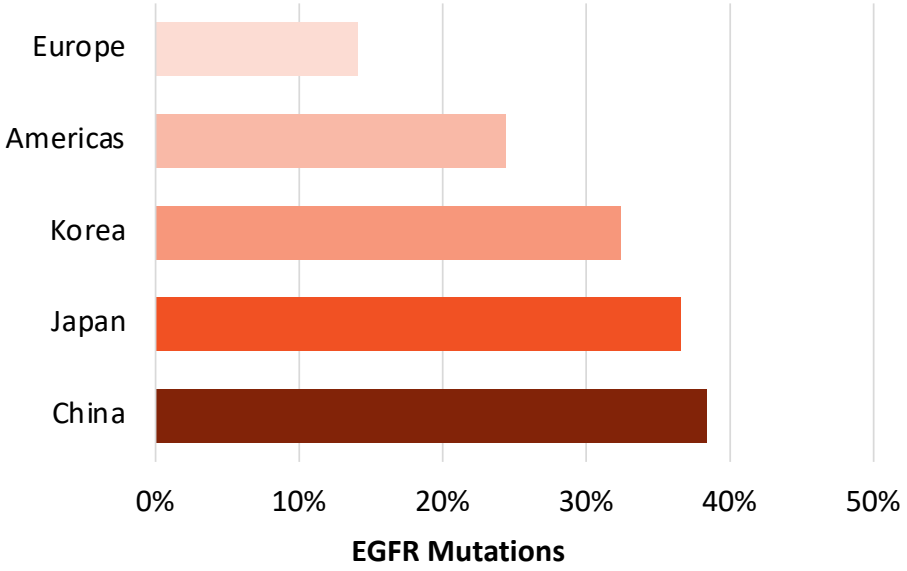
EGFRm Non-Small Cell Lung Cancer



- EGFR-mutated (EGFRm) non-small cell lung cancer (NSCLC) is a subtype of lung cancer characterized by specific gene mutations in the epidermal growth factor receptor (EGFR) that drive uncontrolled cell growth[1]
- The most common and treatable mutations are deletions in exon 19 (E19del) and a point mutation in exon 21 (L858R)[2]
- A greater than US$10 billion a year market

1. John, T. et al. Three-Year Safety, Tolerability, and Health-Related Quality of Life Outcomes of Adjuvant Osimertinib in Patients With Resected Stage IB to IIIA EGFR-Mutated NSCLC: Updated Analysis From the Phase 3 ADAURA Trial. J. Thorac. Oncol. 18, 1209–1221 (2023).
2. Qi, Y.-T., Hou, Y. & Qi, L.-C. Efficacy of Next-Generation EGFR-TKIs in Patients With Non-Small Cell Lung Cancer: A Meta-Analysis of Randomized Controlled Trials. Technol. Cancer Res. Treat. 19 (2020).

EGFR Mutations in NSCLC[1]



EGFR mutations more prevalent in:

- Asian patients
- Females (44%) than males (24%)
- Non-smokers (49%) than current or former smokers (22%)
- Adenocarcinoma (38%) than non-adenocarcinoma (12%) NSCLC

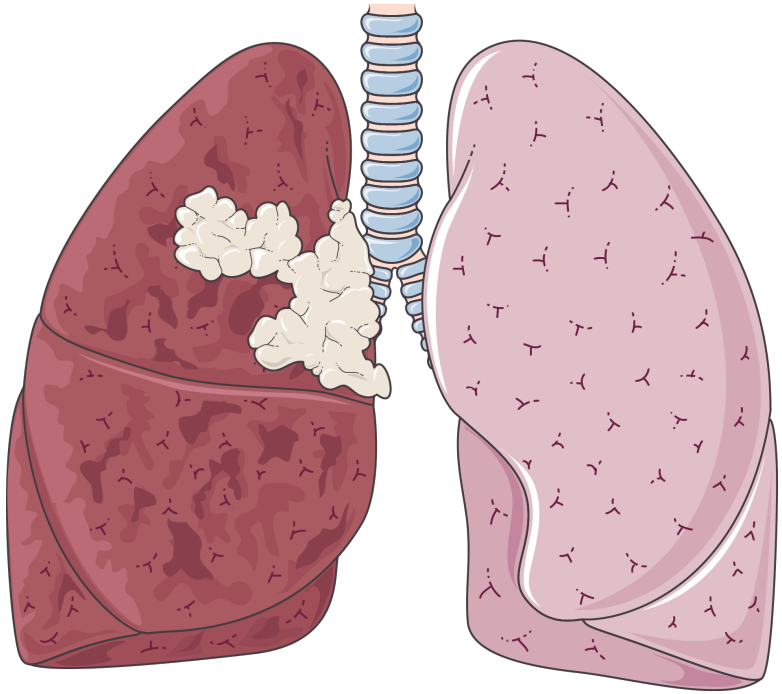
High prevalence of EGFR mutations in Asia, is driving development of many new EGFR TKIs in this region

1. Zhang YL, Yuan JQ, Wang KF, et al. Oncotarget. 2016;7(48):78985-78993

EGFRm NSCLC Treatment with TKIs

- EGFRm NSCLC responds poorly to immunotherapy[1]
- Current mainstay of treatment are 3rd generation EGFRm Tyrosine Kinase Inhibitors (TKIs)[2]
- EGFRm TKIs are highly effective with >80% of patients with targetable mutations responding to treatment[2]
- Enormous market >US$10 billion in 2024[3]
  - 14 EGFRm TKIs approved in USA & China; 8 in Phase 3
  - Osimertinib (Tagrisso®) alone had sales of US$6.6 billion in 2024
  - Many small, medium & large pharma players

Intensely competitive commercial market with no significant clinical differentiation between any of the 3rd generation EGFRm TKIs



1. Zhang, W. et al. What is the optimal first-line regimen for advanced non-small cell lung cancer patients with epidermal growth factor receptor mutation: a systematic review and network meta-analysis. BMC Pulm. Med. 24, 620 (2024).
2. Veccia, A. et al. Osimertinib in the Treatment of Epidermal Growth Factor Receptor-Mutant Early and Locally Advanced Stages of Non-Small-Cell Lung Cancer: Current Evidence and Future Perspectives. Cancers 17, 668 (2025).
3. Frost & Sulivan, Innovative Small Molecule Drug Market Report. (2024).

EGFRm NSCLC TKI Competitive Landscape

Drug Name	Brand Name	Target(s)	Mutation Subtypes	Gen	Company	Clinical Stage	Approvals	2024 Sales (US$m)
Osimertinib	**Tagrisso**	**EGFR, HER2, HER4**	**Ex19del, L858R, T790M**	**3rd**	**Astrazeneca**	**Approved**	**US, EC, CN**	**6580**
Dacomitinib	Vizimpro	EGFR, HER2, HER4	Ex19del, L858R	2nd	Pfizer	Approved	US, CN	~200
Afatinib	Gilotrif	EGFR, HER2, HER4	Sensitive mutations	2nd	Boehringer Ingelheim	Approved	US, CN	690 (2022)
Erlotinib	Tarceva	EGFR	Ex19del, L858R	1st	Astellas/ Roche	Approved	US, CN	~1200
Gefitinib	Iressa	EGFR	Ex19del, L858R	1st	Astrazeneca	Approved	US, CN	~250
Icotinib	Conmana	EGFR	Ex19del, L858R	1st	Betta Pharma	Approved	CN	~100
Befotertinib	Surmana	EGFR	Ex19del, L858R, T790M	3rd	Betta Pharma	Approved	CN	<30
Rezivertinib	Ruibida	EGFR	T790M	3rd	Beta Pharma	Approved	CN	Approved in 2024
Furmonertinib	Ivesa	EGFR	Ex19del, L858R, T790M	3rd	Allist Pharmaceutical	Approved	CN	~500
Almonertinib	Ameile	EGFR	Ex19del, L858R, T790M	3rd	Hansoh Pharma	Approved	CN	~500
Rilertinib	Sanrisso	EGFR	T790M	3rd	Sanhome Pharmaceutical	Approved	CN	Approved in 2024
Lazertinib	**Lazcluze**	**EGFR, HER2, HER4**	**Ex19del, L858R, T790M**	**3rd**	**Yuhan Corporation / Jansen**	**Approved**	**US, EC, CN**	**141 (Q1 2025)**
Zorifertinib	Zorifer	EGFR, HER2, HER4	Ex19del, L858R	3rd	Alpha Biopharma/ Astrazeneca	Approved	CN	Approved in 2024
Olmutinib	Olita	EGFR	Ex19del, L858R, T790M,G719X, L861Q	3rd	Hanmi Pharmaceutical	Approved	SK	~10

CN, China; EC, European Commission; Gen, generation; SK, South Korea; US, United States.

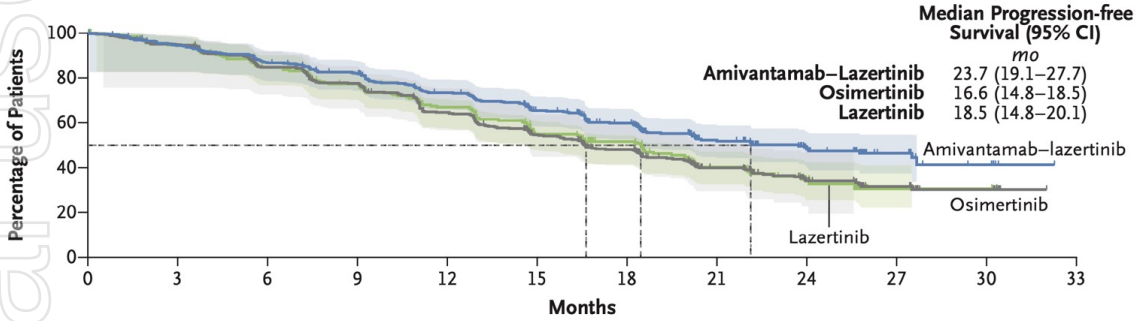
EGFRm NSCLC TKI Competitive Landscape

Drug Name	Target(s)	Mutation Subtypes	Gen	Company	Indication(s)	Clinical Stage
KP-673	EGFR	Ex19del, L858R, T790M, G719X, L861Q	3rd	Zentalis Pharmaceuticals	NSCLC	I/II
Almonertinib	EGFR	Ex19del, L858R, T790M, G719X, L861Q	3rd	Hansoh Pharmaceutical	NSCLC	III
BBT-207	EGFR	Ex19del, L858R, C797S	4th	Bridge Biotherapeutics	NSCLC	I/II
BBT-176	EGFR	Ex19del, L858R, L861Q, C797S	4th	Bridge Biotherapeutics	NSCLC	I
JIN-A02	EGFR	C797S, T790M	4th	J Ints Bio	NSCLC	I/II
BLU-945	EGFR	C797S, T790M	4th	Blueprint Medicines	NSCLC	I/II Terminated
H002	EGFR	C797S	4th	RedCloud Bio	NSCLC	I/II
TAS3351	EGFR	C797S	4th	Taiho Oncology	NSCLC	I/II Terminated

EC, European Commission; FDA, US Food and Drug Administration; NMPA, National Medical Products Administration (China).

The $10B Problem - Universal TKI Resistance

MARIPOSA Phase 3 PFS Trial Data[1]

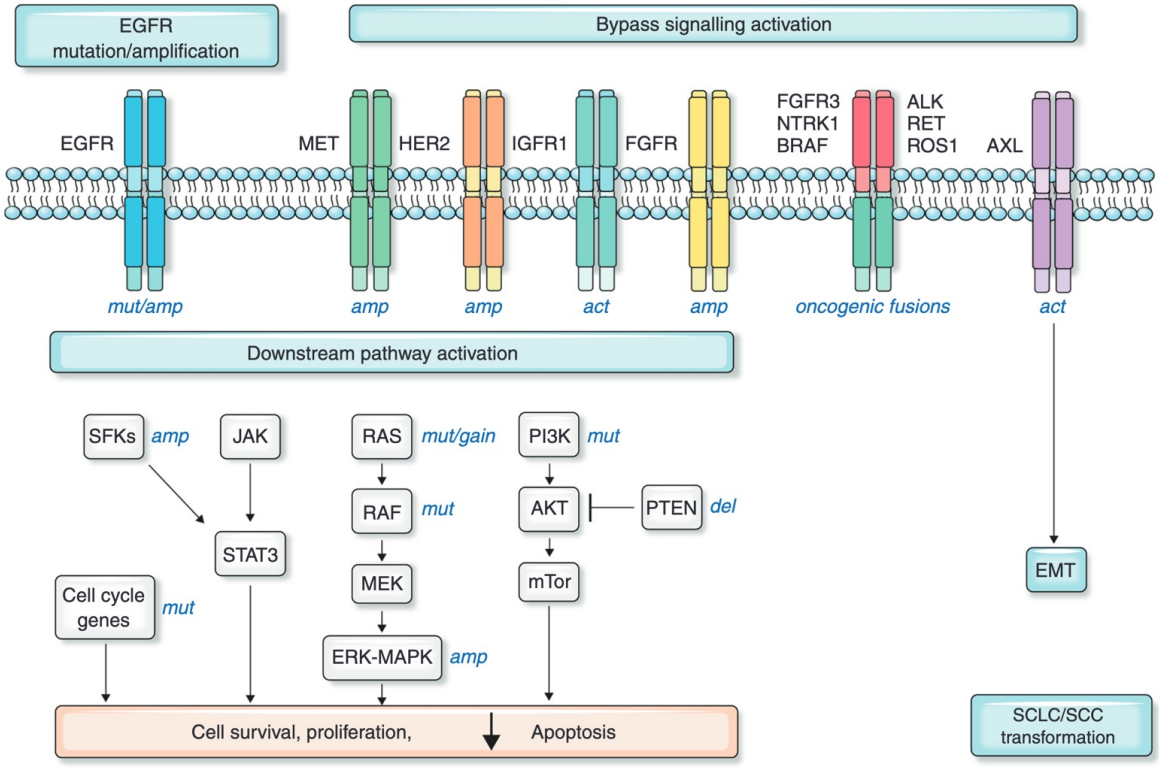


- Despite 14 approved EGRFm TKI and 8 in P3, virtually all patients develop resistance to EGFRm TKI therapy – the median progression free survival (PFS) is 18 months[1]
- No clinical difference between any of the 3rd generation EGFRm TKIs in regards time to resistance
- Slowing resistance development would increase TKI sales in the billions – double time to resistance, double sales of TKIs
- 4th generation EGFRm TKIs have been disappointing in the clinic
- Why? – two fundamental reasons

1. Cho, B. C. et al. Amivantamab plus Lazertinib in Previously Untreated EGFR-Mutated Advanced NSCLC. N. Engl. J. Med. 391, 1486–1498 (2024).

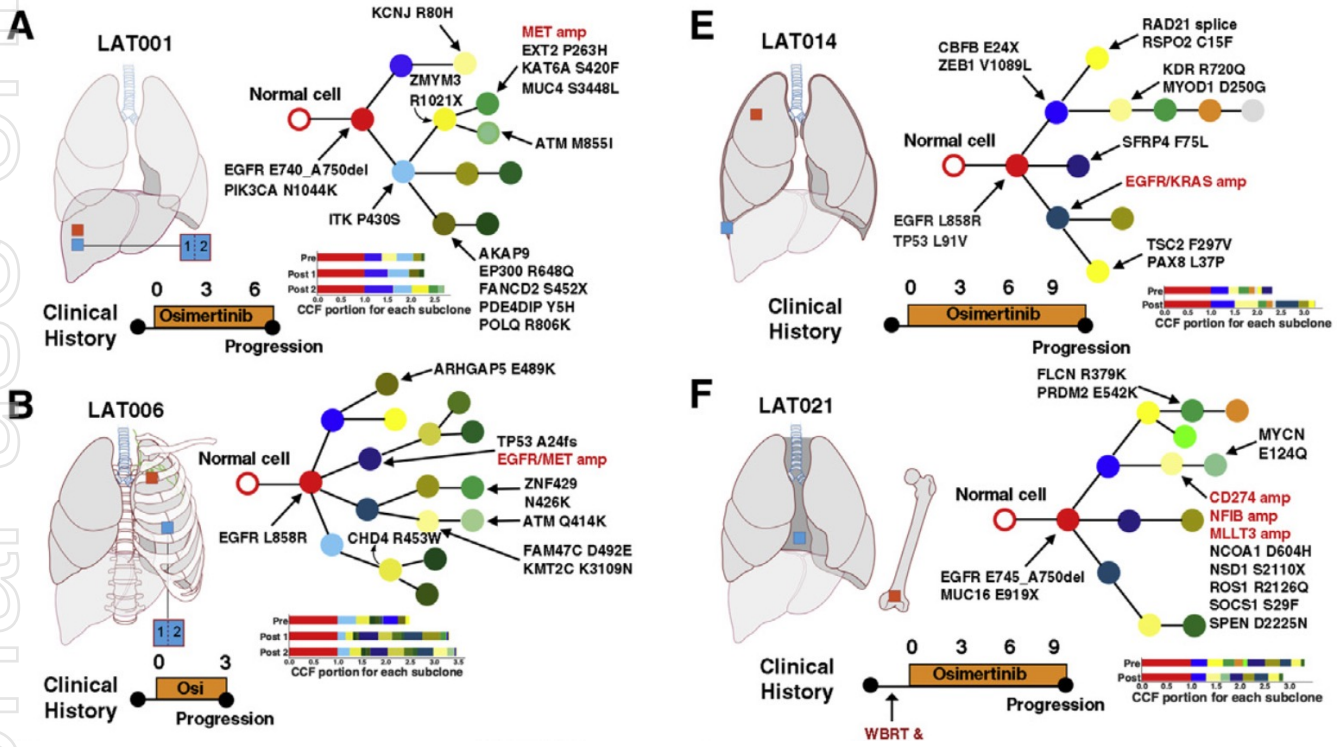
EGRFm TKI Resistance – Bypass Signalling

- EGRF TKI resistance can arise through activation of alternative cell growth signalling pathways
- Can be present even before EGFRm TKI treatment!
- Multiple bypass and other resistance pathways can be activated in a single patient – **the subclone problem**



Schematic representation of the known mechanisms of resistance to osimertinib (Leonetti, A., Sharma, S., Minari, R., Perego, P., Giovannetti, E., Tiseo, M., 2019. Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. Br. J. Cancer 121, 725–737. 2019).

Subclones in EGFRm NSCLC Resistance



Clinical history of individual EGFRm NSCLC patients and resistance subclone progression on osimertinib therapy (Roper et al.. Clonal Evolution and Heterogeneity of Osimertinib Acquired Resistance Mechanisms in EGFR Mutant Lung Cancer. Cell Rep Med. 2020)

Majority of EGFRm NSCLC patients on TKI therapy have 2 or more independent pathway resistance subclones present upon disease progression

Treatment with any single new target drug selects for the unconstrained growth of subclones driven by other resistance pathways

Urgent need for new treatments that can target multiple resistance pathways simultaneous

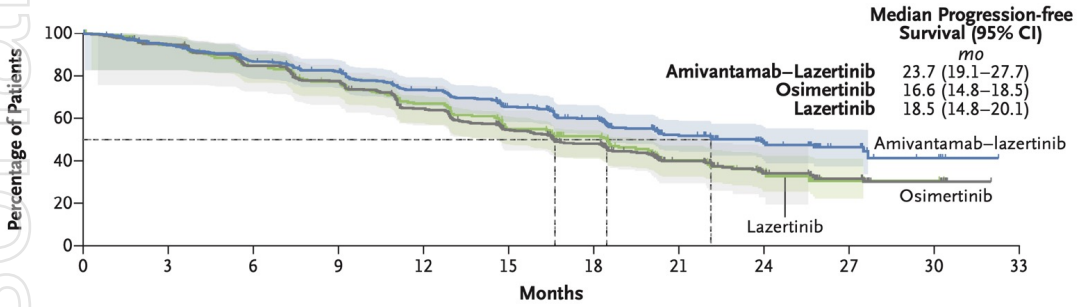
Current Approaches to EGFRm TKI Resistance

Combine EGRFm TKIs with other anticancer treatments

- Targeted agents (e.g. MARIPOSA)
- Chemotherapy (e.g. FLAURA2)

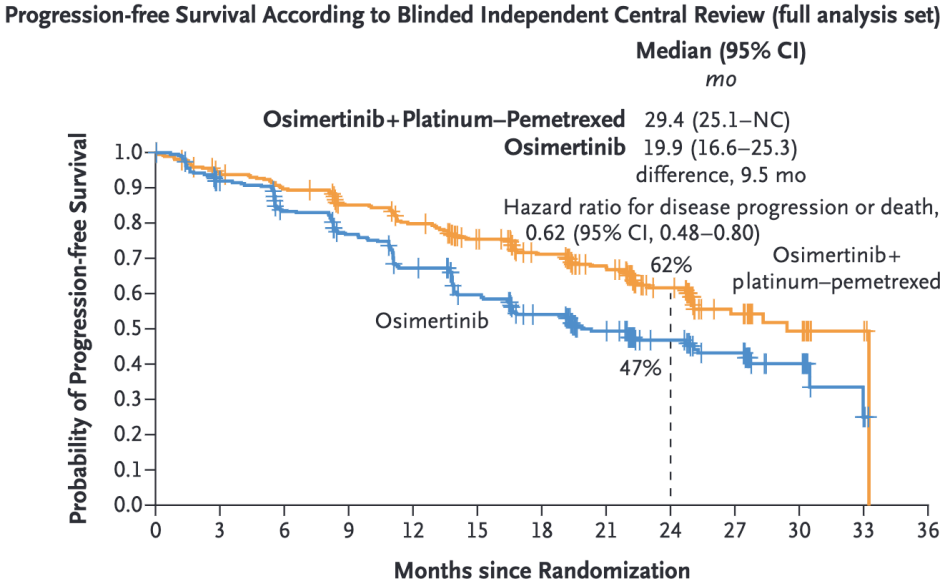
Benefit from these approaches are mixed – Why?

MARIPOSA



Cho, B. C. et al. Amivantamab plus Lazertinib in Previously Untreated EGFR-Mutated Advanced NSCLC. N. Engl. J. Med. 391, 1486–1498 (2024).

FLAURA2



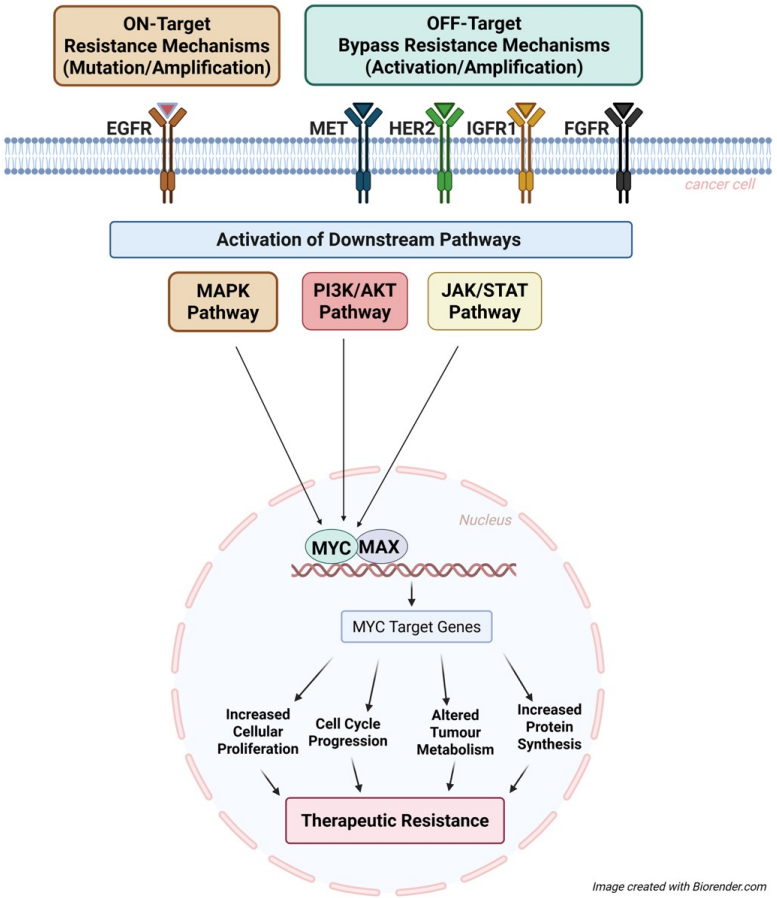
Planchard, D. et al. Osimertinib with or without Chemotherapy in EGFR-Mutated Advanced NSCLC. N. Engl. J. Med. 389, 1935–1948 (2023).

What is Needed to Delay TKI Resistance?

Any successful treatment MUST

- **Be able to prevent/delay bypass signalling** – block signalling downstream of all signalling pathways (e.g. MYC/MAX)
- **Be able to target the different resistance subclones together** – need to target multiple resistance pathways, not just a single pathway
- **Be able to be used indefinitely** – no lifetime or dose cycle limits for patients (e.g. doxorubicin or platinum drugs)
- **Moderate additional toxicity** – patient quality of life is paramount
- **Be proprietary** – otherwise who pays for the practice changing Phase 3 trials?

Example – issues with using Topo2α targeting in EGFRm TKI resistant NSCLC



Targeting Topo2α in TKI resistant EGFR NSCLC

The Journal of Clinical Investigation RESEARCH ARTICLE

DNA topoisomerase II inhibition potentiates osimertinib's therapeutic efficacy in EGFR-mutant non–small cell lung cancer models

Zhen Chen,[1] Karin A. Vallega,[1] Dongsheng Wang,[1] Zihan Quan,[2] Songqing Fan,[2] Qiming Wang,[3] Ticiana Leal,[1] Suresh S. Ramalingam,[1] and Shi-Yong Sun[1]

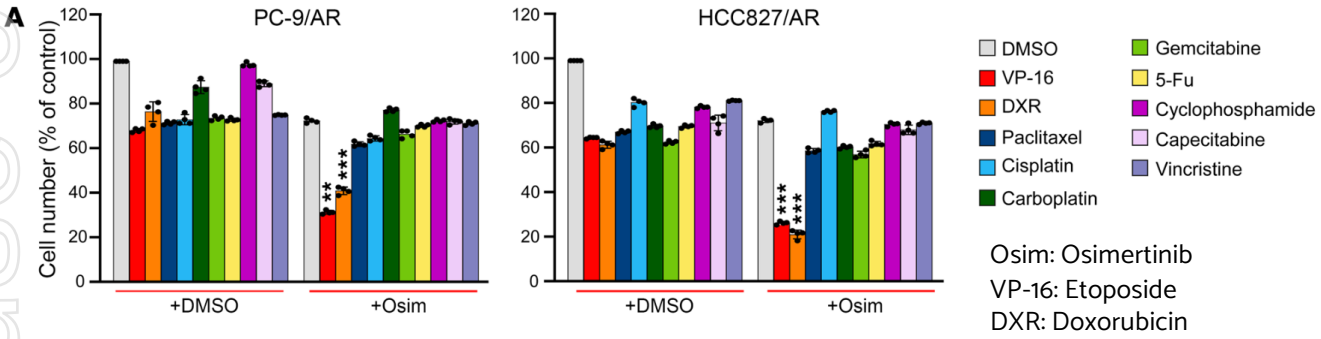
[1]Department of Hematology and Medical Oncology, Emory University School of Medicine and Winship Cancer Institute, Atlanta, Georgia, USA. [2]Department of Pathology, The Second Xiangya Hospital, Central South University, Changsha, Hunan, China. [3]Department of Internal Medicine, The Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China.

Development of effective strategies to manage the inevitable acquired resistance to osimertinib, a third-generation EGFR inhibitor for the treatment of EGFR-mutant (EGFRm) non–small cell lung cancer (NSCLC), is urgently needed. This study reports that DNA topoisomerase II (Topo II) inhibitors, doxorubicin and etoposide, synergistically decreased cell survival, with enhanced induction of DNA damage and apoptosis in osimertinib-resistant cells; suppressed the growth of osimertinib-resistant tumors; and delayed the emergence of osimertinib-acquired resistance. Mechanistically, osimertinib decreased Topo IIα levels in EGFRm NSCLC cells by facilitating FBXW7-mediated proteasomal degradation, resulting in induction of DNA damage; these effects were lost in osimertinib-resistant cell lines that possess elevated levels of Topo IIα. Increased Topo IIα levels were also detected in the majority of tissue samples from patients with NSCLC after relapse from EGFR tyrosine kinase inhibitor treatment. Enforced expression of an ectopic *TOP2A* gene in sensitive EGFRm NSCLC cells conferred resistance to osimertinib, whereas knockdown of *TOP2A* in osimertinib-resistant cell lines restored their susceptibility to osimertinib-induced DNA damage and apoptosis. Together, these results reveal an essential role of Topo IIα inhibition in mediating the therapeutic efficacy of osimertinib against EGFRm NSCLC, providing scientific rationale for targeting Topo II to manage acquired resistance to osimertinib.

Reference information: *J Clin Invest*. 2024;134(10):e172716.

- Topo2α has been discovered to be important in TKI resistance in EGFRm NSCLC
- Topo2α inhibitors are highly effective in TKI resistant tumours with high levels of Topo2α
- Topo2α inhibitors synergise with EGFRm TKIs like osimertinib even in TKI resistant tumours

Osimertinib Resistant EGFRm NSCLC – osimertinib + chemotherapy drugs



Osim: Osimertinib
VP-16: Etoposide
DXR: Doxorubicin

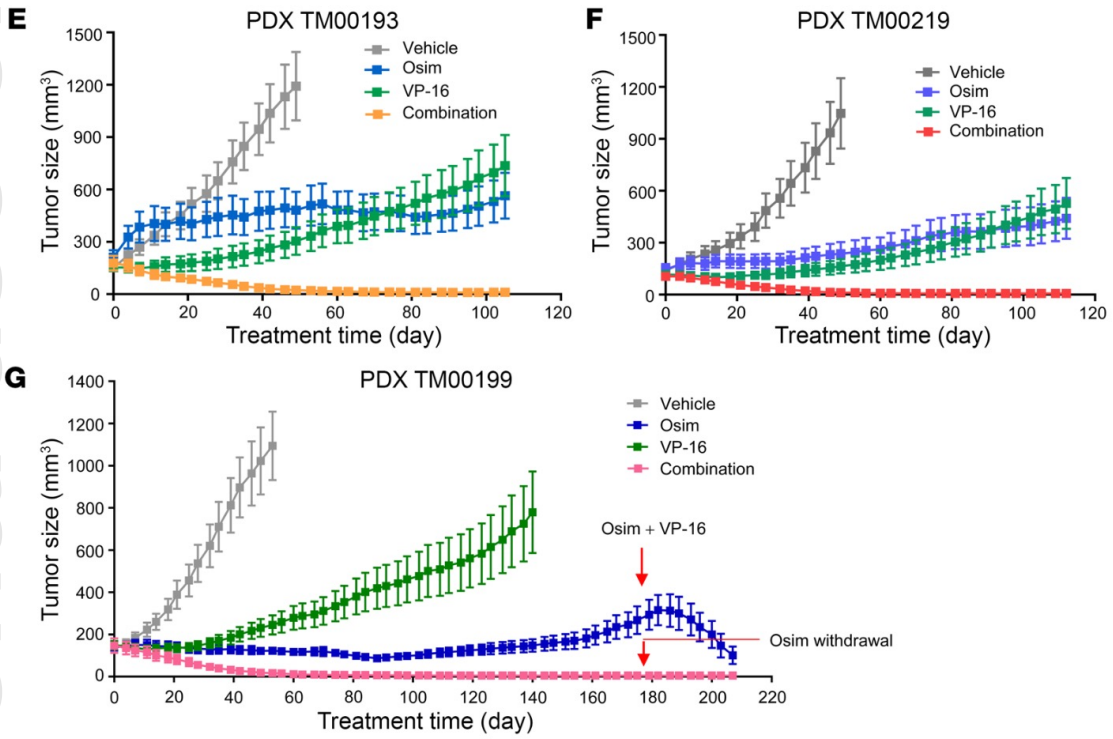
Topo2α levels are elevated in **>60%** of tumours from EGFRm TKI-resistant patients

Synergy with osimertinib was only seen with known Topo2α inhibitors (doxorubicin & etoposide) and not any other chemotherapeutic drug that is used in NSCLC

FLURA2 trial used the standard-of-care platinum drugs in combination with osimertinib

Reference information: *J Clin Invest*. 2024;134(10):e172716.

Osimertinib + Topo2α Inhibition in PDX EGFRm TKI Resistant NSCLC Models



Etoposide + osimertinib can eliminate TKI resistant tumors

Adding etoposide once osimertinib resistance has arisen can control tumor growth

So why aren't etoposide or doxorubicin viable solutions to EGFRm resistance?

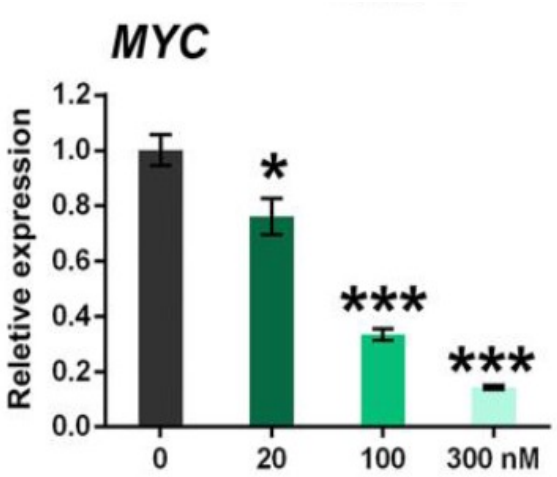
- Don't prevent bypass signaling
- Only target one TKI resistance pathway
- Lifetime limits to dosing
- Generic drugs

Reference information: *J Clin Invest*. 2024;134(10):e172716.

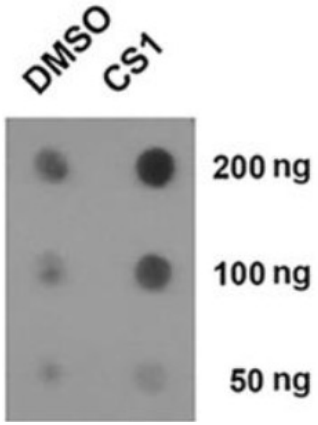
(E,E)-bisantrene activity in TKI resistant EGFRm lung cancer

Bisantrene's G4-binding targets multiple TKI resistance pathways in EGRFm NSCLC

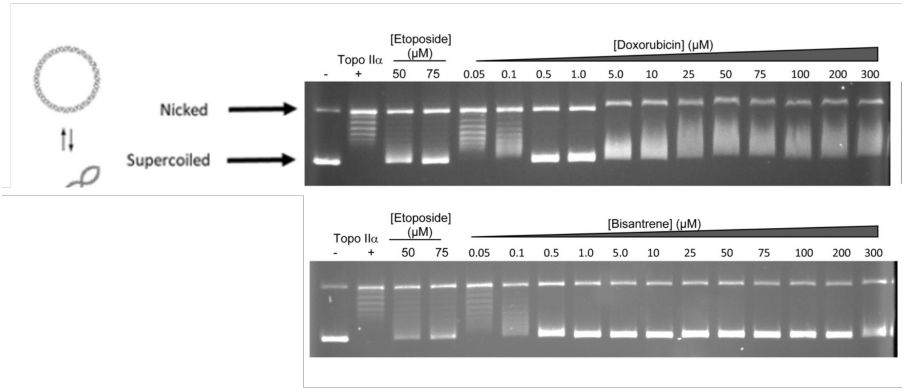
Silences MYC and other oncogene expression[1]



Increases m^{6}A RNA levels[1]



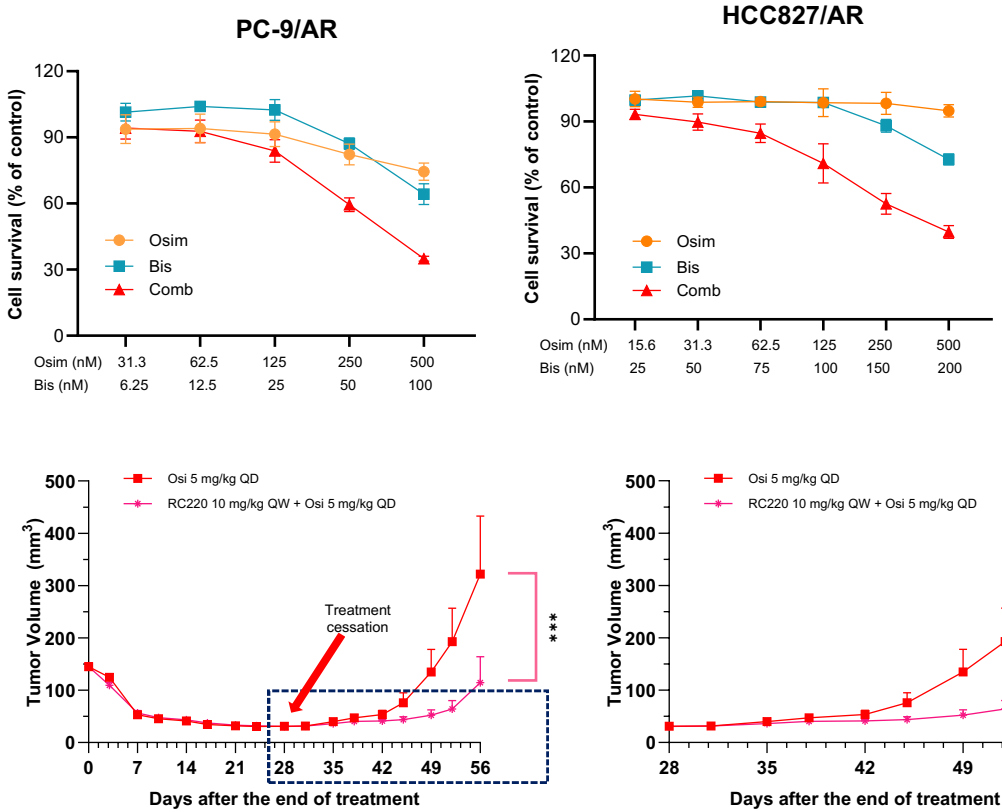
Inhibits Topo2α[2]



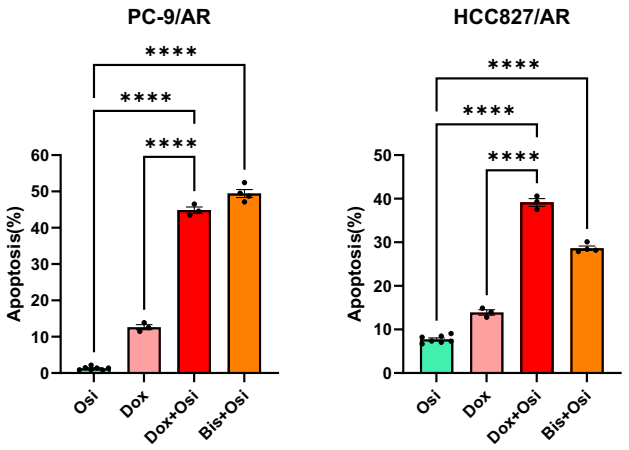
1. Su, R. et al. Targeting FTO Suppresses Cancer Stem Cell Maintenance and Immune Evasion. Cancer Cell 38, 79-96.e11 (2020).
2.. Unpublished data (Race Oncology)

(E,E)-bisantrene in EGFRm NSCLC - Preclinical

Synergise with osimertinib in TKI resistant EGRFm NSCLC cells

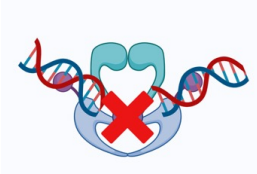
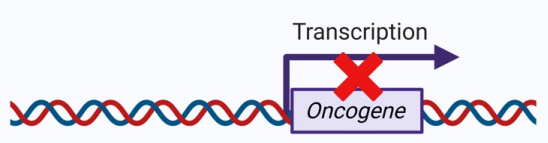
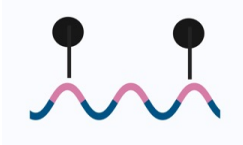


Increase apoptosis in TKI resistant EGFRm NSCLC cells

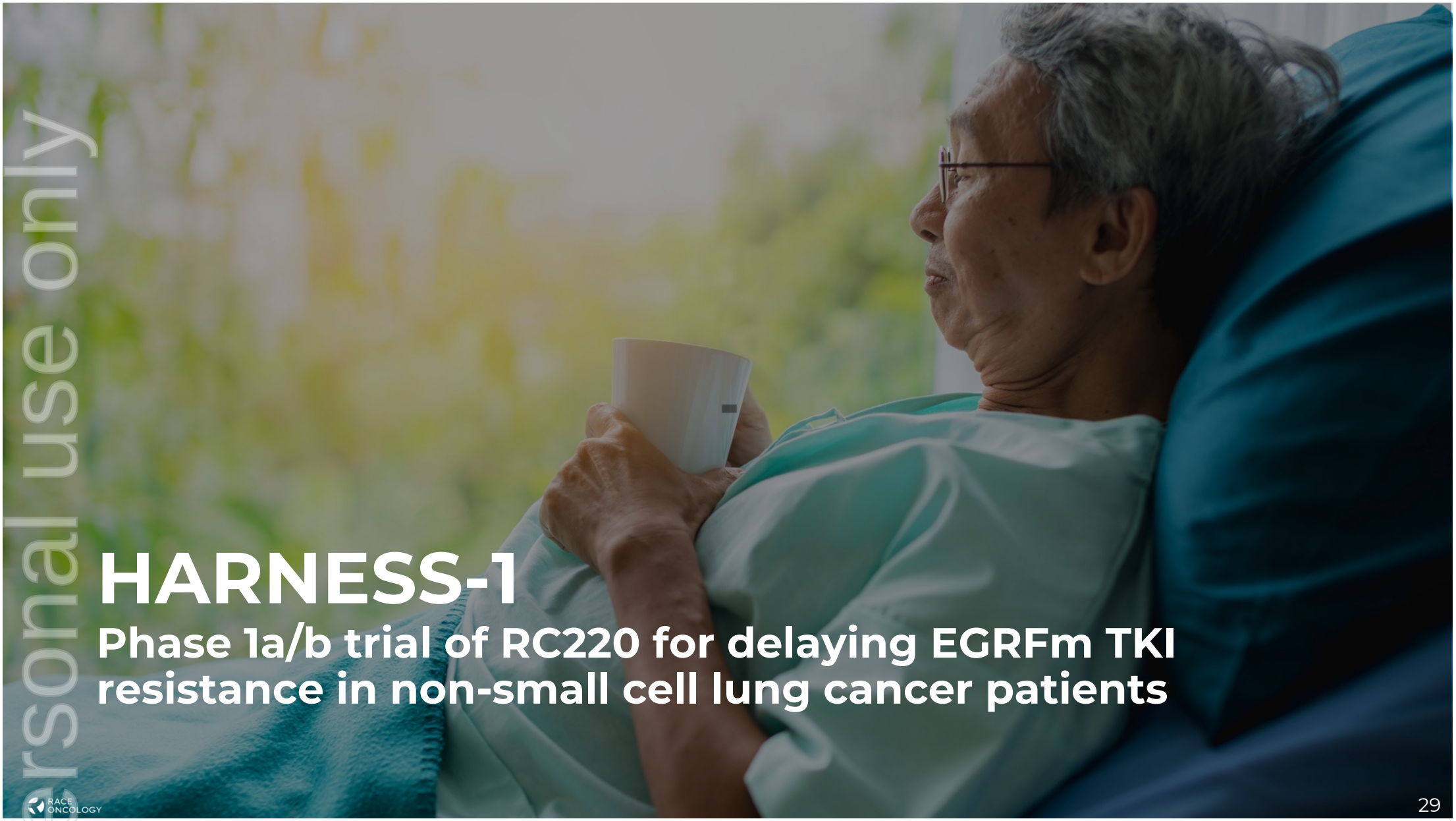


Delays EGRFm NSCLC tumour regrowth in mouse models

Important EGFRm TKI Resistance Pathways Targeted by (E,E)-bisantrene

TKI Resistance Pathway	(E,E)-bisantrene	Effect
Increased Topo2α activity[1]	Inhibits Topo2α	
Bypass signaling[2]	Silences MYC and other oncogene expression	
Decreased m^{6}A RNA levels[3]	Increases m^{6}A RNA levels	

1. Chen, Z. et al. DNA topoisomerase II inhibition potentiates osimertinib's therapeutic efficacy in EGFR-mutant non-small cell lung cancer models. J. Clin. Investig. 134, e172716 (2024).
2.. Chen, Z. et al. Targeting MKK3/c-Myc interaction to overcome osimertinib acquired resistance in EGFR mutant lung cancer. Cancer Lett. 633, 218010 (2025).
3. Fan, S., Lv, X., Zhang, C., Zeng, B., Liang, Y., Chen, D., Xu, Z., Li, P., Wu, S., Liu, H. and Luo, K., 2024. METTL14-Mediated Bim mRNA m6A Modification Augments Osimertinib Sensitivity in EGFR-Mutant NSCLC Cells. Molecular cancer research: MCR, 22(11), pp.1051-1063.



HARNESS-1

Phase 1a/b trial of RC220 for delaying EGRFm TKI resistance in non-small cell lung cancer patients

HARNESS-1. HAlt Resistance in NSCLC with EGFR Sensitising mutationS

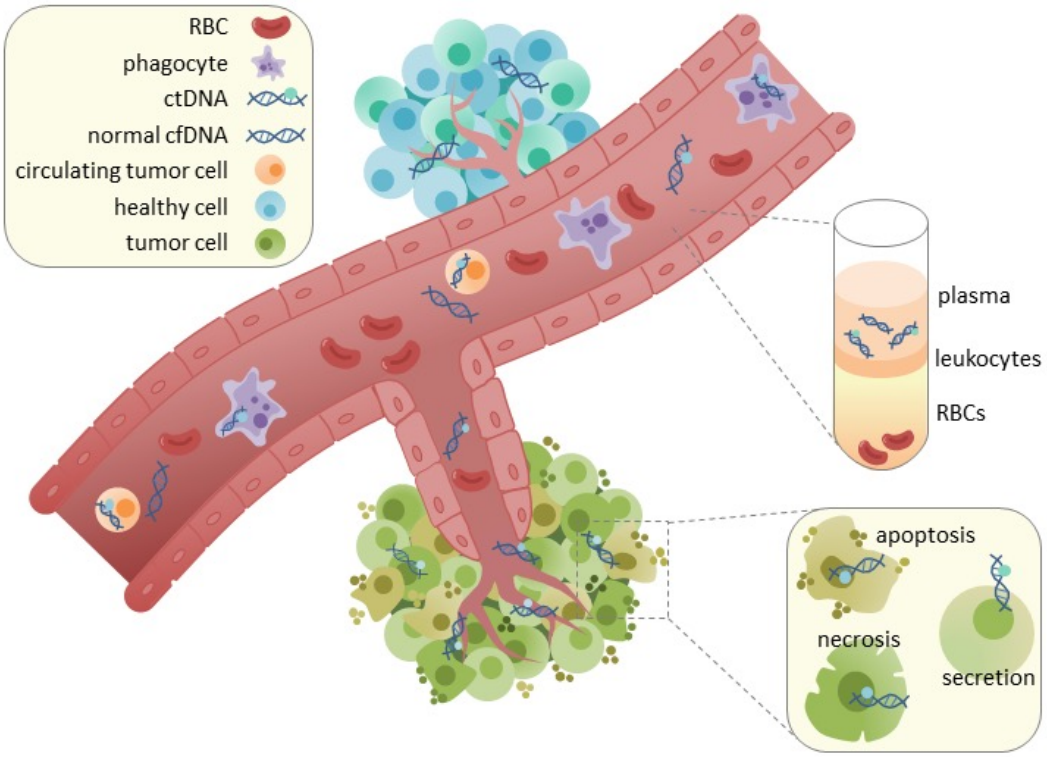
A Race Oncology sponsored Phase 1a/b trial of RC220 + osimertinib in EGFRm NSCLC patients who are tumour positive by ctDNA with the aim of delaying TKI resistance

- **Endpoints:** Safety, maximum tolerated combined dose, changes in ctDNA positivity, progression free survival and overall survival
- **Sites:** Five in Australia (Sydney, Melbourne, Brisbane)
- **Patients:** ~100 ctDNA screening, Phase 1a (12-40), Phase 1b (40)
- **Cost:** ~A$11.5m before R&D tax rebate
- **Time:** Phase 1a (9-12 months), Phase 1b (~9 months)
- **First patient:** Q1 2026 (assuming all approvals granted as expected)

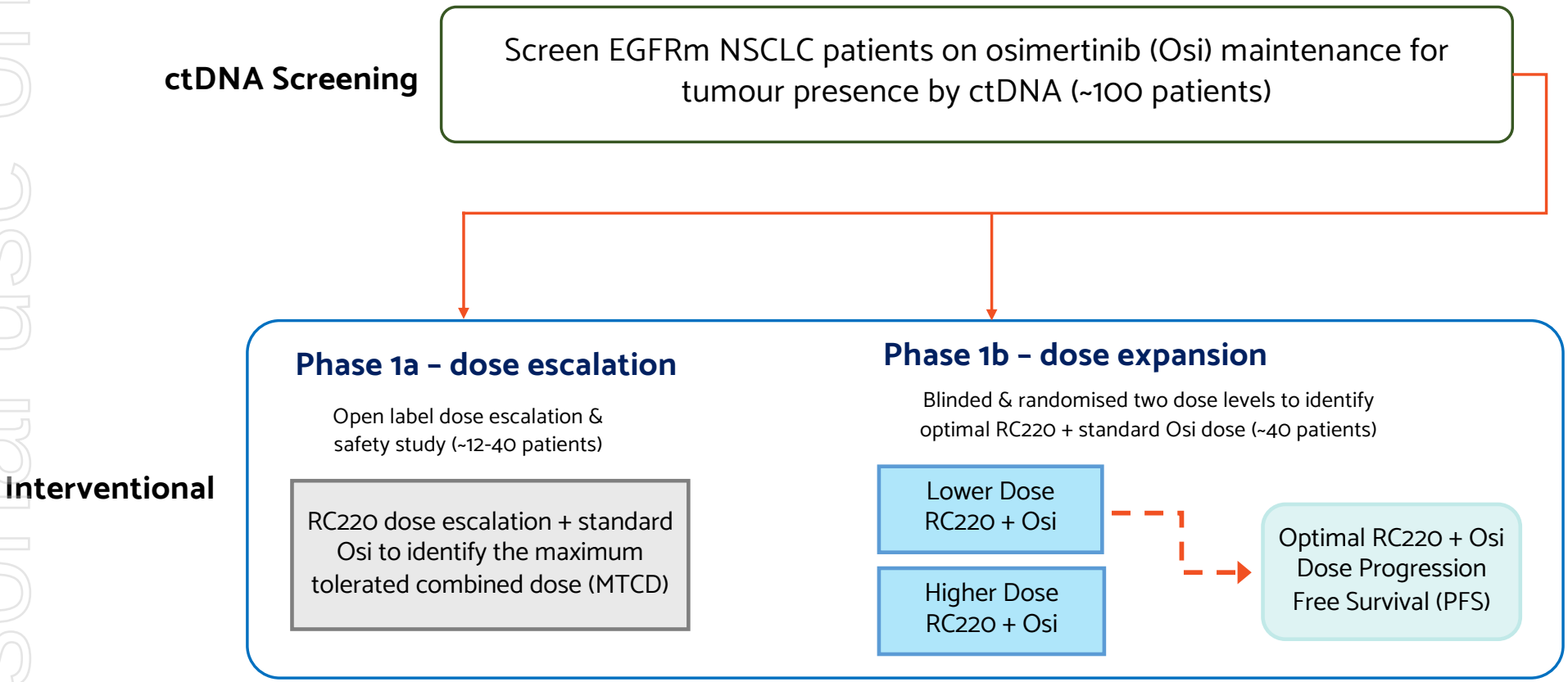
HARNESS-1 planning is highly advanced with the trial protocol written, HREC (ethics) application submitted, CROs contracted, and sites and clinicians recruited

Circulating Tumour DNA (ctDNA)

- Tumours release DNA into the bloodstream when they die
- ctDNA can be isolated from blood and used to detect the presence of the cancer or success of a treatment in a patient
- Patients with detectable ctDNA after treatment relapse more frequently and sooner
- Cancer treatments efficacy can be measured via conversion of ctDNA positive patients to ctDNA negative



HARNESS-1 Phase 1a/b Trial Overview



HARNESS-1 Trial Checklist

Requirement	Feature of EGFRm NSCLC	Check
Large existing market	>US$10 billion p.a. for EGFRm TKIs	✓
Supportive preclinical & clinical data	G4 binding targets more than three of the known EGFRm TKI resistance pathways	✓
High clinical need	Very high – few options for EGFRm TKI progressing patient	✓
Proprietary companion drug	3rd generation EGFR TKIs	✓
Many pharma players	14 EGFRm TKI approved in China & USA, 8 in Phase 3	✓
Rapid & low-cost POC trial	ctDNA(+) to ctDNA(-)	✓
Large effect size	Use of ctDNA	✓
Possibility of FDA accelerated approval	Datopotamab from Phase 2 data (2025) Zongertinib from Phase 1b data (2025)	✓
Template trial design	ctDNA approach can be applied to resistance of any TKI	✓

AML Phase 3 Program

Rapid pathway to approval and optimal use of RC220 in Acute Myeloid Leukemia

RC110 in Acute Myeloid Leukemia

Phase 2 trials of (E,E)-bisantrene RC110 in r/r AML

- RC110 as a mono agent: **40% overall response rate.**[1]
- RC110 in combination with nucleoside antimetabolites: **40% overall response rate.**[2]
- RC110 is an effective salvage agent in late-stage, very heavily pre-treated r/r AML patients.

1. Canaani J, Danylesko I, Shemtov N, et al. Eur J Haematol. 2021;106(2):260-266
2. Danylesko I, Shimoni A, Avigdor A, et al. Br J Haematol. 2025;00:1-10

Received: 13 September 2020 | Revised: 1 November 2020 | Accepted: 2 November 2020
DOI: 10.1111/ejh.13544

ORIGINAL ARTICLE

Haematology WILEY

A phase II study of bisantrene in patients with relapsed/ refractory acute myeloid leukemia

Jonathan Canaani | Ivetta Danylesko | Noga Shemtov | Maya Zlotnick | Kira Lozinsky | Ohad Benjamini | Ronit Yerushalmi | Meital Nagar | Chen Dor | Avichai Shimoni | Abraham Avigdor | Arnon Nagler

Abstract

Objectives: To determine the current role of bisantrene, an anthracene with anthracycline-like activity which was shown in earlier studies to be effective therapy in relapsed/refractory acute myeloid leukemia with no discernible cardiotoxicity, in the treatment of patients with R/R AML.

Methods: This phase 2, single-center study (NCT03820908) enrolled adult R/R AML to receive bisantrene (250 mg/m^2 daily for 7 days) which was administered via an intravenous infusion over 2 hours on days 1-7. Disease assessment included routine blood work and bone marrow studies.

Results: In all, 10 patients were enrolled with a median of 3 lines of prior therapy including seven patients who had relapsed following allogeneic stem cell transplantation. The most frequently reported grade ≥3 treatment-attributed hematologic AE was thrombocytopenia, whereas the most frequently reported grade ≥3 treatment-attributed non-hematologic AE was mucositis. Of the 10 patients, one (10%) achieved a complete remission and three patients achieved a partial remission resulting in an overall response rate of 40%. Next-generation sequencing of patient samples identified a wide array of mutations associated with activated signaling, splicing, and epigenetic modification.

Conclusions: In view of the observed low toxicity, a follow-up study combining bisantrene with complementary anti-leukemic therapy is planned.

KEYWORDS
acute myeloid leukemia, clinical trials, molecular cytogenetics

1 | INTRODUCTION

ORIGINAL PAPER
Haematological Malignancy - Clinical

Bisantrene in combination with fludarabine and clofarabine as salvage therapy for adult patients with refractory or relapsed acute myeloid leukaemia (AML)—An open-label, phase I/II study

Ivetta Danylesko | Avichai Shimoni | Abraham Avigdor | Meirav Kedmi | Irina Amitai | Noga Shem-Tov | Ronit Yerushalmi | Borje S. Andersson | Arnon Nagler

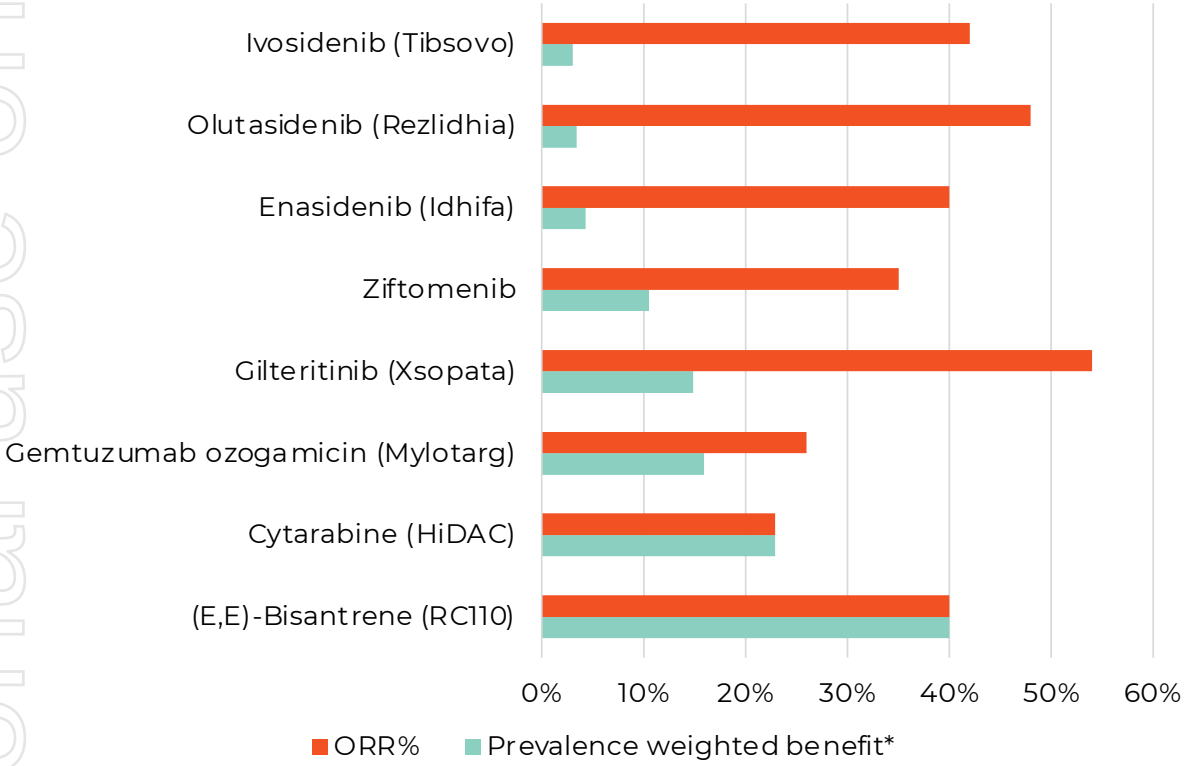
Summary

Bisantrene (Bis), an anthracene derivative with topoisomerase-II inhibitory activity and low cardiotoxicity, may enhance its efficacy when combined with nucleoside analogues such as clofarabine (Clo) and fludarabine (Flu) in preclinical acute myeloid leukaemia (AML) studies. We conducted a phase I/II open-label study (NCT04989335) to evaluate the safety and efficacy of Bis/Clo/Flu in relapsed/refractory AML. Twenty-one patients (median age; 47 years, 55% female) received Flu (10 mg/m^2), Clo (30 mg/m^2) and Bis (250 mg/m^2) intravenously for 4 days. Sixteen had relapsed post-allogeneic stem cell transplantation, and six had extramedullary disease (EMD). Liver toxicity occurred in 10 patients but resolved. No significant cardiac toxicity was observed. Efficacy was assessable in 15 patients, while in six patients, it could not be evaluated due to early non-relapse mortality occurring within 30 days of treatment initiation, before the first post-treatment assessment. Six of the 15 patients responded: five achieved complete remission, and one with EMD achieved a partial remission, yielding a 40% response rate. Responses were transient, but six patients, including four undergoing second allo-HSCTs, proceeded to allo-HSCT within 1–3 months post-treatment. The Bis/Clo/Flu regimen demonstrated a tolerable safety profile and potential as a bridging therapy in high-risk, heavily pre-treated AML.

KEYWORDS
acute myeloid leukaemia, chemotherapy: refractory/relapsed

INTRODUCTION

Performance of different AML drugs as second line treatments



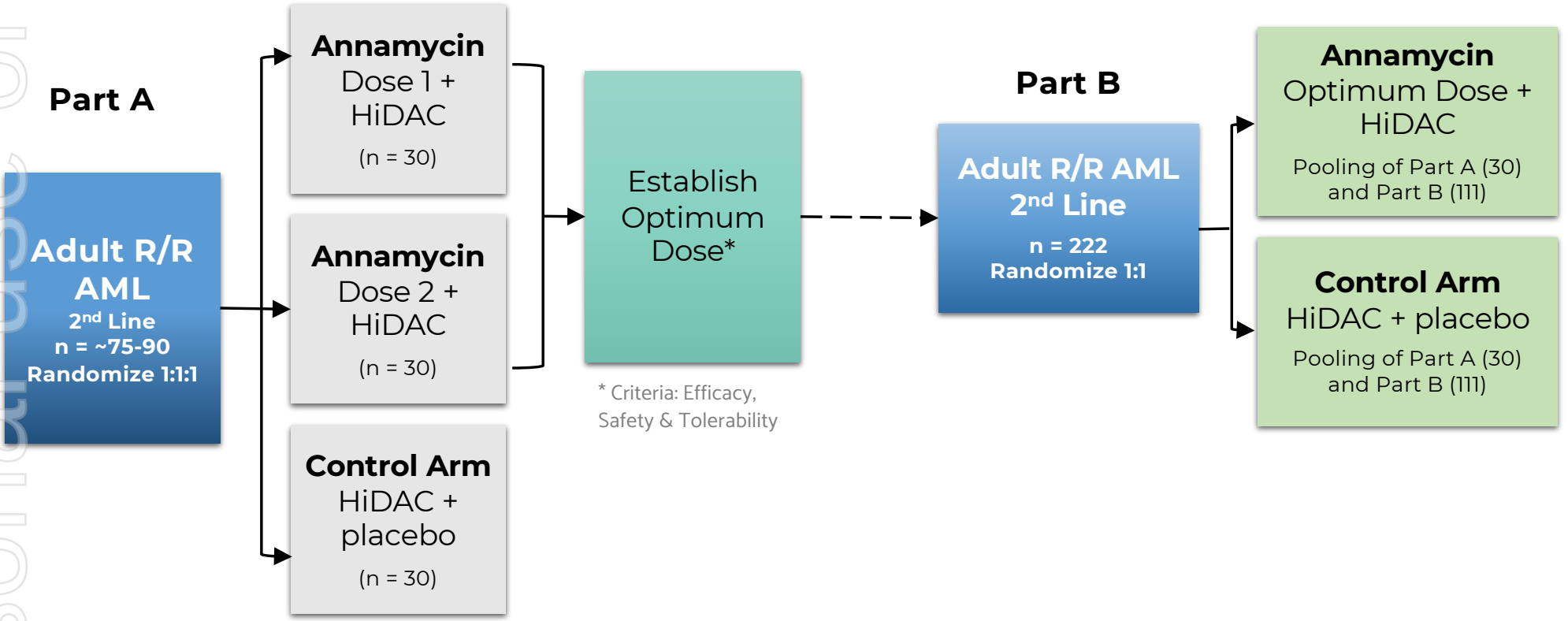
RC110 offers a high prevalence weighted benefit as a mono agent therapy for r/r AML patients

So what trial design to use for FDA approval?

ORR, overall response rate.

* Prevalence weighted benefit for ORR accounts for patient eligibility based on the prevalence of targeted gene mutations/rearrangements (eg, *IDH1*, *IDH2*, *FLT3*, *NPM1*, *KMT2A*r) or overexpressed proteins (eg, CD33+) in r/r AML.

Moleculin's FDA/EMA-agreed Phase 3 Trial Design (2025)

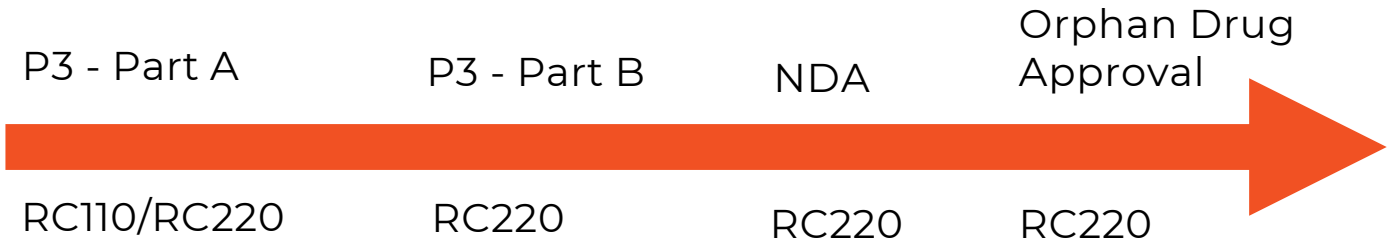


Doses and adaptive design recommended by FDA in end of Phase 1B/2 meeting; Primary Endpoint = CR rate at ~ 1 month; May reduce Part A to 75 subjects if dose optimization possible at first unblinding.

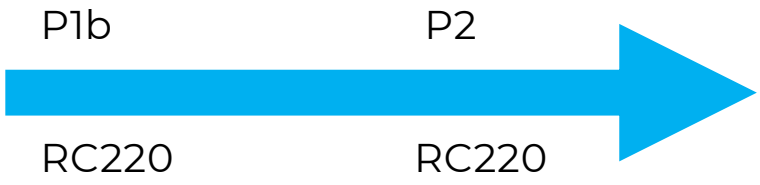
R/R AML, relapsed and refractory acute myeloid leukemia.

Parallel AML Trial Plan

Approval Path (Race Oncology Sponsored)



Optimal Use Path (Investigator Sponsored)

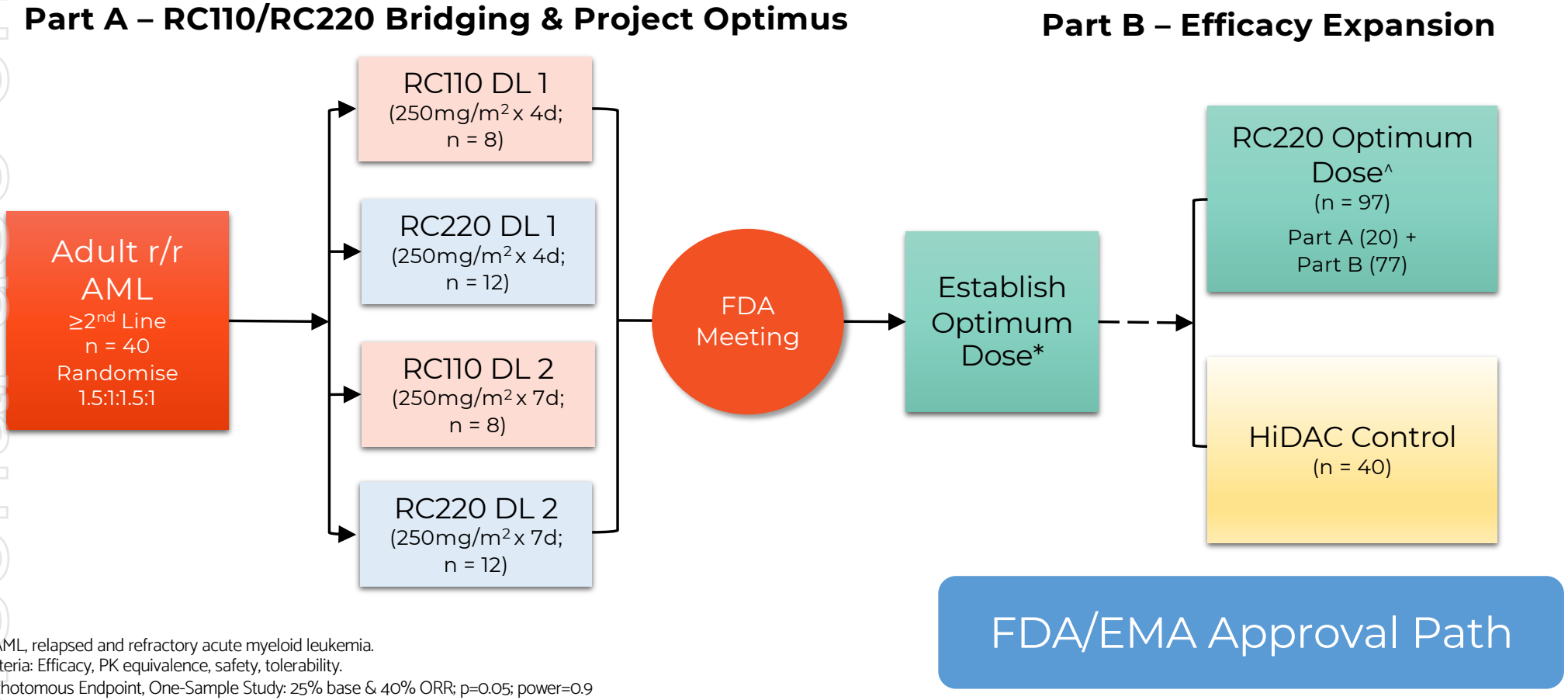


Approach uses stagged parallel trials to both gain approve of RC220 for AML AND identify how to best use it in this disease

Approval Phase 3 trial uses a two-stage bridging + efficacy expansion design

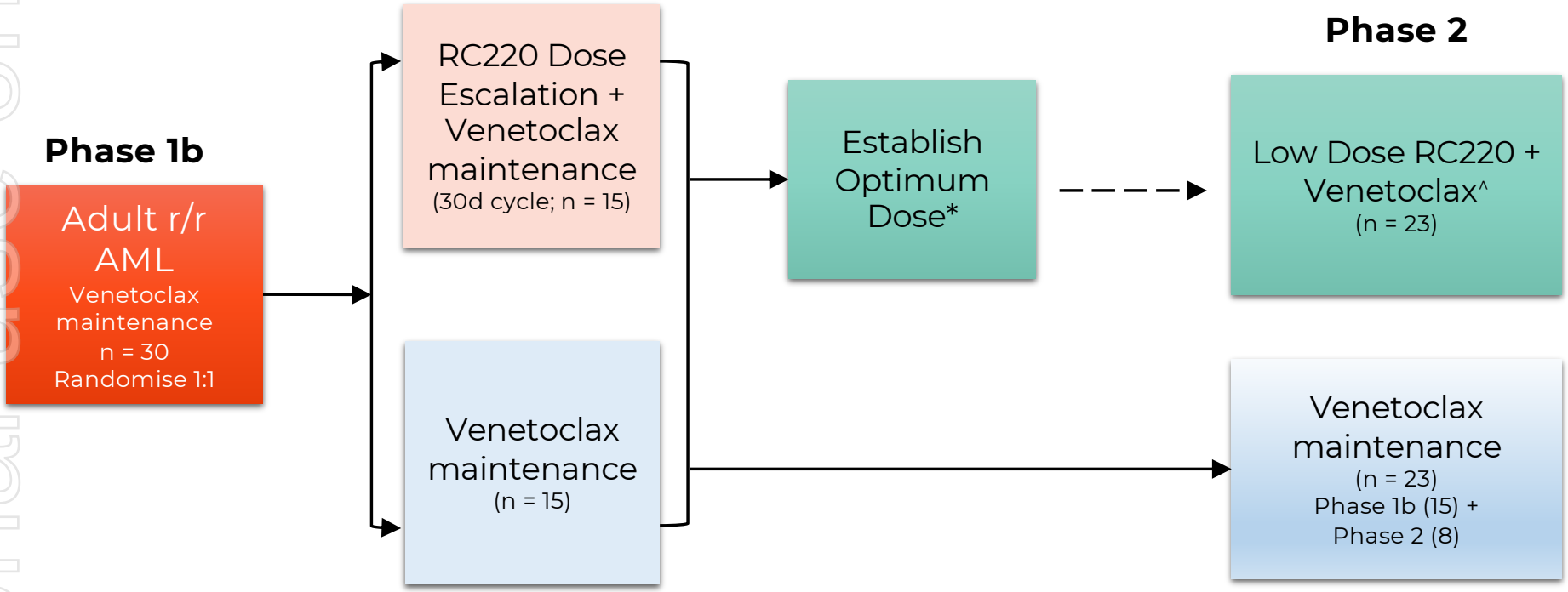
Optimal use trial is a later run IST aimed at showing how to best use RC220 in combination with other AML treatments

Adaptive Phase 3 Trial Design for FDA/EMA Approval of RC220 for r/r AML



r/r AML, relapsed and refractory acute myeloid leukemia.
* Criteria: Efficacy, PK equivalence, safety, tolerability.
^ Dichotomous Endpoint, One-Sample Study: 25% base & 40% ORR; p=0.05; power=0.9

Example Phase 1b/2 Investigator Sponsored Trial for delay of venetoclax resistance in AML



RC220 Optimal Use Path

* Criteria: Efficacy, safety, tolerability.
^ Continuous Endpoint, Two Independent Sample Study: 15m median vrs 12m median PFS; p=0.025; power=0.9

Why Parallel Phase 3 & Phase 1/2 AML Trials?

1. **Rapid path to RC220 FDA/EMA approval** by bridging RC220 from RC110
2. Builds on a 2025 FDA-agreed trial design for r/rAML (Moleculin model)
3. **MYC biomarker** – generates compelling clinical POC demonstrating MYC targeting
4. Opportunity for paediatric PRV from possible paediatric sub-study
5. **Capital efficient design**

Phase 3 Pivotal Trial

- FDA orphan drug indications like AML only requires one Phase 3 trial for approval (RC220 already has Orphan Drug Designation from the FDA)
- **~$7m for Bridging + Project Optimus stage** (funded from options)
- ~$13m for dose expansion stage (not yet funded)

Phase 1b/2 IST Trial

- Australian-based investigator sponsor trial (not yet funded)
- ~$4m for 60 patients before R&D tax rebate

Summary

Two new clinical trials announced with clear paths to value creation

- **Phase 3 in AML** (RC110/RC220 Bridging & Project Optimus Stage)
- **Phase 1a/b in EGFRm Lung Cancer**

Both **trials can be funded from piggyback option conversions ($25m)** – 18% converted already + 12% owned by CEO

Planning well underway for both trials, but **major activities will not be initiated until we have the funds to complete the new trials**

We wish to thank all our shareholders for their continued support and enthusiasm

RACE ONCOLOGY

AT THE HEART OF CANCER CARE

Questions

Race Oncology

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AT THE HEART OF CANCER CARE

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