Mereo BioPharma

Virtual R&D Day

November 24 2020

Mereo BioPharma Group plc

NASDAQ: MREO, AIM: MPH

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Mereo Biopharma Virtual R&D Day - Agenda

- Welcome, introductions and Agenda **Denise Scots-Knight, PhD, CEO Mereo Biopharma**
- Etigilimab : TIGIT as a target/MOA and anti-PD-1/PDL-1 combination approach **Tim Yap, MBBS, PhD, FCRP, Associate Professor, Dept of Investigational Cancer Therapeutics, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center**
- Overview of Phase 1a/1b data **John Strickler, MD, Associate Professor of Medicine, Member of the Duke Cancer Institute**
- Development strategy – phase 1b/2 and biomarkers **John Lewicki, PhD, CSO Mereo & Ann Kapoun, PhD, SVP Translational R&D Mereo**
- Etigilimab Q&A
- Neutrophil Elastase in lung disease : AATD and COVID 19 **Mark Dransfield, MD, Professor and Interim Director, Division of Pulmonary, Allergy and Critical Care Medicine, University of Alabama**
- Alvelestat : development overview, previous data **Alastair Mackinnon, MD, CMO Mereo & Jackie Parkin, MD, Therapeutic Head Mereo**
- Overview other pipeline programs and upcoming milestones **Denise Scots-Knight, PhD, CEO Mereo**
- Alvelestat/Other Q&A

Today's Speakers

John Strickler, MD,
Associate Professor of Medicine, Member of the Duke Cancer Institute

Tim Yap, MBBS, PhD, FCRP,
Associate Professor, Dept of Investigational Cancer Therapeutics, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center

Mark Dransfield, MD,
Professor and Interim Director, Division of Pulmonary, Allergy and Critical Care Medicine, University of Alabama

Dr. Denise Scots-Knight
Chief Executive Officer

Dr. John Lewicki
Chief Scientific Officer

Dr. Ann Kapoun
SVP Translational Research & Development

Dr. Alastair Mackinnon
Chief Medical Officer

Dr. Jackie Parkin
Therapeutic Area Head, Respiratory and Endocrinology

Dr. Brian Schwartz
Non-Executive Director

Our Core Purpose, Strategy & Vision Guide Us

SUMMARY	Mission	Strategy	Our Track Record	Fundamentals
• #1 priority – the patients we seek to serve • Identify and refine novel targets with strong scientific rationale • Develop & commercialize innovative medicines to treat patients with rare diseases and cancer • Seek partners to unlock value for the large opportunities where more resources required • Reach broadest range of patients possible • Partner of choice	Improving lives of patients with oncology and rare disease by unlocking the potential of novel targets **#1 priority – the patients that we seek to serve**	• In-licence or acquire programs for oncology and rare diseases with strong scientific rationale / clinical data based on targets with strong scientific rationale • Focus on core competences – translational R&D, development, CMC, regulatory, rare diseases • Collaboration with the right partners to unlock the value of our programs • Commercialize where it makes sense and match with strategic partnerships	• Acquired/in-licensed 6 programs with Phase 1b/2 data in risk sharing structures since mid-2015 • Delivered three successful Phase 2 studies to-date with a Phase 2 and Phase 1b/2 ongoing • Global out licensing of one program with partnering for three additional programs ongoing • Aim to retain regional commercial rights for our rare disease programs	**Our partners** NOVARTIS AstraZeneca OncXerna • Listed on LSE (AIM : MPH) and NASDAQ (MREO) • Well financed with cash runway into 2022 • Significant news flow into Q4 and 2021

Late Stage Diversified Clinical Pipeline

Core Programs

Product Candidate / Indication	Phase 1a	Phase 1b	Phase 2	Phase 3	Next Milestones
Etigilimab Solid tumors					Phase 1b/2
Alvelestat Alpha-1 antitrypsin deficiency COVID-19					Phase 2 AATD Phase 1b/2 COVID
Setrusumab Osteogenesis imperfecta					Extension study Phase 3 – Partner

With partnering opportunities on non-core programs

Product Candidate / Indication	Phase 1	Phase 2	Phase 3	Financing Milestones
Acumapimod Acute exacerbations of COPD				Separate funding
Leflutrozole HH Infertility				Partner
Navicixizumab Ovarian Cancer				Partnered ~ $300M in milestones + royalties

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Etigilimab

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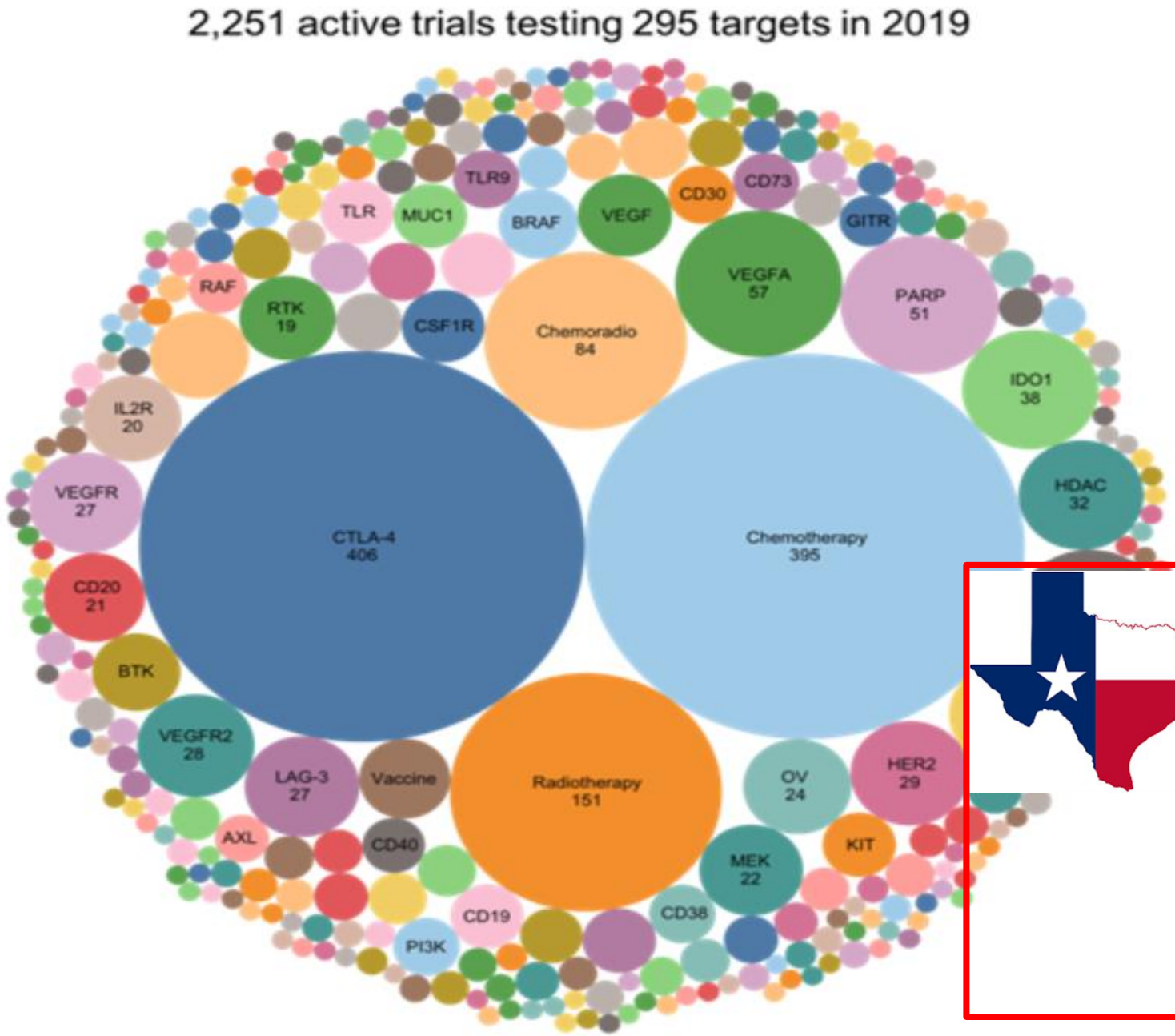
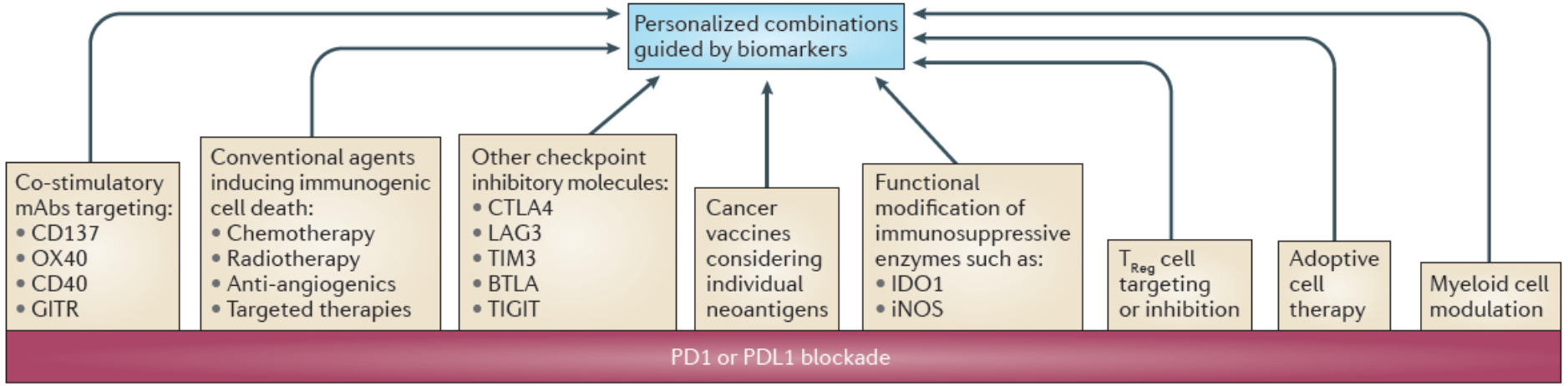
TIGIT

Dr. Timothy A. Yap MBBS
PhD FRCP



Is IO the new Chocolate?
Chocolate makes everything better

Most IO-IO Combos Use Anti-PD-1/PD-L1 as Backbone



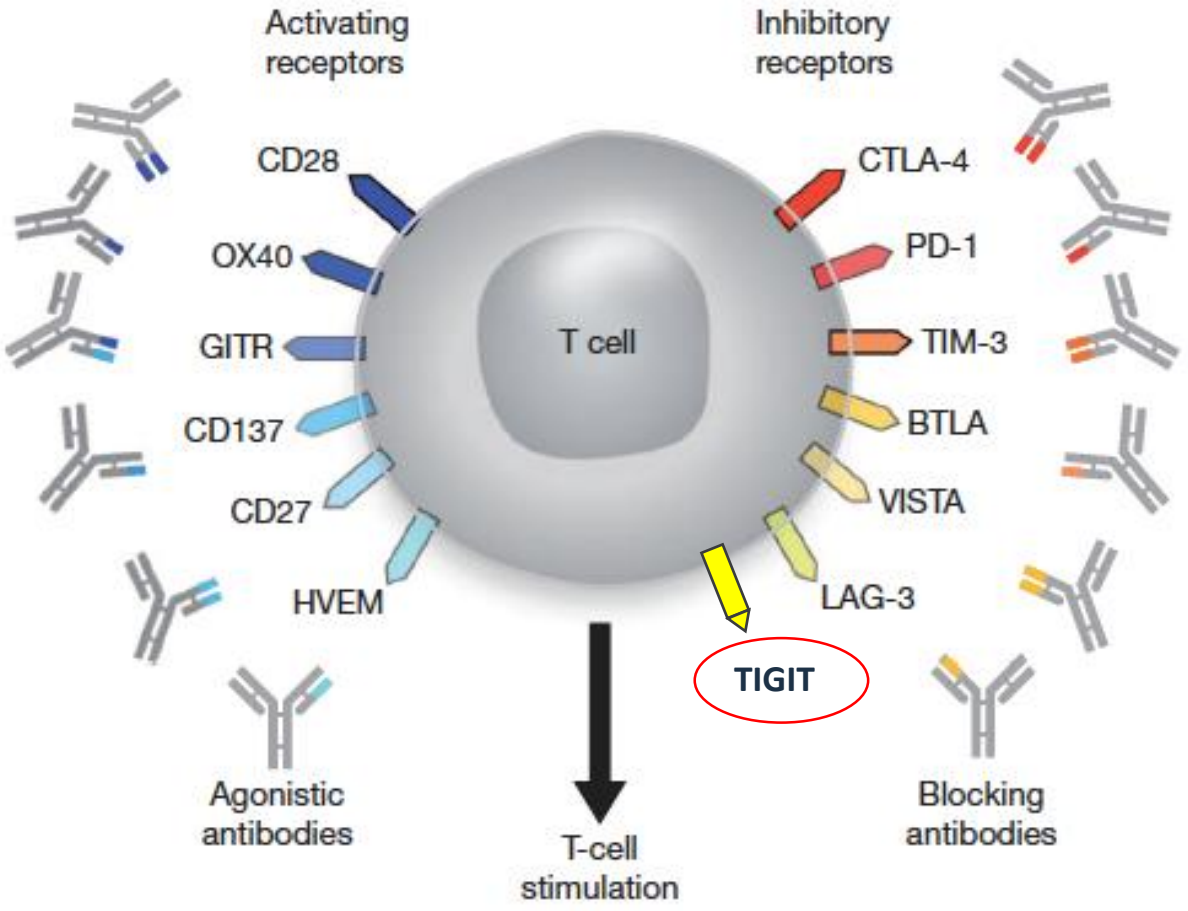
However, most combos are not based on strong supporting biology

"Our paradigm of … let's just add something onto existing therapy may not be correct."
– FDA OCE Director Richard Pazdur

We need new targets driven by strong biology

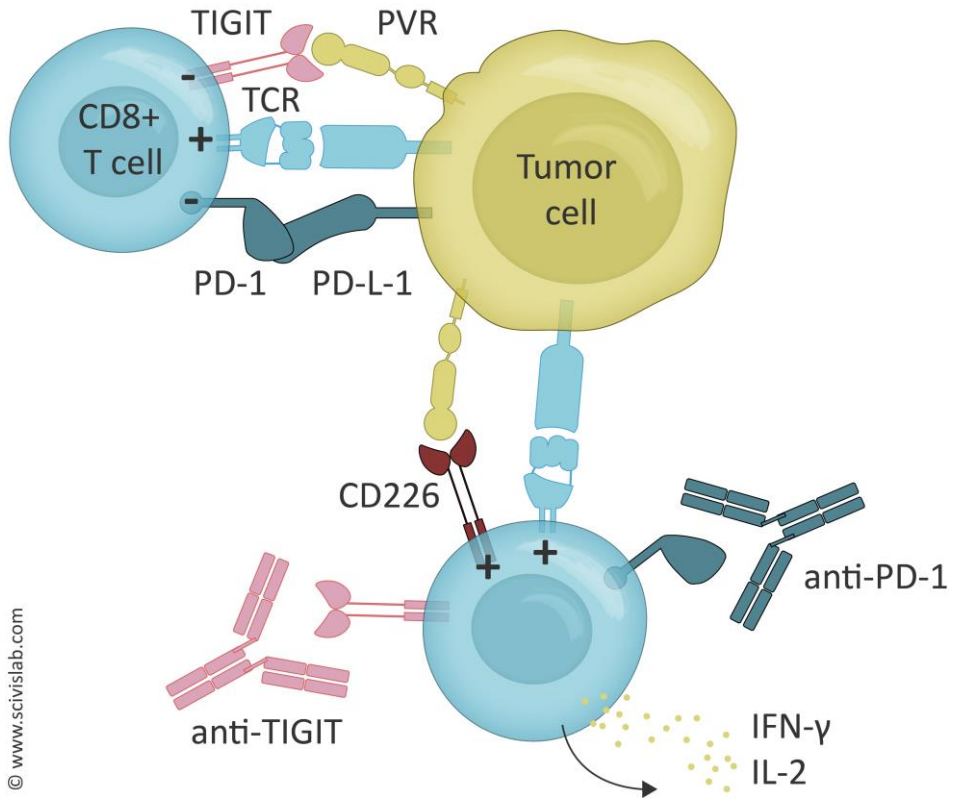
Melero, .., Haanen Nature Reviews Cancer 2015

TIGIT: The New Kid on the Block



Mellman, Nature 2011

TIGIT is a Negative Regulator of T Cell Responses



T cell Immunoreceptor with Ig and ITIM domains (TIGIT)

Negative regulator of T cell response:

- Competes with CD226 for PVR, disrupts CD226 activation, and directly inhibits T cells

Expressed on CD4, CD8 and NK cells and is elevated upon activation

Highly expressed on regulatory T cells (Tregs)

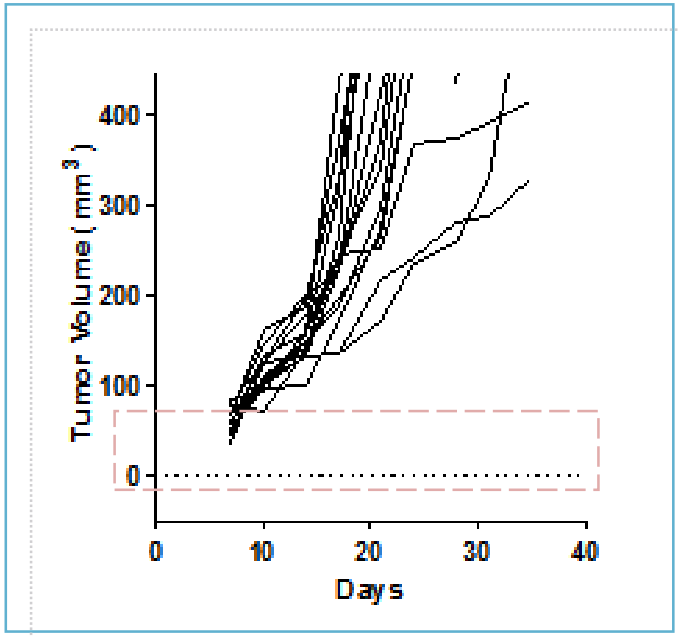
Human tumors co-express high levels of TIGIT and PD1

Co-blockade of anti-TIGIT and anti-PD1 elicits tumor rejection preclinically (Johnson et al., 2014, Cancer Cell)

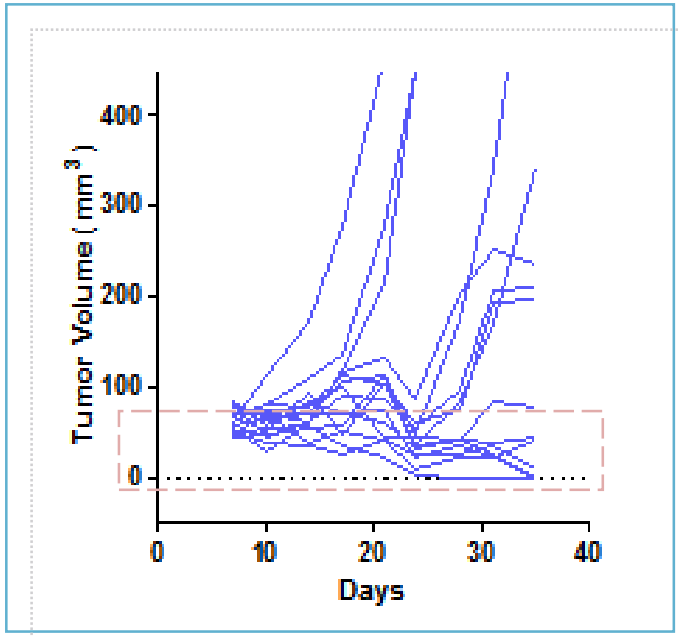
Do we have good drugs against TIGIT?

Etigilimab is an IgG1 Anti-TIGIT Antibody with Inhibitory and ADCC Characteristics

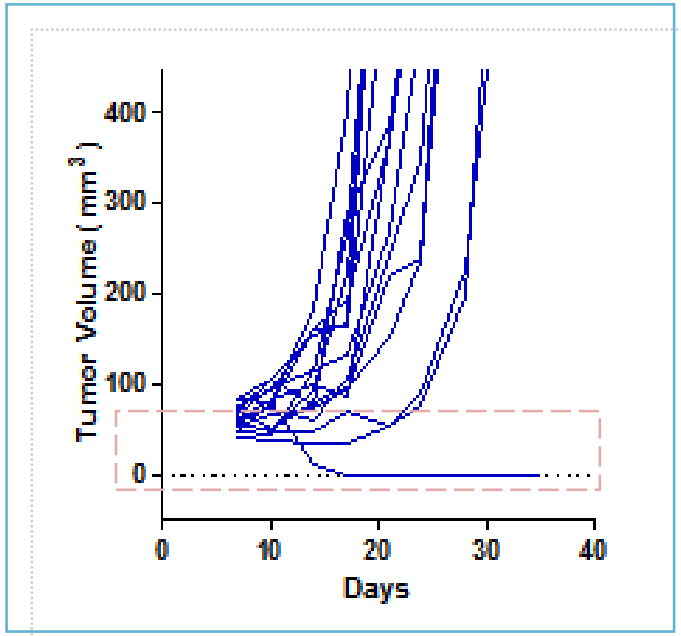
Control Ab



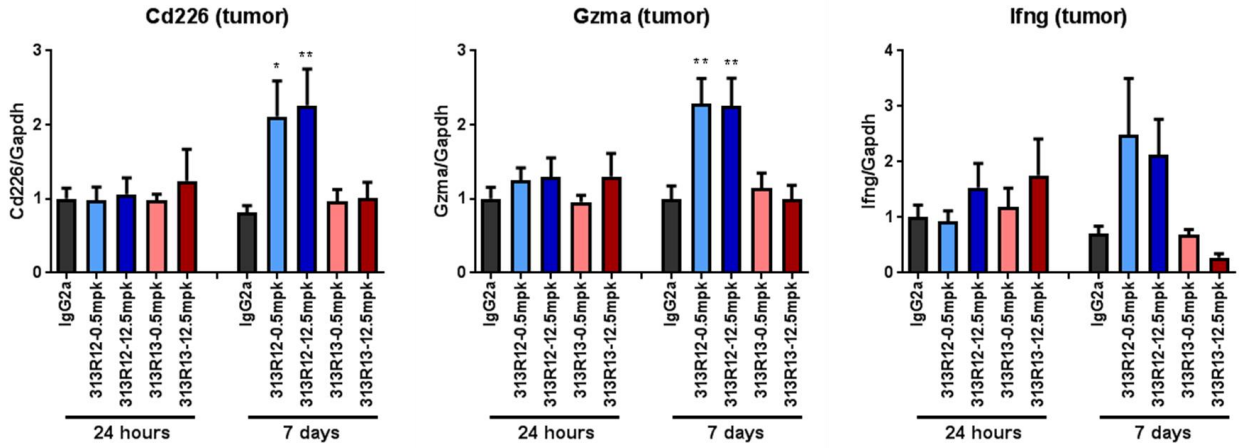
Effector function competent

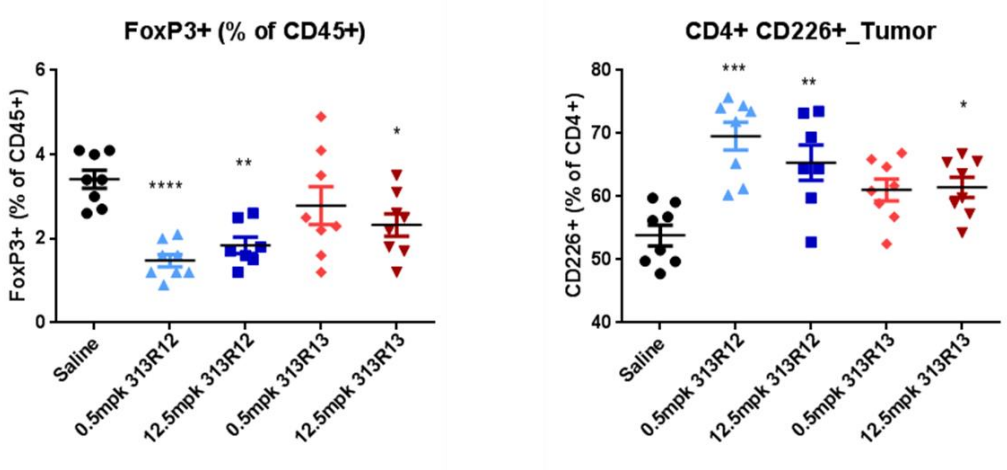


Effector function silent



Fc Receptor Binding Important for Biomarker Changes & Efficacy in Preclinical Models





313R12:
effector function competent

313R13:
effector function incompetent

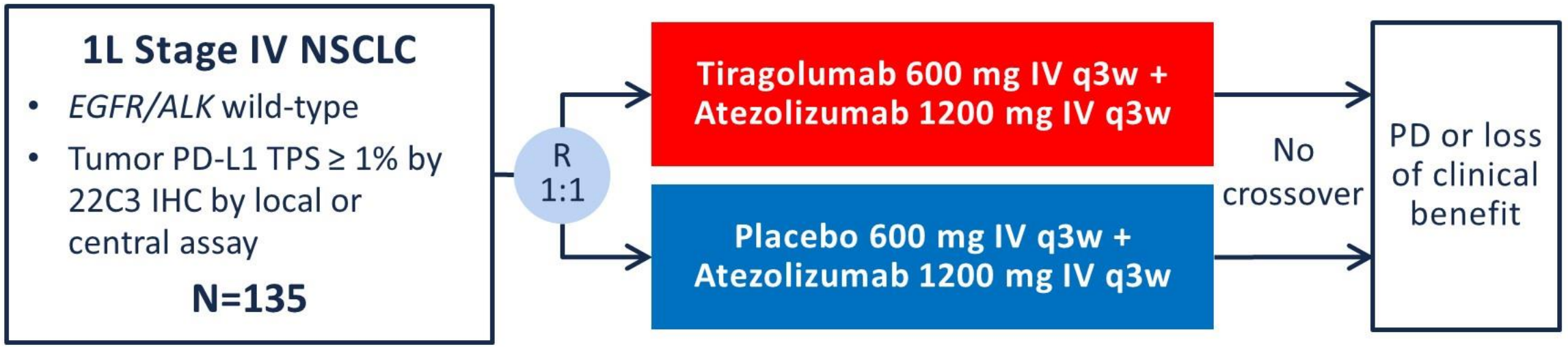
- Control
- 0.5 mpk 313R12
- 12.5 mpk 313R12
- 0.5 mpk 313R13
- 12.5 mpk 313R13

313R12: Mereo's surrogate anti-mouse antibody used for preclinical studies; comparable affinity to etigilimab (anti-human TIGIT)

Argast et. al. AACR 2018

–TIGIT Clinical Landscape

CITYSCAPE Study Design



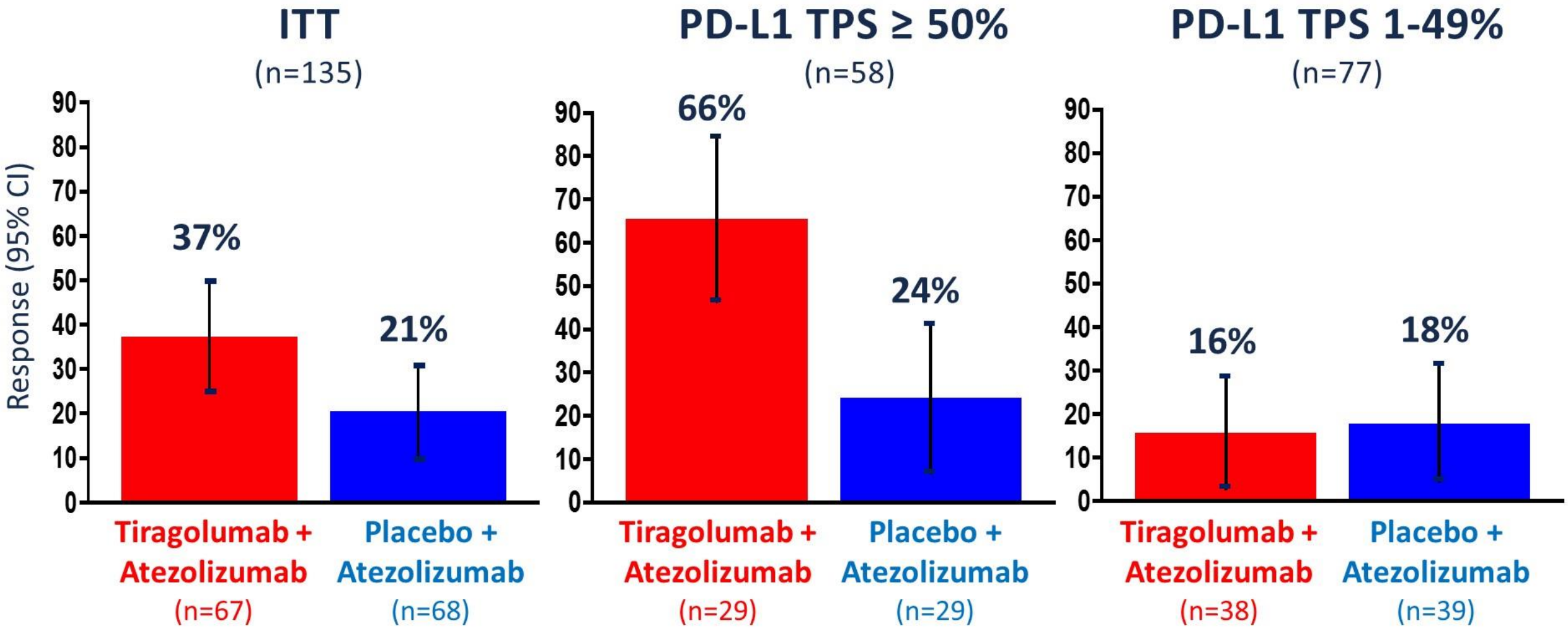
Stratification Factors:

- PD-L1 TPS (1-49% vs ≥ 50%)
- Histology (Non-Squamous vs Squamous)
- Tobacco use (yes vs no)

- **Co-Primary Endpoints: ORR** and **PFS**
- **Key Secondary Endpoints: Safety,** DOR, OS, Patient-reported outcomes (PROs)
- **Exploratory Endpoints:** Efficacy analysis by PD-L1 status

DOR = duration of response; IHC = immunohistochemistry; ORR = confirmed overall response rate; OS = overall survival; PD = progressive disease; PFS = progression free survival ; q3w = every 3 weeks; R = randomized; TPS = tumor proportion score

Updated Confirmed Overall Response Rate (ORR)



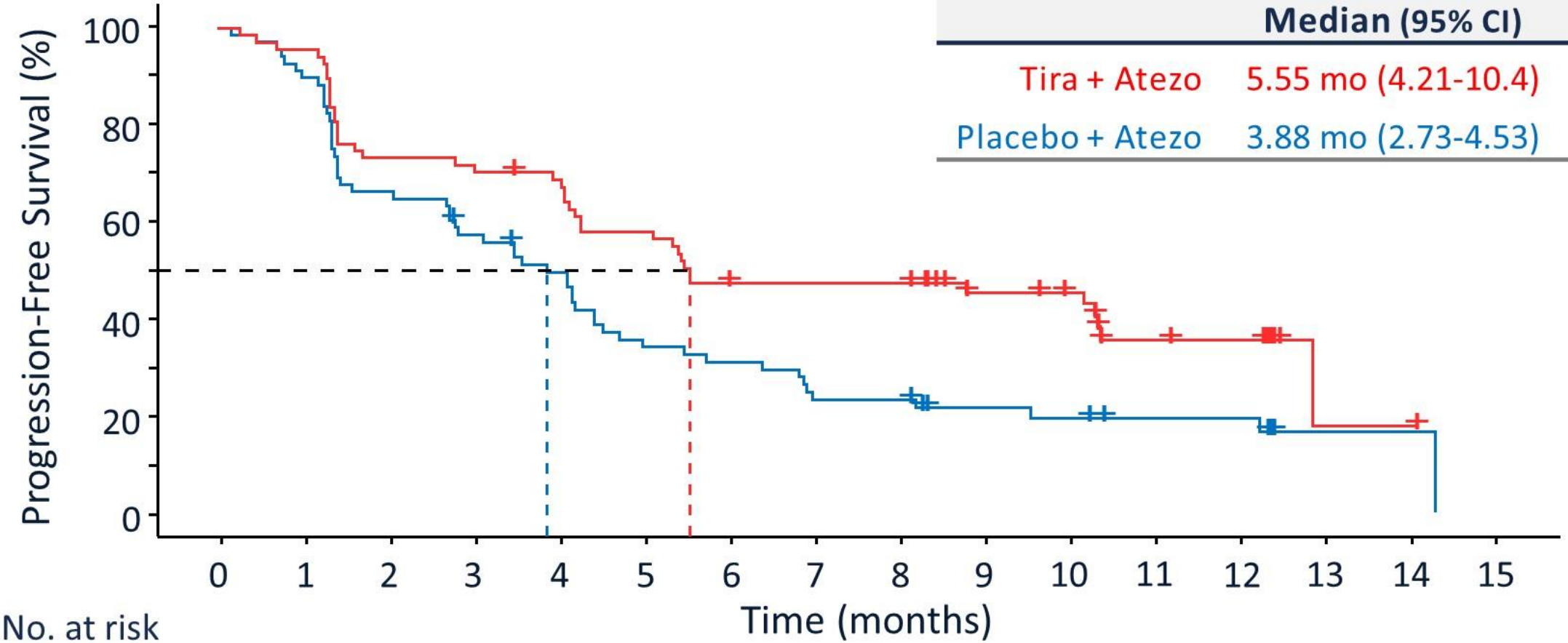
ITT = intention-to-treat; TPS = tumor proportion score

Updated data cutoff: 02 Dec 2019

Updated Investigator-Assessed PFS: ITT

	Median (95% CI)	HR (95% CI)
Tira + Atezo	5.55 mo (4.21-10.4)	0.58* (0.38-0.89)
Placebo + Atezo	3.88 mo (2.73-4.53)	

*stratified HR



No. at risk																
T + A	67	64	49	48	45	38	31	30	30	22	20	10	9	1	1	0
P + A	68	61	45	38	32	22	20	15	15	10	9	7	7	1	1	0

Events
41 (61%)
55 (81%)

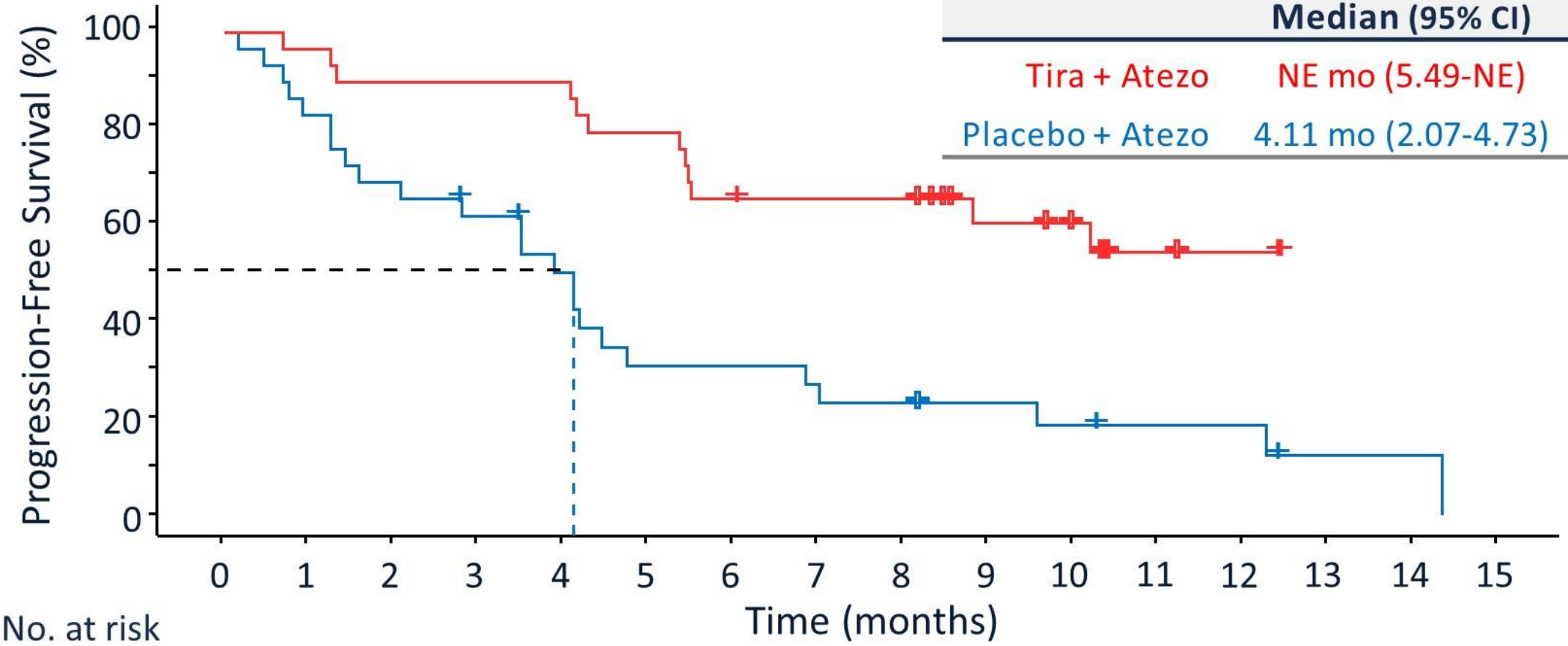
ITT= intention-to-treat; P+A = placebo + atezolizumab; T+A = tiragolumab + atezolizumab

Follow data cutoff: 02 December 2019

Updated Investigator-Assessed PFS: PD-L1 TPS ≥ 50%

	Median (95% CI)	HR (95% CI)
Tira + Atezo	NE mo (5.49-NE)	0.30* (0.15-0.61)
Placebo + Atezo	4.11 mo (2.07-4.73)	

*unstratified HR



No. at risk																
T + A	29	28	26	26	26	23	19	18	18	12	10	4	3	0	0	0
P + A	29	24	20	17	13	8	8	6	6	5	4	3	3	1	1	0

Events
12 (41%)
24 (83%)

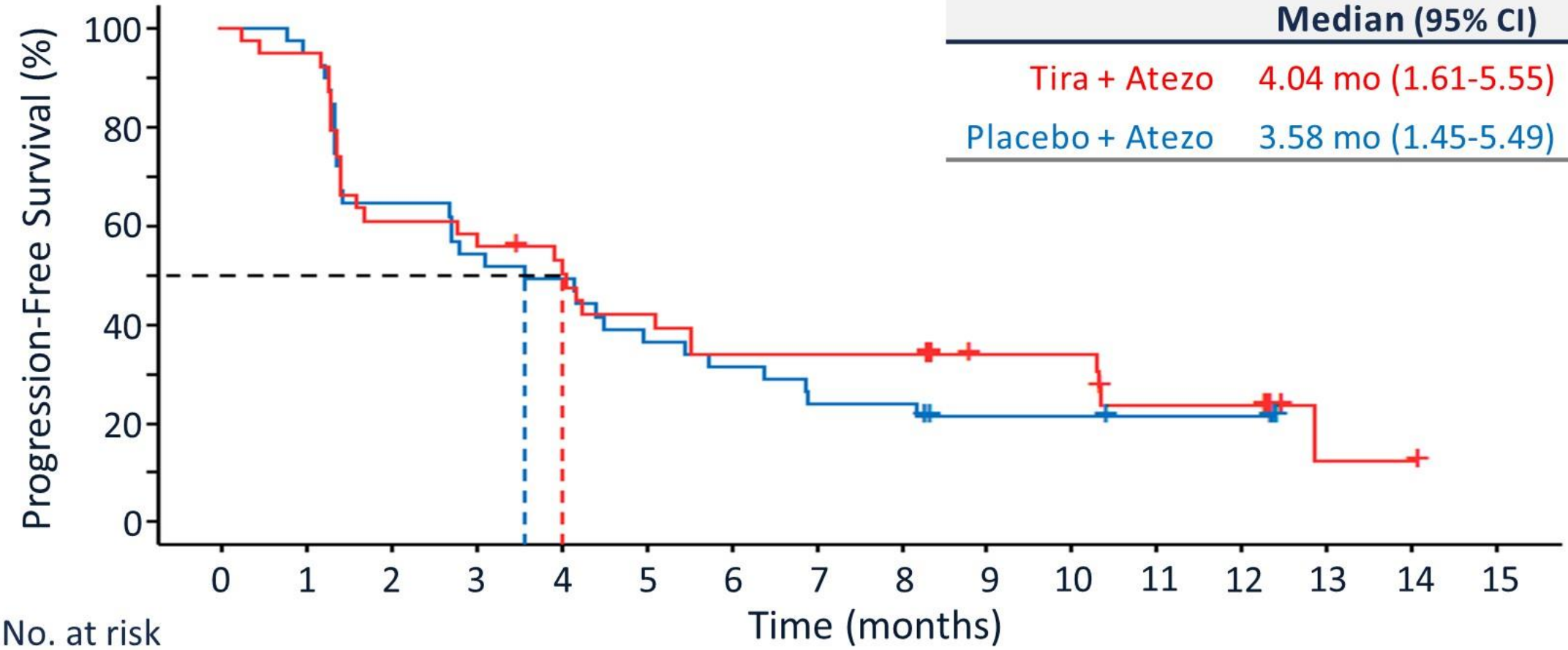
NE = non-evaluable; P+A = placebo + atezolizumab; T+A = tiragolumab + atezolizumab; TPS = tumor proportion score

Follow data cutoff: 02 December 2019

Updated Investigator-Assessed PFS: PD-L1 TPS 1-49%

	Median (95% CI)	HR (95% CI)
Tira + Atezo	4.04 mo (1.61-5.55)	0.89* (0.53-1.49)
Placebo + Atezo	3.58 mo (1.45-5.49)	

*unstratified HR



No. at risk																Events
T + A	38	36	23	22	19	15	12	12	12	10	10	6	6	1	1	0	29 (76%)
P + A	39	37	25	21	19	14	12	9	9	5	5	4	4	0	0	0	31 (80%)

NE = non-evaluable; P+A = placebo + atezolizumab; T+A = tiragolumab + atezolizumab; TPS = tumor proportion score

Follow data cutoff: 02 December 2019

Safety and Efficacy of Vibostolimab, an Anti–TIGIT Antibody, Plus Pembrolizumab in Patients With Anti–PD-1/PD-L1–Naive NSCLC

Table 4. Response Summary Based on Investigator Assessment per RECIST v1.1 in Patients With Anti-PD-1/PD-L1-Naive NSCLC

	Vibostolimab + Pembrolizumab N = 41	
All Patients	**Without Confirmation**	**With Confirmation[a]**
Responders, n	12	10
ORR, % (95% CI)	29 (16-46)	24 (12-40)
CR, n (%)	1 (2)	1 (4)
PR, n (%)	11 (27)	9 (22)
SD, n (%)	11 (27)	12 (29)
PD, n (%)	14 (34)	14 (34)
Not available,[b] n (%)	4 (10)	5 (12)
Median DOR,[c] months (range)	–	NR (4-17+)
Patients With Available PD-L1 Data	**Without Confirmation**	**With Confirmation[a]**
TPS ≥1%: responders, n	6	4
TPS ≥1%: ORR, % (95% CI)	46 (19-75)	31 (9-61)
TPS <1%: responders, n	3	3
TPS <1%: ORR, % (95% CI)	25 (6-57)	25 (6-57)

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Response confirmation per RECIST v1.1.
[b]Patients with no postbaseline assessment available for response evaluation or patients with insufficient data for assessment of response per RECIST v1.1.
[c]From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there was no progressive disease at the time of the last disease assessment.

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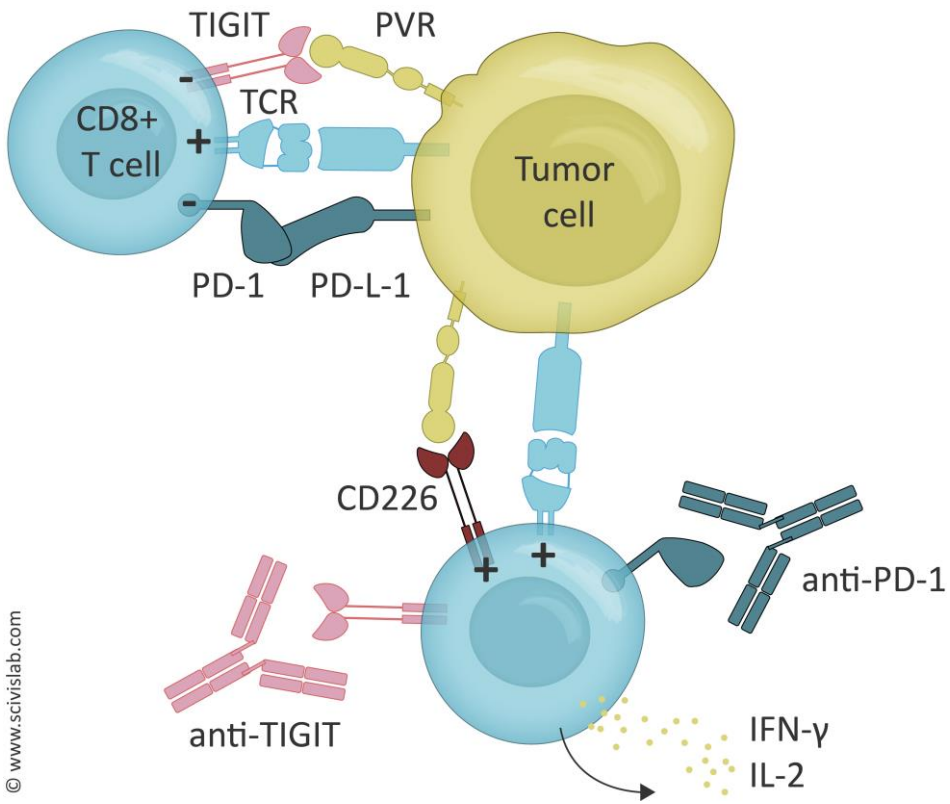
J. Niu et. Al, Phase 1, Presented at the ESMO Virtual Congress 2020; September 19-21, 2020

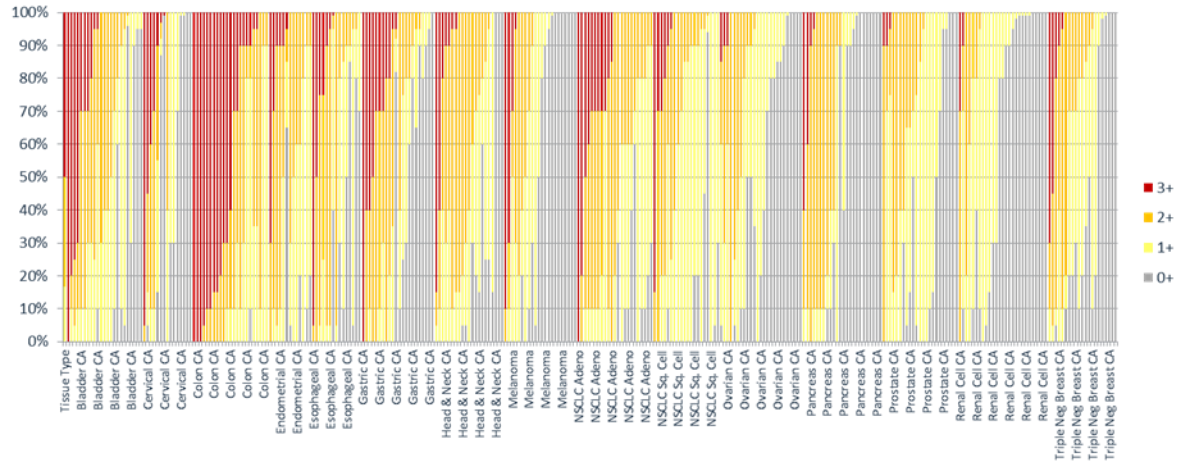
Summary Clinical Data

	Tiragolumab	Vibostolimab	Etigilimab
Type of drug	Anti-TIGIT human IgG1 mAb	Anti-TIGIT humanized IgG1 mAb	Anti-TIGIT humanized IgG1 mAb
Trial	Ph II randomized	Ph I dose escalation	Ph I dose escalation
ORR monotherapy	**0%**	**3% (1/34)**	**0% (0/18)**
DCR monotherapy	17%	35%	39%
ORR combo with anti-PD1 or anti-PD-L1	**37%**	**24% (10/41)**	**N/A**

Potential of PVR and TIGIT as Predictive Biomarkers



- High levels of PVR are associated with poor prognosis in multiple cancers
- PVR/TIGIT potential involvement in resistance to IO
- Potential important role of biomarkers beyond PD-L1, e.g. TIGIT, PVR, CD226



PVR IHC

Where is the TIGIT Field Heading?

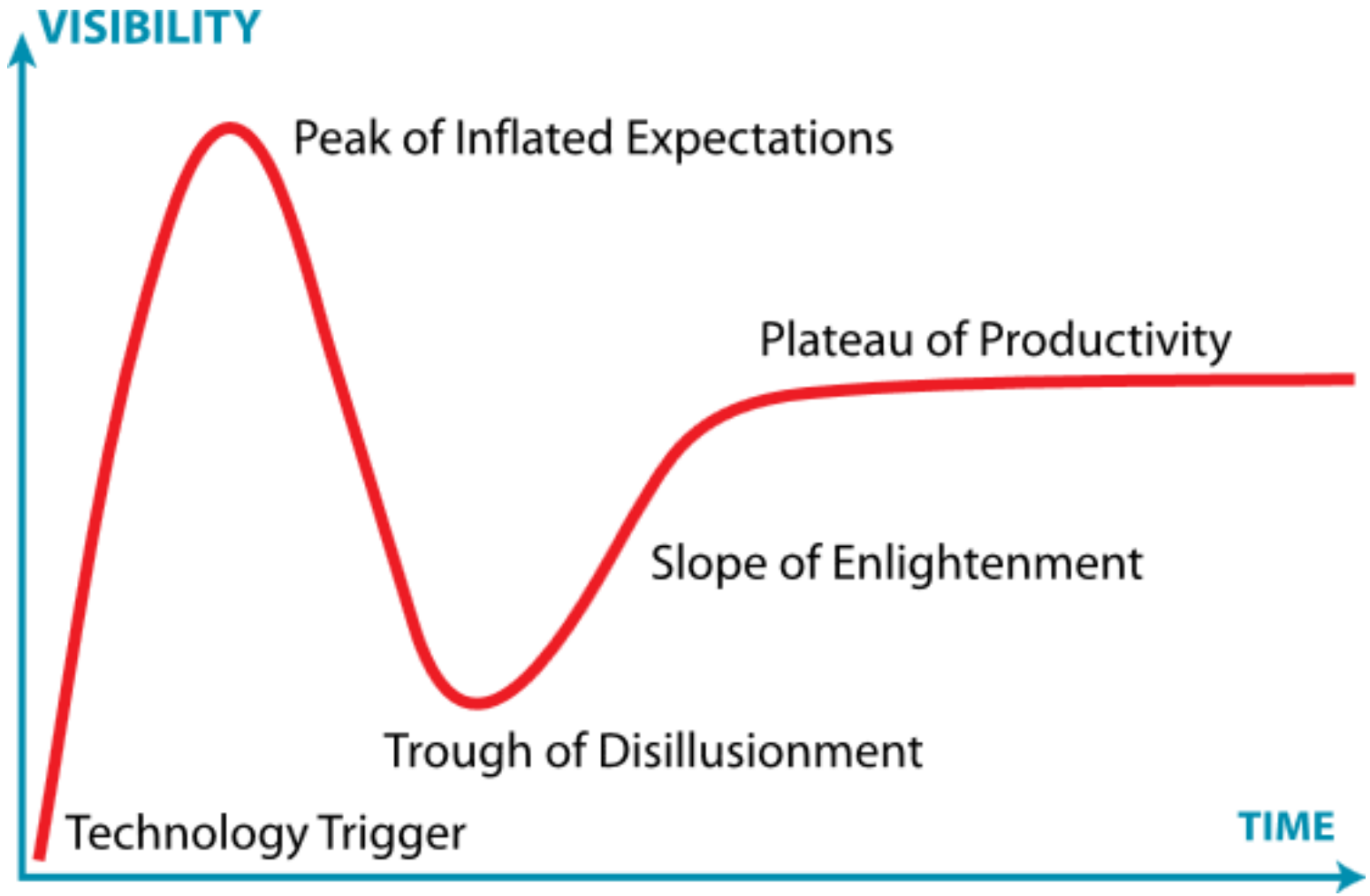
- Etigilimab is a potent and active IgG1 anti-TIGIT antibody
- Monotherapy unlikely to represent registration strategy
- Combination with PD-1/L1 inhibitors is promising line of sight to FDA approval
- Upcoming anti-TIGIT + PD-1/L1 inhibitor trials will define:
  - Specific tumor types beyond NSCLC (‘moving away from the crowd’)
  - Molecular biomarkers of response, e.g. TIGIT expression

The Innovation Cycle (aka Gartner's Hype Cycle)

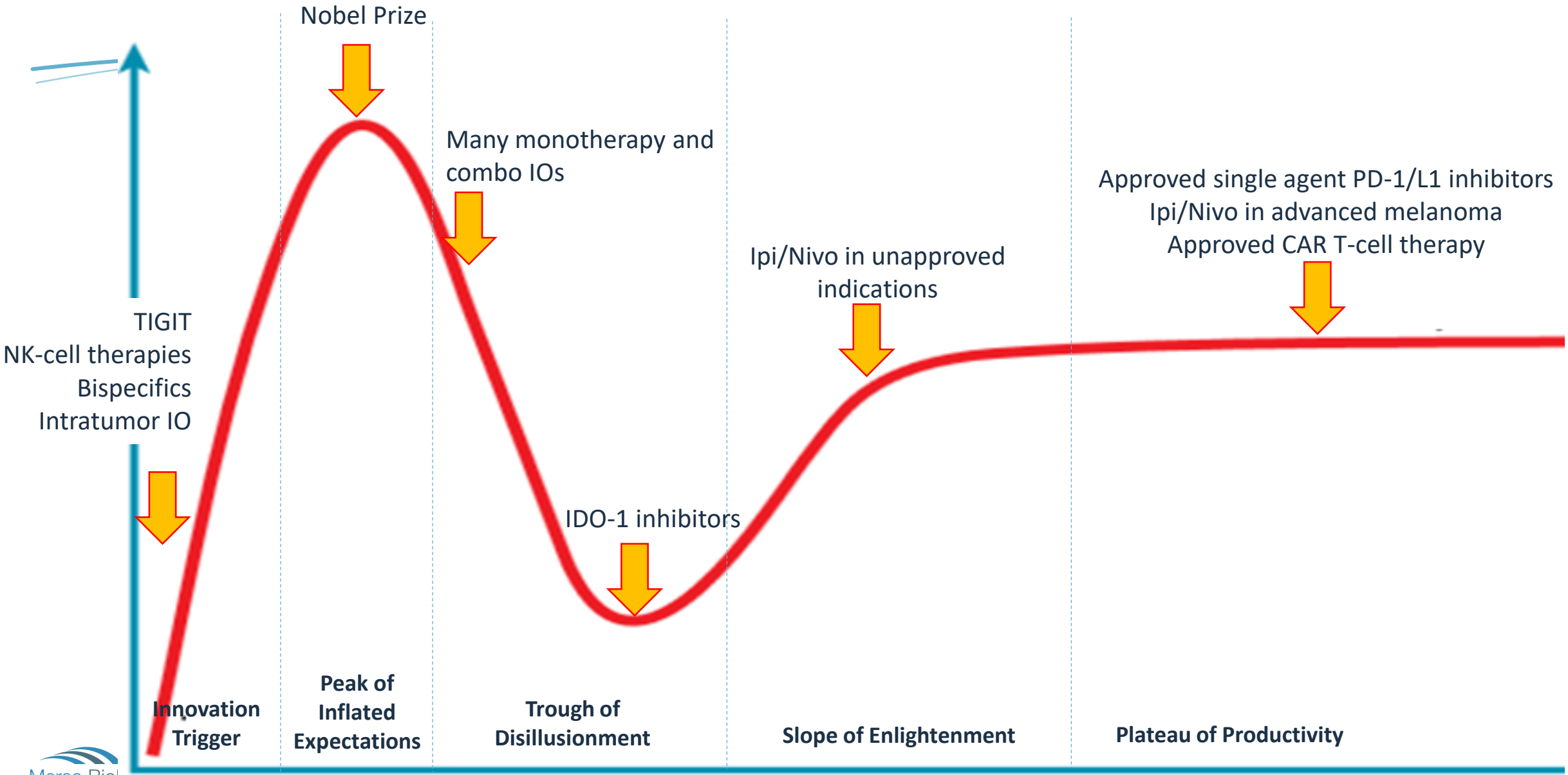
GRAPHICAL REPRESENTATION OF THE MATURITY, ADOPTION AND SOCIAL APPLICATION OF SPECIFIC TECHNOLOGIES

FIVE KEY PHASES OF A TECHNOLOGY'S LIFE CYCLE

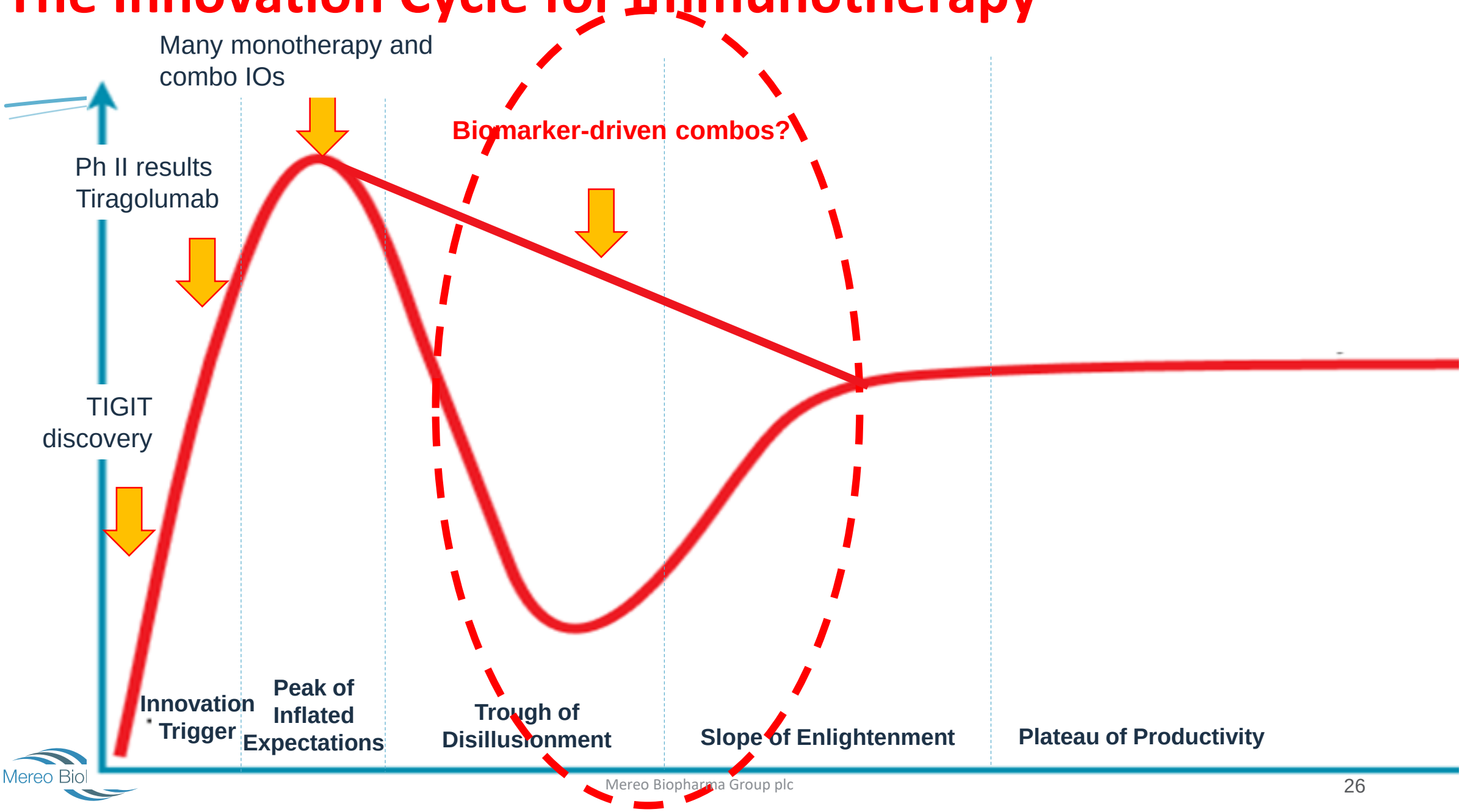
1. Technology Trigger
2. Peak of Inflated Expectations (hype)
3. Trough of Disillusionment
4. Slope of Enlightenment
5. Plateau of Productivity



Gartner's Hype Cycle for Immunotherapy



The Innovation Cycle for Immunotherapy



Take Home Messages

- Promising antitumor activity observed in NSCLC, but also in patients who have progressed on or after prior anti-PD(L)-1 treatment in other cancers
- Optimal trial designs should be guided by shared knowledge from pre-clinical, translational and early clinical data
- Further translational studies warranted to better understand mechanisms of response and resistance

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Etigilimab

Dr. John Strickler, MD

Phase 1 Study Design

Phase 1a

Dose Escalation

Tumor types for inclusion in dose escalation cohort:

- Histologically confirmed advanced relapsed or refractory solid tumors
- All patients heavily pretreated

20mg/kg Q2W
N=3+3

10mg/kg Q2W
N=3+3

3mg/kg Q2W
N=3+3

1mg/kg Q2W
N=3+3

0.3mg/kg Q2W*
N=3+3

Phase 1b

Dose Escalation

Tumor types for inclusion in dose escalation cohort:

- Histologically confirmed advanced relapsed or refractory solid tumors
- Refractory to or progressed after prior anti-PD1/L1 treatment
- All patients heavily pretreated

20mg/kg Q2W + nivolumab
N=3+3

10mg/kg Q2W + nivolumab
N=3+3

3mg/kg Q2W + nivolumab
N=3+3

Baseline Characteristics

	Phase 1a	Phase 1b	Total
M/F	10/13	6/4	16/17
Tumor Type			
Head and Neck	4	1	5
Uterine	4	0	4
CRC	3	1	4
Gastric	0	3	3
MSS CRC	3	0	3
TNBC	2		2
Pancreatic Cancer	2	0	2
Other	5	5	10

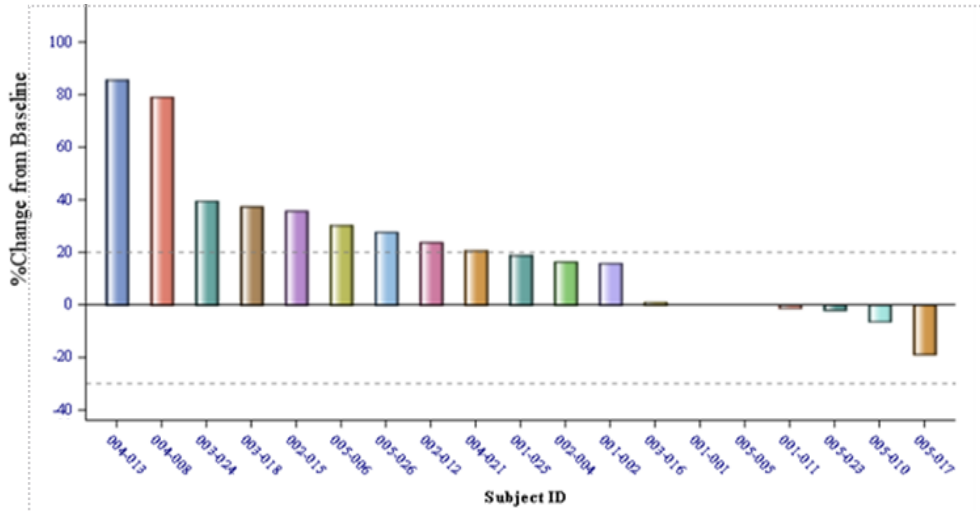
RECIST Response Data

Dose	Phase 1a	Phase 1b	Total
Complete Response	0	0	0/33 (0%)
Partial Response	0	1	1/33 (3%)
Stable Disease	7	1	8/33 (24%)
Progressive Disease	13	6	19/33 (58%)
Not Evaluable	3	2	5/33 (15%)
Clinical Benefit Rate	7	2	9/33 (27%)

Phase 1a Best % Reduction in Target Lesion Size & Duration on Study

etigilimab monotherapy

Waterfall Plot of Best Percentage Change in SLD from Baseline (ITT Population)

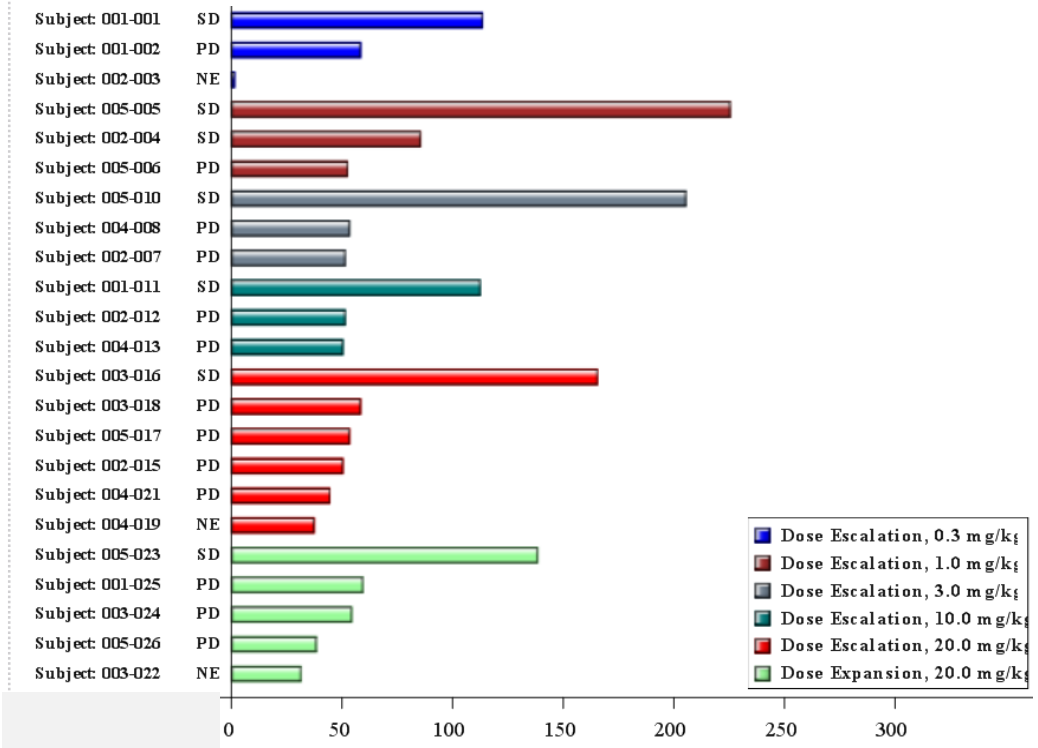


Patient	Dose	Cancer
004-013	10mg/kg	adenocarcinoma of the pancreas
004-008	3mg/kg	CRC MSS adenocarcinoma of the colon
003-024	20mg/kg*	HNSCC
003-018	20mg/kg	triple negative breast cancer
002-015	20mg/kg	pancreatic adenocarcinoma
005-006	1mg/kg	CRC MSS
005-026	20mg/kg*	Lung
002-012	10mg/kg	CRC MSS colorectal adenocarcinoma
004-021	20mg/kg	metastatic endometrial / papillary serous

Patient	Dose	Cancer
001-025	20mg/kg*	Endometrial
002-004	1mg/kg	endometrial adenocarcinoma of uterus
001-002	0.3mg/kg	CRC MSS adenocarcinoma
003-016	20mg/kg	CRC MSI
001-001	0.3mg/kg	CRC MSS
005-005	1mg/kg	salivary duct
001-011	10mg/kg	endometrial
005-023	20mg/kg*	parotid
005-010	3mg/kg	Fallopian
005-017	20mg/kg	endometrial

*Expansion cohort

Duration on Study

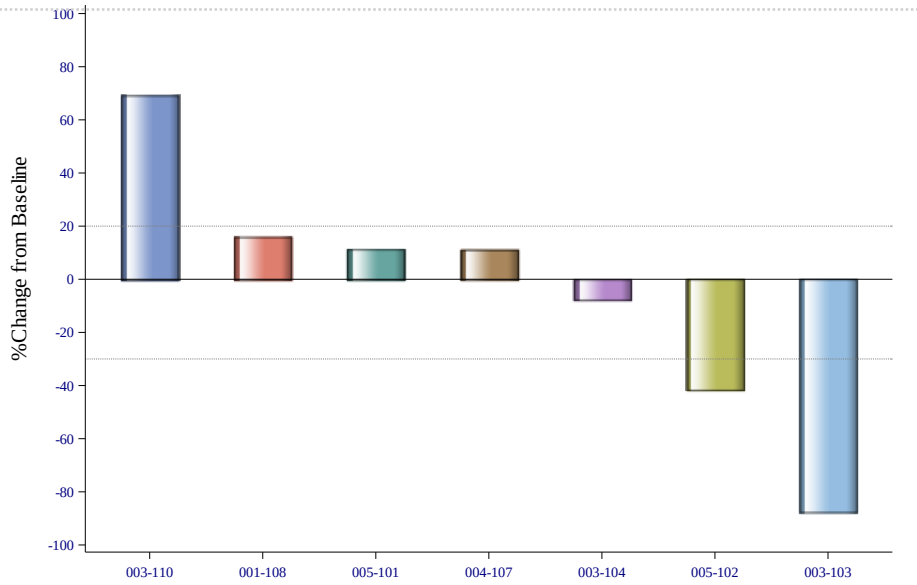


23 patients enrolled

Phase 1b Best % Reduction in Target Lesion Size & Duration on Study

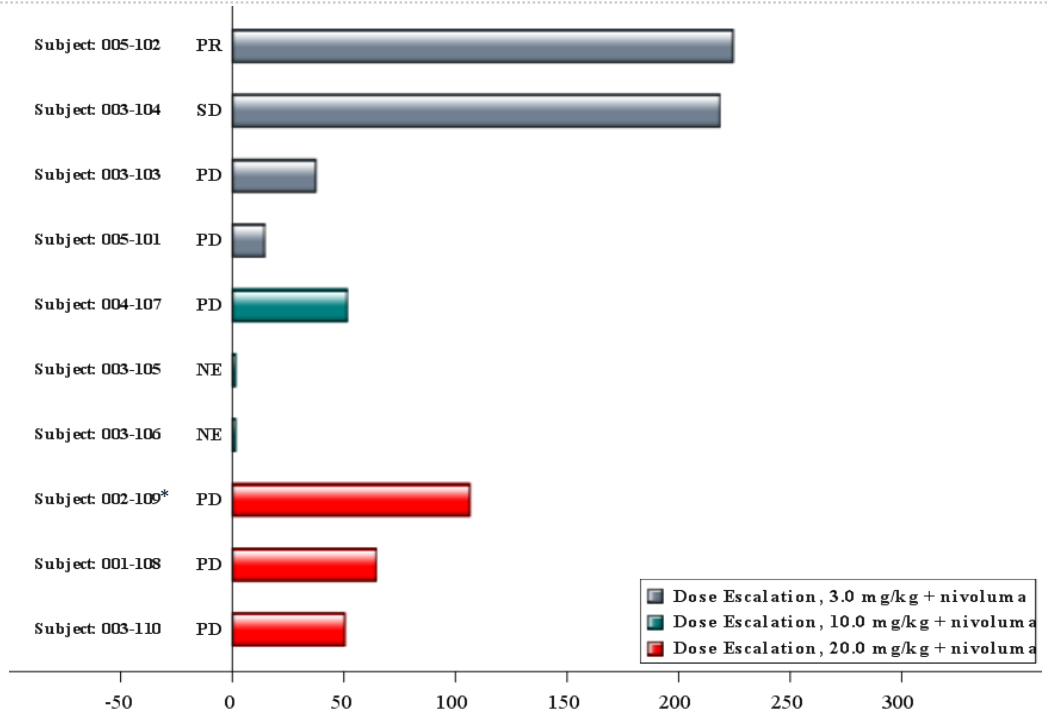
etigilimab + nivolumab

Waterfall Plot of Best Percentage Change in SLD from Baseline (ITT Population)



Patient	Dose	Cancer
003-110	20mg/kg	Head and Neck cancer, tonsils to lung
001-108	20mg/kg	Gastric Cancer MSS adenocarcinoma
005-101	3mg/kg	NSCL adenocarcinoma
004-107	10mg/kg	Renal Cell carcinoma MSS adenocarcinoma
003-104	3mg/kg	Gastric cancer MSS adenocarcinoma
005-102	3mg/kg	Ovarian serious metastatic
003-103	3mg/kg	Colon CRC MSI adenocarcinoma

Duration on Study



*HCC

Phase 1a Safety Data

Related AEs ≥ 5%

Adverse event, n (%)	Number (%)
Pruritis	4 (17%)
Fatigue	3 (13%)
Nausea	3 (13%)
Rash	3 (13%)
Rash maculopapular	3 (13%)
Chills	2 (9%)
Cough	2 (9%)
Rash macular	2 (9%)

≥ Grade 3 Related AEs

Adverse event, n (%)	Number (%)
Rash	1 (4%)
Rash Macular	1 (4%)
Rash Maculopapular	1 (4%)
ALT Increased	1 (4%)
AST Increased	1 (4%)
Hypophosphatemia	1 (4%)

Immune Related Adverse Events

Adverse event, n (%)	Number (%)
Skin Disorders	8 (35%)
Pruritis	3 (13%)
Rash	3 (13%)
Rash Maculopapular	3 (13)%
Rash macular	1 (4%)
Rash pruritic	1 (4)%
Skin disorder	1 (4%)
Autoimmune Hepatitis	1 (4%)

Generally safe and well tolerated

Phase 1b Safety Data

Phase 1b: ≥Grade 3 Related AEs (n = 10)*

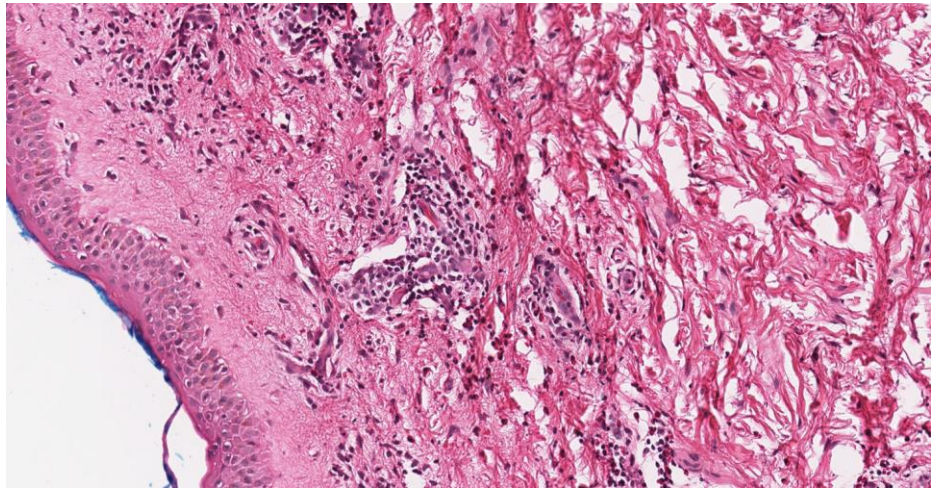
Adverse event, n (%)	Number (%)
Rash	2 (20%)
Rash maculopapular	1 (10%)
ALT increased	1 (10%)
AST increased	1 (10%)

Phase 1b: Immune-Related Adverse Events (n=10)*

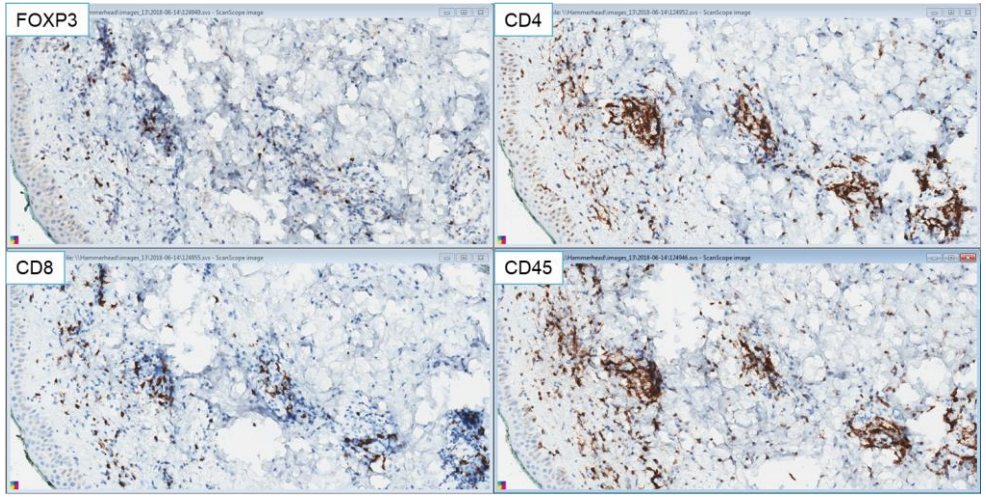
Adverse event, n (%)	Number (%)
Skin Disorders	5 (50%)
Pruritis	2 (13%)
Rash	2 (20%)
Rash pruritic	2 (20%)
Dermatitis psoriasiform	1 (10%)
Rash maculopapular	1 (10%)
Autoimmune hepatitis	1 (10%)
Infusion reaction	1 (10%)

Patient 005-010 Rash
Example rash

- Pt 005-010, 3 mg/kg, Grade 1-3 rash in multiple areas, topical steroids, skin biopsy on day ~150
- Pathology: perivascular lymphocytic inflammatory infiltrate with scattered eosinophils
  - Typical rash seen with other checkpoint inhibitors
  - Received biopsy in-house and stained with CD45, CD4, CD8 and FoxP3
- Rashes seen with checkpoints are diverse, dermal immune eruptions, lichenoid patterns (scaling)



20X



10X

Phase 1 Clinical & Biomarker Findings

- Seven subjects (30%, n=23) had stable disease as their best response in the single-agent Phase 1a cohort
  - Majority of patients are heavily pretreated and have tumor types typically non-responsive to anti-PD1 agents
- One partial response and 1 stable disease evident in initial Phase 1b (combination with nivolumab) cohorts (n=8 evaluable, n=7 with tumor assessments)
- No DLTs were observed; etigilimab generally well tolerated
- Etigilimab elicited adverse events consistent with immune system activation
- The pharmacokinetic profile of etigilimab is linear, with an estimated T1/2 of 6 days; and no evidence of anti-drug antibodies were observed
- Target engagement of etigilimab demonstrated in Phase 1a patients in blood by flow cytometry, NGS gene expression, and DNA methylation analysis

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Etigilimab: A Differentiated Development Strategy

Dr. Ann Kapoun, SVP Translational R&D, PhD
Dr. John Lewicki, Chief Scientific Officer, PhD

Mereo's etigilimab Has Key Differentiating Features

High affinity IgG1 antibody

- IgG1 backbone activates antibody-dependent cellular cytotoxicity (ADCC). Preclinical data suggest advantages of this backbone over competitor ADCC-null anti-TIGIT mAbs

Phase 1a and Phase 1b dose escalation and safety data available

- Active IND and drug product in place
- Potential early clinical signals observed: 30% SD in Phase 1a; 1PR in Phase1b. Majority of patients are heavily pre-treated and some in non-IO responsive tumor types

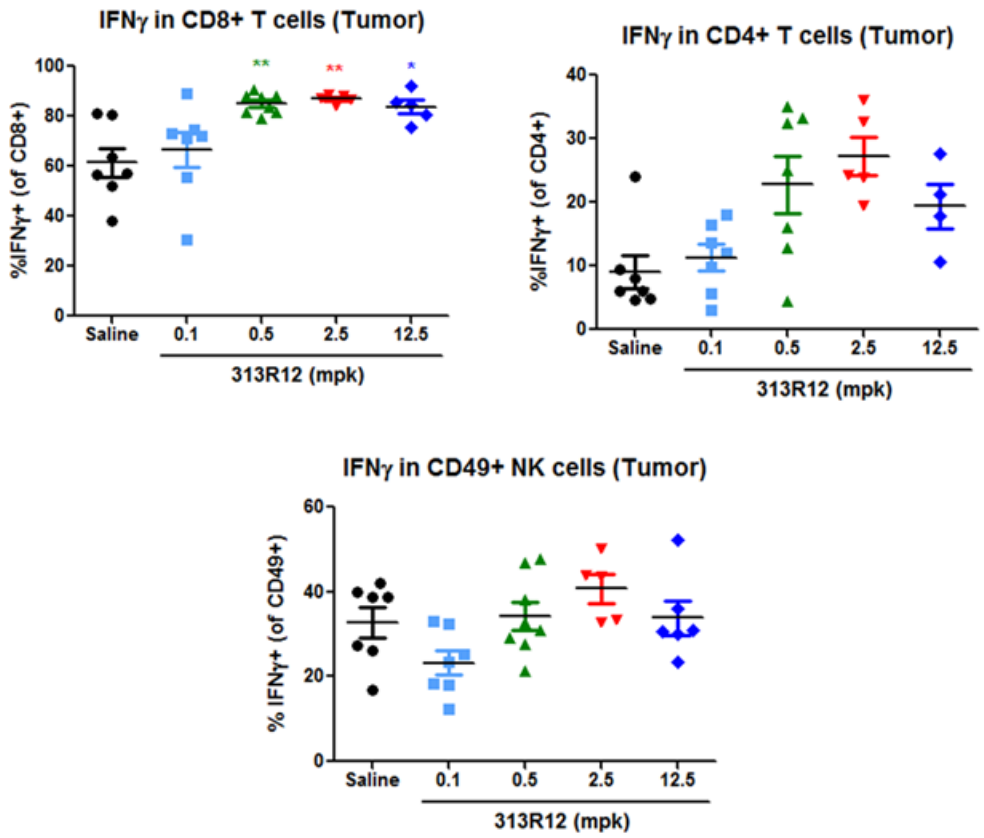
Advanced Biomarker capabilities in place

- Target engagement of etigilimab demonstrated in Phase 1a patients
- Identified tumors with high expression of TIGIT/PVR based on survey of large cohorts of tumors tissues
- Biomarker methods established to evaluate and enable future patient stratification and selection, e.g. IHC for PVR, TIGIT, PVRL2, FOXP3, CD226 and multiple panels for >15 immune related tumor parameters

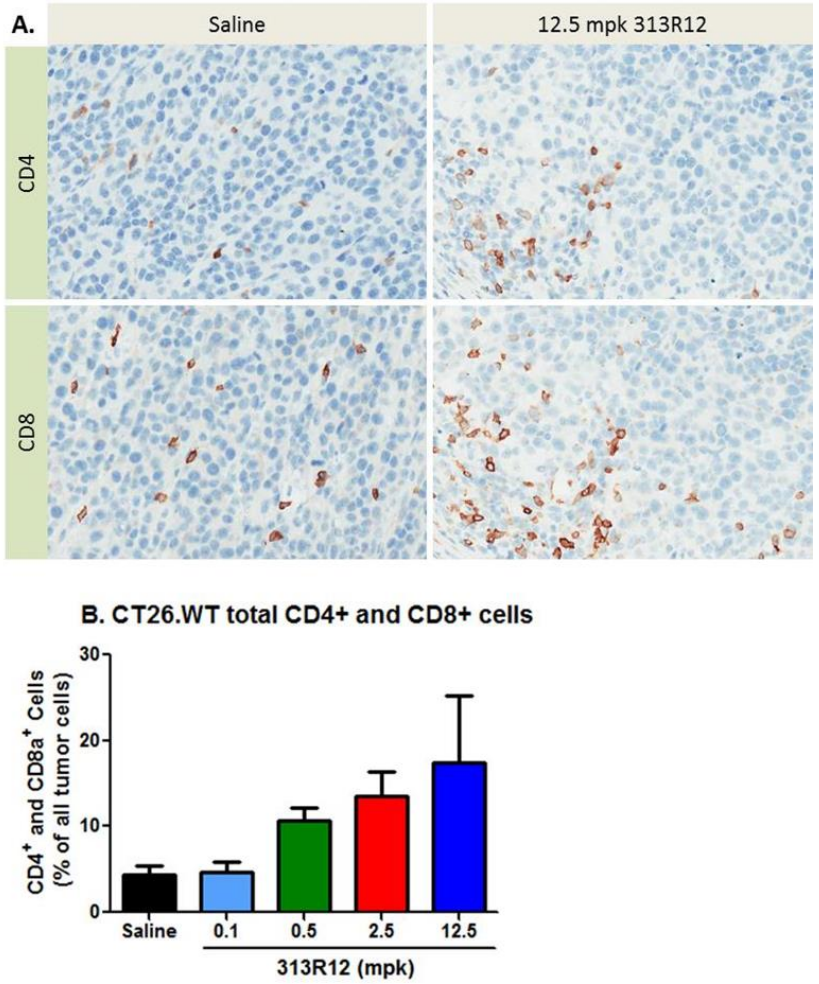
Innovative Phase 1b/2 Trial Design

Non-clinical Biomarkers and Evidence of T Cell and NK Cell Activation

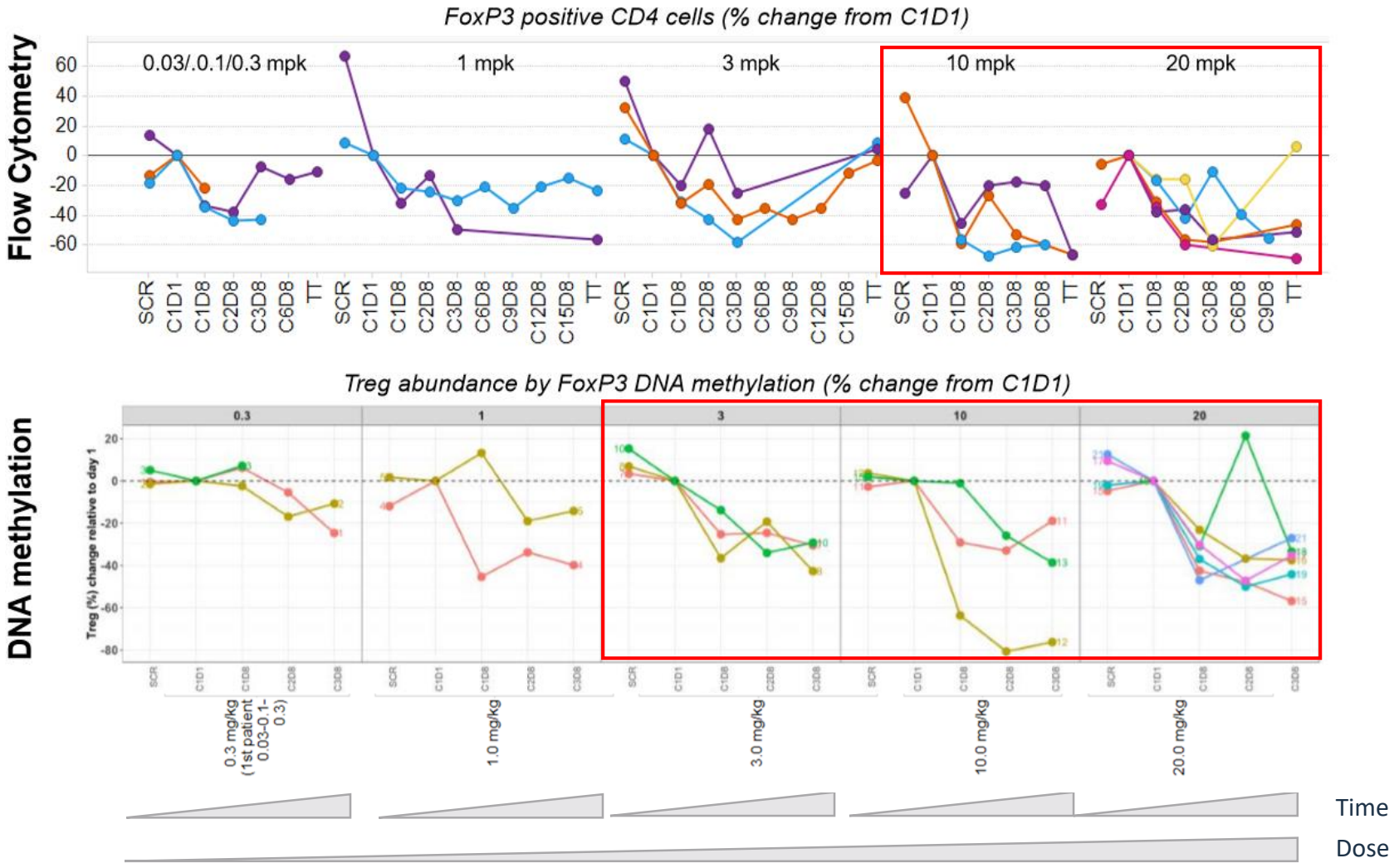
Anti-TIGIT Promotes Activation of CD8⁺ and CD4⁺ T Cells and NK Cells in the Tumor Microenvironment (FLOW)



Anti-TIGIT Increases CD4+ and CD8+ Cell Frequency in CT26.WT Tumors (IHC)



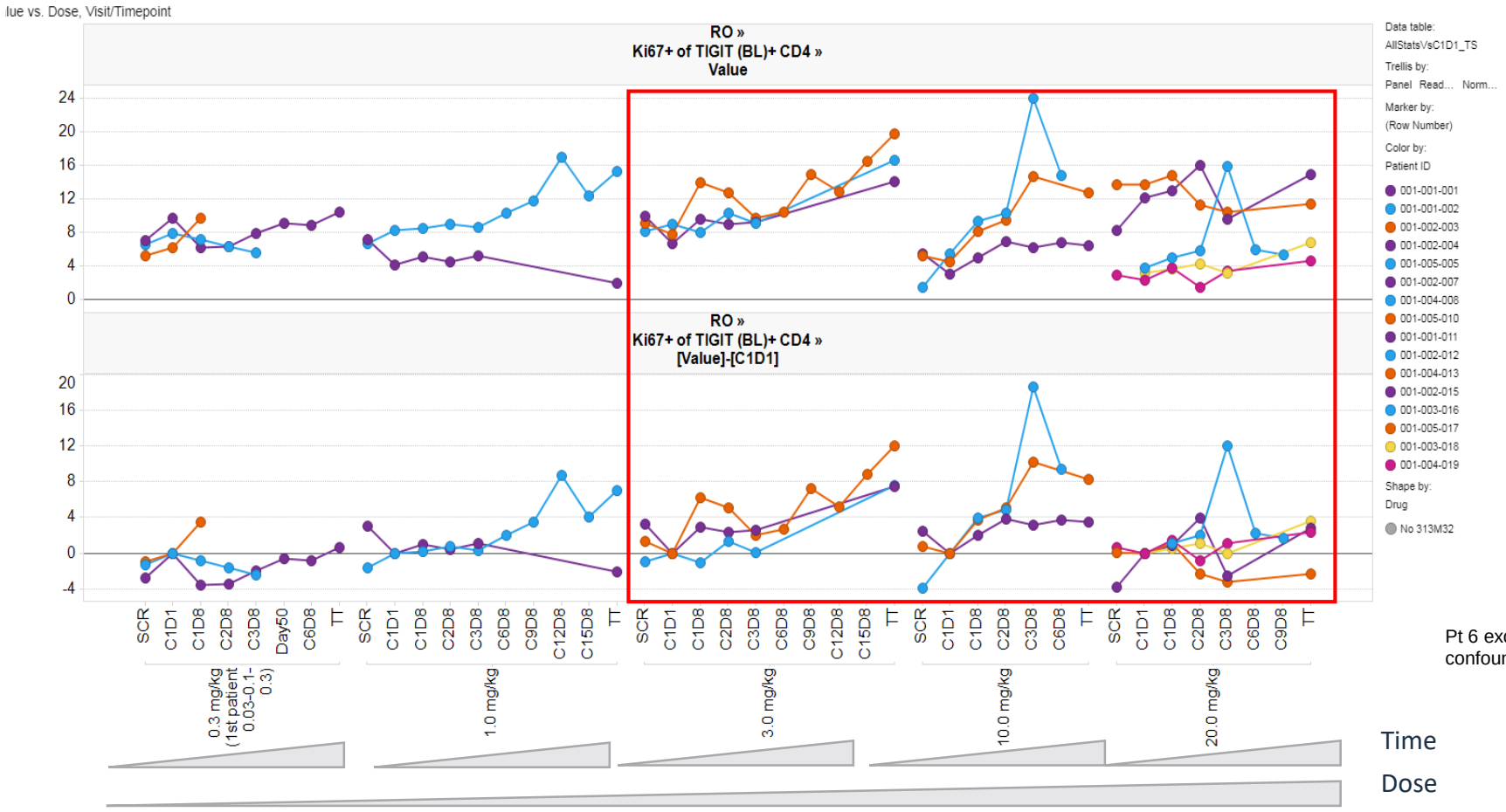
Etigilimab Decreased the Number of Treg Cells in Circulation and Changed FoxP3 DNA Methylation in Phase 1a Patients



Sharma et al

Huang et al

Etigilimab Increased Markers of Cell Proliferation in T and NK Cells of Phase 1a Patients



Pt 6 excluded due to confounding CML

Increases in Ki67+ observed in CD4 T cells as well as NK & Treg

Sharma et al

Anti-TIGIT Phase 1a Biomarker Summary

Target engagement of etigilimab demonstrated in Phase 1a patients by multiple modalities: flow cytometry, NGS gene expression, and DNA methylation analysis

- Activated immune cells measured by increases in Ki67+TIGIT+CD4 as well as NK cells and increased in intracellular cytokines
- Reduced Tregs in circulation, with a corresponding increase in the CD8/Treg ratio
- Regulation of Treg associated genes by etigilimab

Factors & Analyses Influencing Design of Phase 1b/2 Trial

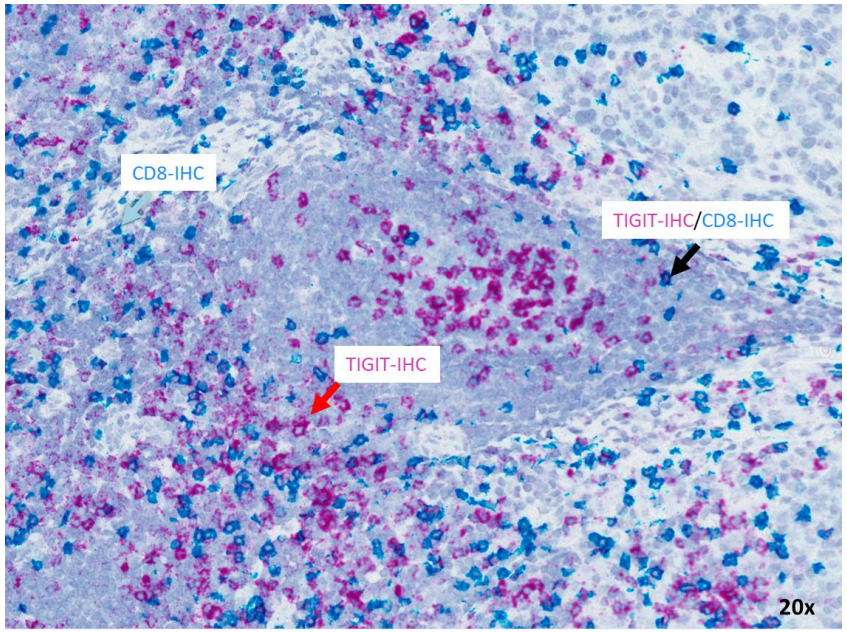
- Survey of large cohorts of tumors for TIGIT/PVR/PD-1 expression, including internal IHC expression data
- Study includes tumor types with high PVR/TIGIT and co-expression with PD1
- Tumors showing responsiveness to anti-PD-1/L1 including rare tumors
- Potential future patient selection in cohort(s) based on biomarker (PDL1, PVR, TIGIT)
- Strong biology rationale and early clinical signals

Huang D-W et. al. Onco Targets Ther. 2017; Braun M. et. al. Immunity 2019; Stamm H. et. al. Oncoimmunology 2019; Lee B-R et. al. JCI Insight 2020; Yang Z-Z et. al. Clin. Cancer. Res. 2020; Lepletier A. et. al. Clin Cancer Res. 2020

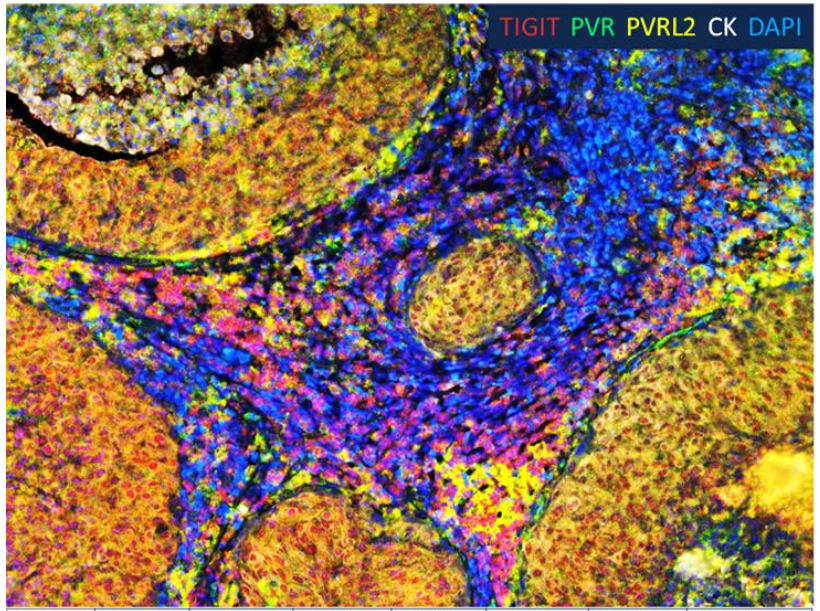
Biomarker Capabilities in Place

Example TIGIT & PVR Immunohistochemistry

- TIGIT biomarker single & multiplex IHC/IF assays developed with image analysis
- These assays were used to survey large cohorts of tumor tissues for indication selection
- Robust multiplex IHC assays and staining for PVR, TIGIT, and ~15 immune related tumor parameters including TIGIT, PVR, PVRL2, CD226, CD4, CD8, FOXP3, PD1, PDL1
- TIGIT and PVR assays developed and establishing as CLIA-validated to enable prospective pt selection at central lab



H&N



Specimen ID	Tumor type	% TIGIT	% PVR	% PVRL2	TIGIT:PVR	TIGIT:PVRL2	TIGIT:PVR or PVRL2
CR-9-1264-2	Head &Neck	30%	10%	8%	824	756	1216

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Biomarker Analysis of TIGIT Expression and Correlation with PD1 Expression

IHC and gene expression analyses of large tumor cohorts were used to:

- Rank tumors for high PVR/TIGIT expression and co-expression with PD1
- Interrogate histological subtypes and rare tumors where anti-TIGIT plus anti-PD1 may show clinical activity and be amenable for patient selection with IHC assay in central labs

TIGIT

Code	Tumor	>3rd Quartile (100.3)	Total Samples	Freq	Rank
DLBC	Lymphoid Neoplasm Diffuse Large B-cell Lymphoma	46	48	95.83%	1
TGCT	Testicular Germ Cell Tumors	88	150	58.67%	2
LUAD	Lung adenocarcinoma	267	515	51.84%	3
HNSC	Head and Neck squamous cell carcinoma	235	520	45.19%	4
SKCM	Skin Cutaneous Melanoma	206	470	43.83%	5
LUSC	Lung squamous cell carcinoma	214	502	42.63%	6
CESC	Cervical squamous cell carcinoma and endocervical adenocarcinoma	127	305	41.64%	7
KIRC	Kidney renal clear cell carcinoma	181	533	33.96%	8
STAD	Stomach adenocarcinoma	132	415	31.81%	9
BRCA	Breast invasive carcinoma	344	1097	31.36%	10
PAAD	Pancreatic adenocarcinoma	51	178	28.65%	11
BLCA	Bladder Urothelial Carcinoma	109	408	26.72%	12
MESO	Mesothelioma	20	87	22.99%	13
SARC	Sarcoma	56	259	21.62%	14
UCEC	Uterine Corpus Endometrial Carcinoma	114	545	20.92%	15
THYM	Thymoma	24	120	20.00%	16
CHOL	Cholangiocarcinoma	7	36	19.44%	17
ESCA	Esophageal carcinoma	33	184	17.93%	18
THCA	Thyroid carcinoma	86	505	17.03%	19
LIHC	Liver hepatocellular carcinoma	57	371	15.36%	20
COAD	Colon adenocarcinoma	65	460	14.13%	21
READ	Rectum adenocarcinoma	16	166	9.64%	22
LAML	Acute Myeloid Leukemia	16	173	9.25%	23
UVM	Uveal Melanoma	6	80	7.50%	24
OV	Ovarian serous cystadenocarcinoma	20	305	6.56%	25
UCS	Uterine Carcinosarcoma	3	57	5.26%	26
PRAD	Prostate adenocarcinoma	26	497	5.23%	27
KIRP	Kidney renal papillary cell carcinoma	13	290	4.48%	28
ACC	Adrenocortical carcinoma	2	79	2.53%	29
LGG	Brain Lower Grade Glioma	4	516	0.78%	30
GBM	Glioblastoma multiforme	1	161	0.62%	31
KICH	Kidney Chromophobe	0	66	0.00%	32
PCPG	Pheochromocytoma and Paraganglioma	0	179	0.00%	32

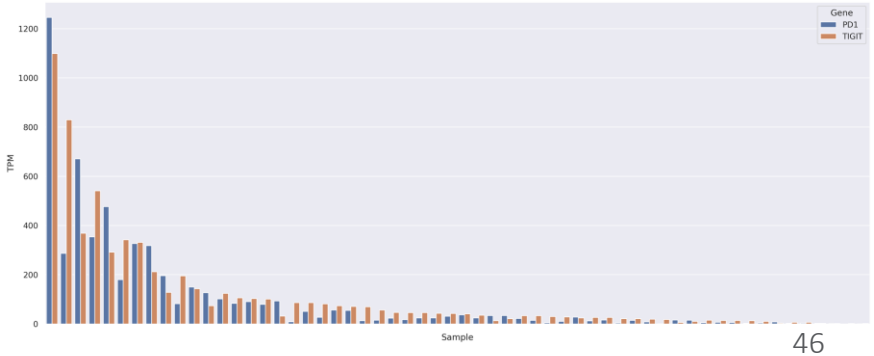
Prevalence of TIGIT gene expression in tumor types as available from TCGA. The quartile RSEM value of TIGIT gene expression is ~100.

PVR

Percentage of Cases for each Indication with ≥50% of Tumor Cells with PVR staining at ≥2+:		
Group	Tumor Indication	% of Cases with Staining ≥50% at ≥2+
High	Colon CA	83%
	Bladder CA	57%
	Endometrial CA	54%
	H&N CA	52%
	Lung Adeno CA	52%
	Gastric CA	50%
Moderate	Esophageal CA	47%
	Pancreatic CA	42%
	Cervical CA	33%
	Melanoma	32%
	Lung Squam CA	30%
	TNBC	29%
	Prostate CA	22%
Low	Ovarian CA	20%
	Leukemia	15%
	RCC	7%
	T-cell Lymphoma	6%
	B-cell Lymphoma	0%

Rare tumor 1

Rare tumor 2

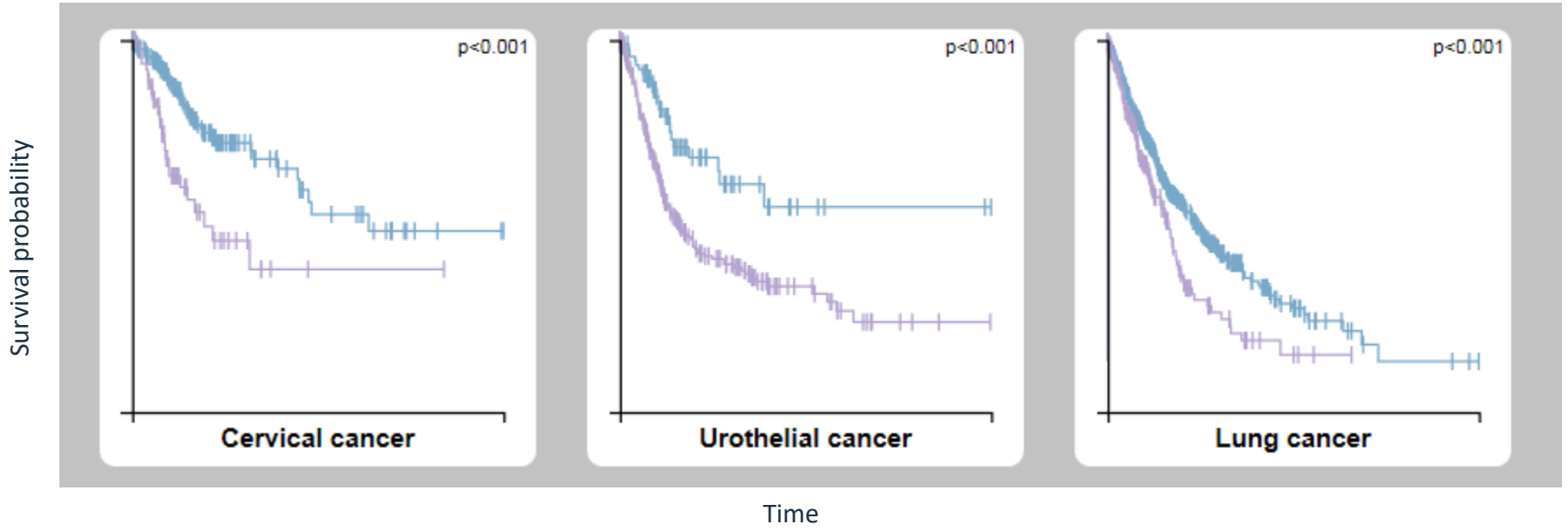


PVR Signaling as a Resistance Mechanism in Tumors

- Emerging data suggests the following:
  - High levels of PVR associated with poor prognosis in cancer patients
  - High PVR expression associated with resistance to anti-PD1 therapy

Huang D-W et. al. Onco Targets Ther. 2017; Braun M. et. al. Immunity 2019; Stamm H. et. al. Oncoimmunology 2019; Lee B-R et. al. JCI Insight 2020; Yang Z-Z et. al. Clin. Cancer. Res. 2020; Lepletier A. et. al. Clin Cancer Res. 2020

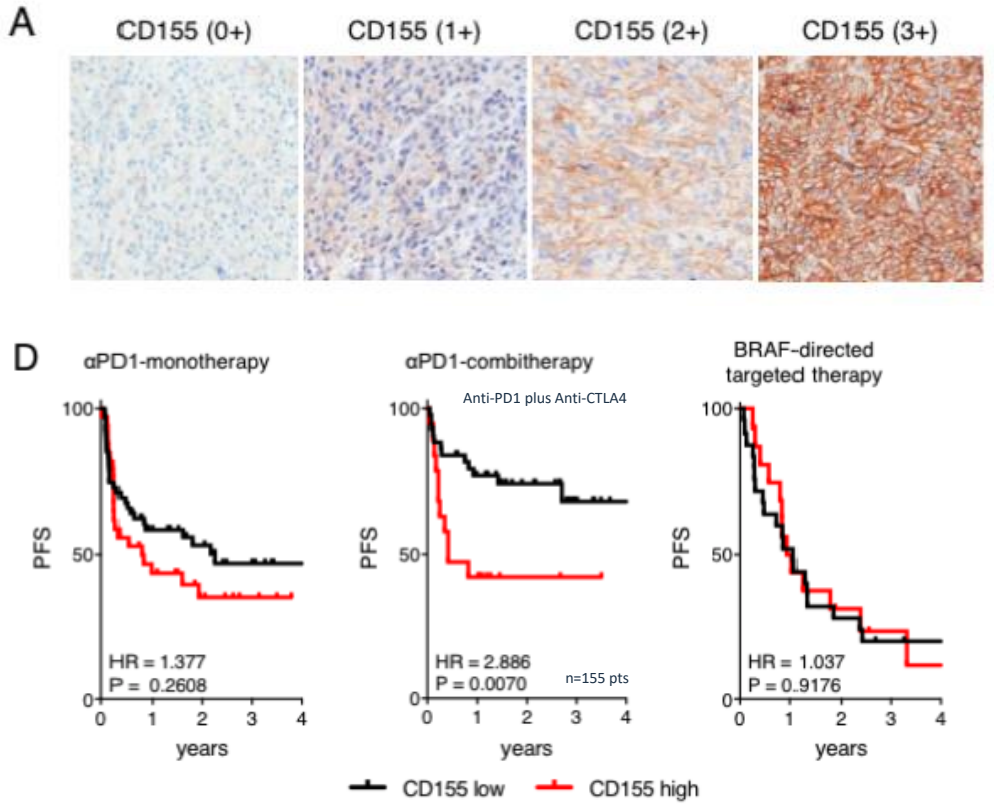
High PVR Expression Associated with Poor Clinical Outcome



TCGA
Blue=low PVR
Purple=high PVR

High PVR Expression Associated with Reduced Response to Anti-PD1 Immunotherapy

Melanoma



Lepletier A. et. al. Clin Cancer Res. 2020

Phase 1b/2 Basket Study

- Clinical design influenced by the following observations:

  - Survey of large cohorts of tumors for TIGIT/PVR/PD-1 expression, including internal IHC expression data
  - Study includes tumor types with high PVR/TIGIT and co-expression with PD1
  - Tumors showing responsiveness to anti-PD-1/L1 including rare tumors
  - Potential patient selection in cohort(s) based on biomarker (TMB, PDL1, PVR, TIGIT)
  - Correlation between high PVR and clinical outcomes
  - Strong biology rationale and signals from anti-TIGIT clinical data

ACTIVATE Study Design
Etigilimab Phase 1b/2 Basket Study

Primary endpoint
- Overall Response Rate

Secondary
- Safety and Tolerability
- PK/PD
- Duration of response

Exploratory
- Biomarker
- PFS
- OS

Simon two-stage design allowing for dynamic decision making and flexible design
~ 100 subjects

- HNSCC*
- Cervical carcinoma*
- Gastric/GE carcinoma*
- Endometrial carcinoma
- TMB-H, MSS tumors
- Rare Tumor
  e.g. Sarcoma, Salivary gland

Initiation of Phase 1b/2 study planned for this quarter

Flat dosing Q2W

*PDL1+

ACTIVATE Study Design
Etigilimab Phase 1b/2 Basket Study

- Received the study may proceed letter from FDA
- 12-15 months study duration
- Anticipating initial data in 2H2021
- Site initiation ongoing in US and EU; top sites and investigators in place

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Q&A

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Alvelestat

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Professor Mark Dransfield
Neutrophil Elastase-Driven Diseases: Alpha-1 Antitrypsin and COVID-19

Neutrophil Elastase- A critical protease in health and agent of disease

- Highly aggressive protease, normally constrained in neutrophil cytoplasmic granules (uM) until activation
  - Physiological role in intracellular killing and degradation of bacteria
- Dysregulated response identified as critical pathogenic mechanism in inflammatory disease
- During neutrophil activation granule contents are translocated to cell surface and released as soluble enzyme and within extracellular vesicles (exosomes) leading to:
  - Local degradation of elastin within tissue matrix
  - Diffusion of soluble elastase and exosomes into adjacent tissue spreads damage and initiates inflammation
- Uncontrolled NE particularly damaging in lung
  - Respiratory parenchyma has highest concentration of elastin -comprises 20–30% connective tissue
- Escalating body evidence for extent of pathogenic role for NE through Neutrophil Extracellular Trap (NET) formation in diseases of systemic inflammation beyond the lung

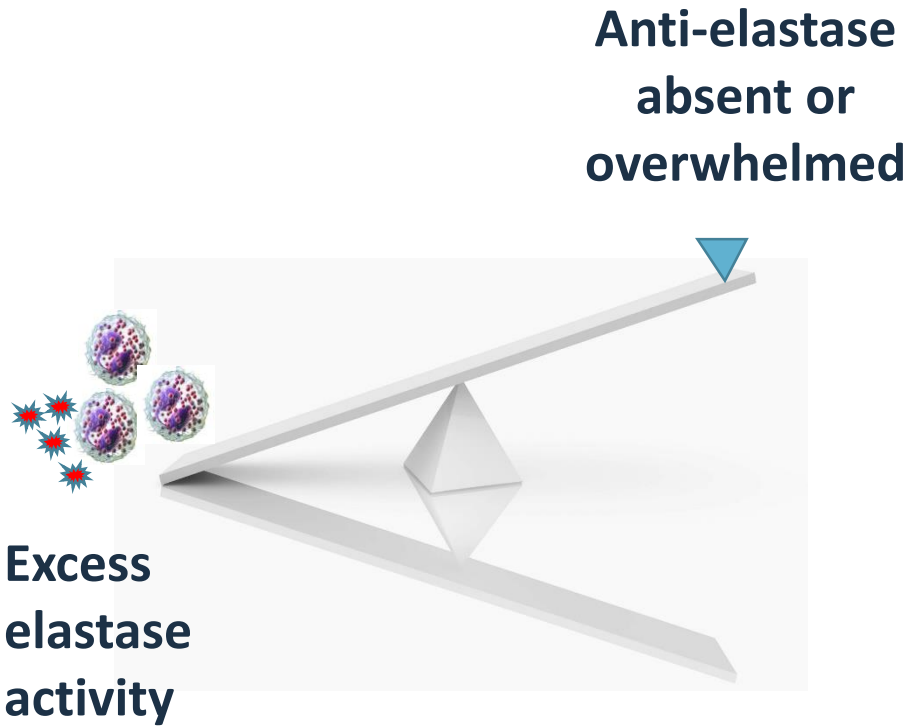
Pathogenesis of Lung Disease – a Critical Balance between Physiological Inhibitor (alpha-1 antitrypsin) and NE

Steps leading to Proteinase/Anti-Proteinase concept of pathogenic role of NE in lung damage

- Recognition of the genetic deficiency of the physiological inhibitor of HNE (alpha-1 antitrypsin) as a rare cause of aggressive early-onset lung disease
- Experimental observations that instillation of NE into lungs of animal models induced emphysema

Demonstration that membrane bound NE is relatively resistant to the physiological inhibitor alpha-1 antitrypsin (α1AT) if protein at low levels or alternatively overwhelmed by high concentrations of elastase

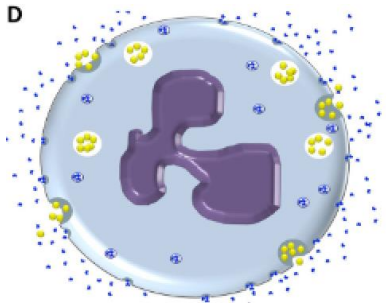
Recent recognition that neutrophil activation releases NE-containing exosomes, resistant to α1AT (steric hindrance), and induce emphysema in animal models

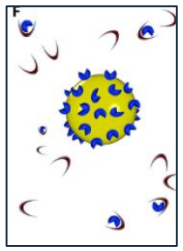


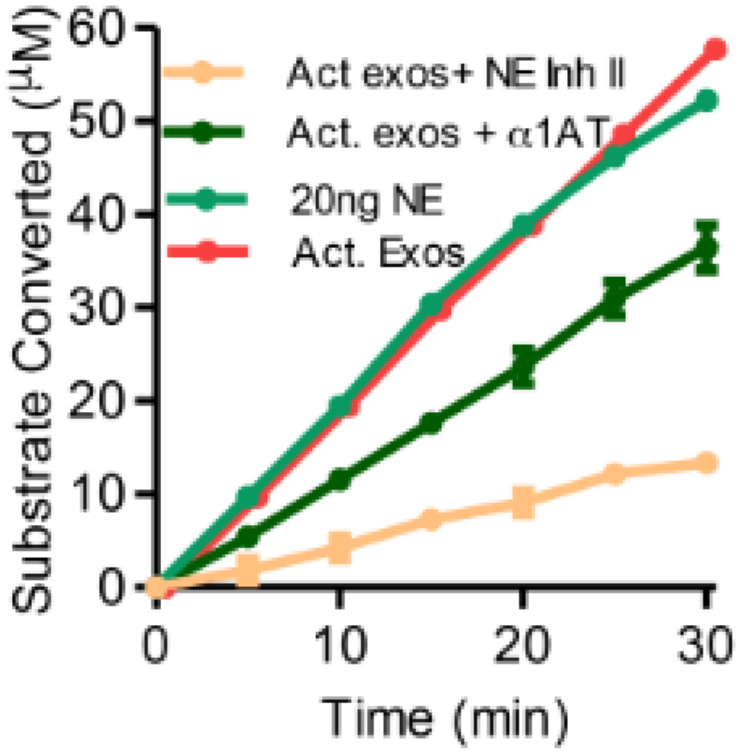
Identification of Exosomes in NE-driven Pathology (COPD)

Key Findings

- Exosomes from activated PMNs harbor surface NE
- Activated PMN exosomes bind and degrade Extra Cellular Matrix via NE
- Activated PMN exosomes are relatively resistant to α1-AT, but are inhibited by small molecule NEi
- CD66b/NE PMN exosomes reside in COPD patients and transfer a COPD phenotype to mice







NE activity of activated exosomes with small molecule NE Inhibitor, α1-AT, or PBS control

Cell. 2019; 176(1-2): 113–126. Activated PMN Exosomes: Pathogenic Entities Causing Matrix Destruction and Disease in the Lung. Genschmer et al.

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Alpha-1 Antitrypsin Deficiency Lung Disease

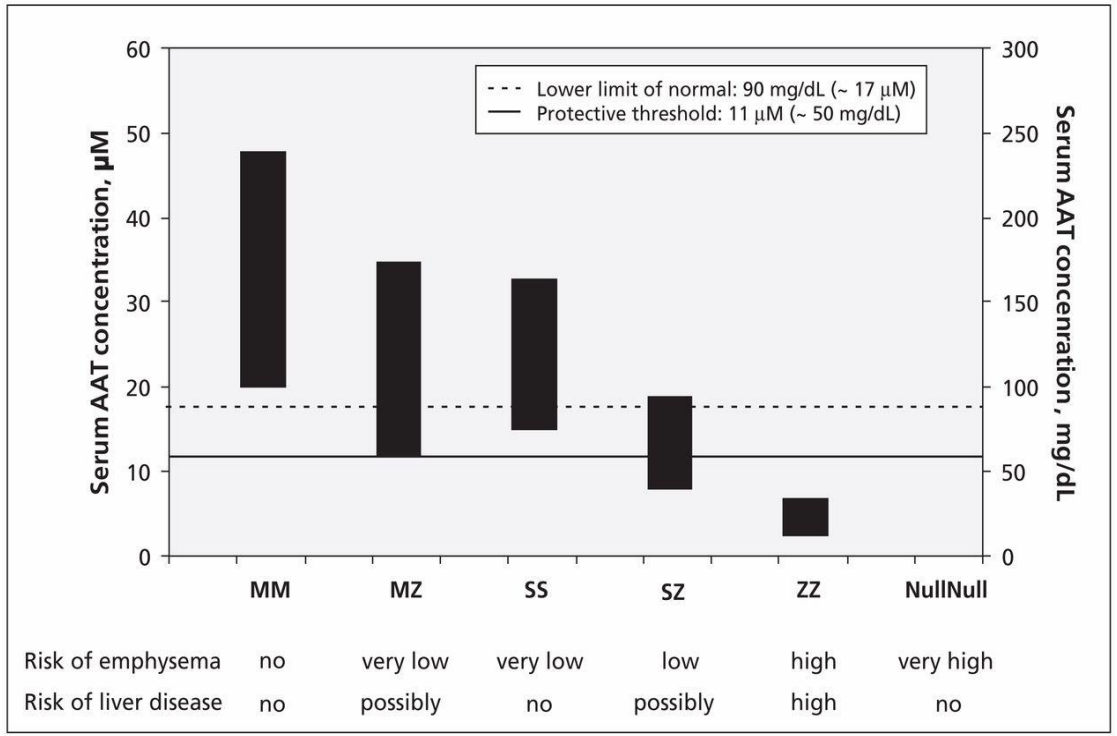
Alpha-1 Antitrypsin Deficiency Lung Disease: a Disorder of Physiological Elastase Inhibitor Deficiency

Genetic condition

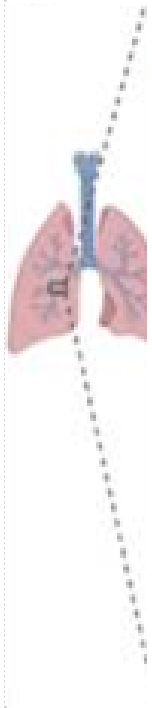
- Autosomal co-dominant inheritance – MM (normal), MZ, SZ, ZZ and null
- Severity of disease related to level of α1AT Homozygotes (ZZs) and nulls have most severe deficiency and disease
- PiZZs misfolded α1AT 'trapped' in liver – 'loss of function' mutation with systemic deficiency with liver disease mainly in children due to accumulation of polymerised α1AT

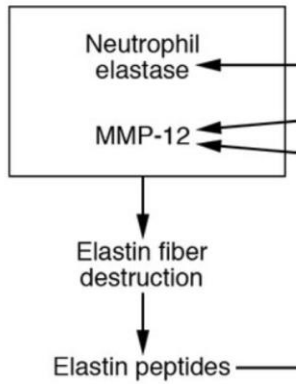
AATD-Lung Disease

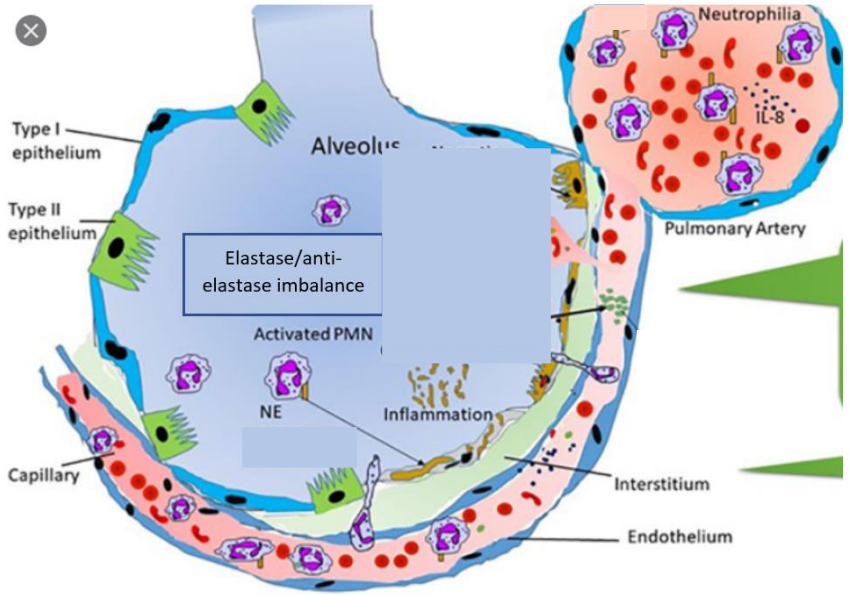
- Prevalence in US ~ 80-100,000, diagnosis often missed/delayed
- Presents age 20 to 50 – SOB, shortness of breath, cough and reduced exercise tolerance
- Unopposed proteases → progressive alveolar & structural damage → emphysema
- May progress to chronic oxygen therapy, lung surgery, transplant and death



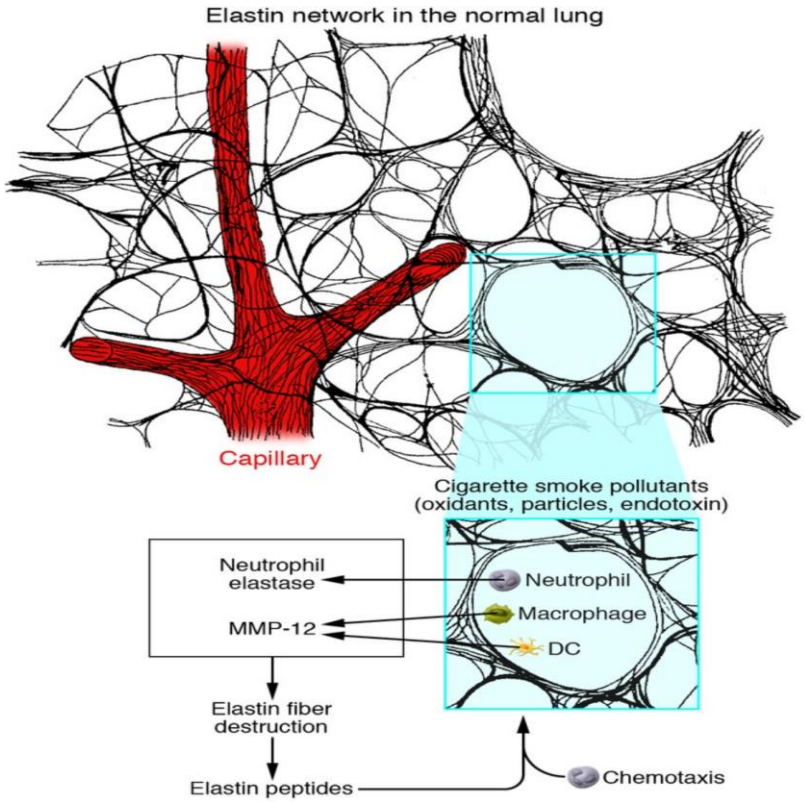
The Role of NE in Pathogenesis of AATD Lung Disease

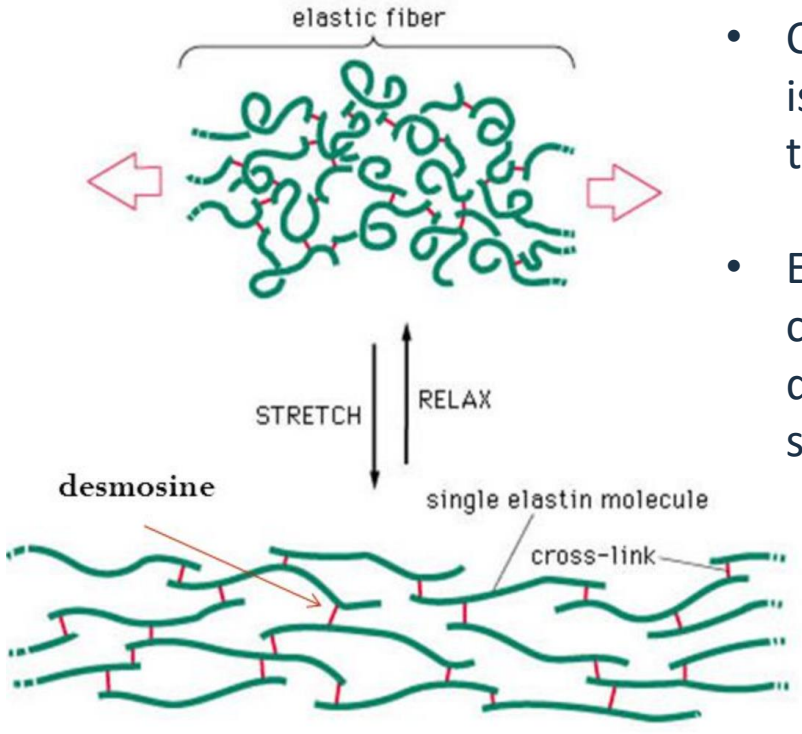






Failure to Control Elastase is Destruction of the Lung Structure Leading to Early-onset Emphysema





- Cross-linking amino acids desmosine and isodesmosine are released on exposure to elastase
- Elastin fragments detected in body fluids can be used as markers for elastin-degrading diseases along with other NE specific markers of eg A-alpha val)

Credit: 'Fibrous Proteins' Malik Alqab

Relationship of Elastin Breakdown Markers and Severity of Lung Disease in AATD-LD Supports the Potential Importance of Controlling Elastase

- Levels of elastin breakdown highest at site of pathology (lung), but also raised in plasma
- Desmosine/isodesmosine correlate with disease severity:
  - Plasma levels of DES/IDES significantly correlate with FEV_1 and DLCO (Ma et al 2017)
  - Lung tissue loss:
    - Reduced DES/IDES associated with slower lung density decline (CT imaging)
- Longitudinal studies demonstrate progressive increase in DES/IDES over time
- Replacement of alpha-1 antitrypsin (IV augmentation) associated with decrease in DES/IDES levels

The Effect of Alpha-1 Proteinase Inhibitor on Biomarkers of Elastin Degradation in Alpha-1 Antitrypsin Deficiency: An Analysis of the RAPID/RAPID Extension Trials. Ma et al Chronic Obstr Pulm Dis. 2017;4(1):34-44

Clinical Management

- **'COPD' maintenance treatment**, personal lifestyle management, e.g., avoidance of smoking and pollution
- Testing of family to enable lifestyle choices
- **Intravenous plasma-derived augmentation therapy**, weekly, approved in N. America and EU, but clinical efficacy not uniformly recognized by physicians or payors:
  - Limited penetration into lung
  - Inability to 'titrate' up to cover periods of acute lung inflammation. elastase activity and lung damage
  - Growing evidence that higher doses may be needed for clinical efficacy with cost and convenience implications

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Neutrophil Extracellular Traps

COVID-19- Immunopathology

For 80% infections with SARS-Cov 2 causes mild or asymptomatic disease

For others, the infection is characterized by dyspnea, hypoxemia, with acute respiratory distress syndrome (ARDS), shock, and multi-organ failure:

- Direct damaging effects of viral infection, compounded by a dysregulated and damaging hyper-responsive immune reaction
- Characterized by elevation of pro-inflammatory cytokines, acute phase reactants, and neutrophilia/lymphocytopenia
- Coagulopathy with microthrombi contributing to organ failure-
- Neutrophil Extracellular Traps (NETs) have been identified as a potential key driver of SARS-CoV-2 pathogenesis

Evidence for NETosis Driving Pathogenesis in SARS-Cov2

Networks of DNA fibers, extruded from activated neutrophils:

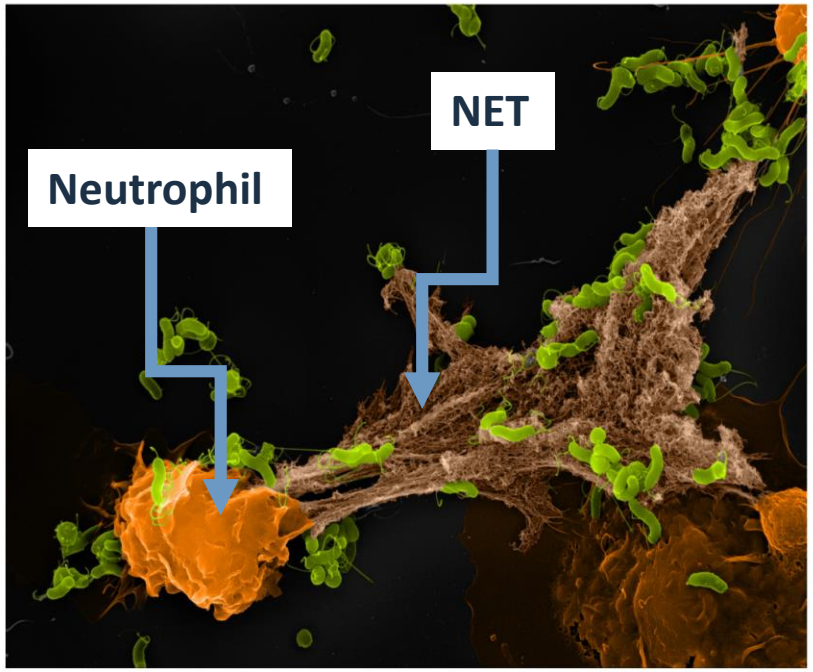
- Studded with histones, myeloperoxidase and NE
- Can be be 10x size of neutrophil

NET effects align with pathogenic features of COVID-19:

- Cytotoxic to endothelial/epithelial cells; act as Damage Associated Molecular Pattern Molecules- cytokine release[1]
- Activate platelets and coagulopathy- scaffold for thrombus

In patients:

- NET biomarkers correlate with COVID-19 disease severity, poor clinical outcomes in hospitalized patients
- Present at post-mortem in lungs, heart, and thrombi[2,3]

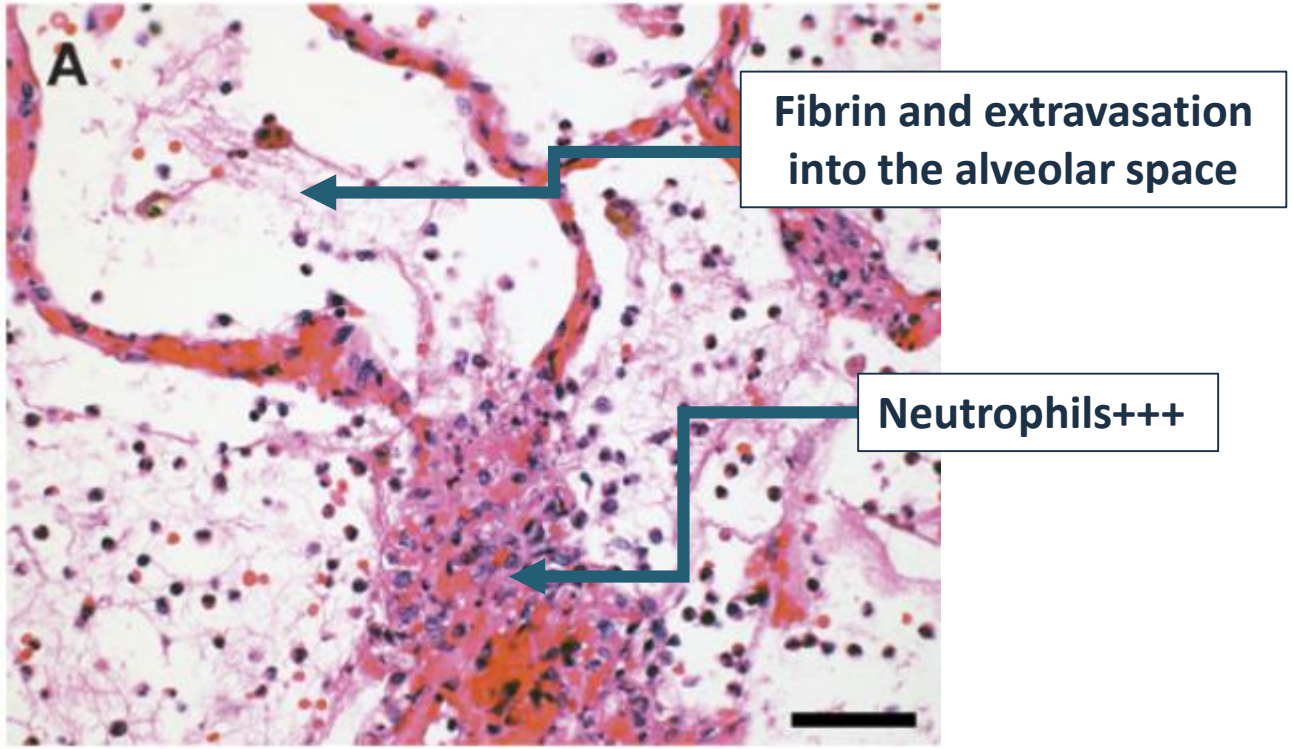


Colorized scanning electron micrograph of human neutrophils (orange) with NETs (brown) after co-culture with *Helicobacter pylori (green)*
VOLKER BRINKMANN

[1]Kim et al 2019 [2]Barnes et al 2020 [3]Zuo et al 2020

Pathology of Organs and Vessels from Patients who Succumbed to COVID-19 are Closely Associated with Excessive Neutrophil/NET Activity

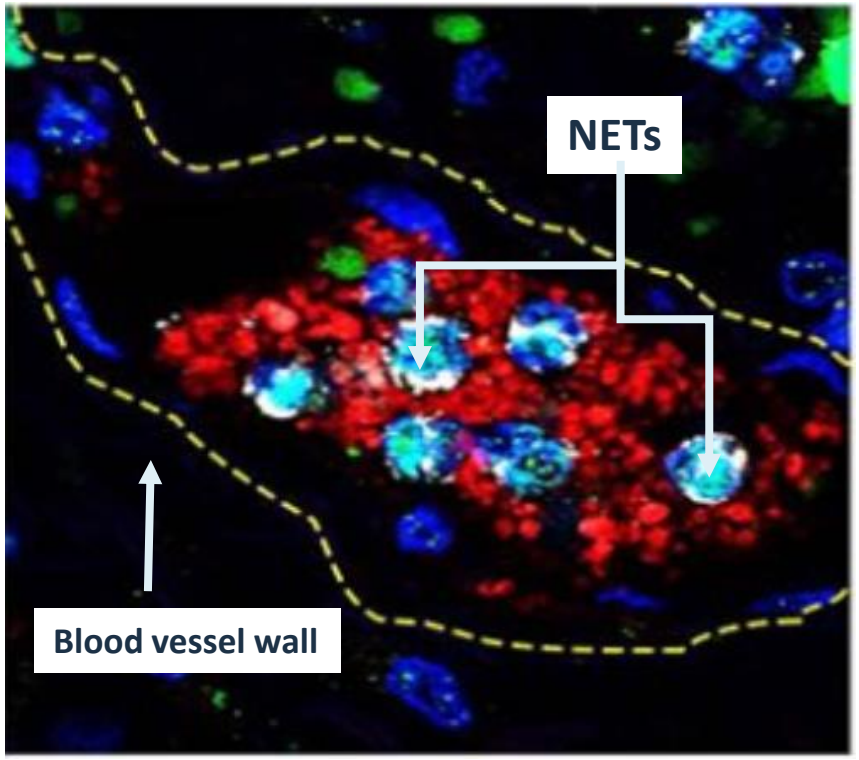
Neutrophilic Inflammation



Extensive neutrophil infiltration in Lung

Adapted from Barnes et al 2020

Immuno-Thrombosis



NET structures associated with blood clots in vessels

Adapted from Xue-Yan He and David Ng, Egeblad Lab/Cold Spring Harbor Laboratory

Critical Role of Neutrophil Elastase in Formation and Inflammatory Activity of NETs

Elastase is essential and sufficient for NET formation[4]

- **NE knock-out mice and NE inhibitor treated neutrophils fail to make NETs**
- **In models of NET-induced Acute Respiratory Distress Syndrome (ARDS), pecific NE inhibitors (alvelestat or anti-NE antibody) attenuated both NET formation and ARDS [5]**

NE is required for ongoing activity of NETs once formed[5]

- **NE inhibitors protected against cell death and inflammatory effect of administration of pre-formed NETS**

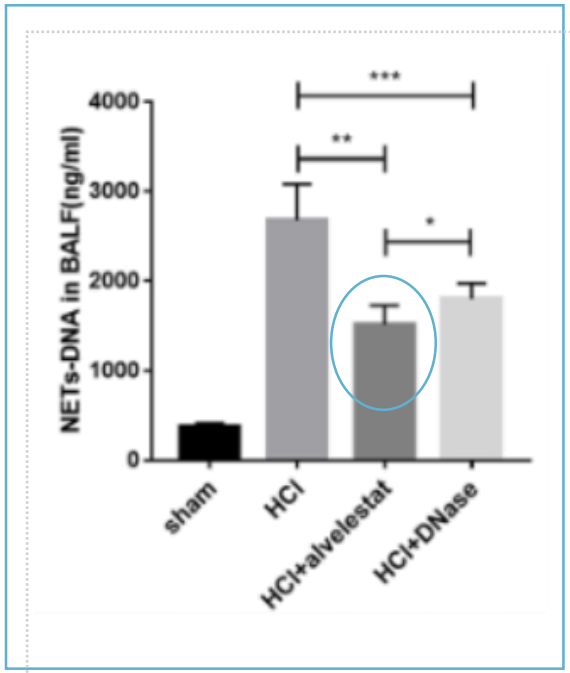
In COVID-19, the physiological inhibitor of NE, Alpha-1 antitrypsin, is overwhelmed[6]

[4]Papayannopoulos et al 2010 [5] Li et al 2018 [6]McElvanay et al 2020

Alvelestat Inhibits both NET Formation and Inflammatory Activity of Pre-formed NETs in Mouse Model (Li et al 2018)

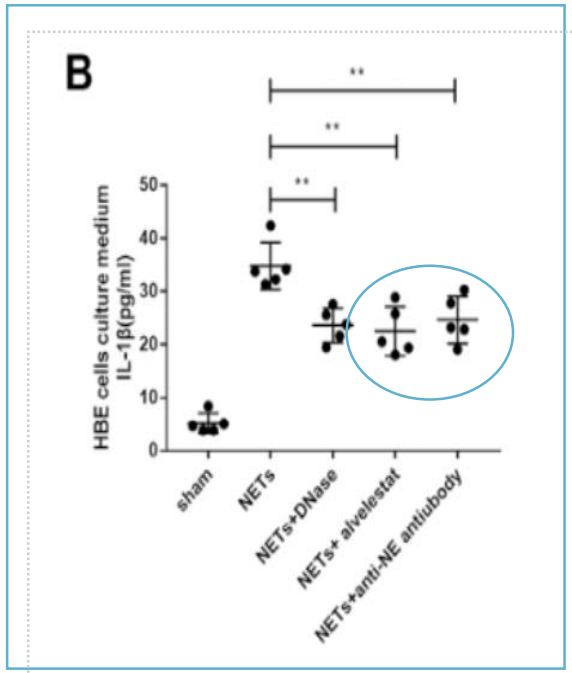
Inhibition of Activity of Exogenous NETs

Inhibition of NET Formation

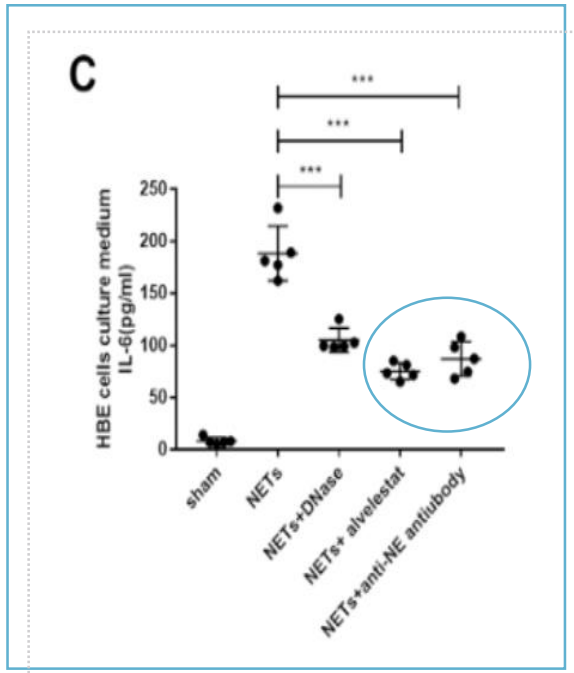


NET-DNA in Bronchiolar lavage after acid-aspiration. * p < 0.05, **p < 0.01, ***p < 0.001

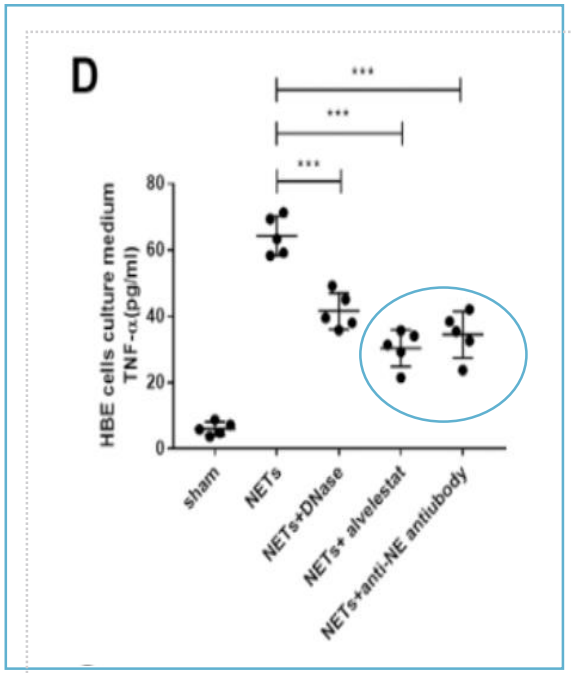
IL-1β



IL-6

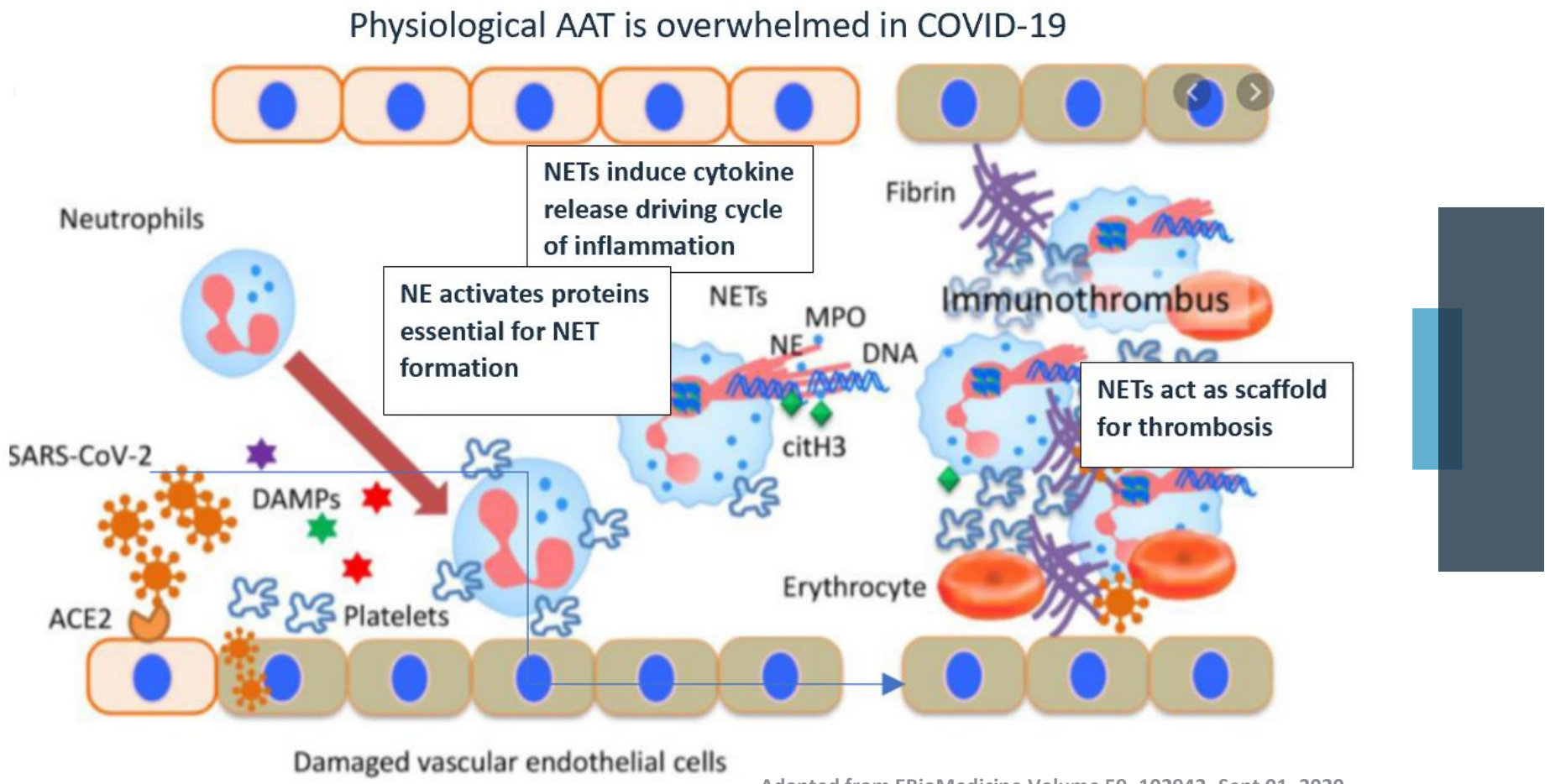


TNF-α



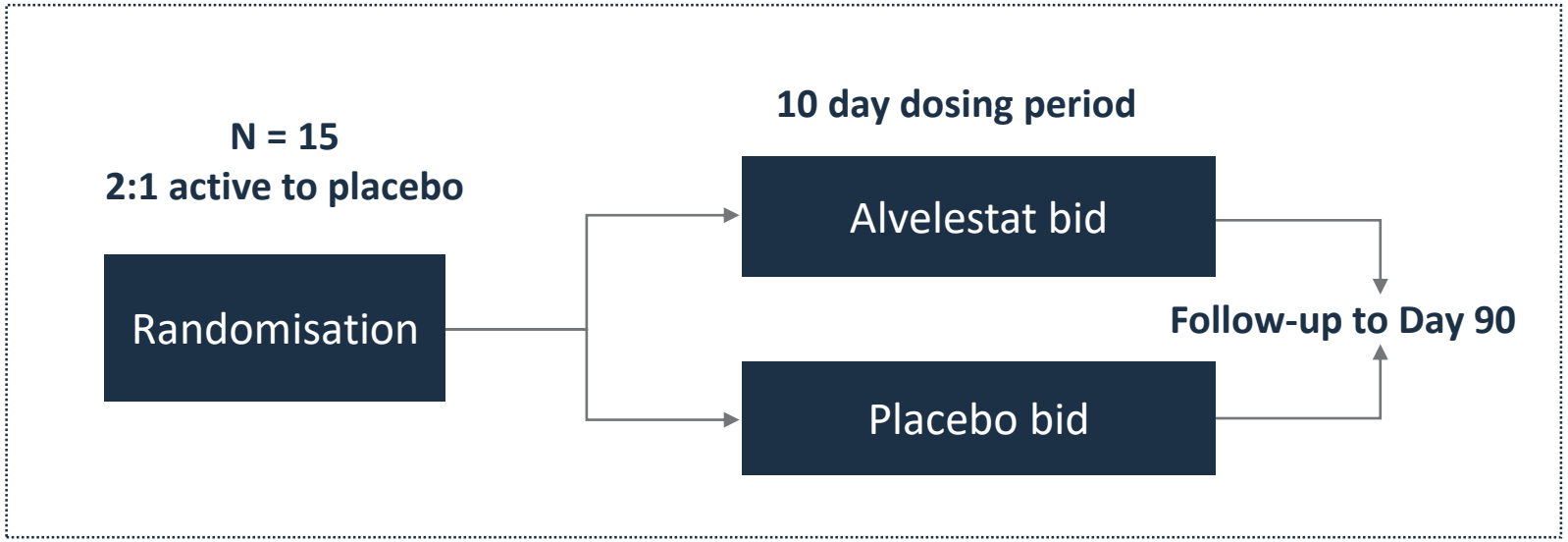
Administration of exogenous NETs in HBE cells ~~(B–D)~~ increased the levels of IL-1β, IL-6, and TNF-α in the supernatant of culture medium, ~~whereas~~ anti-NE antibody, alvelestat or DNase preincubation substantially decreased these cytokines (* p < 0.05, **p < 0.01, ***p < 0.001).

Neutrophil Elastase in NETosis-driven Disease (COVID-19)



Adapted from EBioMedicine Volume 59, 102942, Sept 01, 2020

Testing the Hypothesis in COVID-19 Phase 1b/2 Investigator-initiated Study "COSTA" (Prof. Mike Wells, UAB)



Trial Population

- > 18 years, hospitalized
- Moderate/Severe SARS-CoV-2 infection (WHO grade 3-5)
- Not on invasive ventilation

Primary Endpoint

- Safety and tolerability (Day 60)
- Mortality (Day 90)

Secondary Endpoints

Pharmacodynamic Biomarkers of:

- NETosis
- Inflammation
- Elastase

Clinical outcomes

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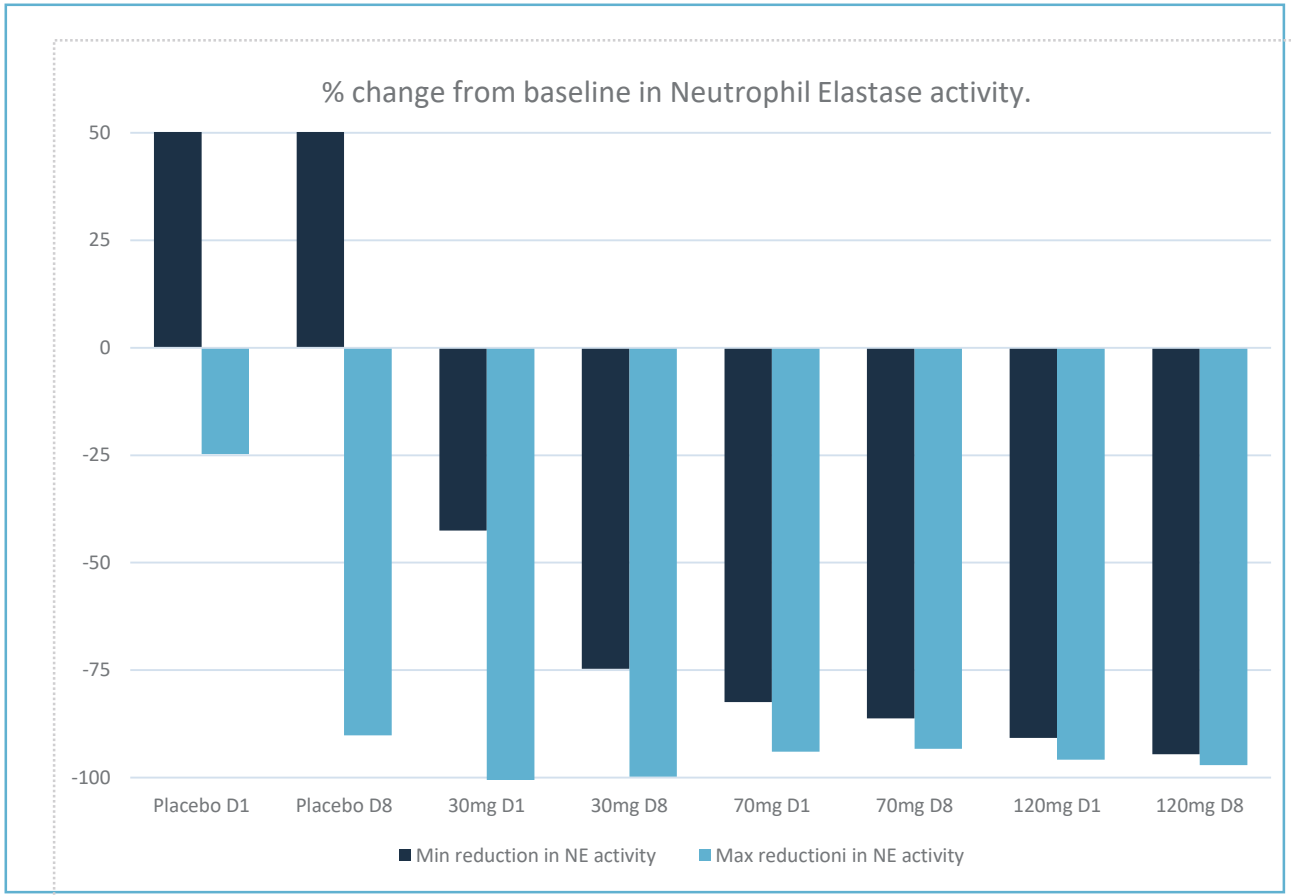
Alvelestat (MPH-966)

Alvelestat Mechanism of Action

- Potent, reversible, oral inhibitor of neutrophil elastase (NE)
- Compared to natural inhibitors i.e., alpha-1 antitrypsin native protein
  - Comparable association constant
  - Not susceptible to oxidative inactivation at sites of inflammation
  - Active against both soluble and cell-bound NE
  - Well-characterised exposure-response profile – significant lung penetration
- Safety established in >1000 subjects
- Activity in pre-clinical models of NE and NETosis pathology
- Studies underway include:
  - AATD (NE)
  - COVID-19 (NETosis)
- Potential mechanistic indication expansion

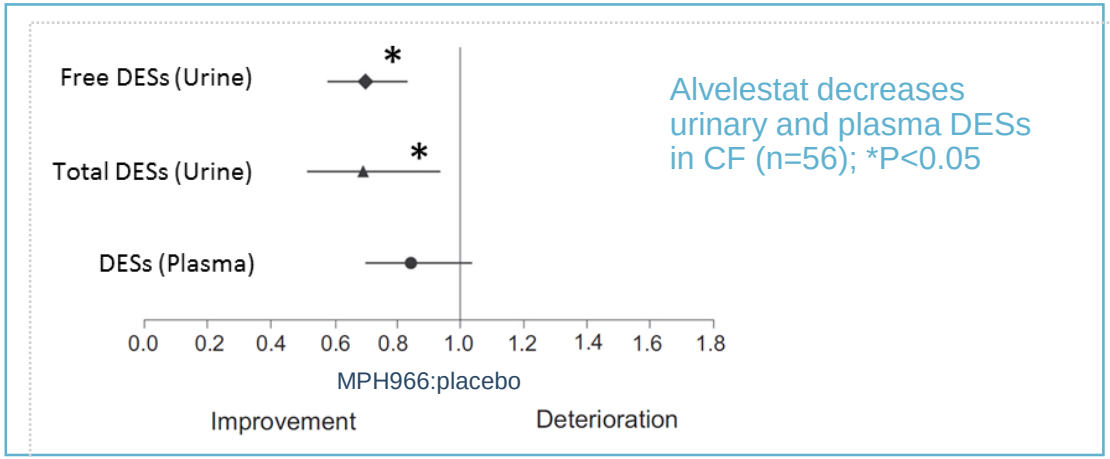
Inhibition of Neutrophil Elastase Activity



- MAD study – once daily dosing
- 3 cohort study; 9 subjects per cohort
- In each cohort, 6 received active, 3 placebo. Placebo from each cohort pooled.
- In placebo arm patients had increases in NE activity – 2 patients > 50% at separate time points
- One 30mg patient had > 100% reduction in NE, due to unusually low reaction to zymosan stimulation

Signal Seeking in Neutrophil-driven Diseases (1) Cystic Fibrosis

Desmosine week 4 Ratio alvelestat:placebo



Pro-Inflammatory Cytokines at week 4

Cytokine	Ratio alvelestat:placebo	P Value
IL-6 (sputum)	0.59	0.006
RANTES (sputum)	0.77	0.100

Efficacy, safety and effect on biomarkers of AZD9668 in cystic fibrosis. Elborne et al. Eur Respir J 2012; 40: 969–976

Trial Summary

- Double-blind, placebo controlled
- ≥ 16 years
- Clinical diagnosis of CF
- FEV1 > 40% predicted
- 60 mg alvelestat or placebo BD for 4 weeks
- Randomized = 56 (27 alvelestat, 29 placebo)

Signal Seeking in Neutrophil-driven Diseases (2)
Bronchiectasis – Anti-inflammatory and Clinical Effect

Spirometry at week 4		
Lung Function Parameter	**Improvement over placebo LSM(SEM)**	**P Value**
FEV_1	100 mls (34.0)	0.006
SVC	130 mls (74.0	0.079

Pro-Inflammatory Cytokines at week 4		
Cytokine	**Ratio alvelestat:placebo**	**P Value**
IL-6 (sputum)	0.72	0.058
RANTES (sputum)	0.63	0.018
IL-8 (blood)	0.74	0.085

Trial Summary

- Double-blind, placebo controlled
- 18- 80 years
- Non-CF bronchiectasis, stable for 6 weeks
- 60 mg alvelestat or placebo BD for 4 weeks
- Randomized = 38 (16 alvelestat, 22 placebo)

Phase 2 study of a neutrophil elastase inhibitor (MPH966) in patients with bronchiectasis. Stockley et al. Respiratory Medicine (2013) 107, 524- 533

Alpha-1 Antitrypsin Deficiency (AATD) – High Unmet Medical Need

Genetic Condition

Progressive life-threatening disease; lack of or deficiency in key protein creates damage to lungs

Autosomal co-dominant inheritance; genetics create MM (normal), MZ, SZ, ZZ and null

Homozygotes (ZZs) and Nulls have severe A1AT protein deficiency and disease, estimated prevalence ~ 50,000 US, 60,000 EU – significant under-diagnosis

A rare, serious genetic disorder that results in early onset pulmonary disease

Alpha-1 Antitrypsin Deficiency (AATD) – Disease Impact

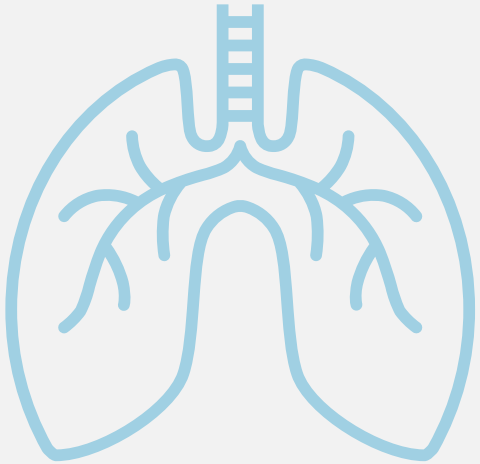
AATD-Lung Disease

Natural protease inhibitor
is either absent or levels are insufficient and dysfunctional

Unopposed neutrophil elastase → progressive and severe lung damage – early onset emphysema

Presents age 20 to 50
shortness of breath, cough and reduced exercise tolerance, can progress to chronic oxygen therapy, lung transplant and death

A rare, serious genetic disorder that results in early onset pulmonary disease



Current Unmet Need in AATD–Lung Disease

Improved Efficacy

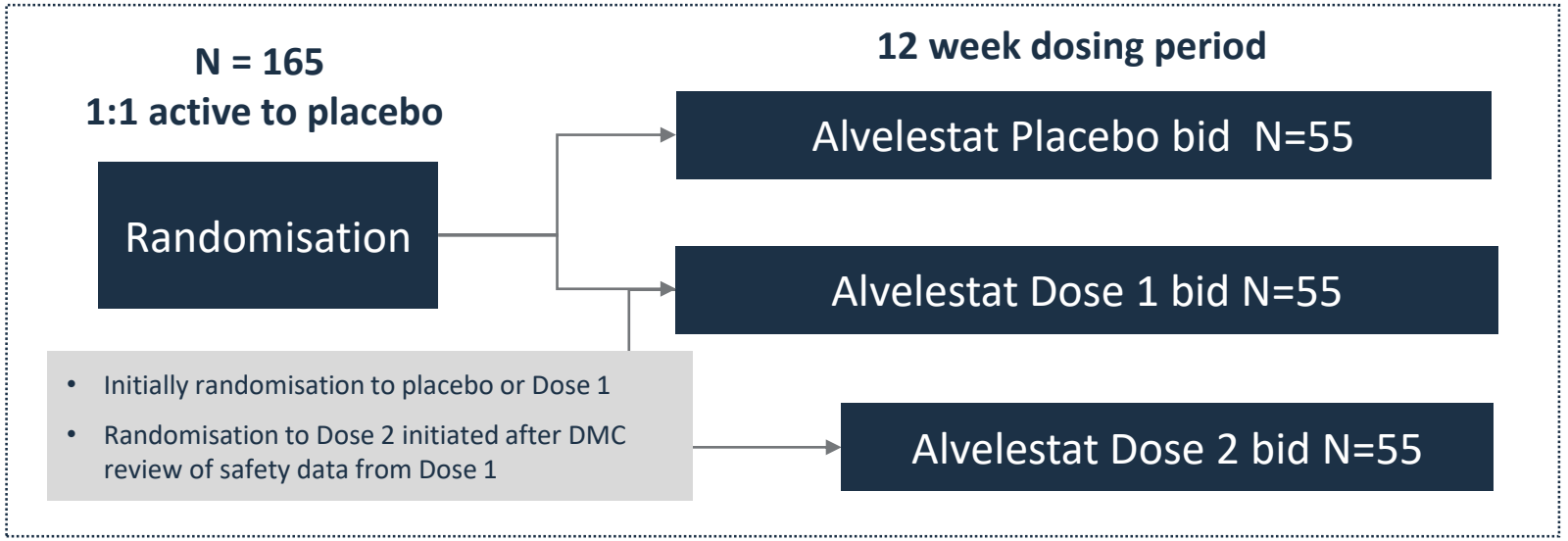
- **Inhibition of elastase forms resistant to alpha-1 antitrypsin**
- **Effective lung penetration**
- **Effective inhibition elastase at times of increase activity, e.g. acute exacerbations**

Convenience

- **Oral therapy benefit for life-long treatment for chronic disease**

ASTRAEUS Phase 2 Study Design (NCT03636347) in Alpha-1 Antitrypsin Deficiency

A 12-week Study Treating Participants Who Have alpha1-antitrypsin-related COPD with Alvelestat (MPH966) or Placebo. (ASTRAEUS)



Trial Population

- Age ≥18 and ≤80 years
- Pi*ZZ, Pi*Z Null, or Pi*Null genotype/phenotype,
- Anti-alpha1 antitrypsin <11uM
- Emphysema, FEV1 ≥25% predicted
- No augmentmentation therapy within 6 months of dosing

Primary Endpoint

- Within-individual % change in plasma desmosine/isodesmosine

Secondary Endpoints

- Safety and tolerability
- Other blood biomarkers of neutrophil elastase activity
- St. George's Respiratory Questionnaire
- Forced expiratory volume in 1 second (FEV_1)

Desmosine/Isodesmosine Rationale for Primary Endpoint- supported by Secondary Endpoints of Inflammation, Lung Damage, Lung Physiology and Exacerbations

Progressive increase over time along with disease progression in patients with AATD-LD (ZZ/null)

- **Dynamics of change in target population appropriate for 12 week POC endpoint**

Correlation with AATD-relevant measures of lung function and imaging

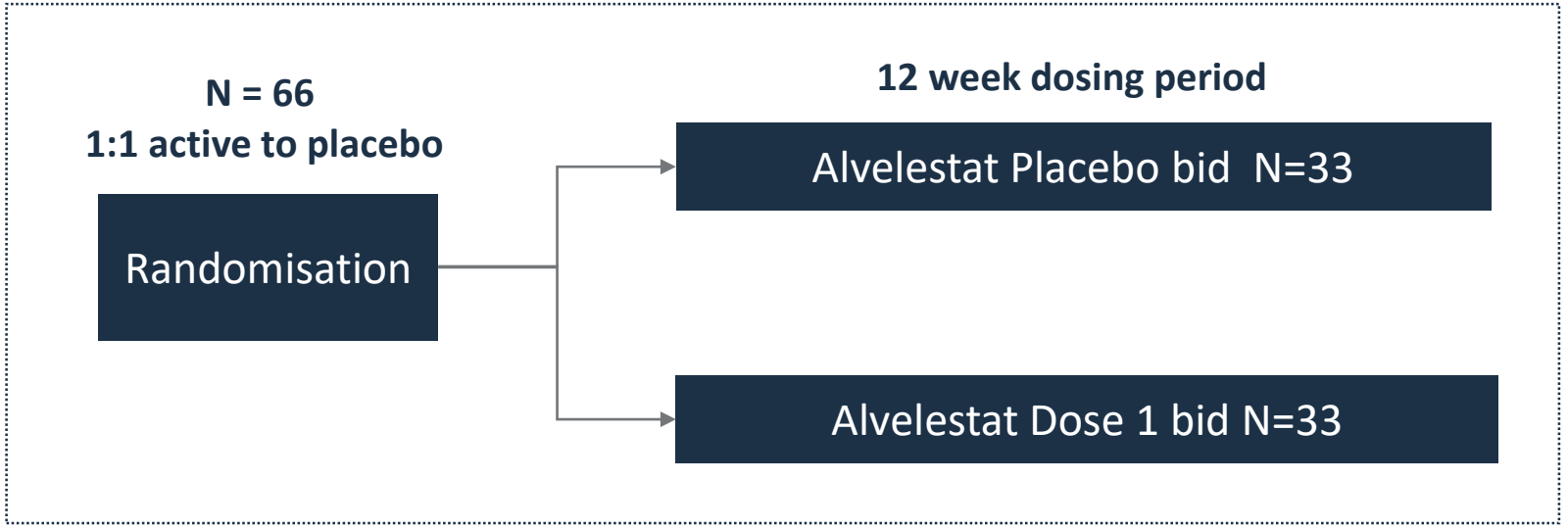
- **Transfer factor**
- **FEV_1**
- **CT Densitometry**

Known assay performance, including in study population

- **Plasma levels correlate with endothelial lining fluid in lung**

Fregonese et al COPD 2011; 8:329-333; Ma et al Chronic Obstr Pulm Dis. 2017; Stolk et al Respir Res 2005; Fregonese et al Eur Respir J 2007

Alvelestat (MPH966) for the Treatment of ALpha-1 ANTitrypsin Deficiency "ATALANTa" (Investigator-initiated – Mark Dransfield, UAB)



Primary Endpoint

- Within-individual % change in plasma desmosine/isodesmosine (week 12)
- Safety and tolerability

Trial Population

- Age ≥18 and ≤80 years
- Pi*ZZ, Pi*SZ, Pi*Z Null, or Pi*Null genotype/phenotype
- Emphysema, FEV1 ≥25% predicted
- Not currently receiving augmentation OR on stable augmentation for at least 12 weeks prior to screening

NETosis in Systemic Inflammatory Diseases Brings Potential of Mechanistic Indication Expansion

Scientific Rationale

- NETosis a pathogenic mechanism highly dependent on neutrophil elastase
- Drives hyper-inflammatory and thrombotic tendency common to a range of serious inflammatory disorders
- Evidence for enhanced NETosis driving pathology in systemic immuno-inflammatory, autoimmune and vasculitic diseases

COVID-19

- Body of existing and rapidly growing evidence for NETosis in disease
- Appropriate disease to test the concept and potentially address high unmet need

SUMMARY
Alvelestat Key Differentiating Features

Profile for long term treatment of AATD lung disease and NETosis-driven diseases

Oral, twice daily dosing

High neutrophil elastase inhibition > 90% at doses trialed

Combination of twice daily dosing and high neutrophil elastase inhibition allows for 24/7 enzyme coverage

Highly specific neutrophil elastase inhibition – reduces potential for side effects

Rapid onset of action < 4 hours to > 90% enzyme inhibition

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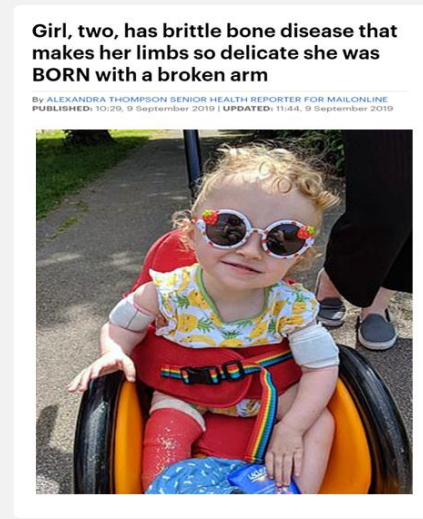
Setrusumab (BPS-804)

Osteogenesis Imperfecta (OI)

- Rare genetic bone disease, key symptoms include:
  - frequent bone fractures, skeletal deformities, pain and respiratory insufficiency
- 85-90% linked to a mutation in Type I collagen[1,2]
- Tangible symptomatology leads to **early diagnosis**:
  - more than 55,000 patients in US and EU-5
- Children have highest unmet need – disease management pathways in key centres
- Adult opportunity is significant – progressive condition, patients remain symptomatic but often burden is overlooked and patient management less organized than children
- Well established patient groups – OIFE and OIF > 50 years old
- Despite the above – NO FDA or EMA approved therapies
- Setrusumab (BPS-804) is an antibody targeting sclerostin
- Orphan designation EU and US, PRIME (Priority medicine) designation by EMA and Pediatric Rare Disease designation by FDA


The twins 'made of glass': 17-month-old sisters defy the odds after doctors gave them a 'zero per cent chance of survival' because of a rare disease that caused them to endure fractures in the WOMB

By ALEXANDRA THOMPSON SENIOR HEALTH REPORTER FOR MAILONLINE
PUBLISHED: 12:11, 9 September 2019 | UPDATED: 15:09, 9 September 2019


Girl, two, has brittle bone disease that makes her limbs so delicate she was BORN with a broken arm

By ALEXANDRA THOMPSON SENIOR HEALTH REPORTER FOR MAILONLINE
PUBLISHED: 10:29, 9 September 2019 | UPDATED: 11:44, 9 September 2019

1. Based on Osteogenesis Imperfecta Foundation estimates; 2. Based on Orphanet estimates;

Summary of Phase 2B Data

Hierarchical primary end-point based on HRPQCT

- Trabecular vBMD at the radius improved at high dose but not statistically significant Total vBMD statistically significant increases at high and medium doses (+4.1% p=0.004)
- Bone strength (Failure Load and Bone Stiffness) dose dependent increases - statistical significance at the high dose (+2% p=0.037) and (+2.2%, p=0.022)

Secondary end-points based on areal bone mineral density measured by DXA

- Dose dependent statistically significant changes in areal BMD at 6 and 12 months at all doses and in all OI phenotypes (+4.4% p<0.001 at 6 months and +8.8% p,0.001 at 12 months at the high dose
- Dose dependent increase in areal BMD at all the anatomical sites tested (femoral neck and total hip) (3.2% p=0.022 and 2.3% p=0.009 at the high dose

Study not powered to show a difference in fracture rates but a trend of reduction in fractures observed in the high dose cohort (15% of high dose patients fracturing versus 25-35%)

Largest clinical study in adults with OI demonstrating the highest increase in areal BMD changes especially in the more severe patient population Type III/IV

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Upcoming Milestones

Late-Stage Diversified Clinical Pipeline

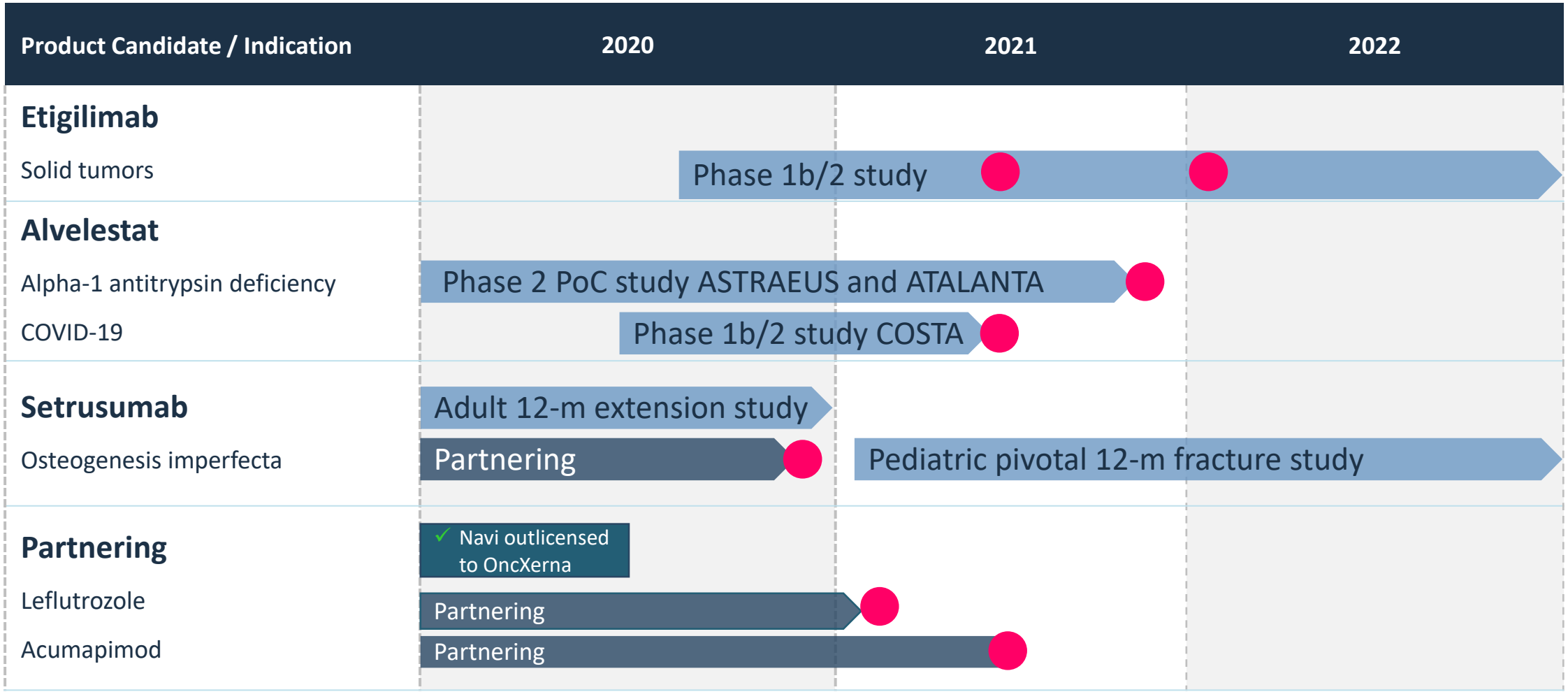
Core Programs

Product Candidate / Indication	Phase 1a	Phase 1b	Phase 2	Phase 3	Next Milestones
Etigilimab Solid tumors					Phase 1b/2
Alvelestat Alpha-1 antitrypsin deficiency COVID-19					Phase 2 AATD Phase 1b/2 COVID
Setrusumab Osteogenesis imperfecta					Extension study Phase 3 – Partner

With partnering opportunities on non-core programs

Product Candidate / Indication	Phase 1	Phase 2	Phase 3	Financing Milestones
Acumapimod Acute exacerbations of COPD				Separate funding
Leflutrozole HH Infertility				Partner
Navicixizumab Ovarian Cancer				Partnered ~ $300M in milestones + royalties

Mereo Upcoming Key Milestones & Opportunities



Key data or milestone event

Investment Highlights

Developing therapeutics for oncology and rare diseases based on novel targets with strong biological rationale

Etigilimab is an anti-TIGIT antibody which actively engages FcyR in a Phase 1b/2 oncology basket study

Alvelestat is an oral neutrophil elastase inhibitor in Phase 2 studies for AATD and COVID

Setrusumab is an anti-sclerostin antibody proven to build bone in Osteogenesis Imperfecta Patients in a Phase 2b study in adults

Additional Programs for partnering or partnering income

- Acumapimod for AECOPD
- Leflutrozole for infertility
- Navicixizumab partnered with OncXerna ($300M + royalties)

Multiple near-term clinical and pipeline milestones

Highly experienced management team with significant expertise in drug development and oncology and rare diseases

Well funded with cash runway into 2022

Mereo BioPharma

Q&A

Mereo BioPharma

Thank You

Mereo BioPharma Group plc

NASDAQ: MREO, AIM: MPH

Mereo BioPharma Group plc

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