CTA-directed TCR-T: serious events and clinical evidence

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Clinical experience can modestly relax the RNA screen. It cannot clear every peptide, isoform or receptor from the parent protein.

Grant one existing RNA ladder step for a reviewed treated TCR-T cohort without an identified grade 4-5 specificity-related signal. Cap at Enhanced-negative. Preserve normal-protein and clinical-injury exclusions. Trial registration and unknown reporting do not qualify.

SAE seriousness is different from CTCAE severity. The following pages include fatal, serious and important severe events; this is a targeted review, not an exhaustive SAE list or pooled incidence estimate.

Clinical-adjusted RNA ceilings

Tier	Baseline IHC ladder	With clinical credit
Vital	4 / 8 / 16 / 32	8 / 16 / 32 / 32
Protected	8 / 16 / 32 / 64	16 / 32 / 64 / 64
Manageable	16 / 32 / 64 / 128	32 / 64 / 128 / 128

Columns follow missing/unusable, Approved-negative, Supported-negative and Enhanced-negative IHC. Native TPM/nTPM retain nominal policy values; corneal CP10K uses its existing /100 policy. These are not measured clinical toxicity limits.

CTAG2 / LAGE-1A

CTAG2 already passes the current screen. LAGE-1A shares SLLMWITQC with NY-ESO-1, recognized by c259 in lete-cel. HPA v23 heart RNA is 5.1 nTPM; Enhanced-negative IHC already gives the capped 32 nTPM ceiling. Other CTAG2 isoforms and peptides are not clinically cleared.

Letetresgene autoleucel / NY-ESO-1 c259

CTAG1A: CTA; CTAG1B: CTA; CTAG2: CTA

Peptide(s): SLLMWITQC
HLA-A*02:01; HLA-A*02:05; HLA-A*02:06

RNA credit: One step, capped

20 treated: Advanced/metastatic myxoid/round cell liposarcoma

No grade 4-5 event was attributed to peptide-specific recognition of normal tissue. Grade 4 cytopenias occurred; one late cardiac death remained potentially treatment-related without an established specificity mechanism.

This is a curation conclusion about reported attribution, not an author-reported zero-event rate or proof of safety.

Letetresgene Autoleucel in Advanced/Metastatic Myxoid/Round Cell Liposarcoma

Fatal cardiac arrest, day 161

1 patient(s); grade 5. Treatment: potentially related. Specificity: not established.

Progressive disease, hypotension, renal insufficiency and intervening radiation/pazopanib complicate attribution. The report does not establish CTAG2-mediated heart injury.

Primary event source

Guillain-Barre / inflammatory demyelinating neuropathy

2 patient(s); grade unreported. Treatment: suspected. Specificity: not established.

Authors suspected treatment association and discussed indirect immune effects. No identified peptide cross-reaction explains the cases. Case reports have no independent treated-cohort denominator and confer no favorable credit.

Primary event source

IMA203

PRAME: CTA

Peptide(s): SLLQHLIGL
HLA-A*02:01

RNA credit: One step, capped

40 treated: PRAME-positive advanced solid tumors

No treatment-related deaths after IMA203 infusion were reported. Severe cytopenias and CRS occurred; no clinical renal toxicity was seen despite weak reactivity in one in-vitro renal donor.

Normal peptide non-detection is assay-limited; this does not clear all PRAME peptides.

Autologous T cell therapy for PRAME+ advanced solid tumors in HLA-A*02+ patients: a phase 1 trial

Grade 4 transaminitis during a grade 3 CRS episode

1 patient(s); grade 4. Treatment: related. Specificity: not established.

Recorded as part of CRS, without evidence that the TCR recognized PRAME in hepatocytes.

Primary event source

Afamitresgene autoleucel / c1032

MAGEA4: CTA

Peptide(s): GVYDGREHTV
HLA-A*02:01; HLA-A*02:02; HLA-A*02:03; HLA-A*02:06

RNA credit: One step, capped

38 treated: MAGE-A4-positive advanced solid tumors

Two possibly treatment-related deaths occurred: aplastic anemia and ischemic stroke. Marrow evaluation did not support MAGE-A4-directed injury; high-dose conditioning and inflammation were considered contributors.

The fatal stroke has no demonstrated specificity mechanism; neither death is relabelled unrelated.

Autologous T cell therapy for MAGE-A4+ solid cancers in HLA-A*02+ patients: a phase 1 trial

52 treated: Synovial sarcoma or myxoid/round cell liposarcoma

No grade 5 adverse events or treatment-related deaths were reported; severe cytopenias and mostly low-grade CRS remained important regimen toxicities.

No identified specificity event in this selected cohort does not establish a population-wide zero risk.

SPEARHEAD-1: a single-arm phase 2 trial of afamitresgene autoleucel in advanced synovial sarcoma and myxoid/round cell liposarcoma

Fatal aplastic anemia, day 55

1 patient(s); grade 5. Treatment: possibly related. Specificity: not supported.

No marrow MAGE-A4 or enrichment of engineered T cells was detected; conditioning and systemic inflammation were considered contributors.

Primary event source

Fatal ischemic cerebrovascular accident, day 17

1 patient(s); grade 5. Treatment: possibly related. Specificity: not established.

Occurred after grade 3 neurotoxicity; no demonstrated MAGE-A4-specific brain injury mechanism was reported.

Primary event source

MAGE-A3 affinity-enhanced a3a receptor

MAGEA3: Unsafe

Peptide(s): EVDPIGHLY
HLA-A*01:01

RNA credit: None

2 treated: One melanoma and one multiple myeloma patient

Fatal cardiac injury was attributed to T-cell cross-recognition, with titin identified as the likely unintended antigen.

The finding blocks credit for this receptor; it does not prove that MAGE-A3 protein was present in heart or that every MAGE-A3 receptor is unsafe.

Identification of a Titin-Derived HLA-A1-Presented Peptide as a Cross-Reactive Target for Engineered MAGE A3-Directed T Cells

Fatal cardiac injury with titin cross-recognition

2 patient(s); grade 5. Treatment: related. Specificity: suspected.

Mechanistic work identified titin as the likely unintended target; MAGE antigens were not detected in patient heart samples.

Primary event source

IMA202

MAGEA1: CTA

Peptide(s): KVLEYVIKV
HLA-A*02:01

RNA credit: One step, capped

16 treated: MAGE-A1-positive advanced solid tumors

Severe cytopenias and one grade 3 CRS occurred. No on-target/off-tumor toxicity was observed; fatal dyspnea was considered unrelated.

The primary paper header lists other MAGEA1 trials; IMA202-101 identity is independently linked by the Columbia trial listing. No objective RECIST responses were required for this safety-only credit.

First-in-human dose escalation trial to evaluate the clinical safety and efficacy of an anti-MAGEA1 autologous TCR-transgenic T cell therapy in relapsed and refractory solid tumors

Fatal dyspnea

1 patient(s); grade 5. Treatment: unrelated. Specificity: not supported.

Investigators considered this death unrelated to treatment; severe conditioning cytopenias and grade 3 CRS occurred in the cohort.

Primary event source

ADP-A2M10 / MAGE-A10 c796

MAGEA10: CTA

Peptide(s): GLYDGMEHL
HLA-A*02:01; HLA-A*02:06

RNA credit: One step, capped

11 treated: Advanced non-small cell lung cancer

One grade 4 CRS and one treatment-related death after repeat infusion/intensified conditioning. Investigations favored conditioning over MAGE-A10-mediated marrow injury.

Patient marrow antigen testing was limited by specimen quality; absence of engineered-cell enrichment does not prove no risk.

Phase I clinical trial evaluating the safety and efficacy of ADP-A2M10 SPEAR T cells in patients with MAGE-A10+ advanced non-small cell lung cancer

Grade 4 CRS

1 patient(s); grade 4. Treatment: related. Specificity: not established.

Required intensive supportive care; symptoms resolved. The subsequent death of this patient was attributed to disease progression.

Primary event source

Fatal marrow aplasia, sepsis and respiratory distress after repeat infusion

1 patient(s); grade 5. Treatment: related. Specificity: not supported.

Authors favored intensified lymphodepletion; patient marrow antigen testing was limited. Fatality was 98 days after the second infusion.

Primary event source

TBI-1301

CTAG1A: CTA; CTAG1B: CTA; CTAG2: CTA

Peptide(s): SLLMWITQC
HLA-A*02:01; HLA-A*02:06

RNA credit: None

9 treated: NY-ESO-1-positive advanced solid tumors

One grade 3 lung injury with TCR-T infiltration; resolved with steroids. Authors favored cytokine-mediated capillary leak but could not exclude normal-peptide recognition.

Retain unresolved specificity as a review hold for this product; do not borrow favorable c259 evidence to clear TBI-1301.

NY-ESO-1-specific redirected T cells with endogenous TCR knockdown mediate tumor response and cytokine release syndrome

Steroid-responsive lung injury with TCR-T infiltration

1 patient(s); grade 3. Treatment: related. Specificity: unresolved.

Cytokine-mediated capillary leak was favored, but normal-peptide recognition remained a possibility. Below grade 4 does not mean clinically irrelevant.

Primary event source

NCI HLA-A*02-restricted MAGE-A3/A9/A12-reactive TCR

MAGEA3: Unsafe; MAGEA9: CTA; MAGEA12: Unsafe; MAGEA9B: CTA

Peptide(s): KMAELVHFL; KVAELVHFL
HLA-A*02:01

RNA credit: None

9 treated: Advanced cancers

Two deaths among three neurological cases in nine treated patients. The original MAGE-A12 attribution is challenged by later EPS8L2 cross-reactivity evidence; neither is established as the unique clinical cause. Severe product-specific injury remains a block on favorable credit.

Brain staining recognized multiple MAGE-family proteins; MAGE-A12 attribution is supported but not uniquely proven.

Cancer regression and neurological toxicity following anti-MAGE-A3 TCR gene therapy

Fatal neurological injury after MAGE-A3/A9/A12-reactive TCR; causal peptide unresolved

2 patient(s); grade 5. Treatment: related. Specificity: suspected.

Two deaths among three neurological cases in nine treated patients. The original MAGE-A12 attribution is challenged by later EPS8L2 cross-reactivity evidence; neither is established as the unique clinical cause. Severe product-specific injury remains a block on favorable credit.

Primary event source