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A Phase 1, First-in-Human, Open-Label, Dose Escalation Study of MGD019, an Investigational Bispecific PD-1 × CTLA-4 DART® Molecule in Patients with Advanced Solid Tumors

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PRESENTER DISCLOSURE INFORMATION

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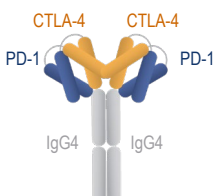
Research support (to the institution for clinical trials):

- Alexo
- Alpine Immune Sciences
- Amgen
- Apexian
- Asana
- Ascentage
- Astellas
- AstraZeneca
- Beigene
- Bolt Biotherapeutics
- Bristol-Myers Squibb
- Celgene
- Compugen
- Coordination
- Constellation
- CytomX
- Effector Therapeutics
- Eli Lilly
- Epizyme
- Exelixis
- Formation Biologics
- Forty Seven
- Genmab
- Ikena
- Innovent Biologics
- InhibRx
- Incyte
- Ipsen
- Jounce Therapeutics
- KLUS Pharma
- Lexicon
- Loxo
- Livzon
- MacroGenics
- Merck
- Mersana
- Northern Biologics
- Novocure
- Odonate Therapeutics
- Pfizer
- QED
- Regeneron
- Sapience
- Shattuck Labs
- Symphogen
- Syros
- TaiRx
- Tempest Therapeutics
- Tesaro
- Treadwell Therapeutics

MGD019: Bispecific Molecule Engineered for Co-Blockade of PD-1 & CTLA-4

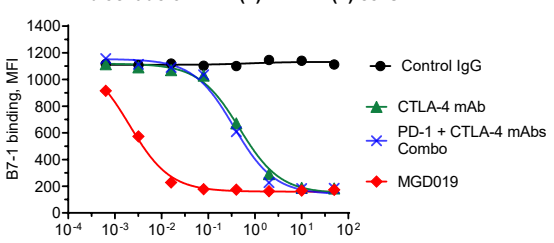
- PD-1 and CTLA-4 are checkpoint molecules with complementary mechanisms of action
- Dual blockade has yielded enhanced efficacy with approved agents, albeit with increased toxicity
- MGD019, an investigational DART molecule:
  - Maintains uncompromised PD-1 blockade versus benchmark mAbs
  - Blocks **both** PD-1 and CTLA-4 pathways with potentially **enhanced CTLA-4 blockade** on dual-expressing cells prevalent in TME

MGD019



PD-1 × CTLA-4
Tetravalent Bispecific
DART Molecule

CTLA-4 blockade on PD-1(+)/CTLA-4(+) cells



10-100 fold enhanced activity by MGD019 relative to PD-1/CTLA-4 mAb combination

DART bispecific platform:

- Diabody based structure
- Flexible design supports various configurations (e.g. bivalent or tetravalent)

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MGD019 is Well Tolerated in Non-human Primates

GLP Toxicology Results Compare Favorably to Ipilimumab + Nivolumab Preclinical Profile

Finding	PD-1 × CTLA-4 bispecific (MGD019)			PD-1 mAb (Retifanlimab)	PD-1 + CTLA-4 two mAb combo[a]
	10 mg/kg	40 mg/kg	100 mg/kg	≥100 mg/kg	
Adverse clinical signs	–	–	–	–	+[b]
Body weight loss	–	–	–	–	+
Increased spleen weight	+	++	++	–	+
Lymphoid hyperplasia/hypertrophy in spleen	–	+	++	–	++
Gastrointestinal tract inflammation	–	–	–	–	+[c]
Cytokine induction	–	–	–	–	not reported
T cell expansion	+	++	++	+	++
Ki67$^+$ CD8$^+$ T cell increase	+	++	+++	+/++	not reported
ICOS$^+$ CD4$^+$ T cell increase	+	++	+++	N/A	not reported

"+" = observed, with quantification (e.g., +, ++, +++); "–" = not observed

[a] Selby M., et al., *Preclinical Development of Ipilimumab & Nivolumab Combination Immunotherapy: Mouse Tumor Models, In Vitro Functional Studies, & Cynomolgus Macaque Toxicology. PLoS One. 2016 Sep 9;11(9):e0161779*

[b] Dose-related diarrhea; decreased food consumption at high dose [50 mg/kg anti-PD-1 + 10 mg/kg anti-CTLA-4]

[c] Large intestine: diffuse lymphoplasmacytic inflammation in the lamina propria with concurrent enlargement of the colonic or pelvic lymph nodes.

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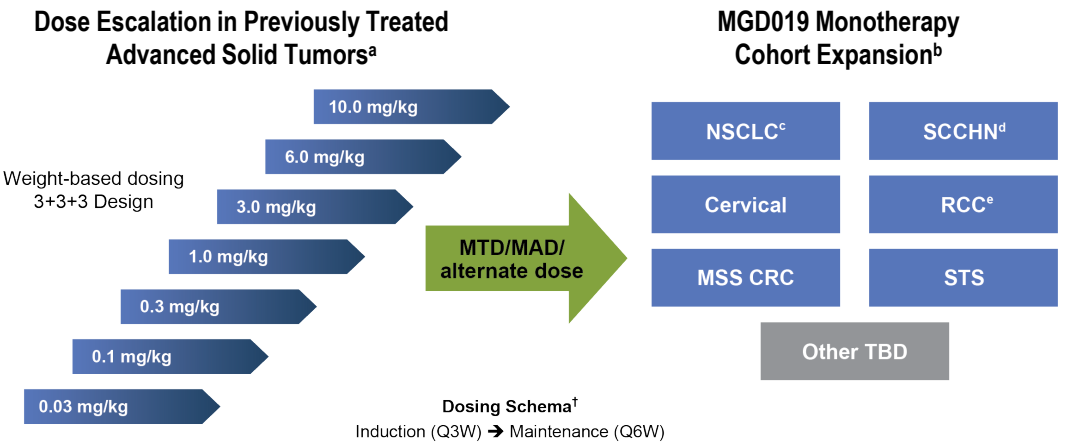
MGD019 Phase 1 Trial Design

- **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; STS = soft tissue sarcoma; MSS CRC = microsatellite stable colorectal cancer; Q3W/Q6W = every 3 or 6 weeks. ClinicalTrials.gov identifier: NCT03761017. [a] Additional patients backfilled at dose levels of interest (3, 6, and 10 mg/kg) after completion of Dose Escalation. [b] Enrollment of select monotherapy expansion cohorts at recommended Phase 2 dose [RP2D] of 6.0 mg/kg are forthcoming. [c] Separate NSCLC cohorts for checkpoint-inhibitor (CPI) naïve and experienced patients. [d] SCCHN cohort of CPI-experienced patients. [e] RCC cohort of CPI-naïve patients. † Induction Period (Q3W) for 24 weeks followed by Maintenance Period (Q6W) until study completion. Data cutoff: July 21, 2020.

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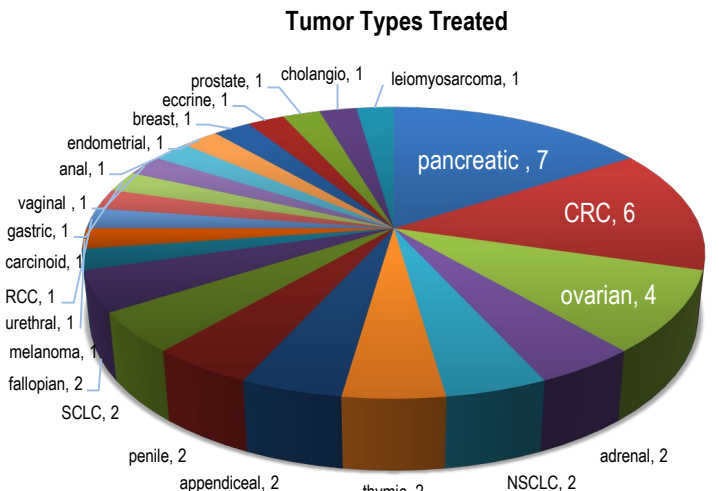
Heavily Pre-treated Population Representing Diverse Tumor Types

Baseline Demographics

	Dose Escalation 0.03 – 10 mg/kg (n=43)
Median age (range), years	62 (30, 85)
Gender, n (%)	
Male	21 (48.8)
Female	22 (51.2)
ECOG PS, n (%)	
0	14 (32.6)
1	29 (67.4)
Median prior lines of therapy (range)	3 (1, 10)
Prior Checkpoint Inhibitor	
Yes	17 (39.5)
No	26 (60.5)



Data cutoff: July 21, 2020

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End of Treatment Disposition

Escalation Dose Levels	0.03 – 1.0 mg/kg	3.0 mg/kg	6.0 mg/kg	10.0 mg/kg	Total
Patients Treated, n	15	7	8	13	43
Response-Evaluable Patients, n (%)	12 (80)	7 (100)	3 (37.5)	8 (61.5)	30 (69.8)
Median duration of therapy, weeks (min, max)	11.6 (1.3, 60.4)	14.1 (6.0, 34.9)	6.6 (4.3, 24.1)[a]	12.1 (3.1, 36.1)	12.0 (1.3, 60.4)
Active Patients, n (%)	0 (0)	2 (28.6)	5 (62.5)	1 (7.7)	8 (18.6)
Reasons for discontinuation, n (%)					
Disease Progression	14 (93.3)	3 (42.9)	3 (37.5)	5 (38.5)	25 (58.1)
Adverse Event	-	1 (14.3)	-	5 (38.5)	6 (14.0)
Death	-	-	-	-	-
Patient/Physician decision/withdrawal	1 (6.7)	1 (14.3)	-	1 (7.7)	3 (7.0)
Not Reported	-	-	-	1 (7.7)	1 (2.3)

[a] Ongoing patients in 6.0 mg/kg cohort (n=5) remain active early in their 1st cycle of treatment. Data cutoff: July 21, 2020.

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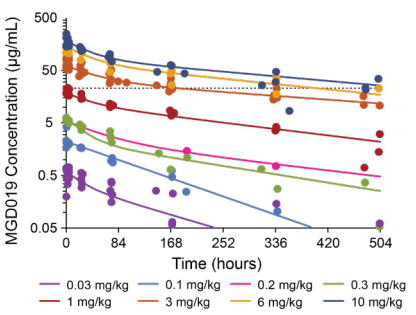
Pharmacokinetics and Receptor Occupancy

Linear PK (1.0 – 10.0 mg/kg dose range) and Sustained Receptor Occupancy (≥ 1.0 mg/kg Q3W)

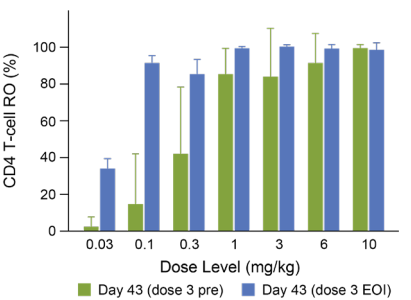
First Dose PK



Estimated $t_{1/2}$ = 298 hours (~12 days)

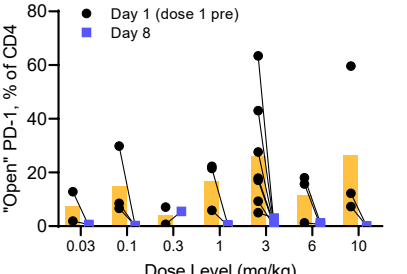
First-dose PK profiles of 0.03 to 10 mg/kg. Symbols and solid lines represent observed data and model fitted median curves, respectively. "Target" refers to published serum trough concentration of pembrolizumab at 2 mg/kg Q3W (23.6 µg/mL) [CDER, KEYTRUDA (pembrolizumab) Clinical Pharmacology and Biopharmaceutics Review(s). 2014]

Receptor (PD-1) Occupancy



MGD019 peripheral PD-1 receptor occupancy for CD4+ T cells collected 21 days after second infusion (green) compared to measured immediately after third infusion (blue).

PD-1 Blockade

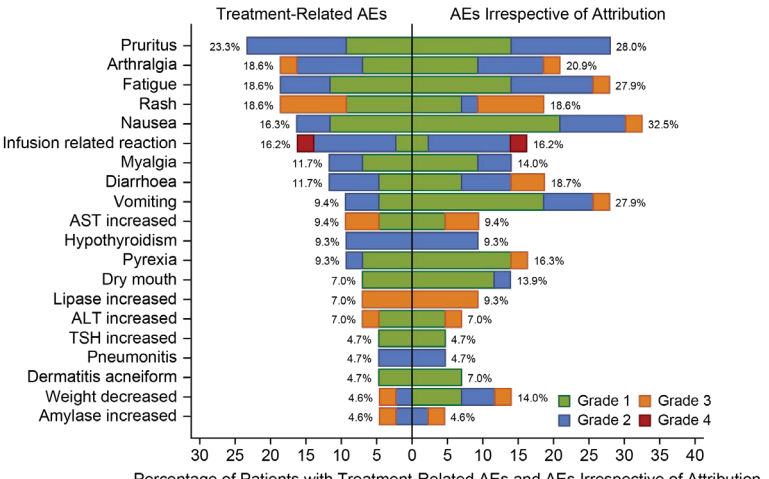


MGD019 blocks binding of competing anti-PD-1 mAb (J105) to peripheral CD4+ T cells of patients. Connected symbols represent individual patients before and after (day 8) MGD019 administration.

MGD019 Dose Escalation: Safety Summary

- Generally well-tolerated at dose levels < 10 mg/kg
- Despite no DLTs, intolerability at 10 mg/kg evident with increased incidence of Grade 3 irAEs, including:
  - Myocarditis (1)
  - Enterocolitis (1)
  - Hepatitis (1)
  - Bullous dermatitis (1)
  - Maculopapular rash (3)
- irAEs recovered with immunosuppression and/or treatment interruption/discontinuation

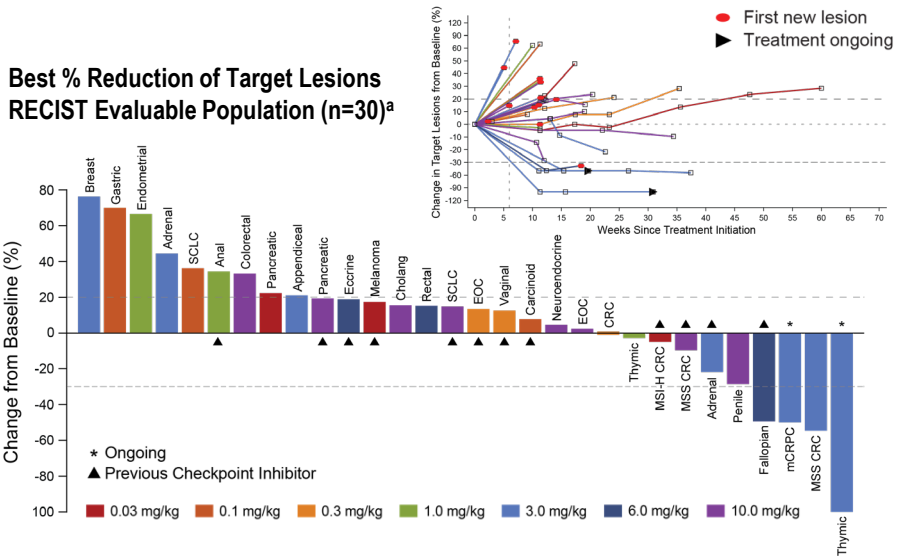
Overall AE Totals	No. (%) of Patients	
	All Grades (N=43)	≥ Grade 3 (N=43)
AE (irrespective of causality)	42 (97.7)	26 (60.5)
Treatment-related AE (TRAE)	34 (79.1)	14 (32.6)[a]
SAE (irrespective of causality)	18 (41.9)	16 (37.2)
Treatment-related SAE	6 (14.0)[b]	4 (9.3)
AE leading to discontinuation	8 (18.6)	8 (18.6)



[a] Includes one Grade 4 TRAE (IRR), occurring in setting of baseline pleural effusion. No Grade 5 TRAEs have been reported. Seven of 14 patients experiencing Grade ≥ 3 TRAEs (50%) occurred at 10 mg/kg dose level. [b] Treatment related SAEs (n=6) include Gr3 myocarditis, Gr3 enteritis, Gr3 enterocolitis, Gr2 arthralgia, Gr2 pneumonitis, and Gr3 bullous dermatitis (n=1, each), four of which occurred at 10 mg/kg. Data cutoff: July 21, 2020.

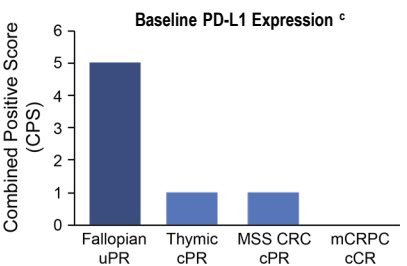
MGD019 Dose Escalation: Preliminary Activity

Best % Reduction of Target Lesions
RECIST Evaluable Population (n=30)[a]



Objective Responses (n=4):

- Microsatellite stable CRC – cPR
- Metastatic type AB thymoma – cPR
- Serous fallopian tube carcinoma[b] – uPR
- mCRPC – cCR
- 10 patients with SD as best response



Preliminary Results[d]:

- *All Dose Levels*: ORR 13.3%; DCR 43.3%
- *Doses ≥ 3 mg/kg*: ORR 22.2%; DCR 50.0%

[a] Based on patients with baseline and post-treatment tumor measurements. [b] Previously refractory to anti-PD-L1 therapy in combination with anti-CD47 mAb. [c] PD-L1 expression determined per Agilent PD-L1 (22C3) pharmDx kit; CPS = number of PD-L1 + cells (tumor and immune)/total number of viable tumor cells x 100. [d] Includes the unconfirmed PR. Data cutoff: July 21, 2020

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Patient Vignettes

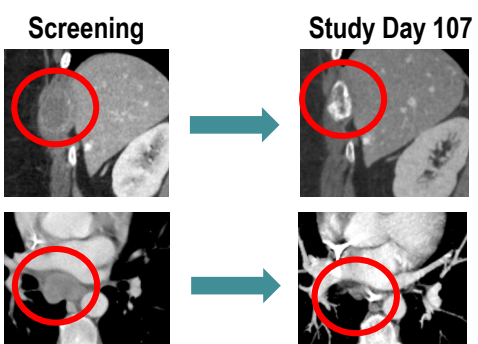
Anti-tumor Activity in Tumors Conventionally Unresponsive to Checkpoint Inhibition

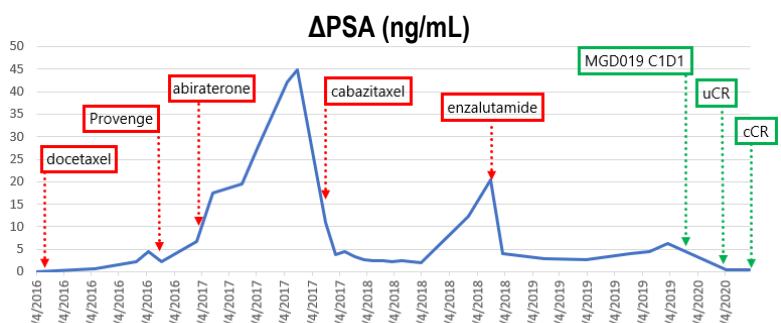
33-year-old female with CRC (3.0 mg/kg)

- MSS disease, low TMB (5 mutations/mB), KRAS mutation
- Clinical course: worsening of celiac disease and Grade 3 enteritis
- Treatment Response: confirmed PR with complete resolution of rib mass and 3 cm subcarinal lymph node (images below); resolution of CEA: 23 (pre-MGD019) to <1 ng/mL
- Off-treatment due to enteritis, with persistent response

61-year-old male with mCRPC (3.0 mg/kg)

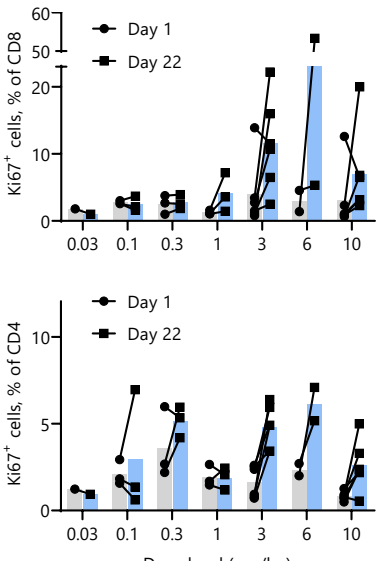
- Post 6 prior lines of systemic therapy; disease limited to LNs
- Clinical course: immune-mediated hypothyroidism and transaminitis
- Treatment Response: confirmed CR with complete resolution of disease; resolution of PSA (0.5 ng/mL)
- Remains on MGD019 treatment (35+ weeks)





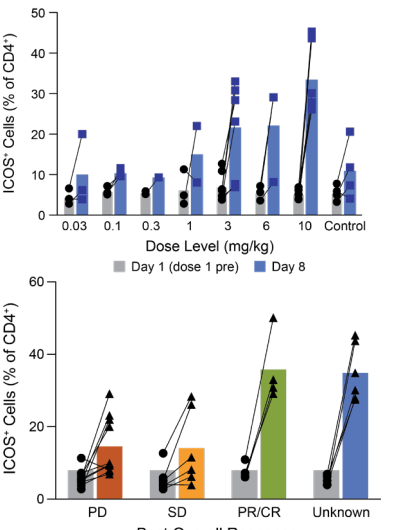
Pharmacodynamics of PD-1 and CTLA-4 Blockade

T cell Proliferation (Ki67)



MGD019 increases fraction of Ki67+ T cells in patients' PBMCs.

ICOS Upregulation by Dose Level and BoR



Dose-dependent ICOS upregulation on peripheral CD4 T-cells attributable to CTLA-4 arm based on cross-comparison with other MacroGenics' PD-1 based molecules.

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MGD019 (PD-1 × CTLA-4 DART Molecule): Conclusions

Purpose-designed bispecific checkpoint inhibitor

- Effects independent or coordinate blockade of PD-1 and CTLA-4
  - Enhanced CTLA-4 blockade on dual-expressing TILs vs. PD-1/CTLA-4 mAb combination
  - Maintains uncompromised PD-1 blockade vs. anti-PD1 mAb benchmarks
- GLP toxicology results compare favorably to that of ipilimumab + nivolumab preclinical profile

Encouraging activity in tumors traditionally unresponsive to checkpoint blockade

- Generally well tolerated at doses < 10 mg/kg
- Full peripheral PD-1 blockade evident at doses ≥ 1 mg/kg
- Dose-dependent ICOS upregulation evident in responding patients
- Responding patients with low PD-L1 expression at baseline

Enrollment in select monotherapy expansion cohorts at RP2D of 6.0 mg/kg forthcoming