



Corporate Overview

Q4 2024

Forward Looking Statements / Safe Harbor

This presentation contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995. These statements may include the use of words or phrases such as “expects,” “plans,” “will”, “should”, “projects,” or other similar words or phrases. These statements are predictions that are based on current information and they may not come to fruition. There are risks and unknowns that mean that Inspirna's actual results may change materially from the expected results. Inspirna has no approved drugs available for sale & marketing at this time and may never have an approved drug. Inspirna is highly dependent on its lead investigational drug candidate, which is in clinical development and may not reach regulatory approval(s). Inspirna faces significant risks involved in drug development including drug substance and drug product manufacturing & stability, contracting with contract research organizations (CROs) and clinical trial sites to conduct its clinical trials, and identifying and hiring high quality and trustworthy employees. Additional risks involve general regulatory and market risks, and competition from many cancer drug candidates in development. Inspirna may reach approval for RGX-202 (ompenaclid), RGX-104 (abequolixron), and/or RGX-019 and still not recoup the investment in the program if there are substantial pricing changes outside of its control, undue competition, or lack of demand or reimbursement due to alternative treatments or safety concerns. Inspirna's RNA-DRIVER platform has not yet yielded an approved drug and may not do so with existing or future drug candidates. Its success is based on several scientific activities being recapitulated in different tumor types and settings. It is also reliant on the availability of human tumor tissues, mouse models, genetic sequencing technology, bioinformatics expertise and adequate research staff and scientific leadership. Inspirna is highly dependent on patent protection for its programs, including licensed intellectual property, and the company is still prosecuting patent protection for key aspects of its programs in the US and abroad. You are cautioned not to rely on Inspirna's forward-looking statements, which are only made as of the date hereof. Inspirna is under no obligation to update these statements.



Company Highlights

- Inspirna's mission is to develop first-in-class drugs to treat cancer types of high-unmet medical need
- Lead drug candidate ompenaclid is a novel small molecule SLC6A8 inhibitor with activity in **pan-RAS mutant** colorectal cancer currently in Phase 2 development
- Second program abequolixron is a small molecule LXR agonist in Phase 1b/2 development for lung and endometrial cancer
- Robust pipeline generated using novel miRNA-DRIVER platform to discover key drivers of cancer
- Strong management team supported by top-tier institutional investors, collaborators and advisors

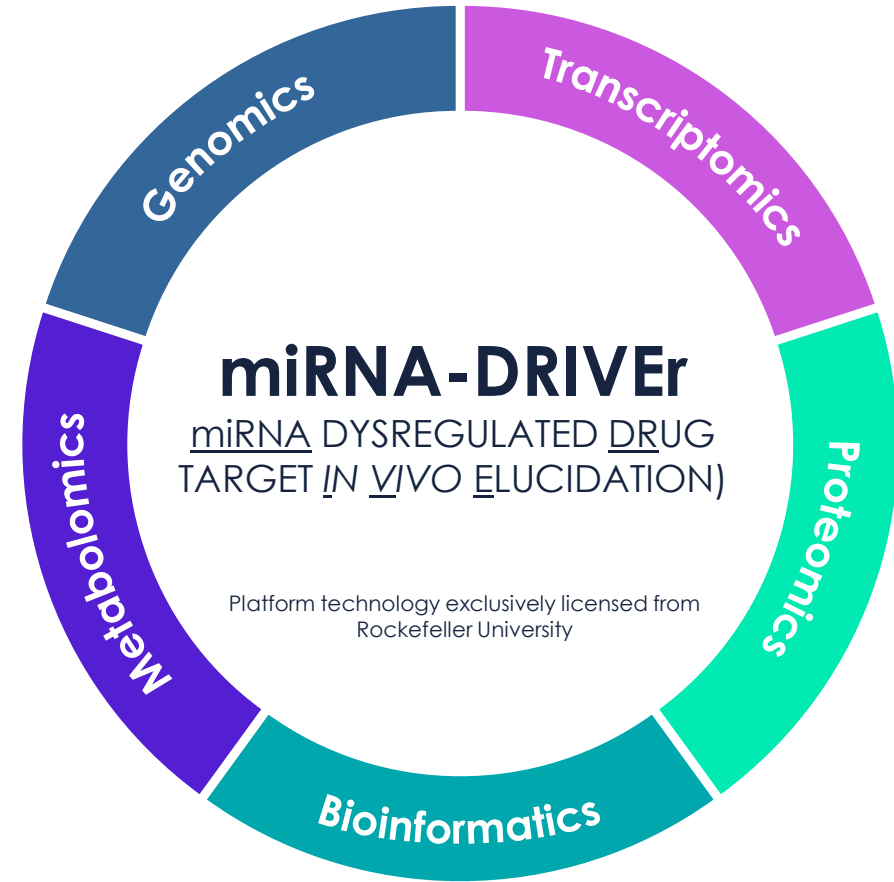
SLC6A8 -Solute Carrier family 6 member 8, LXR- Liver X Receptor, miRNA-DRIVER- miRNA DYSREGULATED DRUG TARGET IN VIVO ELUCIDATION

miRNA-DRIVER: Proprietary and clinically-validated platform to discover actionable targets of miRNA dysregulation

Platform technology exclusively licensed from Rockefeller University

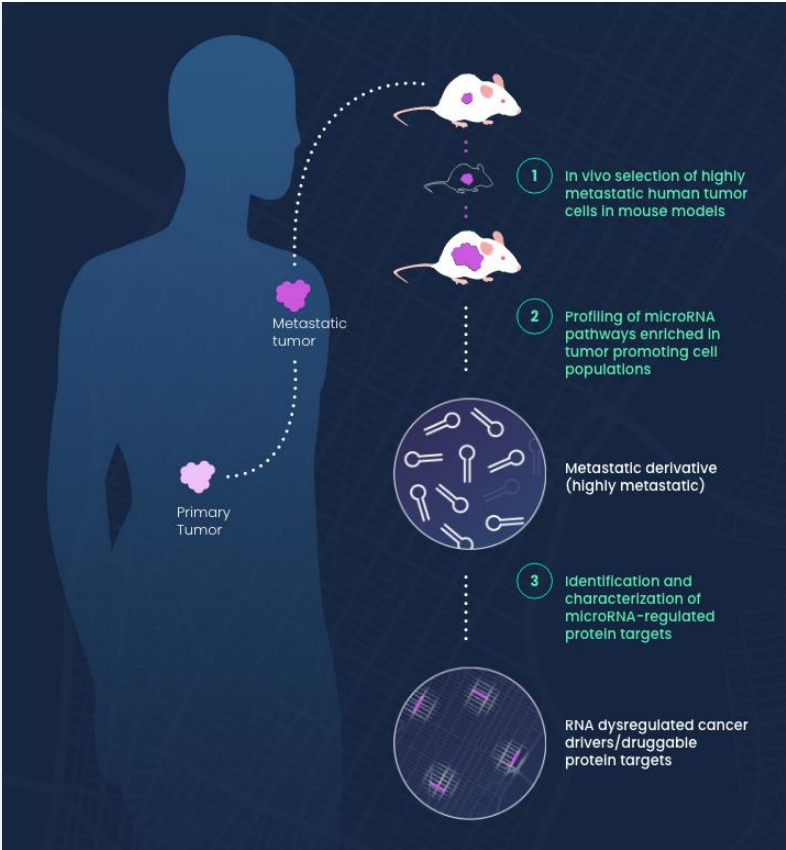
Why target miRNA regulated pathways?

- Micro RNAs (miRNAs)* have important functions in controlling many cell properties:
 - Regulate gene expression at the post-transcriptional level;
 - Modulate cell growth and differentiation;
 - Regulate pathways and networks via coordinated activities;
 - Act as control nodes or hubs in regulatory networks; and
 - Act co-operatively with other miRNAs and with transcription factors, which are frequent targets of miRNAs.
- miRNA dysregulation is a frequent contributor to cancer growth and progression.
 - Delineating miRNA functional effects requires elucidation of their upstream regulators and downstream targets.

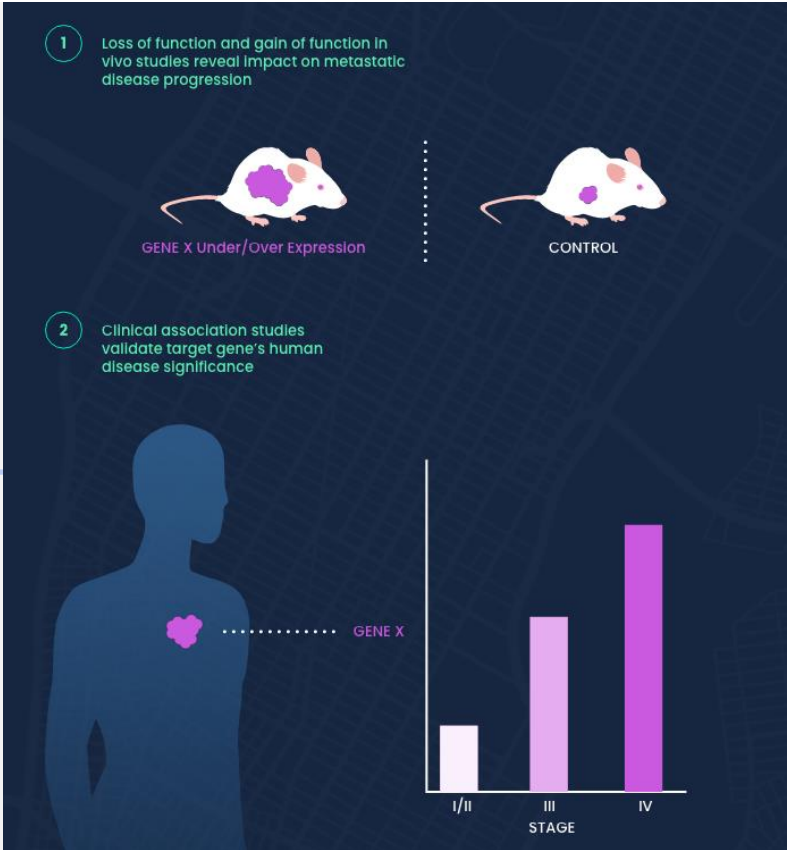


Overview - miRNA-DRIVER platform

RNA-DRIVER platform reveals actionable RNA-dysregulated cancer targets



We **discover** critical targets that drive the growth of metastatic disease.



We test and **validate** the role of the discovered gene in driving metastatic disease.

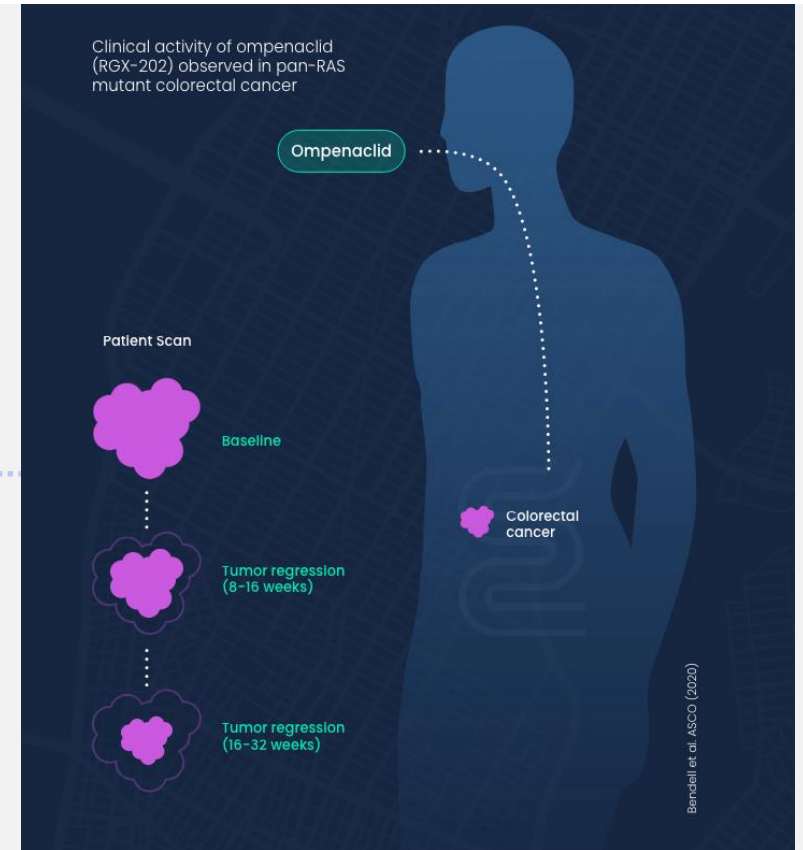
Overview - miRNA-DRIVER platform (continued)

First-in-class targets discovered and developed

RNA-DRIVER platform reveals actionable RNA-dysregulated cancer targets (continued)

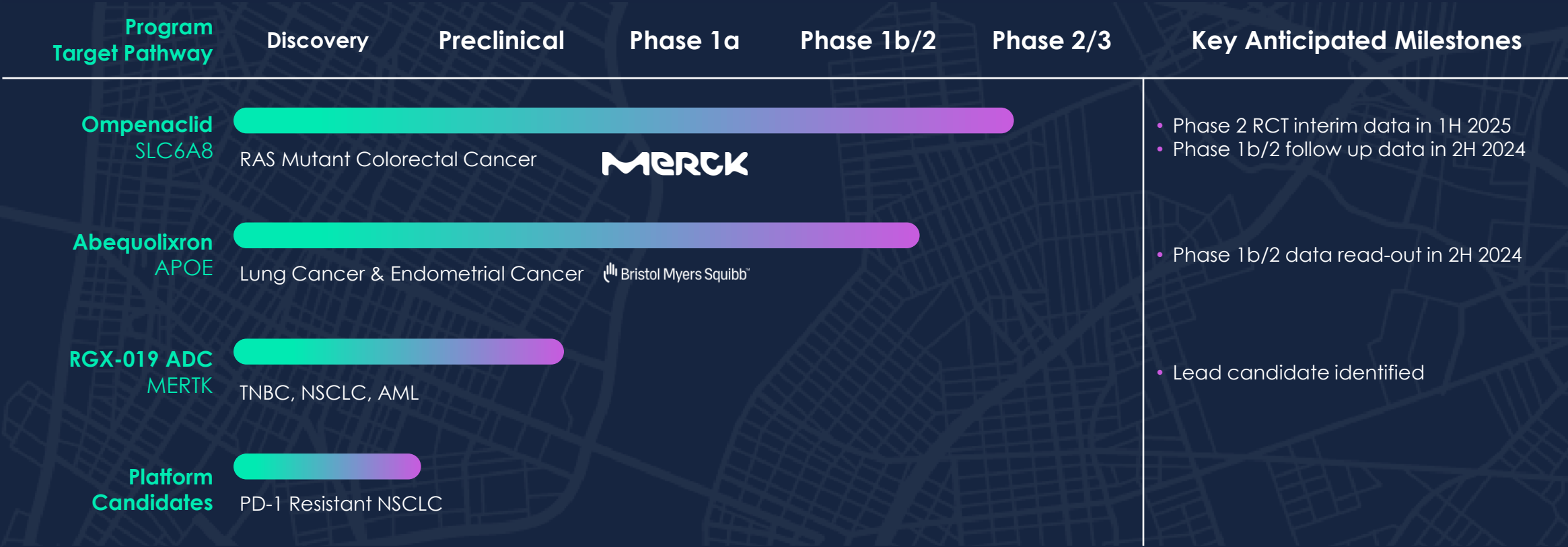


Our experienced team **develops** new drug candidates suitable for clinical evaluation.



We then **transform** cancer medicine by leveraging RNA biology driven insights.

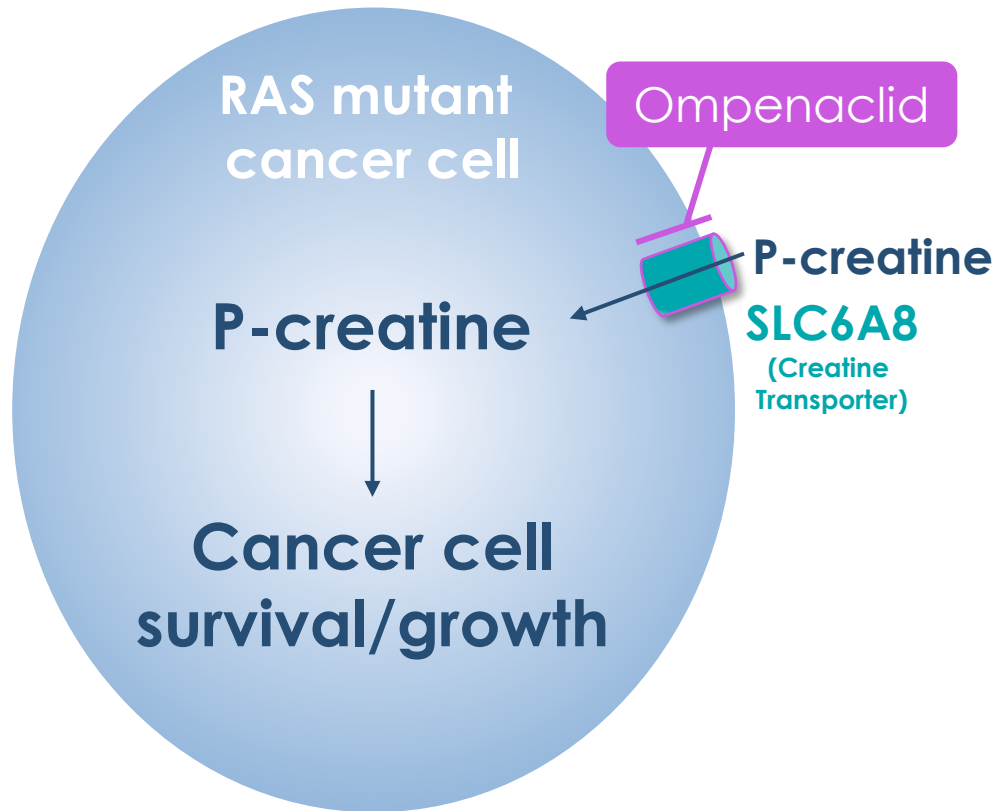
Inspirina's First-in-Class Oncology Pipeline



Ompenaclicid (RGX-202)

- First-in-class orally-administered small molecule SLC6A8 inhibitor
- Targets key pathway that drives RAS mutant tumor growth
- Monotherapy clinical activity in RAS mutated relapsed/refractory metastatic colorectal cancer (CRC) demonstrated during Phase 1
- Clinical activity in combination with standard-of-care (SOC) demonstrated in patients with pan-RAS mutated second line advanced or metastatic CRC in an ongoing Phase 1b/2 trial
- Excellent safety profile with no dose-limiting toxicities observed as a single agent or in combination with SOC in Phase 1 dose escalations
- Completing enrollment of a Phase 2 double blinded randomized controlled trial
- Phase 3 preparation activities underway to enable a global pivotal trial
- Issued global patent protection to 2040+

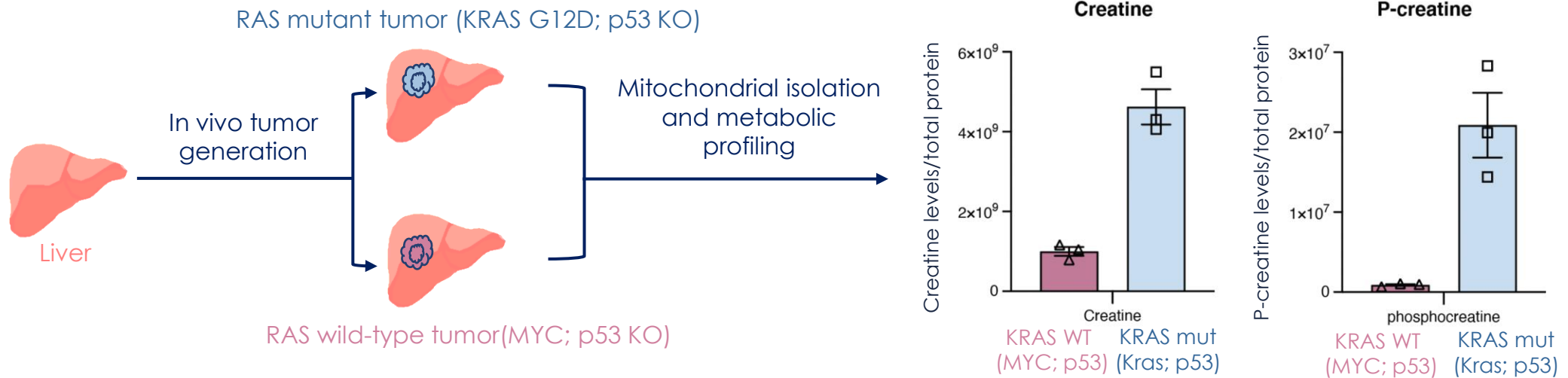
Ompenaclid mechanism of action



- Ompenaclid is an oral small-molecule competitive inhibitor of the SLC6A8 creatine transporter
- Blockade of SLC6A8 by ompenaclid depletes creatine and phospho-creatine in RAS mutant cancer cells, resulting in impairment of ATP synthesis and induction of apoptotic cancer cell death

RAS mutated cancers are dependent on activated creatine metabolism

- RAS mutant tumors significantly activate creatine metabolism
- Metabolic profiling demonstrates substantial increase in creatine and phospho-creatine (P-creatine) levels in the mitochondria of RAS mutant tumors relative to RAS wild-type (WT) tumors or healthy tissue



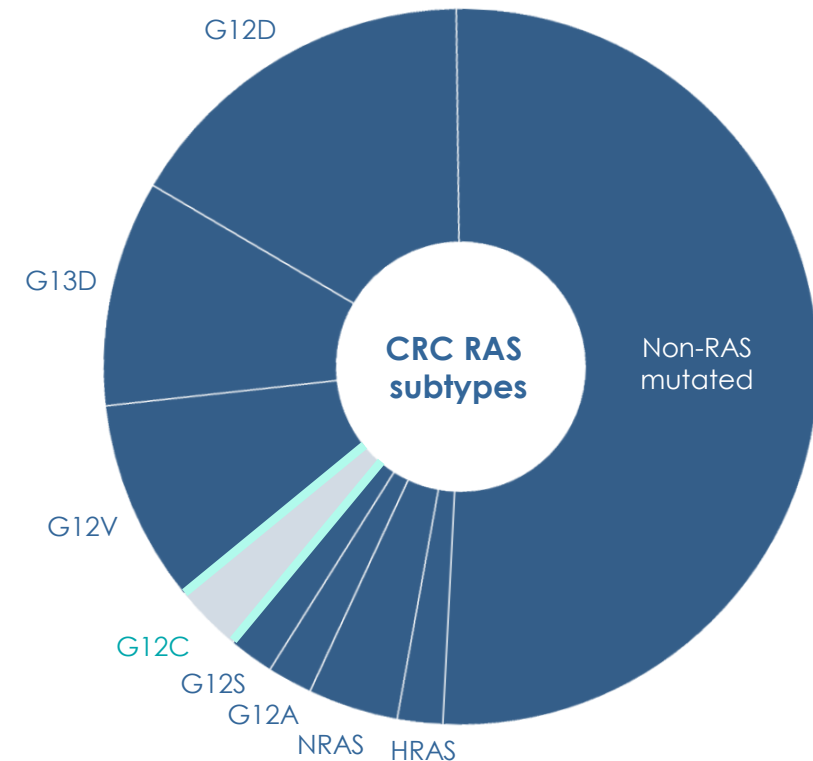
Creatine and phosphocreatine levels were measured in the mitochondria of p53 KO liver tumors that harbor either a KRAS G12D mutation or MYC overexpression. Tumors were induced by hydrodynamic injection of a plasmid carrying a p53 CRISPR construct to knock out p53, a mitochondrial tag and either MYC or KRAS G12D overexpression constructs.

RAS-mutated colorectal cancer (CRC) remains a high-unmet medical need requiring a novel targeted therapy

- CRC is the 3rd most common cancer diagnosed in the United States
- ~45% of patients with CRC have RAS-mutated cancer
- Only ~3% of CRC can be addressed with targeted KRAS G12C inhibitors currently in development

mCRC KRAS G12C mutation patients in USA **at peak sales year ~2,000**

Potentially addressable CRC patient population
(KRAS G12C inhibitors)



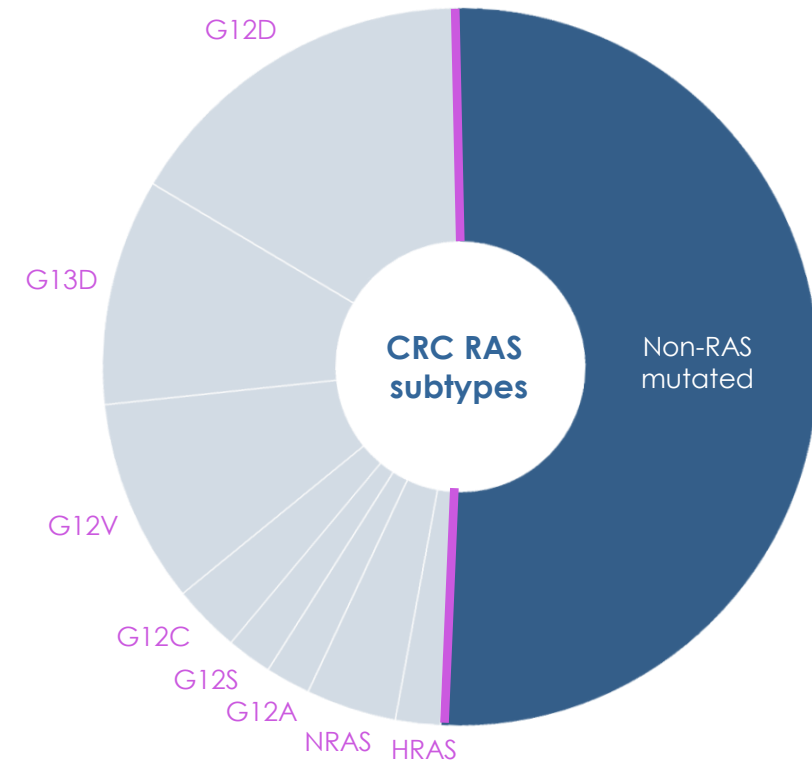
Ompenaclid is a first-in-class clinical stage SLC6A8 inhibitor with activity in pan-RAS-mutated CRC

Ompenaclid targets an essential dependency in pan-RAS-mutated tumors with potential to address ~45% of CRC patient population

mCRC pan-RAS mutation patients in USA **at peak sales year ~20,000**

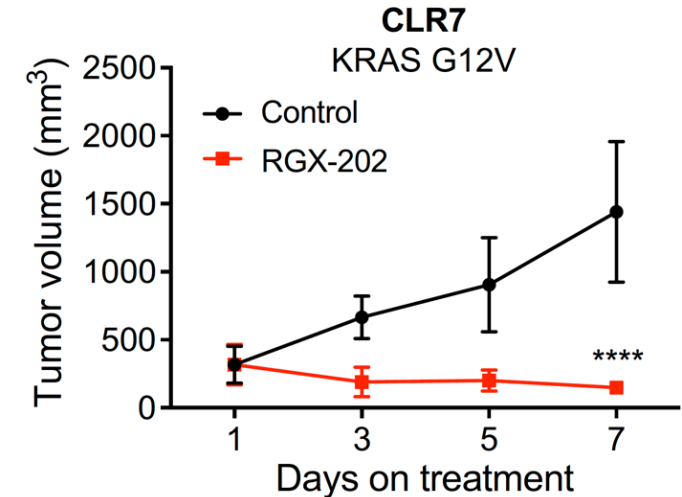
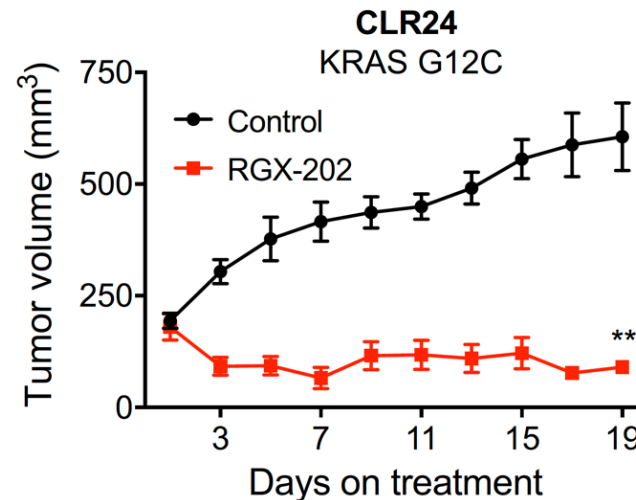
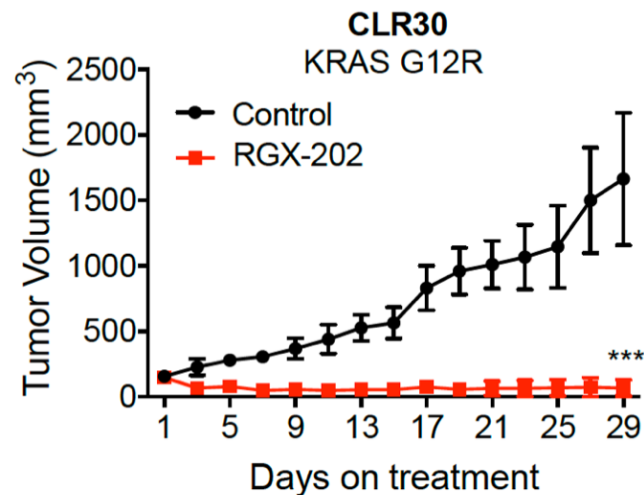
- Clinical activity observed against RAS-mutated CRC tumors (e.g. G12V, G13D, G12D, etc.) outside of G12C mutant cancers
- Orally-administered drug candidate with excellent safety profile observed to date

Potentially addressable CRC patient population (ompenaclid)



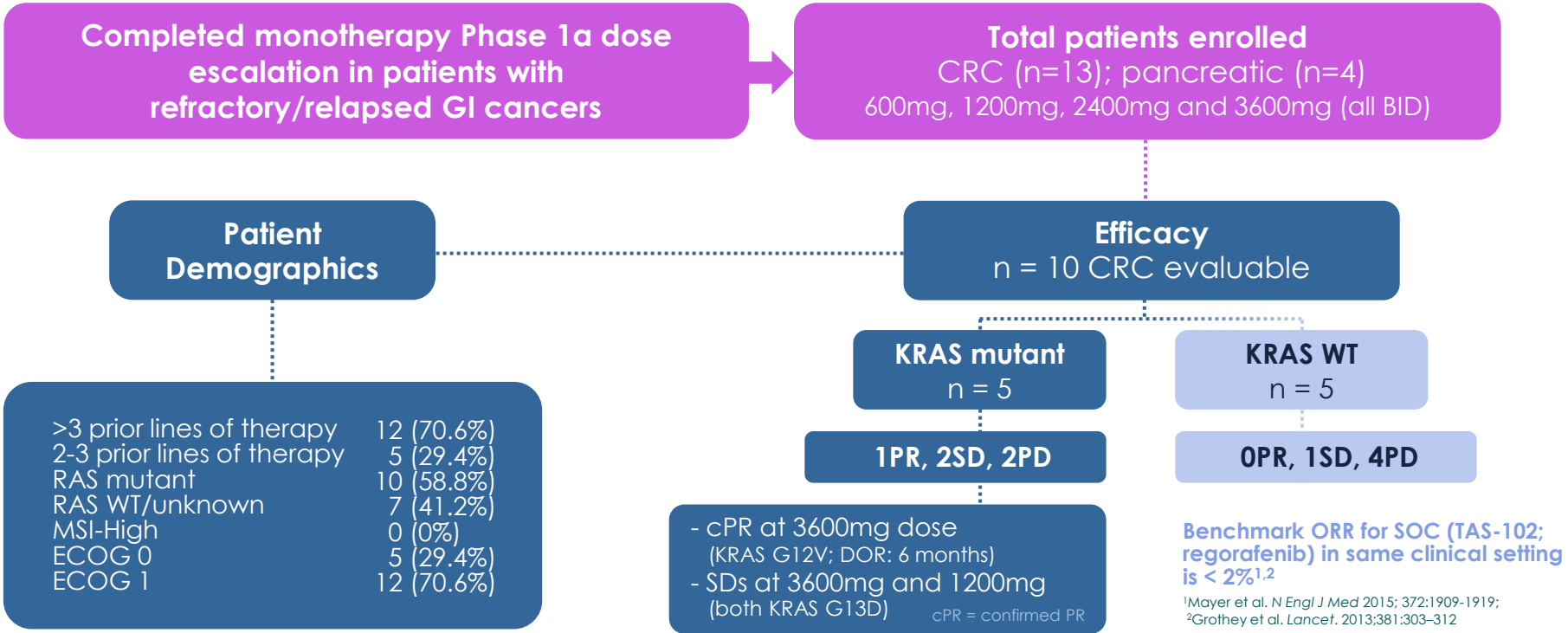
Ompenaclid has potent anti-tumor activity in CRC models across RAS mutant subtypes

Regressions of large established KRAS mutant CRC tumors treated with ompenaclid (RGX-202) (patient derived xenografts)



Treatment with control or RGX-202 at 800 mg/kg (daily) started when average tumor size reached 250 mm³ (CLR7), 200 mm³ (CLR24) and 150 mm³ (CLR30), n = 5 per cohort; ****p<0.0001 ***p<0.001, **p<0.01

Ompenaclicid monotherapy dose escalation Phase 1 *Efficacy Overview*

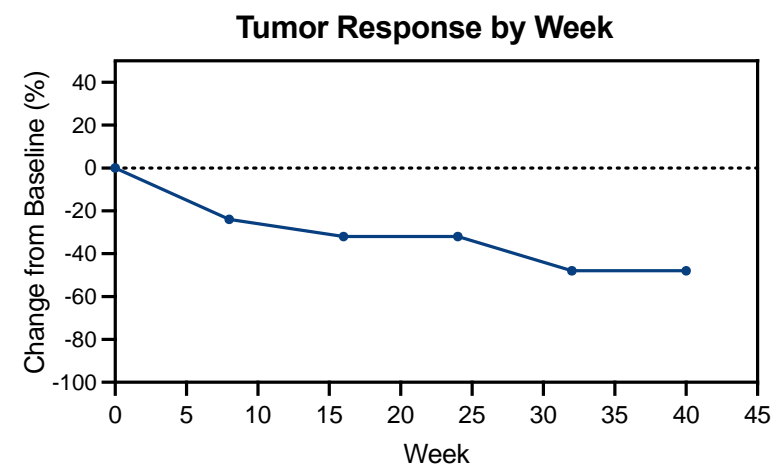
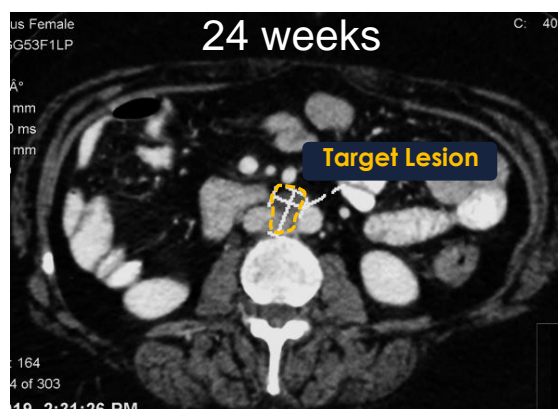
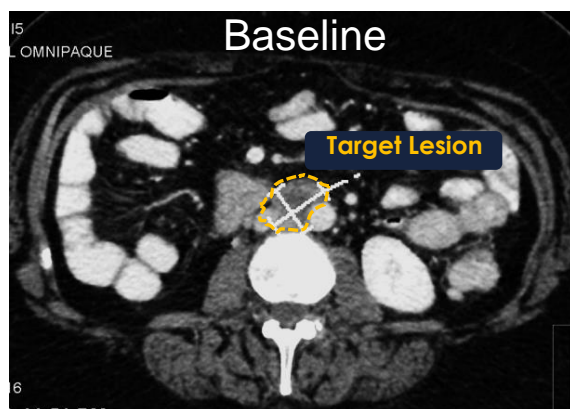


- Safety demonstrated
- Anti-tumor activity observed in KRAS mutant CRC at doses >2400mg BID
- Moved program rapidly into combination 2L setting on strength of preclinical and initial phase 1 monotherapy data

Ompenacnid single agent clinical activity – Phase 1 data presented at ASCO 2020

Confirmed Partial Response (PR) with single-agent ompenacnid in 55-year-old woman with KRAS^{G12V} mutant colon cancer

- Patient had 6 prior lines of therapies including regimens containing 5-FU, oxaliplatin, irinotecan, and bevacizumab (standard-of-care)
- Treated with ompenacnid monotherapy in Phase 1a dose escalation study
- PR by RECIST 1.1 at 16 weeks (confirmed at 24 weeks) with progression at week 40 with growth of a non-target lesion (6-month duration of response; 48% tumor shrinkage)



2L CRC is a setting of high unmet medical need

- The most commonly used standard-of-care (SOC) regimen for 2L metastatic CRC is FOLFIRI* + bevacizumab
- The benchmark efficacy data for this regimen in published clinical studies¹⁻⁵ are:
 - **Response Rate (ORR): ~15%**
 - **Median PFS: ~6 months**
- Patients with KRAS mutant tumors trend towards worse outcomes with standard-of-care than those with KRAS WT tumors

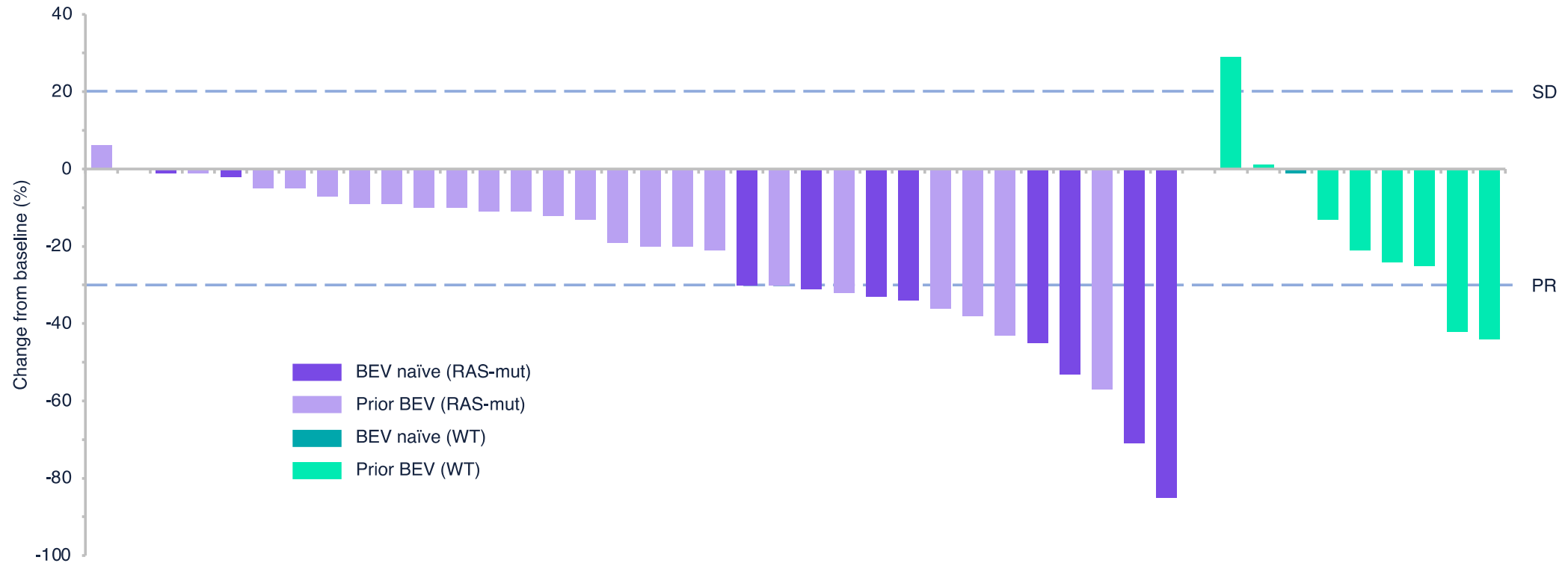
*FOLFIRI: FOL – [folinic acid \(leucovorin\)](#), F – [fluorouracil \(5-FU\)](#), IRI [irinotecan \(Camptosar\)](#),

Efficacy Overview

41% ORR observed in RAS mutant patients
30% ORR (ITT) observed in RAS mutant patients

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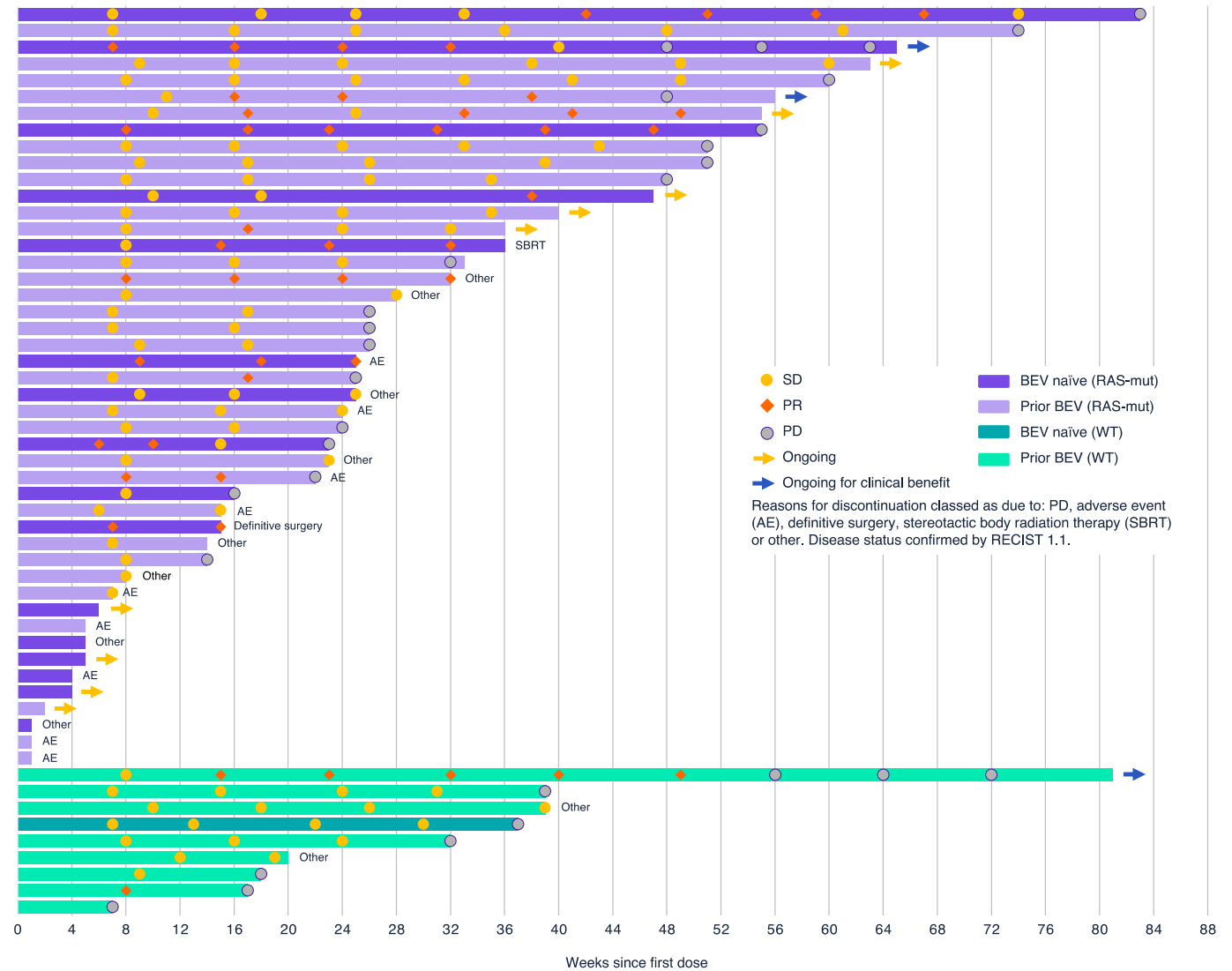
Best response in all evaluable patients (n=43)



Percentage change from baseline of tumors in evaluable patients. Data cut-off 4 Jun 2024; open database, data subject to change. Presented at ESMO 2024.

Duration of treatment and response in all patients (n=55)

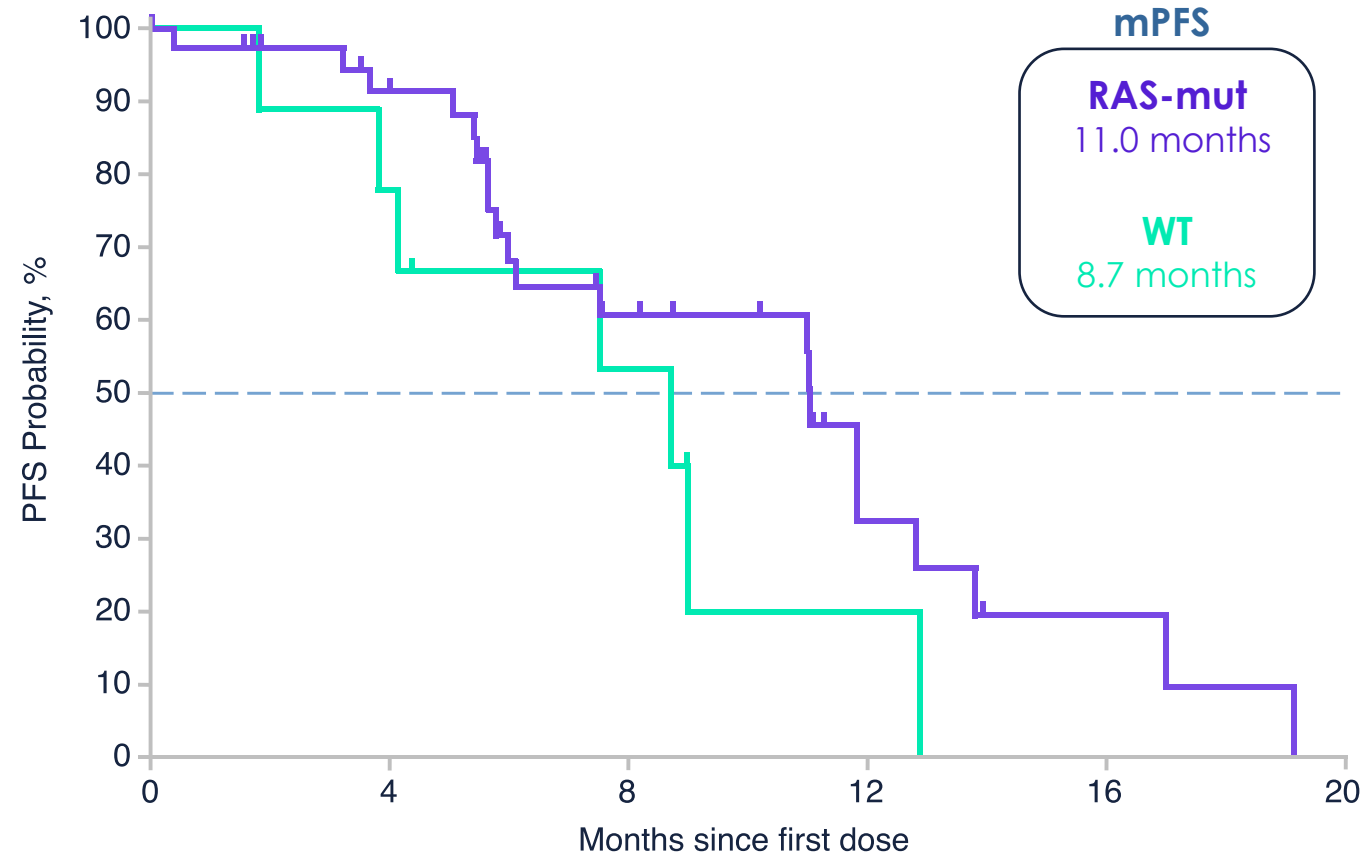
Data cut-off 4 Jun 2024; open database, data subject to change. Presented at ESMO 2024.



PFS in RAS-mut vs WT mCRC

Ompenaclid + SOC increased PFS in RAS-mut vs WT mCRC.

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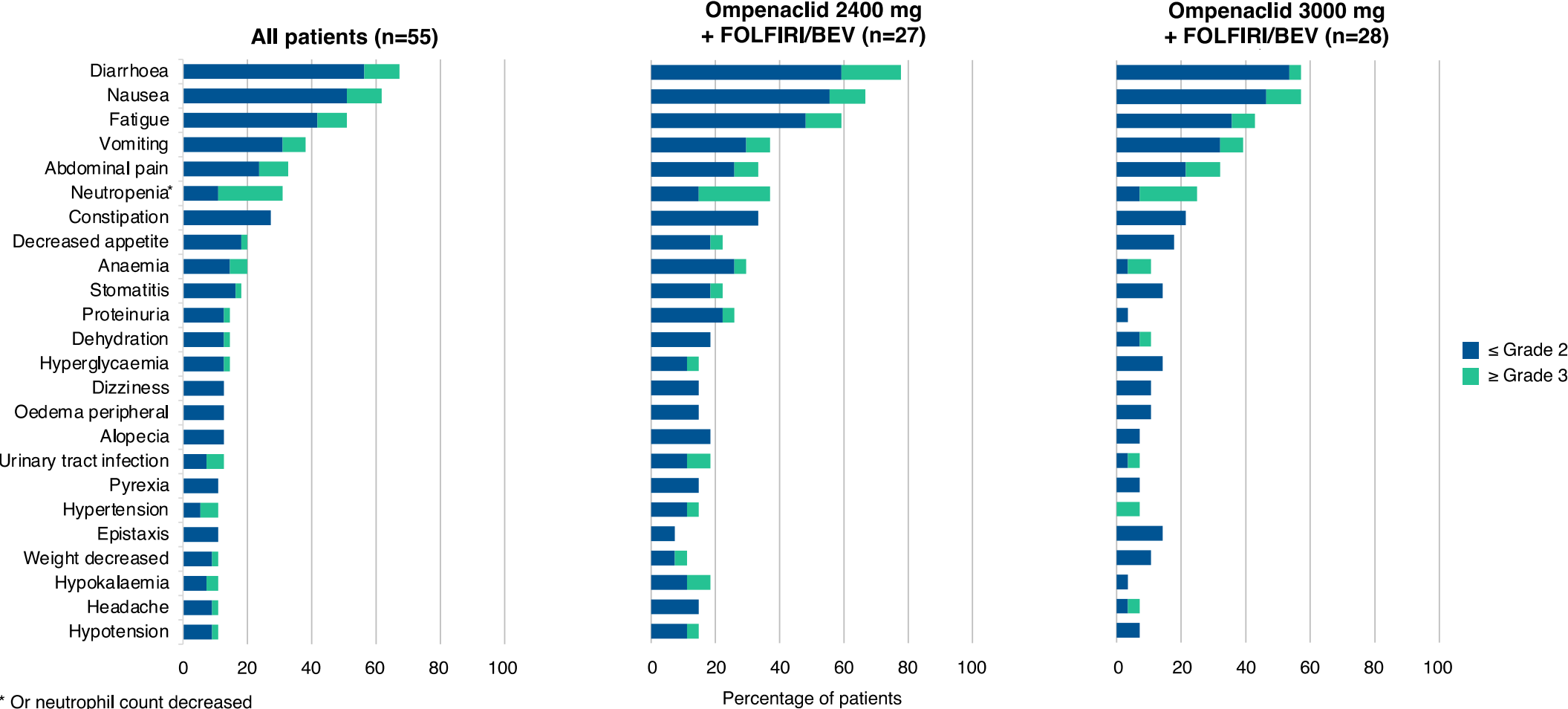


PFS analysis included all patients enrolled (n=55). PFS data are not yet final as of the cut-off date 4 Jun 2024 due to continuing patient follow-up and the limited number of PD events. Presented at ESMO 2024.

Safety summary – ompenacnid + FOLFIRI/ bevacizumab

- In the Dose Escalation Phase, there were no DLTs observed for either the 2400 mg BID or 3000 mg BID dose with the combination.
- The most common Grade ≤ 2 TEAEs were diarrhea (56%) and nausea (51%).
- The most frequent Grade ≥ 3 TEAEs were neutropenia (20%), diarrhea (11%) and nausea (11%).
- The only Grade 5 TEAE was 1 patient with an intestinal perforation, deemed related to BEV.
- At the evaluated dose levels, ompenacnid added to FOLFIRI/BEV was well tolerated.

Ompenaclid Safety – TEAEs occurring in $\geq 10\%$ of patients



Ompenacnid + FOLFIRI/ Bev compared to historical SOC with FOLFIRI combined with Bev or other approved anti-angiogenic inhibitors

	Ompenacnid (Bevacizumab)	RAISE* (Ramucirumab)	VELOUR** (Aflibercept)	ML18147*** (Bevacizumab)
ORR (WT and RAS)	41% (RAS only) ¹ 30% (RAS only, ITT) ¹	13%	19%	5%
DCR (WT and RAS)	100% (RAS only) ¹	74%	85%	88%
mPFS (RAS)	11.0 months¹	5.7 months	Unreported	5.5 months
mOS (RAS)	19.1 months²	12.9 months	12.6 months	10.4 months
mPFS (WT and RAS)		5.7 months	6.9 months	5.7 months
mOS (WT and RAS)		13.3 months	13.5 months	11.2 months

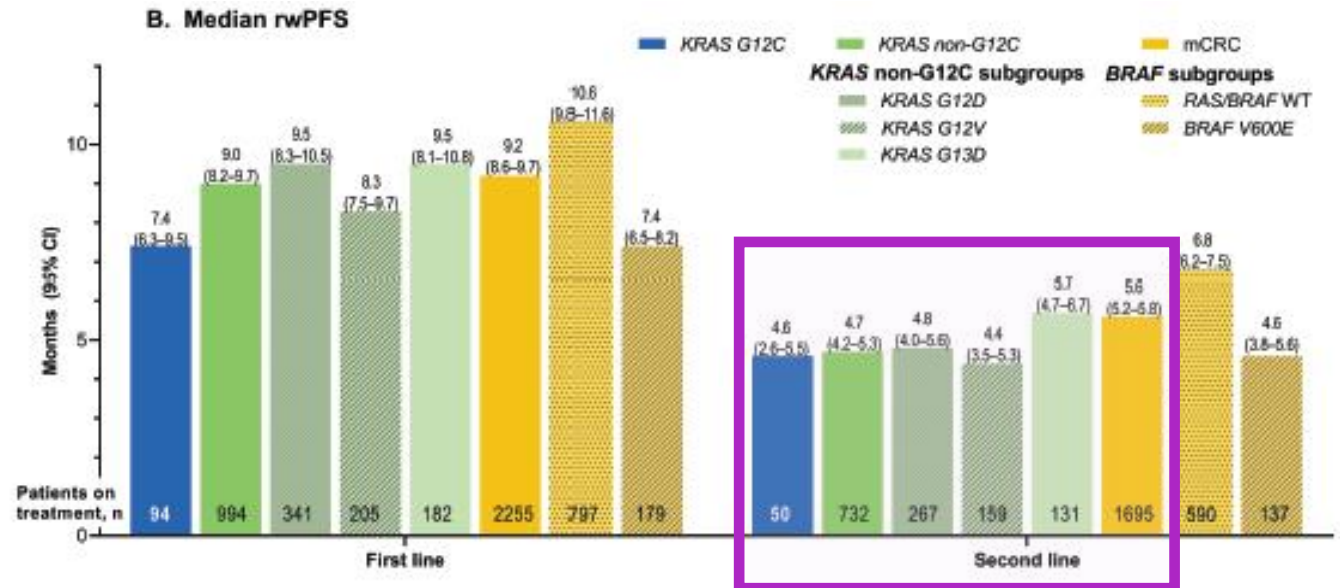
*Patients had either prior Oxaliplatin- or Irinotecan- first line therapies and Investigators had the option to use either Oxaliplatin- or Irinotecan-based second line therapies

1. ESMO 2024, Hendifar et al.
2. ESMO 2023, Hendifar et al.

Real-world data on PFS in 2nd line RAS mutant mCRC

- Largest and most robust real world / RWE study in over 6000 mCRC patients, with and without RAS mutations
- Treatment patterns are generally comparable in patients in mCRC with or without the KRAS p.G12C mutation and consistent across successive LOT*
 - Since anti-VEGF therapy introduced over a decade ago in 2L CRC, standard of care unchanged

* LOT- line(s) of treatment

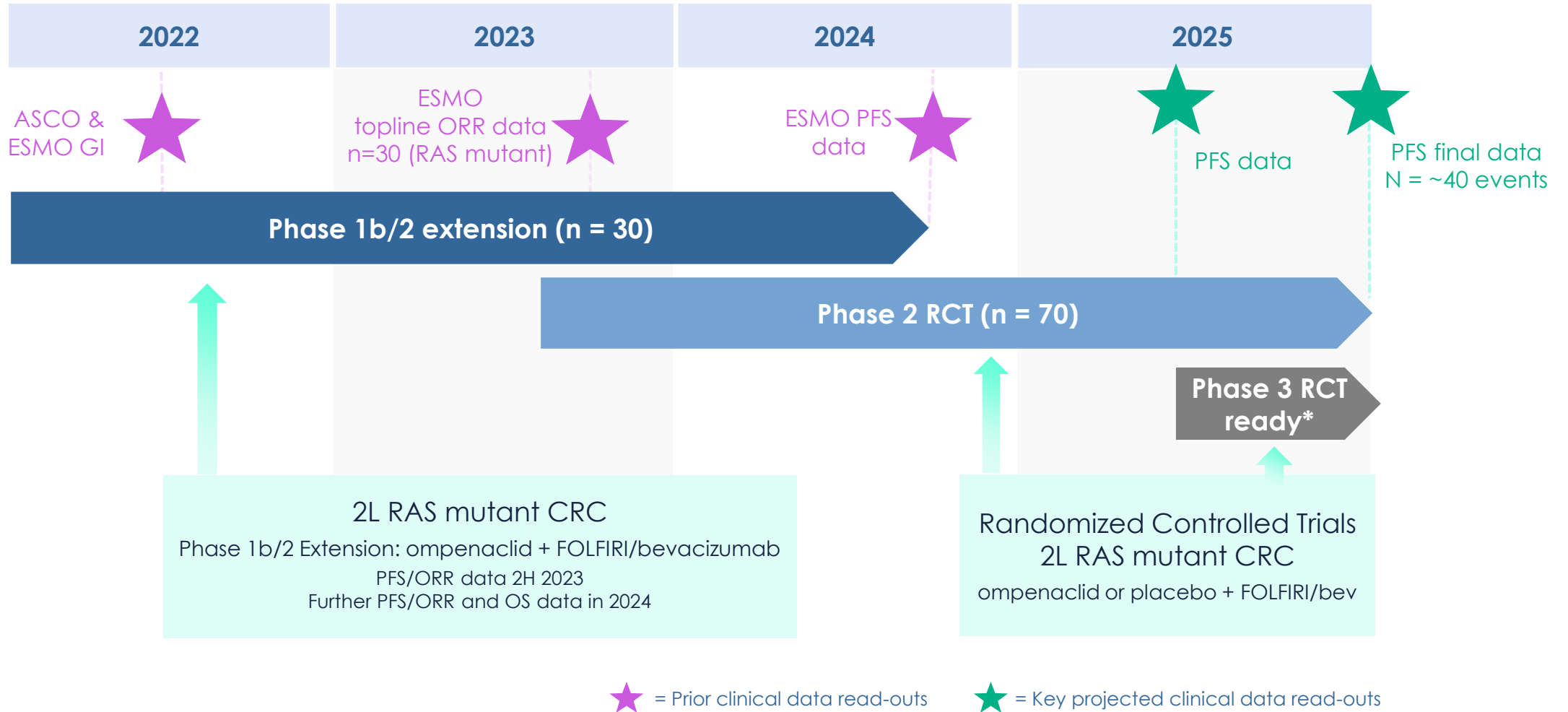


- Median (95% CI) rwPFS in second line settings
 - KRAS G12C cohort – 4.6 (2.6-5.5) months
 - KRAS non-G12C cohort – 4.7 (4.2-5.3) months
 - mCRC overall cohort – 5.6 (5.2-5.8) months

In Phase 1b/2, Ompenacilid demonstrates a meaningful clinical effect in 2L mCRC on top of standard of care of FOLFIRI + Bevacizumab

Projected clinical data read-outs for ompenacldid

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Licensing Agreement with Merck KGaA, Darmstadt, Germany

Announced in January 2024 to Accelerate the Global Development of Ompenaclid

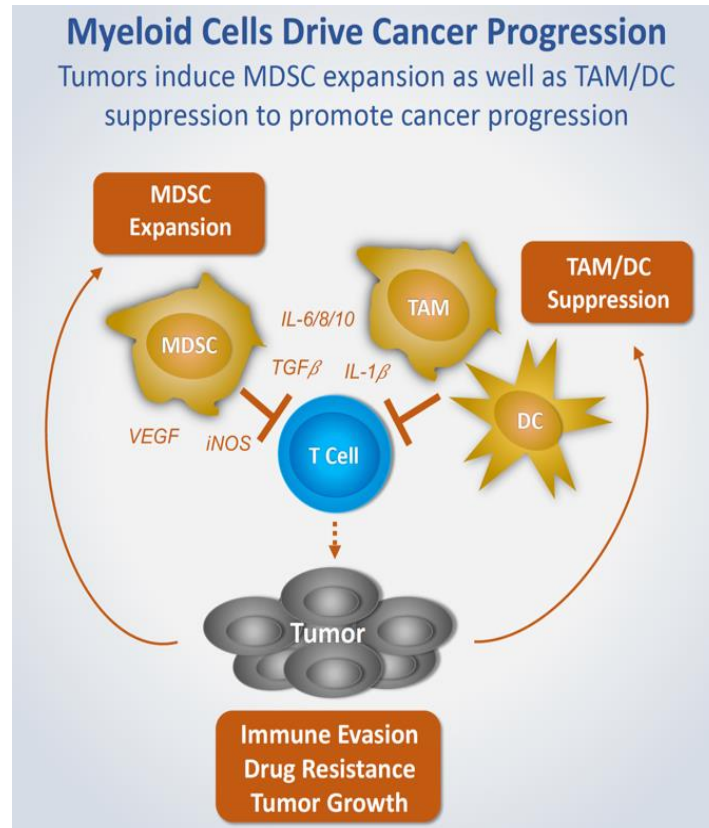
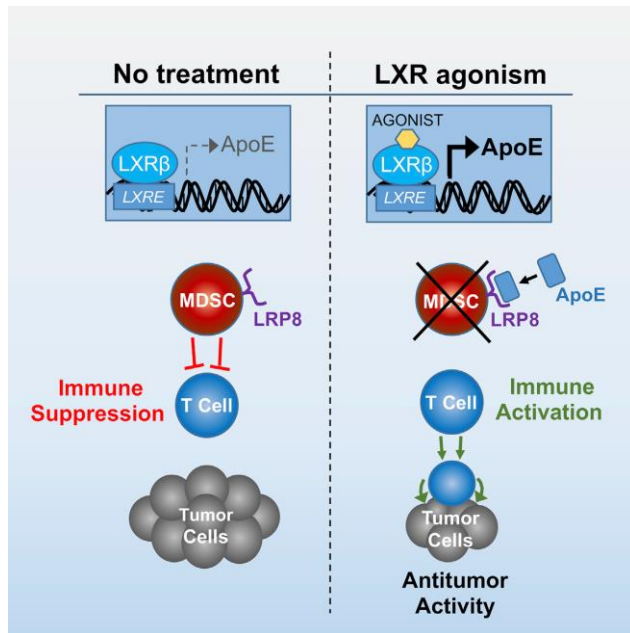
Inspirna Receives \$45M Upfront Payment

- **Merck KGaA, Darmstadt, Germany receives exclusive license to ompenaclid outside of US**
 - Option to co-develop and co-promote ompenaclid in US
- **Further collaboration focused on follow-on compounds targeting SLC6a8**
 - Inspirna will lead pre-IND activities, and retain co-development/co-commercialization rights in US
- **Inspirna receives \$45M upfront payment**
 - Eligible to receive milestone payments with tiered royalty rates in low teens on net sales outside of US, upon achievement of certain development and sales milestones for ompenaclid
 - Eligible to receive development, regulatory and sales milestone payments for each follow-on compound targeting SLC6A8, along with up to double-digit royalties on net sales outside of US

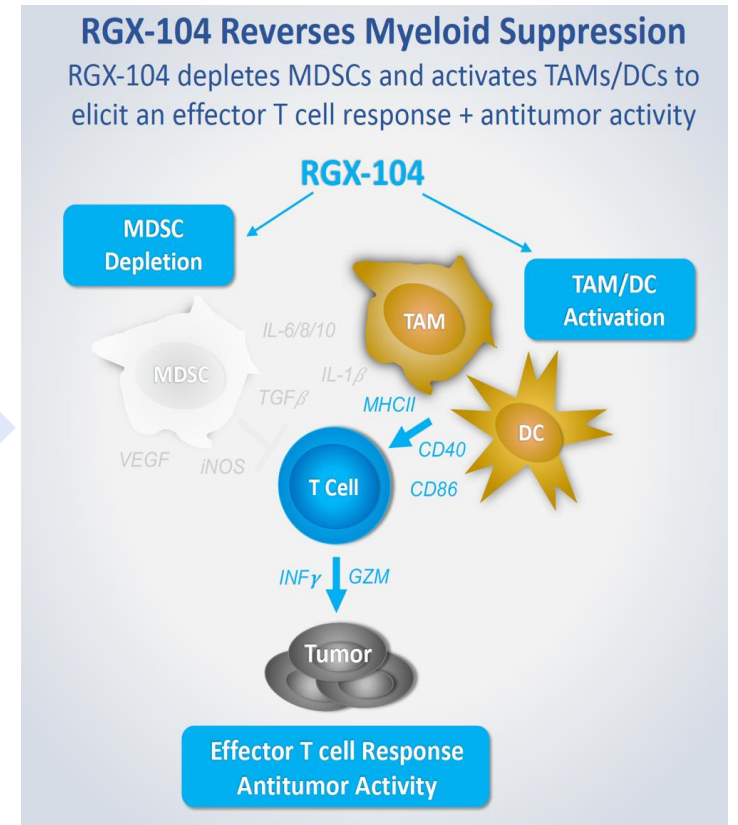
Abequolixron (RGX-104)

- Potent small molecule LXR beta selective agonist that activates APOE to target immune-suppressive tumor myeloid cells, while also inhibiting tumor angiogenesis
- Monotherapy activity in lung cancer demonstrated during Phase 1
- Clinical activity in combination with docetaxel demonstrated in an ongoing Phase 1b/2 clinical trial in patients with non-small cell lung cancer and small-cell lung cancer
- Compound was originally discovered by GlaxoSmithKline for the treatment of cardiovascular disease and exclusively licensed to Inspirna
- Ongoing collaboration with Bristol-Myers Squibb to evaluate abequolixron in combination with ipilimumab for the treatment of endometrial cancer
- Issued global patent protection to 2040

RGX-104 is a first-in-class clinically active LXR agonist that reverses myeloid suppression by targeting ApoE

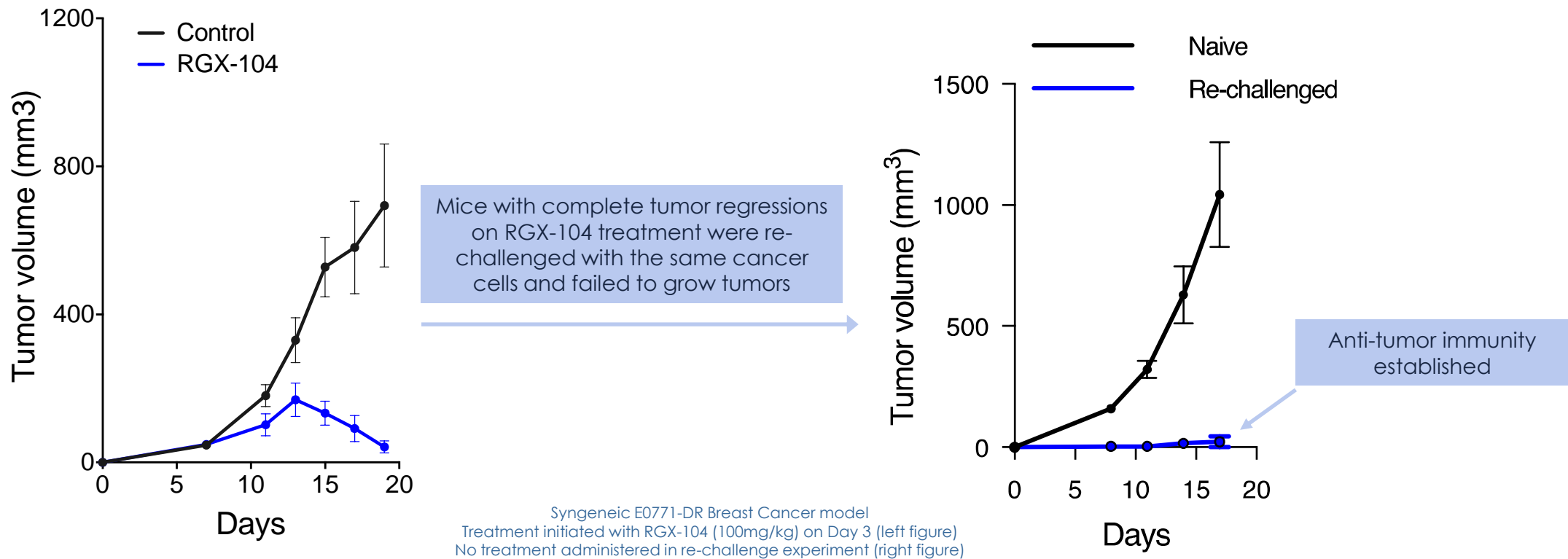


RGX-104



RGX-104 induces anti-tumor immunity in tumor models

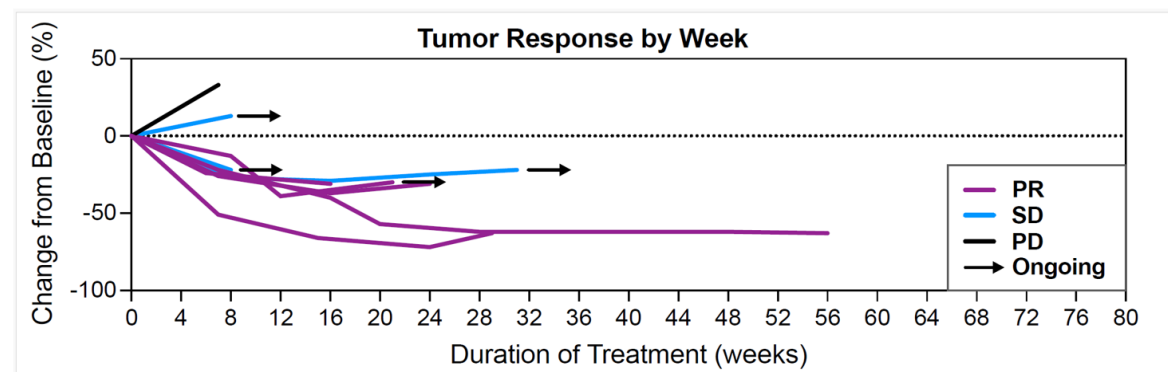
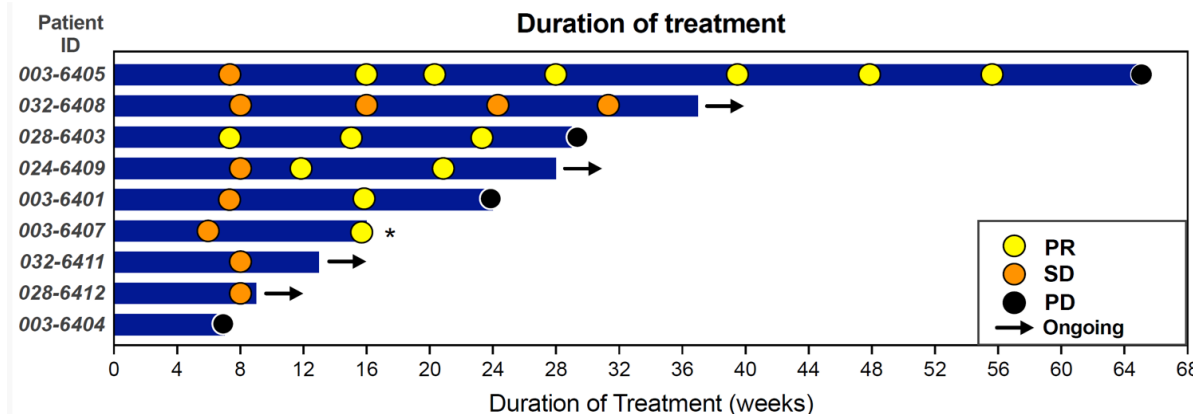
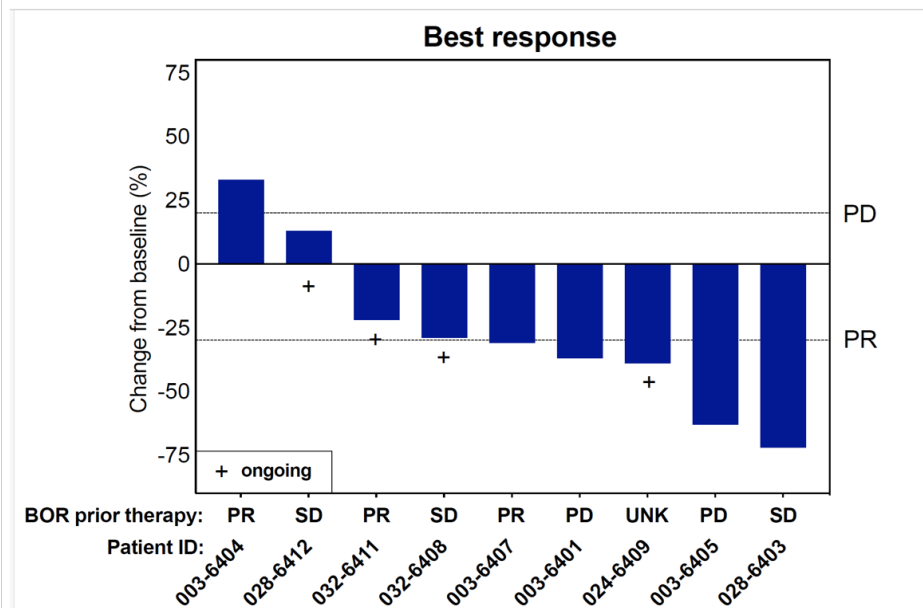
RGX-104 has demonstrated potent immune-modulating and anti-tumor activity in numerous preclinical tumor models spanning different tumor types * 1-6



Clinical Activity Observed in 2/3L NSCLC (RGX-104 + docetaxel)

Benchmark Data for 2/3L NSCLC: From Lung-MAP S1800A Trial

- 166 patients randomized to Pembro +Ramucirumab(R) vs SOC (IC of docetaxel+R; docetaxel, pemetrexed, gemcitabine)
- mOS 14.5 mo for P+R vs 11.6 mo for SOC (significant);
- mPFS 4.5 mo for P+R vs 5.2 mo for SOC arm (NS);
- ORR 22% for P+R vs 28% SOC, respectively (NS)



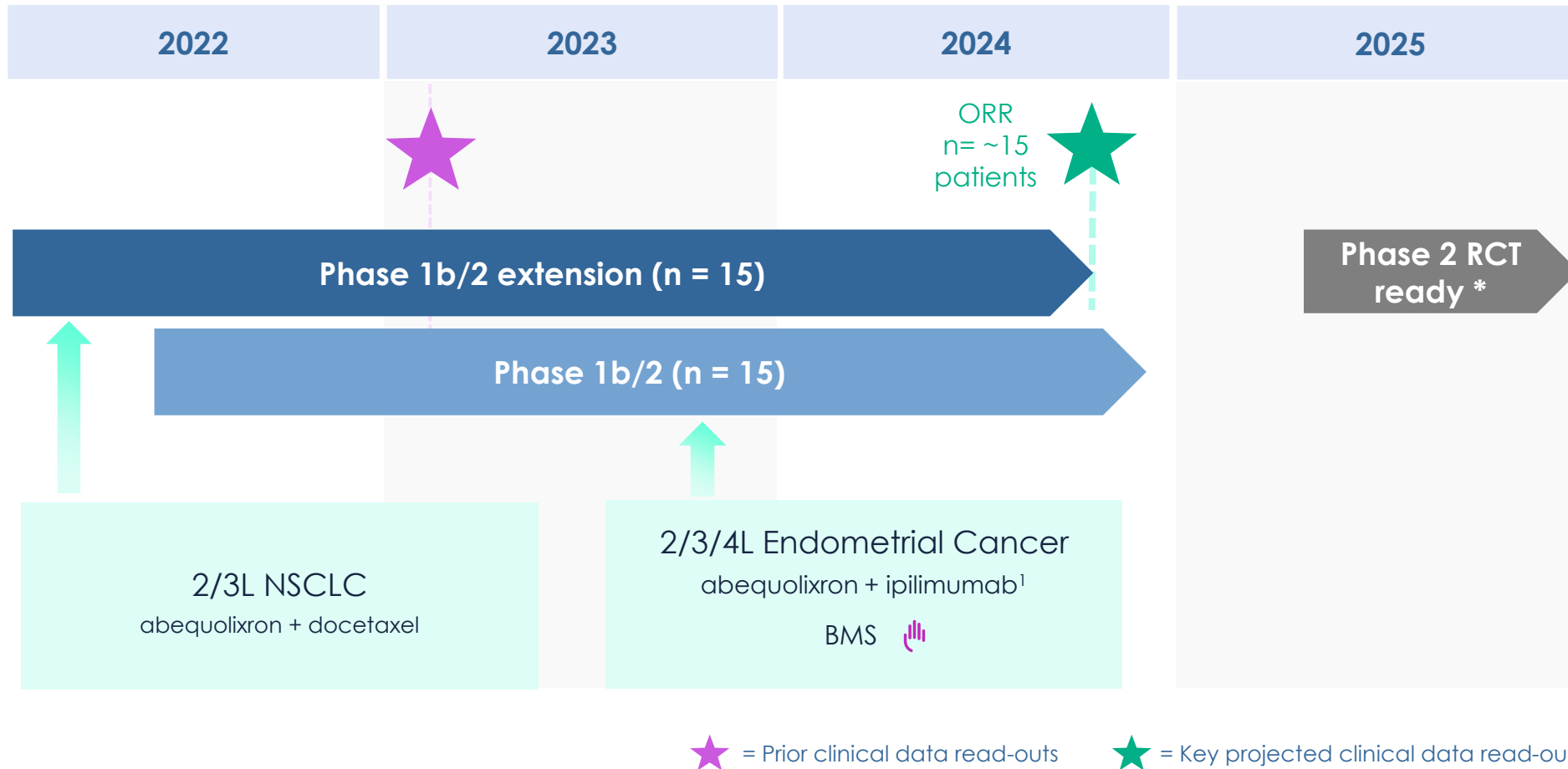
Patients were evaluable for RECIST 1.1 response if they completed at least one treatment cycle and had at least one follow-up scan for RECIST 1.1 assessment. 3 patients were not evaluable for ORR response: 024-6402 – PI decision; 001-6406, baseline scans only and 6 weeks on treatment. 038-6410 – Withdrew consent (1 week on treatment)

*Patient discontinued due to AE's weight loss and persistent nausea. 028-6403 had PD due to CNS lesions

Data cut-off 11/30/2023; Open database, data subject to change

Projected clinical data read-outs for abequolixron

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Supported by Top-Tier Institutional Investors and Academic/Industry Collaborators

Investors



Collaborators

Merck KGaA, Darmstadt, Germany



THE UNIVERSITY OF TEXAS
**MD Anderson
Cancer Center**
Making Cancer History®

Management Team

Track record of advancing transformative science & innovative therapies



Usman "Oz" Azam, MD
Chief Executive Officer

Novartis; TMUNITY; Empryrean



David M. Darst, MBA
COO/ CFO & Co-Founder

Apellis; POTENTIA; OrbiMed



Karim Benhadji, MD
Chief Medical Officer

Taiho Oncology; Eli Lilly



Anne Assmus, PhD
Head of Business
Development

Affimed; Morphosys



Nayomi Thomas
Associate Director
of HR & Legal

JP Morgan Chase;
Viagogo



Darren Wong, PhD
SVP of Translational
Medicine

Exarta Therapeutics; Concert
Pharmaceuticals; Medivation



Steve Wald, MS
SVP, Chemistry &
Pharmaceutical Sciences

Epizyme; Sepracor



Kimberly Hoffman
VP, Clinical & VP,
Clinical Operations

MERCK; Pfizer;
Northern Biologics



Isabel Kurth, PhD
VP, Research

ISREC Foundation
Recherche Cancer;
The Rockefeller
University



**Osamu Takahashi,
MD, PhD**
VP, Clinical
Development

Taiho Oncology;
Gilead Sciences;
AstraZeneca



Corey Sohmer, MBA
VP, Finance &
Accounting

Actinium
Pharmaceuticals;
Cyclacel

Advisors and Board of Directors

Deep experience in oncology drug development

Scientific and Clinical Advisors

Masoud Tavazoie, MD, PhD (Inspirna co-founder)

- Former Inspirna CEO

Sohail Tavazoie, MD, PhD (Inspirna co-founder)

- Professor & Director of Metastasis Center, Rockefeller University; oncologist, MSKCC
- President, American Society of Clinical Investigation

Jean-Pierre Bizzari, MD

- Former Executive VP & Global Head of Oncology, Celgene
- Current Board Director, Compugen, Transgene, Halozyme

Josep Taberner, MD, PhD

- Head of Medical Oncology at Vall d'Hebron University Hospital
- Former President of ESMO

Alan Venook, MD

- Head of GI Oncology Program, UCSF

Hossein Borghaei, DO, MS

- Head of Thoracic Oncology, Fox Chase Cancer Center

Yelena Janjigian, MD

- Chief, GI Oncology Division, MSKCC

Antoni Ribas, MD PhD

- Professor, UCLA; Director of Tumor Immunology

Siavash Kurdistani, MD

- Chair of Biological Chemistry, UCLA; Associate Director, Gene Regulation

Board of Directors

Dieter Weinand, MS (Chairman)

- Former CEO, Pharmaceuticals Division at Bayer AG
- Current Chairman of Replimune, Mnemo

Usman “Oz” Azam, MD

- CEO, Inspirna

Peter Van Vlasselaer, PhD

- Former CEO of ARMO, iPierian, Arresto, Avidia

Eric Rowinsky, MD

- Director of Biogen; Former CMO, ImClone Systems

Antoine Papiernik, MBA (investor)

- Managing Director, Sofinnova Partners

Raymond Camahort, PhD (investor)

- Partner, Novo Ventures

Michael Ginder, CFA (investor)

- Research Analyst, Sands Capital

Priscilla Sugianto, MD (investor)

- Principal, Vivo Capital

Jue Pu, MS (investor)

- Director of Investments, Lepu Medical

Summary

- Inspirna is a clinical stage biotechnology company headquartered in New York City that is developing first-in-class novel therapeutics to treat cancer types of high-unmet medical need
- Our miRNA-DRIVER* platform has delivered novel targets that are now being evaluated in tumor types that present significant commercial opportunities with multiple clinical data catalysts in the near future.
 - Lead candidate ompenaclid is a novel small molecule that inhibits SLC6A8 with activity in patients with RAS mutant colorectal cancer, currently in Phase 2 development and Phase 3 ready by 2025
 - Second program abequolixron is a potent small molecule LXR beta selective agonist that activates APOE currently in Phase 1b/2 development for lung cancer and endometrial cancer
- Led by an experienced management team, supported by top-tier institutional investors, collaborators and advisors