A Phase 1, First-in-Human, Open-Label, Dose Escalation Study of MGD013, a Bispecific DART® Molecule Binding PD-1 and LAG-3 in Patients with Unresectable or Metastatic Neoplasms

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Presenter Disclosure Information

Jason J. Luke, MD, FACP

- Data and Safety Monitoring Board: TTC Oncology
- Scientific Advisory Board: 7 Hills, Actym, Alphamab Oncology, Kanaph, Mavu (now part of AbbVie), Onc.AI, Pyxis, Springbank, Tempest
- Consultancy: Abbvie, Akrevia, Algios, Array, Astellas, Bayer, Bristol-Myers Squibb, Eisai, EMD Serono, Ideaya, Incyte, Janssen, Merck, Mersana, Novartis, PTx, RefleXion, Regeneron, Silicon, Tesaro, Vividion
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- Travel: Akrevia, Bayer, Bristol-Myers Squibb, EMD Serono, Incyte, Janssen, Merck, Mersana, Novartis, Pyxis, RefleXion
- Patents (both provisional): Serial #15/612,657 (Cancer Immunotherapy), PCT/US18/36052 (Microbiome Biomarkers for Anti-PD-1/PD-L1 Responsiveness: Diagnostic, Prognostic and Therapeutic Uses Thereof)

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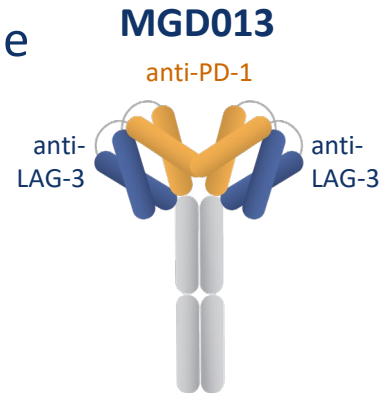
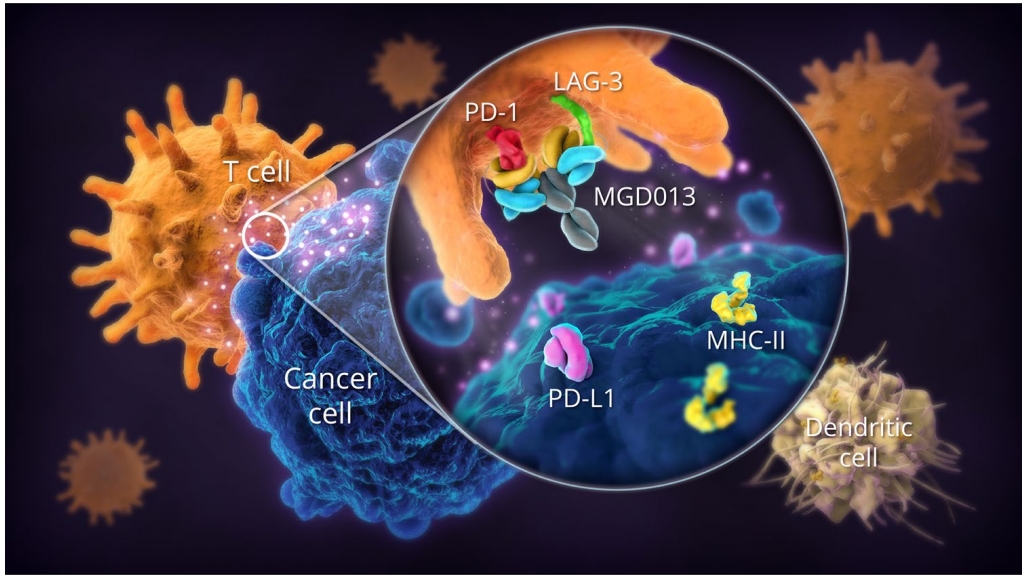
Rationale for Dual Targeting of PD-1 and LAG-3

- Checkpoint molecules are leveraged by tumors or APCs to evade the immune system
- PD-1 and LAG-3 receptors are expressed on “exhausted” T-cells
  - Interactions with corresponding ligands negates anti-tumor T cell activity
- Synergy of anti-PD-1 + anti-LAG-3 mAbs in animal tumor models
  - Combination trials of anti-PD-1 plus anti-LAG-3 are ongoing
- MGD013, an investigational DART protein, targets PD-1 and LAG-3 with a single molecule
  - Greater synergistic T-cell activation (IFN-γ) with MGD013 compared with combination of individual constituents
- DART bispecific platform:
  - Stable diabody format
  - Multiple configurations & applications



PD-1 × LAG-3
Tetravalent Bispecific
DART Molecule



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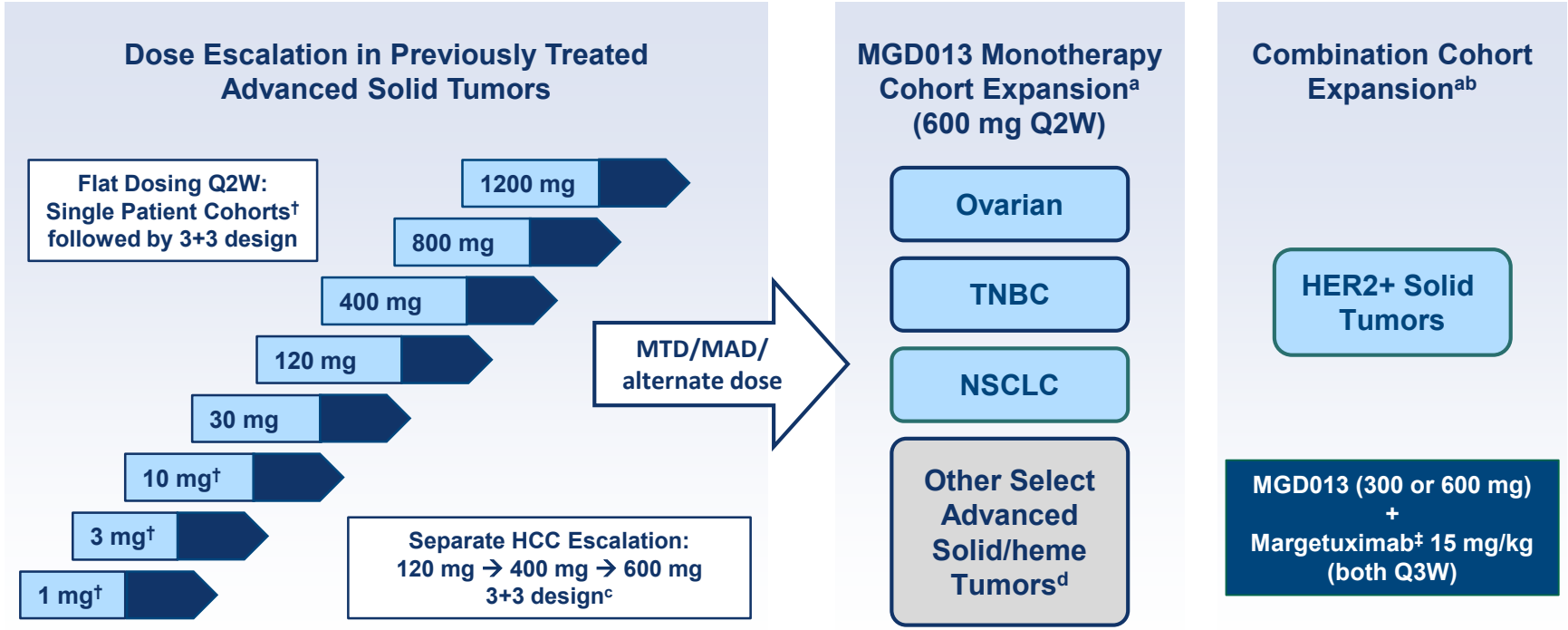
MGD013 Phase 1 Trial Design

- **Primary objectives:**
  - Safety, tolerability
  - DLTs, MTD, MAD
  - Alternate dose
- **Secondary objectives:**
  - Pharmacokinetics
  - Immunogenicity
  - Preliminary activity
- **Exploratory PD objectives:**
  - Receptor/ligand expression
  - Serum biomarkers
  - Gene expression profiling



DLT = dose-limiting toxicity; MAD = maximum administered dose; MTD = maximum tolerated dose; IHC = immunohistochemistry; Q2W = every 2 weeks. ClinicalTrials.gov identifier: NCT03219268. ‡ Margetuximab is an investigational Fc-optimized mAb targeting HER2. [a] Monotherapy and combination expansion cohorts are ongoing. [b] Combination cohort involved a one-step dose escalation followed by expansion. [c] Separate hepatocellular carcinoma (HCC) 3+3 dose escalation initiated after corresponding dose levels cleared in primary Dose Escalation. [d] Other expansion cohorts enrolling patients with SCCHN, SCLC, HCC, cholangiocarcinoma, cervical cancer, gastric/gastroesophageal junction carcinoma, and DLBCL. Data cutoff: April 25, 2020.

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Baseline Demographics

	Dose Escalation 1 -1200 mg Q2W (n=53)	Monotherapy Cohort Expansion 600 mg Q2W (n=205)	Combination Cohort Expansion MGD013 + Margetuximab (n=21)
Median age (range), years	64 (24, 84)	60 (27, 84)	62 (29, 83)
Gender, n (%)			
Male	32 (60.4)	74 (36.1)	7 (33.3)
Female	21 (39.6)	131 (63.9)	14 (66.7)
ECOG PS, n (%)			
0	22 (41.5)	60 (29.3)	12 (57.1)
1	31 (58.5)	145 (70.7)	9 (42.9)
Median prior lines of therapy (range)	2 (1, 9)	2 (1, 9)[a]	2 (1, 7)
Prior Checkpoint Inhibitor			
Yes	23 (43.4)	55 (26.8)	1 (4.8)
No	30 (56.6)	139 (67.8)	20 (95.2)

[a] Monotherapy Cohort Expansion median prior lines of therapy derived from n=200 patients (5 patients without this information available). Data cutoff: April, 25, 2020.

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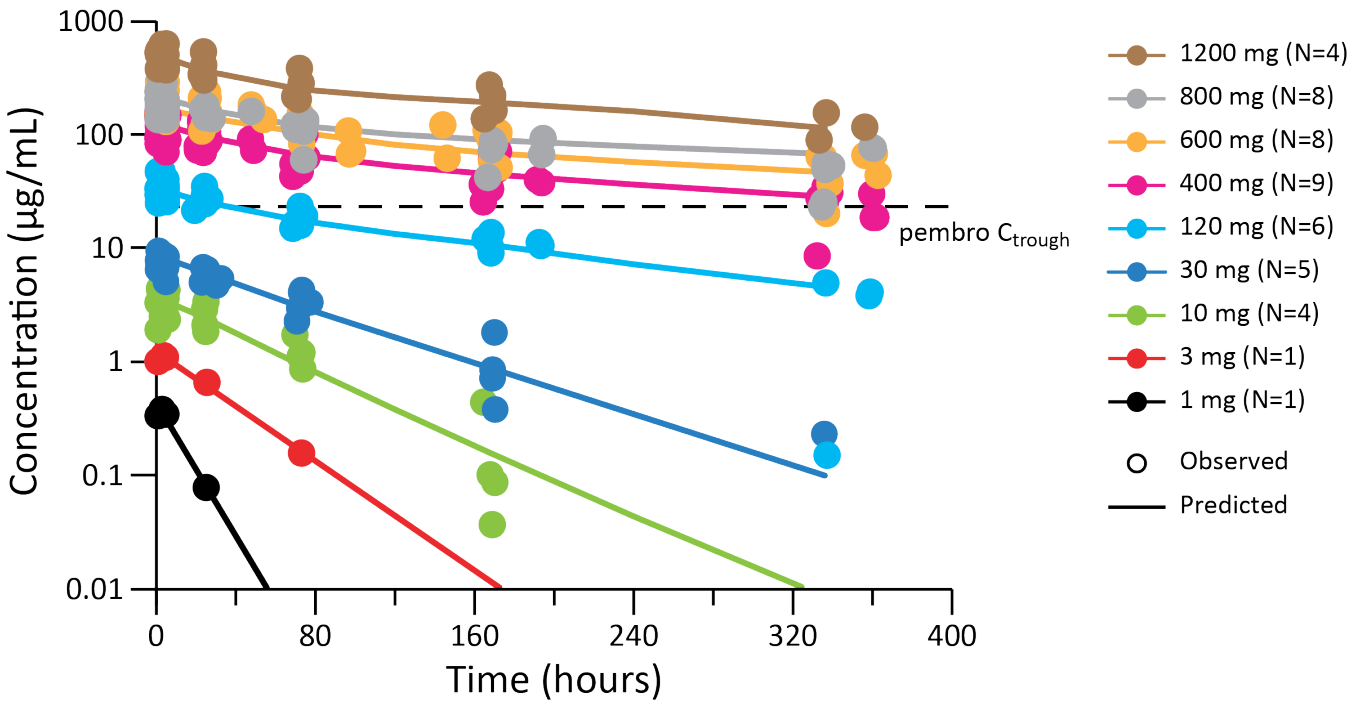
Pharmacokinetics and Receptor Occupancy

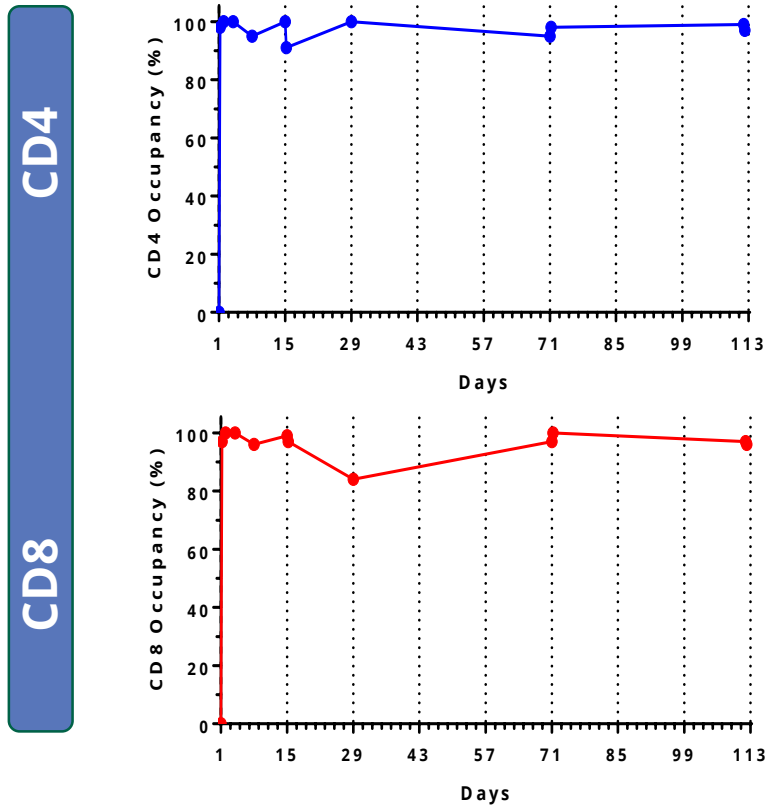
Linear PK (400-1200 mg dose range) and sustained receptor occupancy (≥120 mg)

Pharmacokinetics (1-1200 mg)



Estimated $t_{1/2}$ = 274 hours (~11 days)

Receptor (PD-1) Occupancy (120 mg Q2W)



pembro c_{trough} = published serum trough concentration of pembrolizumab at 2 mg/kg Q3W (23.6 µg/mL)
[CDER, KEYTRUDA (pembrolizumab) Clinical Pharmacology and Biopharmaceutics Review(s). 2014]

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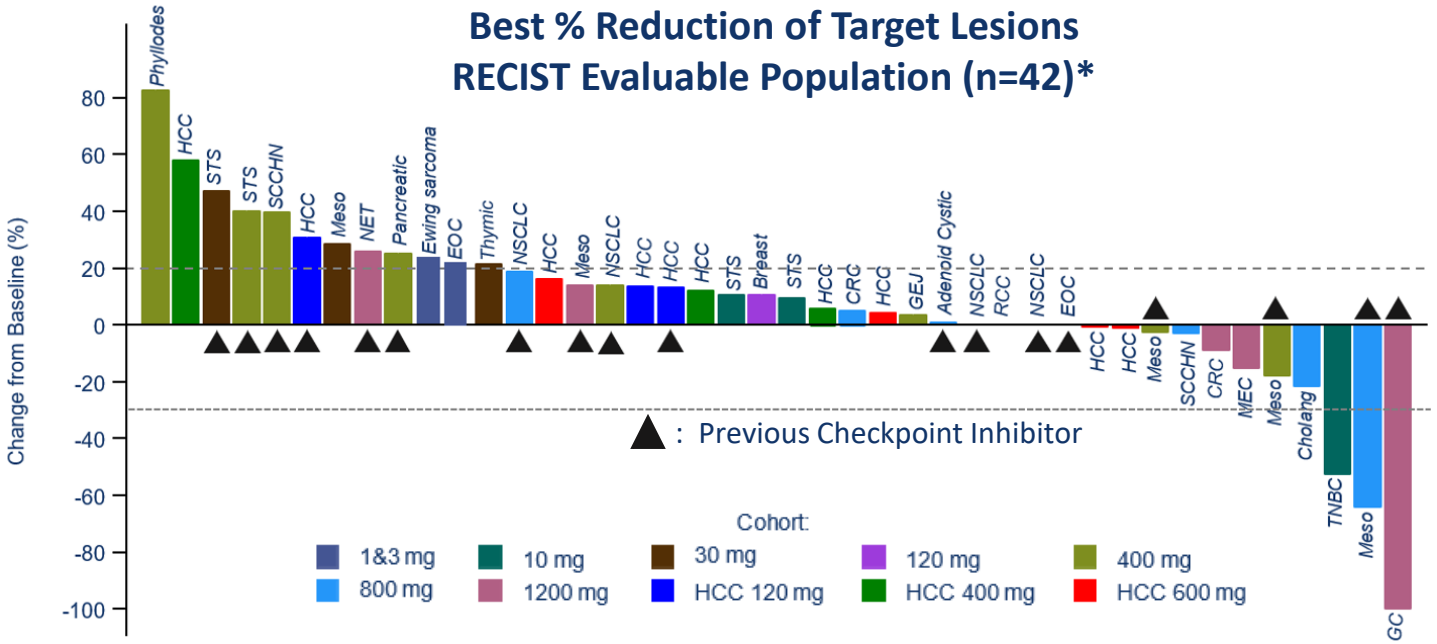
MGD013 Dose Escalation: Results



* Based on patients with baseline and post-treatment tumor measurements. Data cutoff: April, 25, 2020

Immune-Related Adverse Events of Special Interest (AESIs)

	No. (%) of Patients	
	All Grades (N=53)	≥ Grade 3 (N=53)
Rash	7 (13.2)	1 (1.9)
Hypothyroidism	6 (11.3)	0
Immune-mediated hepatitis	2 (3.8)	2 (3.8)
Pancreatitis	1 (1.9)	1 (1.9)
Colitis	1 (1.9)	1 (1.9)
Adrenal insufficiency	1 (1.9)	1 (1.9)
Hyperthyroidism	1 (1.9)	0

<u>Confirmed Partial Responses (n=1, each)</u>:

- TNBC (10 mg)
- Mesothelioma (800 mg)
- Gastric Cancer (1200 mg)

} **Refractory to anti-PD-1 treatment**

- 18 patients with SD as best overall response (DCR = 48.8%)

- Well-tolerated with manageable irAEs
- Safety consistent with anti-PD-(L)1 toxicity profile
- MTD not exceeded or defined at up to 1200 mg Q2W
- Dose limiting toxicities:
  - Immune-mediated hepatitis (1200 mg – primary dose escalation); resolved without sequelae
  - Lipase increase with radiographic evidence of pancreatitis (600 mg – HCC escalation); dose level subsequently cleared

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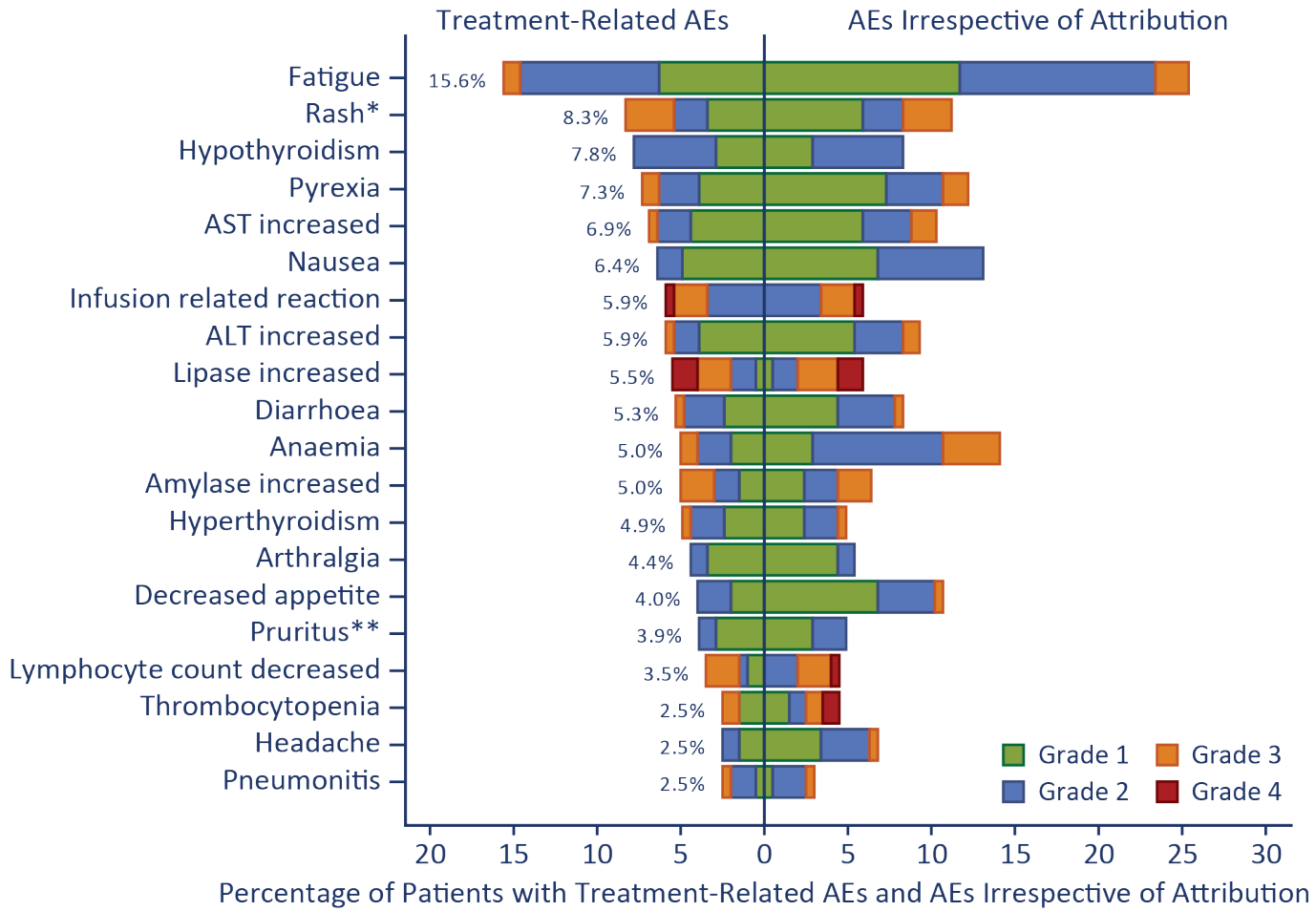
MGD013 Monotherapy Cohort Expansion: Safety

Overall AE Totals	No. (%) of Patients	
	All Grades (N=205)	≥ Grade 3 (N=205)
AE (irrespective of causality)	178 (86.8)	86 (42.0)
Treatment-related AE	118 (57.6)	37 (18.0)[a]
SAE (irrespective of causality)	63 (30.7)	47 (22.9)
Treatment-related SAE	18 (8.8)	11 (5.4)
AE leading to discontinuation	18 (8.8)	16 (7.8)
AESIs in ≥ 2 Patients		
Rash	17 (8.3)	6 (2.9)
Hypothyroidism	16 (7.8)	0 (0.0)
IRR or CRS	13 (6.3)	5 (2.4)
Diarrhoea	11 (5.4)	1 (0.5)
Lipase increased	11 (5.4)	7 (3.4)
Hyperthyroidism	10 (4.9)	1 (0.5)
Arthralgia	9 (4.4)	0 (0.0)
Pneumonitis	4 (2.0)	1 (0.5)
Myalgia	4 (2.0)	0 (0.0)
Peripheral neuropathy	3 (1.5)	1 (0.5)
Hepatitis	3 (1.5)	2 (1.0)
Adrenal insufficiency	2 (1.0)	0 (0.0)



* Includes MedDRA Preferred Terms of *Rash* and *Maculopapular Rash*. ** Includes MedDRA Preferred Terms of *Pruritus* and *Generalized Pruritus*.
[a] Grade 4 drug-related AEs include: lipase increased (n=3), neutrophil count decreased, and IRR (n=1, each). No Grade 5 TRAEs have been reported.
AESI = adverse events of special interest. Data cutoff: April, 25, 2020.

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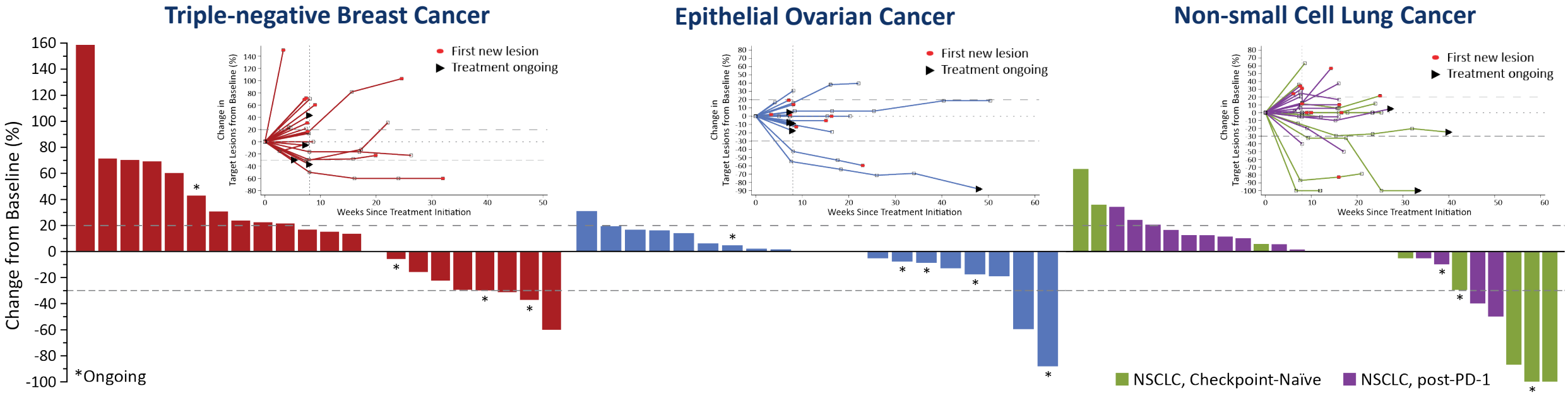
MGD013 Monotherapy Cohort Expansion: Activity

Anti-tumor activity observed in multiple tumor types



	TNBC	EOC	NSCLC, CPI-Naïve	NSCLC, post-PD-1
Evaluable Patients	23	23	14	15
ORR (Confirmed)	4.3% (1/23)	8.7% (2/23)	14.3% (2/14)	0% (0/15)
ORR (Confirmed + Unconfirmed)	17.4% (4/23)	8.7% (2/23)	21.4% (3/14)	13.3% (2/15)
SD	34.8% (8/23)	43.5% (10/23)	50.0% (7/14)	53.3% (8/15)
DCR	39.1% (9/23)	52.2% (12/23)	64.3% (9/14)	53.3% (8/15)

Data cutoff: April, 25, 2020

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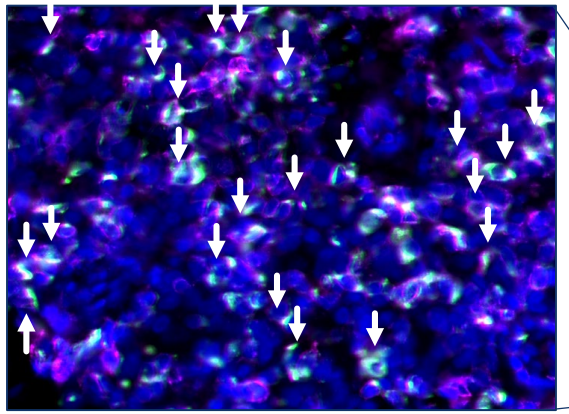
Complete Response after Single MGD013 Administration

27-year-old male with DLBCL progressive disease after CAR-T cell therapy

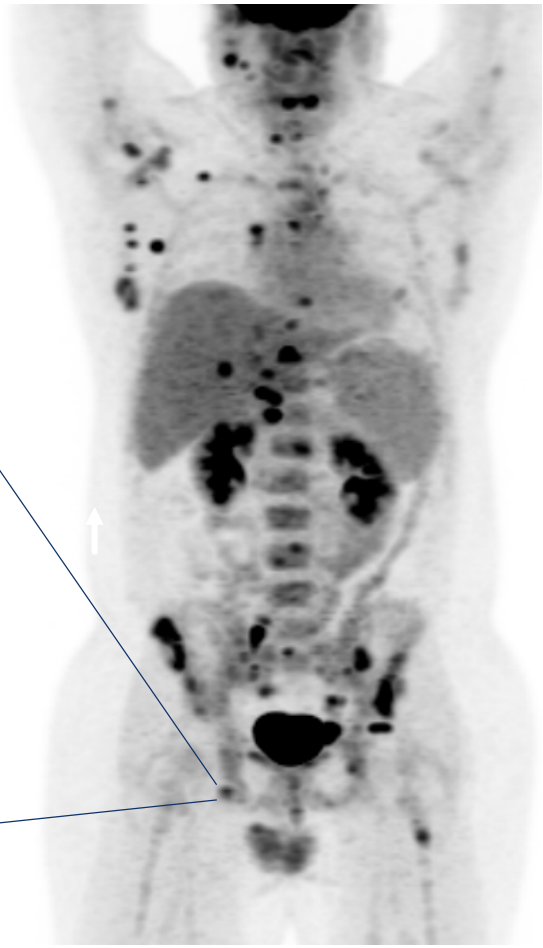
- Relapsed subsequent to DA-R-EPOCH and JCAR017
- Pre-treatment biopsy: High levels of LAG-3 & PD-L1
- Received MGD013, 600 mg x 1
- Admitted on Day 11 for management of Grade 2 CRS
- CR on Day 24 (per Lugano classification)
- No evidence of CAR-T in circulation
- Allogeneic SCT performed
- Currently in remission:
  - 11 months post-MGD013
  - 9 months post-transplant

PD-1/LAG-3 Co-expression

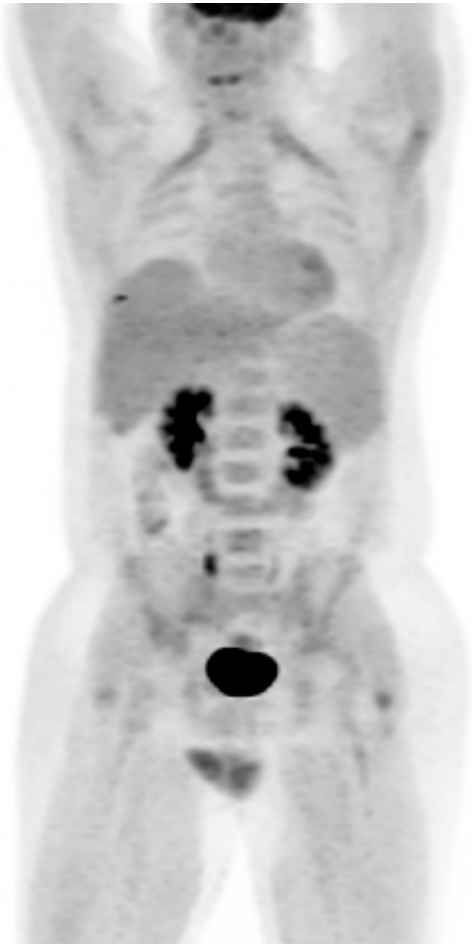


PD-1 (magenta) and LAG-3 (green) co-localized staining

Screening



MGD013
Complete Response - Day 24



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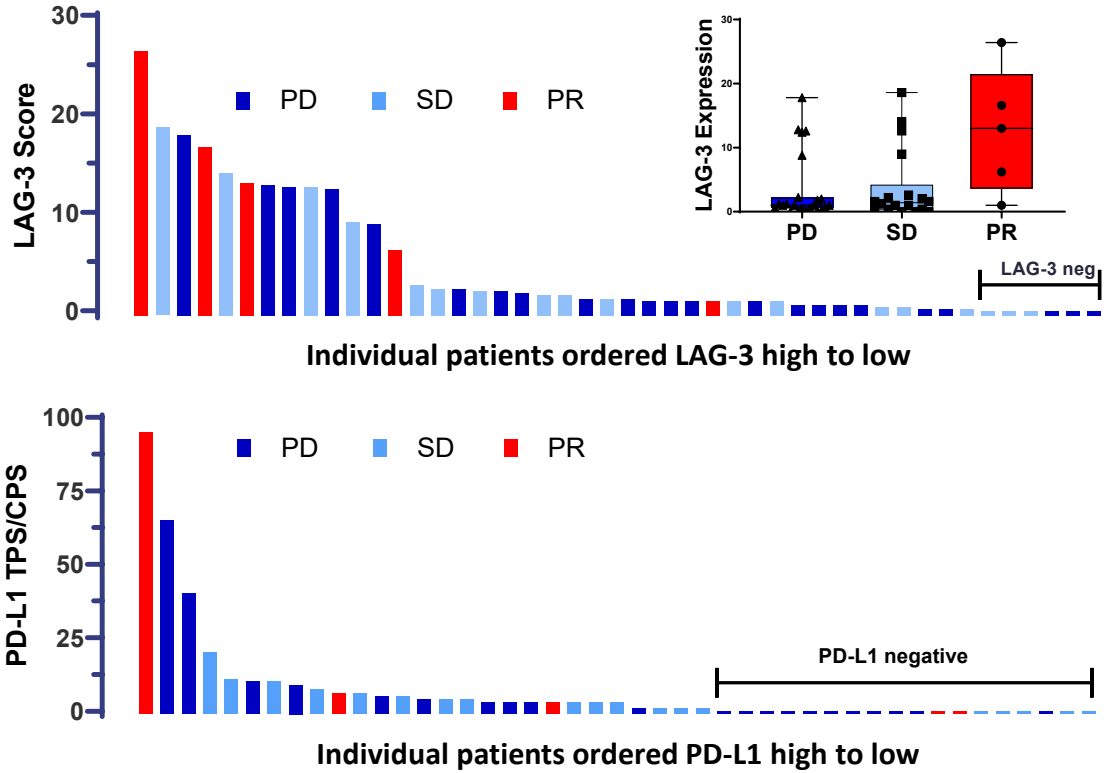
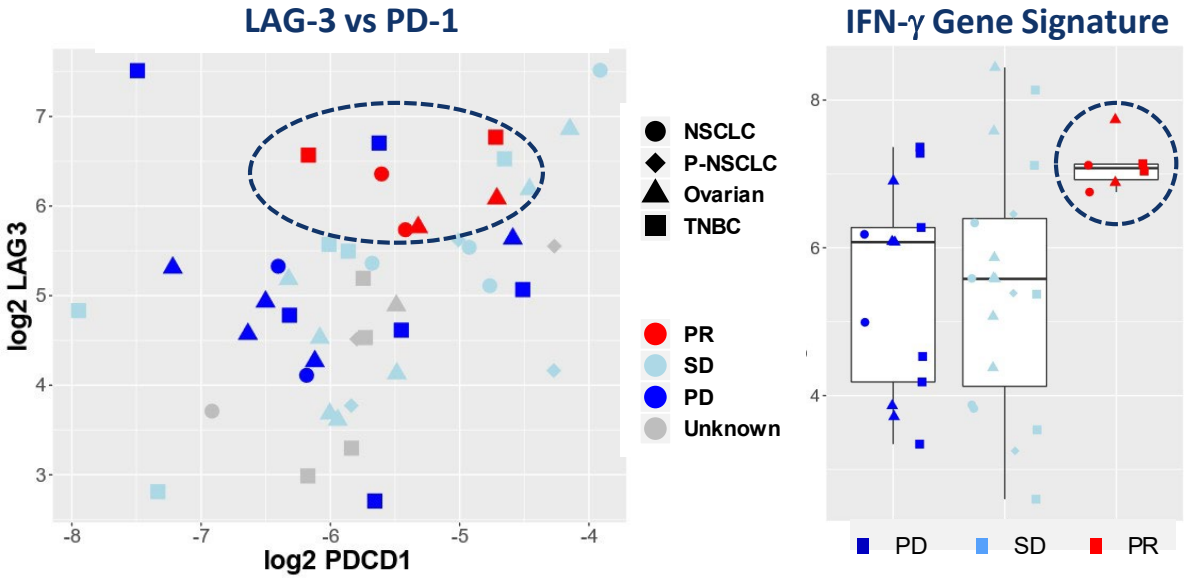
Objective Responses Associated with LAG-3 Expression

Inflammatory interferon-γ signature elevated in patients with clinical response

Retrospective IHC Analyses



Transcript Profiling (Baseline Tumor Biopsy)



Objective responses associated with high baseline LAG-3/PD-1 expression and IFN-γ gene signature (CXCL9, CXCL10, CXC11, STAT1)

Archival biopsies from TNBC, EOC, and NSCLC expansion cohorts analyzed for LAG-3 (N=46) or PD-L1 (N = 45) by IHC. LAG-3 score was determined by calculating mean value of LAG-3+ cells per 40x field across 5 LAG-3+ hot spots (Chen et al., e15086 ASCO 2020). PD-L1 expression was determined per Agilent PD-L1 (22C3) pharmDx kit; TPS (NSCLC) was calculated as per interpretation manual and CPS (EOC, TNBC) calculated as follows: number of PD-L1 + cells (tumor and immune)/total number of viable tumor cells x 100. CPS <1 or TPS <1% was considered negative.

The NanoString PanCancer IO 360™ assay was used to interrogate gene expression, including the abundance of 14 immune cell types and 32 immuno-oncology signatures from archival biopsies from EOC (N= 14) NSCLC (N= 25) and TNBC (N=13) expansion cohorts

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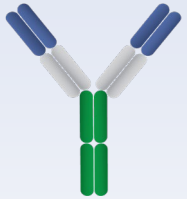
Can Tumors Be Made More Responsive to PD-1 × LAG-3 Intervention?

Enhancing effector-cell activation via Fc-engineered mAb

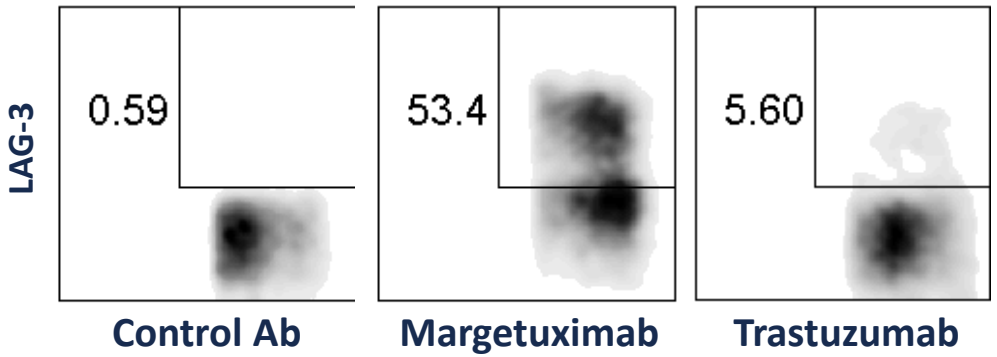
Margetuximab

Investigational Fc-engineered anti-HER2 mAb



- Same anti-HER2 properties as trastuzumab
- Enhanced Fc-mediated effector function[a]
- Superior PFS to trastuzumab in clinical study
  - SOPHIA: Head-to-head Phase 3 study in mBC[b]
- Anti-tumor activity in advanced gastric cancer
  - In combination with anti-PD-1[c]

Margetuximab Enhances LAG-3 Expression by NK Cells



[a] Nordstrom, et al., 2011 *Breast Cancer Research,* 13: R123
[b] Rugo, et al., *ASCO 2019*, Chicago, IL
[c] Catenacci, et al., ASCO GI 2019, San Francisco, CA | Catenacci et al. 2020 *Lancet Oncology*, in press

Human PBMC (Donor # 859) + N87 (HER2+) gastric cancer cells; E:T = 10:1; (IL-2, 20 U/mL)
Control Ab 50ng/mL, margetuximab/trastuzumab, 5ng/mL;. FACS analyses (72h) on $CD3^{-}CD56^{+}$-gated NK cells

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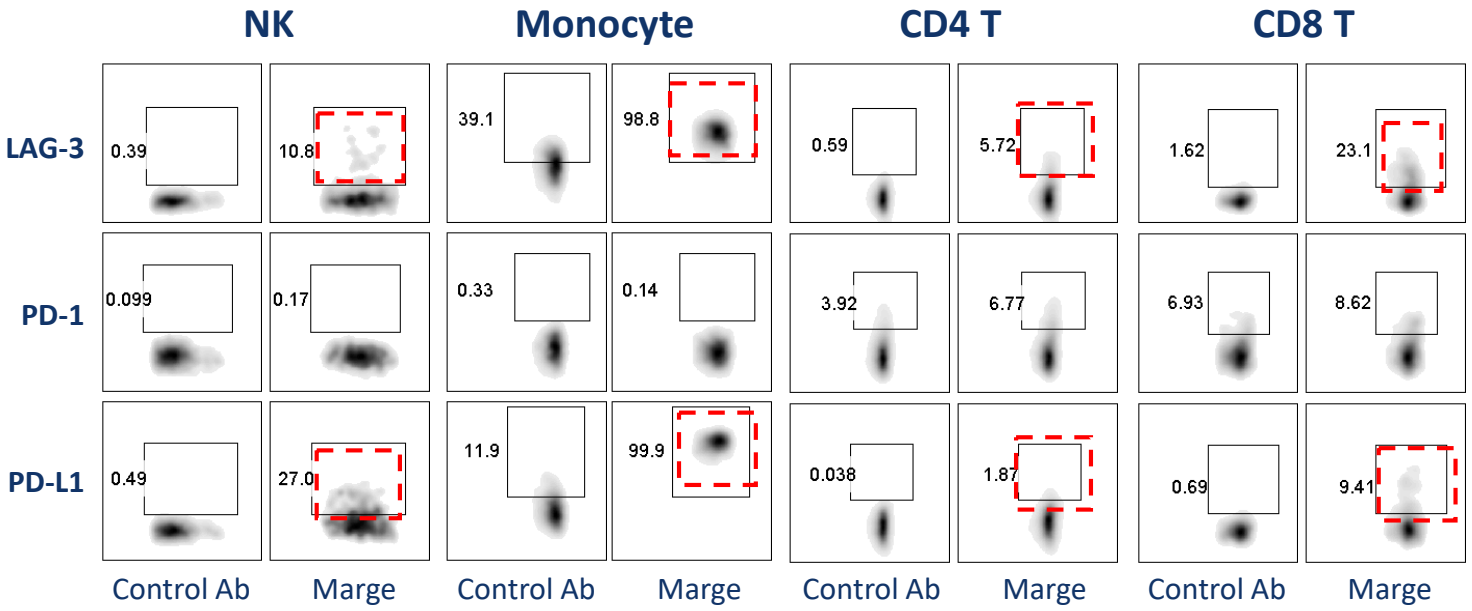
Fc-engineered mAb *plus* PD-1 x LAG-3 DART: Combinatorial Biology

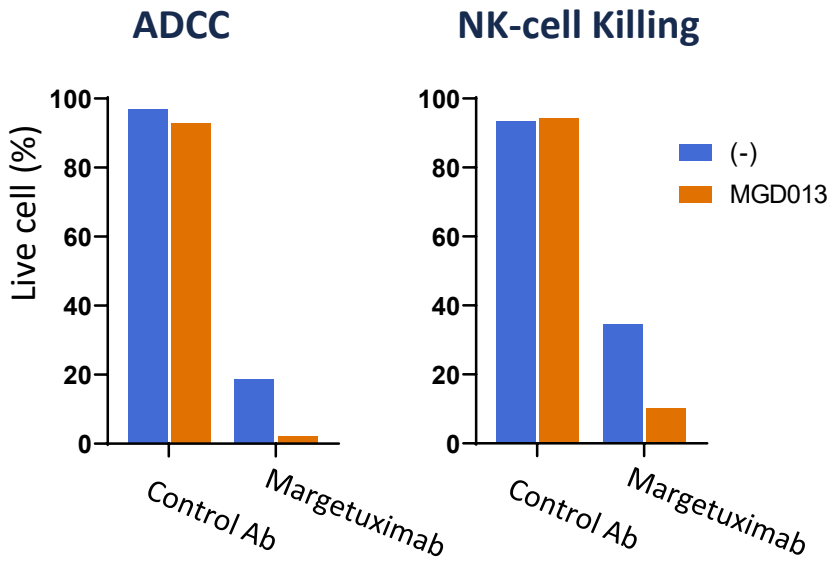
Fc-engineered Margetuximab Up-regulates LAG-3/PD-L1 Expression



Upregulation of LAG-3 and PD-L1 on NK, monocytes and T cells

Human PBMC (Donor # 731) + N87 (HER2+) gastric cancer cells; E:T = 15:1 +/- margetuximab (no supplementary IL-2)

PD-1 x LAG-3 (MGD013) Enhances Lytic Activity of Immune Cells Primed by Fc-engineered mAb (Margetuximab)



ADCC (target: margetuximab opsonized N87, E:T=10) and NK-cell killing (target: K562, E:T=10) mediated by immune cells activated for 6 days by margetuximab +/- MGD013 in the presence of N87 tumor cells.

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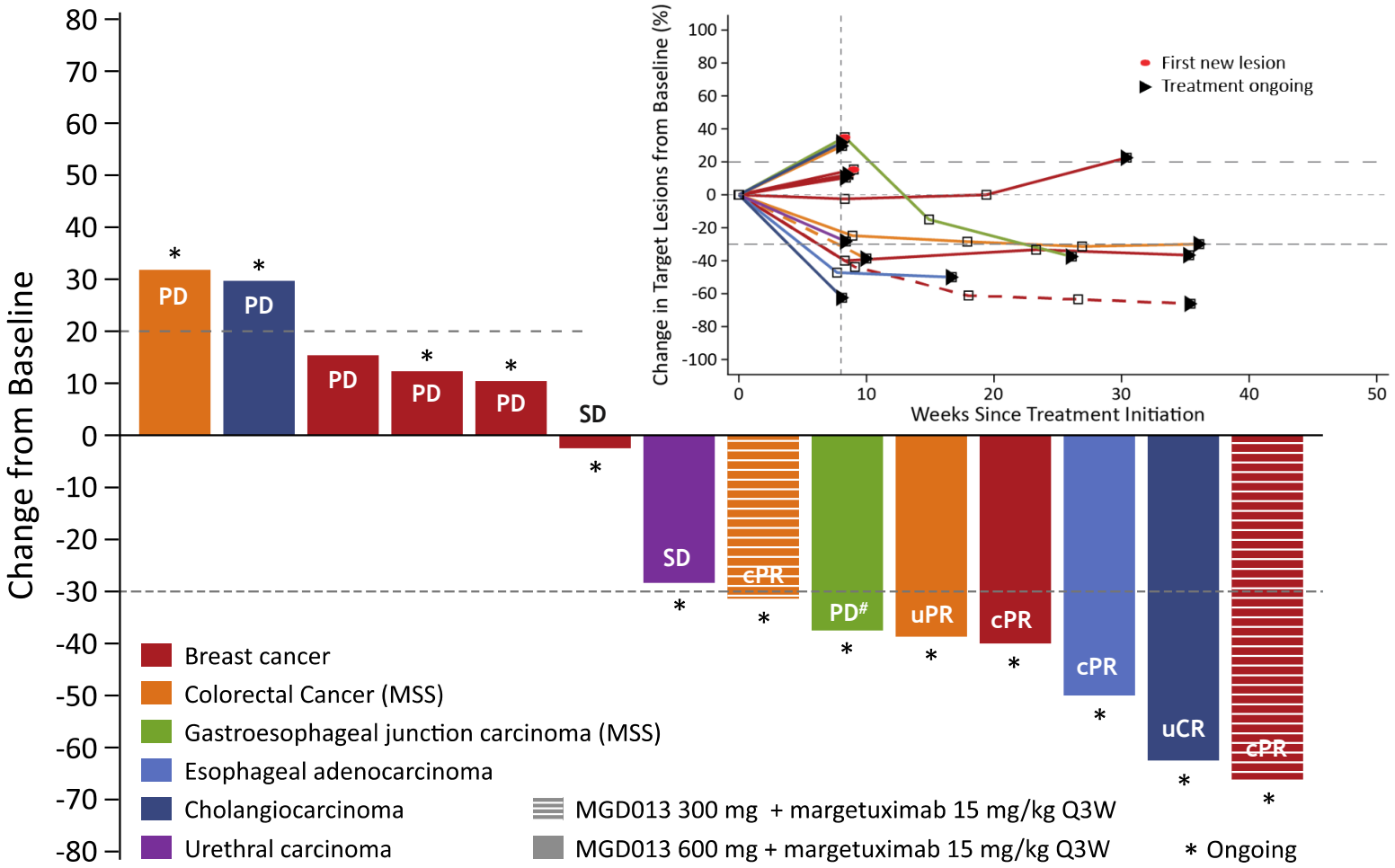
Fc-engineered αHER2 *plus* PD-1 × LAG-3 DART (Margetuximab *plus* MGD013)

Preliminary results in patients with relapsed/refractory HER2+ solid tumors



GEJ pt with apparent pseudo-progression (PD per RECIST), now with 37.5% reduction in target lesions (iPR per iRECIST).

- ORR = 42.9% (6/14 evaluable pts)
  - Includes unconfirmed objective responses
- Well-tolerated
  - Responding patients remain on therapy

Baseline PD-L1 & LAG-3 in # of Responding Patients (N = 6)

PD-L1 CPS:	< 1	1	TBD
N	4	1	1

LAG-3 Score:	< 5	5-15	TBD/NE
N	3	1	2

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Durable Response in Patient Receiving MGD013 *plus* Margetuximab

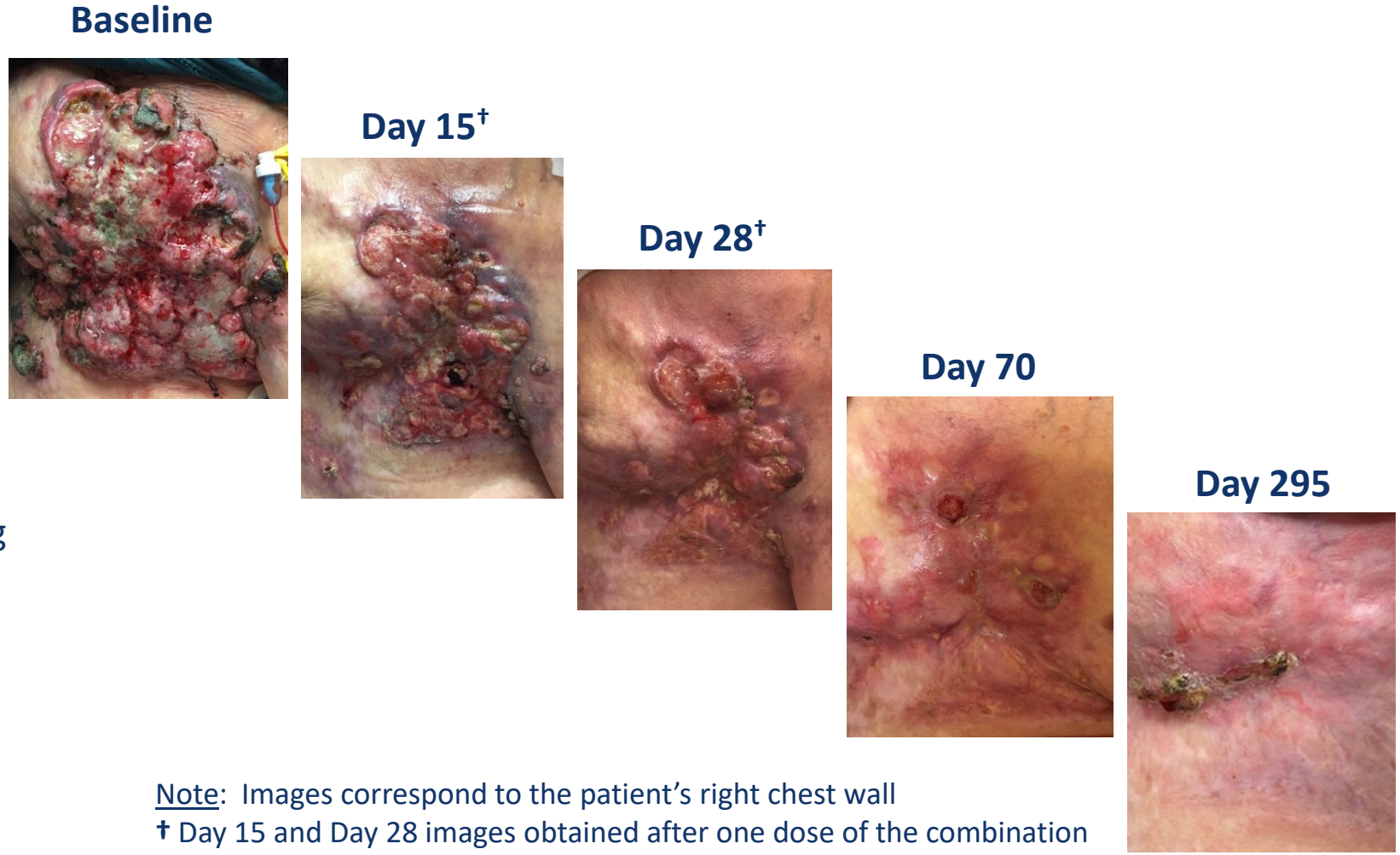
Resolution of chest wall disease with confirmed PR of overall tumor burden

Metastatic HER2+ breast cancer in 67-year-old female

- **Previously progressed on**:
  - 1L pertuzumab/trastuzumab/anastrozole
  - 2L TDM1/anastrozole
  - 3L TDM1

Baseline tumor burden:

- Right breast, liver and lymph nodes
  - PD-L1 CPS: <1; LAG-3 score: 0.8
- Patient remains on treatment in Cycle 15 with improved clinical status and ongoing partial response
  - 1st tumor assessment: -46%
  - 2nd tumor assessment: -61%
  - 3rd tumor assessment: -65%
  - 4th tumor assessment: -66%



Note: Images correspond to the patient's right chest wall
† Day 15 and Day 28 images obtained after one dose of the combination

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MGD013 (PD-1 × LAG-3 DART Molecule): Conclusions

First-in-class bispecific checkpoint inhibitor

- Designed to independently or coordinately block PD-1 and LAG-3
- Well tolerated at doses up to 1200 mg Q2W
- RP2D: 600 mg Q2W or Q3W
- Safety profile consistent with anti-PD-1 monotherapy

Encouraging monotherapy activity in multiple tumor types

- Baseline LAG-3 expression & IFN-γ signature associated with objective response

Compelling preliminary combinatorial activity with margetuximab (Fc-engineered mAb)

- >40% ORR observed in low PD-L1-expressing, relapsed/refractory $HER2^{+}$ tumors
  - Compares favorably to low historical response rates to anti-HER2 ± CPI

Evaluation of MGD013 as monotherapy and in combination with Fc-engineered mAbs (incl. margetuximab) is ongoing

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