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# First-in-human trial in patients with metastatic colorectal cancer using CRISPR-engineered tumor infiltrating lymphocytes in which the intracellular immune checkpoint *CISH* is inhibited

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# Disclosure Information

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## Emil Lou MD, PhD

I have the following relevant financial relationships to disclose:

| | |
|---|---|
| **Employee of:** | University of Minnesota-Twin Cities |
| **Consultant for:** | Elsevier Publishing, Johns Hopkins Press, Colorectal Cancer Alliance, Primum, Myer Research |
| **Advisory Boards** | Minnesota Colorectal Cancer Research Fund & Colon Cancer Coalition (volunteer) |
| **Speaker's Bureau for:** | None |
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# Key Points

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- Immune checkpoint inhibition and T cell-based therapies have not yet been shown to induce consistent and durable tumor regression in common metastatic solid epithelial malignancies
- CISH (Cytokine inducible SH2 containing protein) is a novel intracellular checkpoint target demonstrating tumor-type agnostic, PD-L1 ligand independent mechanisms of enhanced anti-cancer activity
- Given that CISH is classically undruggable, we employed gene and cell therapy as a model system to evaluate the potential safety and efficacy of inhibiting this novel checkpoint
- We treated 12 patients with metastatic treatment-refractory gastrointestinal cancers using *CISH* Knockout TILs (NCT04426669)
- Half of these patients with metastatic colorectal cancer (mCRC) refractory to multiple lines of therapy achieved stable disease.
- A clinical complete response (cCR) was achieved in a young-adult patient with early-onset metastatic colorectal cancer refractory to multiple lines of therapy, including checkpoint inhibitor/combination immunotherapies.

THE LANCET Oncology

E Lou, MS Choudhry, et al. *The Lancet Oncology*, online publication today

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# CISH is a novel ligand-independent intracellular checkpoint not targetable by cell surface blockade

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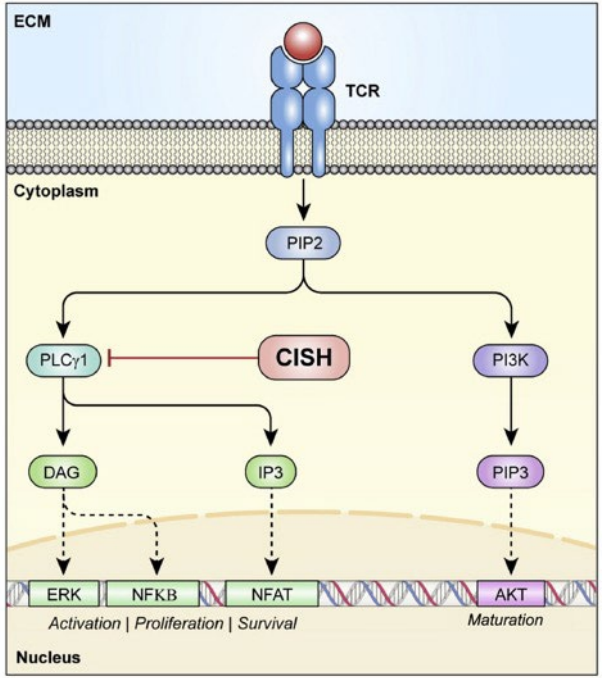
- In 2022, researchers from the National Cancer Institute and University of Minnesota reported a key role for the cytokine-induced SH2 protein (CISH) in regulating human T cell function and reactivity to neoantigens.
- CISH is associated with non-functional tumor-infiltrating lymphocytes (TIL)
- CISH KO uncovered TIL neoantigen reactivity
- CISH KO induced hyper-activation but not hyper-maturation
- Cish KO synergized with PD1 blockade *in vivo*




Palmer, Webber…Rosenberg, Moriarity, Restifo. Internal checkpoint regulates T cell neoantigen reactivity and susceptibility to PD1 blockade. *Med*, Oct 2022

# CISH Clinical Trial
# Genetically Modified Cell Therapy

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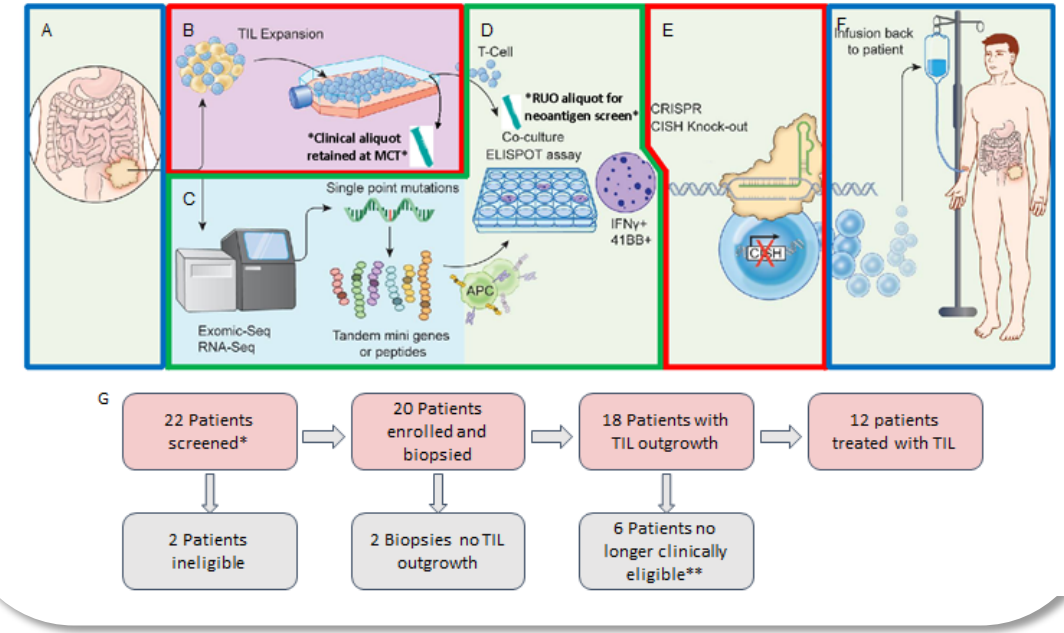
- Tumors were surgically resected for TIL harvest, followed by a rapid expansion protocol and CRISPR/Cas9 knockout (KO) *CISH*
- CISH KO, neoantigen-reactive TILs were expanded, then infused following non-myeloablative lymphocyte depleting (LD) chemotherapy (cyclophosphamide & fludarabine) followed by high-dose IL-2



# Progression-free and overall survival in treated patients

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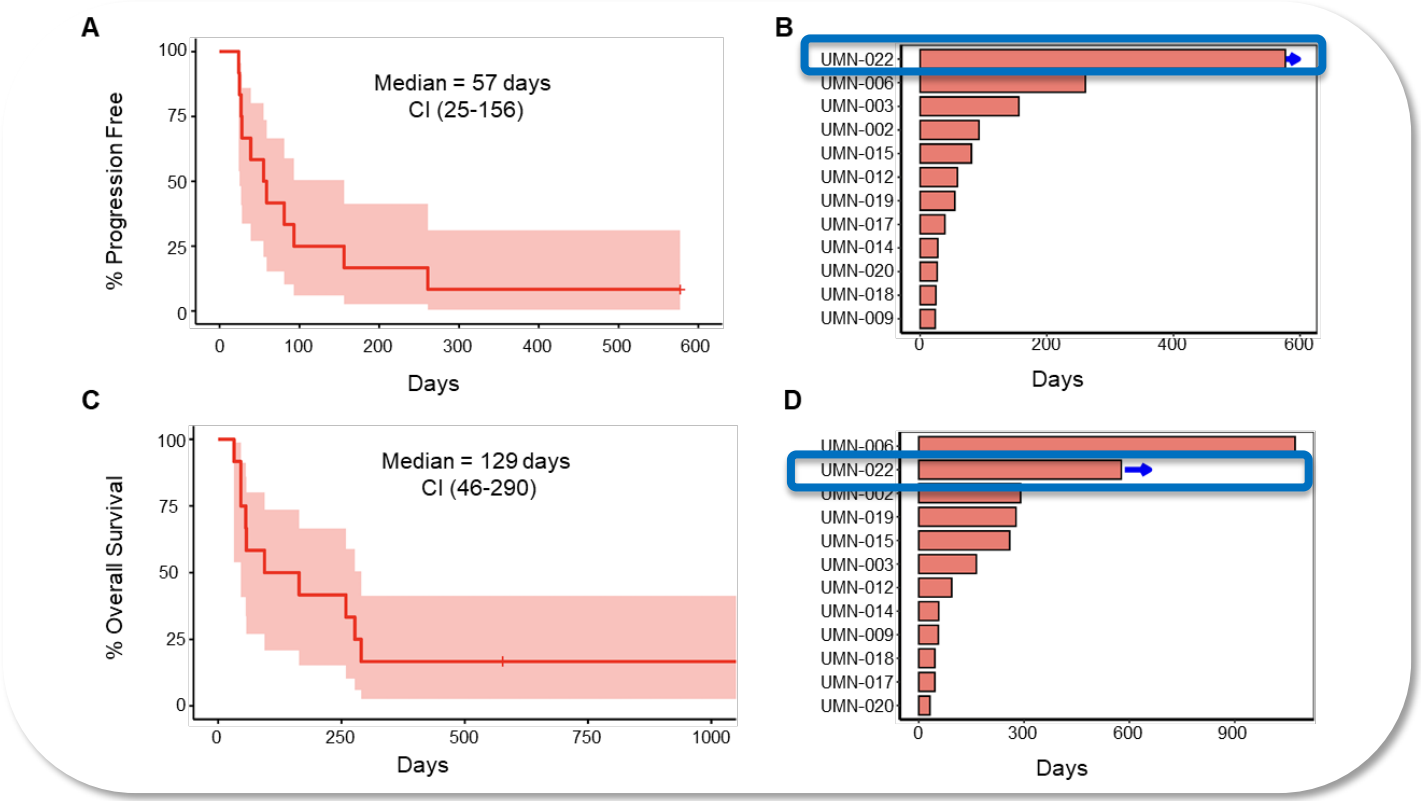

# Durable clinical complete response in young adult patient with CRC refractory to immunotherapy

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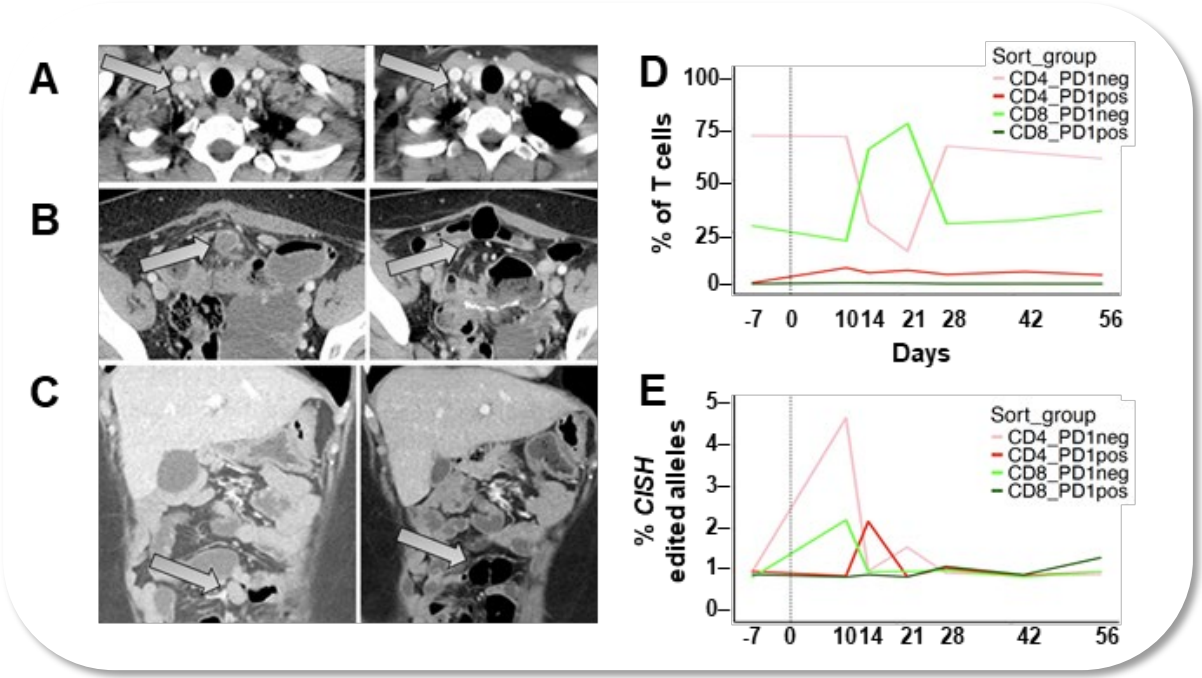
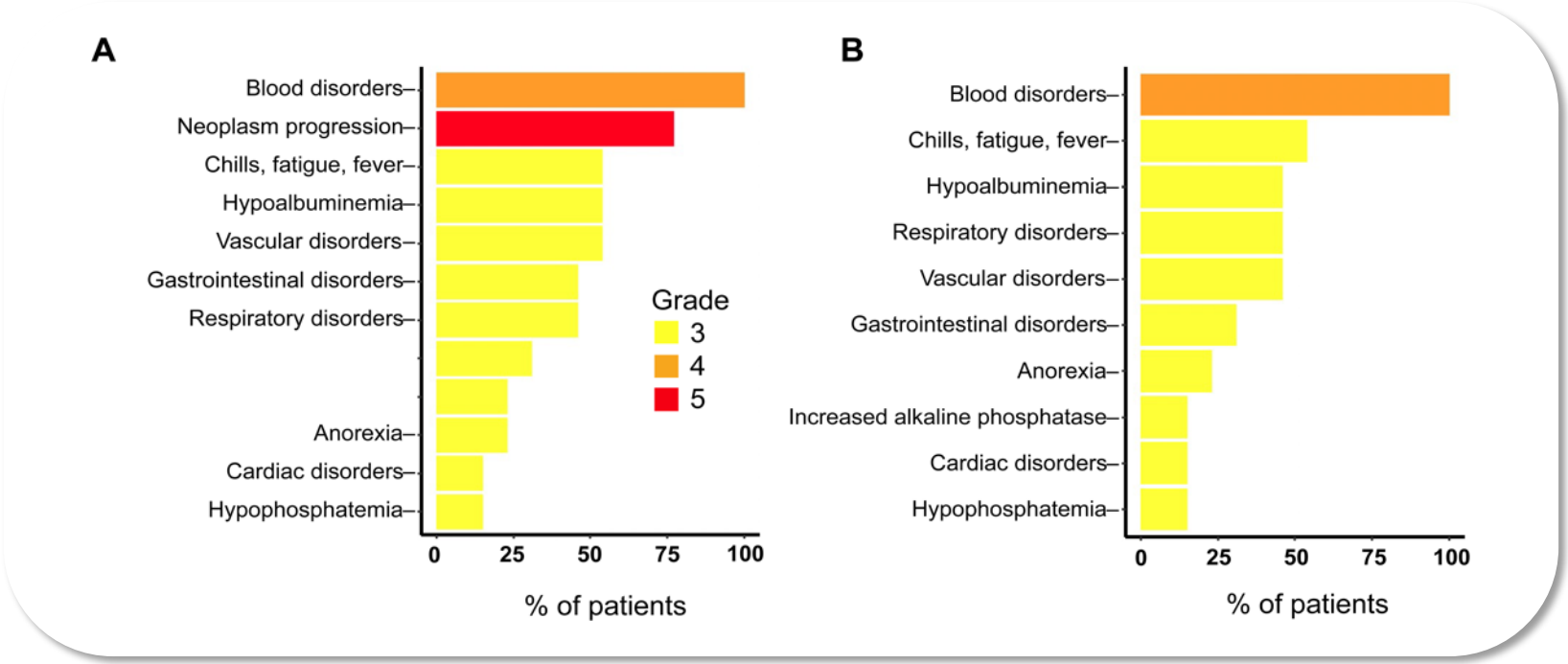
**A durable ongoing complete response (>24 months) was achieved in a patient with microsatellite instability-high (MSI-H) mCRC refractory to chemotherapies and anti-PD1/CTLA-4 combination therapy**



# Adverse events principally stemmed from expected side effects of LD chemotherapy and IL-2





# Attribution of Complete Response to CISH: TIL persistence and TCR repertoire demonstrate KO of CISH

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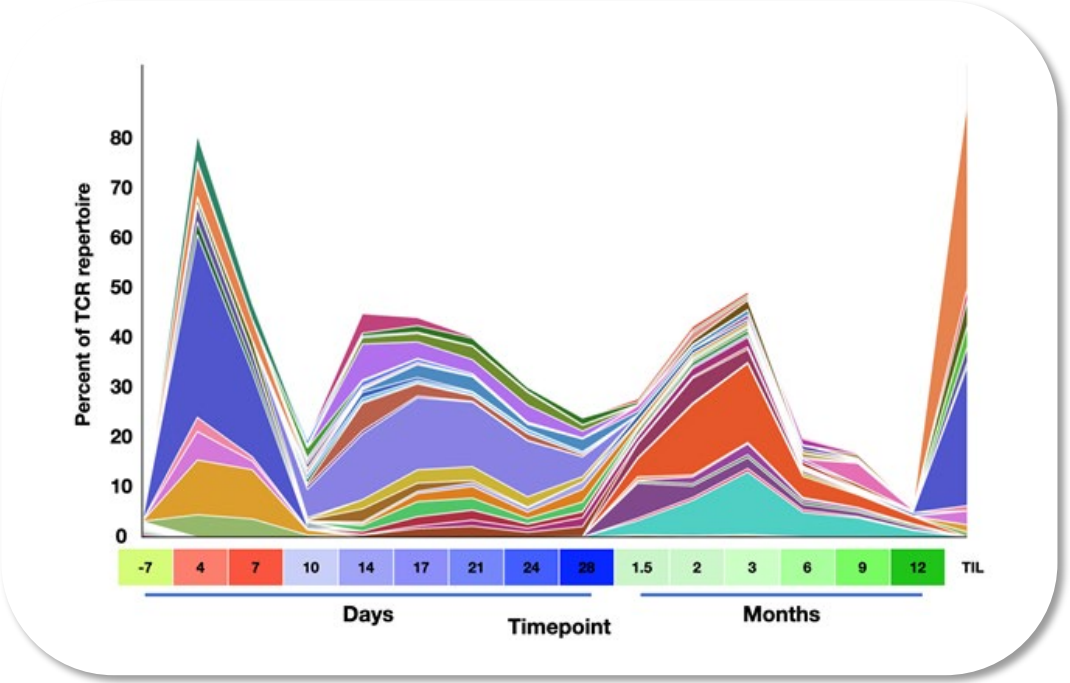
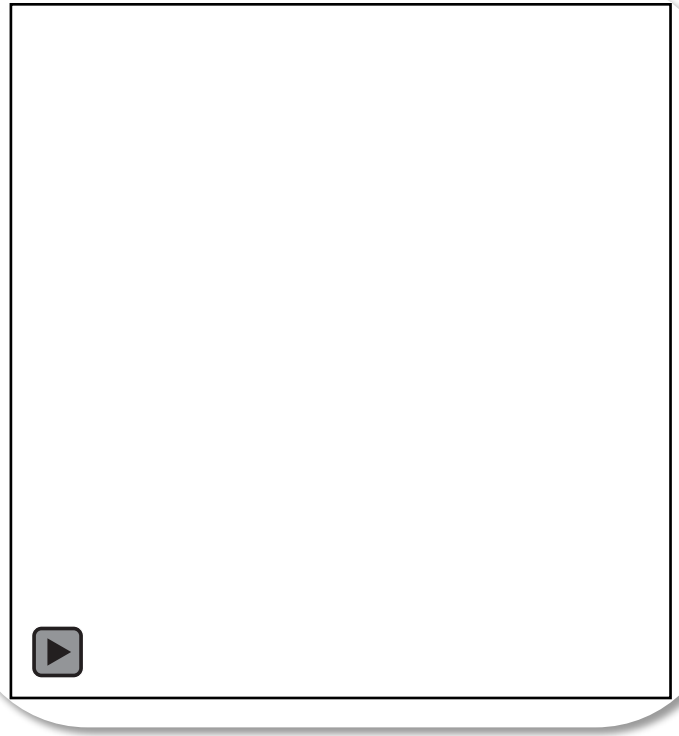
- Persistence and expansion of unique TCR clonotypes detected in neoantigen responsive TIL were temporally consistent with spikes in *CISH* edited alleles detected by NGS assay
- In the patient with Complete Response, four of the clonotypes exhibiting prolonged persistence greater than one-year post-infusion exhibited significantly reduced or undetectable expression of *CISH* compared to the total infused TIL population



# CISH Small Molecule Immune Checkpoint Inhibitor



- These clinical data demonstrating the potential safety and efficacy of the CISH immune checkpoint
- Genetically modified cell therapy provides a robust demonstration of the theoretical PD of CISH biology
- By further improving the theoretical PK or drugability of CISH, we can democratize patient access to a potential next-generation checkpoint inhibitor
- Advanced next-generation small molecule drugging strategies to CISH are well underway



# Conclusions

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- CRISPR engineering led to KO of *CISH* in T cells with high-efficiency (>90%) without detectable off-target editing
- We safely dosed patients at all five dose levels (range: $1.91e^{8}$ to $9.93e^{10}$ cells)
- No dose-limiting toxicities attributable to the *CISH*-KO TIL product were observed
- Adverse events were consistent with established risks of LD chemotherapy, IL-2, or disease progression
- A durable ongoing complete response (>24 months) was achieved in a patient with microsatellite instability-high (MSI-H) mCRC refractory to anti-PD1/CTLA-4 combination therapy, which appears consistent with CISH checkpoint biology
- Given these data and clinical proof-of-concept, next-generation small molecule drugging modalities to inhibit the CISH checkpoint are actively underway

# Acknowledgements & Thank You

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