MOLECULAR TEMPLATES

Corporate Presentation

March 2024

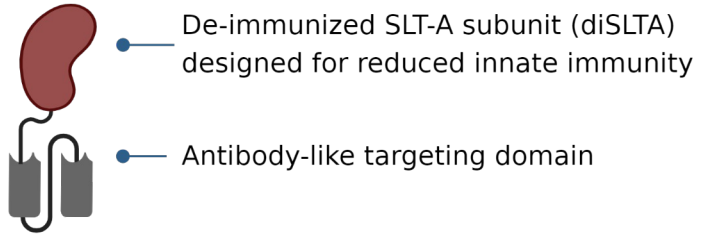
Forward looking statements

Except for statements of historical fact, the statements in this presentation are forward-looking statements, including, but not limited to, statements regarding the future development of our proprietary Engineered Toxin Body (ETB) technology; statements relating to the development of MT-6402, MT-5111, MT-0169, and MT-8421 and our next generation ETBs and preclinical pipeline; statements regarding the safety or potential efficacy of our drug or biologic candidates, including the anticipated benefits of our next-generation ETBs; our belief that our proprietary ETB technology provides for a differentiated mechanism of action that may address some of the limitations associated with currently available cancer therapeutics; statements regarding expected demand and opportunities for certain targets; expected program milestones; the timing, progress and results of pre-clinical studies and clinical trials for our drug or biologic candidates or any future candidates; the timing or likelihood of regulatory filings, including expected timing for submission and approval of various IND applications; our expected receipt of clinical data; the expected timing for providing updates on our pipeline, including MT-6402, MT-5111, MT-0169 and MT-8421, and our earlier stage pipeline of ETBs; our financial performance and future financial position; and statements relating to the outcome of our collaborations as they relate to our ETB platform. These statements constitute "forward-looking statements" within the meaning of Section 27A of the Securities Act and Section 21E of the Securities Exchange Act of 1934, as amended, and are usually identified by the use of words such as "anticipates," "believes," "estimates," "expects," "intends," "may," "plans," "projects," "seeks," "should," "will," and variations of such words or similar expressions. These forward-looking statements reflect our current views about our plans, intentions, expectations, strategies and prospects, which are based on the information currently available to us and on assumptions we have made. Although we believe that our plans, intentions, expectations, strategies and prospects as reflected in or suggested by those forward-looking statements are reasonable, we can give no assurance that the plans, intentions, expectations or strategies will be attained or achieved. Furthermore, actual results may differ materially from those described in the forward-looking statements and will be affected by a variety of risks and factors that are beyond our control. These statements involve risks and uncertainties that can cause actual results to differ materially from those in such forward-looking statements. Important factors that may cause actual results to differ materially from the results discussed in the forward-looking statements include risks and uncertainties, including, but not limited to, (1) our failure to secure and maintain relationships with collaborators; (2) risks relating to clinical trials and other uncertainties of drug or biologic candidate development, including the fact that interim clinical results may not be indicative of future results; (3) risks relating to the commercialization, if any, of our proposed drug or biologic candidates (such as marketing, regulatory, product liability, supply, competition, and other risks); (4) dependence on the efforts of third parties including our strategic partners; (5) dependence on intellectual property; (6) risks from global pandemics including COVID-19; and (7) risks relating to our ability to maintain the listing of our common stock on the Nasdaq Capital Market. Further information regarding these and other risks is included under the heading "Risk Factors" in our filings with the SEC available from the SEC's website (www.sec.gov). Existing and prospective investors are cautioned not to place undue reliance on these forward- looking statements, which speak only as of the date hereof. These forward looking statements reflect management’s current views and we do not undertake to update any of these forward-looking statements to reflect a change in events or circumstances that occur after the date of this presentation except as required by law.

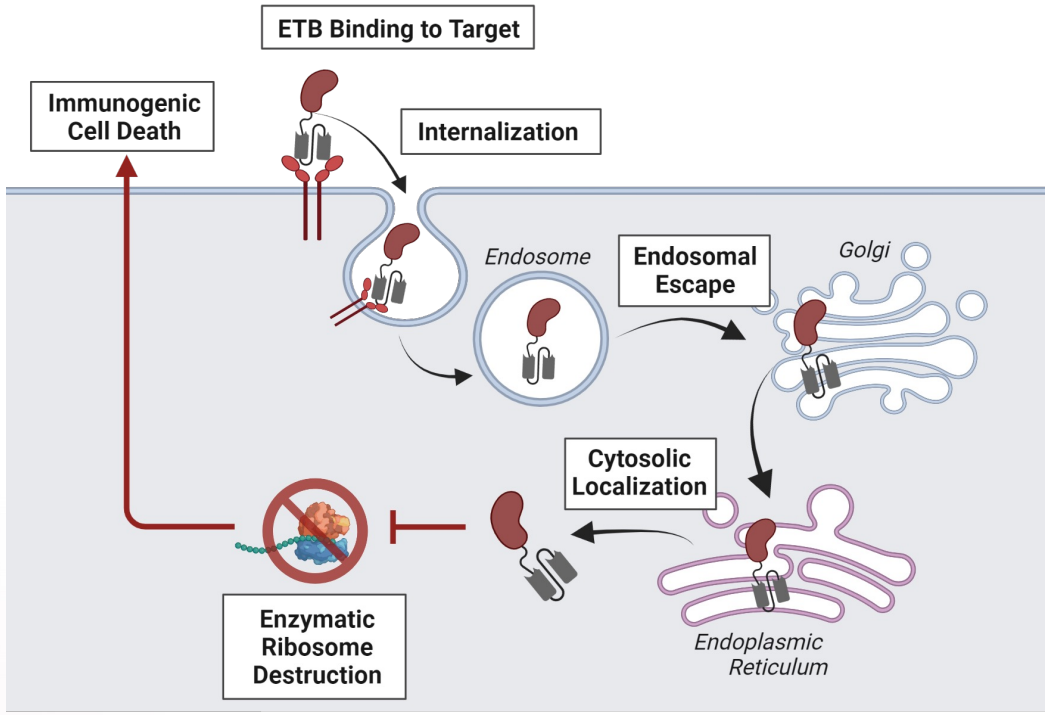
MTEM Platform: Engineered Toxin Bodies (ETBs) leverage novel MoAs for oncology

- **ETBs, next-gen immunotoxins, leverage the unique biology of Shiga-like toxin A (SLTA):**
  - Forced internalization of non-internalizing receptors
  - Potent direct-cell kill via novel mechanism of enzymatic destruction of ribosomes resulting in apoptosis, immunogenic cell death, and T-cell activation
- **ETBs were genetically engineered to eliminate CLS; well-tolerated to date in >100 pts treated**
  - No case of capillary leak syndrome (CLS) reported in any patient
  - No grade 4 or grade 5 events seen; no off-target heme, ocular, lung, or hepatic toxicity seen
- **Compelling evidence of novel pharmacodynamic effects and monotherapy activity in heavily pretreated patients**
  - Novel MOA can drive monotherapy activity in patients with relapsed/refractory disease
- **Novel approach to validated targets in I/O, solid tumors, and hematology**
  - **MT-6402:** PD-L1-targeted TME dismantling and restoration of T-cell function, alteration of tumor immunophenotype, and direct cell-kill of PD-L1+ tumors
  - **MT-8421:** CTLA-4 targeted TME dismantling and restoration of T-cell function
  - **MT-0169:** CD38-targeted direct cell-kill in CD38+ hematologic malignancies

Engineered Toxin Bodies (ETBs)



ETB Mechanism of Action



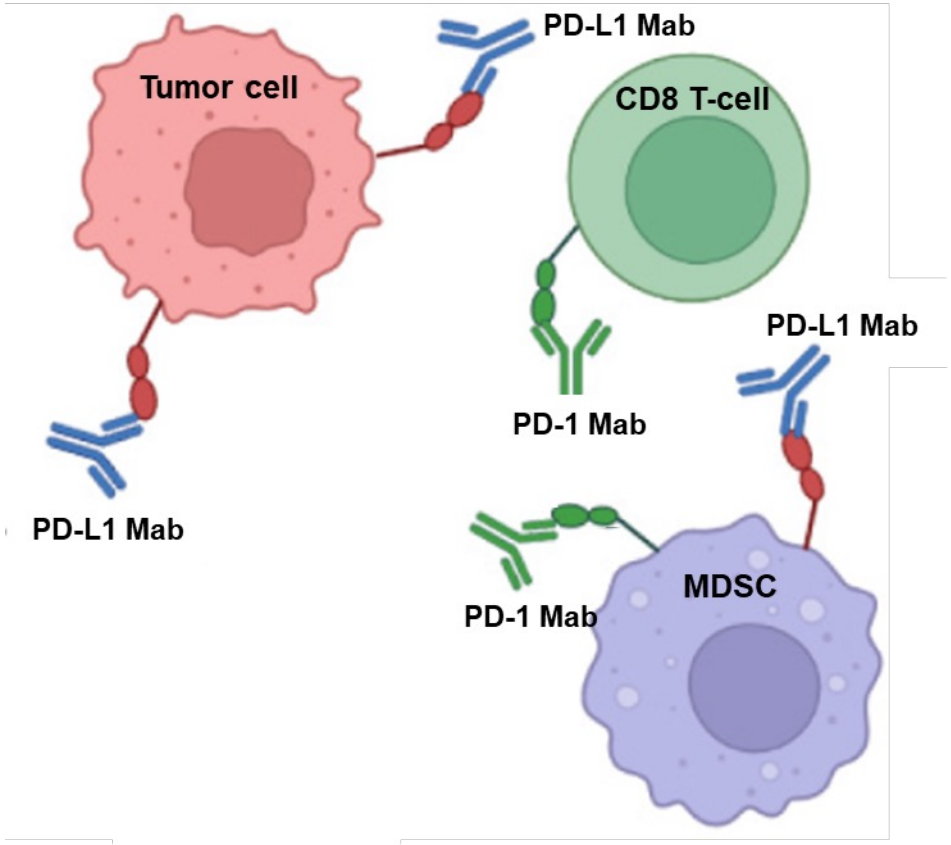
Next-Gen ETB platform shows strong safety with no evidence of innate immunity / CLS

- **Bacterial-based therapeutics (immunotoxins) show high levels of CLS / innate immunity**
  - Approved immunotoxins demonstrate 33-55% rates of CLS in patients with up to 1/3 of patients requiring hospitalization; ~3% Gr 5 CLS
  - 1st-gen ETB MT-3724 (not de-immunized) showed similar rates of CLS as other immunotoxins: 53% CLS with one Gr 5 CLS
- **~4-year campaign of altering surface exposed residues in SLTA to reduce TLR4 / innate cell recognition while maintaining biology (internalization, routing, immunogenic cell kill)**
- **In 100+ patients treated to date with next-gen ETBs, there has not been a single case of CLS**
  - No grade 4 or grade 5 events seen with diSLTA;
  - Off-target heme, ocular, lung, or hepatic toxicity seen with ADCs are not seen with diSLTA

	Treatment	Scaffold	Dose level	CLS (all grades)
Approved Immunotoxins	**Elzonris**	IL-3 diphtheria fusion	12 mcg/kg	55%
	Ontak	IL-2 diphtheria fusion	9 or 18 mcg/kg	33%
	Lumoxiti	CD22 scFv pseudomonas fusion	40 mcg/kg	34%
1st-Gen ETB	**MT-3724**	CD20 scFv wild-type SLTA fusion	5 through 100 mcg/kg (MTD=50 mcg/kg)	53%
Next-Gen ETBs	**MT-6402**	PD-L1 scFv de-immunized SLTA fusion	16 through 100 mcg/kg	**0%**
	MT-8421	CTLA-4 biparatopic VHH de-immunized SLTA fusion	32 and 48 mcg/kg (dose escalation ongoing)	**0%**

MT-6402: A novel approach to the PD-1 / PD-L1 axis

PD-1/PD-L1 checkpoint inhibitors work by sterically inhibiting PD-1/PD-L1 interactions



- **Checkpoint mAbs sterically inhibit PD-1 from binding PD-L1**
  - Checkpoint antibodies are dosed between 200–1200mg per dose
  - The half-life of checkpoint antibodies are between 1 to 4 weeks
  - Dosing and half-life allow for saturating antibody levels to comprehensively and persistently block PD-1/PD-L1 interactions

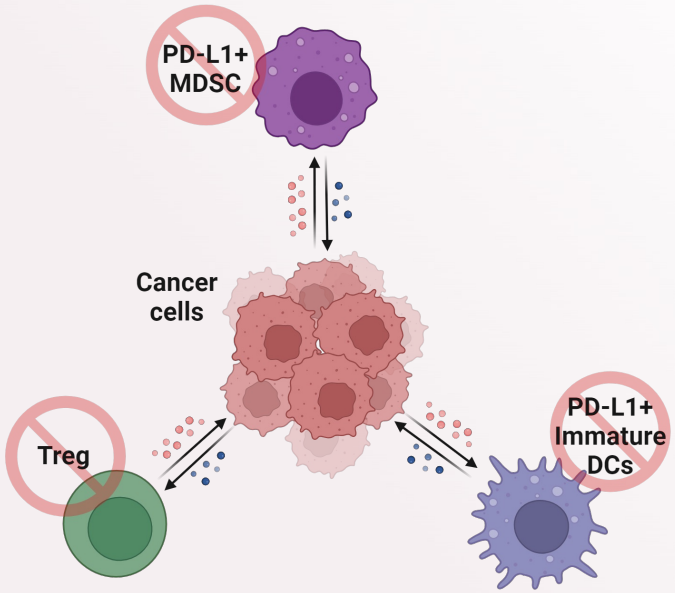
- **MT-6402 does not sterically inhibit PD-1 from binding PD-L1**
  - MT-6402 MTD is 83 mcg/kg: 30 to 180-fold lower checkpoint doses
  - MT-6402 half-life is 2-4 hrs: 50 to 220-fold lower than half-life of checkpoints
  - MT-6402 does not achieve saturating concentrations sufficient to comprehensively and persistently block PD-1 / PD-L1 interactions

MT-6402 – A novel approach to targeting PD-L1 with three unique MOAs

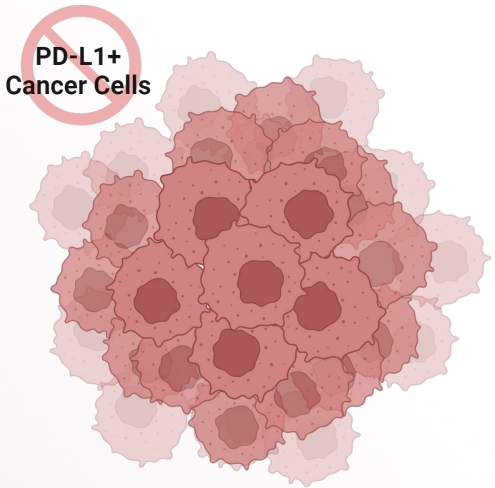
MT-6402 - Targeting PD-L1 via Differentiated MOA

- De-immunized SLT-A subunit (diSLTA)
- scFv binds PD-L1
- Delivery payload: CMV pp65 antigen to alter tumor immunophenotype

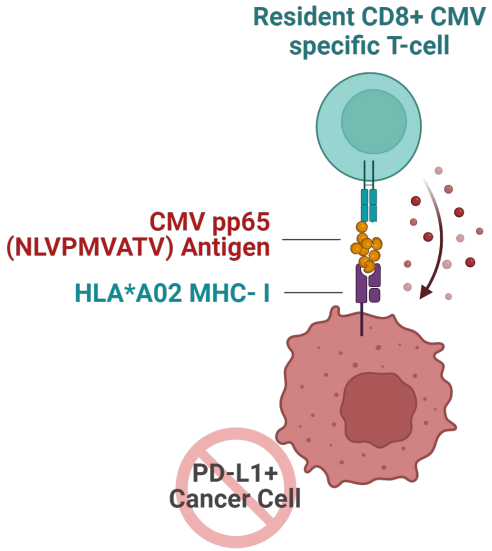
TME Immune Cell Depletion



Tumor Direct-Cell Kill



Antigen Seeding: Immunophenotype Duping

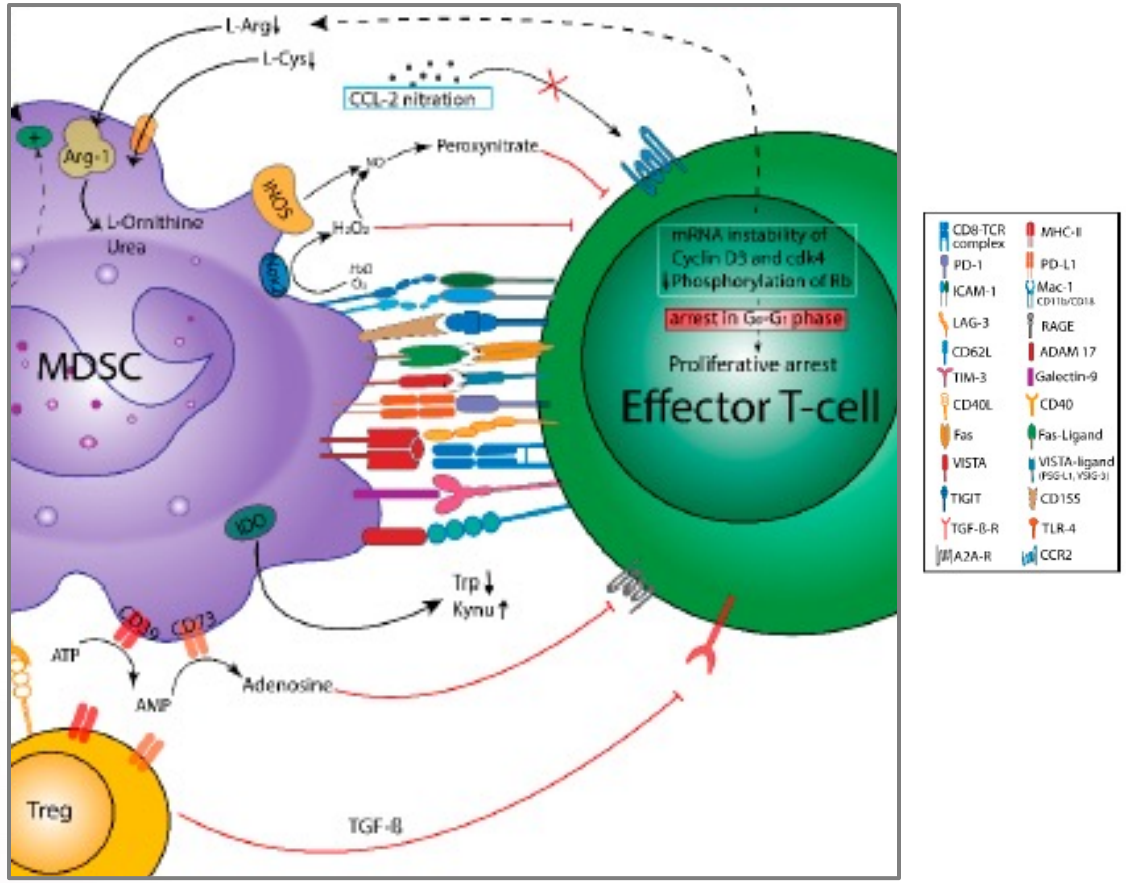


MT-6402: TME Immune Cell Depletion

Unique pharmacodynamic and clinical efficacy through TME dismantling

MDSCs block T-cell function and promote tumor growth

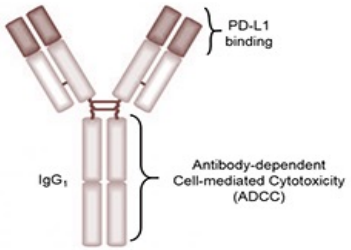
- **Peripheral expression of MDSC correlates with poor prognosis with PD-1 therapy[1,2]**
  - Multiple interactions between MDSCs and T-cells beyond PD-1/PD-L1
- **MDSCs inhibit immune surveillance, induce angiogenesis, and promote metastasis[3]**
- **Expression ADAM17 on MDSC decreases CD62L expression on CD8⁺ T cells inhibiting trafficking**
- **Current PD(L)-1 Mabs do not clear MDSCs**
- **MT-6402 dismantles the TME through internalization and direct cell-kill of PD-L1-expressing immune cells**
  - MT-6402 destroys PD-L1+ immune cells
  - Elimination of MDSCs allows for T-cell function



1. Koh et al, Eur J Immunol. 2020 Nov; 50(11): 1810–1819
2. Ostrand-Rosenberg Annual Review of Cancer Biology, Vol 5, 2021
3. Weber et al, Front Immunol. 2018; 9: 1310
4. Haist et al, *Cancers* 2021: 13(2)

PD-L1 Fc-enhanced mAb vs MT-6402: Immune cell clearance

Avelumab

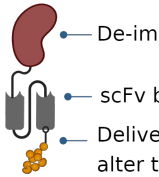


PD-L1 mAb w/ effector function, does NOT eliminate PD-L1+ immune cells

	Pre	Day 15 (n=19)	Pre	Day 43 (n=14)	Pre	Day 127 (n=16)
PD-L1+ CD4	0·09 (0·06-0·09)	0·08 (0·06-0·09)	0·09 (0·06-0·11)	0·07 (0·05-0·09)	0·07 (0·05-0·09)	0·07 (0·05-0·10)
PD-L1+ CD8	0·04 (0·03-0·07)	0·04 (0·03-0·07)	0·05 (0·03-0·09)	0·04 (0·03-0·08)	0·04 (0·03-0·05)	0·04 (0·01-0·06)
PD-L1+ Treg	<0·01	<0·01	<0·01	<0·01	<0·01	<0·01
PD-L1+ NK	0·07 (0·05-0·09)	0·07 (0·04-0·11)	0·08 (0·05-0·14)	0·06 (0·05-0·10)	0·04 (0·03-0·08)	0·05 (0·04-0·07)
PD-L1+ NKT	0·04 (0·03-0·07)	0·04 (0·03-0·06)	0·04 (0·03-0·07)	0·04 (0·03-0·06)	0·02 (0·01-0·03)	0·02 (0·01-0·04)
PD-L1+ B cells	0·7 (0·2-1·2)	0·8 (0·3-1·3)	0·8 (0·3-1·3)	0·8 (0·3-1·3)	1·2 (0·4-1·9)	1·1 (0·4-1·5)
PD-L1+ cDC	0·01 (0·01-0·02)	0·01 (0·01-0·02)	0·01 (0·01-0·02)	0·01 (0·01-0·02)	0·02 (0·01-0·04)	0·01 (0·01-0·02)
PD-L1+ pDC	0·02 (0·01-0·05)	0·01 (0·01-0·03)	0·02 (0·01-0·04)	0·02 (0·01-0·06)	0·02 (0·01-0·07)	0·05 (0·02-0·25)
PD-L1+ MDSC	0·5 (0·4-1·1)	0·9 (0·5-1·6)	0·5 (0·3-0·8)	0·5 (0·4-1·0)	0·6 (0·3-1·8)	1·3 (0·5-2·8)

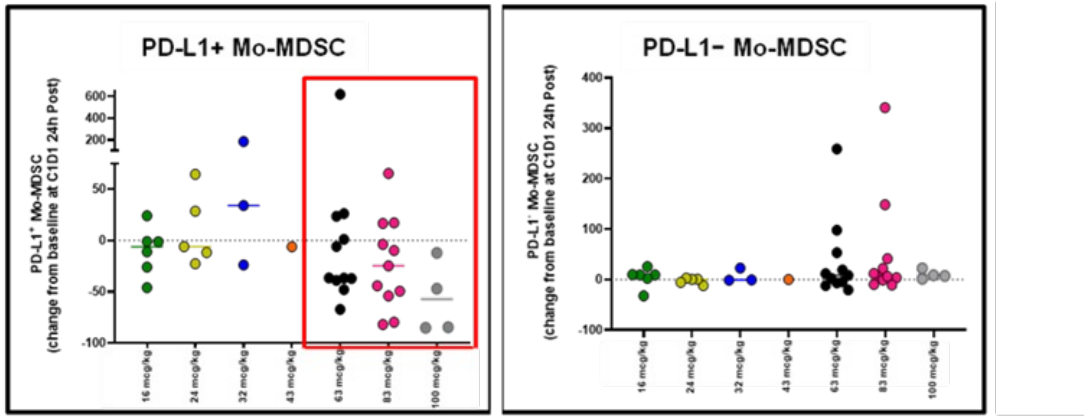
"These studies demonstrate the lack of any significant effect on multiple immune cell subsets, even those expressing PD-L1, following multiple cycles of avelumab."[2]

MT-6402



- De-immunized SLT-A subunit (diSLTA)
- scFv binds PD-L1
- Delivery payload: CMV pp65 antigen to alter tumor immunophenotype

ETB targeting PD-L1 eliminates PD-L1+ immune cells in a target-dependent fashion



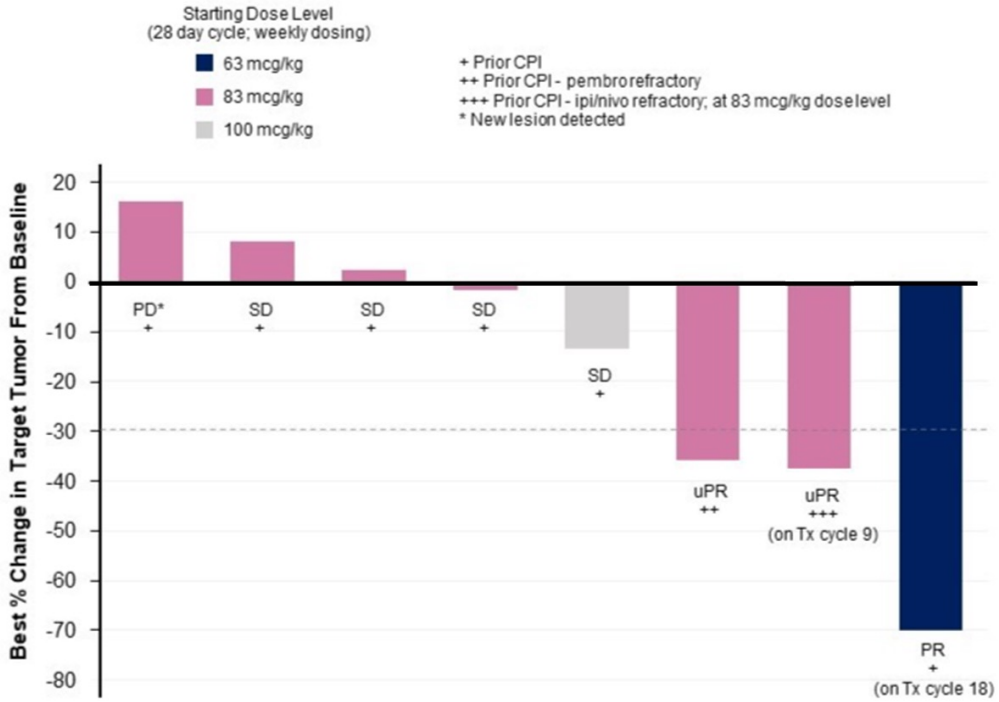
Reduction of PD-L1+ MDSCs in a dose-dependent fashion by MT-6402. No depletion noted on PD-L1- MDSCs. Similar reduction noted for PD-L1+ DCs, monocytes, and other immune cells

1. Heery et al, Lancet Oncol. 2017 18(5): 587-598
2. Donahue et al, *J Immunotherapy Cancer*. 2017. 21;5:20

Compelling signal of monotherapy activity with MT-6402 at higher doses in head and neck cancer

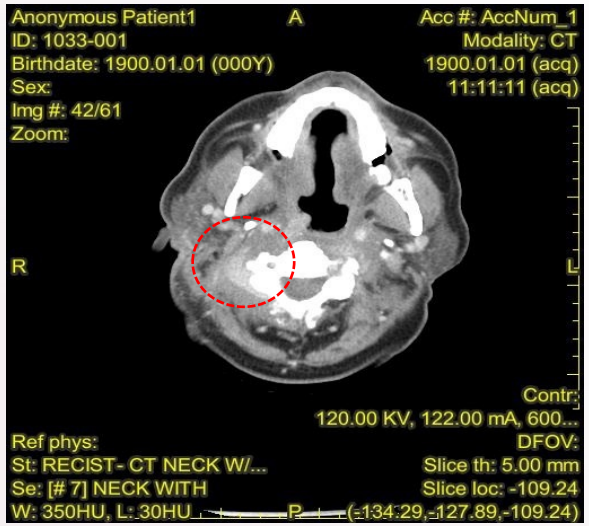
- **Head and neck cancer is the 6th most common cancer**
- **A new I/O approach is needed: ORR with PD-1 therapy is ~15%**
- **10 pts with HNSCC in dose escalation; two considered non-evaluable**
  - Pts dosed at 63, 83 (MTD), or 100 mcg/kg; median # of prior tx >3
- **2 pts currently in responses**
  - 1 pt (63 mcg/kg) has a confirmed PR with 70% reduction in tumor volume at **cycle 18 (1 cycle = 4 weeks)**
  - **1 pt (83 mcg/kg) has an uPR (37% reduction) at cycle 8 w/ reductions of 3%, 9%, and 15% across three previous cycles**
    - **Pt is on tx in cycle 9**
  - **2 pts (one uPR and one 15% reduction) came off tx for gr1 hs-Trop elevation; guidelines now revised to allow pts to continue**
- **No gr 4 or gr 5 drug-related toxicities were observed**
- **All patients with responses/tumor reduction had low PD-L1**
- **Activity seen is I/O; all patients showed evidence of T-cell activation**
  - I/O responses are typically longer duration than chemo responses

Monotherapy Activity with MT-6402 in Low-PD-L1 Relapsed/Refractory SCHNN Patients (N=8)

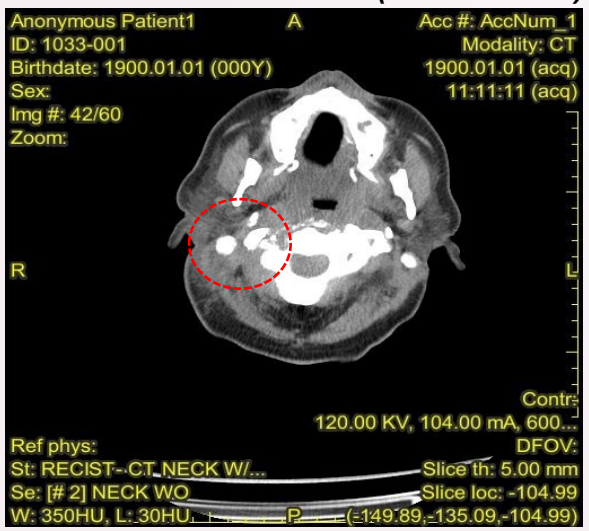


Partial response (70% tumor reduction) in head and neck cancer patient at 63 mcg/kg

Baseline



Post-MT-6402 treatment (8-week scan)

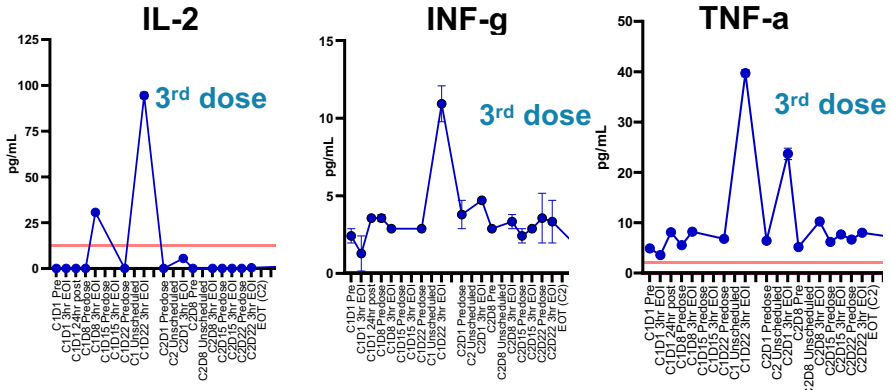


- **50-year-old man with metastatic nasopharynx carcinoma to the bone**
  - Prior tx w/ cisplatin+70 Gy radioTx followed by adjuvant chemo (cisplatin, docetaxel, 5-FU) for 4 mths
  - Tx with pembro + denosumab with disease progression
- **Tumoral PD-L1 expression is low at 2% and patient is not HLA-A*02**
  - Response is mediated by clearance of immunosuppressive cells in the patient
- **Patient remains on treatment in a confirmed response in cycle 16 with 70% tumor reduction**
  - Soft tissue mass adjacent to right C2 vertebral body measured 4.1 x 1.7 cm at baseline
  - After C2, measurement of soft tissue mass was 1.5 x 1.2 cm: 63% reduction and RECIST PR
    - Rapid onset of response consistent with changes in TME markers

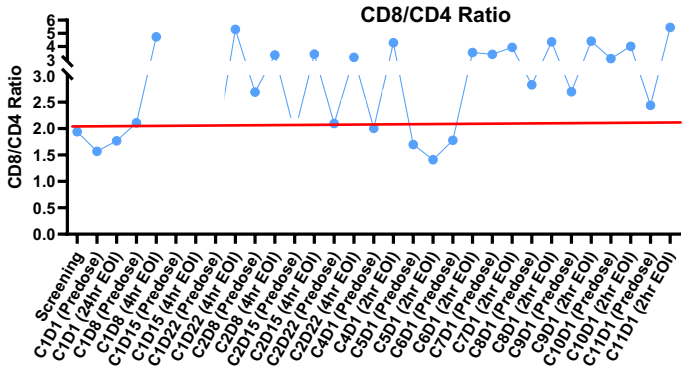
Evidence of potential for deep and long-lasting response with MT-6402

Activation of CD8+ T-cells, elimination of monocytes, and evidence of TME disruption

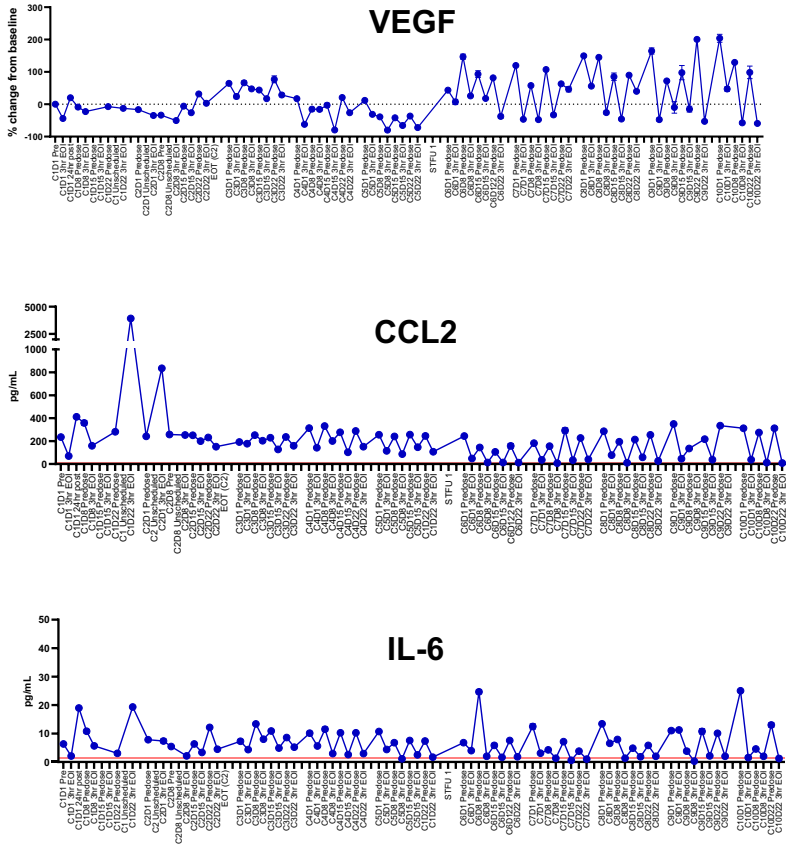
Dramatic increase in cytokines associated with T-cell activation with 3rd dose at week 3



Increase in CD8/CD4 Ratio after each dose



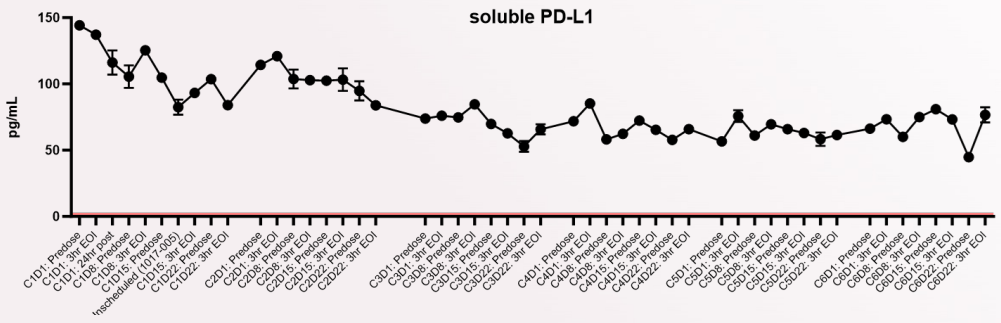
Prolonged modulation of TME-associated markers and decrease of PD-L1+ MDSCs

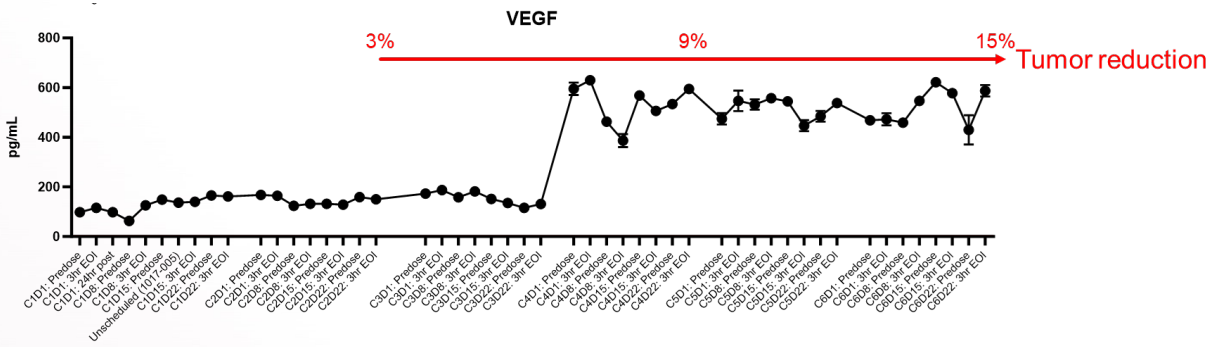


Continued tumor reduction in patient over 6 cycles with PR in cycle 8

- 61-year-old male with squamous cell carcinoma of the oral cavity and CPS score of 10%
  - Patient progressed on Ipi/Nivo within 4 months
  - Progressed on taxol+cetuximab; progressed on carboplatin/5FU/pembrolizumab

- Patient on 83 mcg/kg dose and has received all doses of MT-6402 with no notable AEs
  - Patient has seen continuing reduction in tumor volume at each scan
    - Cycle 2: 3% reduction
    - Cycle 4: 9% reduction
    - Cycle 6: 14% reduction
  - Patient showed a 37% reduction (PR) at cycle 8
    - Continuous reduction in soluble PD-L1
    - Dramatic increase in VEGF (TME remodeling)
  - Patient remains on study in cycle 9

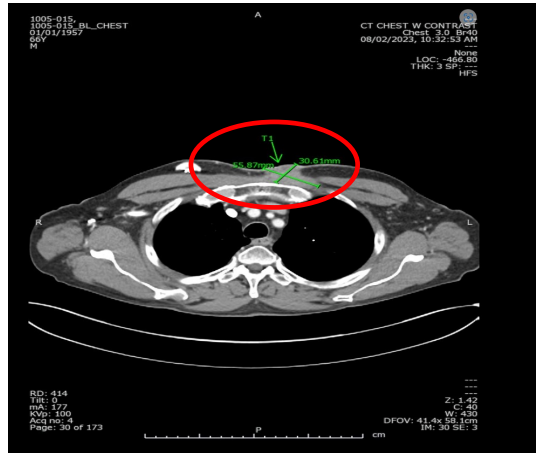




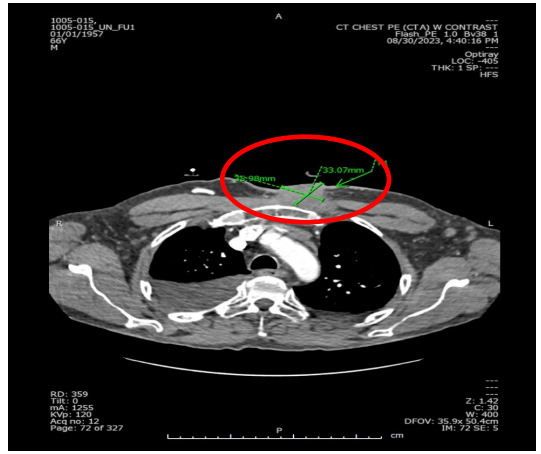
Partial response (unconfirmed) at 83 mcg/kg in head and neck patient refractory to Pembro

- **Pt with a cutaneous skin cancer of the head and neck region had a left anterior chest wall lesion measuring 5.6 cm by 3.1 cm; CPS=10%**
- **Patient had received 6 prior lines of therapy including radiation, abraxane, taxotere, 5-FU, cetuximab, tazemetostat, carboplatin, palbociclib, and pembro**
  - Pt had progressed twice on pembro within two months (monotherapy and combo with tazemetostat)
- **Patient received 2 doses of MT-6402 before coming off treatment**
  - Patient had grade 1 high sensitivity troponin elevation but was asymptomatic with no ECG or ECHO changes (hs-cTnI elevation of 111 ng/L after 2nd dose)
  - Pt had also developed hyponatremia related to excessive alcohol intake
- **The treating physician noted that thickness has dramatically decreased with flattening of most of the elevated lesion and caving-in of the central part like a "volcano crater"**
- **Patient discontinued treatment after CT scan at site showed stable disease, but an external radiology review showed an unconfirmed partial response (36% reduction in the chest wall lesion).**
- **Pt had elevations in TNF-a and IL-2 after 2nd dose of MT-6402, consistent with T-cell activation**

Baseline



After 2 doses of MT-6402

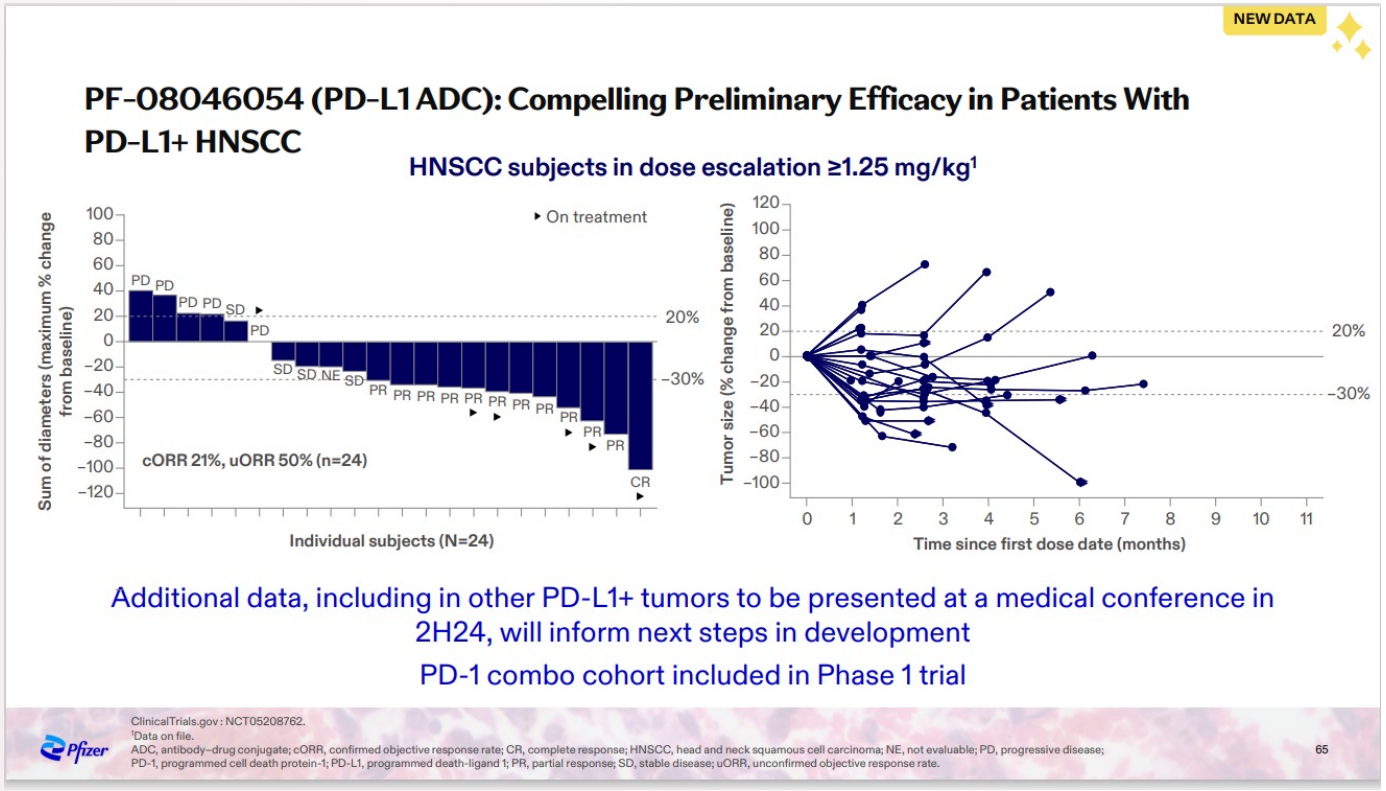


Evidence of potential response activity in checkpoint refractory patients with MT-6402

Tumor reduction in head and neck patient treated at 100 mcg/kg with subsequent dose reduction

- **61-year-old man with metastatic squamous cell cancer of the hypopharynx (HPV-negative) treated at 100 mcg/kg**
  - Previous systemic cancer treatments: carboplatin, paclitaxel, cetuximab combo followed by pembrolizumab
- **Patient had pre-existing cardiac risk factors of hypertension, hyperlipidemia, hypercholesterolemia, and evidence of vascular disease as evidenced by peripheral vascular disorder and cerebrovascular accident**
- **Patient received three doses of MT-6402 before presenting with grade 1 high sensitivity troponin elevation**
  - hs-cTnI elevation of 303 ng/L: EKG and ECHO were normal, and patient had no clinical evidence of cardiotoxicity, but dosing was held
  - hs-CTnI elevation coincided with spike in IL-2 in patient
- **A CT scan showed a 13% reduction in tumor, but disease progression (44% increase) occurred during 3-month treatment interruption**
  - VEGF and other cytokines returned to baseline during treatment interruption
- **Physician restarted treatment at 50% dose reduction after evidence of disease progression while off treatment**
  - No increase in cardiac biomarkers have been noted after the resumption of treatment
  - Patient ultimately progressed again on therapy

Data on Pfizer's PD-L1 ADC with vedotin payload: Presented at Pfizer Oncology Day



Pt ID	Best Response	Est. Tumor Reduction	Time on Study	On Tx	Confirmed (C) / Unconfirmed (U)
1	PD	40%	2.7	N	
2	PD	37%	1	N	
3	PD	22%	1	N	
4	PD	21%	1	N	
5	SD	17%	4	N	
6	PD	0%	2.7	Y	
7	SD	-15%	5.4	N	
8	SD	-19%	1	N	
9	NE	-19%		N	
10	SD	-22%	4	N	
11	PR	-30%	6.4	N	U
12	PR	-34%	2.7	N	U
13	PR	-34%	7.6	N	U
14	PR	-36%	2.5	N	U
15	PR	-37%	5.6	Y	C
16	PR	-39%	4	Y	U
17	PR	-41%	2	N	U
18	PR	-43%	4.4	N	C
19	PR	-51%	2.7	Y	C
20	PR	-62%	2.4	Y	C
21	PR	-72%	3.2	N	U
22	CR	-100%	6	Y	C

- Study on-going since 2022 with multiple tumor types tested
  - 24 HNSCC pts with PD-L1+ HNSCC were treated
- 5 confirmed responses (21%); 7 unconfirmed responses (29%)
  - Only 5 pts remain on study with 7-month follow-up
- Most responses appear transient: mean duration on study for responses is ~4.3 mths
  - Longest on-going response is 6 months
- Responses seen with Pfizer ADC appear to be chemo-responses (ie, more short-lived)
- No info on tox provided; MMAE associated with neuropathy, neutropenia, nausea, etc

- **6 of the 7 patients with unconfirmed PRs have progressed**
  - **Mean time to progression for 6 progressors was 4.1 mths**
  - **Remaining uPR patient has been on 4 months**

- **1 of the 5 confirmed PRs progressed after 4 months**
  - **Mean time on tx for remaining responders is 4.2 mths**

- **Only 3/24 patients have been on study for 6 months or more**
  - **Only 1 of these patients remains on study**
  - **3/8 MT-6402 pts where on study ≥6 mths w/ 2 still on study**

Pfizer ADC data versus MT-6402 in head and neck cancer

Pfizer data is confirmatory of MT-6402 signal in HNSCC

- Both molecules have been tested in multiple tumor types, but HNSCC seems most promising tumor type early on
  - Potential early signs of activity with MT-6402 in NSCLC

MT-6402 is likely to have a similar or better response rate as Pfizer ADC

- Confirmed ORR rate with Pfizer compound is 21%; MTEM expects to have a confirmed ORR of 20% in 2 months
- 2 pts on MT-6402 showed early signs of efficacy but were discontinued or dose interrupted over hs troponin guidelines
  - After a safety review, those guidelines have been altered and those patients would have continued on treatment

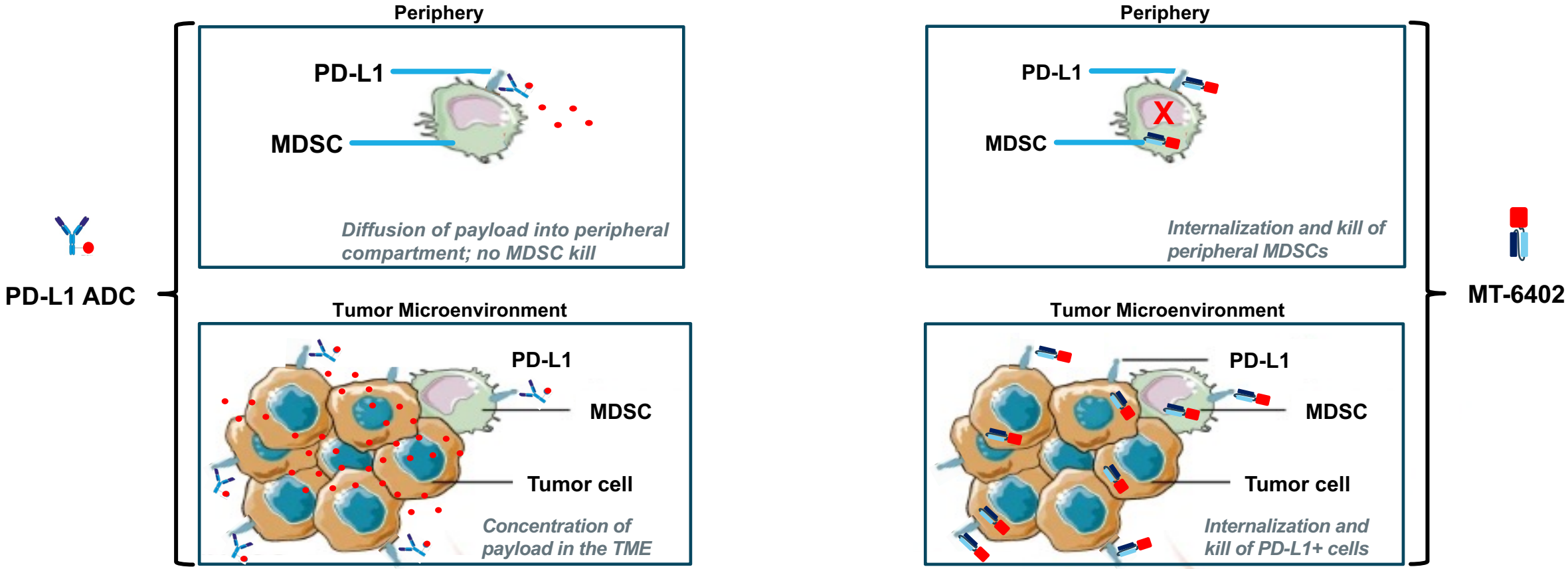
MTEM expects MT-6402 to have a better duration of response than the Pfizer ADC

- 1 response with MT-6402 is on-going at 18 months and another is on-going at 9 months
- Mean time on therapy for patients in a response with Pfizer ADC appears to be ~4 months
- 3 of 8 MT-6402 pts on study for ≥6 months (2 ongoing); 3 of 24 Pfizer pts on study for ≥6 months (1 ongoing)
- Difference in duration of response is due to a difference in MOA (chemo vs I/O)

No grade 4 drug-related toxicities or hematological, hepatic, lung, neuropathy, or ocular toxicity were seen with MT-6402

- Hematological toxicity, neuropathy, and nausea are consistently seen with vedotin payload and are dose-limiting

MOA for MT-6402: MDSC destruction and T-cell activation



PD-L1 is a poorly internalizing receptor

- A cleavable linker allows release of payload outside the cell;
  - Cell entry is dependent on achieving concentration gradient
- Concentration gradient of payload occurs in the TME because of high PD-L1
  - Tumor cells are destroyed via chemo mechanism of action
- A concentration gradient cannot be established in the periphery
  - No peripheral destruction of MDSCs allowing for MDSCs in the TME
- PD-L1 ADCs function through a chemo mechanism of action, not I/O

PD-L1 is a poorly internalizing receptor

- MT-6402 induces internalization and cell kill independent of concentration gradients
- PD-L1+ immune cells are destroyed by MT-6402 in the TME
- PD-L1+ immune cells are destroyed by MT-6402 in the periphery
  - Peripheral MDSC destruction prevents replenishing of MDSCs in the TME
- MT-6402 operates through an I/O mechanism of action

Next steps for MT-6402

Expand on signal in HNSCC

- Initiate study of monotherapy MT-6402 in HNSCC (PD-L1<50%) at MTD
  - Confirm efficacy and safety of MT-6402
  - Demonstrate improved ORR, duration, and safety versus Pfizer ADC
  - ~15 evaluable patients by year end
- Continue to explore MT-6402 in high PD-L1+ tumors
  - Early sign of efficacy in 1 of 3 NSCLC pts treated: Pt on study with near PR (26% reduction) at cycle 4
  - Assess antigen seeding in high PD-L1+ tumors in pts with HLA-A*02 haplotype

Potential to move to phase III study in HNSCC within next ~18 months

- Ipi and Pembro have ~15% monotherapy ORR in HNSCC
- Ipi approved on phase III vs systemic chemo on overall survival (7.5 mths vs 5.1 mths)

Maturing data on MT-6402 and growing interest around ADCs to PD-L1 should allow for BD in near term

- Growing confirmation of activity and ability to contrast with Pfizer ADC makes for a much more credible story

MT-8421: A novel approach to CTLA-4

Depletion of Tregs from the TME

Tregs are the central immunosuppressive cell in the TME: CTLA-4 blockade does not eliminate them

Precision Medicine and Imaging

Clinical Cancer Research

Anti-CTLA-4 Immunotherapy Does Not Deplete FOXP3^{+} Regulatory T Cells (Tregs) in Human Cancers

Anu Sharma[1], Sumit K. Subudhi[1], Jorge Blando[2], Jorge Scutti[2], Luis Vence[2], Jennifer Wargo[3], James P. Allison[2], Antoni Ribas[4], and Padmanee Sharma[1,2]

Check for updates

"Both ipilimumab and tremelimumab increase infiltration of intratumoral CD4^{+} and CD8^{+} cells without significantly changing or depleting FOXP3^{+} cells within the tumor microenvironment."

Review

Addressing the Elephant in the Immunotherapy Room: Effector T-Cell Priming versus Depletion of Regulatory T-Cells by Anti-CTLA-4 Therapy

Megan M Y Hong [1] and Saman Maleki Vareki [1,2,3,4,*]

"Research to date suggests that enhancing anti-CTLA-4-mediated Treg depletion may be the foremost strategy for developing next-generation anti-CTLA-4 antibodies."

RESEARCH HIGHLIGHT

Anti-CTLA-4 immunotherapy: uncoupling toxicity and efficacy

Jonathan Pol[1,2,3,4] and Guido Kroemer[1,2,3,4,5,6]

Cell Research (2018) 28:501–502; https://doi.org/10.1038/s41422-018-0031-9

"general T cell activation outside of the tumor is not required for the tumor growth-restraining effect of ipilimumab"

Tregs are the central immunosuppressive cell in the TME: CTLA-4 blockade does not eliminate them

Precision Medicine and Imaging

Clinical Cancer Research

Anti-CTLA-4 Immunotherapy Does Not Deplete FOXP3$^+$ Regulatory T Cells (Tregs) in Human Cancers

Anu Sharma[1], Sumit K. Subudhi[1], Jorge Blando[2], Jorge Scutti[2], Luis Vence[2], Jennifer Wargo[3], James P. Allison[2], Antoni Ribas[4], and Padmanee Sharma[1,2]

"Both ipilimumab and tremelimumab increase infiltration of intratumoral CD4$^+$ and CD8$^+$ cells without significantly changing or depleting FOXP3$^+$ cells within the tumor microenvironment."

Review

Addressing the Elephant in the Immunotherapy Room: Effector T-Cell Priming versus Depletion of Regulatory T-Cells by Anti-CTLA-4 Therapy

Megan M Y Hong [1] and Saman Maleki Vareki [1,2,3,4,*]

"Research to date suggests that enhancing anti-CTLA-4-mediated Treg depletion may be the foremost strategy for developing next-generation anti-CTLA-4 antibodies."

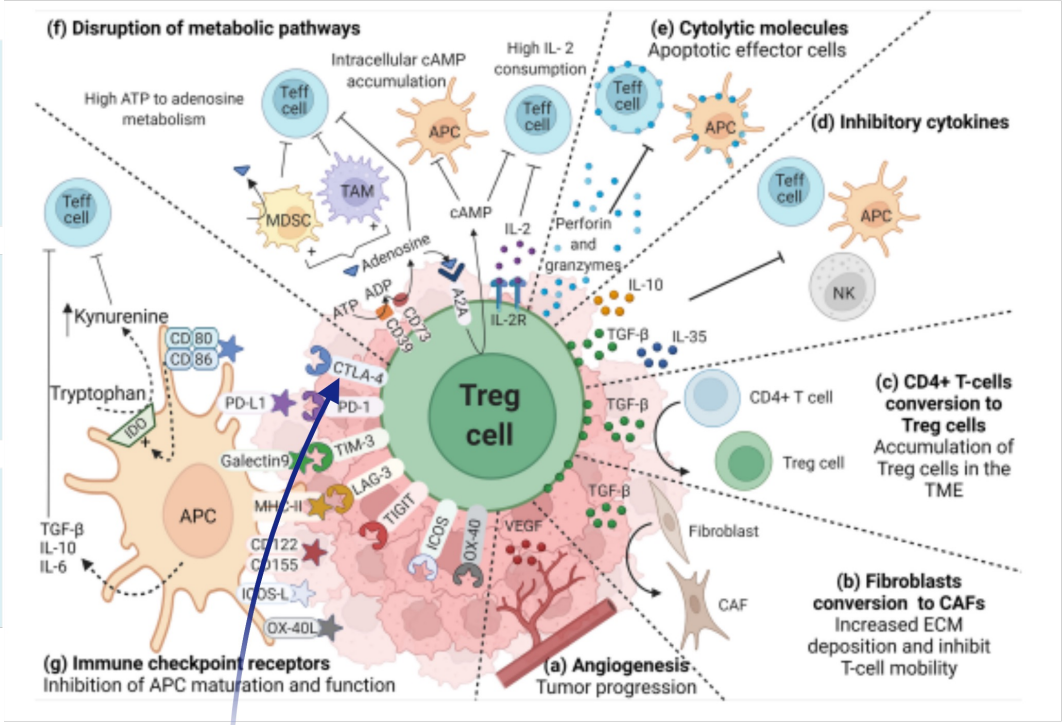
RESEARCH HIGHLIGHT

Anti-CTLA-4 immunotherapy: uncoupling toxicity and efficacy

Jonathan Pol[1,2,3,4] and Guido Kroemer[1,2,3,4,5,6]

Cell Research (2018) 28:501–502; https://doi.org/10.1038/s41422-018-0031-9

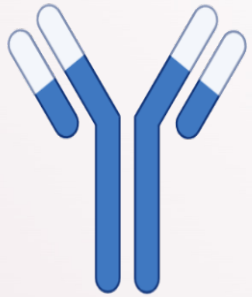
"general T cell activation outside of the tumor is not required for the tumor growth-restraining effect of ipilimumab"



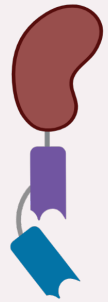
CTLA-4 blockade inhibits only a small portion of a Treg cell's immunosuppressive functionality

MT-8421: ETB dismantling the TME by destroying CTLA-4+ Tregs through a novel MOA

CTLA-4 mAb



MT-8421



Poor single agent activity of Ipi may be due to MOA: effector cell mediated ADCC

MT-8421 MOA: direct cell-kill through ribosomal destruction of CTLA-4 Tregs

Treg depletion by Ipi is dependent on presence of $CD14^{+}CD16^{-}$ non-classical monocytes. Fc-enhanced CTLA-4 mAbs are unlikely to change this.

MT-8421 mechanism of cell kill is independent of effector cell presence

Mab blockade effect is systemic and long-lived and results in peripheral autoimmune toxicity

Short half-life and activity only on high CTLA-4 expressing Tregs in TME to avoid peripheral irAEs

MT-8421 Phase I Study initiated in 4Q23

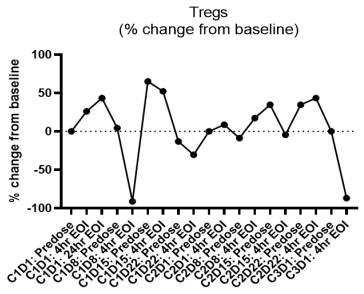
- **Phase I FIH dose-escalation study to explore safety and efficacy with MT-8421 as monotherapy in rel/ref solid tumors**
  - Melanoma, hepatocellular carcinoma, non-small cell lung cancer, renal cell carcinoma, MSI-H/Dmmr cancer, mesothelioma, esophageal squamous cell carcinoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, and cervical carcinoma
- **First cohort completed at 32 mcg/kg with patients enrolled**
  - Gr 2 IRR and Gr 1 rash were only drug-related toxicities noted; Gr 1 rash is suggestive of PD effect
  - Notable lymphocyte changes and cytokine elevations observed
  - Two patients with stable disease at end of cycle 2; one patient with progressive disease
- **Second cohort (48 mcg/kg) now enrolling**

Pts 1002-001 and 1002-003 (SD at C4 and C2, on study) vs Pt 1003-001 (PD at C2, off study)

Checkpoint break signature and effector T-cell phenotype mediated by MOA independent of effector cells

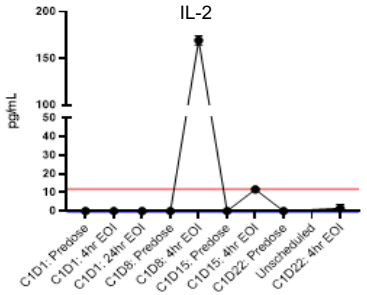
Pt 1002-001 (SD at C2, on study)

Lymphocyte Profile



Tregs eliminated from periphery

Cytokine Profile

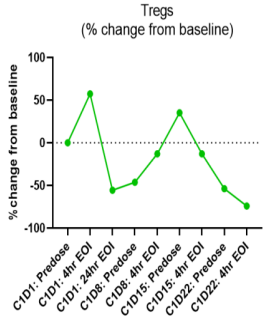


Large spike in IL-2 after 2nd dose

63 y/o male with cutaneous melanoma with metastases to the thoracic lymph node and bone. Disease progression on Ipi+Nivo.

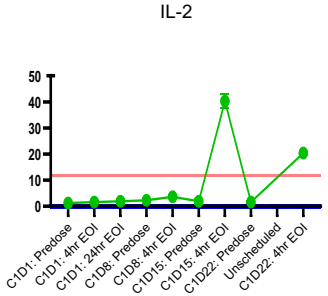
Pt 1002-003 (SD at C2, on study)

Lymphocyte Profile



T-reg depletion into 4th dose

Cytokine Profile

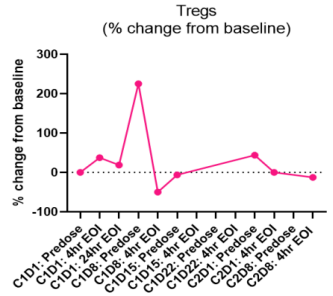


Large increase in NK cell population

43 y/o female pt with melanoma metastatic to lung, bones, and multiple LNs. Received adjuvant pembro, Ipi/ Nivo for metastatic disease and TAK-573 experimental tx

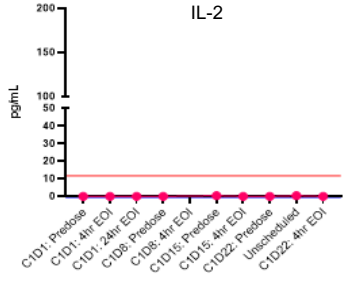
Pt 1003-001 (PD at C2, off study)

Lymphocyte Profile



No major change in Tregs

Cytokine Profile



No elevation in IL-2

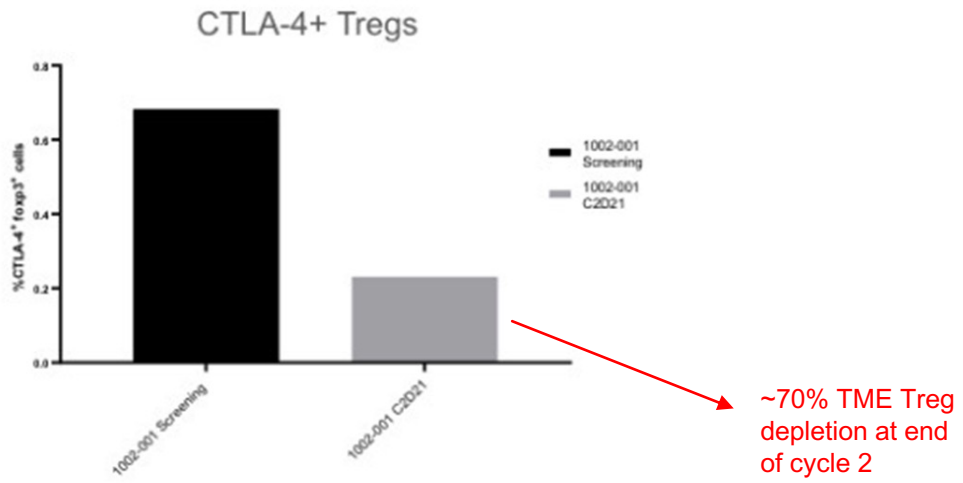
64 y/o male w/ NSCLC and multiple liver mets. Disease progression after chemotherapy with Pembro and Pembro maintenance therapy. PD on experimental therapy.

- Treg depletion and IL-2 spikes not seen with Ipilimumab

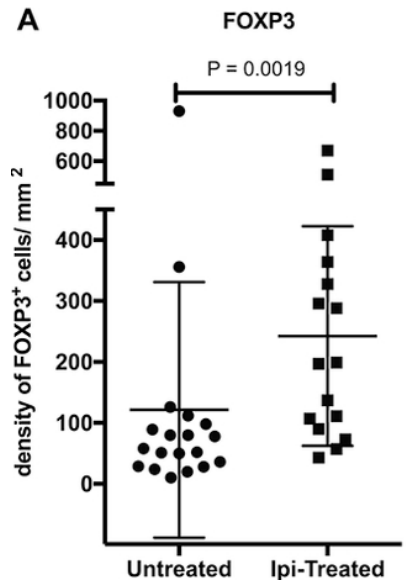
Pt 1002-001 (SD at C4): Treg depletion in the TME

One pt 1002-001) was eligible for pre- and post-treatment tumor biopsies; strong evidence of Treg depletion

Pt 1002-001 (SD at C4, on study)



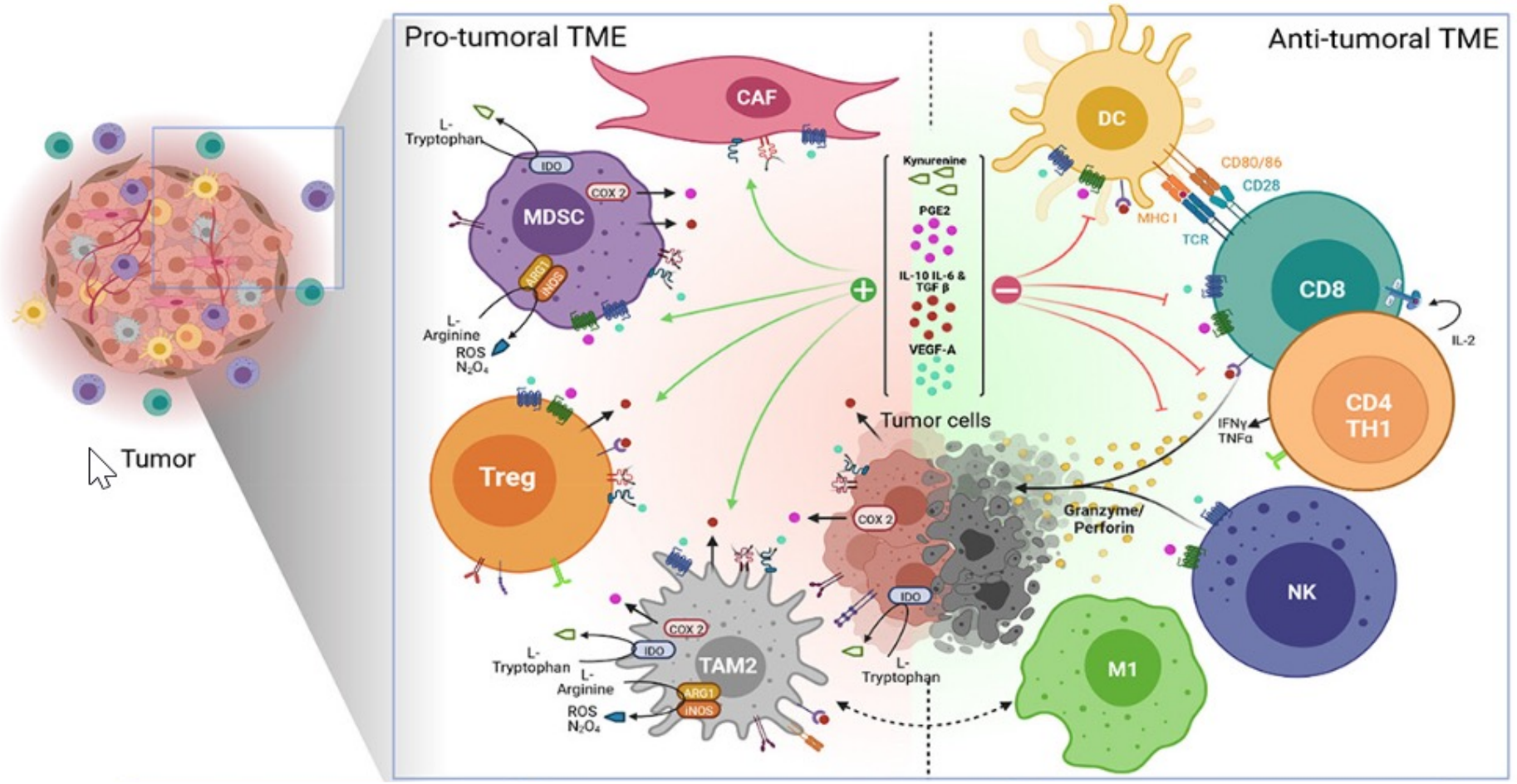
63 y/o male with cutaneous melanoma with metastases to the thoracic lymph node and bone. Disease progression on Ipi+Nivo.



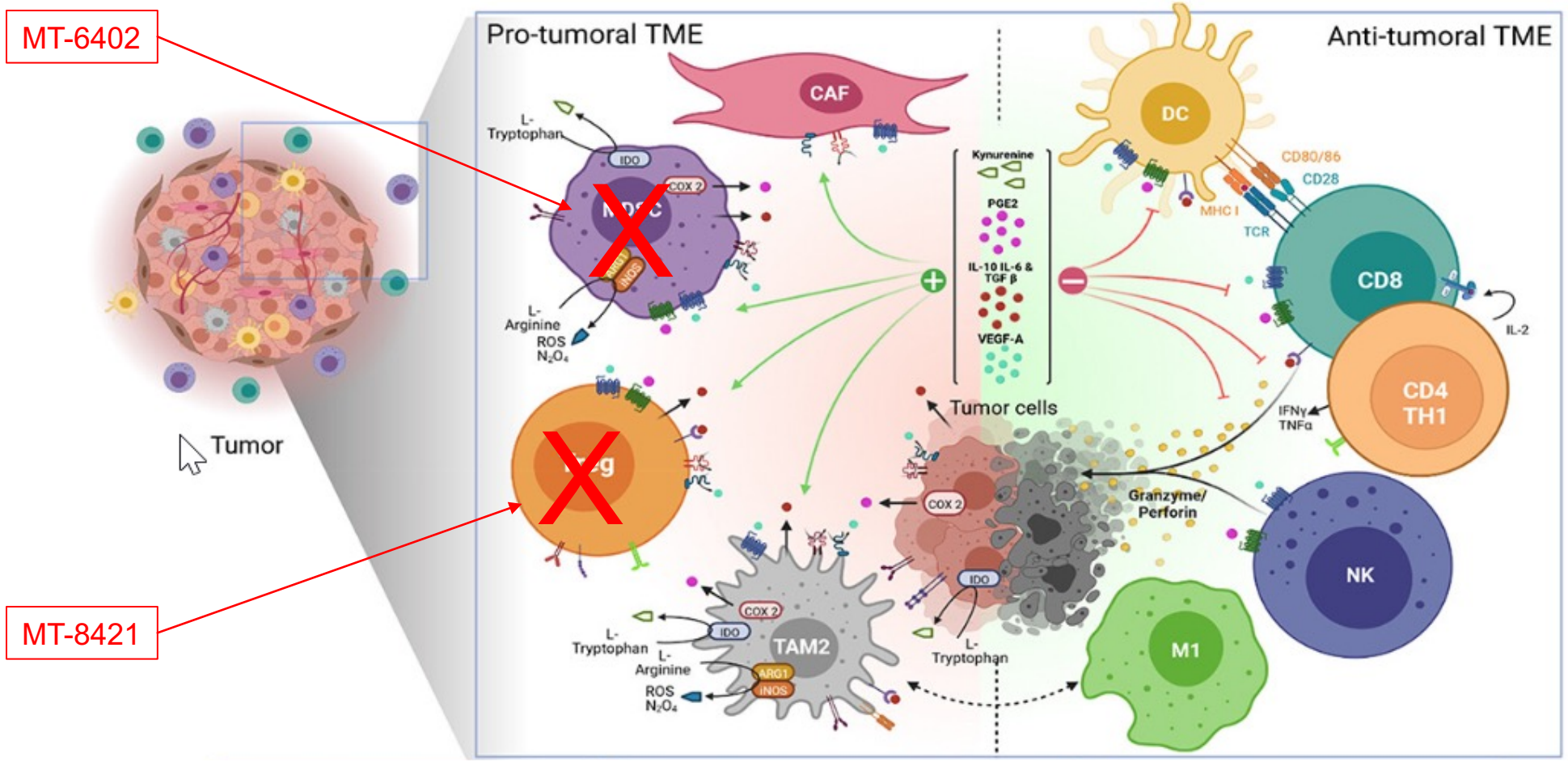
Treg depletion in the TME not seen with Ipilimumab

Sharma et al, *Clin Can Res*, 2019.

Tregs and MDSCs drive TME immunosuppression



Tregs and MDSCs drive TME immunosuppression: MT-6402 and MT-8421 can eliminate these cells



Novel mechanisms of action with focus on validated targets create new axes for pipeline differentiation

	Target	Stage and Timeline	Differentiated MOA and Product Profile
MT-6402	**PD-L1**	Phase 1 Ongoing	• Depletion of PD-L1+ immunosuppressive immune cells and PD-L1+ tumor cells • Delivery of CMV antigen to alter immunophenotype to redirect antigen specific T-cells to tumor (Antigen Seeding)
MT-8421	**CTLA-4**	Phase 1 Ongoing	• Depletion of Tregs via enzymatic direct-cell kill to dismantle TME • No peripheral blockade effect to enhance tolerability
MT-0169	**CD38**	Phase 1 Ongoing	• Clearance of CD38 expressing cells via novel MOA of enzymatic direct cell kill

Substantial clinical data expected throughout the next 12 months from 3 open-label studies