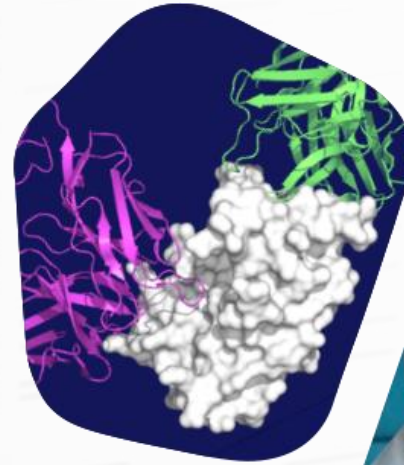**NGM Biopharmaceuticals, Inc.**
NASDAQ: NGM

R&D Day

December 9, 2020

**Novel Biology. Powerful Medicines. Transformative Impact.**

David Woodhouse, Ph.D.
Chief Executive Officer

Safe Harbor Statement

The following series of presentations contain forward-looking statements, including, but not limited to, statements regarding potential indications for, planned development of, and therapeutic potential of, product candidates in NGM's pipeline, including aldafermin, MK-3655 (NGM313), NGM621, NGM120, NGM438 and NGM707; the planned timing of initiation, enrollment and results of NGM's clinical trials; potential future late-stage development of product candidates in NGM's pipeline, including aldafermin and NGM621; the potential activity, complementarity, safety, tolerability and efficacy of NGM's product candidates, including the potential for MK-3655 and aldafermin to be complementary treatments for non-alcoholic steatohepatitis (NASH); the potential roles of ILT2, ILT4 and LAIR1 in cancer and the potential consequences of ILT2, ILT4 and LAIR1 blockade; anticipated regulatory submissions and actions; NGM's option to participate in the economic return of any programs licensed by NGM's collaborator, Merck, and Merck's funding commitments under NGM's collaboration with Merck; NGM's opportunities for value creation and its ability to deliver powerful or transformational treatments; and any other statements other than statements of historical facts. Because such statements deal with future events and are based on NGM's current plans, objectives, estimates and expectations, they are subject to various significant risks and uncertainties and actual results, performance and achievements and the timing of events could differ materially from those described in or implied by the statements herein. Such risks and uncertainties include, without limitation, those associated with the costly and time-consuming pharmaceutical product development process and the uncertainty of clinical success, including risks related to failures or delays in successfully initiating, enrolling or completing clinical trials; the risk that results obtained in NGM's clinical trials to date may not be indicative of results obtained in ongoing or future trials, including pivotal trials, including the risk that ongoing or future studies will not show that aldafermin and/or MK-3655 are tolerable or effective treatments for NASH patients or that NGM621 is a tolerable or effective treatment for geographic atrophy (GA); the risk that preclinical studies or modeling may not be indicative of results in future human clinical trials; the risk that clinical trials of NGM438, NGM707 and NGM120 will not show that NGM438, NGM707 and/or NGM120 are tolerable or effective treatments in cancer indications; the risk that others may discover, develop or commercialize products before or more successfully than NGM, including in NASH; the ongoing COVID-19 pandemic which has adversely affected, and could materially and adversely affect in the future, NGM's business and operations, including NGM's ability to timely supply, initiate, enroll and complete its ongoing and future clinical trials; the time-consuming and uncertain regulatory approval process, including the risk that NGM or Merck may not receive marketing approvals for any of NGM's product candidates in a timely manner, or at all; seeking and maintaining protection of intellectual property; NGM's reliance on third party manufacturers and delays or problems in the manufacture of product candidates; NGM's dependence on its collaboration with Merck for the development and potential commercialization of its product candidates, including the risk that Merck may unilaterally terminate its annual funding of NGM's research and development program; the sufficiency of NGM's cash resources and need for additional capital; and other risks and uncertainties affecting NGM and its research and development programs, including those described under the caption "Risk Factors" and elsewhere in NGM's quarterly report on Form 10-Q for the quarter ended September 30, 2020 and future filings and reports of NGM with the Securities and Exchange Commission. The forward-looking statements contained in the following series of presentations are made only as of the date hereof or as of the dates indicated in the forward-looking statements, even if they are subsequently made available by NGM on its website or otherwise. NGM undertakes no obligation to update or supplement any forward-looking statements after the date hereof, or to update the reasons why actual results may differ or differ materially from those anticipated in the forward-looking statements.
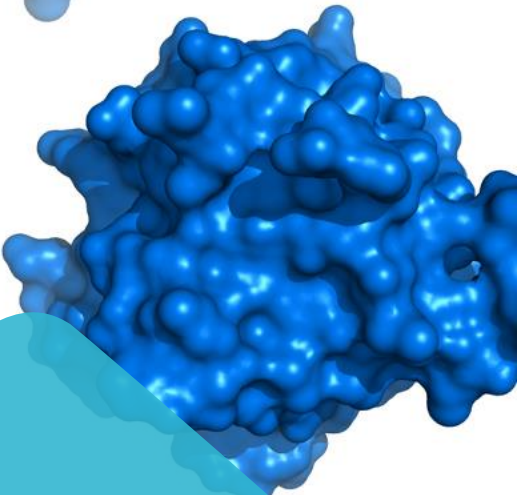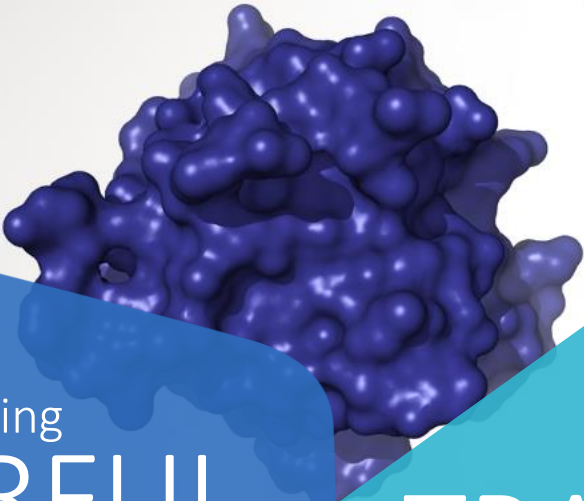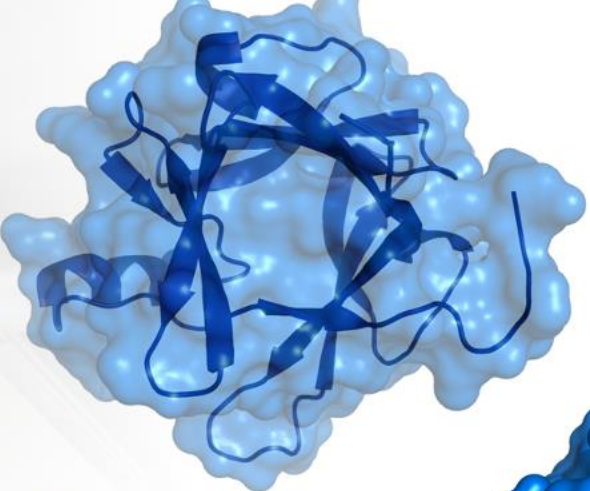
Interrogating
HUMAN
BIOLOGY

Engineering
POWERFUL
BIOLOGICS

To
TRANSFORM
TREATMENT

In
LARGE PATIENT
POPULATIONS

With
SIGNIFICANT
NEED

NGM Bio

Our Vision: Build an Iconic Biologics Therapeutic Company

NGM Approach — NGM

Four Guiding Principles

1. Focus on <u>emerging</u> <u>human</u> <u>biology</u>
2. Develop novel, <u>transformational</u> medicines
3. <u>Multi-pronged</u> approach: parallel drug discovery programs, constant discipline and prioritization
4. <u>Biologics</u>-focused, but modality flexible

REPEATABLE & SCALABLE

DELIVER TRANSFORMATIVE TREATMENTS

3 Therapeutic areas

7 Disclosed programs

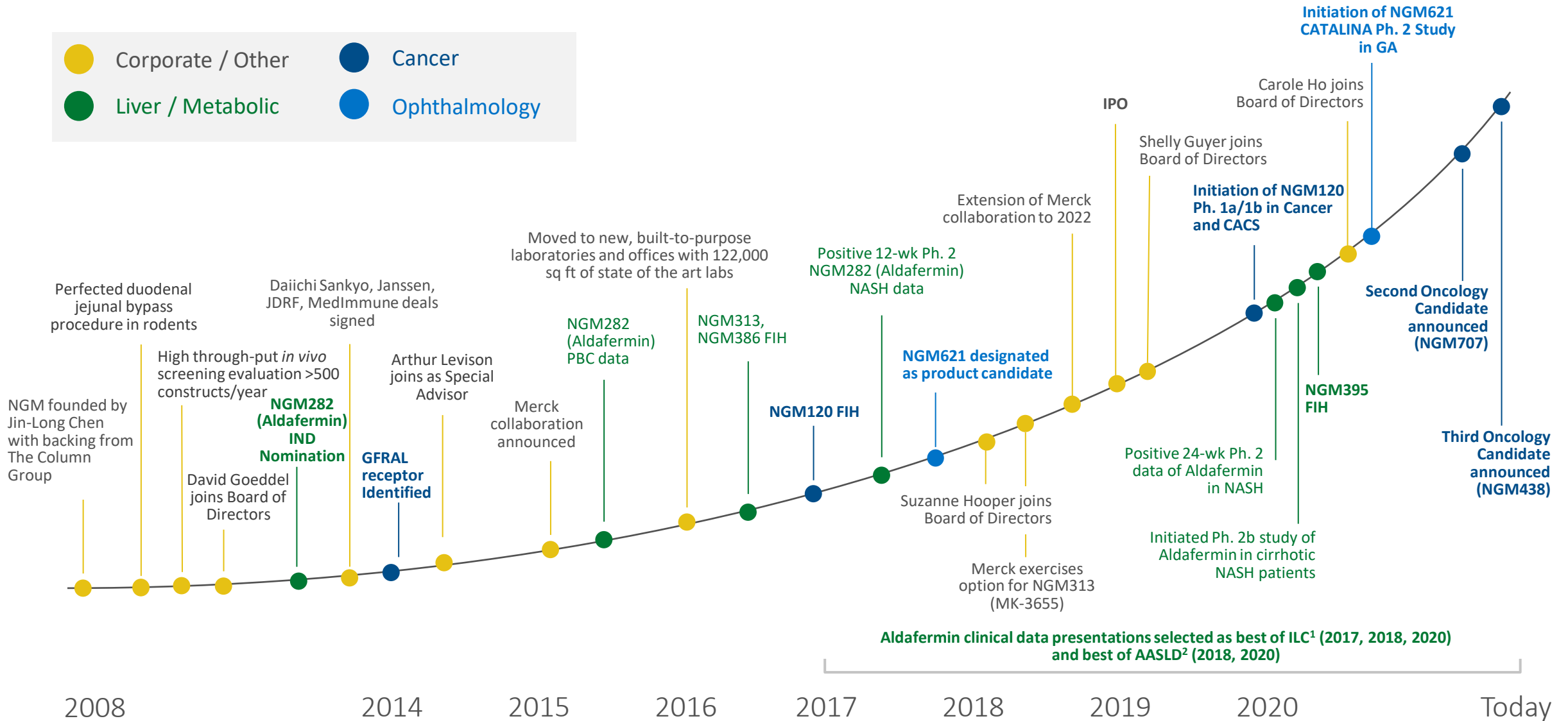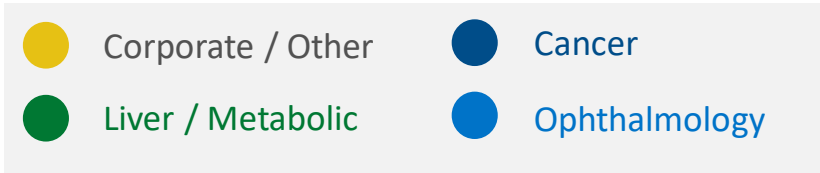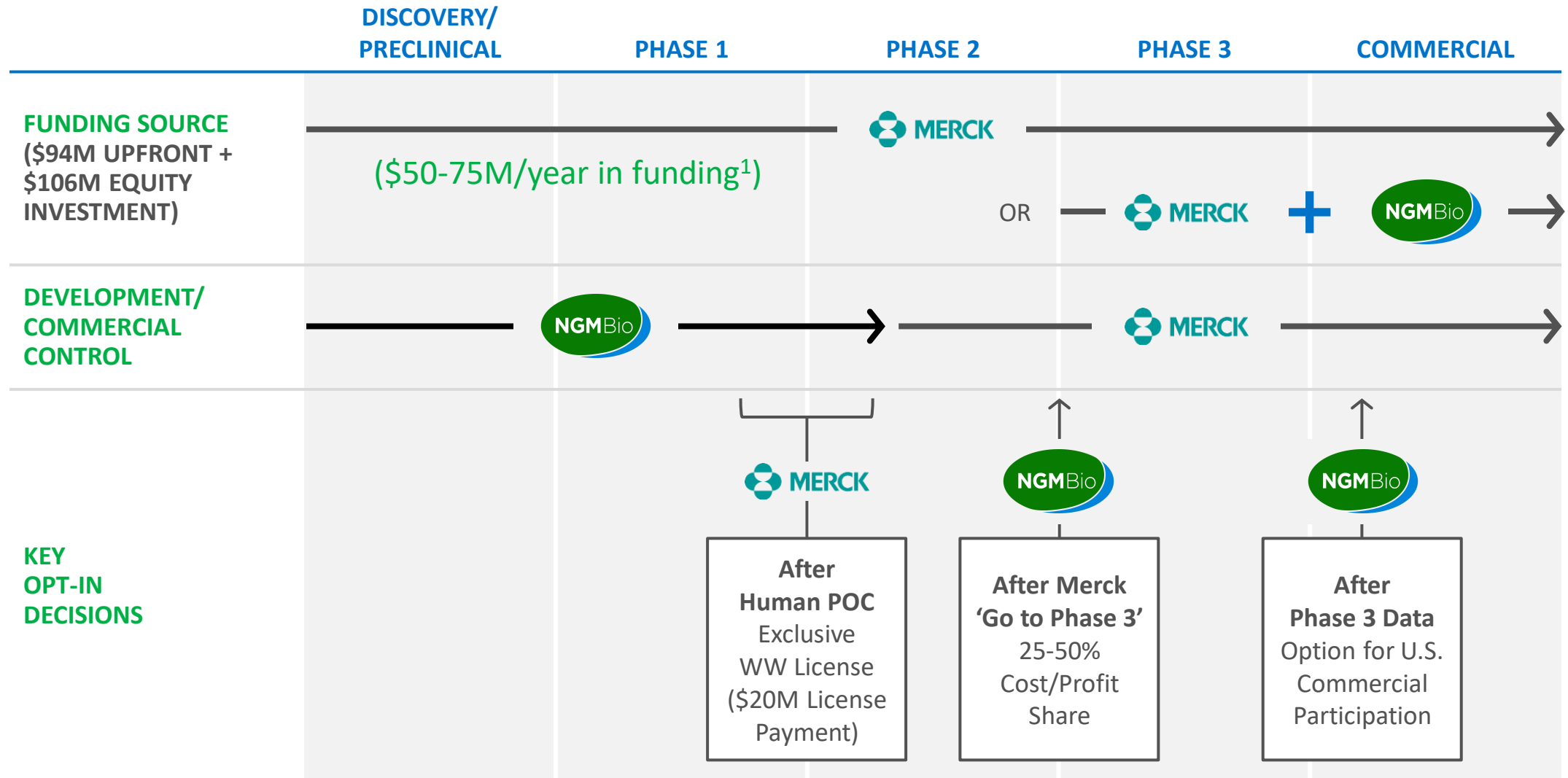**5** Programs in clinical development

3 Programs in Ph2b/Ph3-enabling studies

This Strategy has Fueled our Growth to Date

NGMBio

Legend:
- ● Corporate / Other (gold)
- ● Liver / Metabolic (green)
- ● Cancer (dark blue)
- ● Ophthalmology (light blue)

NGM founded by Jin-Long Chen with backing from The Column Group

Perfected duodenal jejunal bypass procedure in rodents

High through-put *in vivo* screening evaluation >500 constructs/year

David Goeddel joins Board of Directors

Daiichi Sankyo, Janssen, JDRF, MedImmune deals signed

NGM282 (Aldafermin) IND Nomination

Arthur Levison joins as Special Advisor

GFRAL receptor Identified

Moved to new, built-to-purpose laboratories and offices with 122,000 sq ft of state of the art labs

NGM282 (Aldafermin) PBC data

Merck collaboration announced

NGM313, NGM386 FIH

Positive 12-wk Ph. 2 NGM282 (Aldafermin) NASH data

NGM120 FIH

NGM621 designated as product candidate

Extension of Merck collaboration to 2022

Suzanne Hooper joins Board of Directors

Merck exercises option for NGM313 (MK-3655)

IPO

Shelly Guyer joins Board of Directors

Initiation of NGM120 Ph. 1a/1b in Cancer and CACS

Carole Ho joins Board of Directors

Initiation of NGM621 CATALINA Ph. 2 Study in GA

Second Oncology Candidate announced (NGM707)

NGM395 FIH

Positive 24-wk Ph. 2 data of Aldafermin in NASH

Initiated Ph. 2b study of Aldafermin in cirrhotic NASH patients

Third Oncology Candidate announced (NGM438)

Aldafermin clinical data presentations selected as best of ILC[1] (2017, 2018, 2020) and best of AASLD[2] (2018, 2020)

| 2008 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | Today |

[1]American Associate for the Study of Liver Diseases – The Liver Meeting;   [2]EASL International Liver Congress™ ; FIH – First In Human

Merck Partnership Allows Us to Maximize Value of R&D Engine

	DISCOVERY/ PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	COMMERCIAL

FUNDING SOURCE ($94M UPFRONT + $106M EQUITY INVESTMENT)

($50-75M/year in funding[1])

MERCK

OR ——— MERCK ✚ NGMBio ➜

DEVELOPMENT/ COMMERCIAL CONTROL

NGMBio ➜ MERCK ➜

KEY OPT-IN DECISIONS

MERCK

After Human POC
Exclusive WW License ($20M License Payment)

NGMBio

After Merck 'Go to Phase 3'
25-50% Cost/Profit Share

NGMBio

After Phase 3 Data
Option for U.S. Commercial Participation

[1] Merck has committed to provide R&D reimbursement of up to $50 million per year through the current two-year extension of the research phase of our collaboration with Merck through March 16, 2022. If our R&D expenses exceed $50 million in a given year, Merck can either reimburse up to an additional $25 million for use in funding IND-enabling or later-staged activities or provide us with the equivalent value in in-kind services for such activities.

8

Diverse Pipeline, Many Opportunities for Value Creation

Programs to be discussed today:

LIVER & METABOLIC DISEASES

NASH F2/F3	**Aldafermin**	FGF19 Analog	PHASE 2B	Topline Data Expected 2Q21
NASH F4	**Aldafermin**	FGF19 Analog	PHASE 2B	Enrolling
NASH	**MK-3655**	FGFR1c/KLB Agonistic Antibody	PHASE 1A/1B	Ph2b Initiation Expected 4Q20

RETINAL DISEASES

Geographic Atrophy	**NGM621**	Anti-Complement C3 Antibody	PHASE 2	Enrolling

CANCER

Cancer & CACS	**NGM120**	GFRAL Antagonistic Antibody	PHASE 1A/1B	Enrolling
Advanced Solid Tumors	**NGM707**	ILT2/ILT4 Dual Antagonist Antibody	IND-ENABLING STUDIES	Ph1 Initiation Expected Mid-21
Advanced Solid Tumors	**NGM438**	To be discussed later today	IND-ENABLING STUDIES	Ph1 Initiation Expected 4Q21

NASH = non-alcoholic steatohepatitis; FGF = fibroblast growth factor; GDF = growth differentiation factor; KLB = klotho beta; C3 = Component 3; GFRAL = glial cell-derived neurotrophic factor receptor alpha-like; CACS = Cancer Anorexia-Cachexia Syndrome; ILT2 = Immunoglobulin-like transcript 2; ILT4 = Immunoglobulin-like transcript 4

The NGM Team by the Numbers

205 Employees

100+ Researchers

122,000 sq. ft. total footprint including **60,000 sq. ft.** of active lab space

A team that has contributed to **10+** commercially successful medicines

>$500M Received from business development collaborations

37 Patents held

Experienced Management Team

William Rieflin
Executive Chairman

XenoPort   Tularik

David Woodhouse, Ph.D.
Chief Executive Officer

Goldman Sachs

Jin-Long Chen, Ph.D.
Founder and Chief
Scientific Officer

AMGEN   Tularik

Hsiao D. Lieu, M.D.
Senior Vice President,
Chief Medical Officer

Lilly   Genentech
A Member of the Roche Group

Siobhan Nolan Mangini
Chief Financial Officer

Castlight   BAIN & COMPANY

Brian Muma
Vice President,
Human Resources

Roche   ORIC

Hui Tian, Ph.D.
Senior Vice President,
Research

AMGEN   Tularik

Alex DePaoli, M.D.
Senior Vice President,
Chief Translational Officer

AMGEN   InteKrin
THERAPEUTICS

Marc Learned, Ph.D.
Vice President,
Research Operations

AMGEN   Tularik

Valerie Pierce
Senior Vice President,
General Counsel and Chief
Compliance Officer

Jazz Pharmaceuticals   Tularik
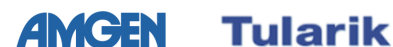
Wenyan (David) Shen, Ph.D.
Senior Vice President,
Biologics and CMC

AMGEN   MERCK

AGENDA

TOPIC	SPEAKERS
Discover, Develop, Deliver	• **David Woodhouse, Ph.D.** - *Chief Executive Officer, NGM*
R&D Blueprint	• **Jin-Long Chen, Ph.D.** - *Founder and Chief Scientific Officer, NGM*
Oncology - Cancer & CACS (NGM120) - Advanced Solid Tumors (NGM707 and NGM438)	• **Alex DePaoli, M.D.** - *SVP and Chief Translational Officer, NGM* • **Daniel Von Hoff, M.D., F.A.C.P.** - *The Translational Genomics Research Institute* • **Robert Schreiber, Ph.D.** - *Washington University School of Medicine* • **Daniel Kaplan, Ph.D.** - *Director, Biology, NGM* • **James Sissons, Ph.D.** – *Director, Biology, NGM* • Oncology Q&A
Geographic Atrophy (NGM621)	• **Erin Henry, Ph.D.** - *Sr. Director, Clinical Development Ophthalmology, NGM* • **Charles Wykoff, M.D., Ph.D.** - *Retina Consultants Houston* • Geographic Atrophy Q&A
NASH (Aldafermin, MK-3655)	• **Hsiao Lieu, M.D.** - SVP and *Chief Medical Officer, NGM* • **Corinne Foo-Atkins, M.D., MBA, MSc** - *VP of Product Strategy, NGM* • **Manal Abdelmalek, M.D.** - *Duke University* • NASH Q&A
Fireside Chat: A Conversation with Merck Research Laboratories	• **Roger Perlmutter, M.D., Ph.D.** - *Executive Vice President and President, Merck Research Laboratories (MRL)* • **Dean Li, M.D., Ph.D.** - *Senior Vice President of Discovery Sciences and Translational Medicine, MRL* • *Moderated by Jin-Long Chen and Bill Rieflin, NGM*
Final Q&A	• **Bill Rieflin** - *Executive Chairman, NGM* • **Jin-Long Chen, Ph.D.** - *Founder and Chief Scientific Officer, NGM* • **David Woodhouse, Ph.D.** - *Chief Executive Officer, NGM* • **Siobhan Nolan Mangini** - *Chief Financial Officer* • **Hsiao Lieu, M.D.** - SVP and *Chief Medical Officer, NGM* • **Alex DePaoli, M.D.** - *SVP and Chief Translational Officer, NGM*
Closing Remarks	• **David Woodhouse, Ph.D.** - *Chief Executive Officer, NGM*

Jin-Long Chen, Ph.D.
Founder, Chief Scientific Officer

Building a Biotech for Long-term Success

Foundational Ingredients
- Build from scratch
- Biology-driven drug discovery
- Guiding focus: patient need

▶ Assemble the Team

▶ Continually Evolve the Tools

▶ Tackle the Tough Problems

NGM R&D Engine:
An Integrated Approach to Create New Medicines

BIOLOGY + TECHNOLOGY ➤ MEDICINE
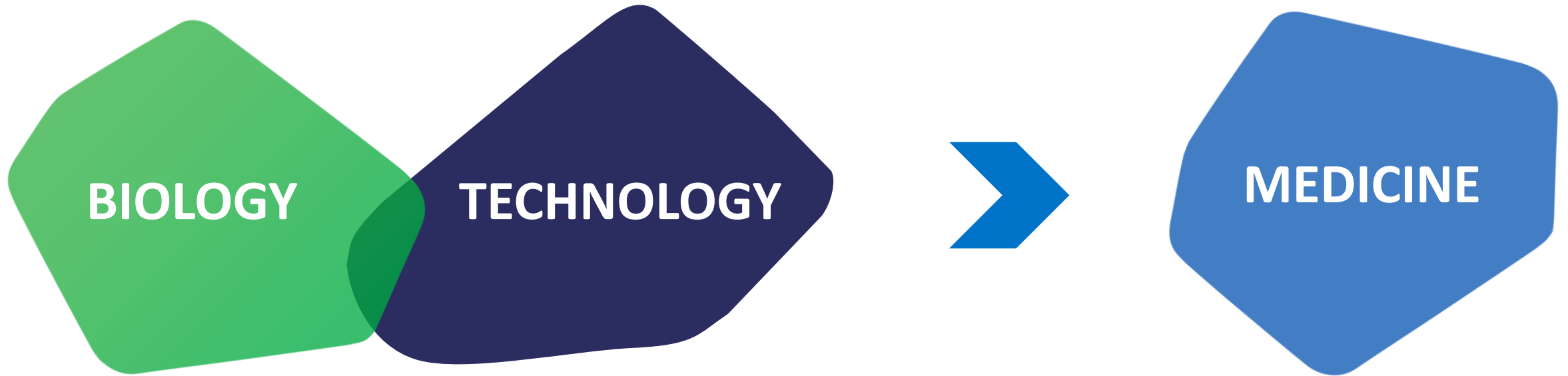
Biology-Driven Drug Discovery: Connecting the Dots

BIOLOGY TECHNOLOGY MEDICINE

Systematic interrogation of complex disease-associated biology

▸ Whole Body Biology

▸ Pathological Tissues

▸ Specialized Cells

▸ Molecules / Targets

Biology-Driven Drug Discovery: Connecting the Dots

BIOLOGY

TECHNOLOGY

MEDICINE

Empirical Approach: Integrated, **powerful,** multi-disciplinary platform

▸ Genetics: human and model systems

▸ Industrial-scale functional genomics
  - *in vivo*-based discovery
  - High content *in vitro* analysis
  - Orphan ligand-receptor matching

▸ Computational biology

Biology-driven Drug Discovery:
Designing Unique Solutions for Complex Problems

BIOLOGY

TECHNOLOGY

MEDICINE

Versatile Biologics Platform

Fit-for-purpose design
▸ Engineered proteins
▸ Engineered antibodies
▸ Multi-specific / multi-functional therapeutics

Flexible targeting
▸ Hormones
▸ Ligands / receptors
▸ Enzymes
▸ Transporters / ion channels
▸ Cell-cell interactions

Tunable pharmacology
▸ Antagonists / inhibitors
▸ Agonists / activators
▸ Modulators
▸ Biased ligands
▸ Multi
- specificity
- functionality
- valency
▸ Tissue specificity

Biology-driven Drug Discovery:
Seamless Integration of Biology and Technology

Unique biological probes

BIOLOGY

TECHNOLOGY

Refined understanding of biology

Delivering powerful therapies
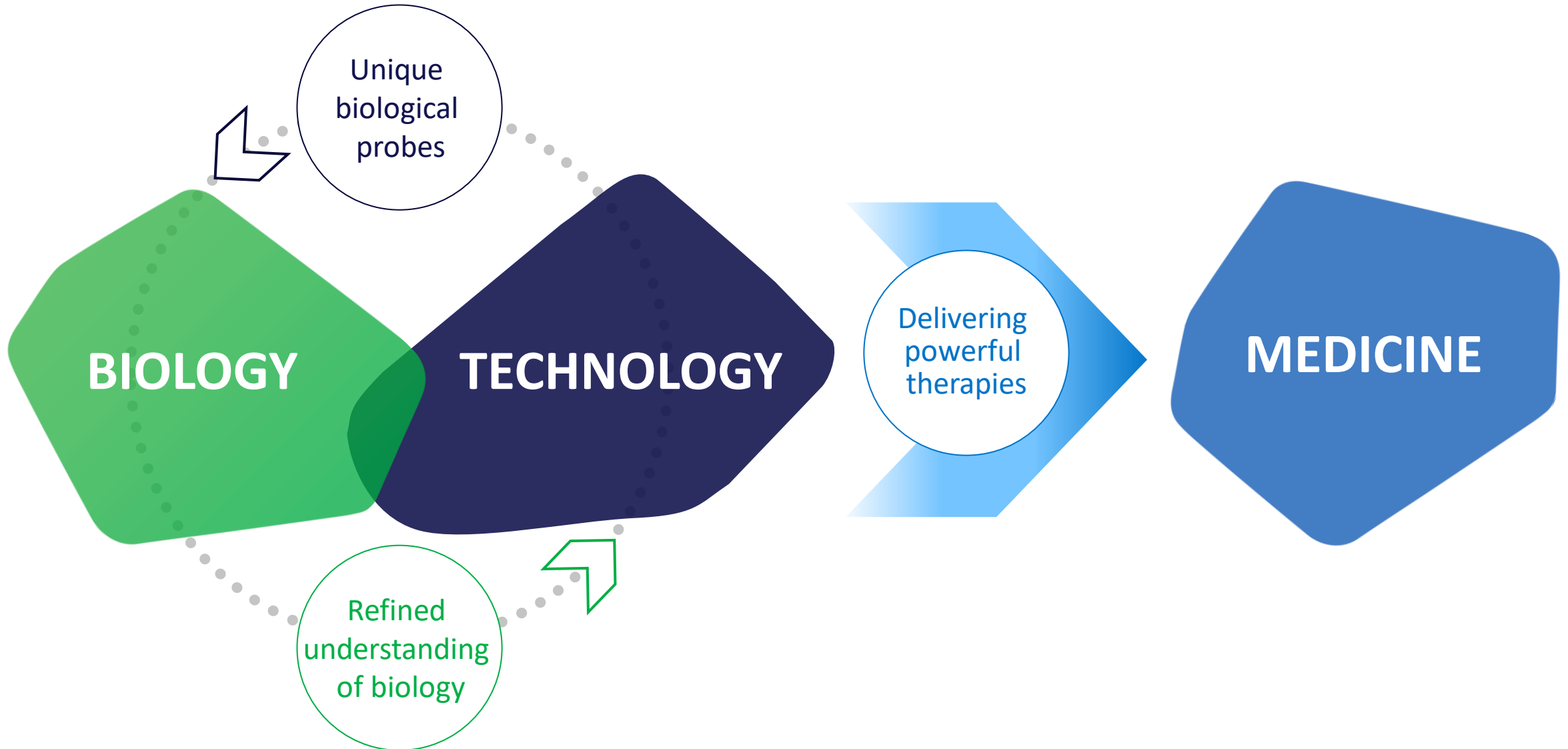
MEDICINE

NGM's Goal: Deliver Powerful Medicines

BIOLOGY **TECHNOLOGY** **MEDICINE**

Focused on:

- **Grievous** diseases
- **Significant** medical needs
- **Impactful** therapies

Liver and Metabolic Diseases
- ‣ Aldafermin
- ‣ MK-3655 / NGM313

Retinal Diseases
- ‣ NGM621

Cancer
- ‣ NGM120
- ‣ NGM707
- ‣ NGM438

Discovery programs
(ongoing)

Alex DePaoli, M.D.
SVP and Chief Translational Officer, NGM

NGM120: An inhibitor of GDF15 Signaling for the Treatment of Cancer and Cancer Anorexia Cachexia Syndrome

Cancer Anorexia Cachexia Syndrome (Cachexia)

- Common 'wasting' syndrome linked to many cancers
  - No effective therapy
  - Significant contribution to morbidity and mortality

- Cachexia is estimated affect **to 60% to 80% of advanced cancer patients** and to be responsible for **~30% of all cancer deaths**[1]

- Weight loss exacerbated by many chemotherapies
  - Often linked to nausea and vomiting
  - May require dose reduction of chemotherapy

- Elevated GDF15 associated with both chemotherapy and cancer cachexia
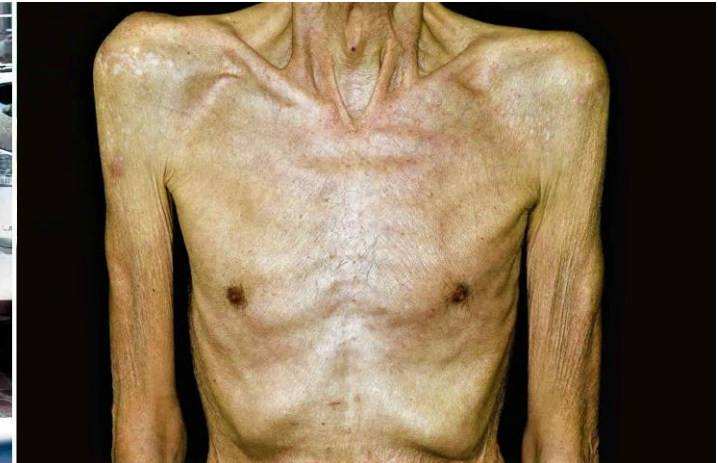
NGM120 is an Antagonist Antibody Inhibiting GFRAL

Potent, first-in-class antibody targeting the GDNF Family Receptor Alpha-Like (GFRAL)

Potential to regulate the GDF15/GFRAL pathway in the brain stem that is known to signal feeding and the autonomic nervous system

Preclinical studies suggest that NGM120 may:
- Reverse human tumor-induced body weight loss in mice
- Reduce tumor growth and improves survival in syngeneic orthotopic pancreatic tumor model
- Prevent cisplatin-induced GDF15-mediated weight loss in mice

Ph1b study of NGM120 in patients with metastatic pancreatic cancer is ongoing
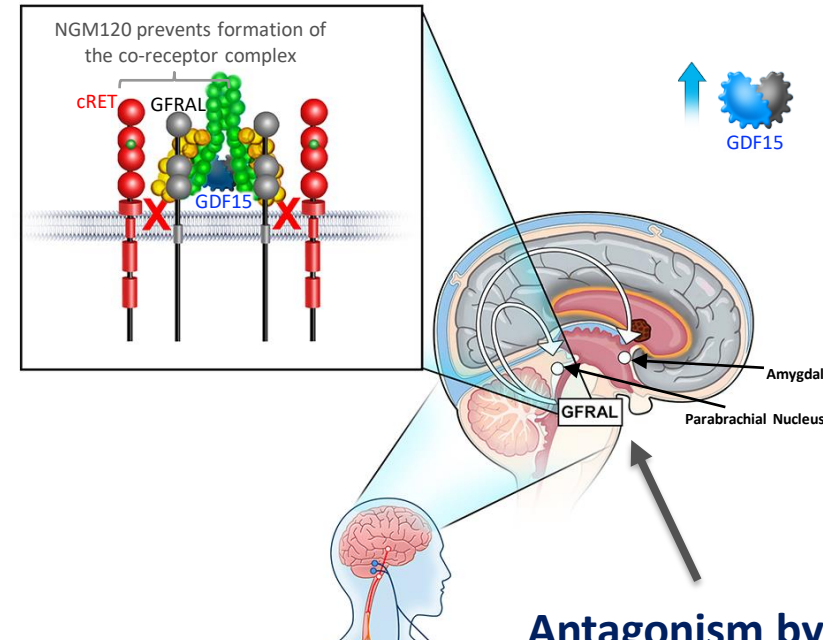
NGM120 prevents formation of the co-receptor complex

cRET GFRAL

GDF15

GFRAL Amygdala Parabrachial Nucleus

GDF15 levels are increased by:
- Tumor
- Chemotherapy
- Infection
- Inflammation
- Other stressors

GDF15

Antagonism by NGM120 may result in:
- Appetite Regulation
- Metabolic Regulation
- Immune Modulation

GDF = growth differentiation factor

Growth Differentiation Factor 15 (GDF15): A Powerful Biological Pathway

- Identified GDF15 'wow biology' through the systematic *in vivo* screening of >1000 secreted factors

- GDF15 is secreted by macrophages, endothelial cells, myocytes, adipocytes, and multiple tumor types in response to cellular stress

- GDF15 regulates feeding, metabolism and immune function

In-Vivo Systematic Screening of Human Genes using AAV*
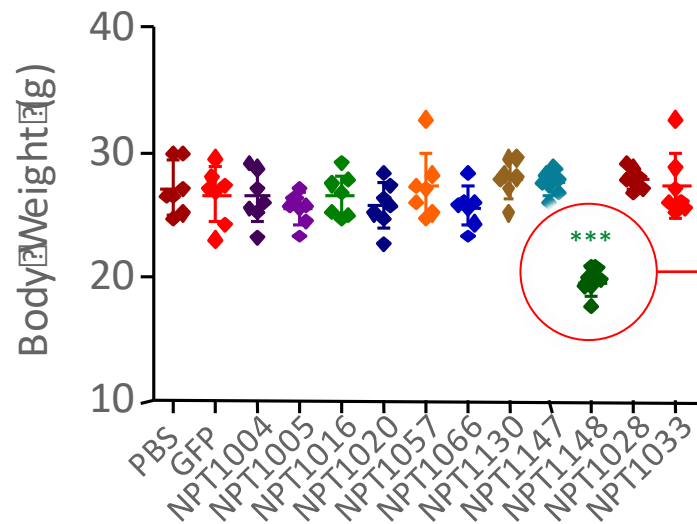
GDF15
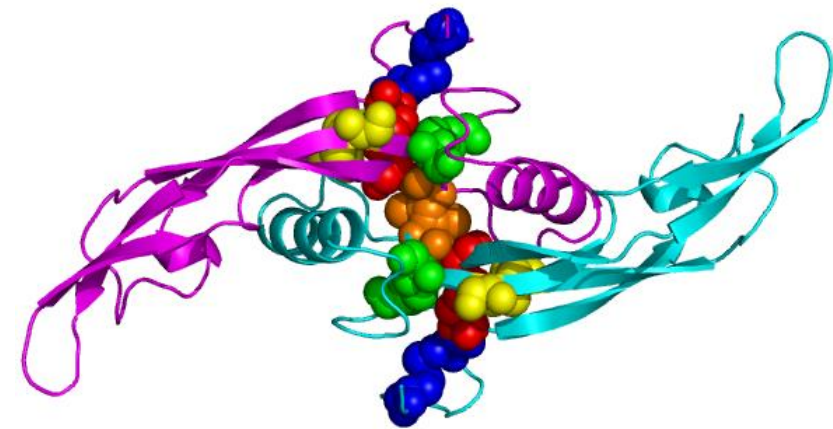
X-ray Crystal Structure of dimeric GDF15
(1.97Å resolution, NGM)

*AAV – Adeno-Associated Virus

Elevated GDF15 Levels are Linked to Poor Survival in Multiple Cancers

Ovarian Cancer

Low GDF15

High GDF15
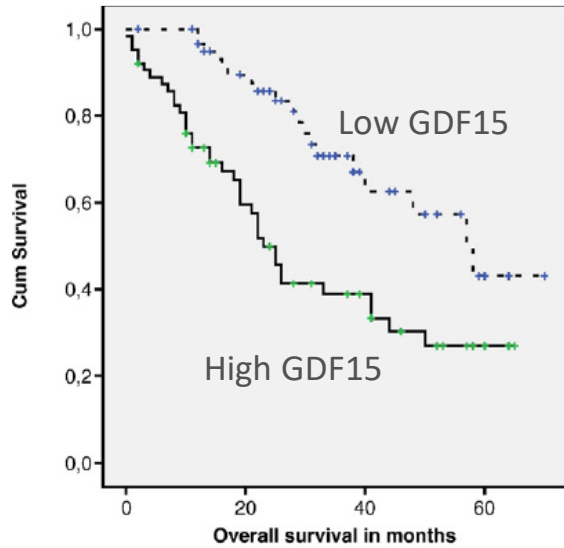
Staff *et al.*, *Gynecologic Oncology* 2010

Prostate Cancer

GDF15 ≤1300 pg/mL

GDF15 1300-3000 pg/mL

GDF15 >3000 pg/mL
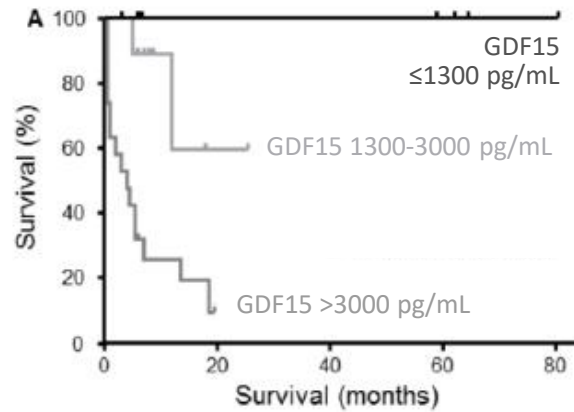
Winand *et al.*, *J Mol Biomark Diagn* 2014

Colorectal Cancer (CRC)

Cumulative proportion surviving (Kaplan–Meier)

Deletion

GDF15<1150 pg/ml, *n* = 47

GDF15≥1150 pg/ml, *n* = 91

$P = 0.022$
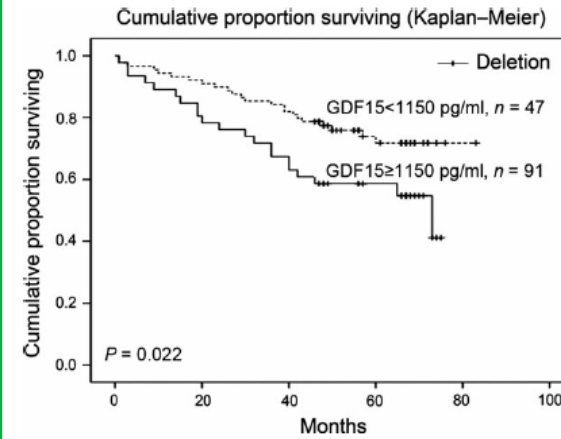
Li *et al.*, *J Cell Mol Med*_2016

Esophageal Cancer

Log-rank $P=0.063$

MIC-1/GDF15 plasma levels ⩽1140 pg ml^{-1}
MIC-1/GDF15 plasma levels ⩾1140 pg ml^{-1}
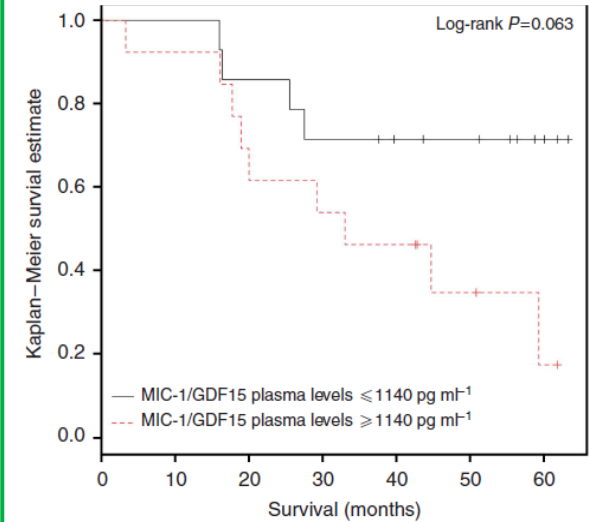
Fisher *et al.*, *BJC* 2015

Identification of GFRAL (GDNF Family Receptor Alpha-Like): The Receptor for GDF15

GDF15 binding to GFRAL

Bound Ligand (molecules/cell x 10³)

[^{125}I-GDF15] (pM)
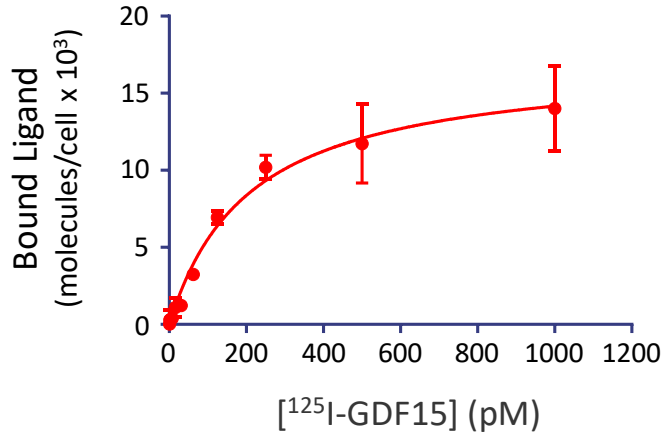
GFRAL-cRET co-receptor complex mediates GDF15 signaling

Signaling (RLU x 10^{-5})

Log [Ligand] (M)

GFRAL + cRET
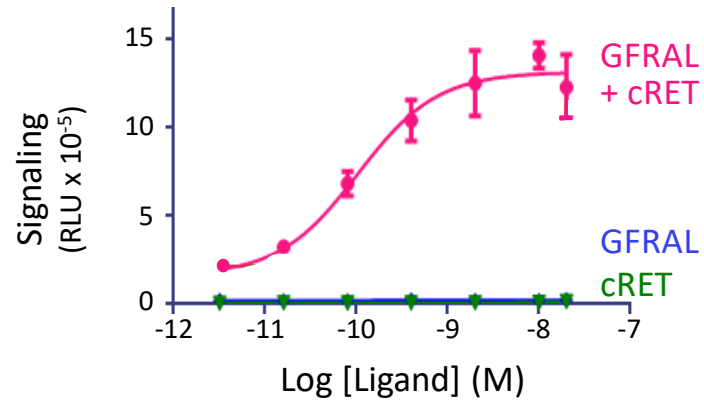
GFRAL

cRET

GDF15-GFRAL-cRET Ternary Complex

cRET

GFRAL

GDF15

GDF15 co-receptor Complex with cRET

cRET   GFRAL
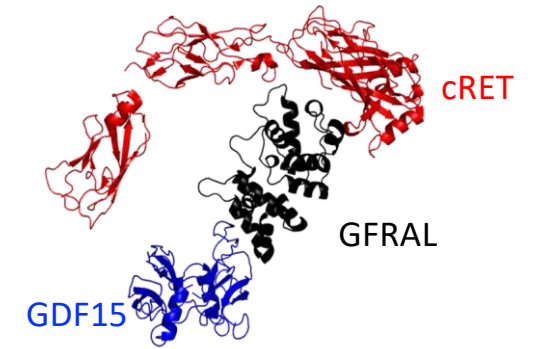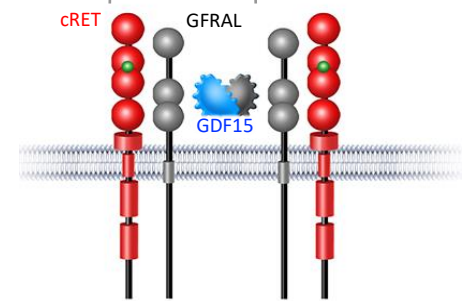
GDF15

The GDF15 Receptor, GFRAL, is Exclusively Expressed in the Brain Stem

NGMBio

GFRAL Gene Expression Profile

Relative Expression Level
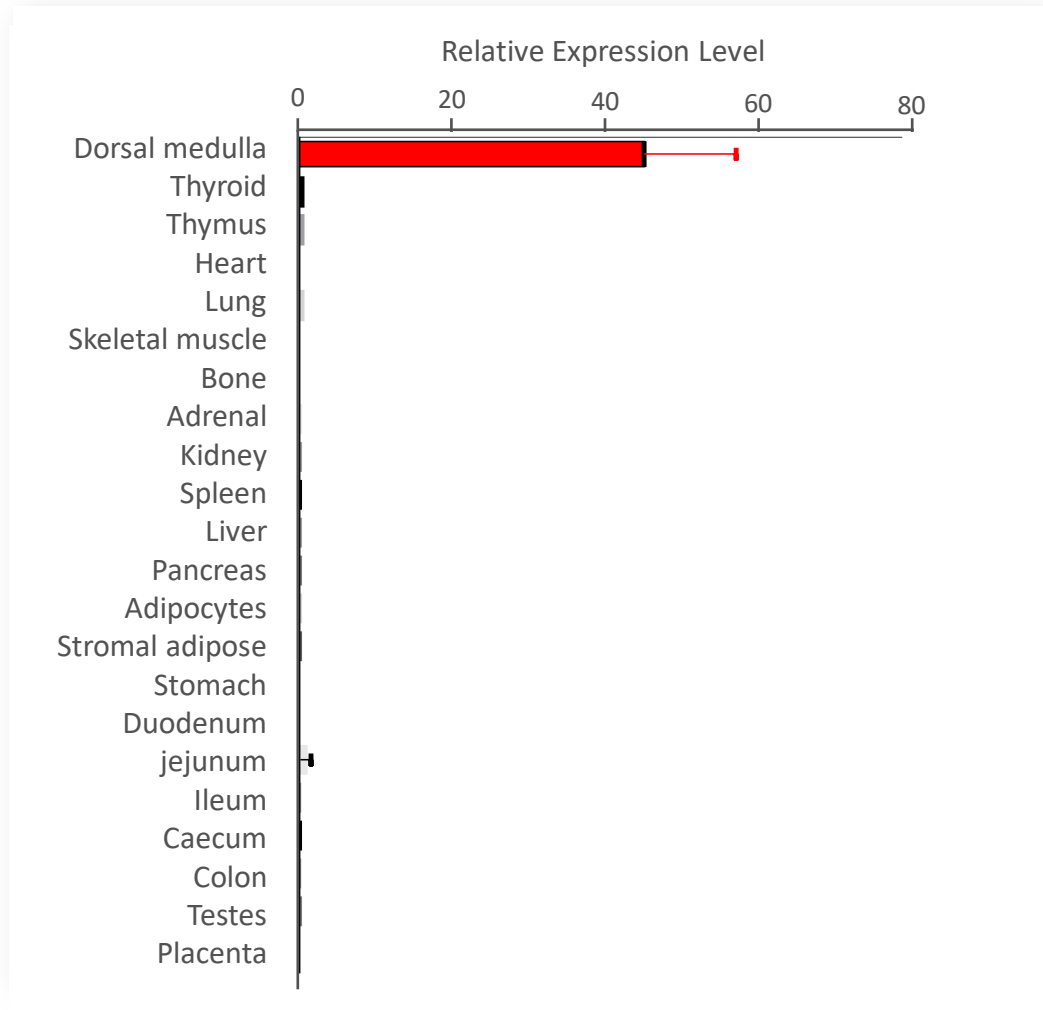
GFRAL Expression in the Dorsal Medulla, Exclusively Expressed in the Brain Stem
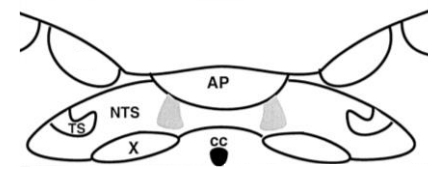
AP: Area Postrema

NTS: Nucleus of Solitary Tract

CC: Central Canal
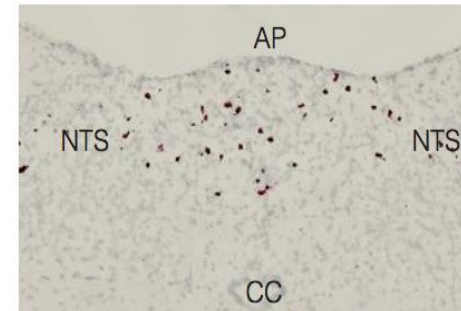
in situ hybridization
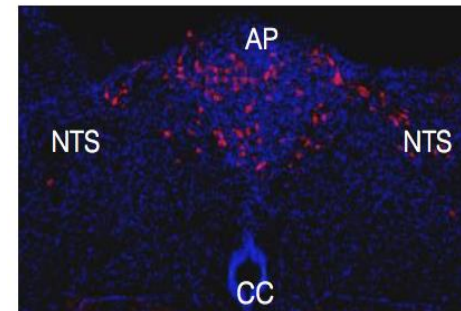
Immunofluorescence

NGM120: An inhibitor of GDF15 Signaling

## GDF15/GFRAL Pathway Modulates Food Intake, Metabolic and Immune Function
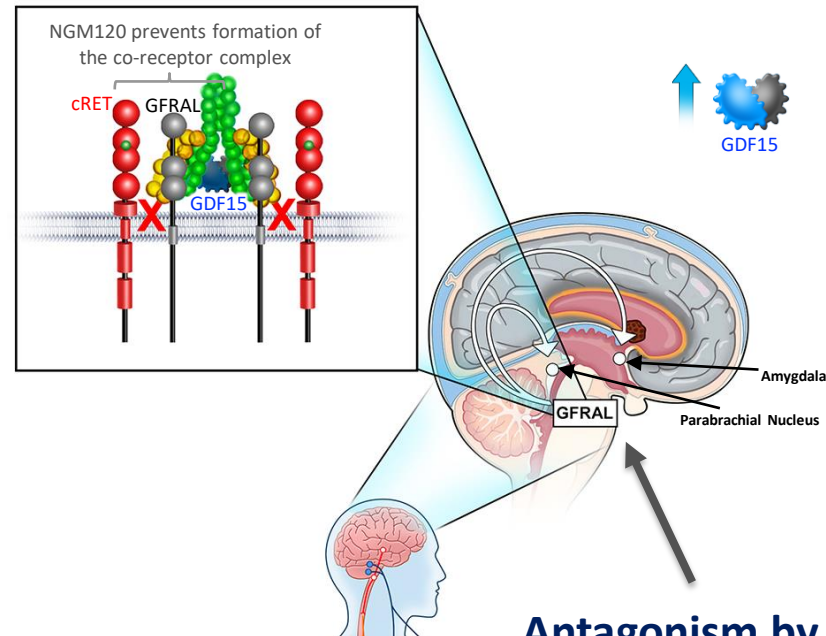
NGM120 prevents formation of the co-receptor complex

cRET GFRAL

GDF15

GFRAL

Amygdala

Parabrachial Nucleus

GDF15 levels are increased by:

- Tumor
- Chemotherapy
- Infection
- Inflammation
- Other stressors

GDF15

Antagonism by NGM120 may result in:

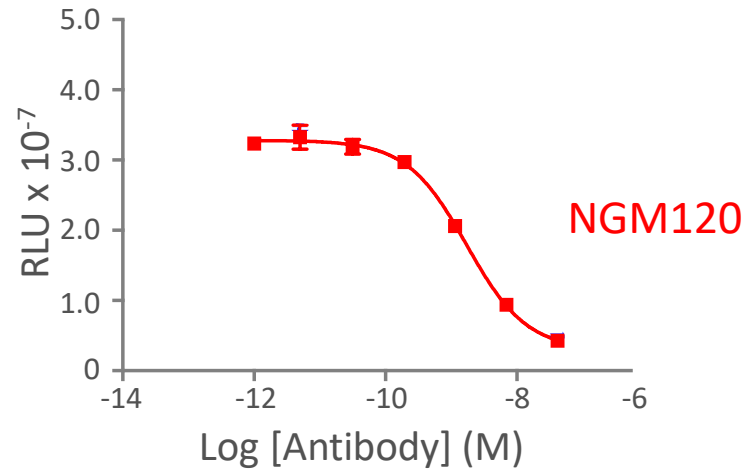- Appetite Regulation
- Metabolic Regulation
- Immune Modulation

NGM120 Binds with High Affinity to GFRAL and Acts as a Non-competitive Antagonist of Receptor-mediated Signaling

NGM120 binding to GFRAL (Biacore)
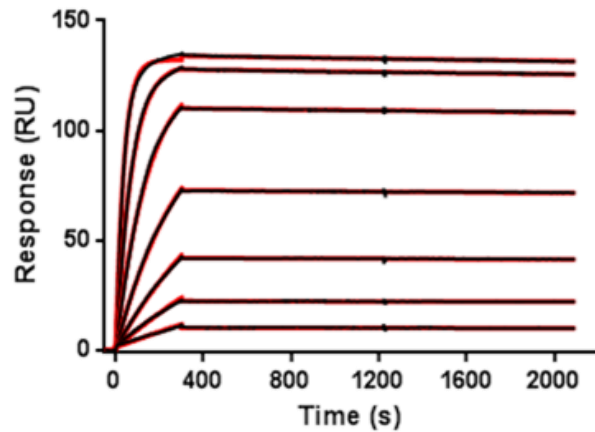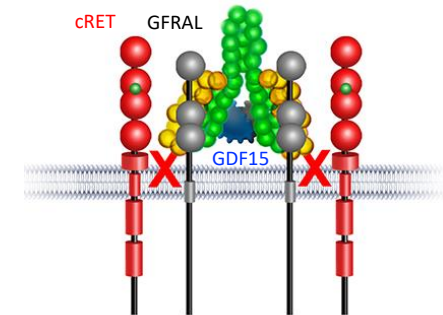
K_D=785 fM
(KinExA)

Inhibition of GDF15 signaling by NGM120

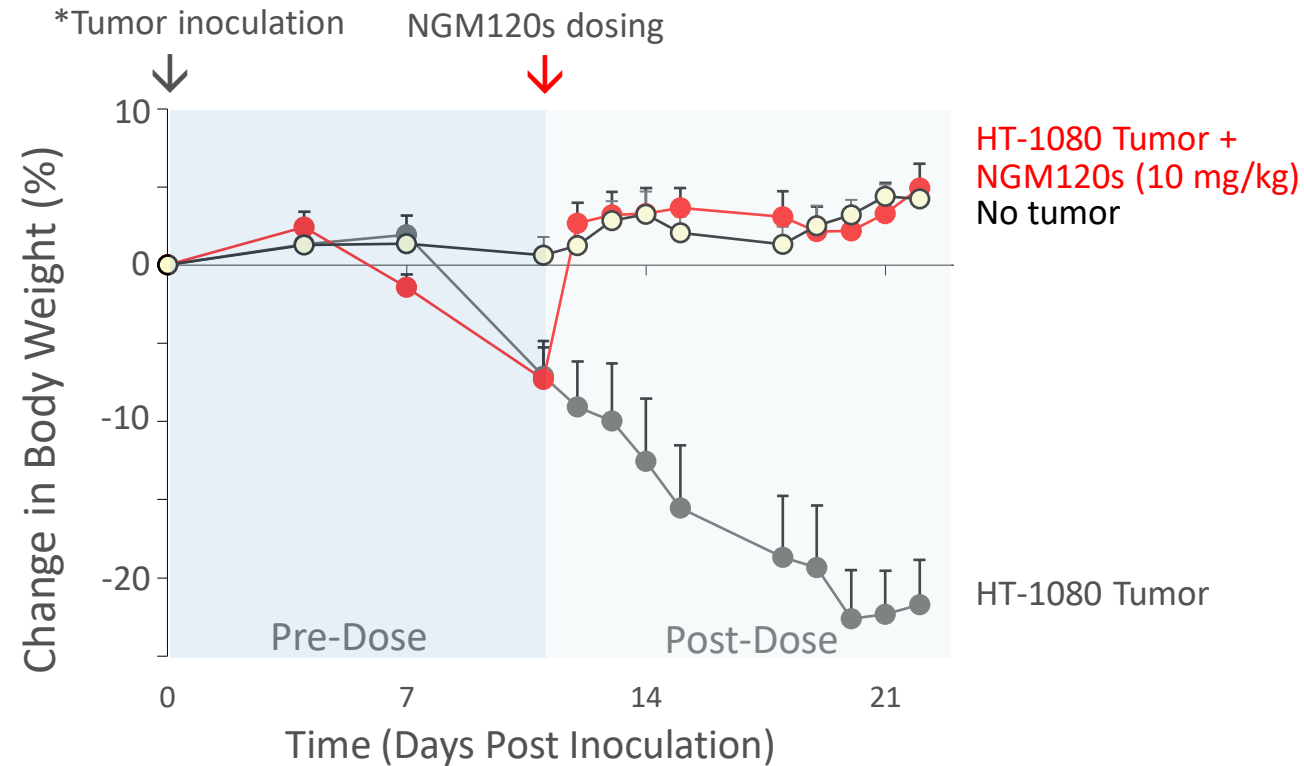NGM120

NGM120 prevents formation of the co-receptor complex

NGM120

cRET

GFRAL

GDF15

GDF15 co-receptor Complex with cRET

cRET   GFRAL

GDF15

Suriben et. al.., Nat Med 2020
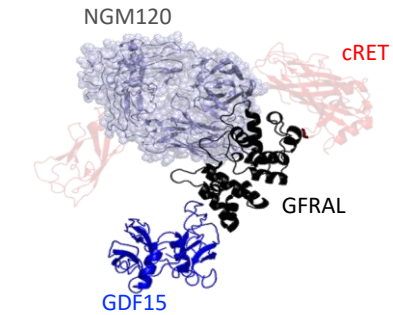
NGM120s Rapidly Reverses Human Tumor-Induced Body Weight Loss in a Murine Cachexia Model

A Murine Model of Cancer Cachexia Syndrome

Study Model: Tumor-bearing (HT-1080 (Human fibrosarcoma cell line)) SCID mice; (n=6/group)
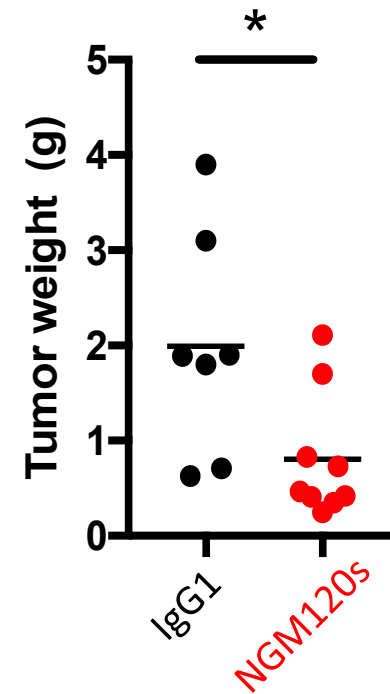
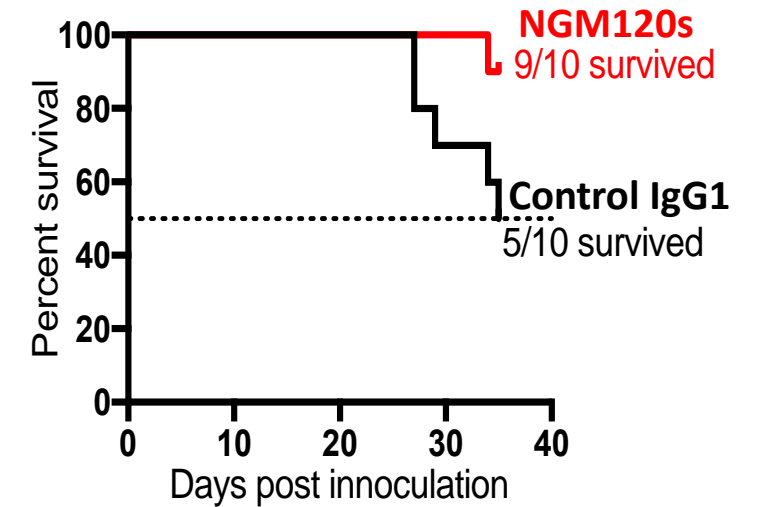# NGM120s Reduces Tumor Growth and Improves Survival in a Pancreatic Tumor Model

Tumor Model

- Orthotopic syngeneic tumor model
- Pancreatic cancer
- NGM120 dosed weekly

Tumor Weight

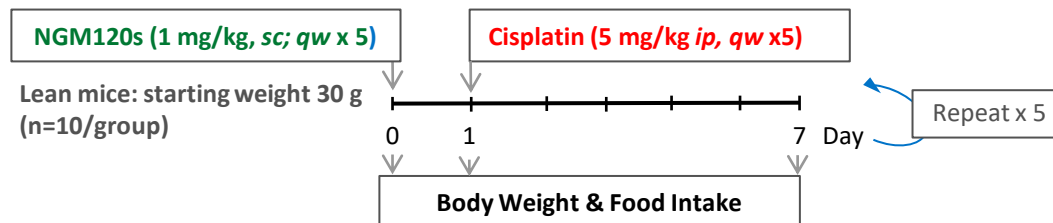**Survival**

NGM120s
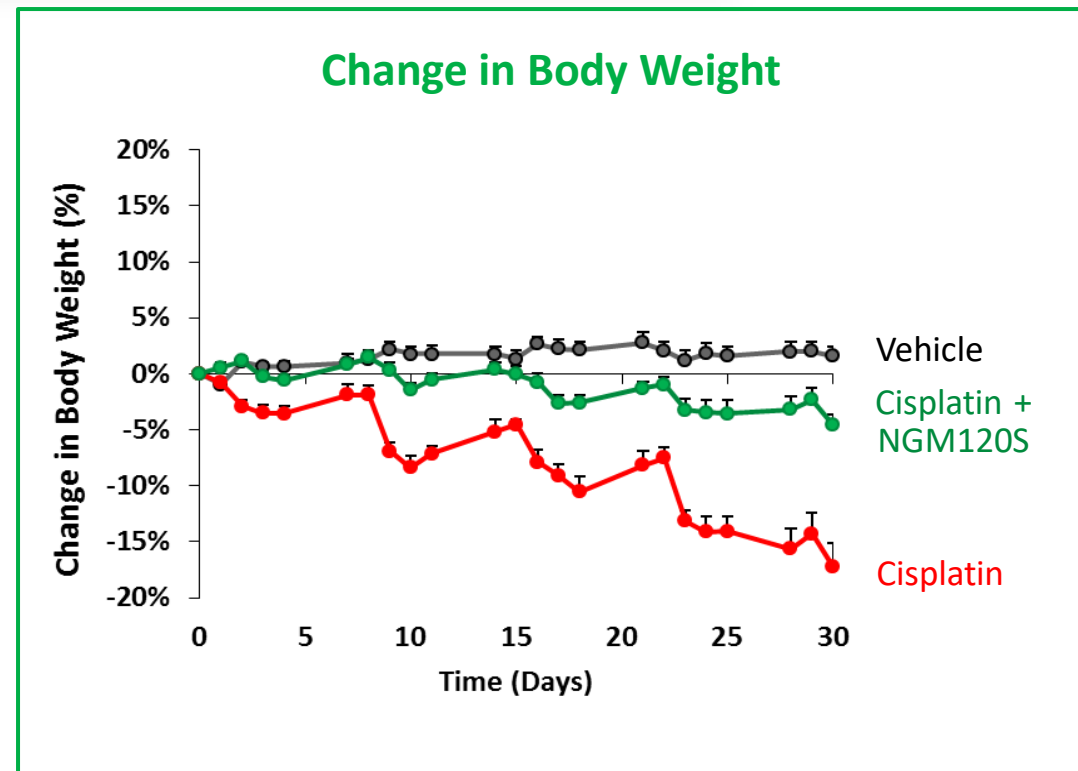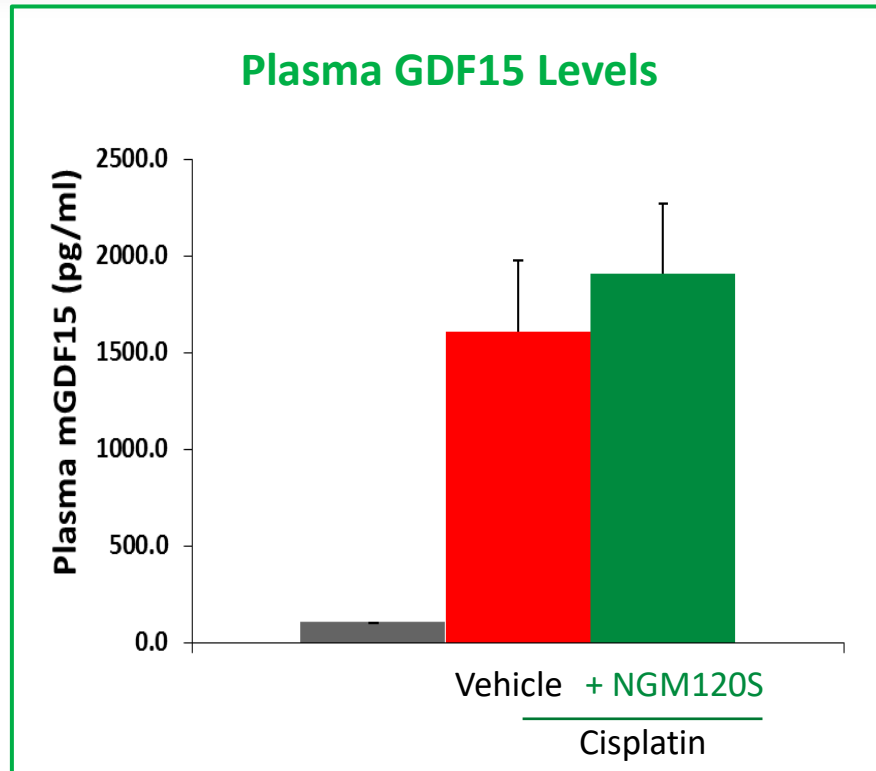9/10 survived

Control IgG1
5/10 survived

NGM120s Prevents Cisplatin-induced GDF15-mediated Weight Loss in Mice

- Administration of NGM120 also preserved lean body mass and muscle function in mice treated with cisplatin

NGM120s (1 mg/kg, *sc; qw* x 5)

Cisplatin (5 mg/kg *ip, qw* x5)

Lean mice: starting weight 30 g (n=10/group)

Repeat x 5

0 1 7 Day

Body Weight & Food Intake

NGM120 Clinical Development in Cancer and Cancer Anorexia-Cachexia Syndrome

- Completed single (n=48) and multiple (n=44) ascending dose cohorts in first-in-human healthy volunteer studies
  - Well-tolerated at all doses
  - No serious adverse events or adverse event of interest
  - $T_{1/2}$ approximately 35 days
- Completed enrollment in dose finding studies for Ph1a monotherapy (n=12) in patients with select solid tumors and Ph1b in combination with gemcitabine and abraxane (n=8) in patients with metastatic pancreatic cancer
- Planned Ph1b expansion study in metastatic pancreatic carcinoma patients
  - Randomized, placebo-controlled study (n=60)
  - Anticipate initiation in 1Q21
  - Metastatic pancreatic carcinoma patients treated with gemcitabine and abraxane and either NGM120 (n=30) or placebo (n=30)
  - Assessment of both cancer and cancer anorexia cachexia syndrome endpoints
    - Tumor assessment by RECIST 1.1, body weight, body composition, functional status and PRO measures

Daniel Von Hoff, MD, F.A.C.P.
Distinguished Professor, The Translational Genomics Research Institute

Perspective on The Clinical Issues

Daniel D. Von Hoff, MD, FACP, FASCO, FAACR

Distinguished Professor, Translational Genomics Research Institute (TGen)
Virginia G. Piper, Distinguished Chair for Innovative Cancer Research, Honor Health
Margaret Givan Larkin Endowed Chair in
Developmental Cancer Therapeutics, Hoag Family Cancer Institute
Professor of Medicine University of Arizona and Mayo Clinic
Distinguished Professor, Department of Medical Oncology and Therapeutic Research,
City of Hope

- 32 years as medical oncologist at the bedside
- Conducted >300 phase I trials with new anticancer and supportive care agents
- PI on pivotal clinical trials for 3 of 4 FDA approved drugs that improve survival for patients with stage IV pancreatic cancer (and approval of multiple other agents)
- Learned to recognize that unique mechanisms of action and the best science based approaches work in the clinic
- Wanting to further improve the situation

Why Did I Contact NGM Bio When I Heard About This Program?

1. Cancer Cachexia (Greek for "bad condition") is a significant clinical problem for our patients
   - "Look – Dad is wasting away"
   - Often looked upon as a "prelude to death" (not only in cancer but AIDS, COPD and cardiac disease)
   - Cachexia is "the last illness you have"
2. Syndrome defined by ongoing loss of skeletal muscle (sarcopenia)
   - With or without loss of fat
   - Functional impairment of performance status
   - Can't be reversed by nutritional support
3. Cachexia
   - Affects 60-80% cancer patients (depending on tumor type and stage)
   - Associated with increased risk treatment failure and a worse survival
   - Contributes to patients demise by
     - Pneumonia (weak respiratory muscles)
     - Thrombosis (pulmonary embolism/stroke)
   - Infection - compromise of immune system

Perhaps Lesser Known Facts About Cachexia

1. Can start a median of 8.7 years before diagnosis of pancreas cancer
   - Signs of breakdown of muscle (branched-chain amino acids in plasma (Mayers et al, Nature Med 2014)
2. Low serum albumin (one measure of nutritional status and of inflammation)
   - Terrible prognostic factor for patients
   - If albumin <3.0 not eligible for therapeutic clinical trials
   - Causes vascular leak (low oncotic pressure)
   - Tremendous edema
   - Ascites (fluid in the abdomen) (10-40% of pts)
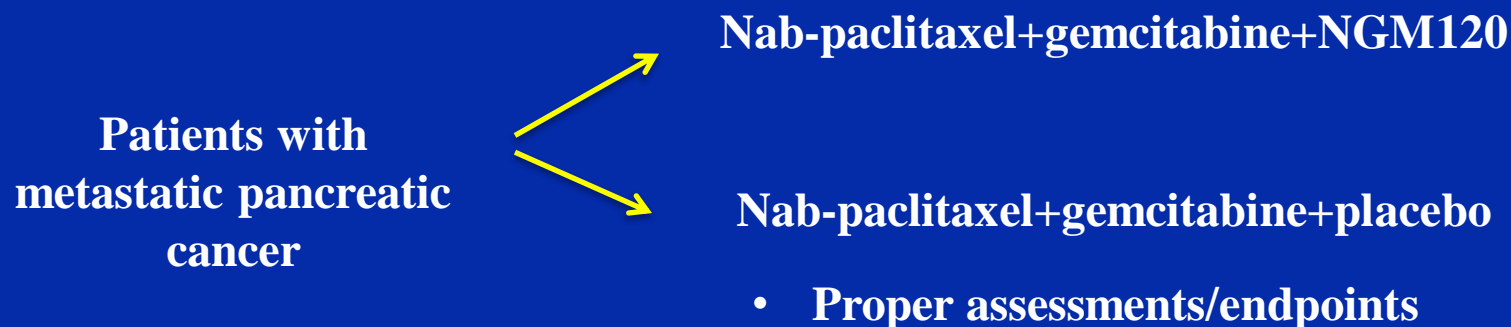

Carrying around excess of 5-6 liters of fluid
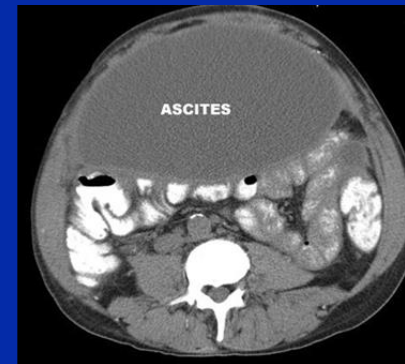
Abdominal pain, can't eat - "I can't go on like this" – Take it off and decreases albumin

Cachexia is a Tremendous Unmet Medical Need – Supportive Care

1. We don't have much approved that we can try (and that work)
   - Megestrol acetate
     - More edema, worry about increased thrombosis
   - Glucocorticoids
     - Immune suppression, diabetes out of control, muscle atrophy
   - Anabolic steroids
     - Liver issues
   - THC-like compounds
     - Marinol
   - Multiple others tried but not approved
     - Ghrelin, L-carnitine, glutamine, omega-3 fatty acids
2. There is a great need in this area of supportive care for our oncology patients
   - Patients are very willing to participate in clinical trials
   - Investigators really anxious to have something to offer their patients

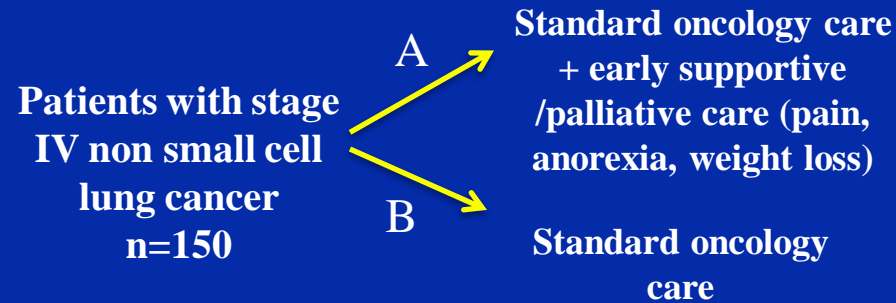# The Proposed Clinical Development Plan Builds on This New Science

1. **Excellent trial design**

   Nab-paclitaxel+gemcitabine+NGM120

   Patients with metastatic pancreatic cancer

   Nab-paclitaxel+gemcitabine+placebo

   - **Proper assessments/endpoints**

2. **Trial is of even more interest because of the potential for antitumor activity of NGM120 by itself**
   - **Documented in a preclinical pancreatic cancer model**

One Final Point Regarding Anything in the Supportive Care Area (Because Improved Survival is A Goal Too)
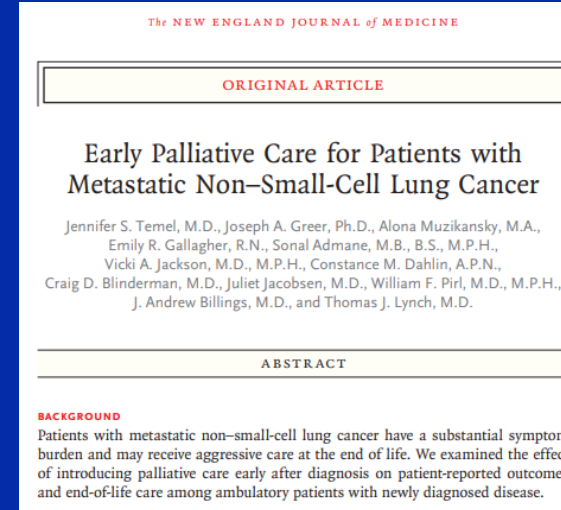
1. **A landmark paper**

Patients with stage IV non small cell lung cancer
n=150

A → Standard oncology care + early supportive /palliative care (pain, anorexia, weight loss)

B → Standard oncology care

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early Palliative Care for Patients with Metastatic Non–Small-Cell Lung Cancer

Jennifer S. Temel, M.D., Joseph A. Greer, Ph.D., Alona Muzikansky, M.A., Emily R. Gallagher, R.N., Sonal Admane, M.B., B.S., M.P.H., Vicki A. Jackson, M.D., M.P.H., Constance M. Dahlin, A.P.N., Craig D. Blinderman, M.D., Juliet Jacobsen, M.D., William F. Pirl, M.D., M.P.H., J. Andrew Billings, M.D., and Thomas J. Lynch, M.D.

ABSTRACT

BACKGROUND

Patients with metastatic non–small-cell lung cancer have a substantial symptom burden and may receive aggressive care at the end of life. We examined the effect of introducing palliative care early after diagnosis on patient-reported outcomes and end-of-life care among ambulatory patients with newly diagnosed disease.

Temel et al, NEJM 363: 733-742, 2010

2. **Results**
   - **Arm A**
     - Better quality of life (p=0.03)
     - Less depression (p=0.01)
     - Longer median survival 11.6 vs 8.9 months (p=0.02)
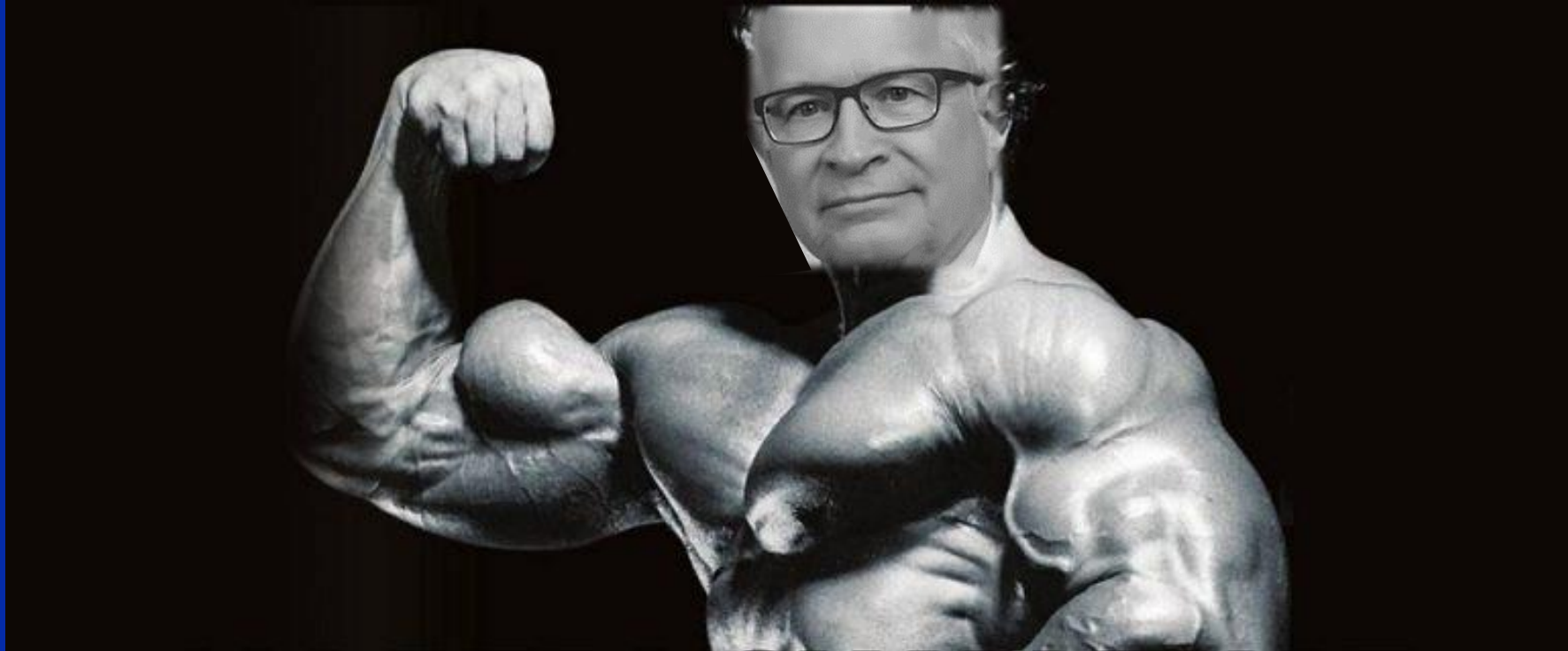
3. **A logical interpretation**
   - Duh – If you feel better, you probably will want to live longer

4. **We need more tools for supportive care - NGM120 could be one of them**

Thank You For Listening!

Robert Schreiber, Ph.D.
Distinguished Professor,
Pathology & Immunology,
Washington University School of Medicine

WHY TARGET THE MYELOID COMPARTMENT IN CANCER?

NGM Bio Research Day
December 9, 2020

Robert D. Schreiber, PhD

Andrew M. & Jane M. Bursky Distinguished Professor

Interim Chief of the Division of Immunobiology

Department of Pathology & Immunology

Director, Bursky Center for Human Immunology & Immunotherapy Programs

Co-Leader of the Tumor Immunology Program at the Siteman Cancer Center

Washington University School of Medicine, St. Louis, MO

Universal Excitement Over Cancer Immunotherapy

Immune Checkpoint Therapy:
Taking the Brakes Off The Immune System

Drake, Lipson & Brahmer Nature Reviews Clinical Oncology 2014
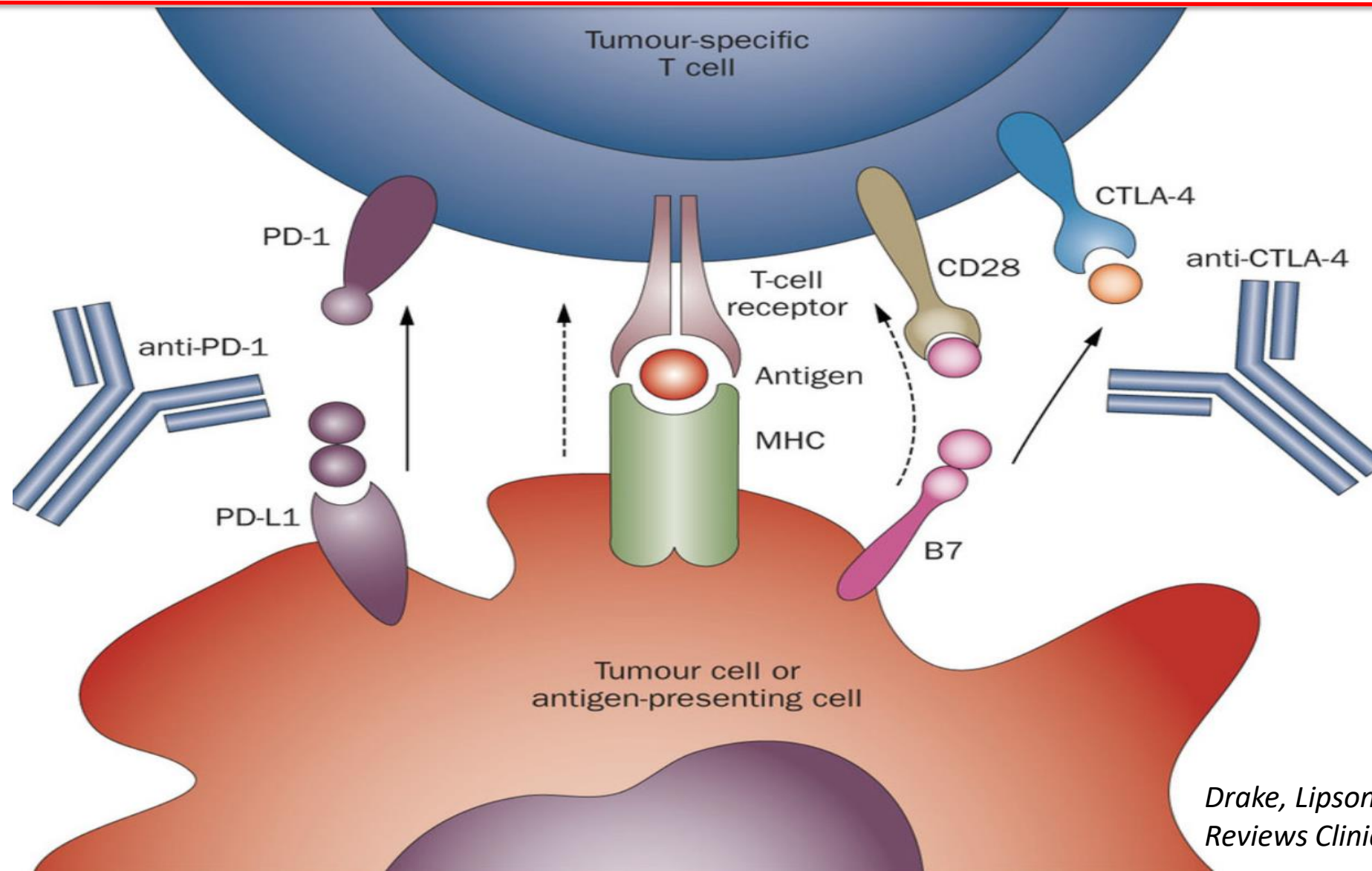
Immune Checkpoint Therapy Can be a Profoundly Effective and Durable Cancer Treatment
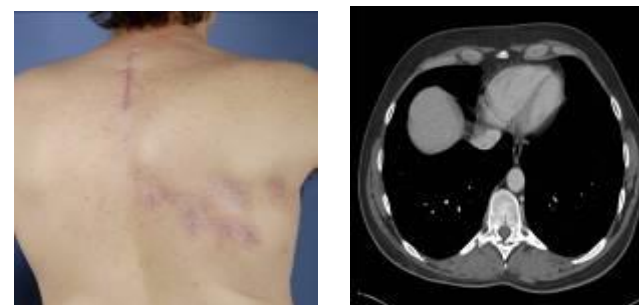

Screening

Week 12
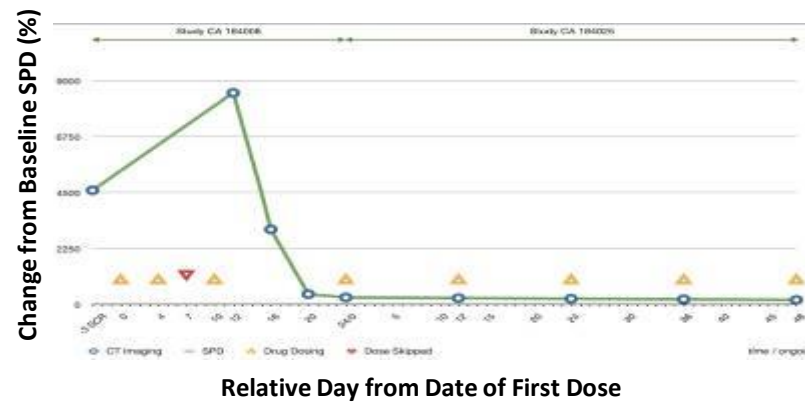**Initial increase in
total tumor burden (mWHO PD)**

Week 16
Responding

Week 72
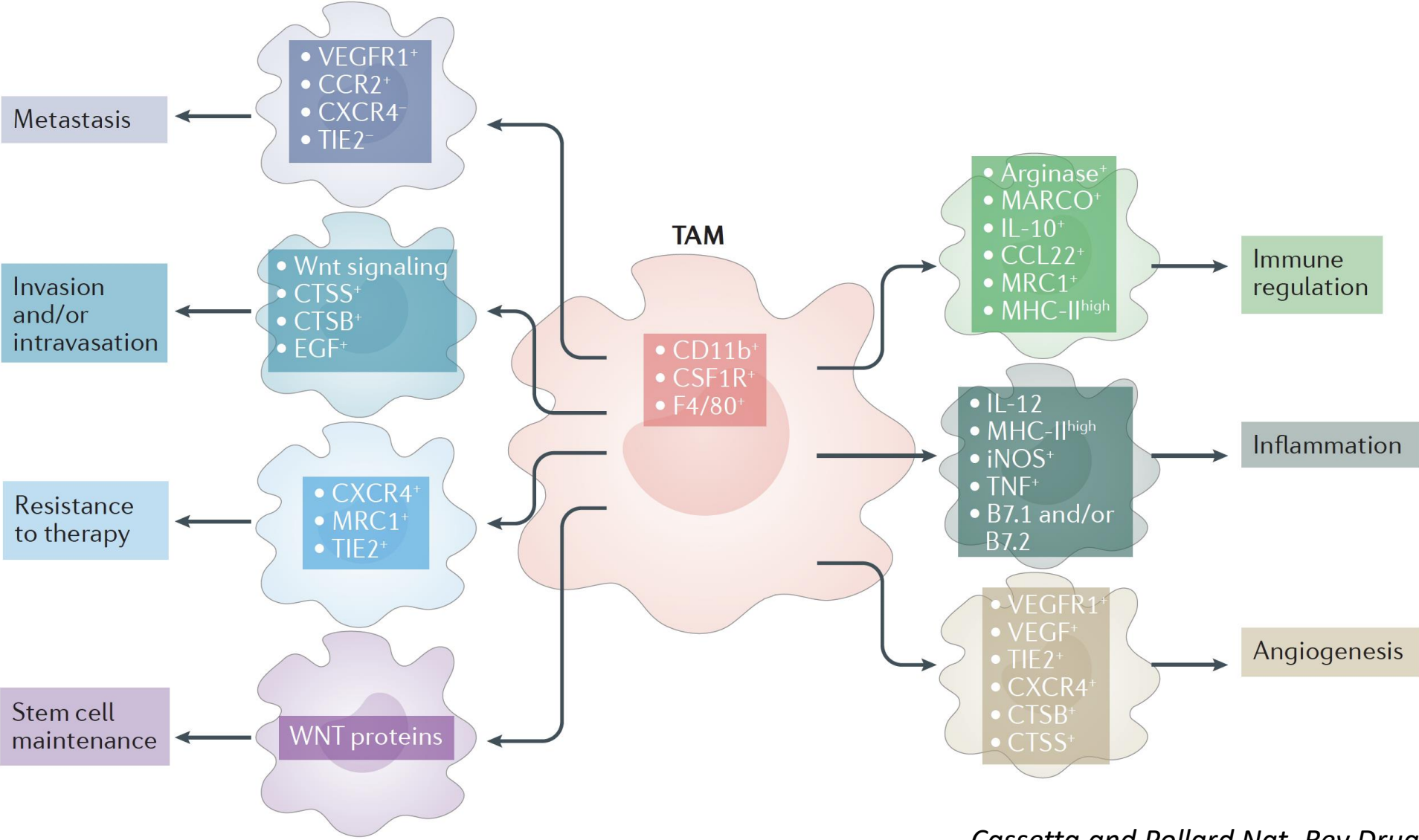**Durable & ongoing response
without signs of IRAEs**

*Hoos et al.
J. Natl Cancer
Inst, 2001*

*Wolchok et al.
Clin Can Res, 2009*

But—There Are Still Many Questions That Need to be Addressed

- How can we increase the success rate (i.e., the effectiveness) of immune checkpoint cancer therapy (ICT)?

- How can we improve the specificity and safety of ICT?

- What additional immune checkpoints should be targeted?

- What are the cellular sources of these additional checkpoints and what are their targets?

# Macrophages Can Promote Tumorigenesis & Depress Tumor Immunity

TAM

- CD11b$^+$
- CSF1R$^+$
- F4/80$^+$

Metastasis
- VEGFR1$^+$
- CCR2$^+$
- CXCR4$^-$
- TIE2$^-$

Invasion and/or intravasation
- Wnt signaling
- CTSS$^+$
- CTSB$^+$
- EGF$^+$

Resistance to therapy
- CXCR4$^+$
- MRC1$^+$
- TIE2$^+$

Stem cell maintenance
- WNT proteins

Immune regulation
- Arginase$^+$
- MARCO$^+$
- IL-10$^+$
- CCL22$^+$
- MRC1$^+$
- MHC-II^{high}

Inflammation
- IL-12
- MHC-II^{high}
- iNOS$^+$
- TNF$^+$
- B7.1 and/or B7.2

Angiogenesis
- VEGFR1$^+$
- VEGF$^+$
- TIE2$^+$
- CXCR4$^+$
- CTSB$^+$
- CTSS$^+$

Cassetta and Pollard Nat. Rev Drug Discovery 2018

The Complexity of the Intratumoral Macrophage Compartment and its Remodeling Following Successful Immunotherapy

Gubin et al, Cell 2018
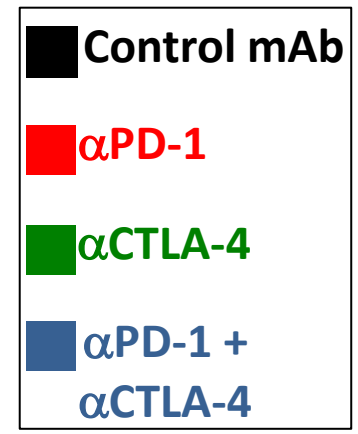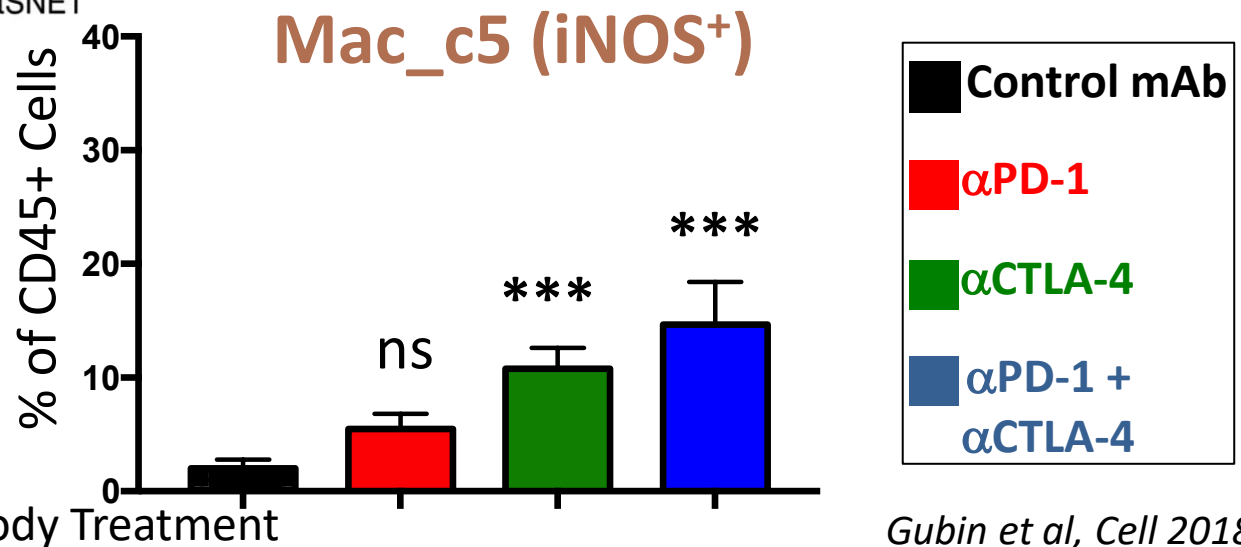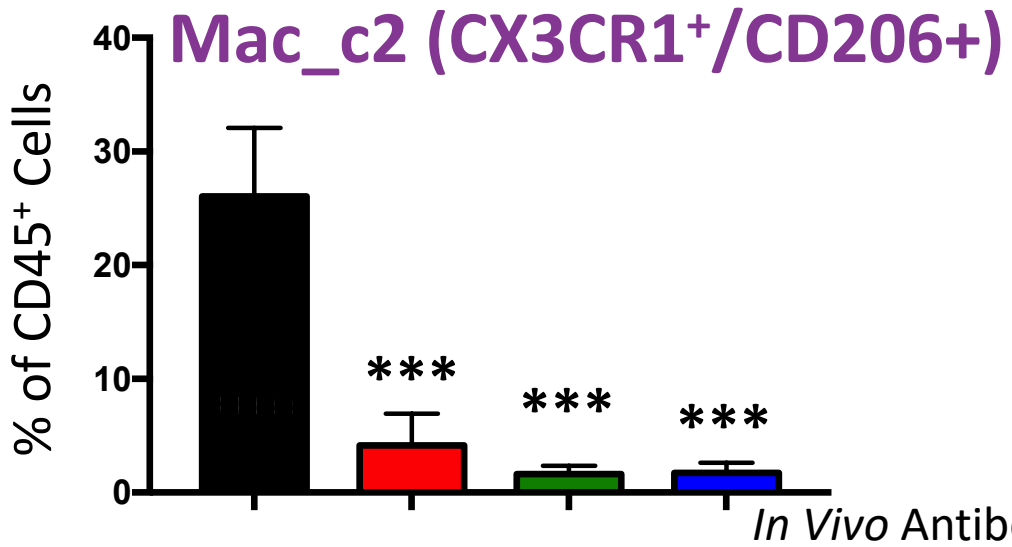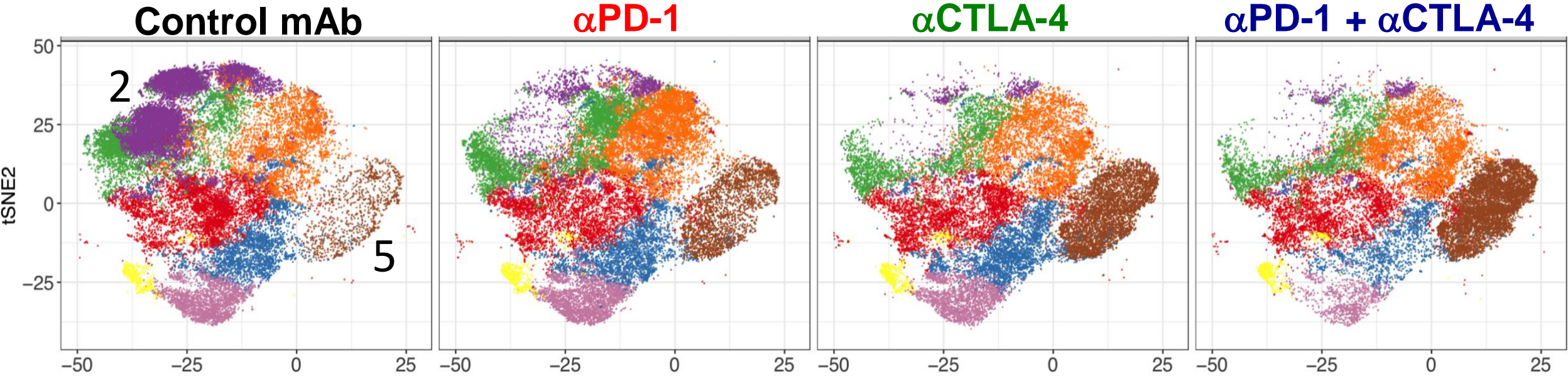
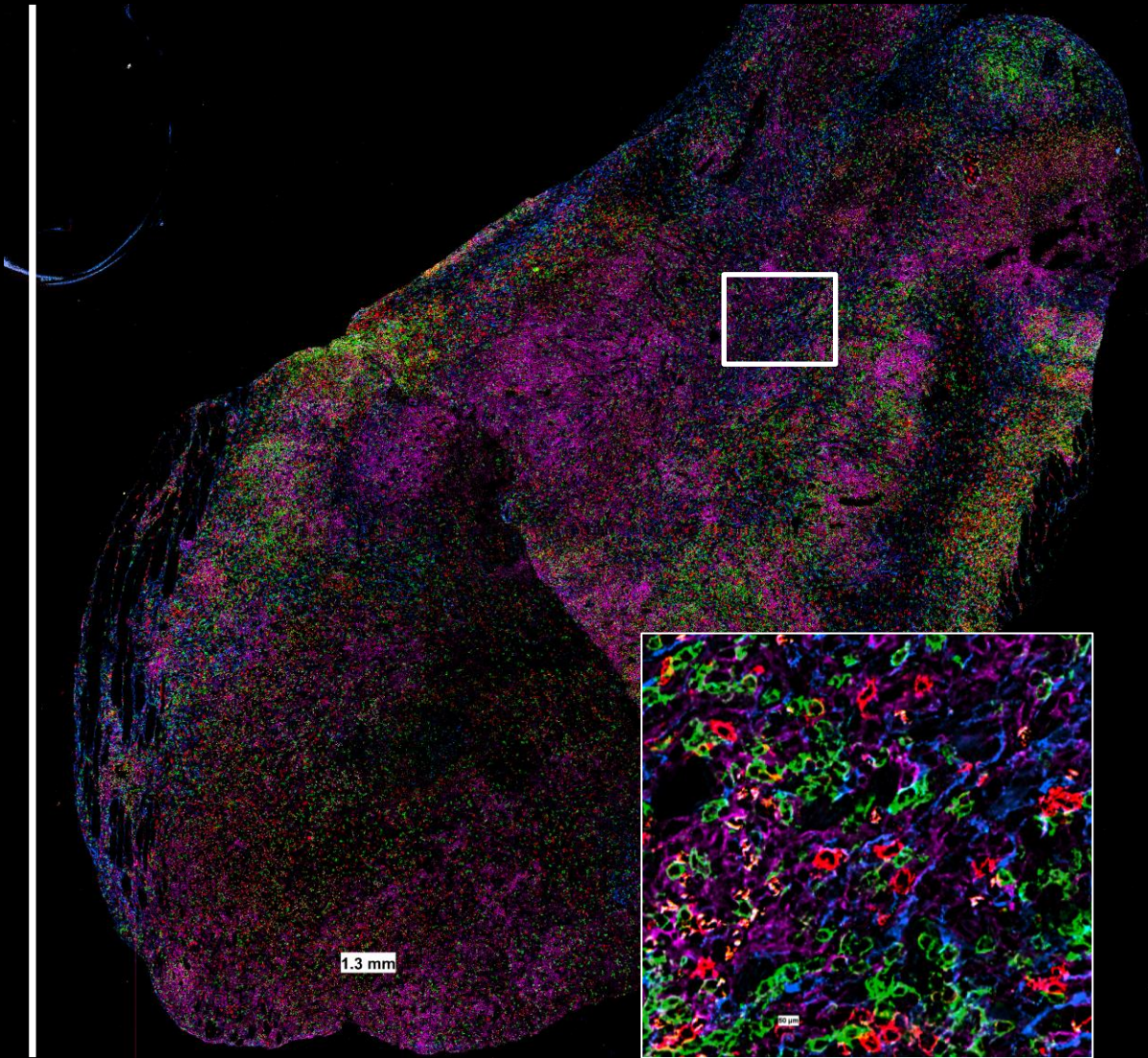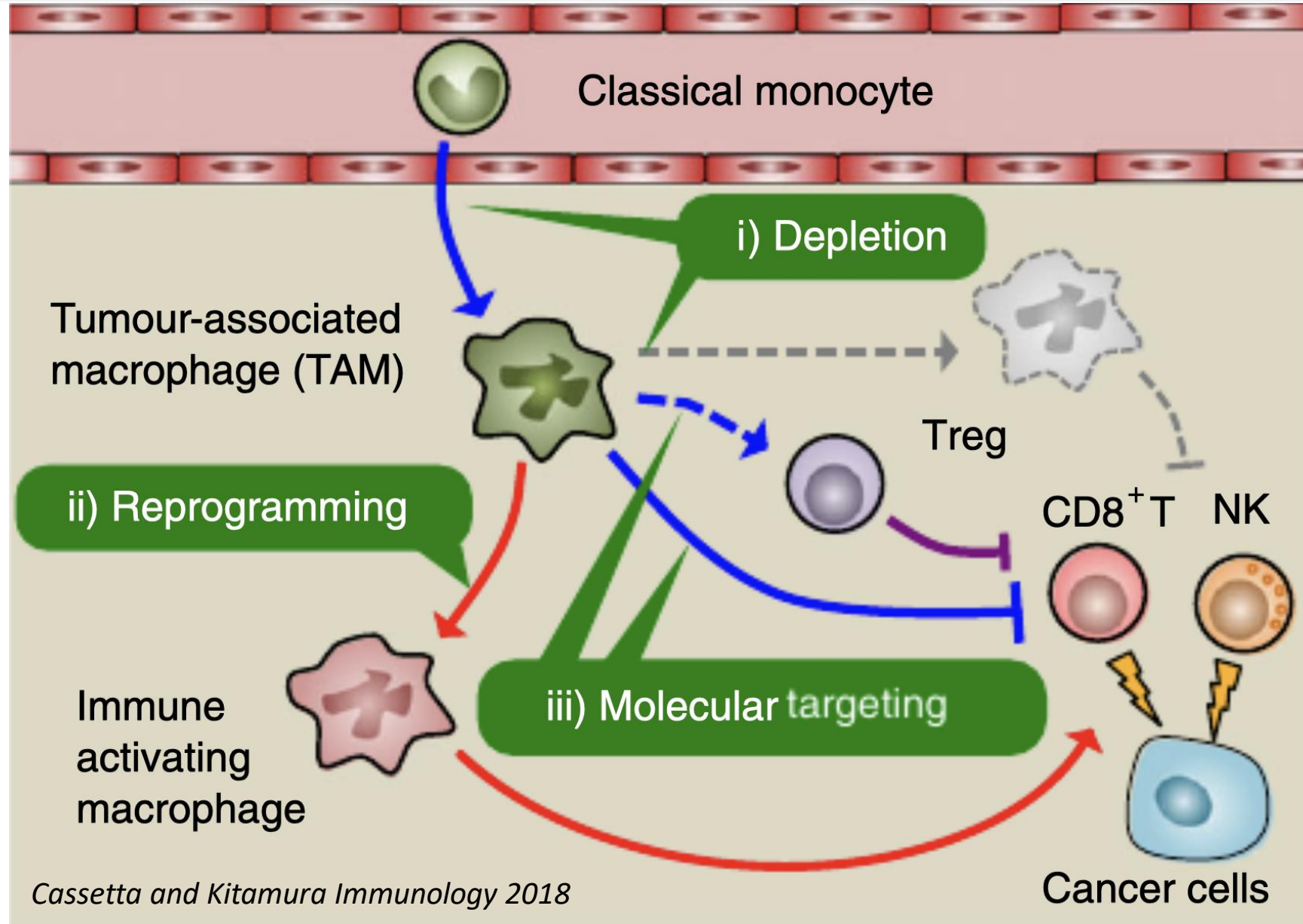**CD140a CD4 CD8 CD11C**

CONTROL

α-CTLA-4/α-PD-1

1.13 mm

1.3 mm
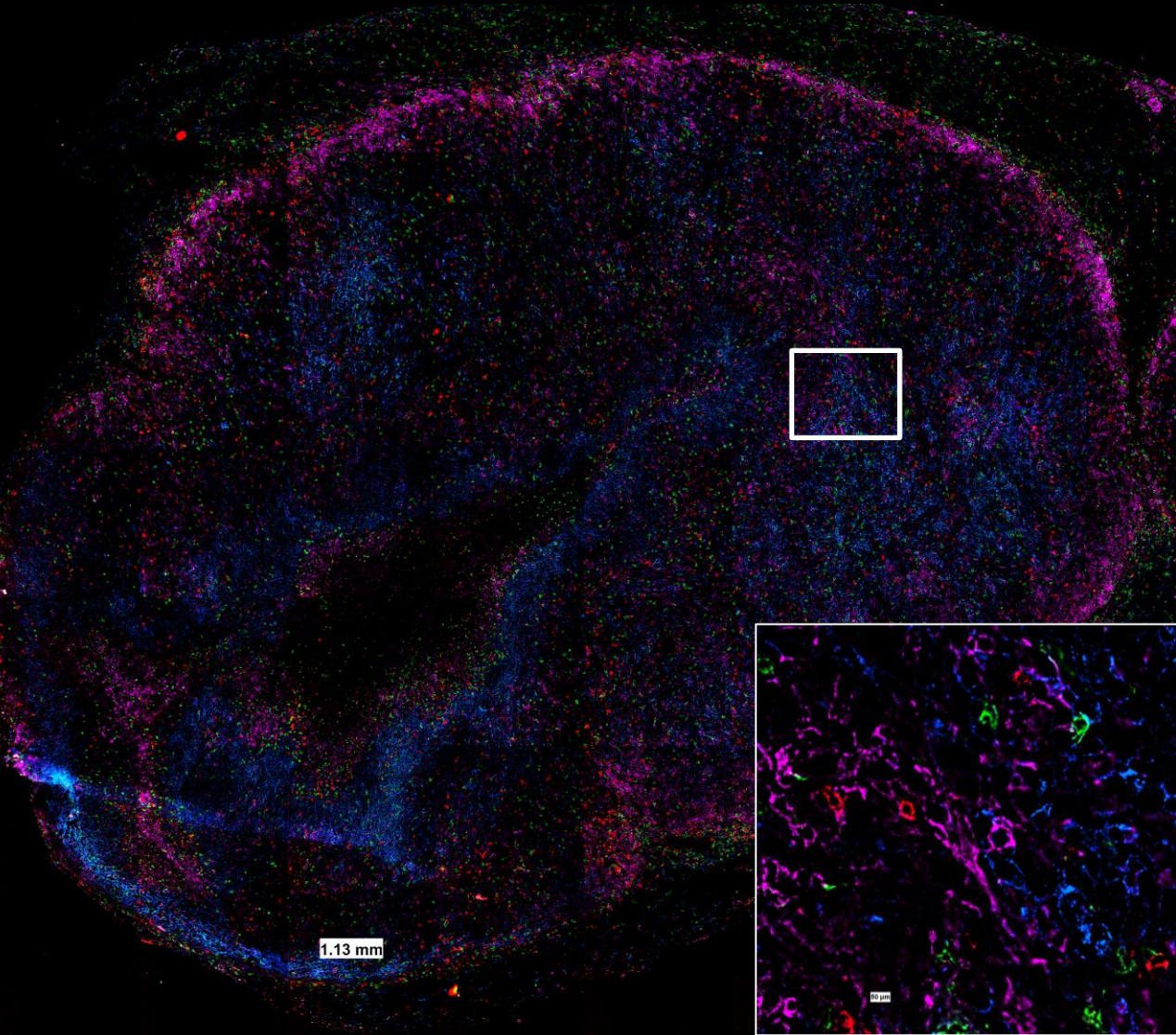
Strategies to Circumvent Myeloid Cell Immunosuppression

Cassetta and Kitamura Immunology 2018

Rationale for Focusing on the Myeloid Compartment

● Most current immunotherapy efforts target the T cell compartment

● However, myeloid cells represent a substantial percentage of hematopoietic cells that reside in tumors and they participate in directing the specificity and action of tumor specific T cells

● Myeloid cells can reversibly take on different activation states and thereby paradoxically facilitate either pro- or anti-tumor functions

● Thus, it would be preferable to <u>re-program</u> these cells (rather than eliminating them altogether) to concomitantly *promote* their capacity to facilitate tumor immune elimination and *reduce* their capacity to facilitate tumor outgrowth
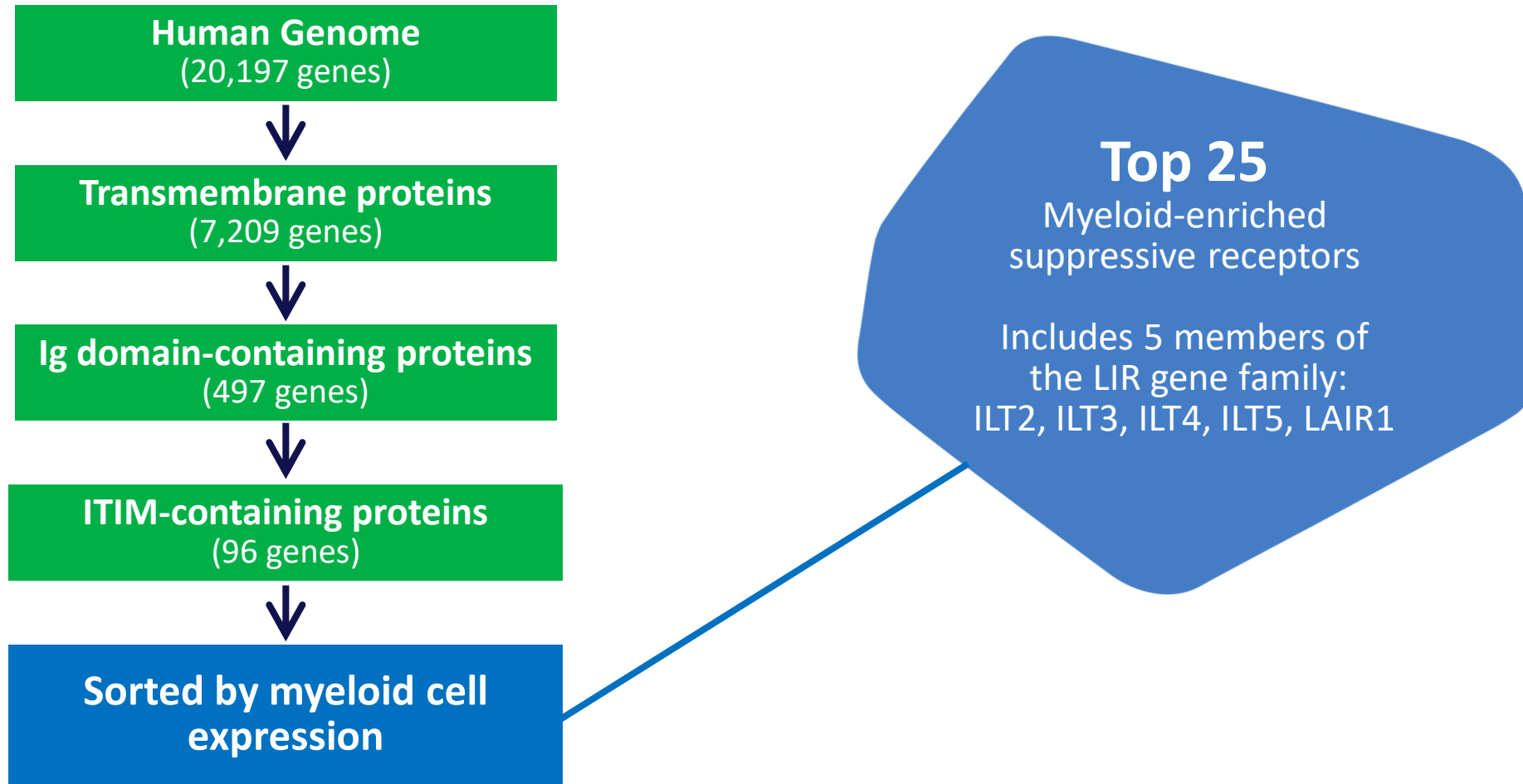
Dan Kaplan, Ph.D.

Director, Biology

James Sissons, Ph.D.

Director, Biology

Selection of LIR Family Receptors as Targets to Induce Myeloid Reprogramming

Human Genome
(20,197 genes)

↓

Transmembrane proteins
(7,209 genes)

↓

Ig domain-containing proteins
(497 genes)

↓

ITIM-containing proteins
(96 genes)

↓

Sorted by myeloid cell expression

Top 25
Myeloid-enriched suppressive receptors

Includes 5 members of the LIR gene family:
ILT2, ILT3, ILT4, ILT5, LAIR1

NGM Bio

Prioritization of LIR Family Receptors that Recognize Ligands Highly Expressed in Tumors

Inhibitory receptors of the LIR locus **evolved to mediate immune tolerance** through interactions with constitutively-expressed ligands

Leukocyte Ig-like Receptor (LIR) locus on human chromosome 19
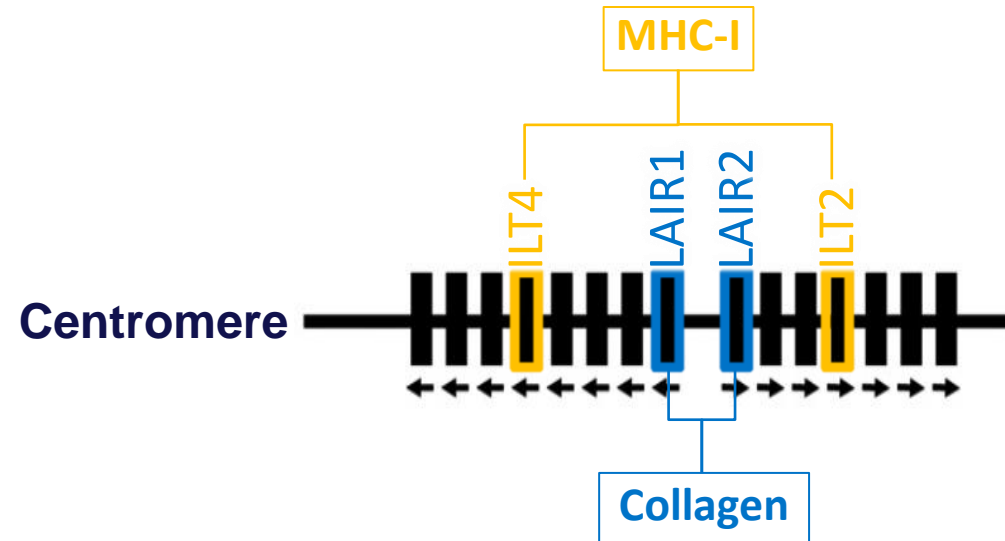
NGM707
Dual antagonist antibody targeting *both* ILT2 and ILT4

NGM438
LAIR1 antagonist antibody

NGM707 in Advanced Solid Tumors

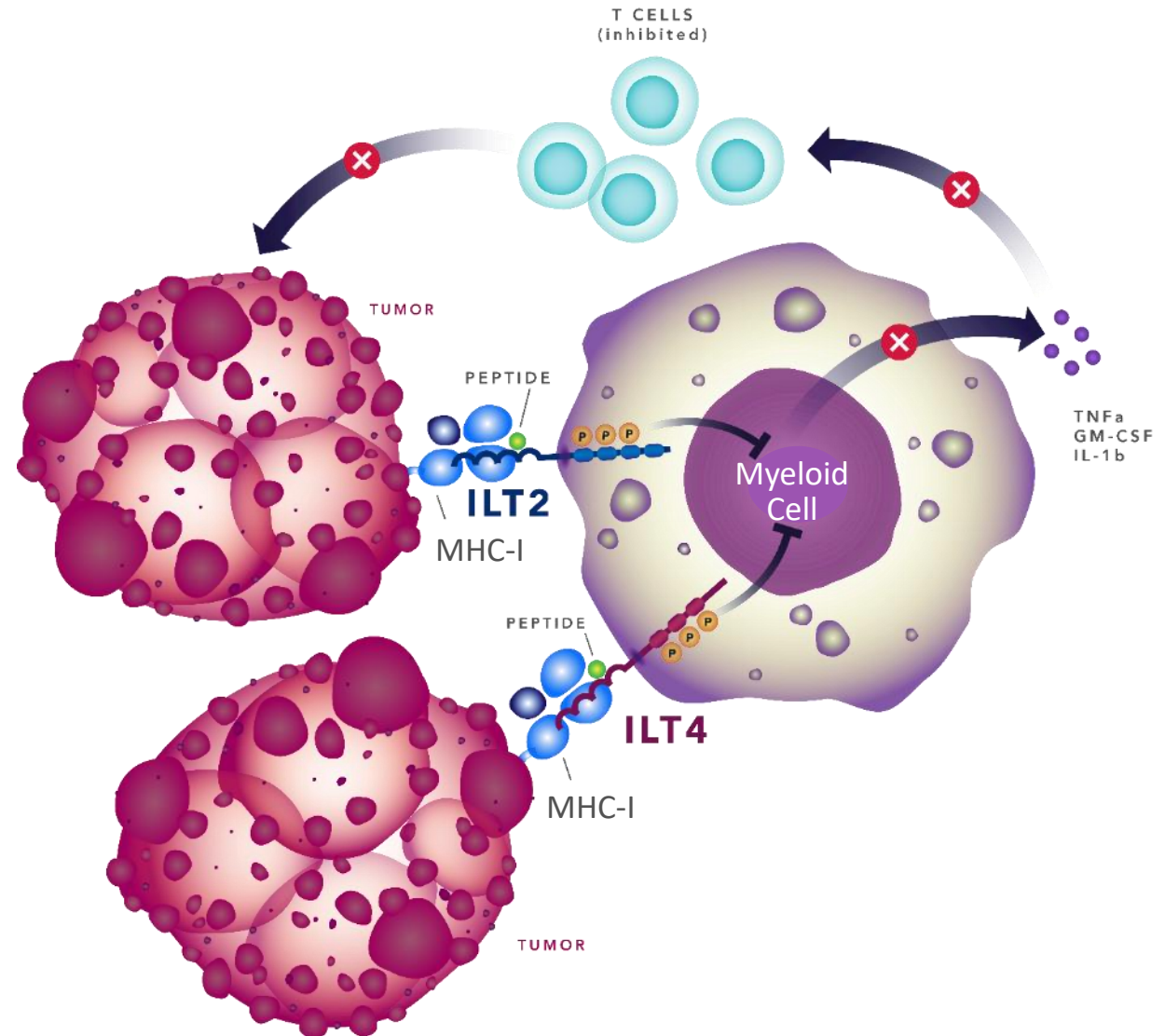# NGM707 is a Dual Antagonist Antibody Inhibiting ILT2 and ILT4

Potent, first-in-class antibody targeting the myeloid-enriched inhibitory receptors ILT2 (LILRB1) and ILT4 (LILRB2)

Potential to reprogram ILT4-expressing myeloid cells and stimulate the activity of ILT2-expressing myeloid and lymphoid cells

Preclinical studies of NGM707 suggest that:
- ILT4 blockade reverses myeloid cell immune suppression
- ILT2 blockade promotes tumor cell killing by NK and CD8+ T cells as well as tumor cell phagocytosis by macrophages
- Dual blockade of ILT2 and ILT4 acts synergistically to reverse suppression of Fc receptor signaling

Plan to initiate first-in-human study of NGM707 in mid-2021

ILT2 = Immunoglobulin-like transcript 2; ILT4 = Immunoglobulin-like transcript 4; NK = Natural killer; FC = fragment crystallizable; MHC = major histocompatibility complex; TNF = Tumor necrosis factor; IL = interleukin, GM-CSF = Granulocyte-macrophage colony-stimulating factor

ILT2 and ILT4: Key Myeloid and Lymphoid Checkpoints and Their Potential Roles in Cancer

## Upregulated in certain cancer types[1-5]

- ILT2 and ILT4 receptors are expressed on myeloid cells (APCs, MDSCs, macrophages, granulocytes) in the tumor microenvironment

- ILT2 additionally exhibits expression on natural killer (NK) cells, B cells and a subset of highly cytolytic T cells

Restrict anti-tumor immunity and promote a tolerogenic state

- By suppressing anti-tumor immune responses, ILT2 and ILT4 may enable tumors to evade immune detection

Contribute to T cell checkpoint inhibitor resistance[6]

- ILT2 and ILT4 are upregulated on macrophages in the tumor microenvironment of certain cancer patients that are non-responders to T cell checkpoint inhibitor therapy


Cancer Cells

B Cells

- ● ILT2 Expression
- ● ILT4 Expression
- ● Dual Expression

Myeloid Cells

T Cells/ NK Cells
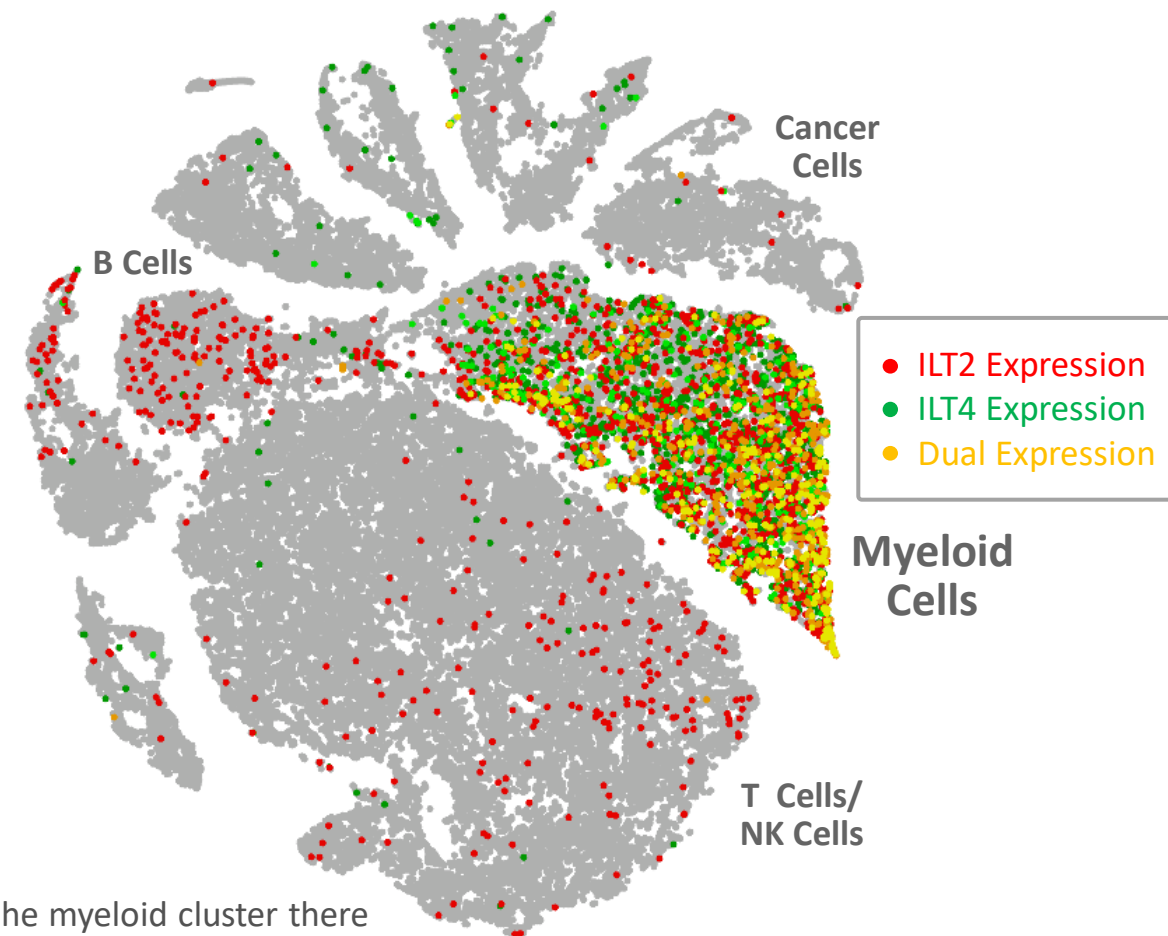
Within the myeloid cluster there are distinct subsets of cells:

ILT2+, ILT4-
ILT2-, ILT4+   *Blocking both ILT2 and ILT4 may provide further benefit*
ILT2+, ILT4+

1. Tirosh et al., Science, 2016   2. Li et al., Nat Genet, 2017   3. Puram et al., Cell, 2017   4. Azizi et al., Cell, 2018   5. Lambrechts et al., Nat Med, 2018   6. Sade-Feldman et al., Cell, 2018
TAM = Tumor-associated Macrophage; APC = Antigen-presenting Cell; MDSC = Myeloid-derived Suppressor Cell

ILT2 and ILT4 May Represent Resistance Mechanisms to T Cell Checkpoint Inhibitors

ILT2 and ILT4 are upregulated in melanoma on macrophages of T cell checkpoint inhibitor non-responders[1]
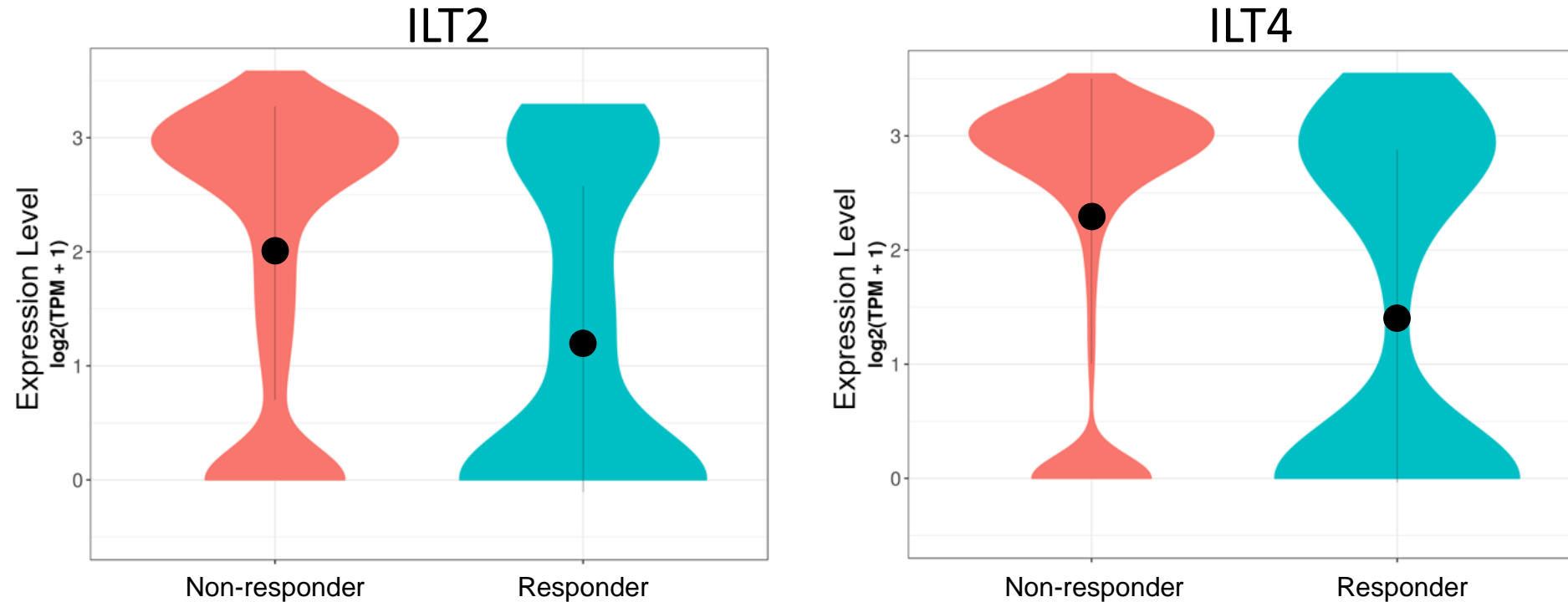
GSE120575 – scRNAseq analysis 48 tumors treated with:

- Anti-PD1 (n=35)
- Anti-PD1+Anti-CTLA4 (n=11)
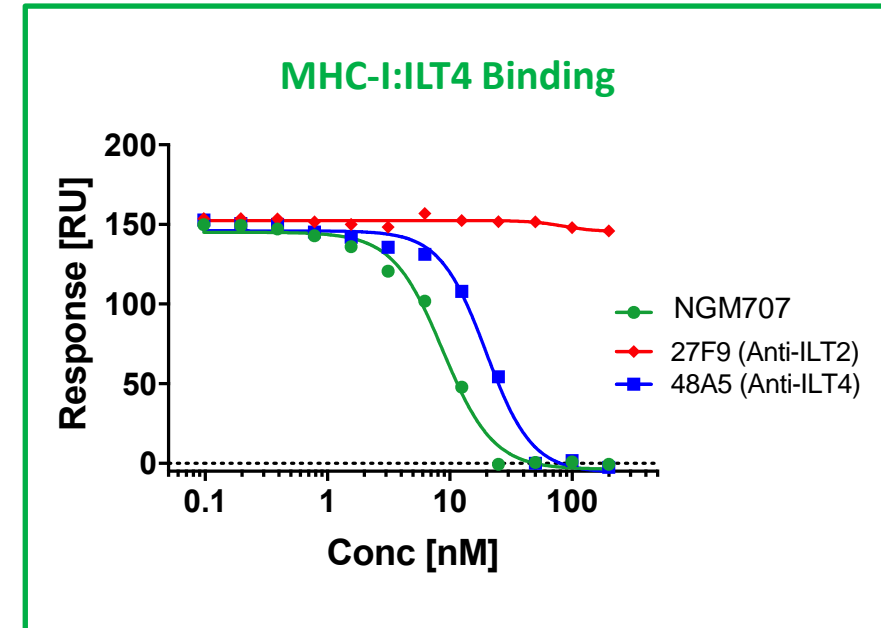- Anti-CTLA4 (n=2)
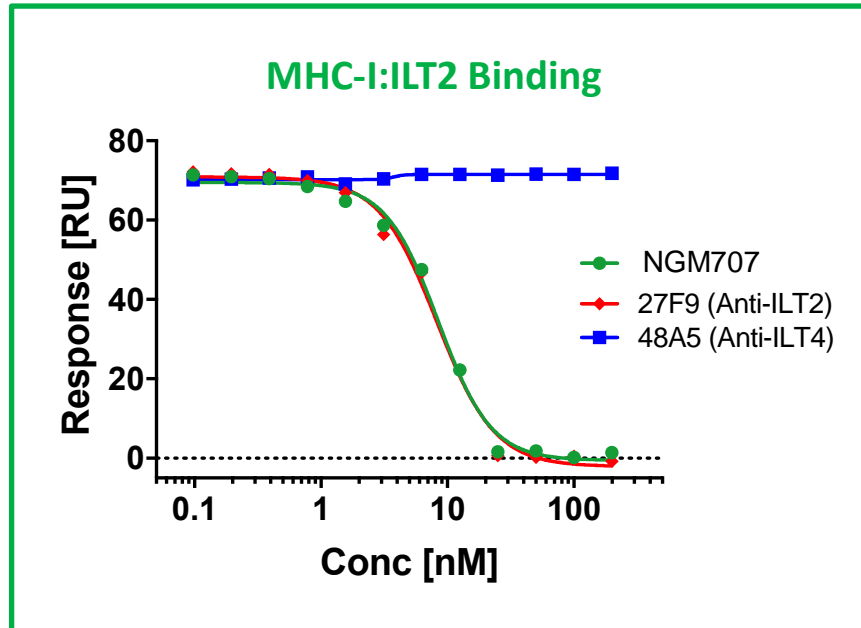
17 responders, 31 non-responders

cluster
- Non-responder
- Responder

NGM707 Molecular Pharmacology

# NGM707 is a Potent Inhibitor of Both ILT2 and ILT4 Interactions with MHC-I

Complete and potent inhibition of MHC-I:ILT2 and MHC-I:ILT4 interactions in Biacore-based binding assays

MHC-I:ILT2 Binding
- NGM707
- 27F9 (Anti-ILT2)
- 48A5 (Anti-ILT4)

MHC-I:ILT4 Binding
- NGM707
- 27F9 (Anti-ILT2)
- 48A5 (Anti-ILT4)

ILT4 Blockade Reprograms Tumor-conditioned Myeloid-derived Suppressor Cells (MDSC)

## ILT4 antagonism enhances T cell activity and proliferation
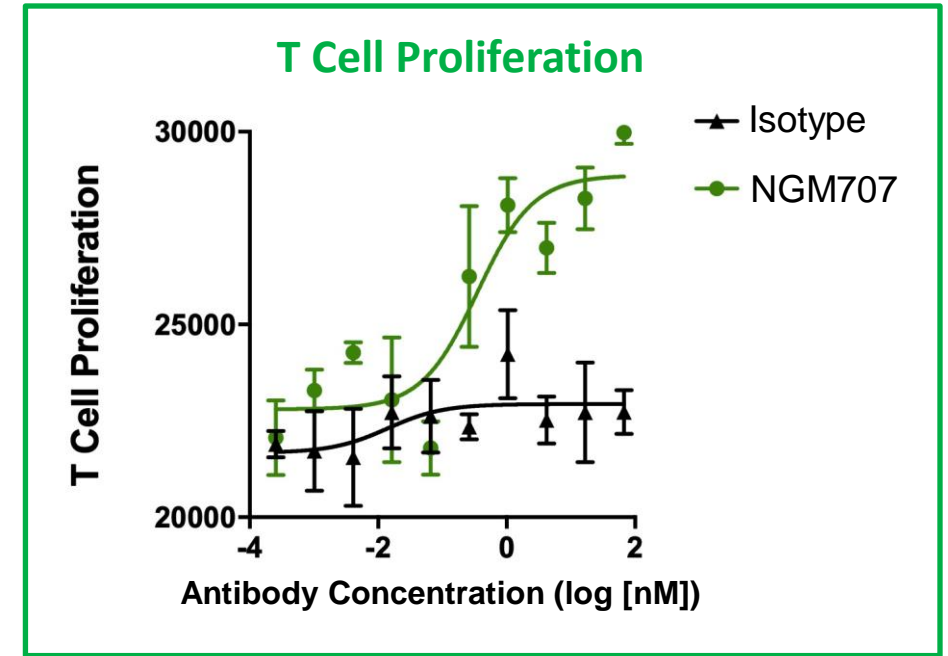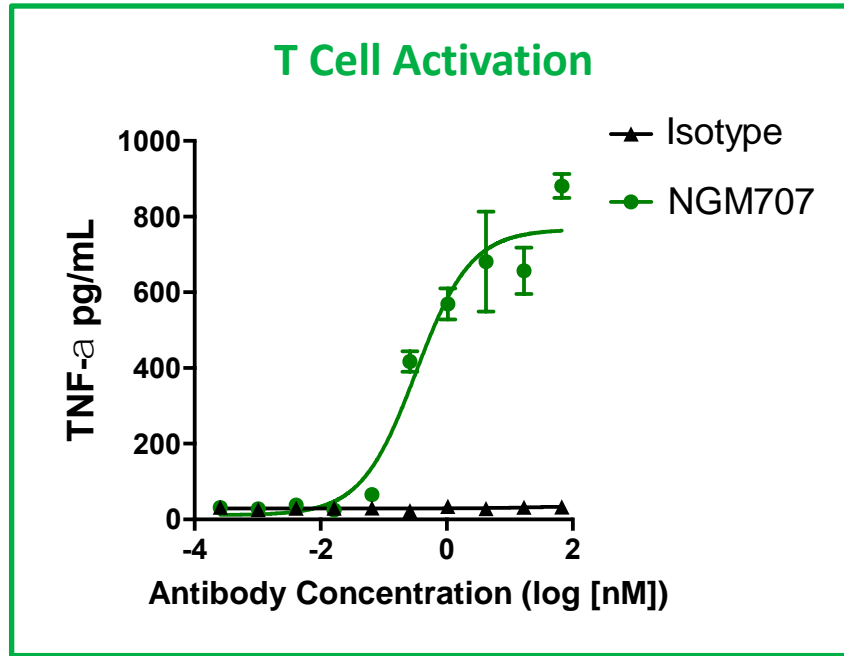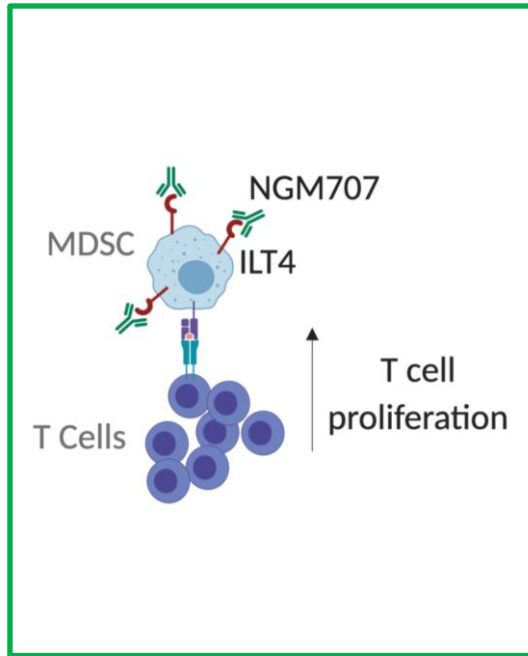
MDSC generated from monocytes using cancer cell-conditioned media (OVISE cells)
MLR performed by mixing MDSC with allogeneic T cells

MDSC = Myeloid-derived Suppressor Cells; OVISE = Ovarian Clear Cell Carcinoma; MLR = Mixed Lymphocyte Reaction; TNF = Tumor Necrosis Factor; CPM = 3H-thymidine Counts Per Minute

ILT2 Blockade Enhances Macrophage Phagocytosis of Tumor Cells

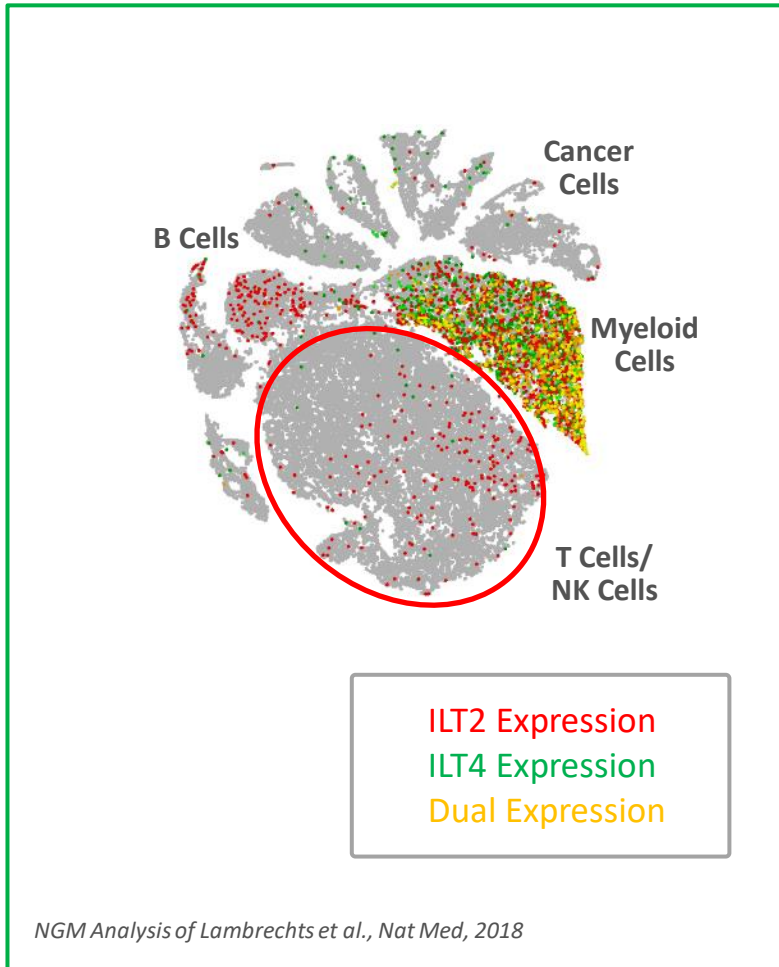- **Increased macrophage phagocytosis of cancer cells with ILT2 blockade**
  - Macrophage phagocytosis may increase tumor killing and potentially drive antigen spread
  - Activity is specific to ILT2/MHC-I interaction despite ILT4 co-expression on macrophages

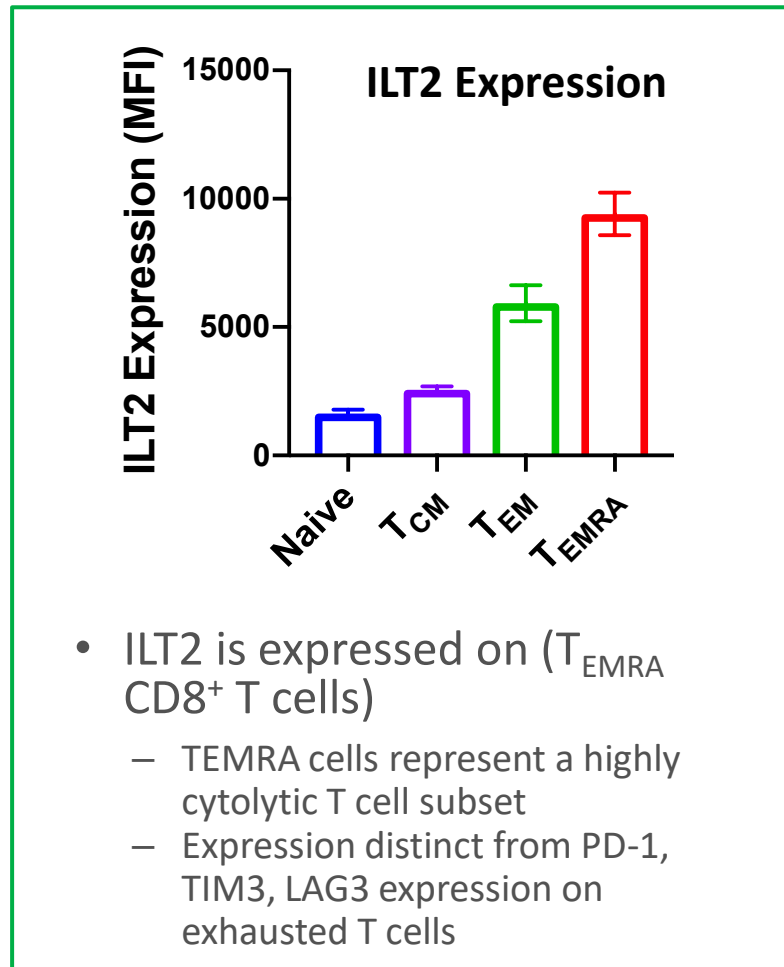## Macrophage Phagocytosis of Tumor Cells
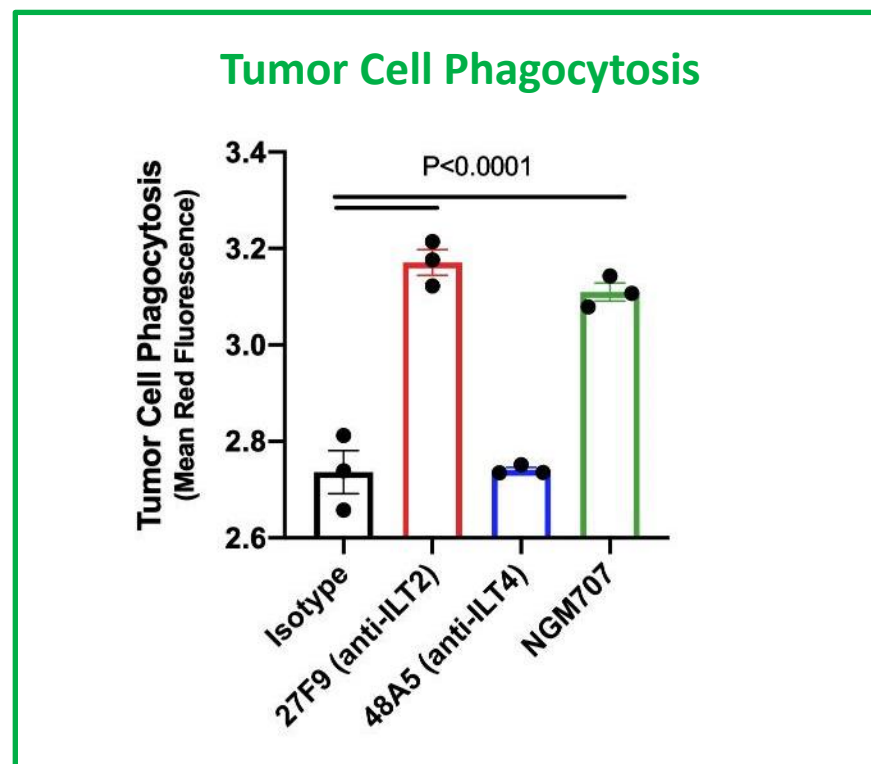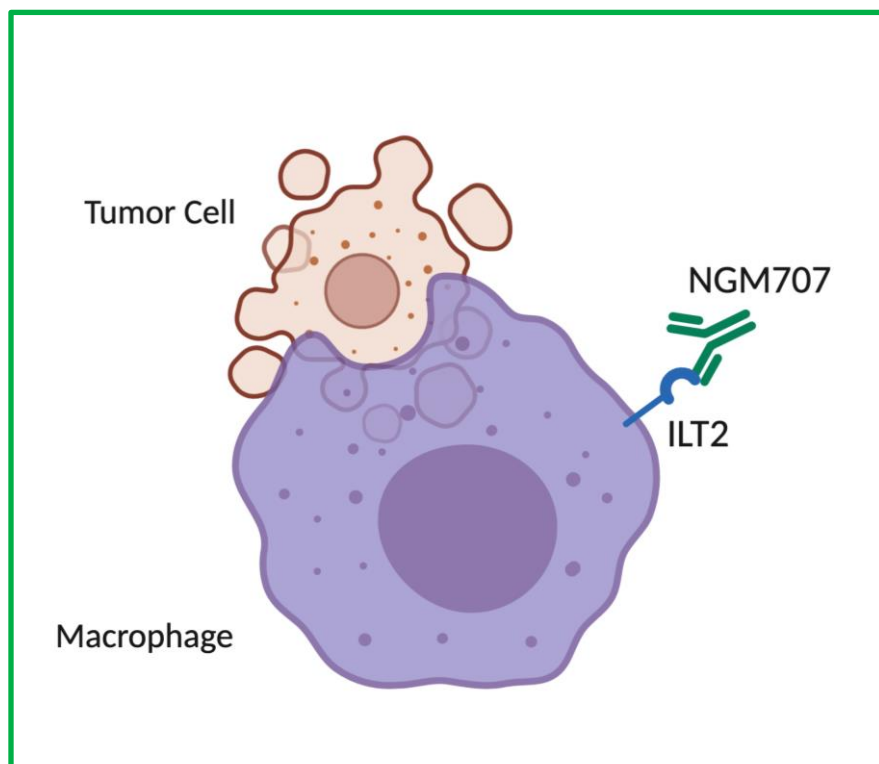
ILT2 Blockade Enhances CD8+ T Cell Cytolytic Activity

Intra-tumoral ILT2 Expression on CD8+ T cells and NK cells (NSCLC)
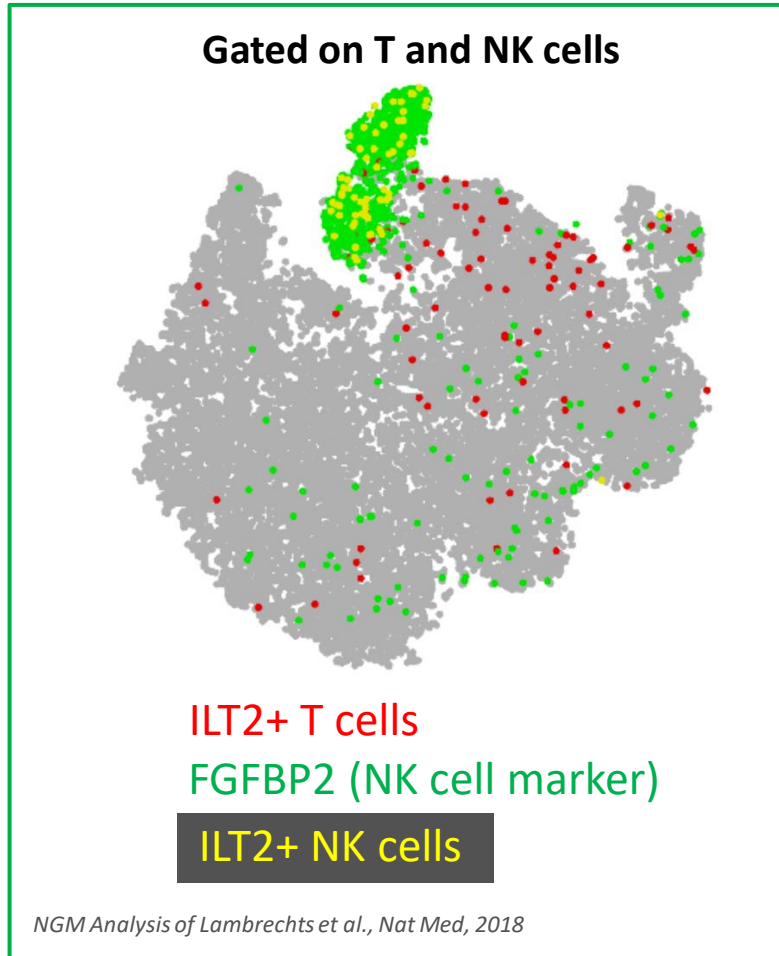

- ILT2 Expression (red)
- ILT4 Expression (green)
- Dual Expression (yellow)

Labels: Cancer Cells, B Cells, Myeloid Cells, T Cells/NK Cells

NGM Analysis of Lambrechts et al., Nat Med, 2018

ILT2+ expression on CD8+ TEMRA T-cells

ILT2 Expression

x-axis: Naive, T_{CM}, T_{EM}, T_{EMRA}
y-axis: ILT2 Expression (MFI), 0–15000

- ILT2 is expressed on (T_{EMRA} CD8$^+$ T cells)
  - TEMRA cells represent a highly cytolytic T cell subset
  - Expression distinct from PD-1, TIM3, LAG3 expression on exhausted T cells

NGM707 enhanced CD8+ T cell cytolytic activity against a tumor B cell line expressing HLA-G

P<0.05

x-axis: Isotype, 27F9 (anti-ILT2), 48A5 (anti-ILT4), NGM707
y-axis: Tumor Killing (%), 35–55
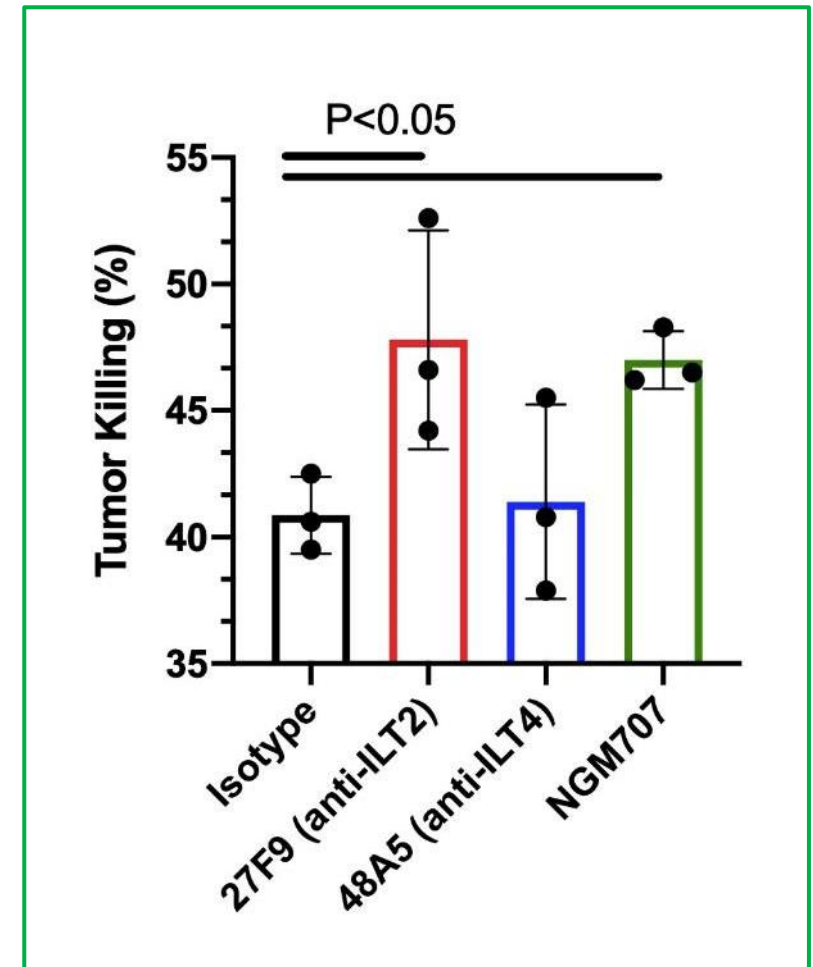
ILT2 Blockade Enhances Primary NK Cell Killing Activity

ILT2 expression on T and NK cells in NSCLC

Gated on T and NK cells

ILT2+ T cells
FGFBP2 (NK cell marker)
ILT2+ NK cells

NGM Analysis of Lambrechts et al., Nat Med, 2018

NGM707 enhances primary NK cell tumor killing activity
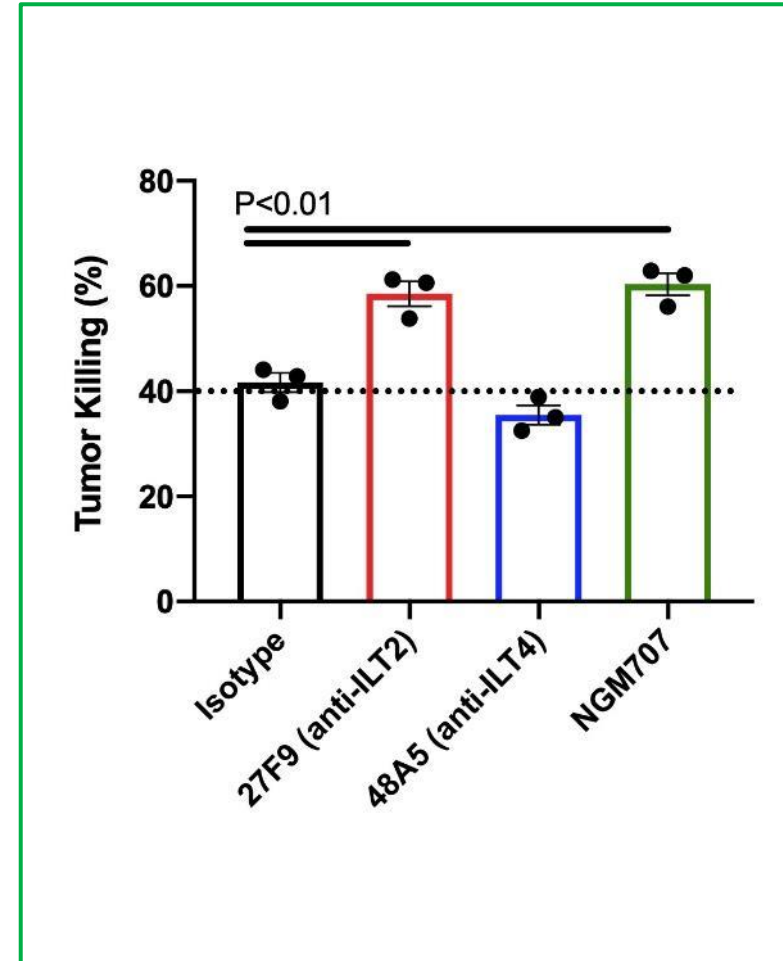
# ILT2 and ILT4 Blockade Act Additively to Enhance Myeloid Cell Activation

- **Fc receptors represent key stimulatory receptors on myeloid cells**
  - Inhibition of Fc receptor signaling by ILT2 and ILT4 promotes a suppressive myeloid cell phenotype

- **Dual blockade of ILT2 and ILT4 strongly potentiates Fc receptor signaling**
  - Blockade of ILT2 or ILT4 alone leads to a modest increase in Fc receptor signaling
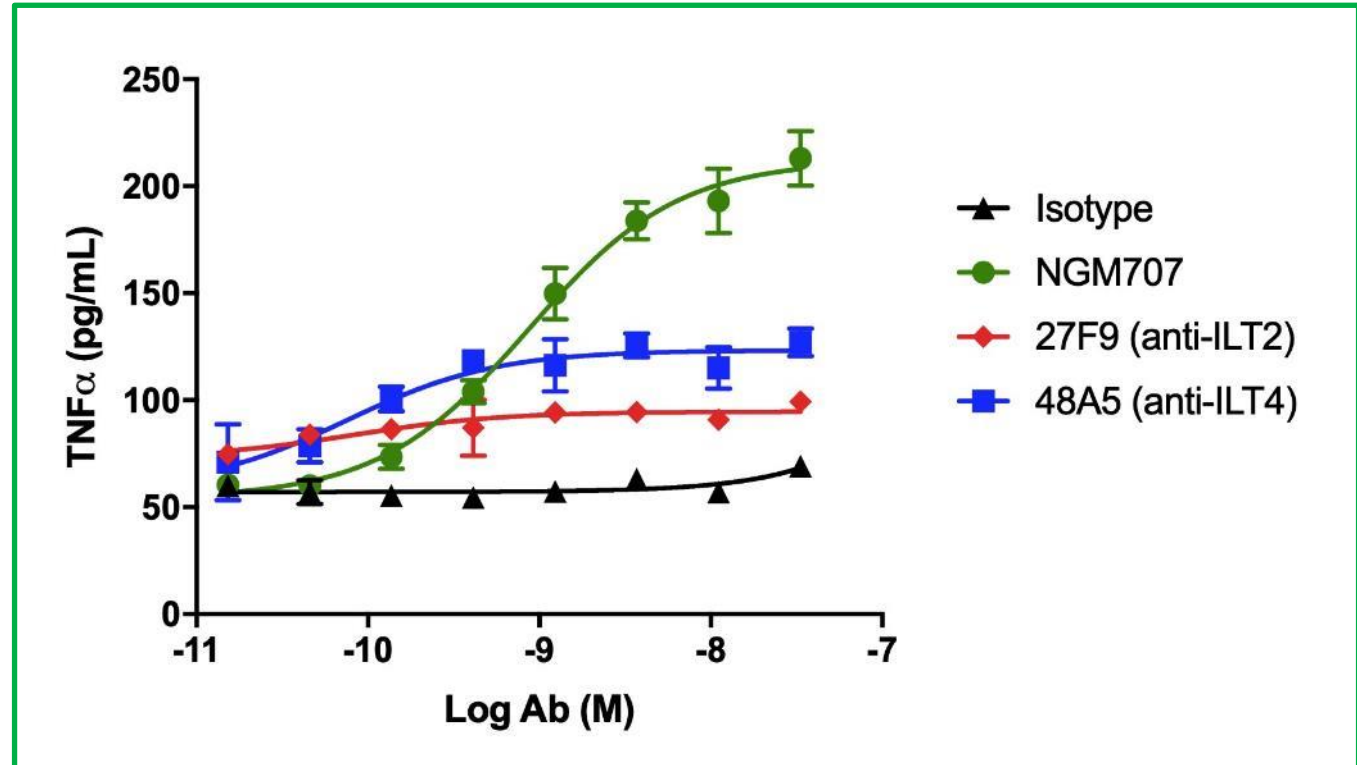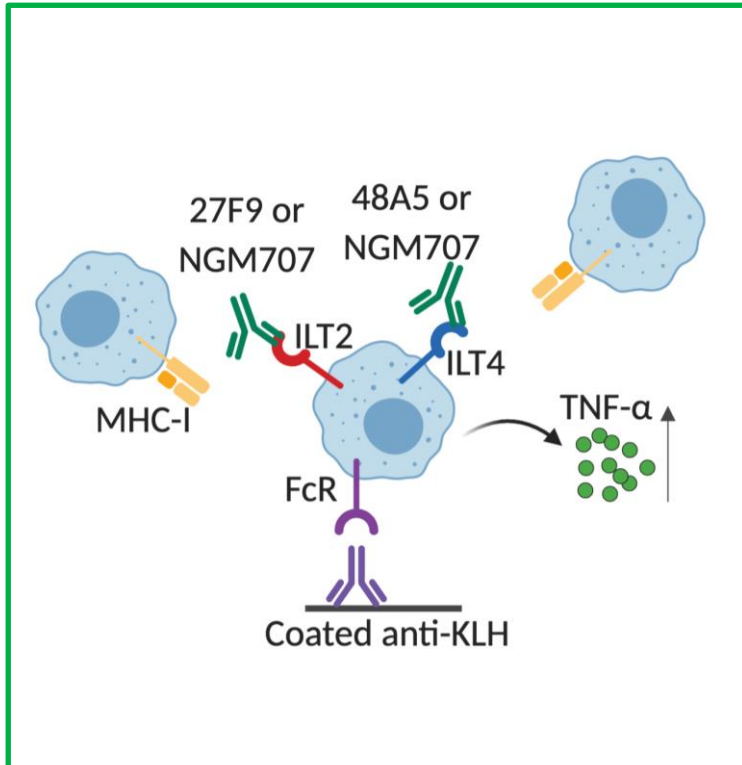
NGM707 and Pembrolizumab Act Additively to Enhance T Cell Activation in a Mixed Lymphocyte Reaction

- NGM707 or pembrolizumab alone **modestly** enhance T cell activation and increase in cytokine secretion (IFNg, IL-2, TNFa, GM-CSF)
- Combination of NGM707 and pembrolizumab leads to an **additive** increase in T cell activation and cytokine secretion
- Monocytes from two individuals differentiated into macrophages and tested in mixed lymphocyte reactions with T cells from 12 individuals
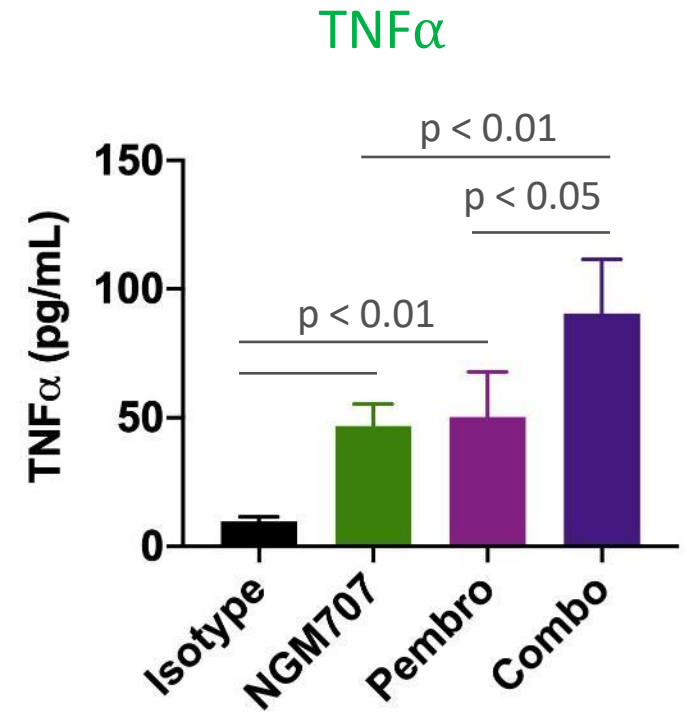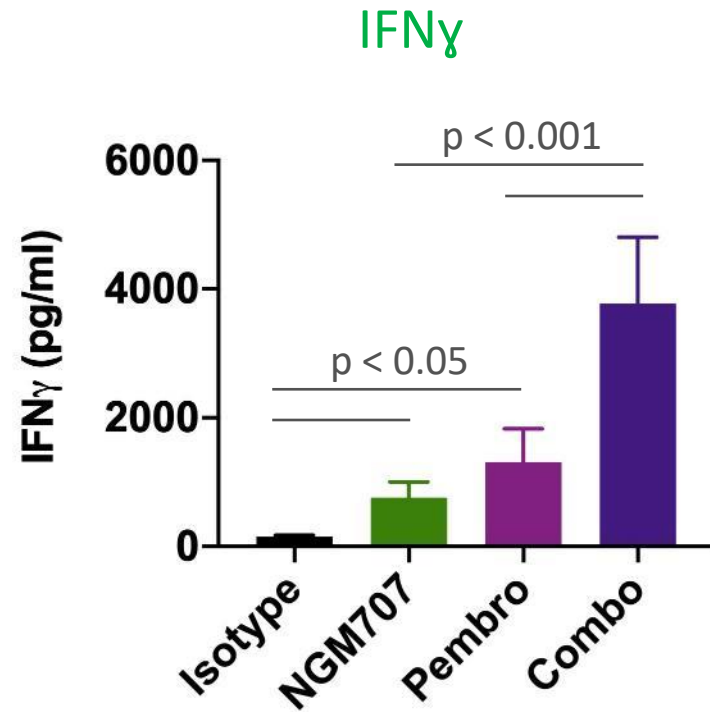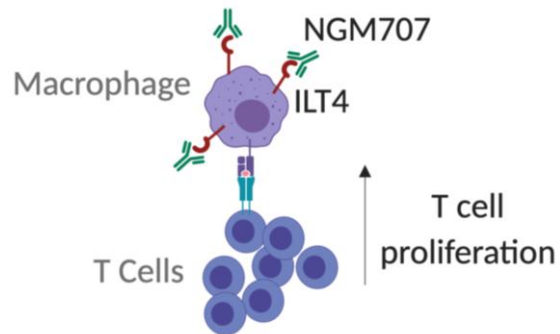
NGM707 is a Dual Antagonist Antibody Inhibiting ILT2 and ILT4

Preclinical studies suggest that NGM707 may:

1. Reprogram tumor-conditioned myeloid-derived suppressor cells to a stimulatory phenotype

2. Enhance macrophage phagocytosis

3. Enhance CD8+ T cell cytolytic activity

4. Enhance primary NK cell killing activity

5. Suppress Fc receptor signaling

6. Act additively with pembrolizumab to enhance T cell activation

➢ **Plan to initiate first-in-human study of NGM707 in mid-2021**

HLA-G = Human Leukocyte antigen-G
ILT2 = Immunoglobulin-like transcript 2; ILT4 = Immunoglobulin-like transcript 4; NK = natural killer; FC = fragment crystallizable; MHC = major histocompatibility complex; TNF = Tumor necrosis factor; IL= interleukin
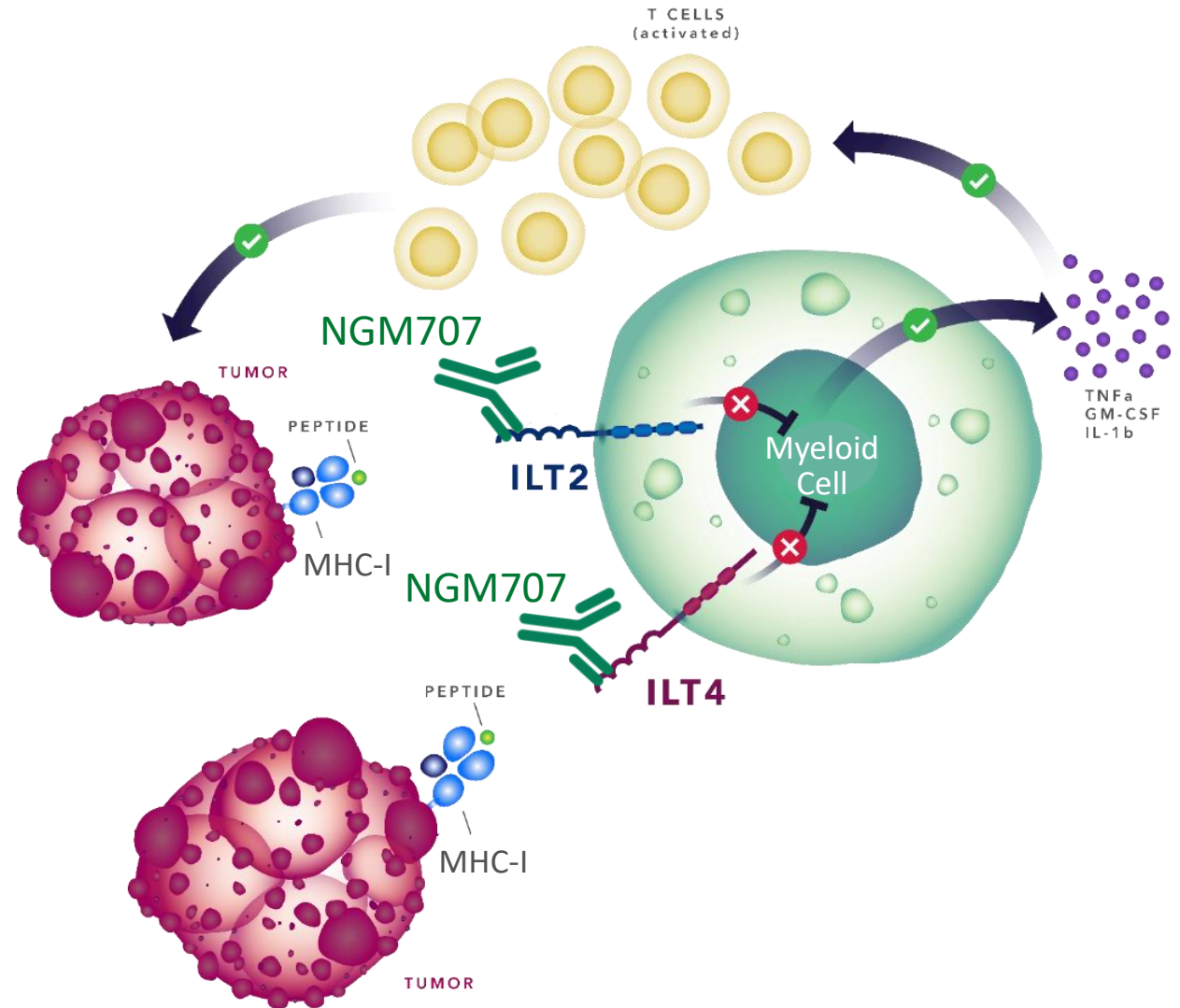
NGM438 in Advanced Solid Tumors

NGM438 is an Antagonist Antibody Inhibiting LAIR1

Potent, first-in-class antibody targeting the myeloid-enriched inhibitory receptor LAIR1

Potential to reprogram LAIR1-expressing suppressive myeloid cells within the tumor via disruption of Collagen-LAIR1 mediated immune cell signaling

Preclinical studies suggest that NGM438 may:
1. Reverse collagen mediated suppression of myeloid cells to a stimulatory phenotype
2. Stimulate inflammatory cytokine production in myeloid and T cells
3. Reprogram collagen suppressed myeloid cells to stimulate T cell activation
4. Enhance cellular proliferation of collagen suppressed T cells

Plan to initiate first-in-human study of NGM438 in 4Q21

LAIR1 = Leukocyte-associated immunoglobulin-like receptor 1
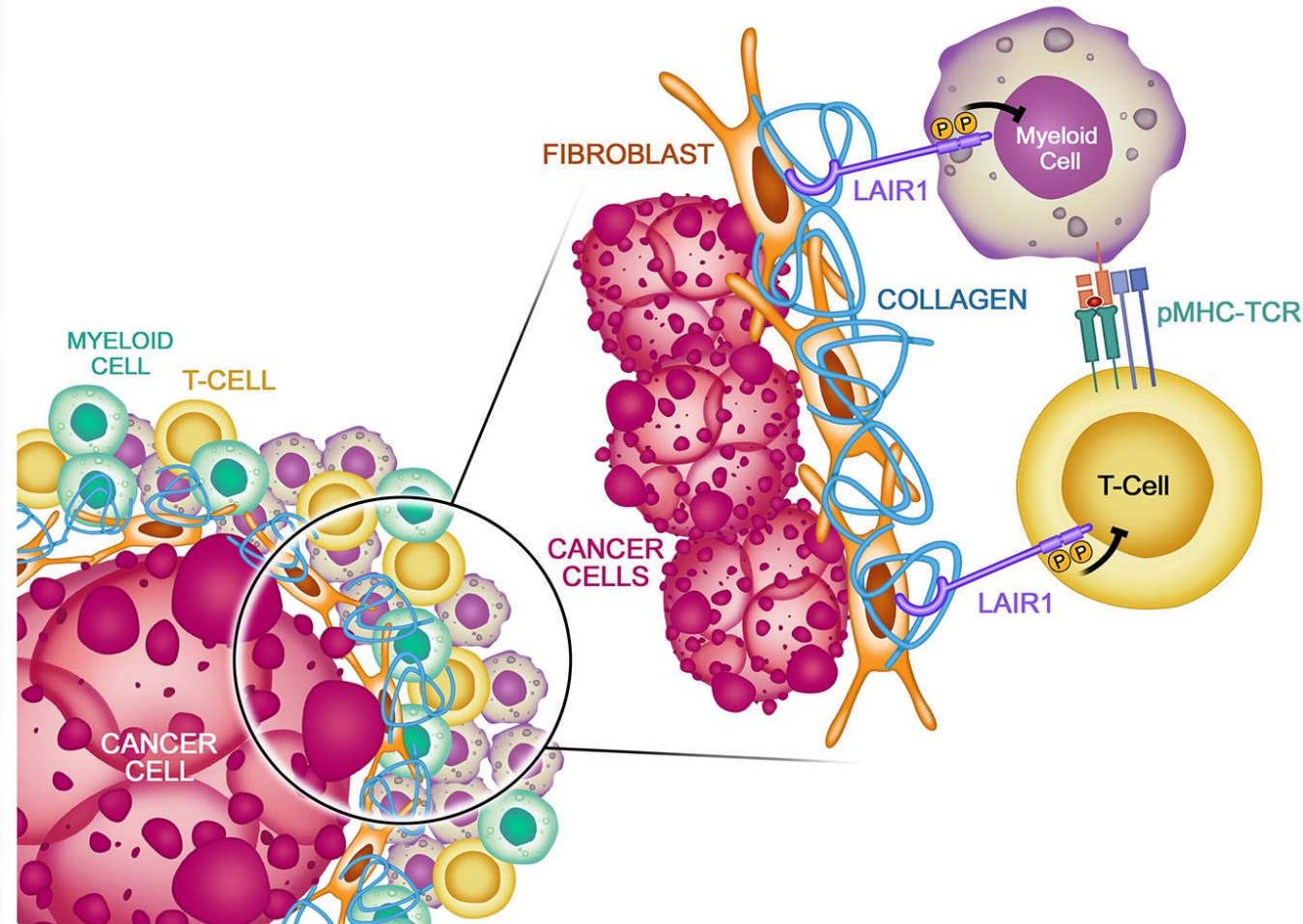
LAIR1: Key Stromal Checkpoint and its Potential Roles in Cancer
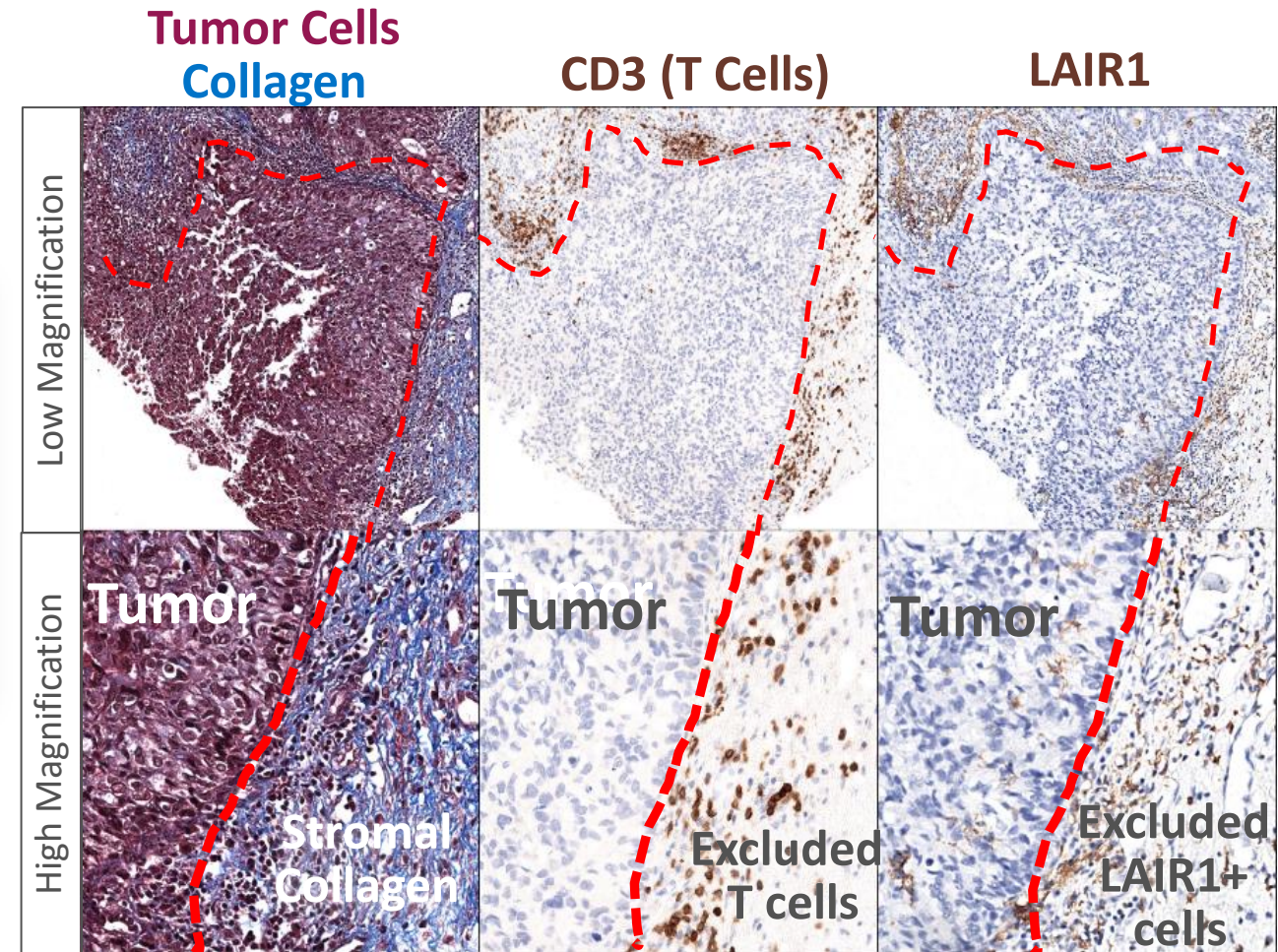
LAIR1 is a collagen-binding inhibitory signaling receptor expressed on immune cells: T cells, B cells, NK cells and myeloid cells[1-2]

LAIR1 and Collagens are upregulated in certain cancer types[3-7] and impose signal-based immune suppression[8-9]

- Collagens act as a stromal checkpoint to physically impede anti-tumor immunity
- Co-localization of LAIR1-expressing immune cells and stromal collagen may impose signaling-based immune suppression

Stromal derived factors, such as Collagen expression, and LAIR1-expressing myeloid cells are associated with poor responses to checkpoint inhibitors

LAIR1-Expressing Immune Cells in Pancreatic Tumor

Pancreatic ductal adenocarcinoma tumor section

1. Meyaard, Immunity, 1997; 2. Guo, Trans Med, 2020, 3. Cao, 2015, Biochem Biophys Res Commun; 4. Wang, Exp Ther Med, 2016; 5. Wu, CP Cancer, 2018; 6. Yang, Head & Neck, 2018 7. Jingushi, Onc. Reports, 2018; 8. Peng, Nat Comm, 2020; 9. Lijun, Oncoimmunology, 2020

# LAIR1-Expressing Myeloid Cells are Present in Many Human Tumors
LAIR1 Expression is Elevated in Myeloid Cells in Checkpoint Inhibitor Non-Responders

LAIR1 RNA Enriched in Myeloid Cells and Lymphoid Cells In NSCLC

Alveolar
Endothelial
Epithelial
Cancer
Cancer
B Cells
Myeloid
Fibroblasts
T/NK Cells

LAIR1
RNA Transcripts
0.04   *≥5*
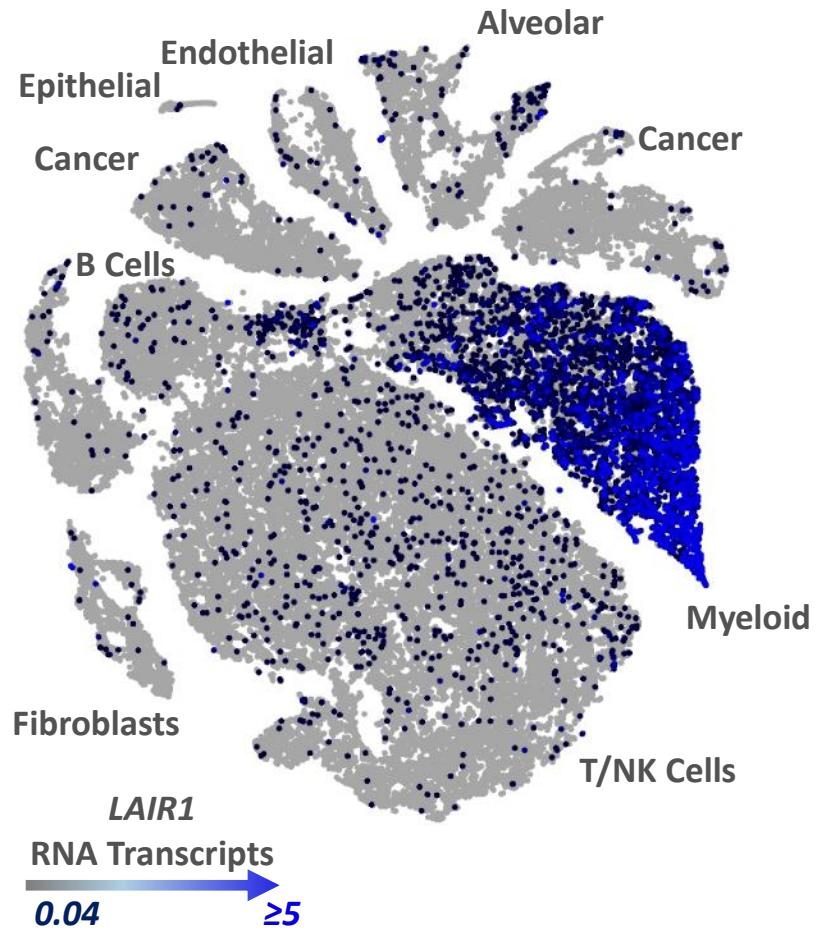
Lambrechts et al., Nat Med, 2018

LAIR1 Expression is Elevated in Macrophages in Checkpoint Inhibitor (CPI) Non-Responders in Metastatic Melanoma

Macrophages

LAIR1 Transcripts Log2(TPM+1)

Non-Responders   **Responders**

LAIR1(%)   65%   29.2%
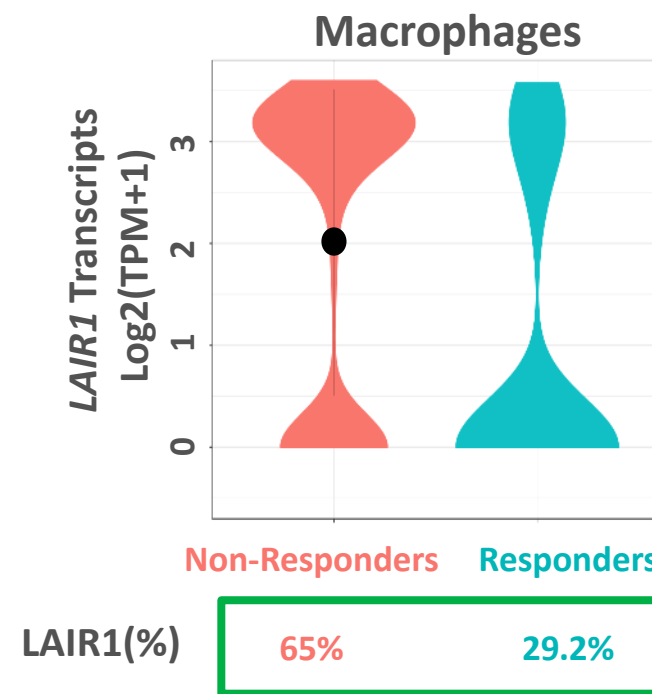
Tumor samples categorized by RECIST/radiological assessment:
35 anti-PD-1, 11 anti-CTLA4+PD-1, 2 anti-CTLA4
Sage-Feldman, *et al.*, 2019

- LAIR1 may represent a novel myeloid checkpoint in checkpoint inhibitor non-responders

- LAIR1 may represent a resistance mechanism to checkpoint inhibitor therapies

NGM438 Molecular Pharmacology

NGM438 is an Antagonist of LAIR1-Collagen Signaling

LAIR1 Reporter Cell Activity Blocking Assay

IC_{50} (M)	NGM438
Collagen 1	3.2×10^{-11}
Collagen 4	3.2×10^{-11}
Tumor Cell Collagens	1.6×10^{-11}
Polymerized Collagen Matrix	3.0×10^{-11}

LAIR1 Reporter cells were incubated on plates coated with ligands with soluble antagonists in the media

Collagen 1

Collagen 4

NGM438
Isotype
control mAb

Tumor Cell Collagens

Polymerized Collagen Matrix

NGM438 Reverses Collagen-Mediated Suppression and Induces Reprogramming in Myeloid Antigen Presenting Cells
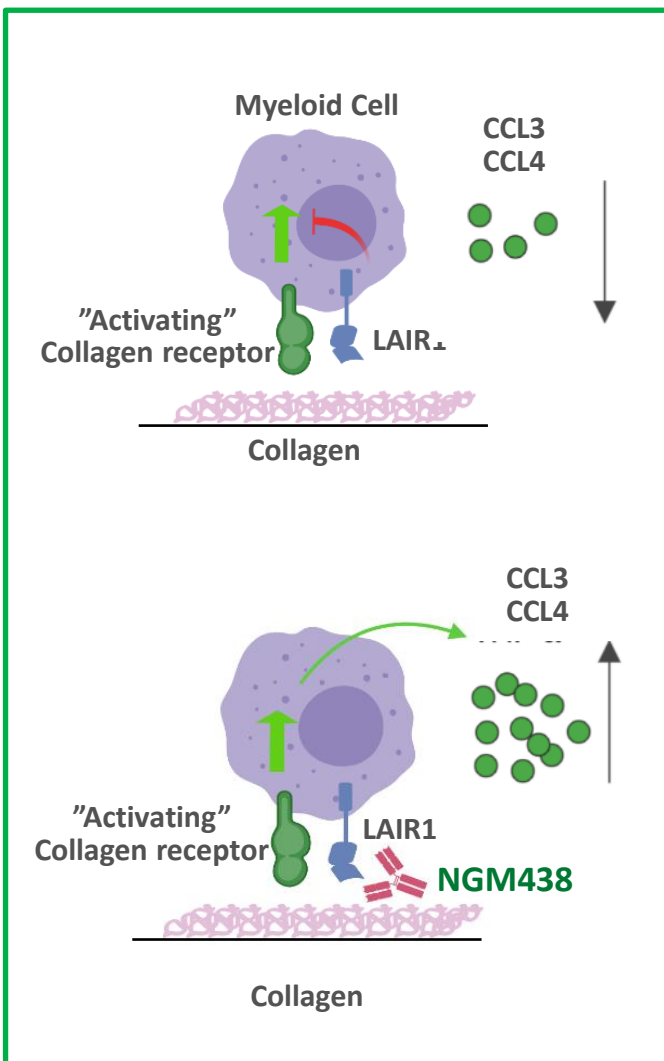
- **Collagen receptors, such as integrins, represent key stimulatory receptors on myeloid cells**
  - Inhibition of activating receptors via Collagen-LAIR1 signaling promotes a suppressive myeloid cell phenotype
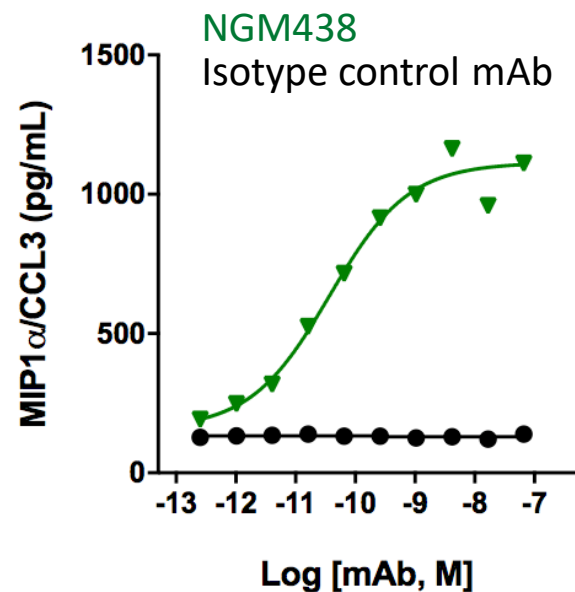- **NGM438 blockade of LAIR1-Collagen binding reprograms myeloid cells to be pro-inflammatory**
  - Blockade of Collagen-LAIR1 leads to a potent increase in inflammatory cytokines, including CCL3 and CCL4 that are involved in recruiting lymphocytes to areas of inflammation

CCL3 production

NGM438
Isotype control mAb

CCL4 production
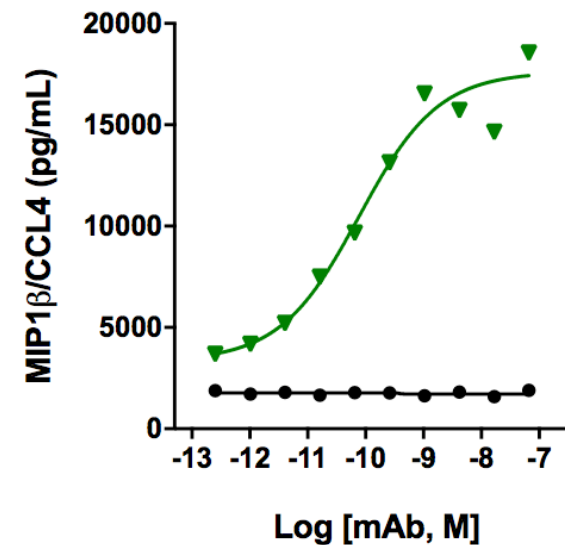
LAIR1 Blockade Reverses Suppression of Myeloid Cells by Collagen Leading to Enhanced T Cell Proliferation

T Cell Proliferation (MLR) is Suppressed by Collagen

NGM438 Reverses T Cell Proliferation Suppression in a Dose-Dependent Manner
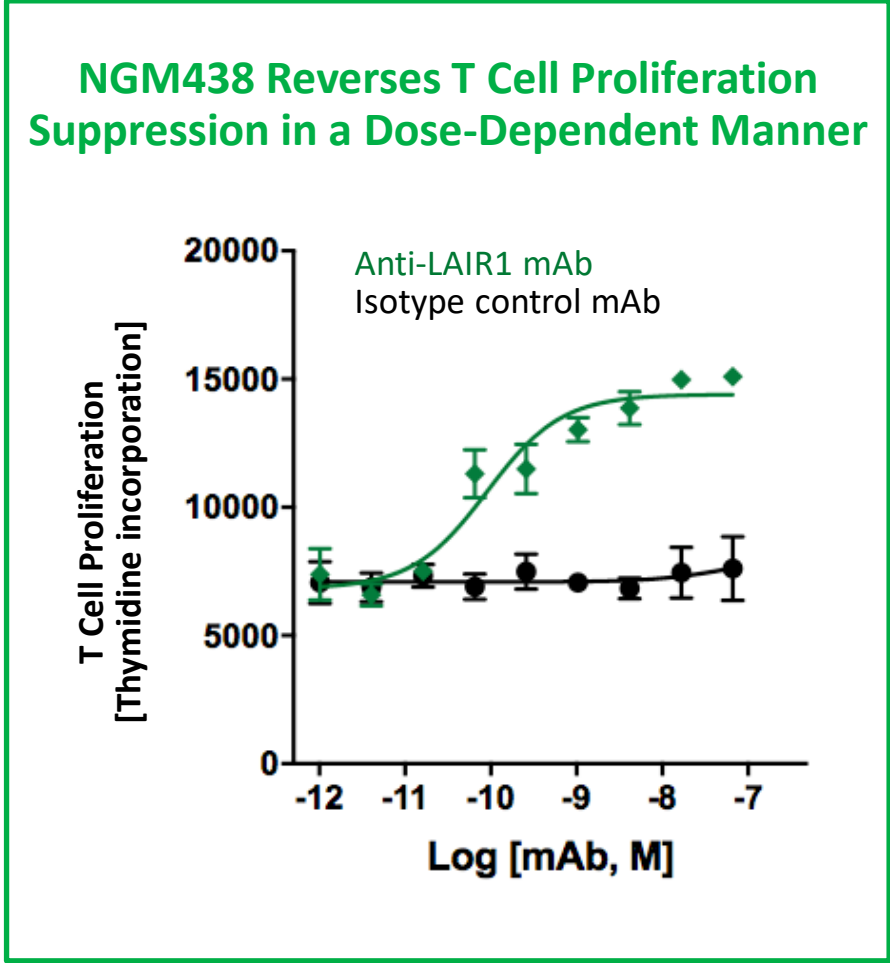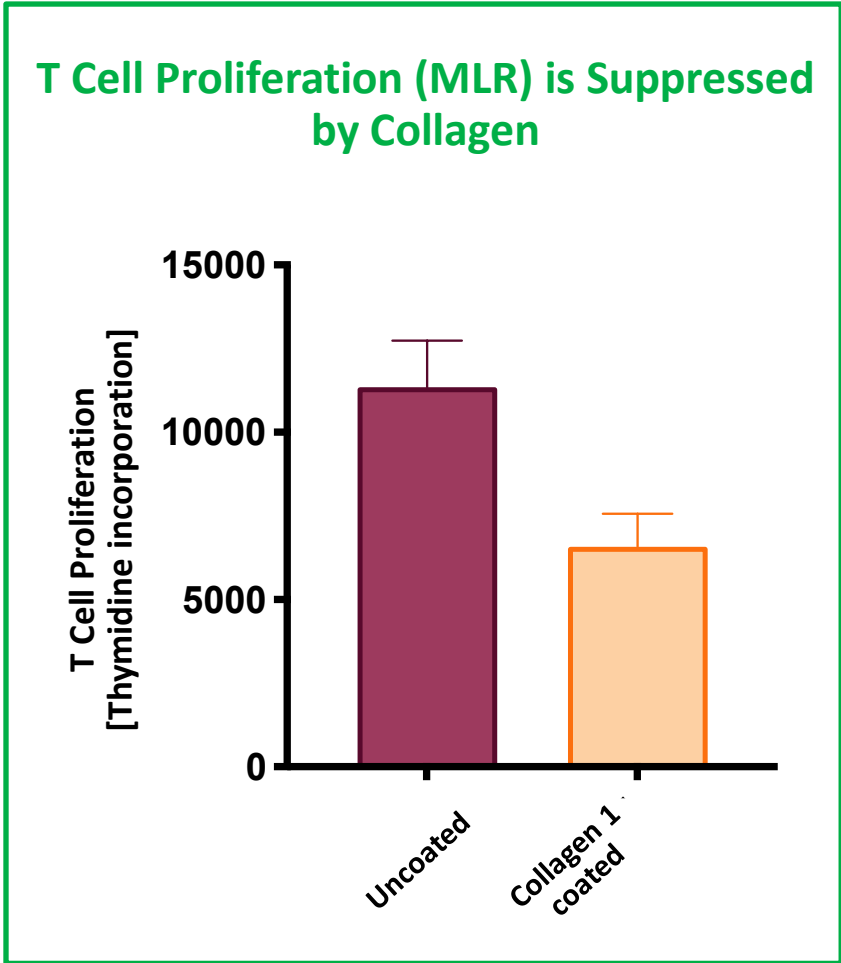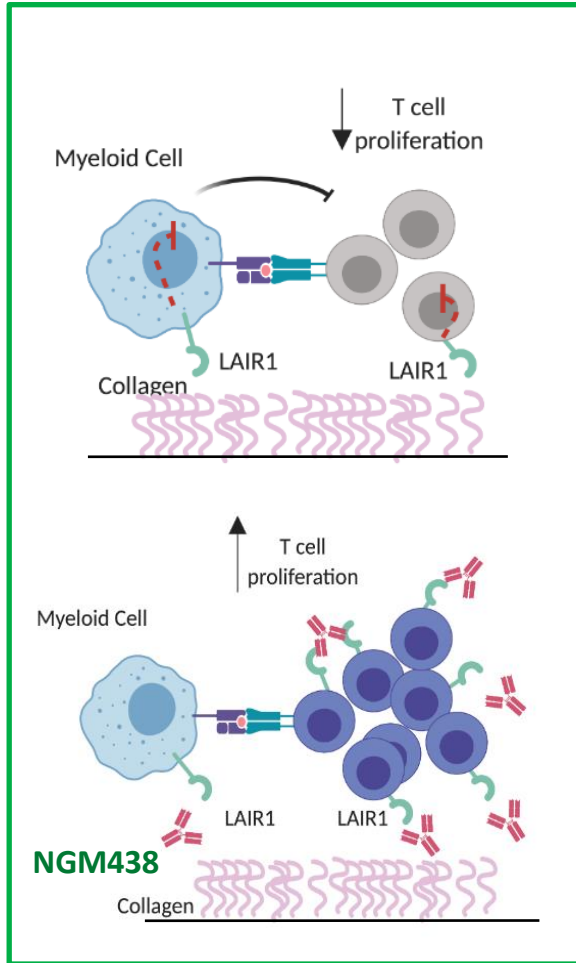
donor-mismatched monocyte-derived dendritic cells and T cells were incubated on plates coated with human collagen type 1 with soluble antagonists in the media

MLR = Mixed Lymphocyte Reaction

NGM438 Enhances Inflammatory Cytokine Secretion and T Cell Proliferation in Collagen-suppressed T Cells

Collagen-Suppressed T cell Assay

T Cell

Collagen-LAIR1 signaling inhibition

LAIR1

collagen

Anti-CD3 mAb

T Cell

IL-2 IFNγ

LAIR1

Cellular proliferation

NGM438

collagen

Anti-CD3 mAb
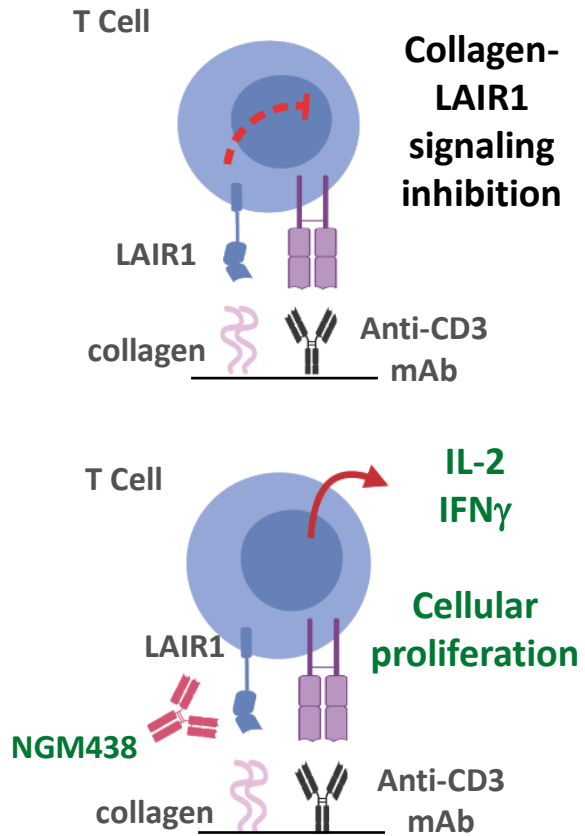
NGM438 Promotes Th1 Cytokine Production

NGM438
Isotype control mAb
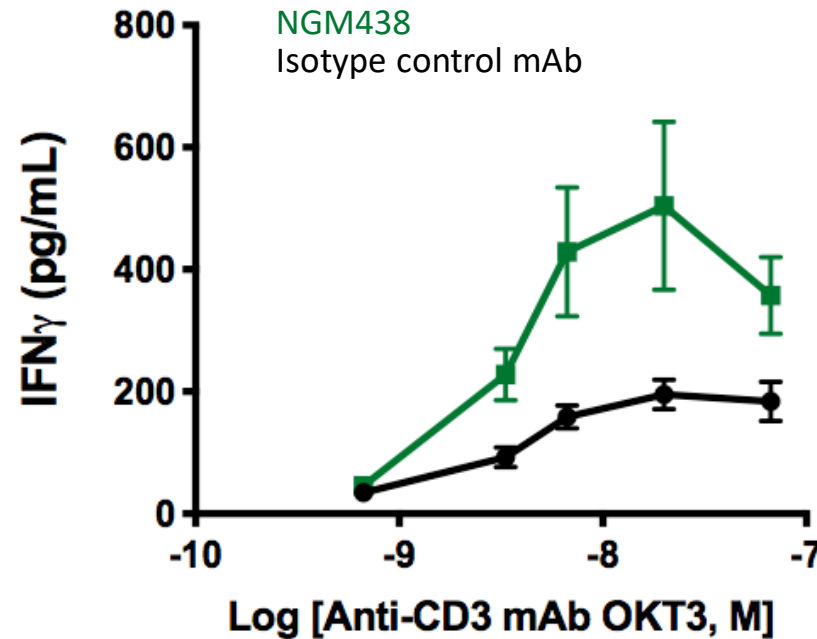
NGM438 Enhances T Cell Proliferation *in vitro*

Human T cells incubated on plates coated with collagen and range of anti-CD3 stimulating mAb with single concentration of soluble antagonist mAbs in the media
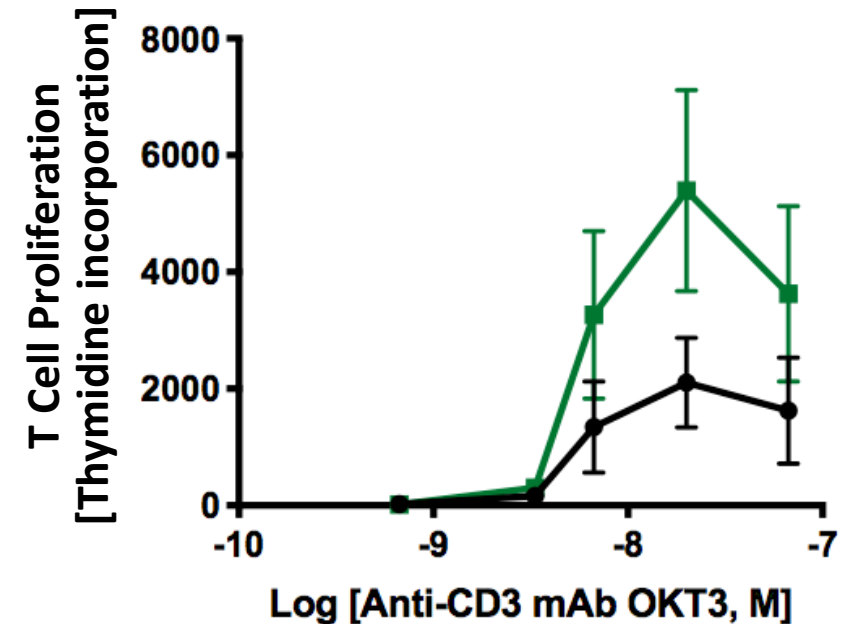
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1. Reverse collagen mediated suppression of myeloid cells to a stimulatory phenotype
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➤ **Plan to initiate first-in-human study of NGM438 in 4Q21**

FcR = fragment crystallizable Receptor

LAIR1 = Leukocyte-associated immunoglobulin-like receptor 1, ECM = Extracellular Matrix
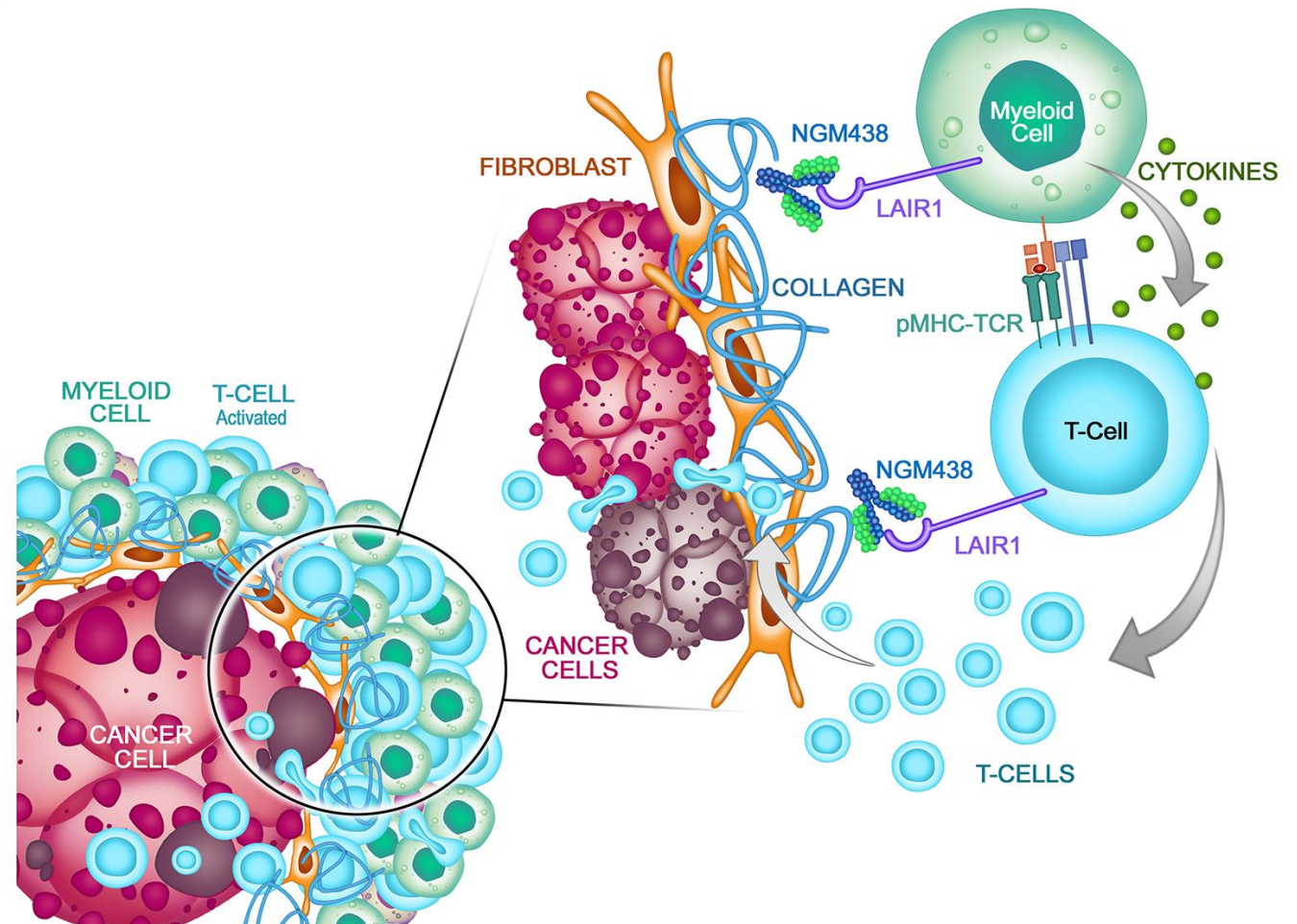
Q&A

Alex DePaoli, M.D.
SVP and Chief Translational
Officer, NGM

Daniel Kaplan, Ph.D.
Director, Biology, NGM

James Sissons, Ph.D.
Director, Biology, NGM

Daniel Von Hoff, MD, F.A.C.P.
Distinguished Professor,
The Translational Genomics
Research Institute

Robert Schreiber, Ph.D.
Distinguished Professor, Pathology &
Immunology, Washington University
School of Medicine

David Woodhouse, Ph.D.
Chief Executive Officer, NGM

NGM621 for Geographic Atrophy Secondary to Age-Related Macular Degeneration (AMD)

Erin Henry, Ph.D.
Head of Ophthalmology

Geographic Atrophy is a Leading Cause of Blindness with no Approved Treatments

- GA and neovascular (wet) AMD are the **advanced forms of AMD**
  - prevalence rates are similar in the US, and both **rise exponentially with age**
  - wet AMD has approved treatment options
  - GA has **no FDA-approved treatments** and is a **leading cause of blindness** in the developed world

- GA affects **>5 million globally** and **~1 million** in the U.S. [1,2]

AMD is the most common cause of blindness in the developed world, accounting for 8.7% of blindness worldwide.[3,4]

Geographic Atrophy | Neovascular (wet) AMD
Pigment clumping
Drusen | Geographic Atrophy
Subretinal Hemorrhage
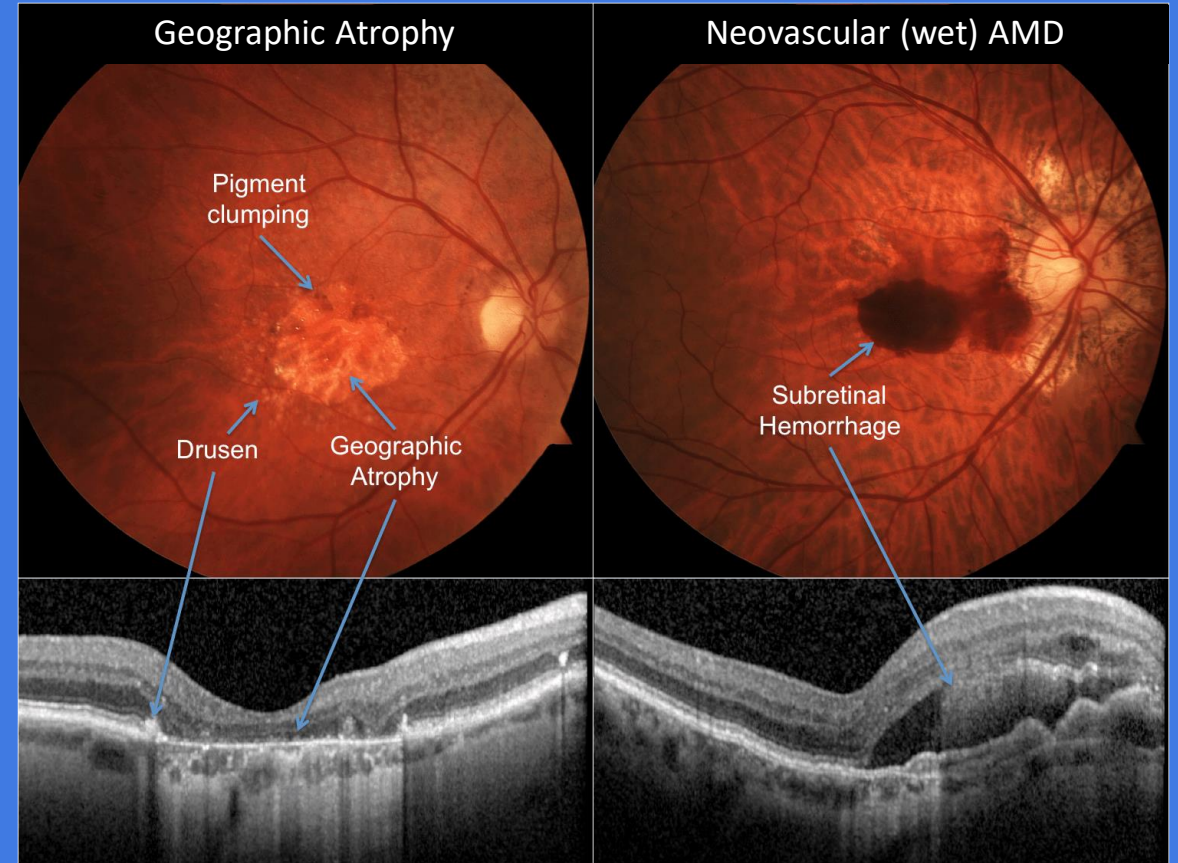
Geographic Atrophy and wet AMD are not mutually exclusive

[1]Fleckenstein, 2018; [2]Friedman, 2004; BrightFocus® Foundation
[3]As of 2016. Eye Vis (Lond). 2016; 3: 34.
[4]Wong et al. NEJM 2014.
https://www.acms.org/2019/03/age-related-macular-degeneration-in-2019

Geographic Atrophy is an Age-Related, Progressive Retinal Degenerative Disease Associated with Irreversible Loss of Vision

GA is characterized by the progressive loss of photoreceptors, retinal pigment epithelium (RPE) and choriocapillaris in the macular region of the retina.

GA typically impacts both eyes, exacting a striking toll on patients' central vision:

- Recent studies have reported,
  - 2/3rds of GA patients became **ineligible to drive** within 2 years of diagnosis
  - 1 in 6 people became **legally blind within 6 years** of diagnosis
  - GA patients on average **lost a line of vision a year** due to their disease progression

- GA disease progression, and accompanying vision decline, may **lead to loss of independence**, poorer quality of life, depression and an increased incidence of falls and fractures

HEALTHY RETINA
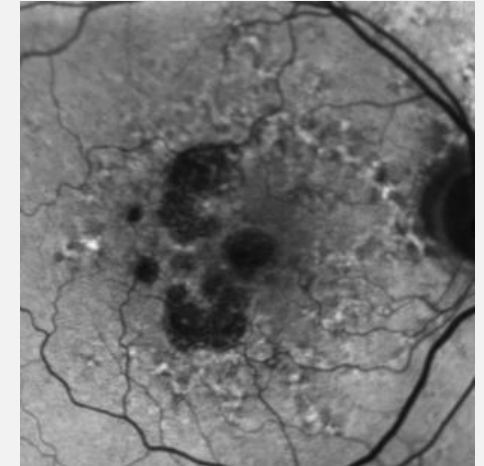
RETINA WITH GA
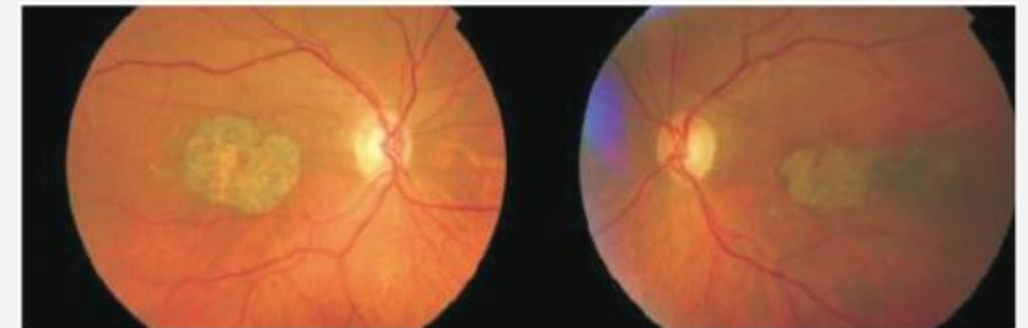
BILATERAL GA
Fundus images show hypopigmented areas in the macula where the RPE and photoreceptors are absent

Chakravarty U et al. Ophthalmology. 2018 Jun;125(6):842-849.

Evidence Strongly Supports the Pathological Role of Dysregulated Complement Activation in GA

GENETIC EVIDENCE

Fritsche et al. Nat Genet 2016
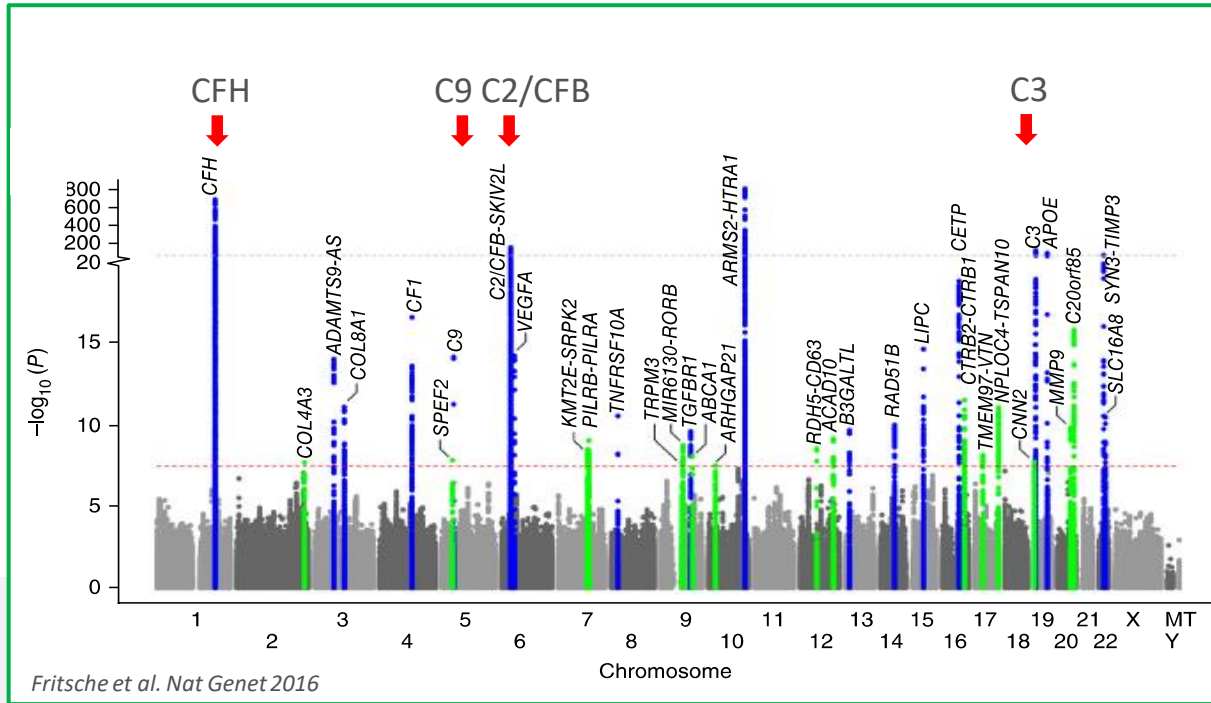
Variants in the complement pathway account for the majority of the known genetic risk for GA/AMD

HISTOPATHOLOGICAL EVIDENCE

C3 Deposition on Photoreceptors Precedes their Degeneration in Human GA Eyes

Retina bordering the GA lesion

Katschke et al. Sci. Reports 2018
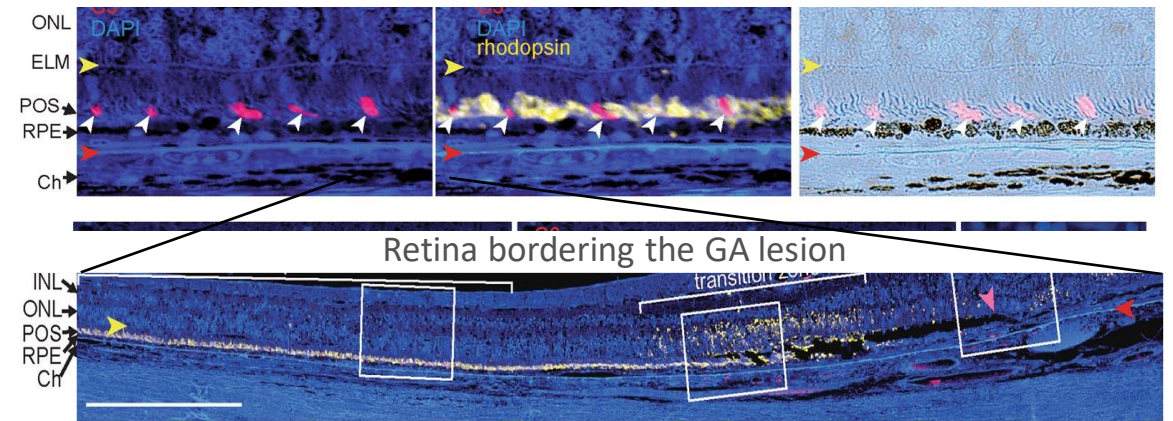
Pathological activation of complement system is strongly implicated in development and progression of GA

NGM621 Targets Complement C3, Blocking All Pathways of Complement Activation

NGM621 Targets Complement C3, Blocking All Pathways of Complement Activation
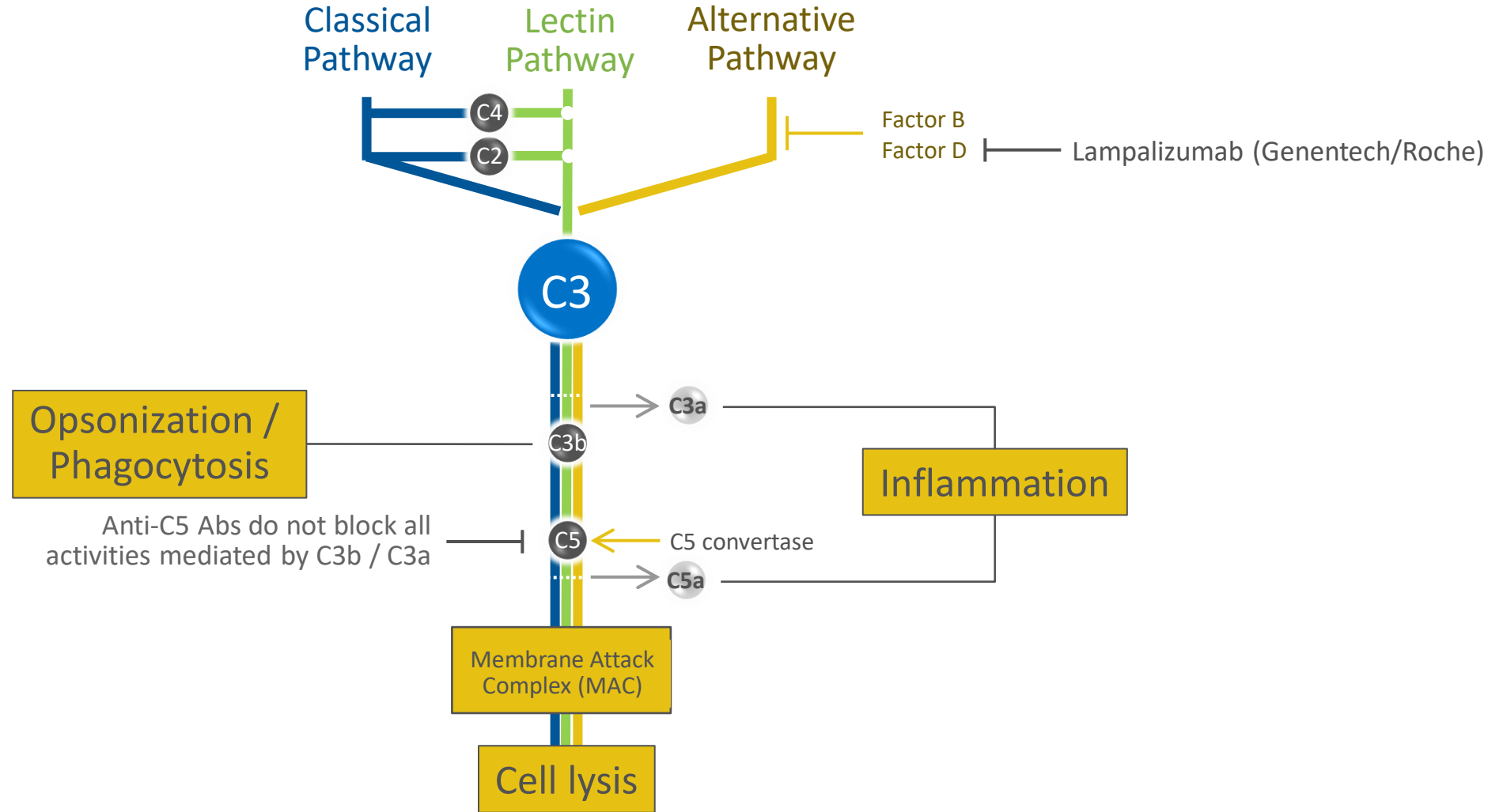
NGM621 for Treatment of Geographic Atrophy
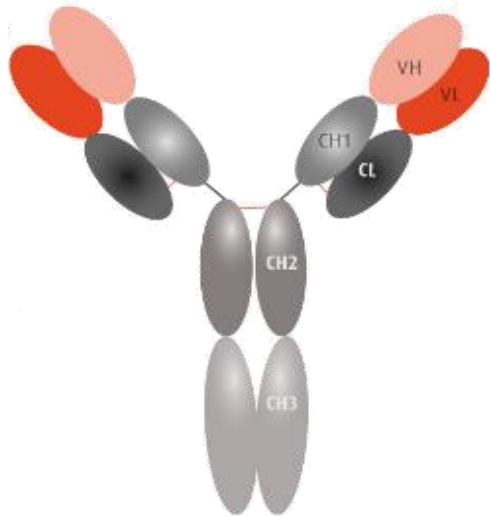
NOVEL C3 INHIBITOR

NGM621

Anti-C3 Monoclonal Antibody

- Dysregulated activation of complement is implicated in GA onset and progression
- NGM621 is designed to inhibit all complement pathway activation

Differentiated Design

- Engineered to potently inhibit C3
- High affinity binding to C3
- Potential for extended dosing up to 2 months (8 weeks)
- Potential to not trigger choroidal neovascularization (CNV) development

NGM621 MOLECULE ATTRIBUTES

Type	Humanized IgG1 monoclonal antibody
Target	Binds & inhibits Complement C3
Affinity	K_D = 0.34 nM, >100 fold specific to C3 over C3b
Potency (hemolytic assays)	AP IC_{50} =2 nM; CP IC_{50} =2 nM (10-50 nM C3 concentration)
Effector Function	2-point mutations in the Fc region eliminate effector function
Route of Administration	Intravitreal Injection
Formulation	Liquid
Dosing Frequency	4 weeks or 8 weeks (QM or Q2M)

Preclinical Data Shows PEG Can Exacerbate CNV Post-Laser Injury

Anti-C3 Ab Reduces Vascular Leakage in Laser Injury-Induced CNV in Mice

	Fundus (Day 0)	Complement activation (Anti-C3d - Day 2)	Vascular Leakage (Fluorescein angiography - Day 7)	Angiogenesis (Isolectin B4 - Day 7)
Anti-KLH (IVT)				
Anti-C3 Ab (IVT)		-41%	-53%	--
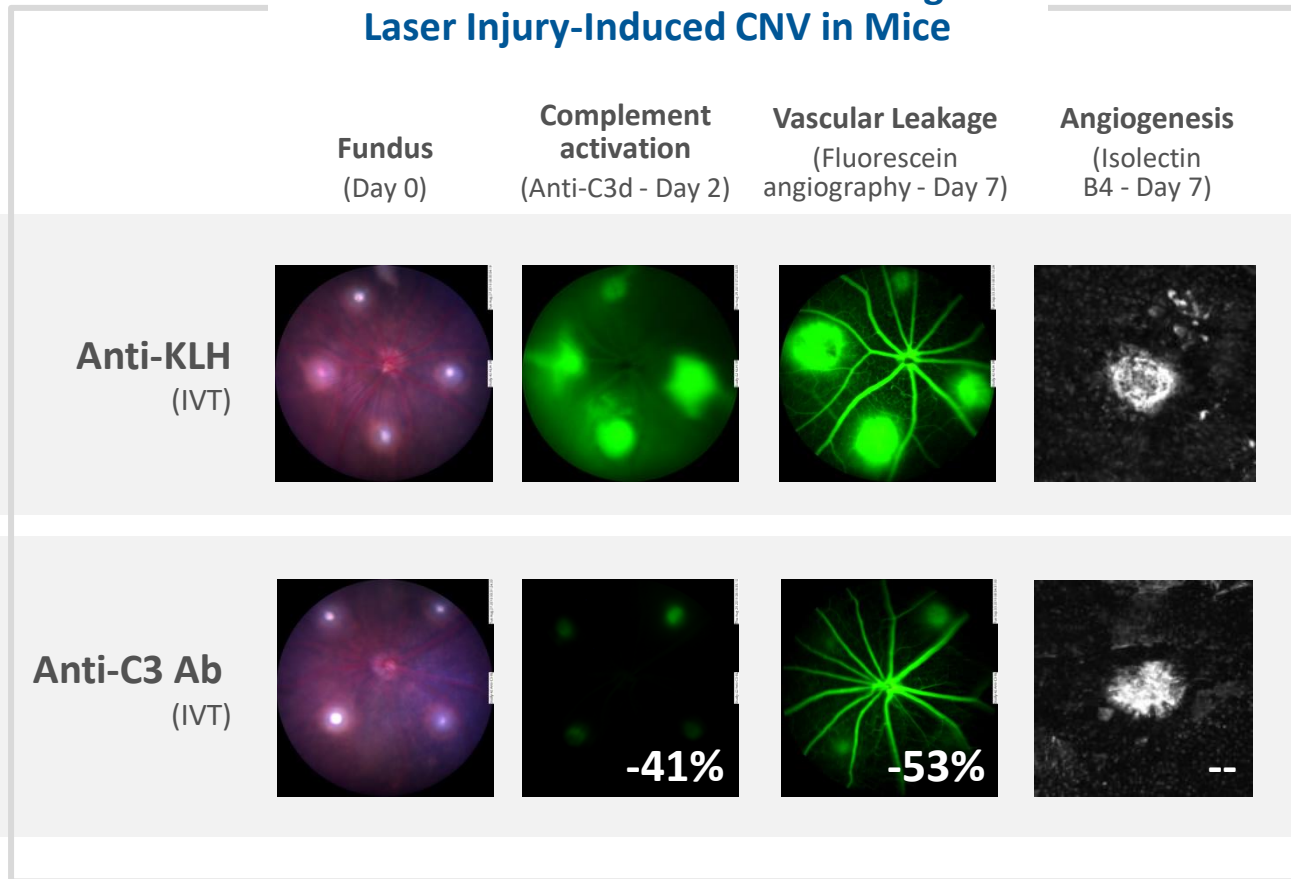
PEG-40KD Exacerbates Laser Injury-induced CNV in Mice

	Fundus (Day 0)	Vascular Leakage (Fluorescein angiography - Day 7)	Angiogenesis (Isolectin B4 - Day 7)
PBS (IVT)			
PEG-40kD (IVT)		+65%	+51%
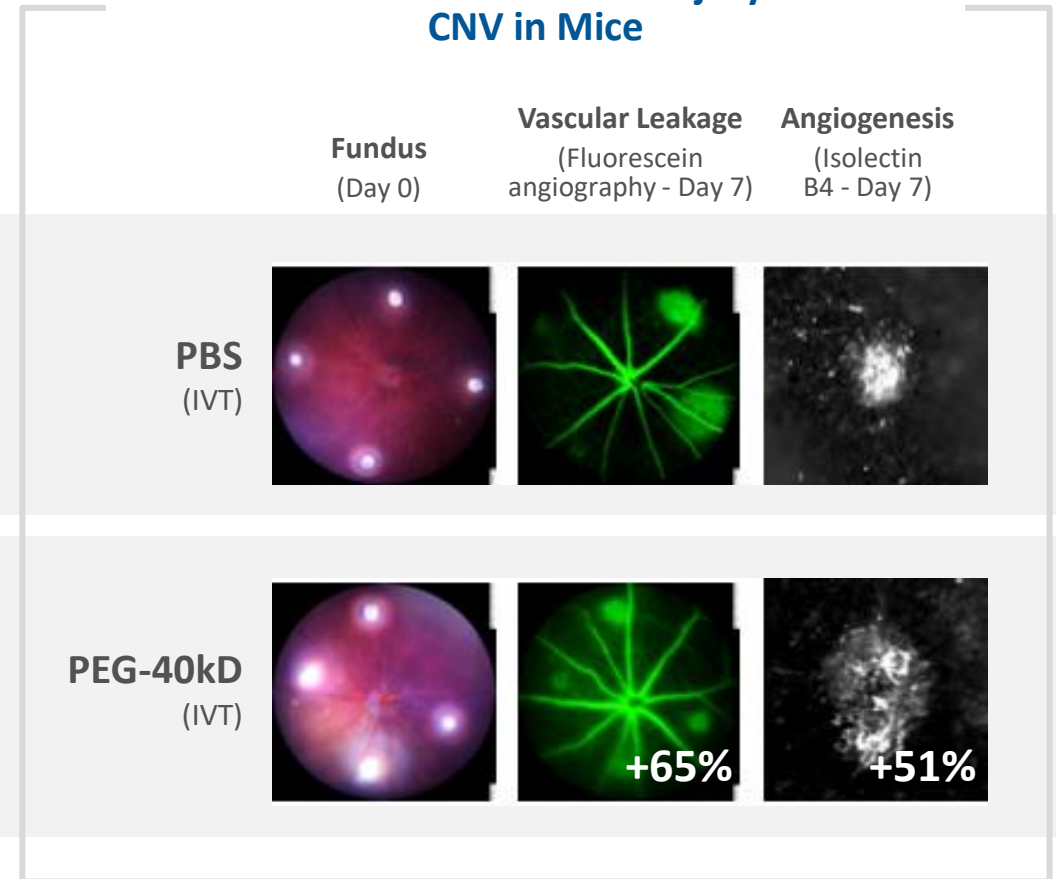
The absence of PEG may provide a safety profile advantage for NGM621.

Clinical Development of NGM621 is Rapidly Advancing

ADVANCING CLINICAL DEVELOPMENT

✓ **Phase 1** in GA patients successfully completed
- ✓ Data presented at AAO in November
- ✓ NGM621 well tolerated
- ✓ No drug-related adverse events or serious adverse events

✓ **Phase 2** sham-controlled, double-masked study for GA (CATALINA) **enrollment ongoing**
- – Evaluating the safety and efficacy of intravitreal NGM621 dosed every 4 or 8 weeks compared to matched sham arms
- – 240 patients from US sites
- – Designed to be a Phase 3-enabling study
- – First-Patient-In achieved July 2020

Charles Wykoff, M.D., Ph.D.
Director of Research
Retina Consultants Houston

RETINA
Consultants of America

Retina
Consultants
Houston

AMD = Leading Cause of Blindness in US

AMD = Leading Cause of Blindness in US
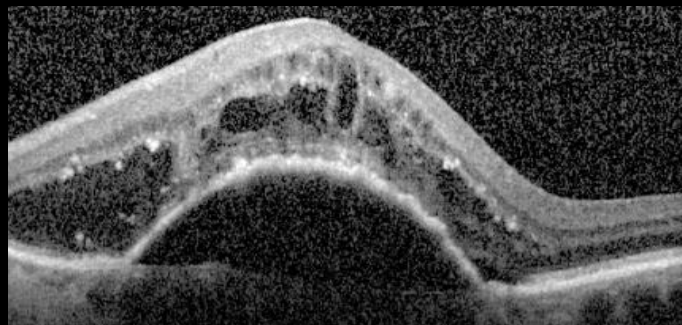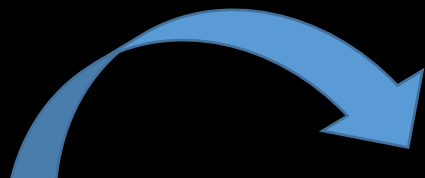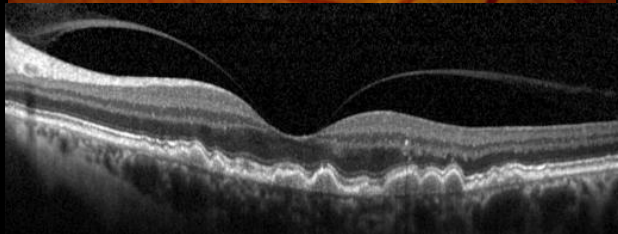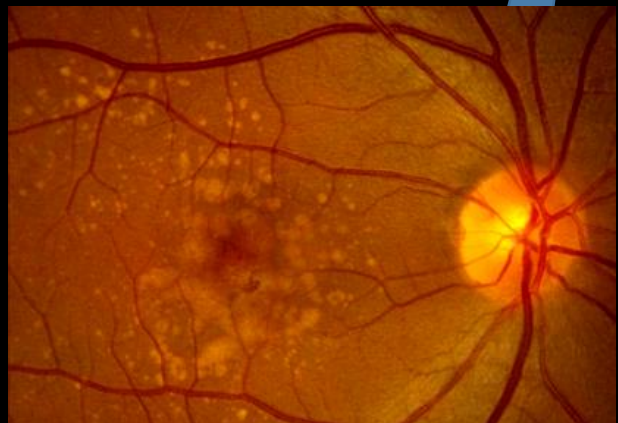
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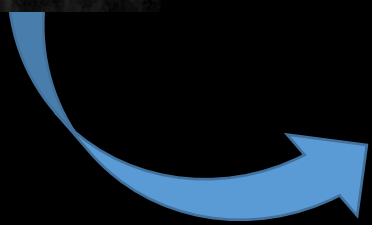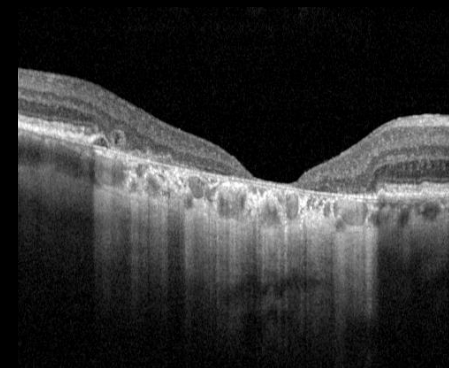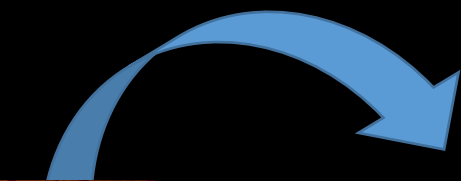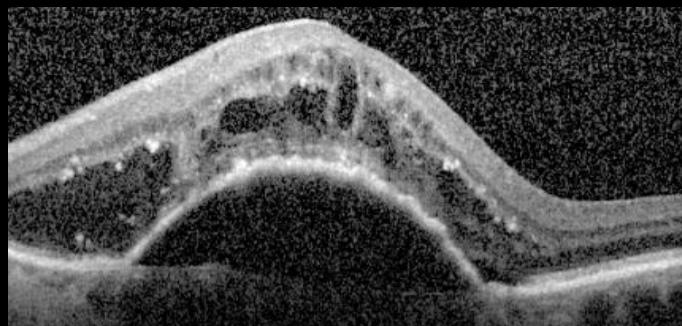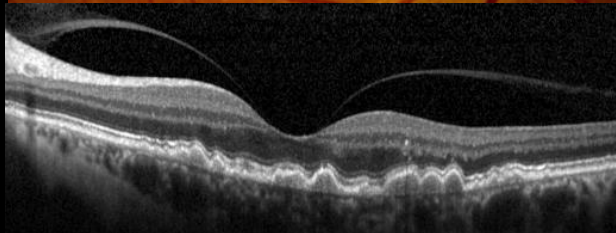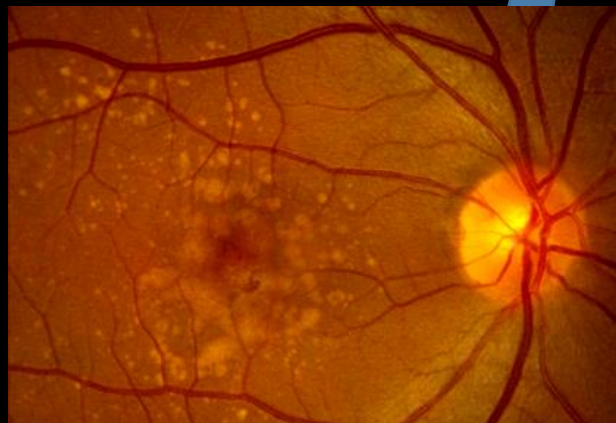
Geographic Atrophy Secondary to AMD

20/20   20/20   20/20   20/40

2009   2013   2016   2019
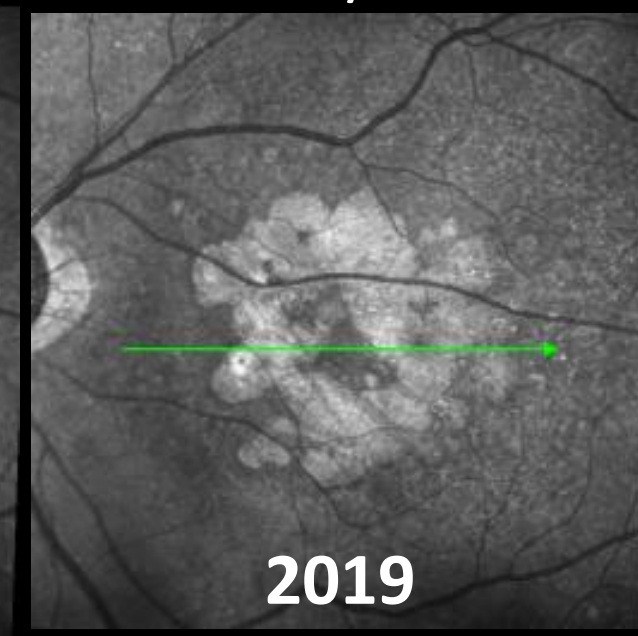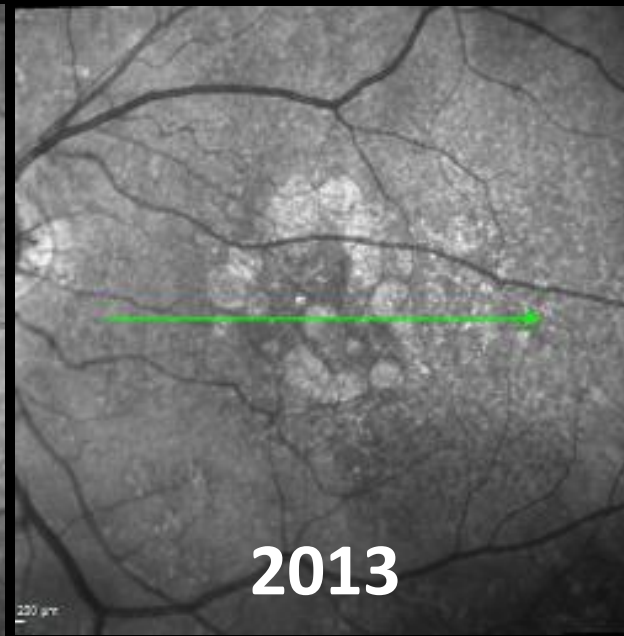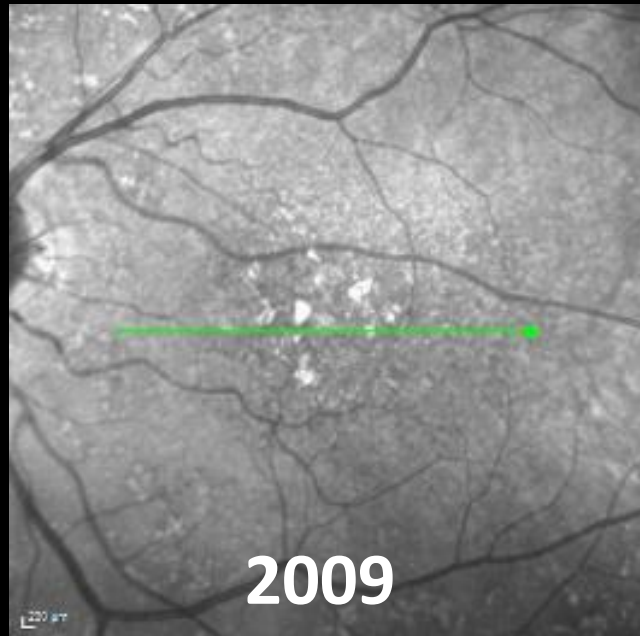
Progressive degeneration of the macula over time

Quantifying the Burden of GA
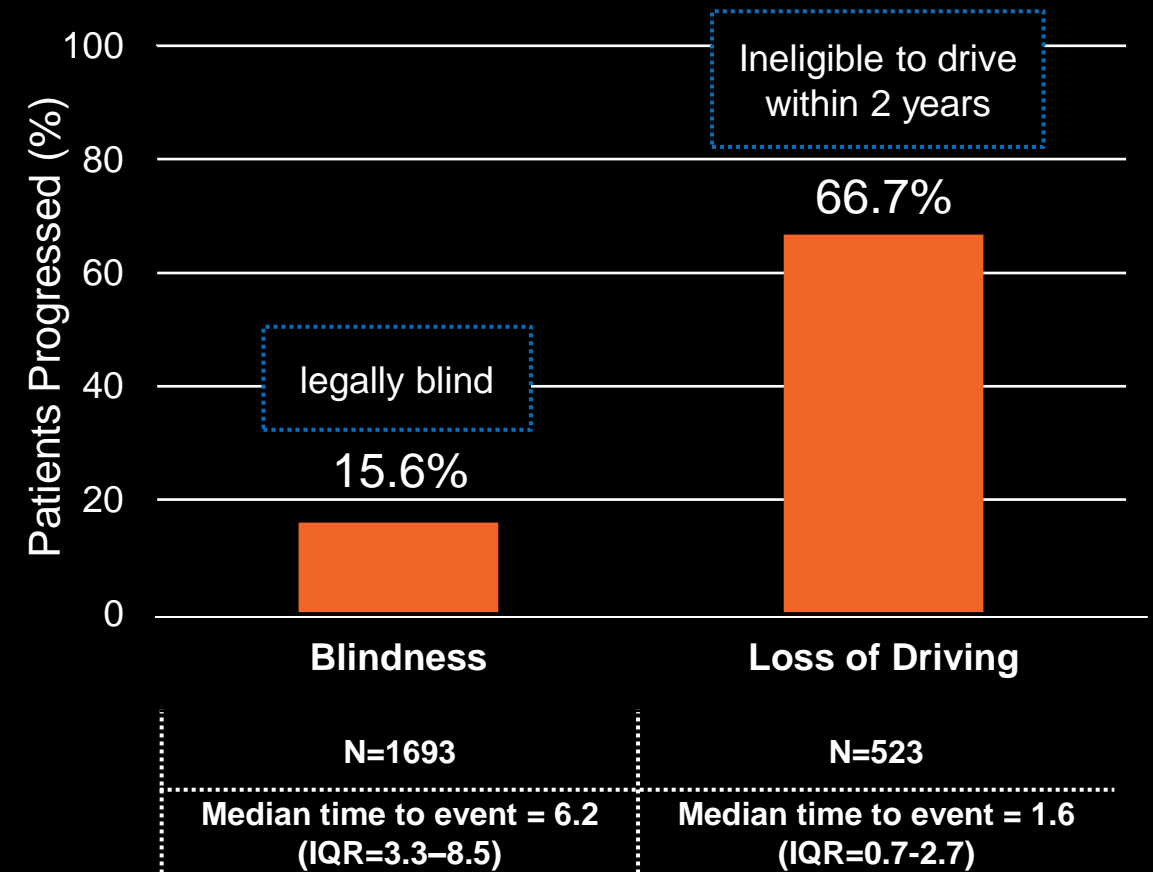
Data from UK EMR systems at 10 clinical sites: 2000 – 2016

- Among patients OU GA
- Loss of 6-10 letters / 2 years
- 2/3rd unable to drive within 2 years

Figure 2. Change in mean visual acuity (VA) from baseline in the worse-seeing (study) eye and better-seeing (fellow) eye through 60 months' follow-up in patients with bilateral geographic atrophy identified in the

Blindness

N=1693

Median time to event = 6.2 (IQR=3.3–8.5)

Loss of Driving

N=523

Median time to event = 1.6 (IQR=0.7-2.7)

Chakravarty U et al. Ophthalmology. 2018 Jun;125(6):842-849.

Goal of Therapy = Reduction of Progression

GA Area

Visual Function

Time

Severe Impairment

*1.93 mm^2/year in lampalizumab phase 3 program sham arm

Goal of Therapy = Reduction of Progression

Rate of Progression
Average: 1.5 - 2.2 mm^2 / year*
Wide range: 0.53 - >4.0 m^2/year

Natural History

Treatment Effect

GA Area

Visual Function

Time

Severe Impairment
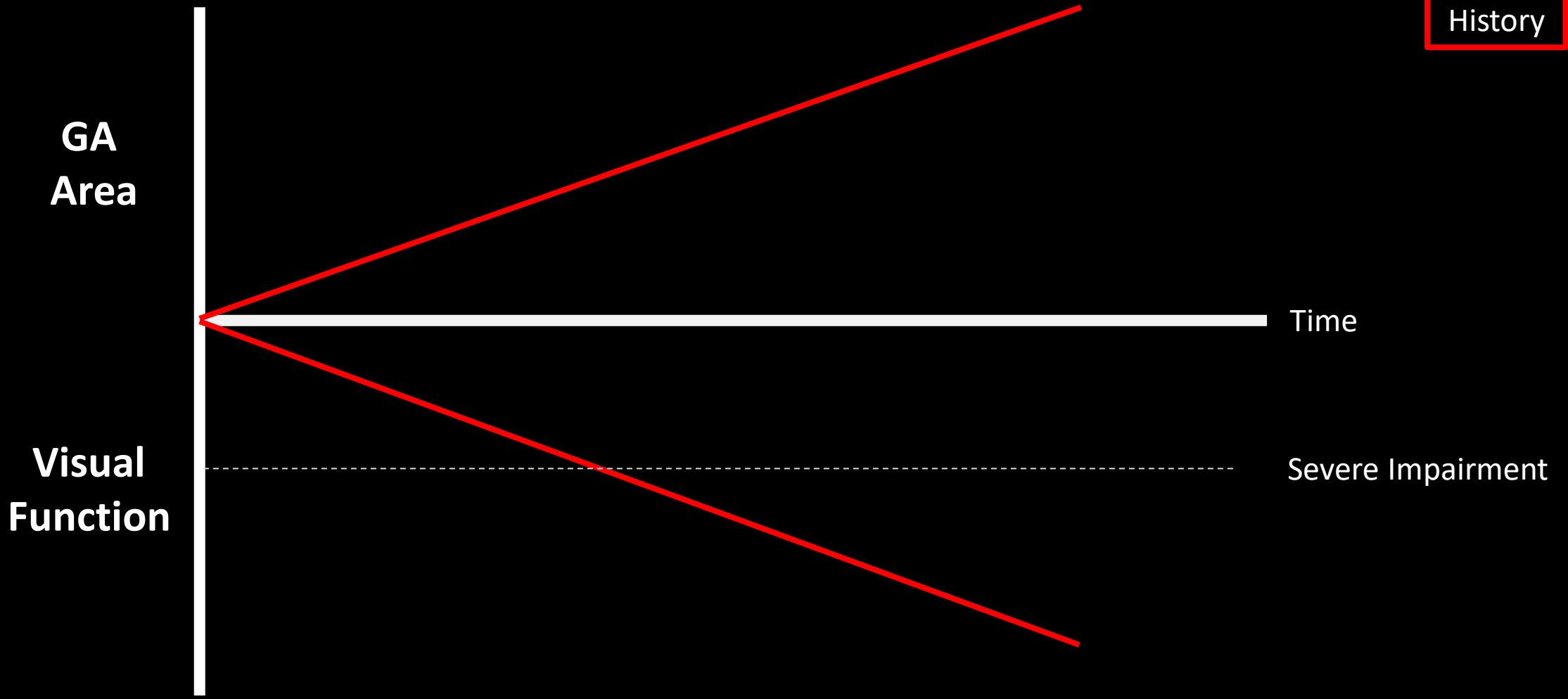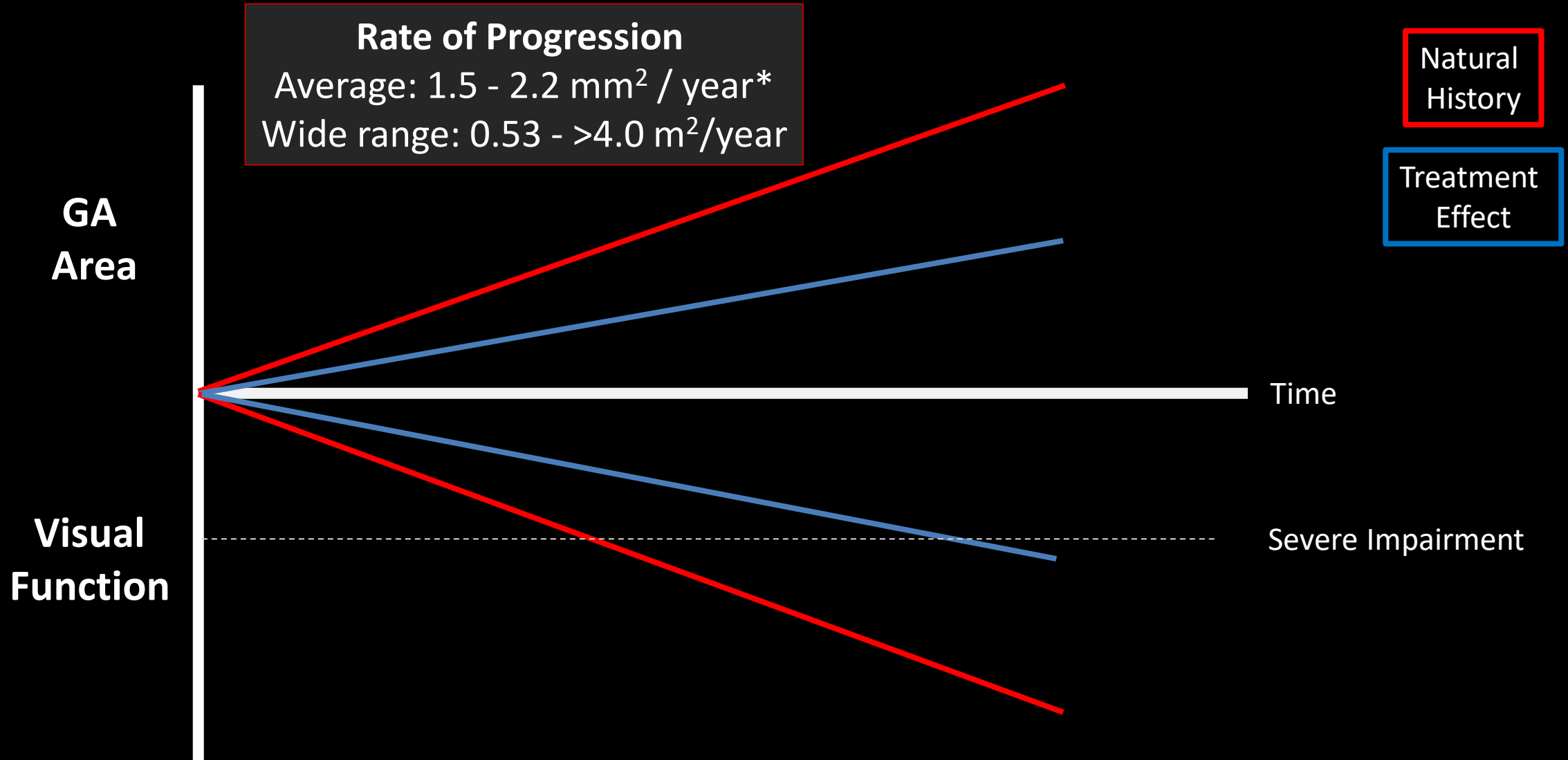
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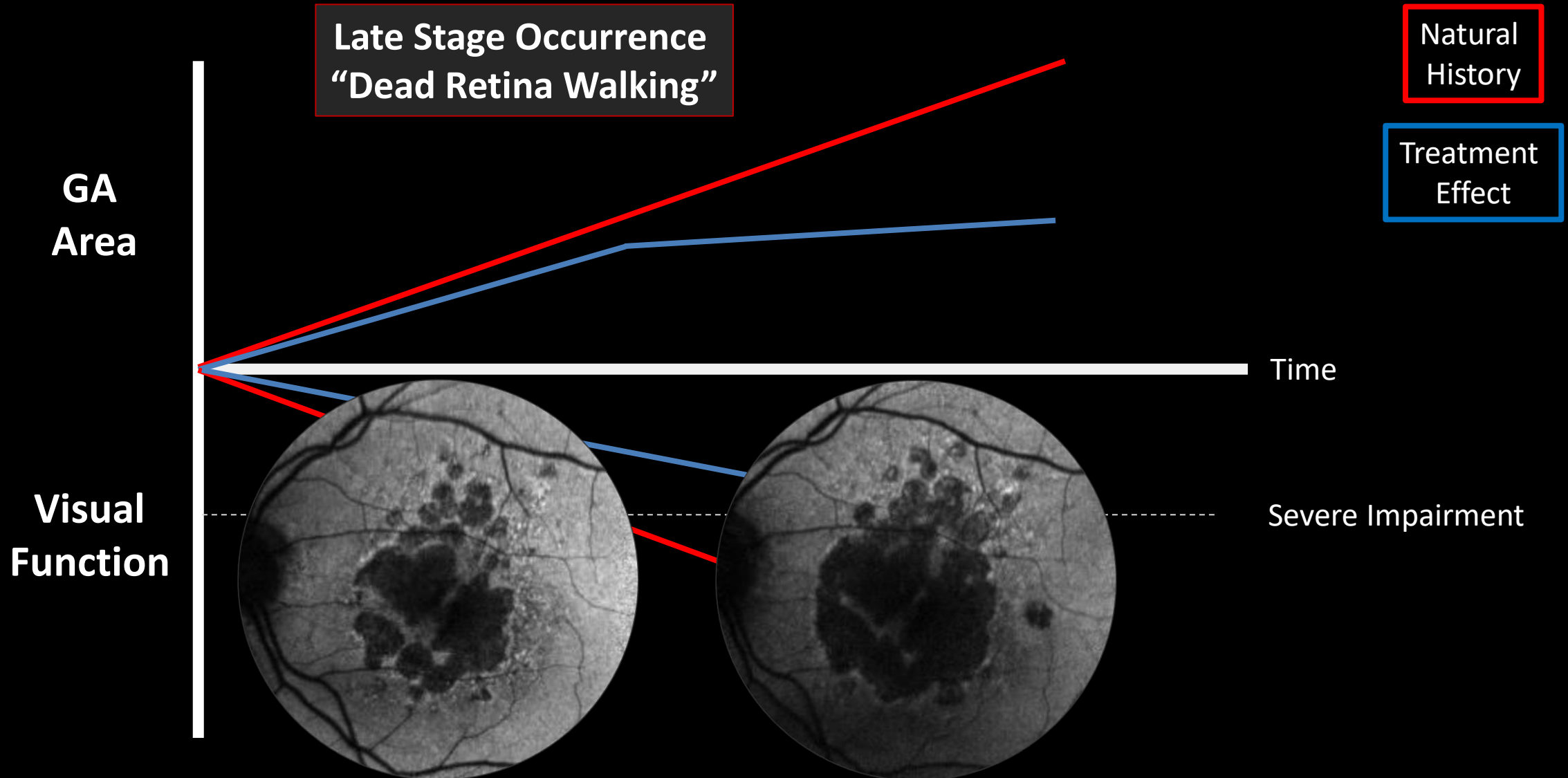
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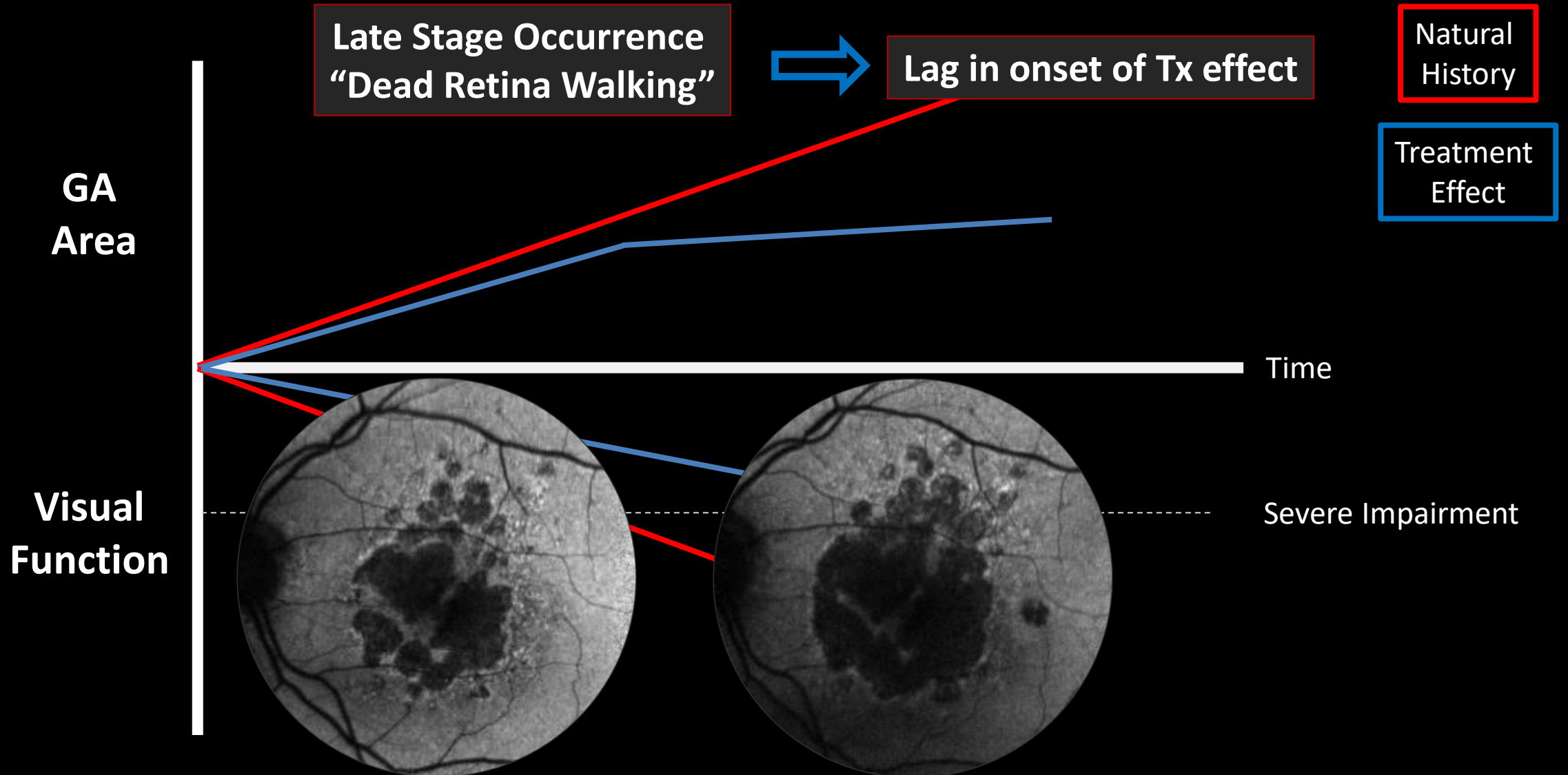
NGM621: Potent Anti-C3 Monoclonal Antibody

NGM621 MOLECULE ATTRIBUTES
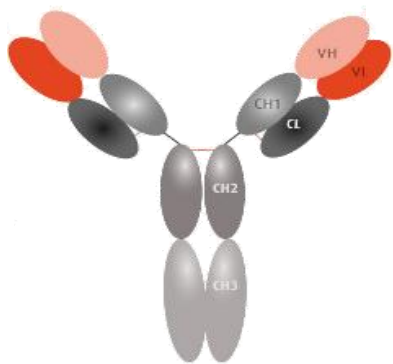
Type	Humanized IgG1 monoclonal antibody
Target	Complement C3
MW	~150 kDa
Affinity	K_D = 340pM
Effector Function	Fc mutations eliminating effector function

NGM621

SCIENTIFIC RATIONALE: NGM621 FOR GEOGRAPHIC ATROPHY

- Complement dysregulation is implicated in GA/AMD; C3 is the central convergence point in the complement cascade
- NGM621 is a novel monoclonal antibody that potently inhibits C3, blocking all complement pathways and associated downstream effects, with the potential for extended dosing without PEGylation

COMPLEMENT CASCADE

Classical Pathway

Lectin Pathway

Alternative Pathway

C4

C2

Factor B
Factor D

NGM621

C3

Opsonization / Phagocytosis

C3b

C3a

Inflammation

C5

C5 convertase

C5a

Membrane Attack Complex (MAC)

Cell lysis

AMD, age-related macular degeneration; GA, geographic atrophy; IgG1, immune globulin G1; PEG, polyethylene glycol.
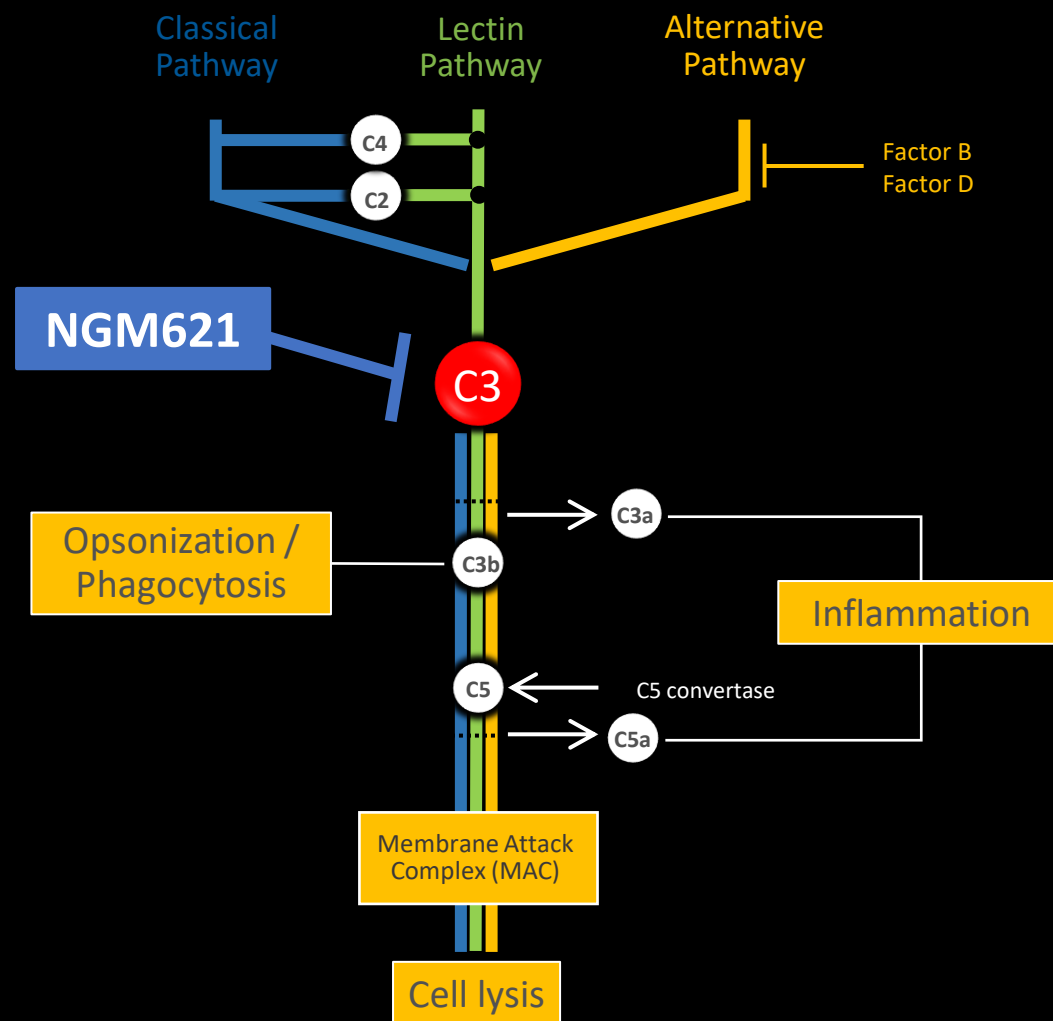
Phase 1 Study Objectives and Design

SINGLE-ASCENDING DOSE COHORTS

15 mg/eye
N = 3

7.5 mg/eye
N = 3

2 mg/eye
N = 3

MFD

MULTIDOSE COHORT

15 mg/eye
Q4W X 2
N = 6
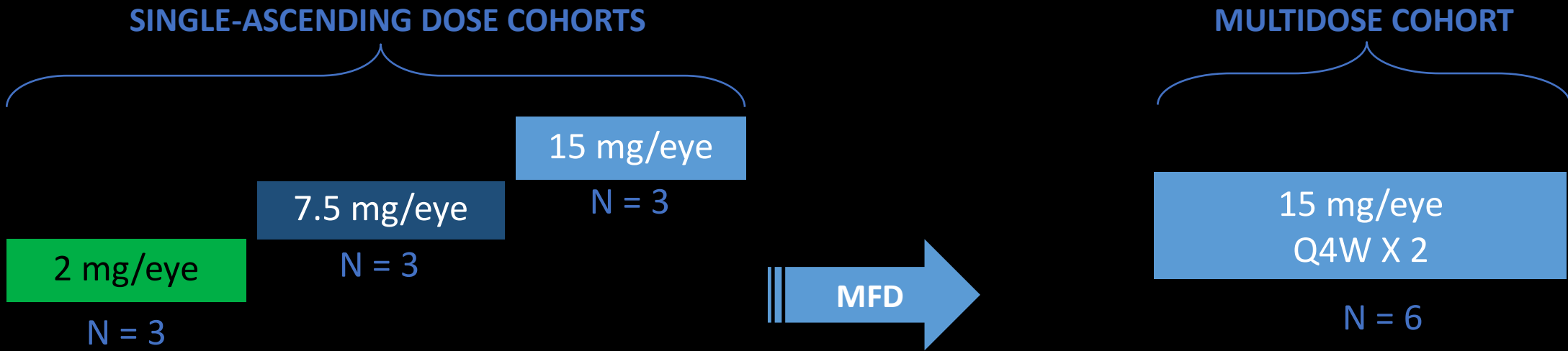
STUDY OBJECTIVES

- **Primary:** To evaluate the safety and tolerability of single and multiple IVT injection(s) of NGM621 in patients with GA

- **Secondary:** To characterize the PK of single or multiple doses of and evaluate immunogenicity of NGM621 (serum ADA levels) NGM621

COHORT DESIGN

- 3 Single-Ascending Dose Cohorts of 2mg, 7.5mg, and 15mg

- 1 Multidose Cohort of 15mg NGM621 given twice, 4 weeks apart

- Patients dosed sequentially, followed for 12 weeks

- Safety review performed after sentinel patient dosed and prior to enrollment proceeded to subsequent cohorts

ADA, anti-drug antibodies; GA, geographic atrophy; IVT, intravitreal; MFD, maximum feasible dose; PK, pharmacokinetics; Q4W, every 4 weeks.
ClinicalTrials.gov NCT04014777.

Phase 1: Key Patient Eligibility and Assessments

PATIENT ELIGIBILITY

- GA secondary to AMD in at least one eye

- ≥50 years of age

- GA lesion size in the study eye of ≥2.5 mm^2
  - If the GA is multifocal, at least one lesion must be >1.5mm^2 with the total lesion size ≥2.5 mm^2 on the Screening FAF

- ETDRS BCVA between 54 and 4 letters (20/80 to 20/400 Snellen equivalent) in study eye
  - Fellow eye must have BCVA of at least 34 letters (Snellen equivalent 20/200)

- No history or evidence of CNV in either eye (including subclinical neovascular AMD)

DOSING AND KEY ASSESSMENTS

- Cohorts 1-3: Single-Ascending Dose
  - NGM621 dosed on Day 1

- Cohort 4: Multidose
  - NGM621 dosed on Days 1 and 28

- All cohorts were followed for 12 weeks (85 days)

- Key Assessments Included:
  - Slit Lamp Biomicroscopy, Fundus Exam
  - Ocular imaging: FAF, CFP, OCT/OCT-A
  - Visual Acuity: ETDRS BCVA & LLVA
  - Vitals / Labs / ECG
  - Serum / Plasma Samples

Phase 1: Patient Demographics and Baseline Characteristics

	SAD Cohort 1 NGM621 2mg (N = 3)	SAD Cohort 2 NGM621 7.5mg (N = 3)	SAD Cohort 3 NGM621 15mg (N = 3)	MD Cohort 4 NGM621 15mg (N=6)	Total (N = 15)
Age Mean (SD) Years	84.3 (3.06)	79.0 (9.64)	76.7 (4.04)	76.5 (7.04)	78.6 (6.66)
Sex					
Male	100.0%	100.0%	33.3%	33.3%	60.0%
Female	0	0	66.7%	66.7%	40%
Race					
White	100.0%	100.0%	100.0%	100.0%	100.0%
BCVA, Mean (SD) ETDRS letter score	19.3 (16.3)	23.7 (16.1)	36.7 (13.3)	38.8 (12.8)	31.5 (14.7)
Snellen Equivalent	20/400	20/320	20/200	20/160	20/250
GA lesion size, Mean (SD) mm²	5.7 (3)	9.6 (8.5)	21.4 (14.5)	18.7 (11.2)	14.9 (10.8)
Unifocal lesions	66.7%	100%	100%	66.7%	80%
Foveal-involved GA (Yes)	66.7%	100%	100%	83.3%	86.7%

BCVA, best corrected visual acuity; GA, geographic atrophy; MD, multidose cohort; SAD, single ascending dose cohort; SD, standard deviation.

105

Primary Analysis: Key Safety & Tolerability Observations

- No safety or tolerability signals observed in any cohort
  - No safety events attributed to study drug
  - No SAEs or deaths
  - No endophthalmitis or IOI
  - No cases of CNV
  - Ocular AEs were representative of those seen with intravitreal injections

- No vision-related safety signals detected
  - On average, patients maintained their visual acuity over the 12-week follow-up

SUMMARY OF ADVERSE EVENTS BY DECREASING FREQUENCY*

	SAD Cohort 1 NGM621 2 mg (N = 3)	SAD Cohort 2 NGM621 7.5 mg (N = 3)	SAD Cohort 3 NGM621 15 mg (N = 3)	MD Cohort 4 NGM621 15 mg (N = 6)	Total (N = 15)
At least one AE	3	3	2	6	14
Conjunctival hemorrhage	0	0	0	3	3
Eye pruritus	0	1	0	1	2
Basal cell carcinoma	1	0	0	0	1
Benign prostatic hyperplasia	1	0	0	0	1
Diarrhea	0	1	0	0	1
Diverticulitis	0	1	0	0	1
Headache	0	0	0	1	1
Hypaesthesia	0	0	0	1	1
Pneumonia	1	0	0	0	1
Sciatica	0	0	1	0	1
Ventricular extrasystoles	0	0	1	0	1

AEs, adverse events; CNV, choroidal neovascularization; IOI, intraocular inflammation; MD, multidose cohort; SAD, single ascending dose cohort; SAEs, serious adverse events.
*Defined as treatment emergent events; includes any events not present prior to initiation of drug treatment or events that were already present that worsen intensity or frequency.

NGM621 Human Serum PK Profile and Ocular PK/PD Modeling Support Dosing Regimen Being Explored in Ongoing CATALINA Phase 2

PHASE 1 SERUM PK POST-IVT SINGLE & REPEAT DOSING

- The serum PK of NGM621 was linear and dose-proportional with low accumulation following every 4-week repeat IVT dosing
- NGM621 serum exposure was below concentrations that produce systemic complement inhibition at the highest IVT dose of 15mg
- All subjects were ADA negative at all timepoints

Mean Serum Concentration-time Profile post-IVT of NGM621
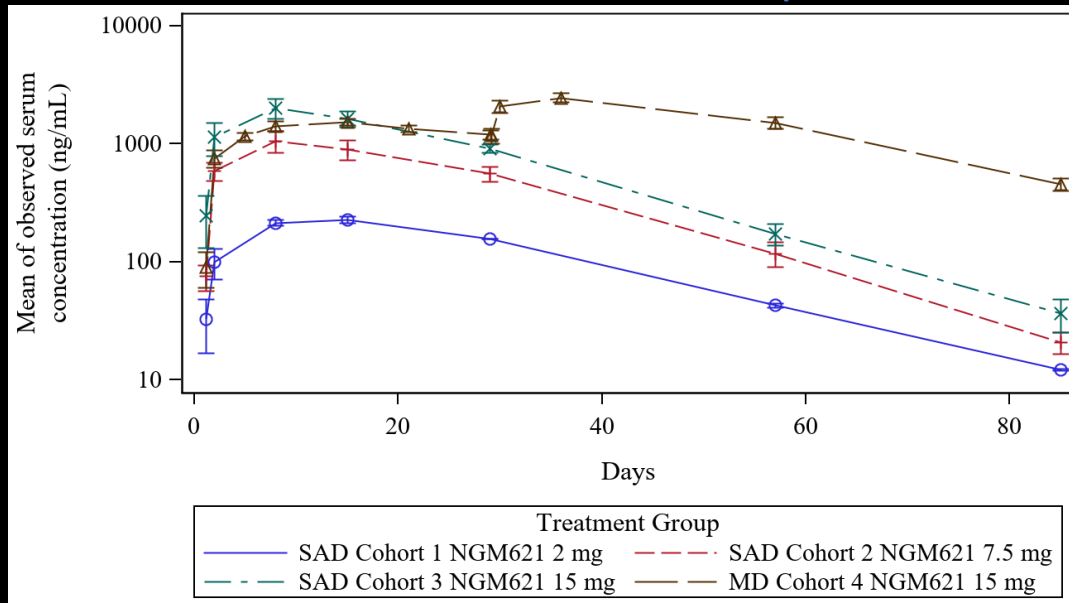
OCULAR PK/PD MODELING*

- Preclinical modeling suggests that NGM621 may achieve >90% C3 target engagement in the eye for 7 weeks following a single IVT dose of 15 mg based on a PK/PD model
- PK/PD modeling and simulation support exploring an every 8-week IVT dosing regimen at the 15 mg dose level

Predicted vitreous humor PK/PD profile
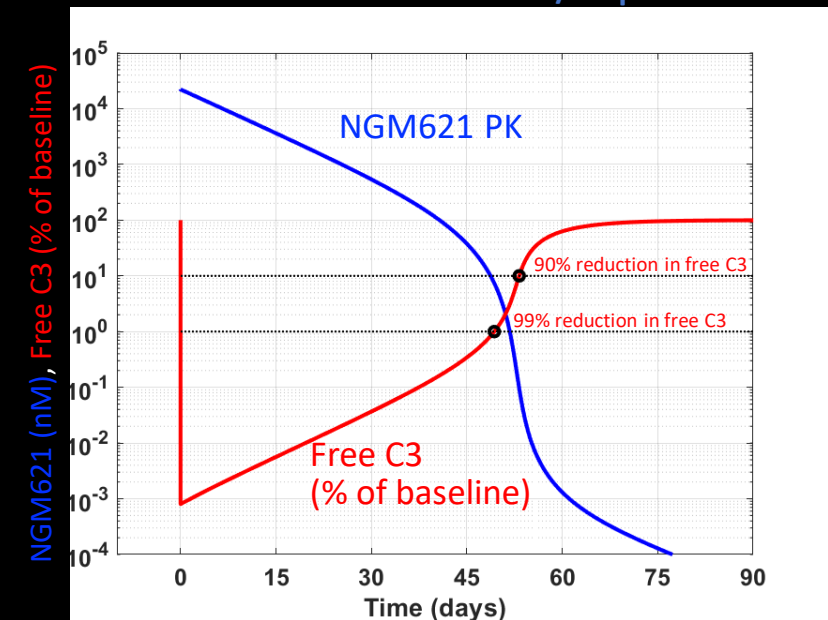
ADA, anti-drug antibodies; IVT, intravitreal; MD, multidose cohort; PD, pharmacodynamics; PK pharmacokinetic; SAD, single ascending dose cohort.
*ocular PK was not collected in Phase 1; model based on pre-clinical ocular PK data.

Encouraging Phase 1 Results Support Continued Clinical Development of NGM621 for GA

- NGM621 up to 15mg was well tolerated in this first-in-human study
  - All patients completed the 12-week follow-up
  - No SAEs
  - No drug-related AEs
  - No CNV

- NGM621 serum exposures appeared dose-proportional indicating linear PK in the studied range
  - PK/PD modeling supports exploring NGM621 dose intervals of up to 8 weeks

THANK YOU TO THE NGM621 PHASE 1 STUDY SITES, INVESTIGATORS, AND PATIENTS!

Principle Investigators: Drs. Brian Berger, Tom Chang, David Eichenbaum, Vrinda Hershberger, Charlie Wykoff

Thank you as well to Harish Shankaran (Merck) for support of the PK/PD modeling work and to Neang Ly (NGMBio) for supporting the PK/ADA analyses efforts.

ADA, anti-drug antibodies; AE, adverse events; CNV, choroidal neovascularization; GA, geographic atrophy; PD, pharmacodynamic; PK, pharmacokinetic; SAEs, serious adverse events.

Now Recruiting: CATALINA Phase 2 GA Study

Dosing with NGM621 every 4 or 8 weeks vs Sham

PATIENTS WITH GA SECONDARY TO AMD; N = 240[1]

Randomized 2:1:2:1

NGM621 Q4W	Sham Q4W	NGM621 Q8W	Sham Q8W

Primary Objective	To evaluate the efficacy and safety of NGM621 IVT injections administered every 4 or 8 weeks in GA patients compared to sham control
Design	Phase 2 Multicenter, Randomized, Double-Masked, Sham-Controlled

1 Target enrollment; enrollment ongoing NCT04465955.
AMD, age-related macular degeneration; FAF, fundus autofluorescence; GA, geographic atrophy; IVT, intravitreal; Q4, every 4 weeks; Q8, every 8 weeks.

Q&A

Charles Wykoff, M.D., Ph.D.
Retina Consultants Houston

Erin Henry, Ph.D.
Head of Ophthalmology, NGM

David Woodhouse, Ph.D.
Chief Executive Officer, NGM

Hsiao D. Lieu, M.D., F.A.C.C.
Chief Medical Officer

NGM Has Deep Expertise in the FGF Pathways

NGM

Licensed to Merck

FGF19 Analogue: aldafermin
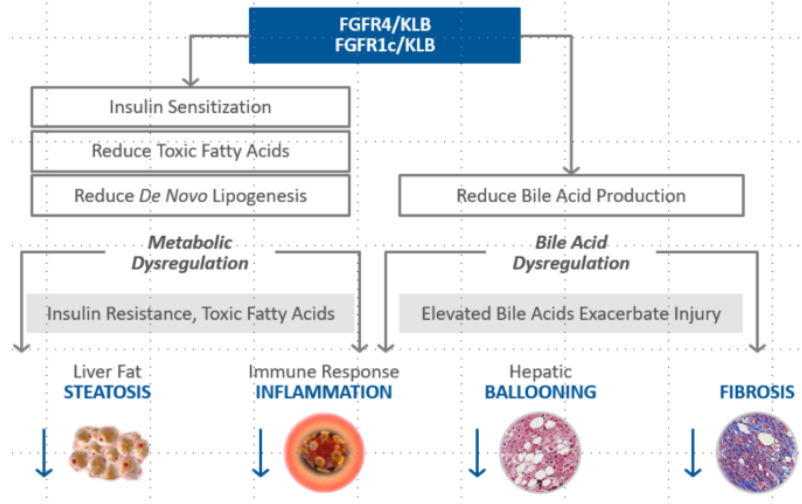
FGFR1c/KLB agonistic Ab: MK-3655 (NGM313)
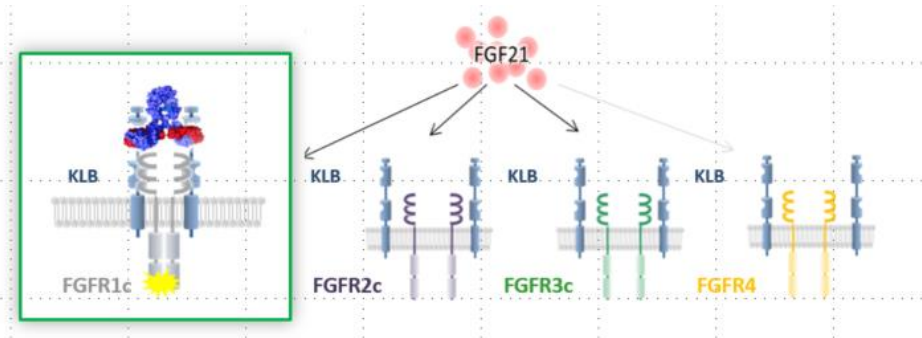
FGF19 and FGF21 pathways impact different benefits to address the needs from the various patient segments of a large heterogeneous NASH population

Higher Unmet Need Especially in Advanced Fibrotic NASH Patients

No / Early / Moderate Fibrosis
All-cause mortality dominated by cardiovascular complications

Advanced Fibrosis

Liver-related Mortality Rates (per 1,000 Patients)[1]

Exponential increase in liver-related mortality

Fibrosis Stage	F0	F1	F2	F3	F4
Liver-related Mortality Ratio (vs. F0) [2]	1x	1.4x	9.6x	**16.7x**	**42.3x**
Drivers of Mortality		Cardiovascular Disease		Liver Disease	
Time to Progression		One Fibrosis Stage Worsening Every <7 Years			

▶ **Advanced Liver fibrosis** has higher rates of mortality and morbidity in NASH[1]

▶ **~ 22%** of F3 patients progress to cirrhosis in 29 months[3]

▶ The higher the fibrosis stage, the greater the urgency to reverse fibrosis quickly

[1] Angulo et al., Gastroenterology 2015;149:389-397; Ekstedt et al., Hepatology 2015;61:1547-1554;
[2] Dulai et al., Hepatology 2017;65:1557-1565
[3] Sanyal et al., Hepatology. 2019 Dec;70(6):1913-1927

Aldafermin Impacts the Key Drivers of NASH Pathogenesis

ALDAFERMIN

FGF19 Analog

FGFR4/KLB
FGFR1c/KLB

ALDAFERMIN

Actions on Implicated Disease Drivers

Insulin Sensitization

Reduce Toxic Fatty Acids

Reduce *De Novo* Lipogenesis

Reduce Bile Acid Production

Metabolic Dysregulation

Bile Acid Dysregulation

Implicated Disease Drivers

Insulin Resistance, Toxic Fatty Acids

Elevated Bile Acids Exacerbate Injury

Liver Fat
STEATOSIS

Immune Response
INFLAMMATION

Hepatic
BALLOONING

FIBROSIS

Resulting Impact on Disease Progression in the Liver

Aldafermin Induces Rapid Fibrosis Regression in 12 Weeks

Baseline: F3

Steatosis

Bridging fibrosis
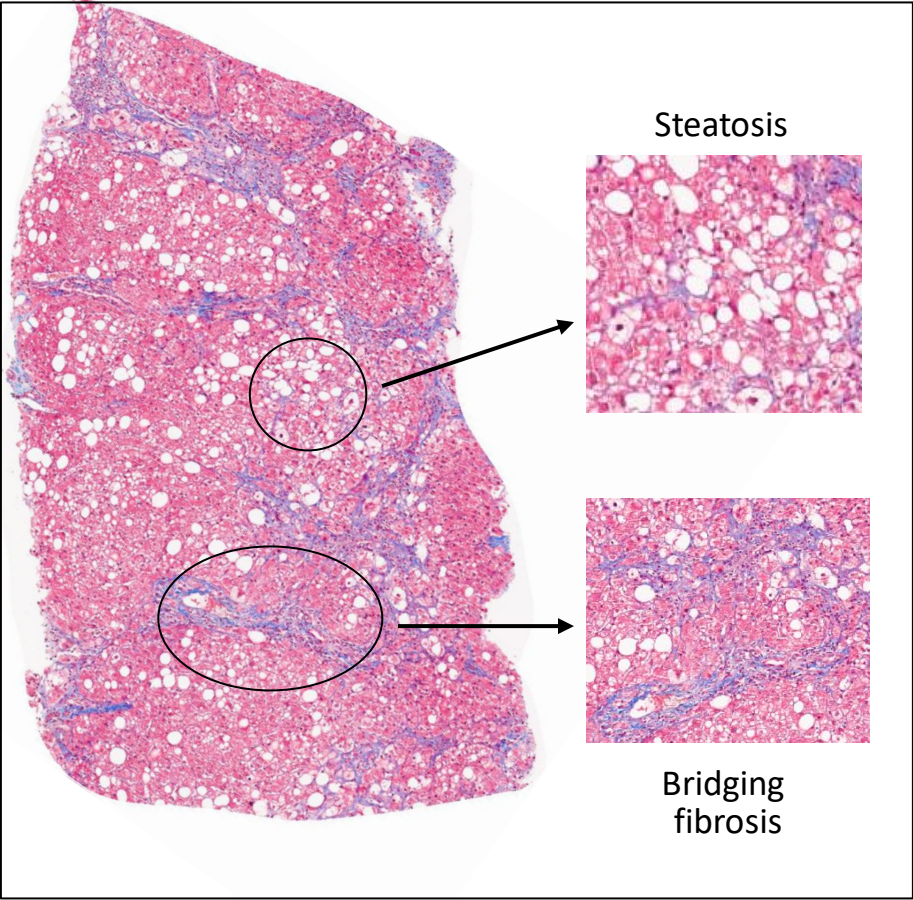
Aldafermin

Week 12: F2
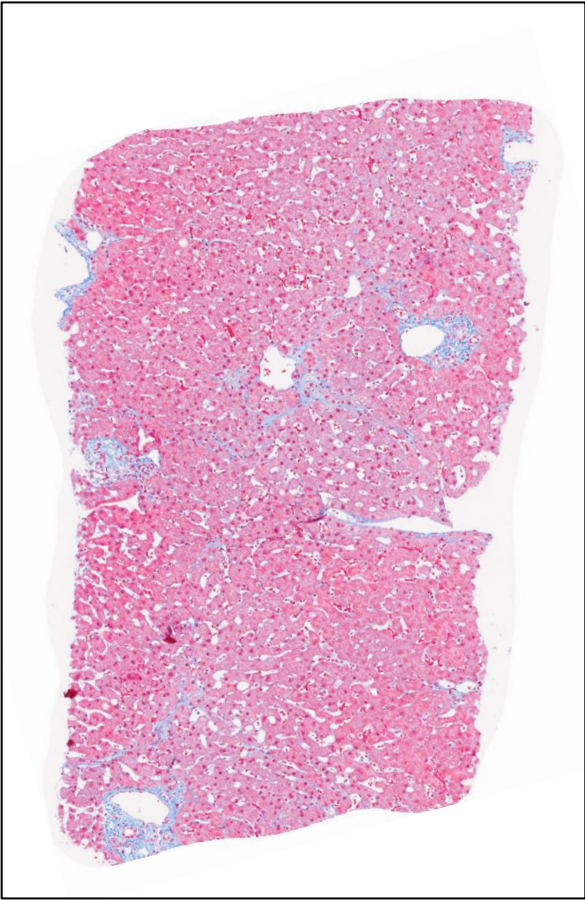
- Blue as indicated by Trichrome stain represents collagen, or fibrosis
- Open white space represents steatosis

Patient 909-202; Liver fibrosis stage by CRN

5

Robust Clinical Evidence in Completed Phase 2 Trial Shows Consistent and Strong Aldafermin Effect in NASH Patients

PHASE 2 STUDIES

○ = Trial size (patients)

Dose Ranging

Placebo-controlled Dose; Longer Duration

| ALPINE 2/3 | ALPINE 4 |

~160 — 24 Weeks — F2/F3

~160 — 48 Weeks — F4

Histologic Proof of Principle

COHORT 4 — 78

COHORT 2/3 — 94 — 12 Weeks

Proof of Activity

COHORT 1 — 55 — 12 Weeks

24 Weeks

Phase 3 Pivotal Trial in Planning

✓ Signal-seeking w/ biomarker data

✓ Introduced biopsy data

✓ Biopsy and biomarkers

ONGOING

↓LFC ↓ALT

↓LFC ↓ALT ↓Fibrosis

↓LFC ↓ALT ↓Fibrosis NASH Resolution

Aldafermin demonstrated strong, consistent results across Phase 2 cohorts

KEY RESULTS

LFC = Liver Fat Content; ALT = alanine aminotransferase; AST; Aspartate Transaminase;

116

Cohort 4: Study Design and Demographics

STUDY DESIGN

| Screening | On-Treatment Study Period | Follow-Up |

Placebo (Subcutaneous Injection, Daily)

Aldafermin (Subcutaneous Injection, Daily)

D-28   D-1   W6   W12   W18   W24   W30

MRI-PDFF

BIOPSY
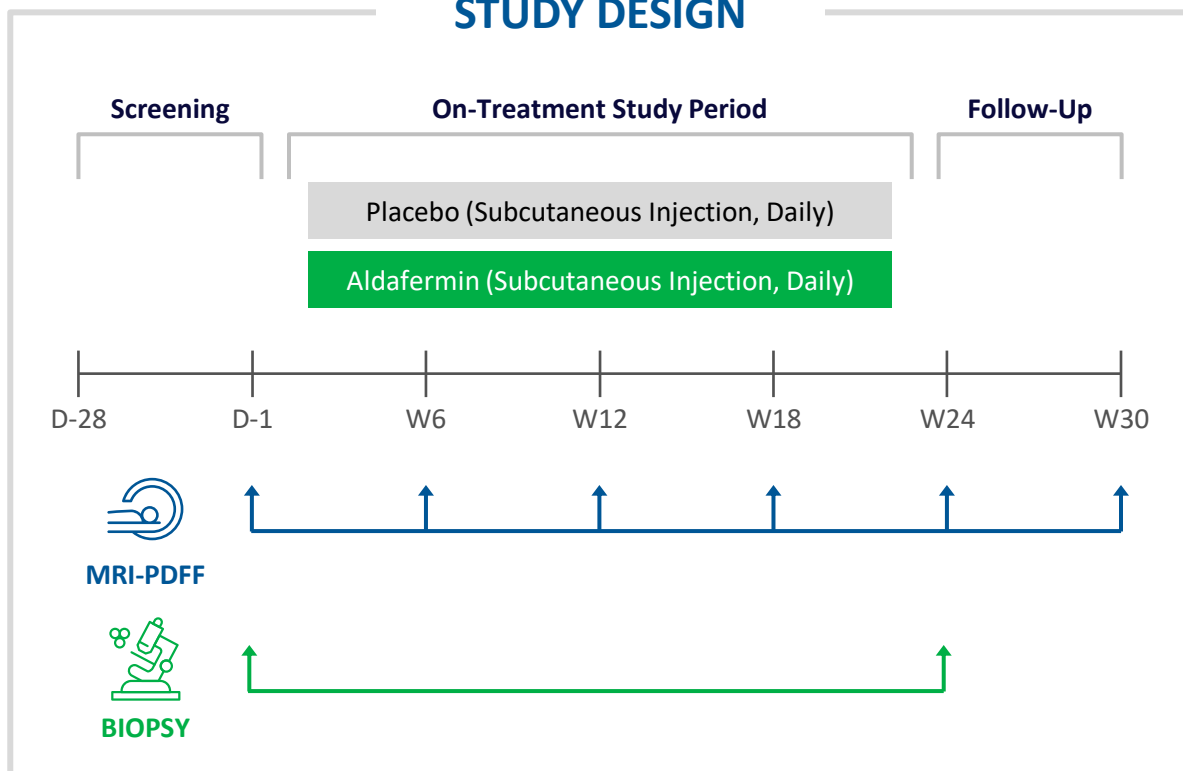
DEMOGRAPHICS AND INCLUSION CRITERIA

Mean Parameters	Placebo (n=25)	Aldafermin 1 mg (n=52)
Age (years)	54.1	53.0
BMI (kg/m^2)	36.8	35.8
Type 2 Diabetes (%)	64%	60%
NAFLD Activity Score (NAS)	5.4	5.7
Fibrosis Stage F3 (%)	41%	46%
LFC (% by MRI-PDFF)	18.5	18.0
ALT (IU/L)	55.1	73.3
AST (IU/L)	44.3	54.5

KEY INCLUSION CRITERIA

- Biopsy-confirmed NASH (**F2 or F3** liver fibrosis by NASH CRN criteria) with NAS ≥4 (1 point in each component)
- Absolute liver fat content (LFC) ≥8% by MRI-PDFF
- ALT > 19 IU/L in females, ALT > 30 IU/L in males

ENDPOINTS

Primary endpoint: change from baseline in absolute LFC (as measured by MRI-PDFF) at W24

Secondary and exploratory endpoints included ALT, AST, biomarkers of fibrosis and effect on liver histology at W24

[1] Liver histology population (aldafermin n=50; placebo n=22); LFC = Liver Fat Content; ALT = alanine aminotransferase; AST; Aspartate Transaminase; MRI-PDFF: magnetic resonance imaging-estimated proton density fat fraction

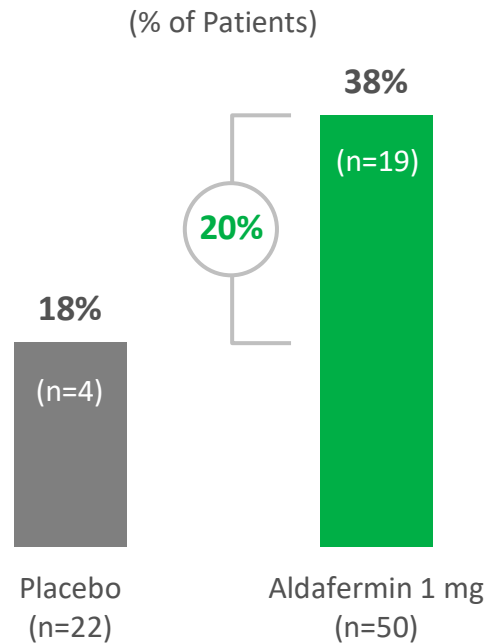# Cohort 4: Efficacy Results on FDA Guided Histological Endpoints

NGMBio

#1

Fibrosis Reversal

Fibrosis Improvement ≥1 Stage with No Worsening of NASH[1] at W24

(% of Patients)

38% (n=19)

20%

18% (n=4)

Placebo (n=22)   Aldafermin 1 mg (n=50)

#2

NASH Resolution

Resolution of NASH without Worsening of Fibrosis[2] at W24

(% of Patients)

24% (n=12)

15%

9% (n=2)

Placebo (n=22)   Aldafermin 1 mg (n=50)

Composite Endpoint

Reverse Fibrosis and Resolve NASH

Fibrosis Improvement and Resolution of NASH[3] at W24

(% of Patients)

$p = 0.015$*

22%* (n=11)

22%

0%

Placebo (n=22)   Aldafermin 1 mg (n=50)

[1] Defined as patients who have an improvement in liver fibrosis by ≥1 stage with no worsening of NASH (no worsening of steatosis, lobular inflammation or hepatocyte ballooning grade) from baseline to W24 (not powered for statistical significance)

[2] Defined as subjects having a NAS score of 0 or 1 for inflammation and 0 for ballooning, with no worsening of fibrosis (no progression of NASH CRN fibrosis stage) from baseline to W24 (not powered for statistical significance)

[3] Defined as patients who have an improvement in liver fibrosis by ≥1 stage AND have a NAS score of 0 or 1 for inflammation and 0 for ballooning at W24 (not powered for statistical significance)

Cohort 4: Strong, Consistent Results Across Non-Invasive Measures

Change in Relative LFC (MRI-PDFF)

Placebo: -13%
1mg: -39%
24W Cohort 4

Change in Relative ALT from Baseline

Placebo: -6%
1mg: -49%
24W Cohort 4

STATISTICALLY SIGNIFICANT
Differences vs Baseline Across All Cohorts

Change in Relative AST from Baseline

Placebo: -1%
1mg: -33%
24W Cohort 4

Change in Relative Pro-C3 from Baseline

Placebo: -4%
1mg: -28%
24W Cohort 4

Relative values are calculated as mean change from baseline; PRO-C3 = pro-peptide of type III collagen

119

Cohort 4: Aldafermin was Well Tolerated and AEs Generally Comparable to Placebo

COHORT 4

TREATMENT EMERGENT ADVERSE EVENTS (TEAE)	Placebo (N=25)	Aldafermin 1 mg (N=53)
Any TEAE	22 (88.0%)	46 (86.8%)
TEAE Leading to Drug Withdrawal	1 (4.0%)	0
Serious Adverse Event (SAE)	3 (12.0%)	2 (3.8%)
Drug-Related TEAE	11 (44.0%)	27 (50.9%)
TEAE Leading to Death	0	0

Most Common (>10%) Adverse Events	Placebo (N=25)	Aldafermin 1 mg (N=53)
Diarrhea	6 (24.0%)	15 (28.3%)
Nausea	6 (24.0%)	5 (9.4.%)
Headache	9 (36.0%)	7 (13.2%)
Fatigue	4 (16%)	3 (5.7%)
Abdominal Distension	3 (12.0%)	7 (13.2%)
Diabetes Mellitus	5 (20.0%)	2 (3.8%)
Peripheral Edema	3 (12.0%)	2 (3.8%)

- All SAEs were deemed to be not related to treatment by site investigator

- No increase in Pruritus (4% Aldafermin vs. 8% placebo)

- No increase in gastrointestinal adverse events

Aldafermin Development Plan
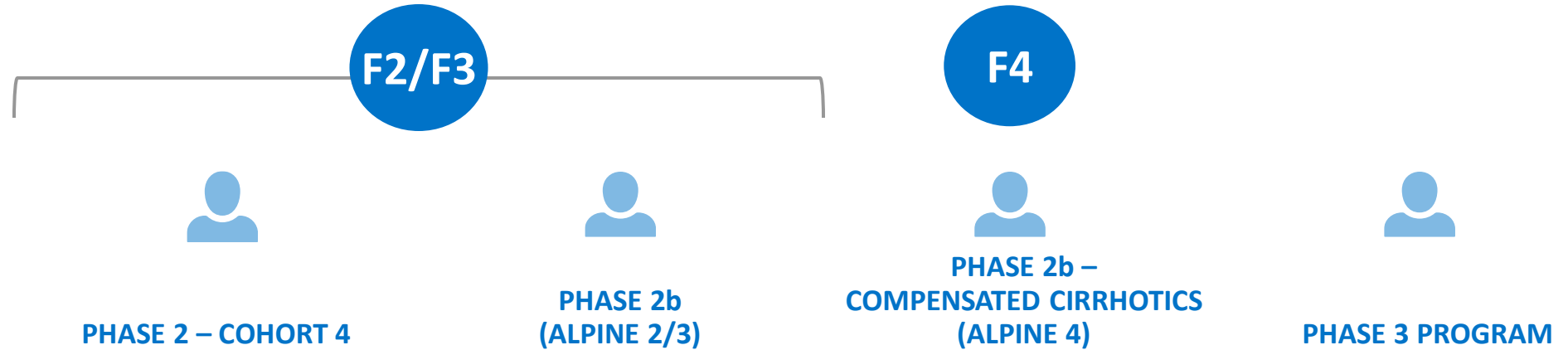
	PHASE 2 – COHORT 4	**PHASE 2b (ALPINE 2/3)**	**PHASE 2b – COMPENSATED CIRRHOTICS (ALPINE 4)**	**PHASE 3 PROGRAM**
Status	Topline Data – Feb 2020 EASL Presentation – Aug 2020	Fully enrolled Topline data expected – 2Q21	Enrolling	Planning
Duration	24 Weeks	24 Weeks	48 weeks	TBD
Aldafermin Dose (# Patients)	Placebo (25)	Placebo (~40)	Placebo (~40)	Placebo
	1 mg (53)	0.3 mg, 1 mg, 3 mg (~40 per dose level)	0.3 mg, 1 mg, 3 mg (~40 per dose level)	Dose Level(s) TBD

MK-3655 in NASH
A Monthly FGFR1c/KLB-specific Agonist Antibody Distinct from FGF21

MK-3655 (NGM313) for the Treatment of NASH

FGF21 analogs have demonstrated variable clinical efficacy in metabolic syndrome patients; native ligand has potential for safety liabilities

MK-3655

FGF21

KLB — FGFR1c

KLB — FGFR2c

KLB — FGFR3c

KLB — FGFR4
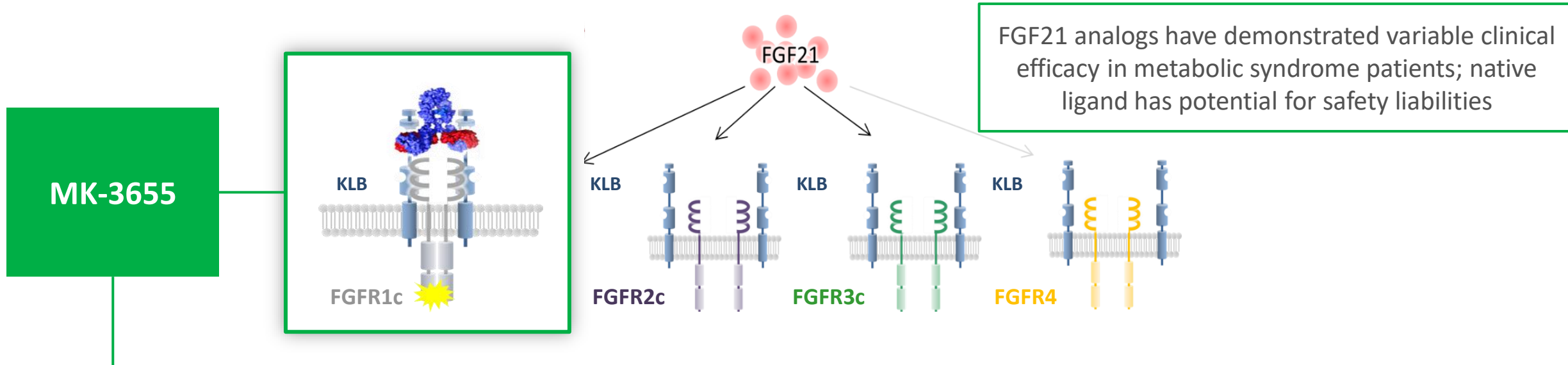
- Agonistic antibody that selectively activates FGFR1c / KLB to regulate energy metabolism

- Potential to be once-monthly injectable insulin sensitizer for treatment of NASH

- Completed Phase 1 SAD/MAD study in obese, insulin resistant subjects and Phase 1b study in subjects with NAFLD

- Single dose of MK-3655 resulted in **significant reductions in liver fat content and improvement in metabolic markers** based on preliminary data from a Phase 1b study in obese, insulin resistant subjects with NAFLD **after five weeks**

- **Merck exercised its option and licensed MK-3655 (NGM313)**

MK-3655 for the Treatment of NASH

Significant Reductions in Liver Fat Content and Improvement in Metabolic Markers (HbA1C) After 5 Weeks

Phase 1b Study in Obese, Insulin Resistant Subjects with NAFLD

Liver Fat Content	HbA1c
Absolute Reductions / Relative Reduction	Absolute Reduction

Liver Fat Content — Absolute Reductions: -6.3% (MK-3655), -4.0% (Pioglitazone)
Liver Fat Content — Relative Reduction: -37.0% (MK-3655), -25.0% (Pioglitazone)
HbA1c — Absolute Reduction: -0.24% (MK-3655), -0.11% (Pioglitazone)

Legend:
- MK-3655 240 mg QM
- Pioglitazone 45 mg QD

MK-3655
Statistically Significant Improvements in
ALT and AST, Triglycerides,
HDL-C, LDL-C, PRO-C3

Pioglitazone
Increased Body Weight by 2.3kg
(vs 1.6kg increase for MK-3655 -
no edema/fluid retention)

Phase 1b Safety: MK-3655 was Well Tolerated and AEs Generally Comparable to Placebo

MK-3655 Safety Results

- Favorable safety and tolerability profile consistent with other MK-3655 studies

- All AEs were mild in severity

- No SAEs or Grade 2/3/4 AEs

- No pattern of AEs or organ system AEs of note

- No hypoglycemia

- Most common AEs (>10%) were injection site reaction (12%) and increased appetite (12%)

- No evidence of safety issues that have been associated with FGF21 analogues in clinical development

    - No tremor, no GI side effects, no effects on cortisol, no blood pressure changes

Aldafermin and MK-3655 Have Potential to be Complementary

Aldafermin

- Data from Cohort 4 Phase 2 study of Aldafermin 1 mg demonstrated:

  1. **Fibrosis reversal and NASH resolution**
  2. **Significant reductions in liver fat content**
  3. **Improvement in metabolic markers**
  - based on data from Phase 2 study in biopsy-confirmed NASH patients with F2-F3 fibrosis **after 24 weeks** of daily treatment[1]

- Each cohort in the Phase 2 study demonstrated strong consistent results and added more evidence of effect

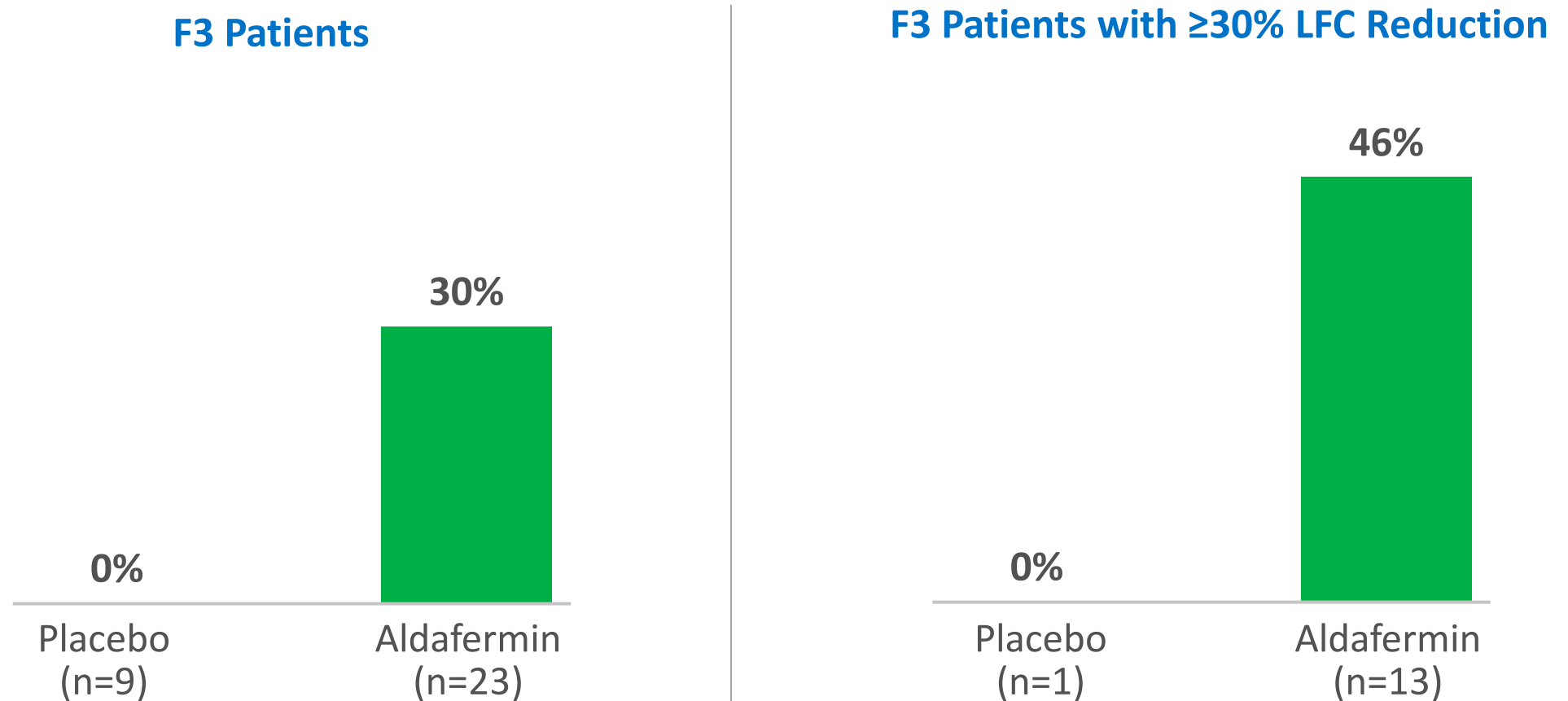- Aldafermin was well tolerated and AEs generally comparable to placebo

MK-3655

- Data from Phase 1b study of single dose of MK-3655 1 mg demonstrated:

  1. **Reductions in HbA1c**
  2. **Significant reductions in liver fat content**
  3. **Improvement in metabolic markers**
  - based on data from a Phase 1b study in obese, insulin resistant subjects with NAFLD **after five weeks**[2]

- Favorable safety and tolerability profile consistent with other MK-3655 studies

- No evidence of safety issues that have been associated with FGF21 analogues in clinical development
  - No tremor, no GI side effects, no effects on cortisol, no blood pressure changes, no bone effects

Aldafermin Phase 3 Development Planning

Cohort 4: Aldafermin Has Demonstrated Higher Anti-Fibrotic Effect in Patients with Advanced Disease (F3)

Fibrosis Improvement ≥1 Stage with No Worsening of NASH[1] at W24

F3 Patients

F3 Patients with ≥30% LFC Reduction

30%

0%

Placebo
(n=9)

Aldafermin
(n=23)

46%

0%

Placebo
(n=1)

Aldafermin
(n=13)

[1] Defined as patients who have an improvement in liver fibrosis by ≥1 stage with no worsening of NASH (no worsening of steatosis, lobular inflammation or hepatocyte ballooning grade) from baseline to W24 (not powered for statistical significance); LFC, liver fat content

NASH Development Landscape: Available Data on Fibrosis Improvement in Patients with Advanced Disease (F3)

Magnitude of Fibrosis Improvement ≥1 Stage with No Worsening of NASH in F3 Patients

30%

No Data Available

Placebo (n=9) — 0%
Aldafermin (n=23) — 30%
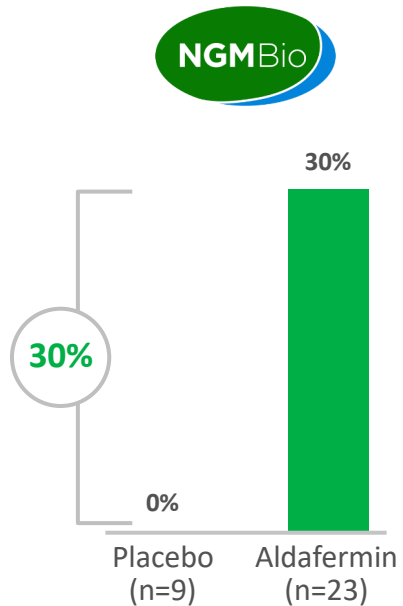
Importance of Fibrosis Improvement in F3 Patients *versus* F2 Patients

- Efficacy in F3 may be more clinically meaningful to clinical hepatologists
  - Preventing progression to cirrhosis is a top priority for F3 patients

- A focus on F3 efficacy may be more clinically meaningful to NASH patients. We continue to gather more data to enable us to:
  - Understand how rapidly aldafermin may work
  - Understand how aldafermin works for the F3 fibrotic liver condition

Liver fibrosis is the most important determinant of mortality and morbidity in NASH[1]

[1]Angulo et al., Gastroenterology 2015;149:389-397; Ekstedt et al., Hepatology 2015;61:1547-1554; Dulai et al., Hepatology 2017;65:1557-1565

Phase 3/4 Program Planning

- We will be discussing a few novel Phase 3/4 designs with FDA

- Planning to enrich patients studied to emphasize F3 subjects
  - May decrease placebo variability and increase the probability of success in Phase 3
  - The higher event rate expected to be experienced by F3 patients in the Phase 4 portion may expedite final approval decision

- Awaiting ALPINE 2/3 data to determine final dose(s) for Phase 3

- Actively planning to start Phase 3

Corinne Foo-Atkins, MD MBA MSc
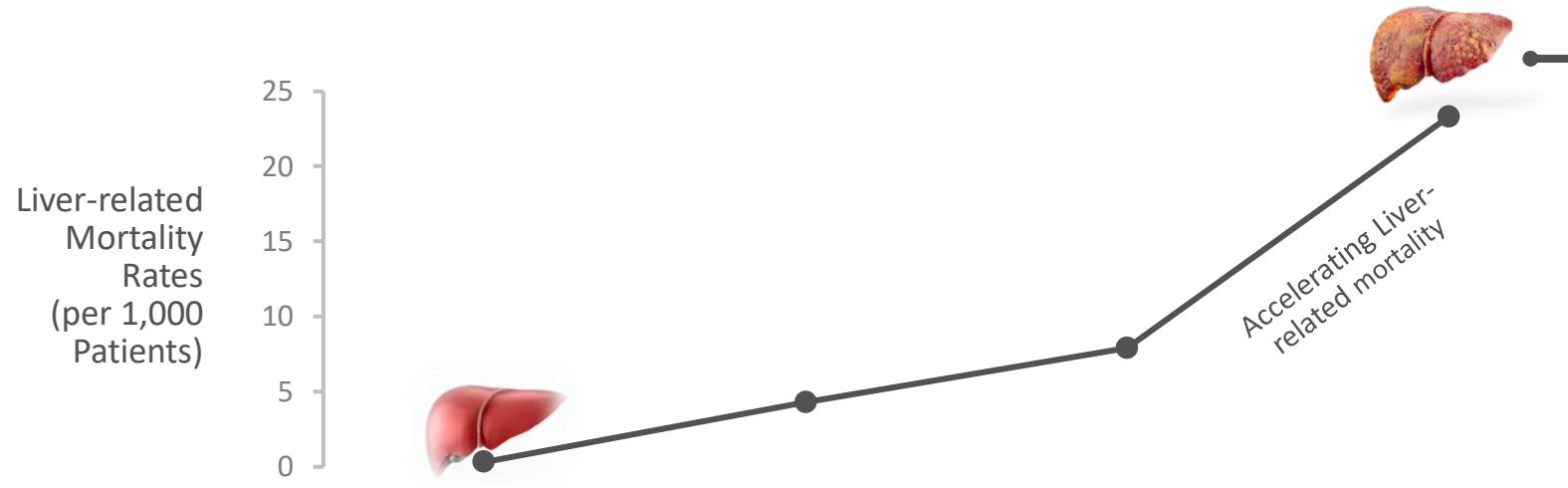
Vice President, Product Strategy

NASH: A Serious and Growing Disease, with Negative Outcomes Linked to Severity of Fibrosis

Liver-related Mortality Rates (per 1,000 Patients)

Accelerating Liver-related mortality

FIBROSIS STAGE	F0/F1	F2	F3	F4
US Prevalence - 2020	11.0M	4.1M	2.6M	1.6M
US Prevalence – 2030 (Est'd)	12.9M	6.1M	4.5M	3.5M

AN INCREASINGLY HEAVY BURDEN OF DISEASE

F4 (cirrhosis) drives negative liver-related outcomes and mortality

- **~7 year median survival**

- **>60% risk of cirrhosis-related complications**: ascites, jaundice, hepatic encephalopathy, variceal bleed, liver cancer, liver transplant

- **3rd leading cause of death:** liver-related complications in NASH cirrhosis (liver failure, variceal bleed, liver cancer)

Cirrhosis regression shown to reduce risk of liver events by 84%

Source: Adams et al, Gastroenterology 2005; 129:113-121. Sanyal A, AASLD 2020

Sources: Dulai et al, Hepatology 2017, 65(5):1557-1565; Singh et al, Clin Gastroenterol Hepatol. 2015, 13(4): 643–654; Estes et al, Hepatology 2018, 67(1): 123-133

F3/F4 NASH Exact a Severe Economic Toll on Both Patients and Society

Estimated average annual costs per U.S. NASH patient

	F0 F1 F2	F3	F4			
			Comp.	Decomp.	HCC	Liver Transplant*
NON-DRUG MEDICAL	$0.4k	$0.6k	$19.6k	$37.0k	$97.0k	$368.1k
DIRECT NON-MEDICAL	$2.8k	$4.8k	$7.5k			
INDIRECT	$7.9k	$13.9k	$21.3k			
Total Annual NASH Economic Burden per Patient**	**$11.1k**	**$19.3k**	**$48.4k** → **$396.8k**			

*Year 1 costs
**Non-drug

FOCUS POPULATIONS

Sources: Younossi AM et al, Hepatology 2016; 64(5):1577-1586, O'Hara J et al, Lancet Preprints (2019). ICER Evidence Report on Obeticholic Acid for NASH (2020).
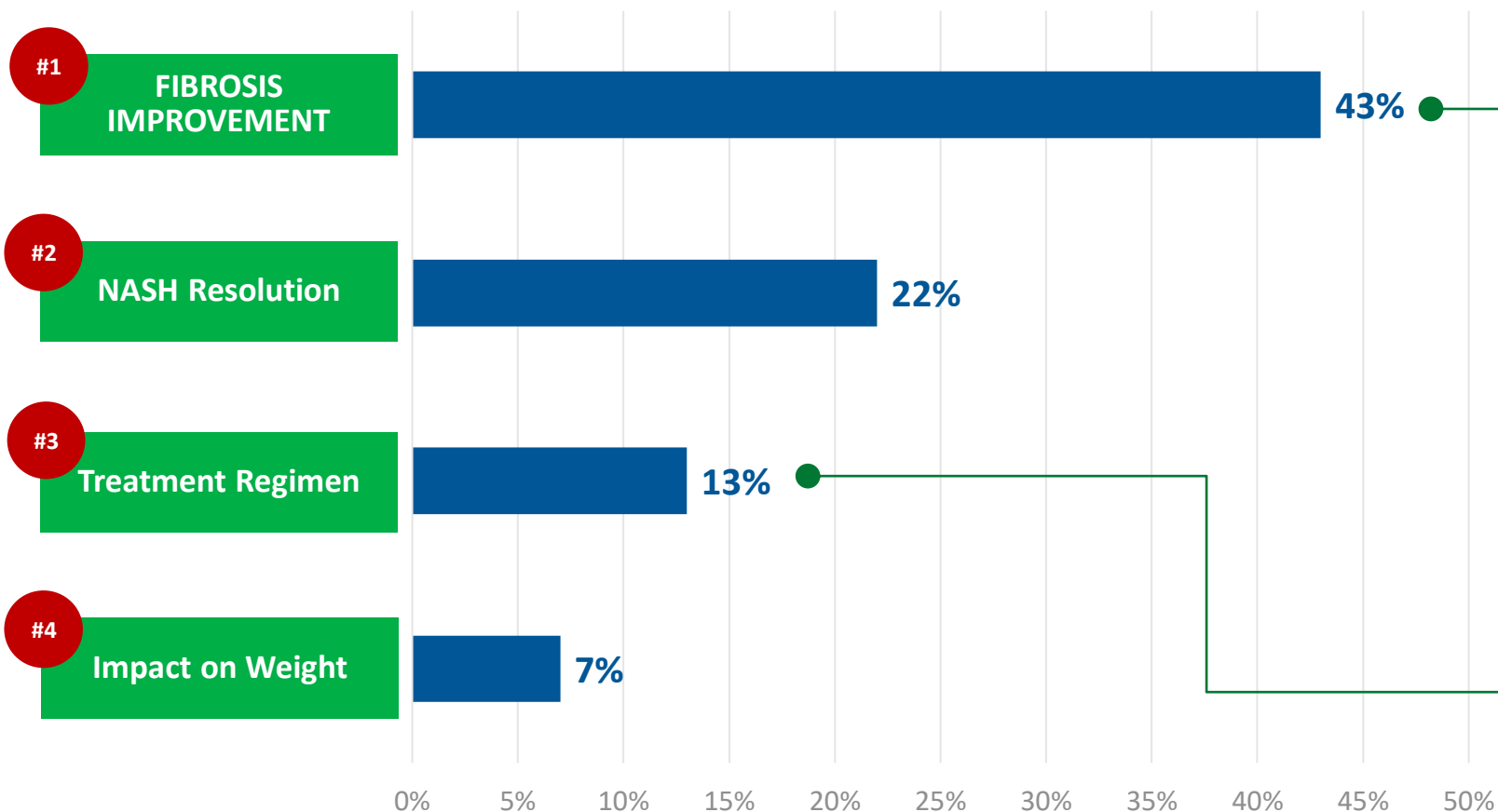
In Prescribing Decisions, Gastros/Heps Likely to be Most Driven by Fibrosis Data

RELATIVE CONTRIBUTION OF DRUG ATTRIBUTES IN NASH THERAPY SELECTION

#1 FIBROSIS IMPROVEMENT — 43%

#2 NASH Resolution — 22%

#3 Treatment Regimen — 13%

#4 Impact on Weight — 7%

0% 5% 10% 15% 20% 25% 30% 35% 40% 45% 50%

> *I would put fibrosis as the single most important factor, because it's a good predictor.* Especially if you have advanced fibrosis, that means there is injury and hopefully it can be reversed. There are more studies on fibrosis to show prognosis-wise in terms of decompensation, in terms of risk for cancer, especially if they're F3 or F4.
>
> **– Gastroenterologist**

Reduced frequency of treatment is relevant to patient compliance, but ~50% of respondents stated **route of administration does not matter** for HCP treatment decisions

15% other factors.

NGM Bio analysis with ~250 hepatologists and gastroenterologists

134

Market Research Indicates that Injectable RoA is an Acceptable Tradeoff for Achieving Greater Efficacy

Representative Patient Profile	**F2, High Liver Fat Content, Obese, Diabetic, Hypertensive**	**F3, High Liver Fat Content/ Mod Inflammation, Obese, Diabetic, Hypertensive**	**F3, Highly Inflamed Liver, Obese, Dyslipidemic, Hypertensive**
Physicians' Selection Criteria for Treatments	✓ High efficacy with quick response ✓ May avoid therapies with weight gain	✓ Strong efficacy and rapid response prioritized ✓ Injectable RoA of less concern	✓ Dyslipidemia a concern for first-line Tx selection ✓ High switch rate to efficacious second-line
Patients' Preferences	✓ Stops progression or even reverses fibrosis or cures NASH ✓ Injections acceptable, particularly if already on other injectable meds ✓ Mild side effects can be tolerated		

Manal Abdelmalek, MD,
Professor of Medicine, Duke University School of Medicine; Director, NAFLD Clinical Research Program, Duke University

Natural History of NAFLD/NASH

HCC, hepatocellular carcinoma.
Younossi ZM, et al. *Hepatology*. 2018;68:349–360; Younossi ZM, et al. *Hepatology*. 2018;68:361–371; Younossi ZM. *J Hepatol*. 2019;70:e17–e32;
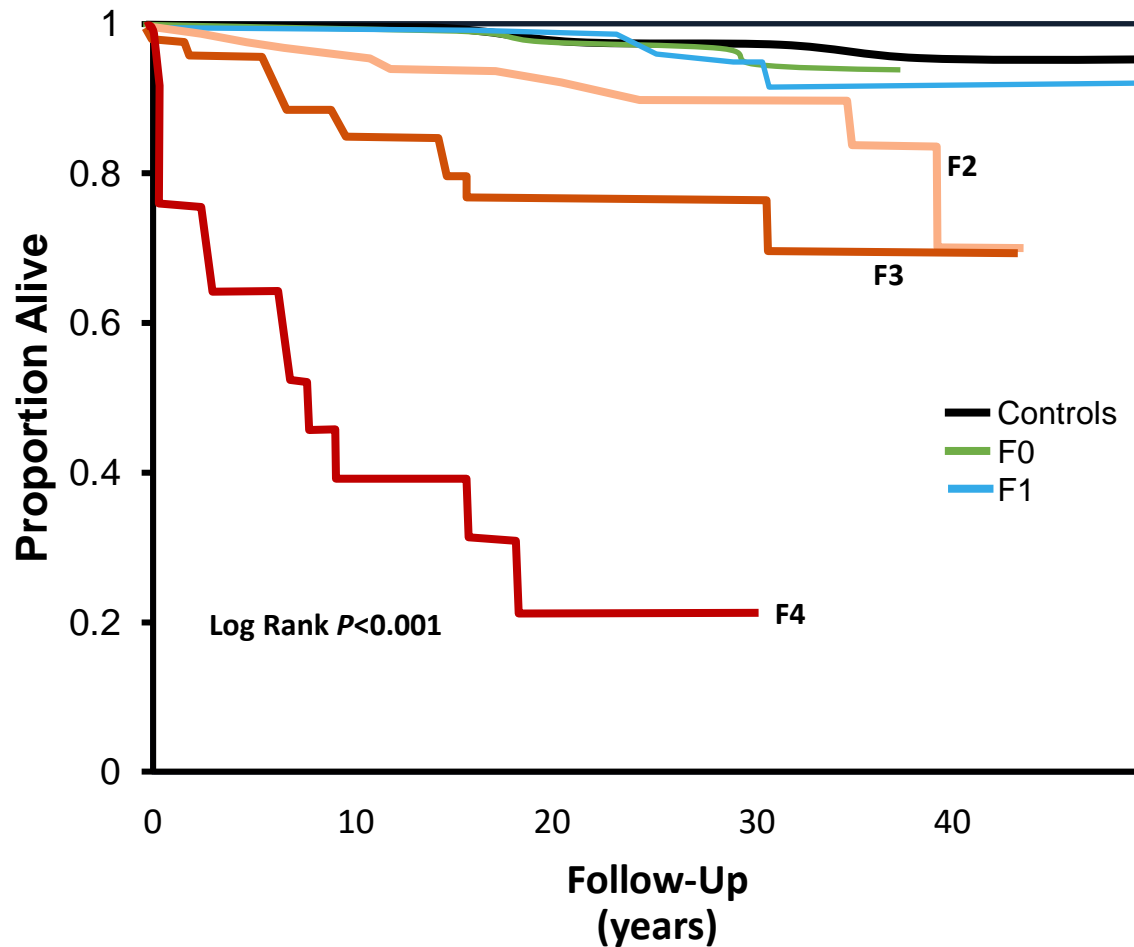Jie Li, et al. *Lancet Gastroenterol Hepatol*. May 2019.
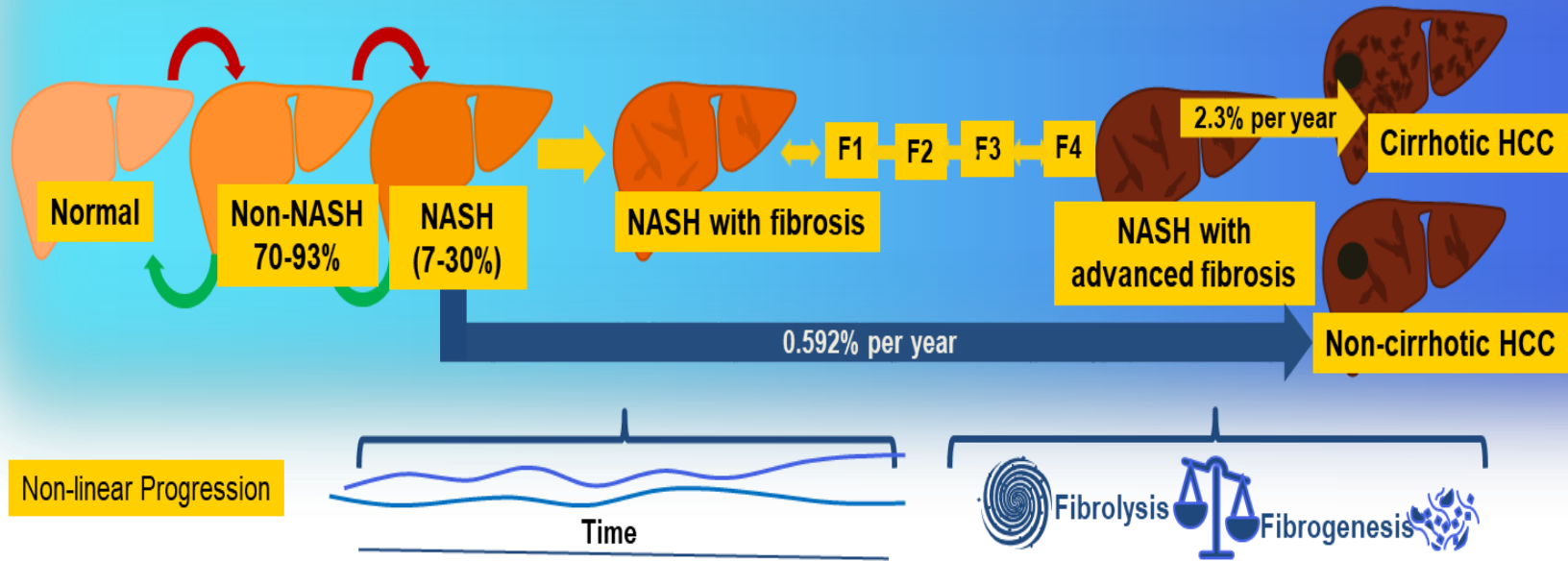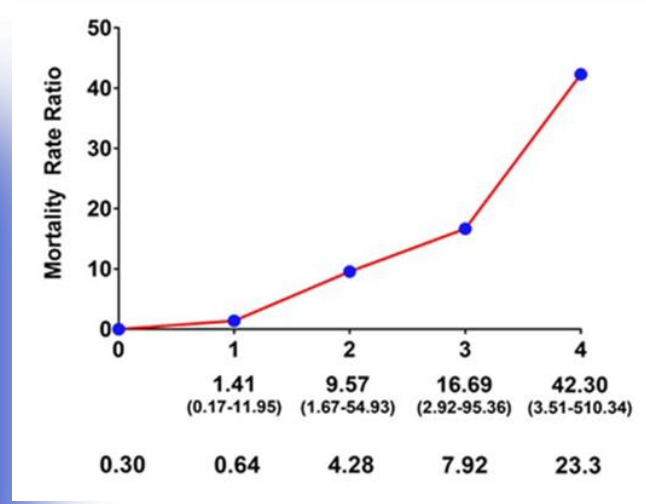
Fibrosis Stage But Not NASH Predicts Mortality

Liver-Related Mortality / All-Cause Mortality survival curves by fibrosis stage (Controls, F0, F1, F2, F3, F4). Log Rank P<0.001.

Angulo et al., Gastroenterology, 2015; 149:389
Ekstedt et al., Hepatology, 2015; 61:1547
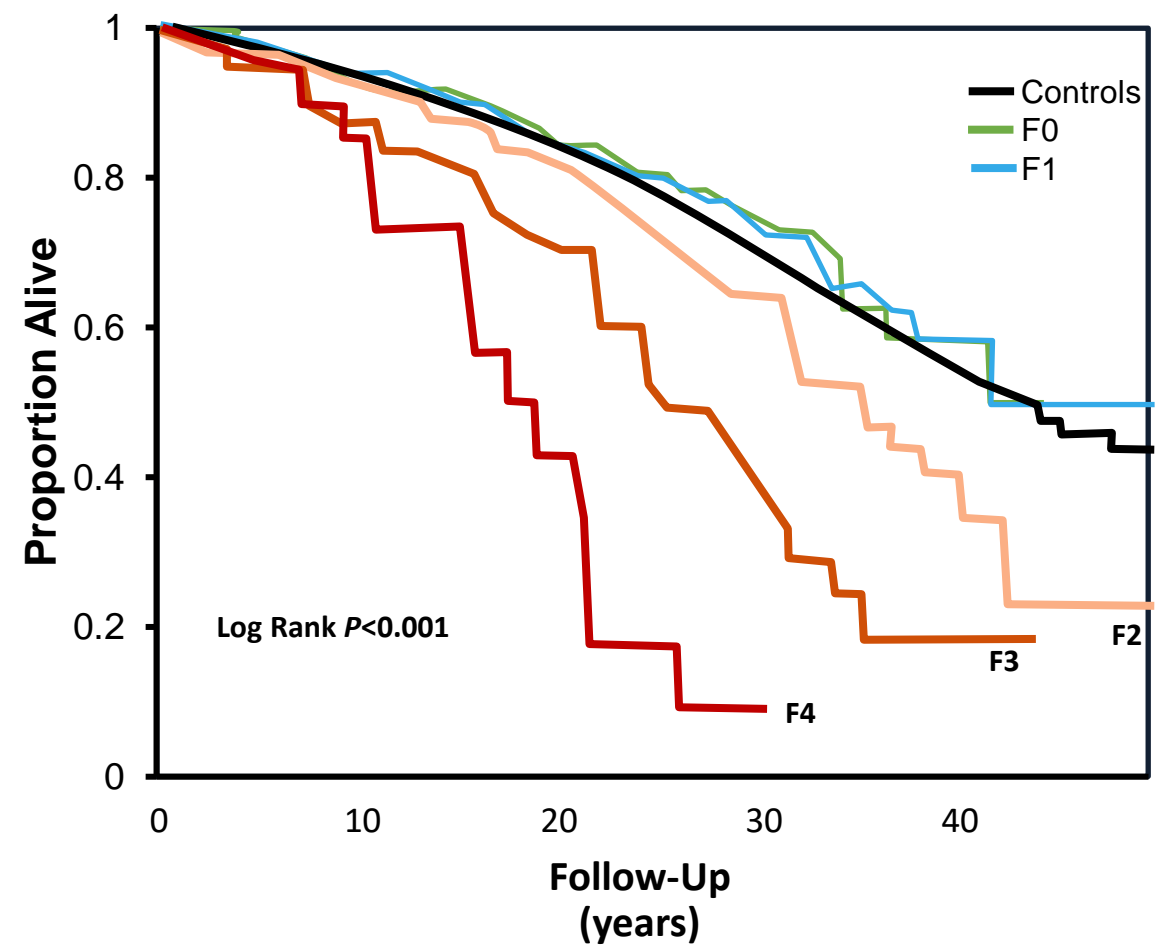
Models Suggest a Growing Clinical Burden Driven by Advanced NASH: Data from the United States

2015

20% of NAFLD is NASH

2030

27% NAFLD will be NASH

Cases of stage 3 fibrosis due to NASH[1]

2 M → 4.5 M

Cases of stage 4 fibrosis due to NASH[1]

1.3 M → 3.1 M

By 2030, there are projected to be nearly 800,000 excess liver deaths
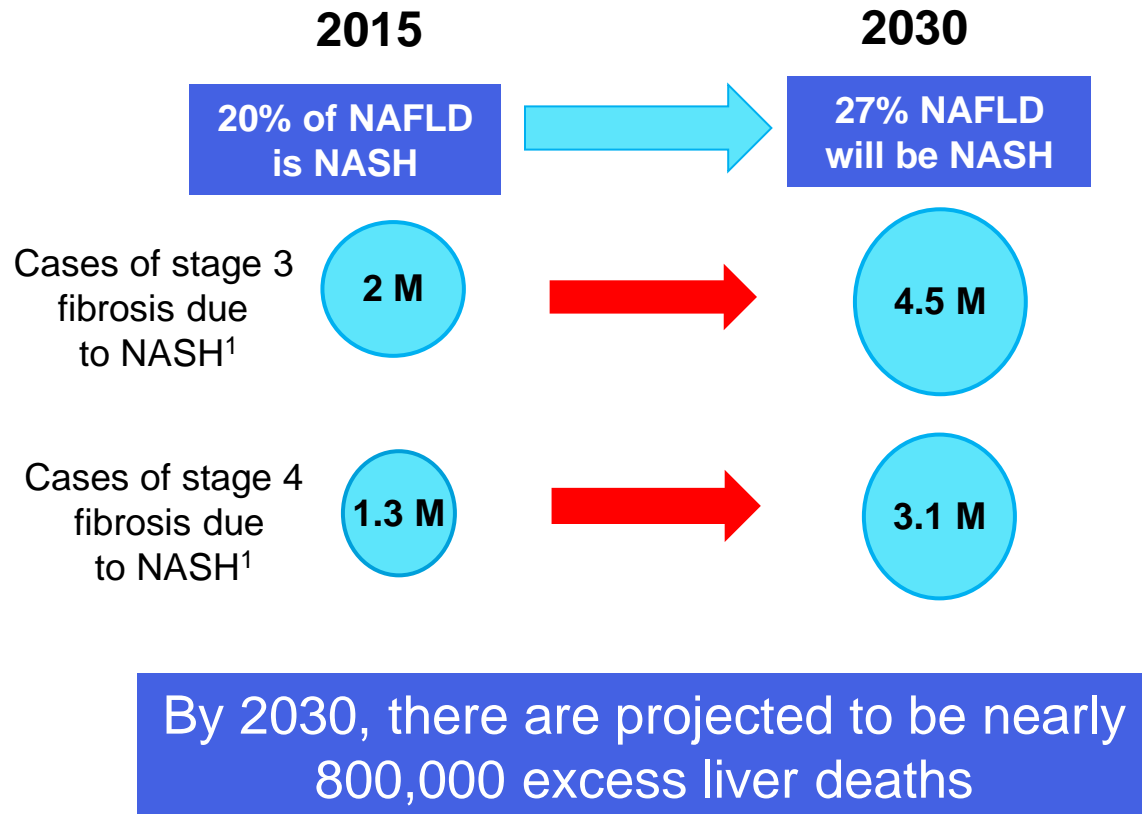
Incident decompensated cirrhosis, HCC and liver-related deaths

Incident-decompensated cirrhosis +168%

Incident liver-related deaths +178%

Incident HCC +137%

Incident cases/deaths

120,000
100,000
80,000
60,000
40,000
20,000
0

2015 2016 2017 2018 2019 2020 2021 2022 2023 2024 2025 2026 2027 2028 2029 2030
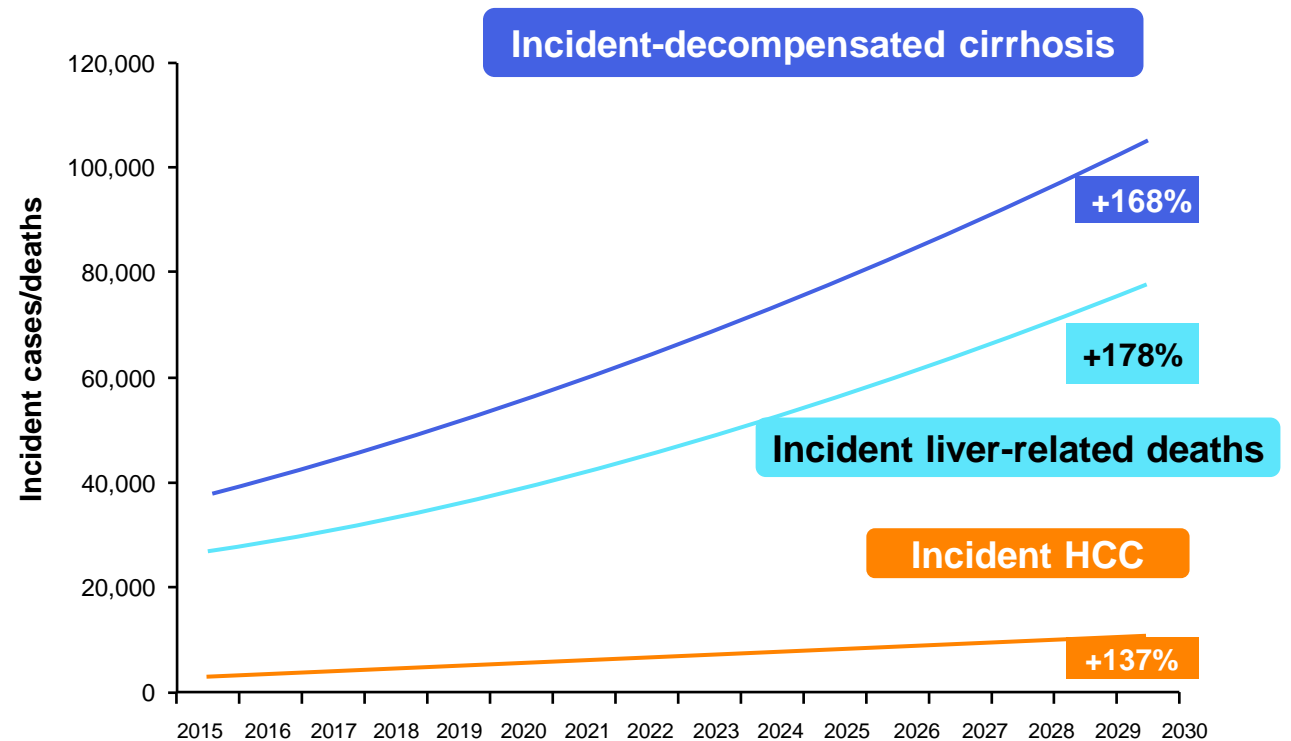
HCC, hepatocellular carcinoma; M, million; T2DM, type 2 diabetes mellitus.
Estes C, et al. *Hepatology*. 2018;67:123–133.

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Goal for Drug Development

CURE

GOAL

FDA APPROVED

FEEL

FUNCTION

SURVIVE
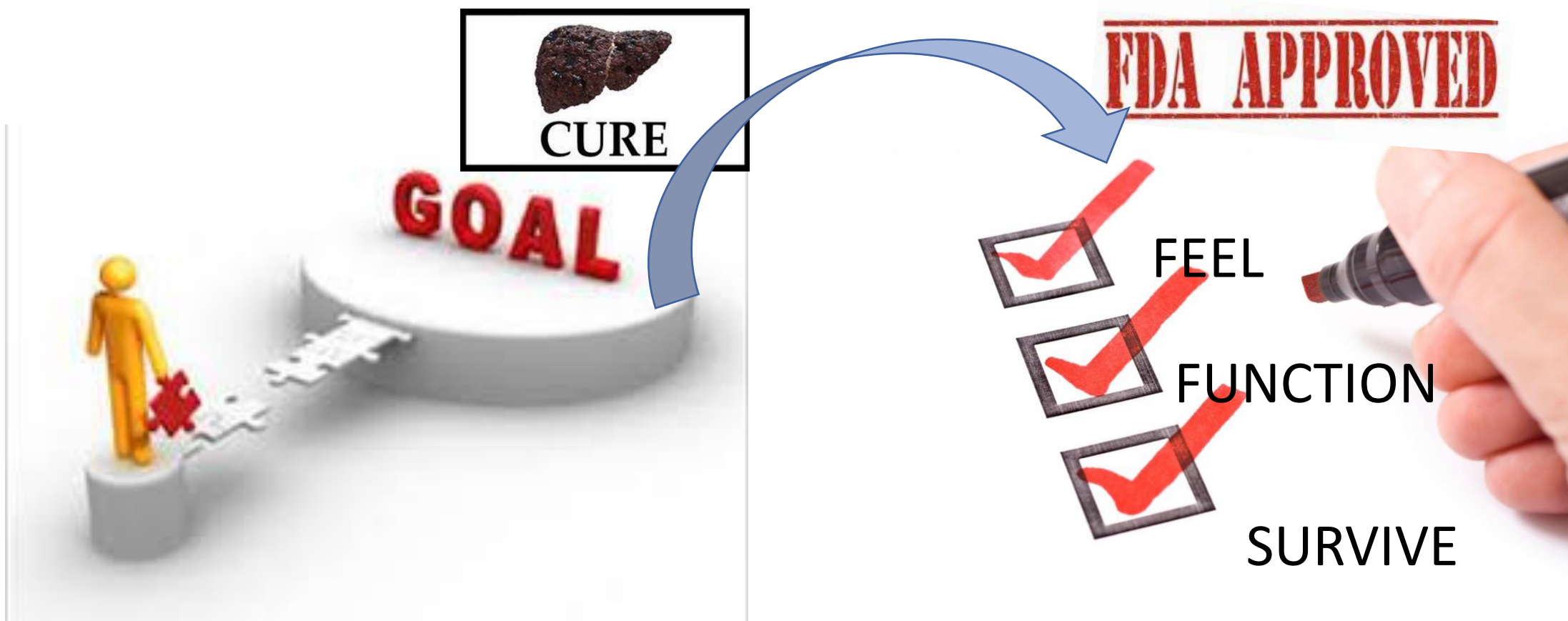
Resolve NASH—strongest predictor of hepatic fibrosis
Improve fibrosis—strongest predictor of morbidity /mortality

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Living with NASH: A Frustrating Ordeal for Patients

TYPICAL PATIENT'S JOURNEY

Vague Discomfort, Constant Fatigue

- NASH mostly picked up through workups for comorbidities

- Relief if told "only fatty liver"
- Fear, shock if told of seriousness
- Angry and frustrated at diagnosis delays (especially if already progressed to cirrhosis)

NASH Diagnosis Frequently Missed or Delayed

Few Treatment Options - Mostly Ineffective

- Defeated, frustrated at limited options and little/no information about NASH
- Dieting ineffective

Monitoring Visits Create Anxiety

- Feeling of desperation about potential progression

MARCELA'S STORY

- 43-year-old
- San Antonio, Texas
- Diagnosed in 2017

Diagnosis

" *For 6 months, I had diarrhea, heartburn, pain in my right upper abdomen, nausea ... my liver function test was very abnormal. My gall bladder was inflamed and was removed, and fortunately the doctor did a liver biopsy, which showed I had F3 disease.*

Management

" *I changed my lifestyle and went on a diet and exercise regimen. And fortunately I got into a clinical trial. I was so motivated for myself and my family.*

Knowing I can prevent cirrhosis, liver cancer, and liver failure keeps me positive.

I'm a single mom and want to be around for my 12-year old.

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142

Bile Acid Dysregulation As a Key Driver of NASH Pathogenesis

- Bile acids accumulate in excess in the liver and blood in chronic liver diseases including NASH

- **Bile acid is a major driver of hepatic inflammation**, perpetuating the pro-inflammatory and pro-fibrotic cascades
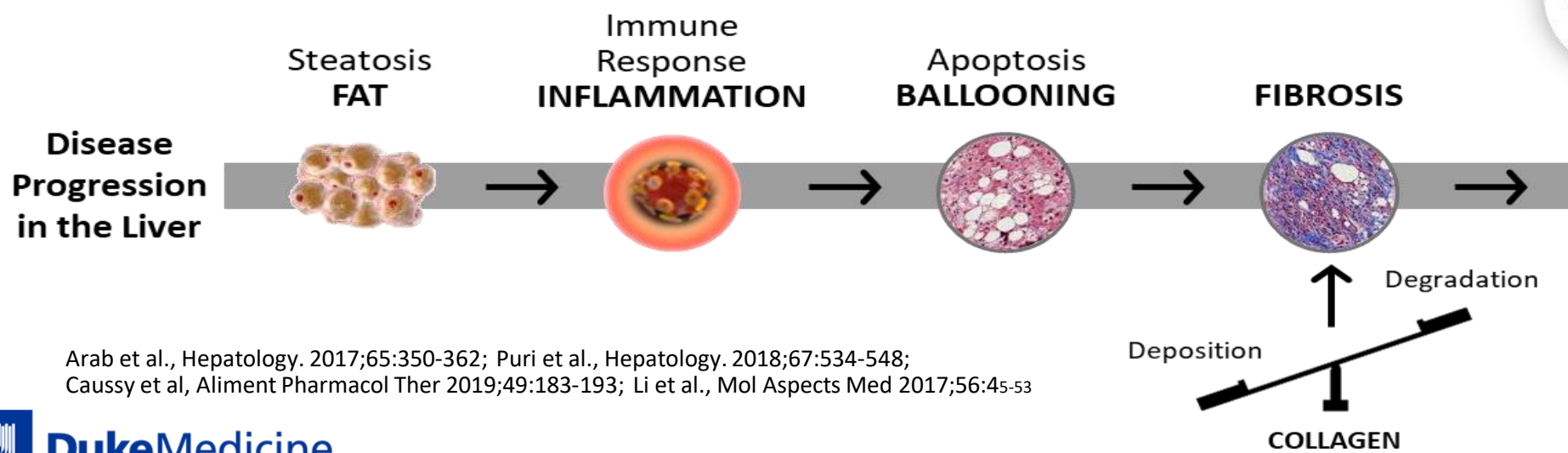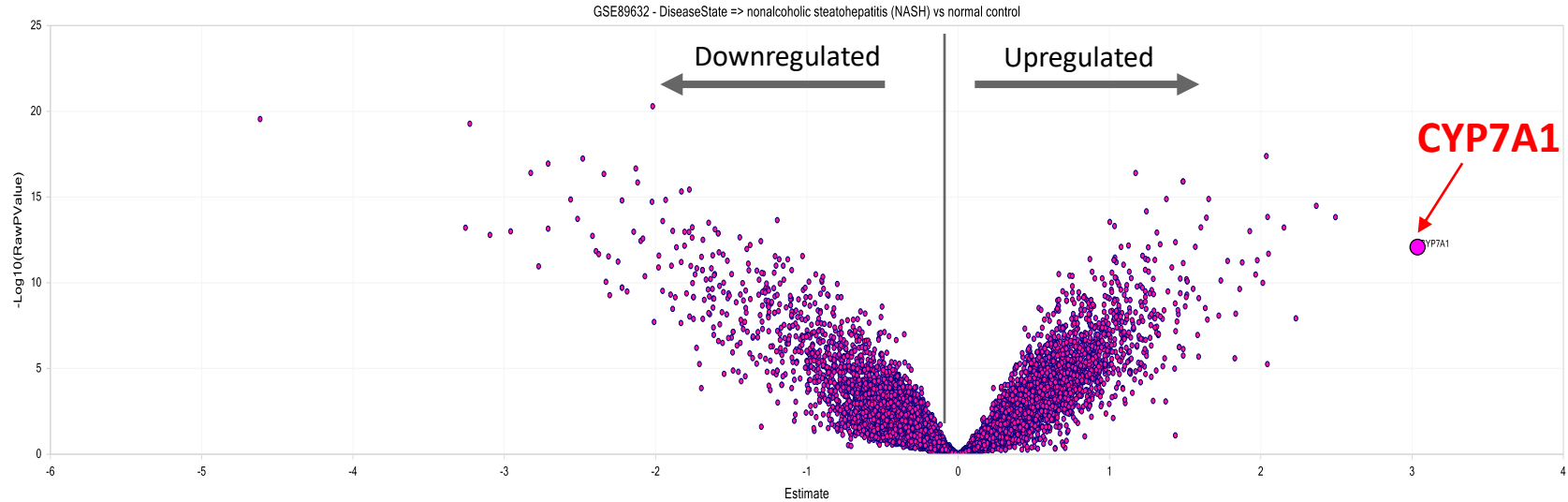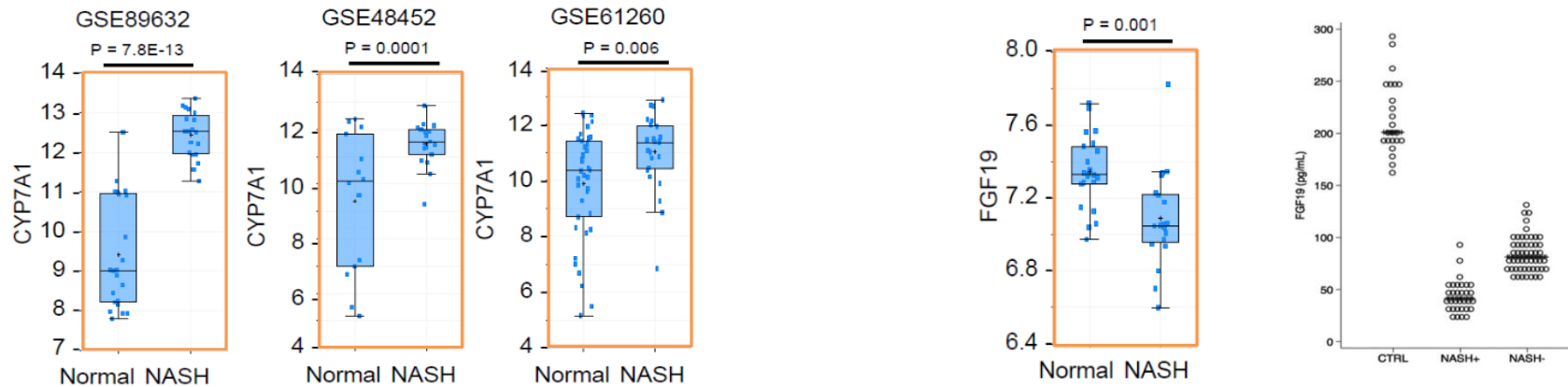
Arab et al., Hepatology. 2017;65:350-362; Puri et al., Hepatology. 2018;67:534-548;
Caussy et al, Aliment Pharmacol Ther 2019;49:183-193; Li et al., Mol Aspects Med 2017;56:45-53

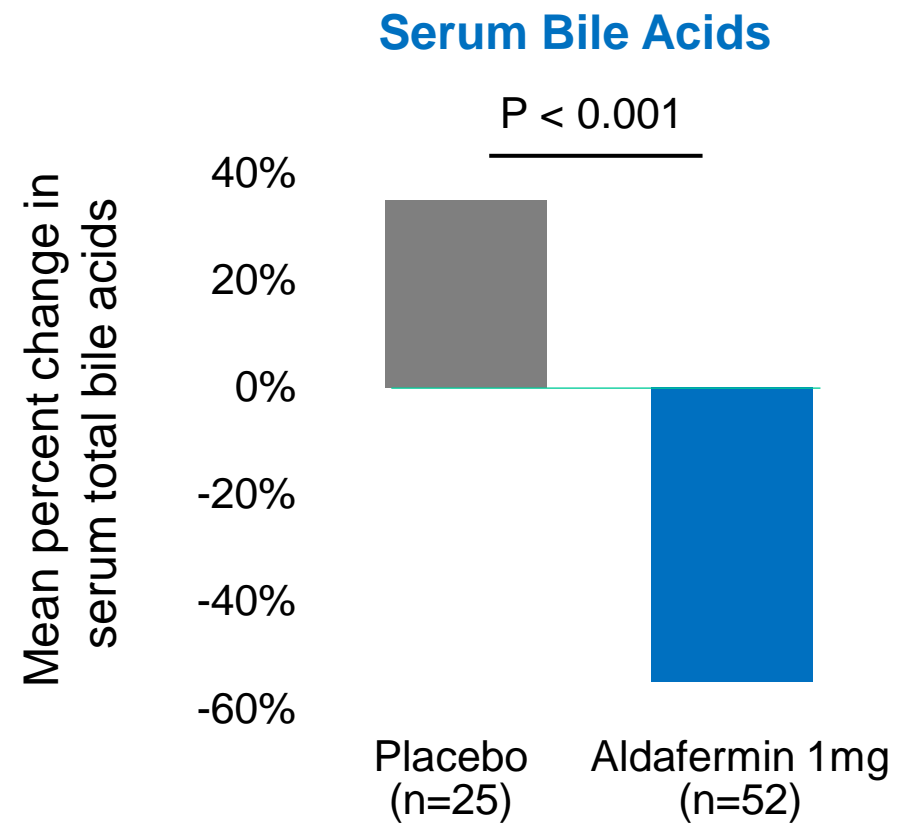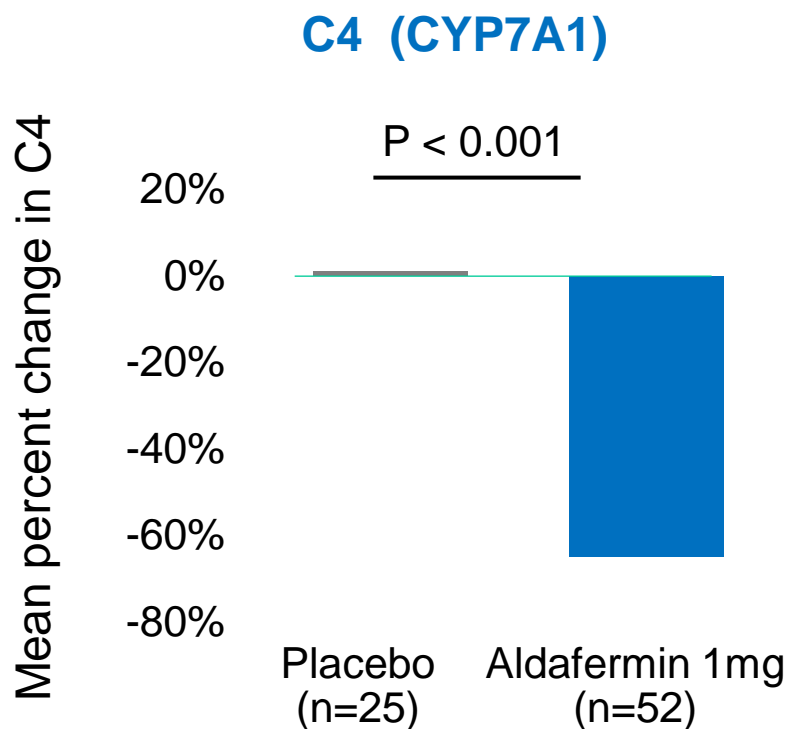# Bile Acid Metabolism is Dysregulated in Patients with NASH

GSE89632 - DiseaseState => nonalcoholic steatohepatitis (NASH) vs normal control

Downregulated ← → Upregulated

CYP7A1

- **CYP7A1 is upregulated in NASH patients**
- **FGF19 is downregulated in NASH patients**

GSE89632 — P = 7.8E-13
GSE48452 — P = 0.0001
GSE61260 — P = 0.006
P = 0.001

Cohort 4 Data: Aldafermin Robustly Reduces Serum Bile Acids and C4

C4 (CYP7A1)

Serum Bile Acids

C4, 7α-hydroxyl-4-cholesten-3-one

My perspective on Regulatory Landscape

FDA Mission
Ensure Public Health

Efficacy Drug
Risk Drug

Safety Drug
Risk Disease

FDA AASLD

"It is imperative that any drug developed for NASH be at least neutral from a cardiovascular risk perspective and ideally also reduce cardiovascular risks"

Hepatology 2015

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My perspective on ICPT Complete Response Letter (CRL)

"In hindsight, I believe that our oversight was shortsighted. At least that's my insight."

1. Lack of protocol driven management of OCA associated LDL-C elevations. –as with phase 2, management left to discretion of PI.

2. Primary outcome with small margin of efficacy over placebo with side effects including pruritus and increase in lipids.

3. Imperfect "gold" standard of histology with poor agreement between 2 different pathologists.

3. Surrogate biomarkers not approval endpoints.

4. No alarm signs (CV events) but want more time and more data to optimize confidence

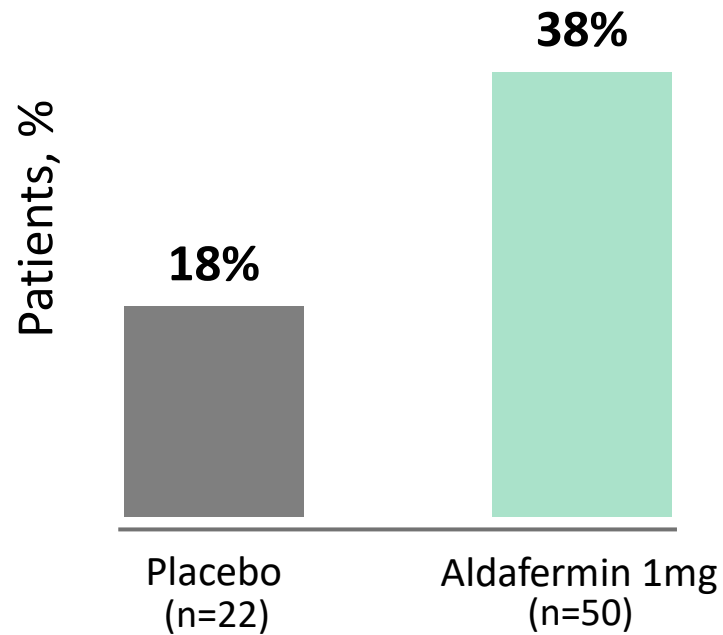PLEASE SLOW DOWN! FOR EVERYONE'S SAFETY

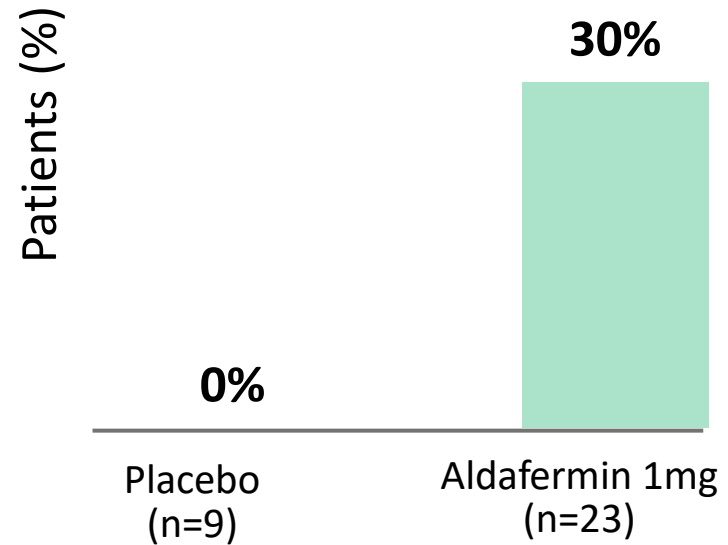Cohort 4 Data: Aldafermin Shows A Robust Fibrosis Regression Data at W24

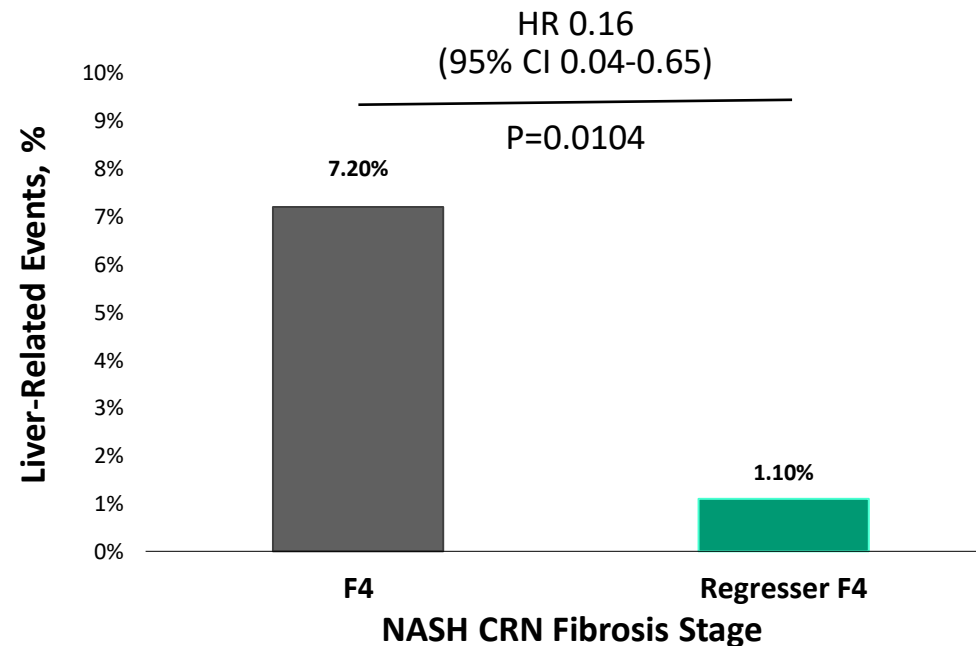Fibrosis Improvement ≥1 Stage with No Worsening of NASH[1]
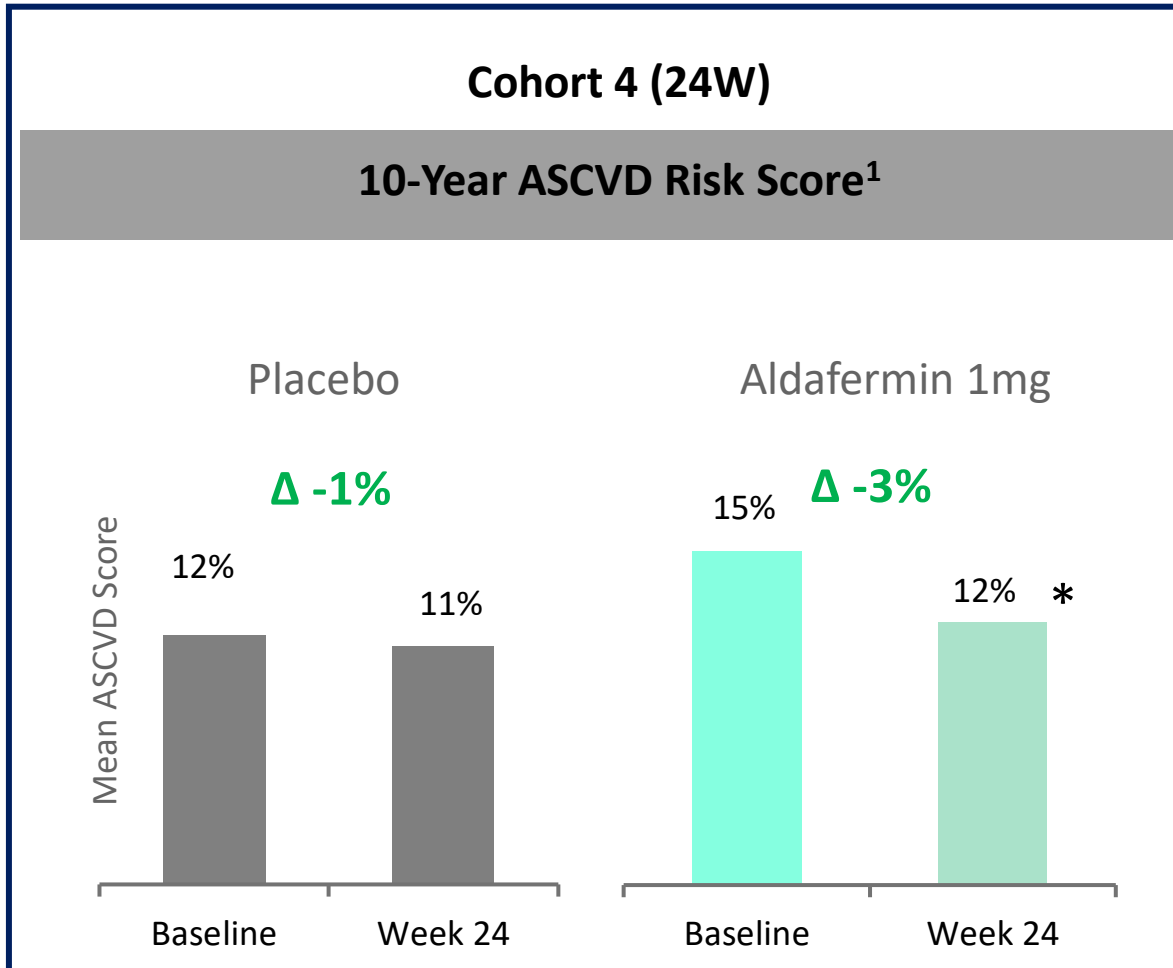
F2/F3 Patients

F3 Patients

148

Fibrosis Regression is Associated with Reduction of Hepatic Events in Compensated Cirrhotic Patients

Fibrosis Regression in F4 Subjects Associated with Reduction of Hepatic Events[1]

[1]Dr Arun Sanyal, Oral Abstract, AASLD, 2020 Stellar-4 data.

Cohort 4 Data: Optimized Lipid Management in NASH Decreases 10-yr ASCVD Risk Score

Cohort 4 (24W)

10-Year ASCVD Risk Score[1]

Placebo

Δ -1%

12%

11%

Mean ASCVD Score

Baseline   Week 24

Aldafermin 1mg

Δ -3%

15%

12% *

Baseline   Week 24

ASCVD Risk

- Optimal lipid management and reduction of ASCVD risk with rosuvastatin in this trial, including mitigating LDL increase from aldafermin

- At baseline, approx. 61% of NASH subjects had diabetes and qualified for statin use based on guidelines

- Only 32% of subjects on a statin at baseline

- In-trial lipid optimization with rosuvastatin at week 2 if LDL-C rise >10 mg/dL from baseline

*P=0.032 *vs.* placebo

[1] 10-year atherosclerotic cardiovascular disease (ASCVD) risk calculator at: http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/

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Concluding Remarks

- Fibrosis –important!
  - Strongest predictor of clinical outcomes
  - Improved fibrosis decreases risk of negative clinic outcomes
- NASH resolution
  - Strongest predictor of fibrosis improvement
- Either NASH resolution without worsening of fibrosis OR Fibrosis improvement without worsening of NASH (or BOTH) are ideal endpoints.
- NASH patients are at increased risk of CVD, cancer, and cirrhosis.
- Risk mitigation strategies to optimize safety and efficacy are essentials
- Given the large population eligible for treatment, *any* drug approved for NASH must have optimally high efficacy to safety profile

THANK YOU

Q&A

Manal Abdelmalek, MD,
Professor of Medicine, Duke University

Corinne Foo-Atkins,
MD MBA MSc
Vice President, Product Strategy

Hsiao D. Lieu, MD
Chief Medical Officer

David Woodhouse, Ph.D.
Chief Executive Officer, NGM

Fireside Chat

Q&A

Bill Rieflin
Executive Chairman, NGM

Jin-Long Chen, Ph.D.
Founder and Chief Scientific Officer, NGM

David Woodhouse, Ph.D.
Chief Executive Officer, NGM

Siobhan Nolan Mangini
Chief Financial Officer, NGM

Hsiao D. Lieu, M.D.
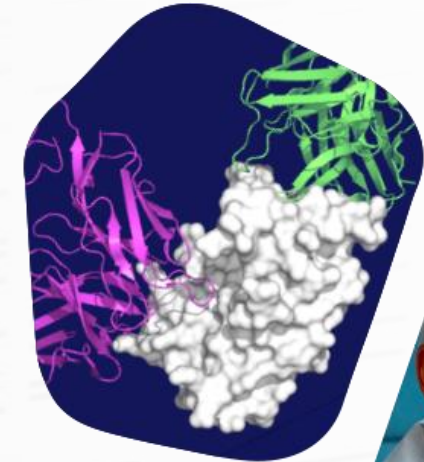Senior Vice President,
Chief Medical Officer, NGM

Alex DePaoli, M.D.
SVP and Chief Translational Officer,
NGM

Closing Remarks

David Woodhouse, Ph.D.
Chief Executive Officer, NGM

Thank You

ir@ngmbio.com

Novel Biology. Powerful Medicines. Transformative Impact.