



XIX CONGRESSO
NAZIONALE
SIES 2026

Targeting Glutamine Metabolism Potentiates T Cell Engager-mediated Immunotherapy in Multiple Myeloma

Vincenzo Raimondi

Firenze | 4-6 marzo 2026
Palazzo degli Affari

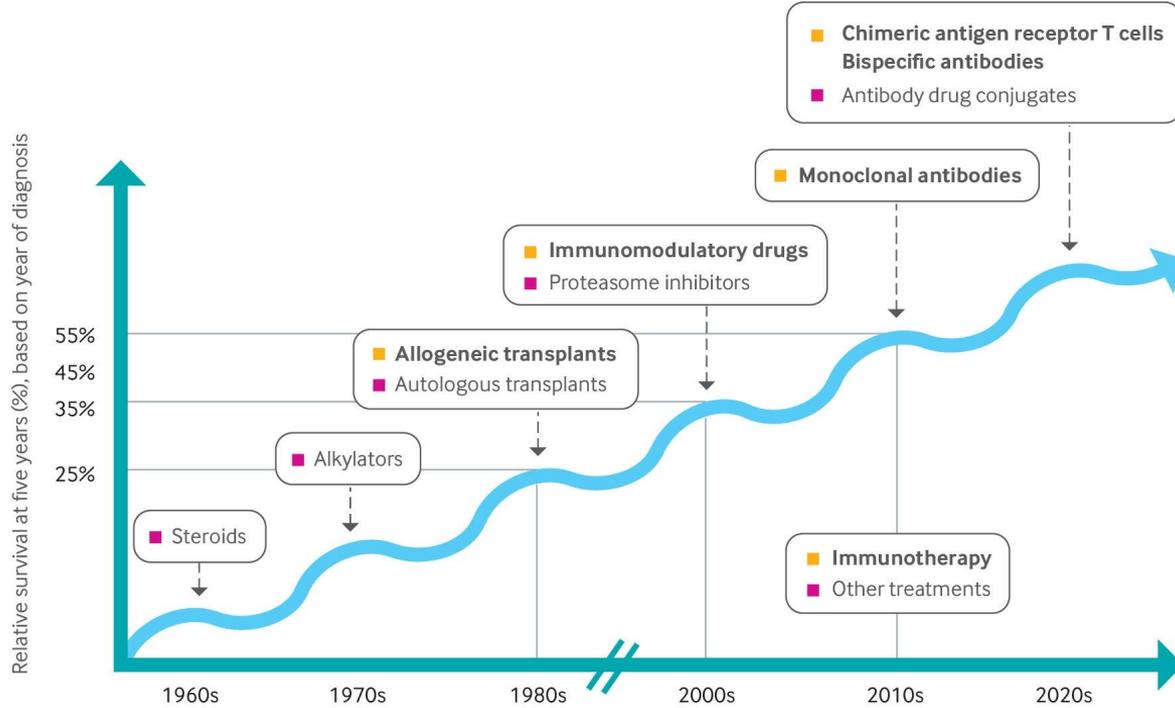


Disclosures of Vincenzo Raimondi

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other



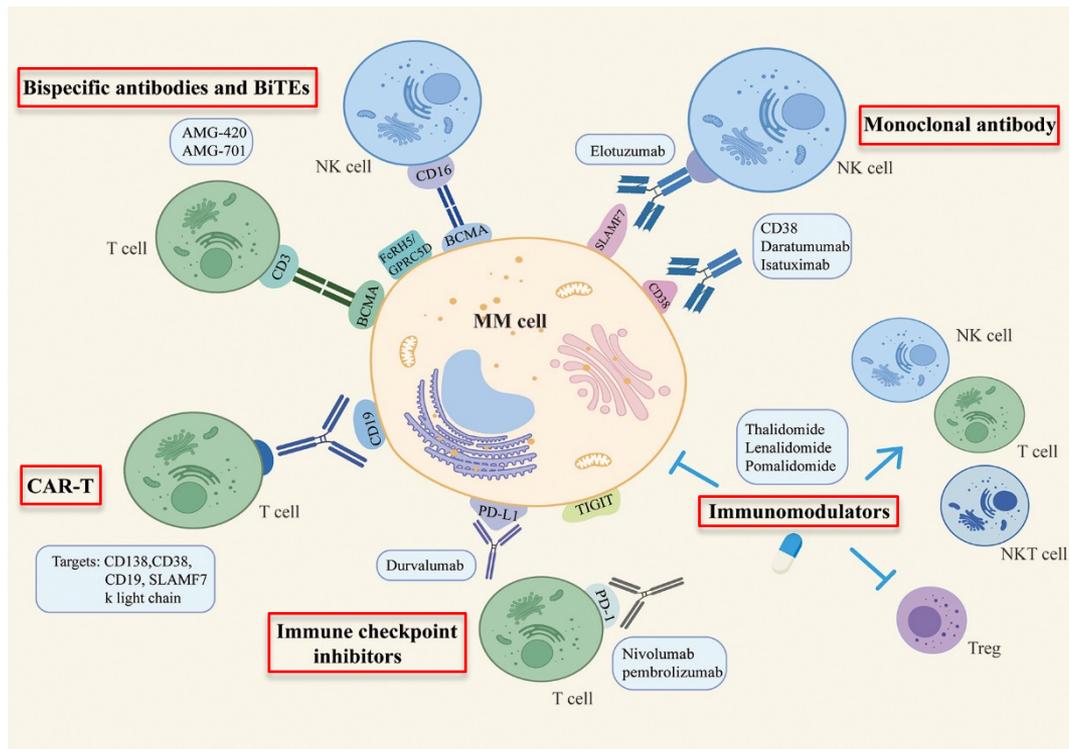
THERAPEUTIC MILESTONES AND SURVIVAL ADVANCES IN MULTIPLE MYELOMA (MM)



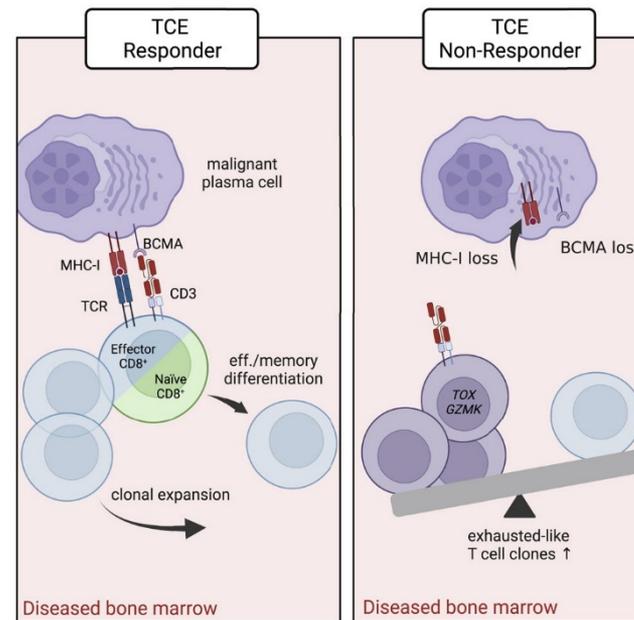
Timeline of drug discovery and year of multiple myeloma diagnosis (by decade)

Shah UA, and Mailankody S. *Bmj* 370 (2020).

IMMUNOTHERAPY IN MM: MECHANISMS AND RESISTANCE



Liu Z, et al. 14 (2023): 1169541.



Friedrich MJ, et al. *Cancer cell* 41.4 (2023): 711-725.

METABOLIC REPROGRAMMING SUSTAINS MM CELL GROWTH

- Metabolic reprogramming is a hallmark of cancer.^{1,2}
- MM cells rewire their metabolism to sustain anabolic growth and to adapt to the tumor

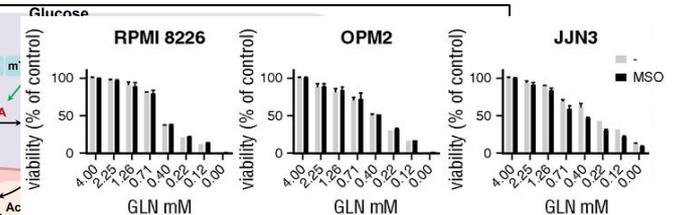
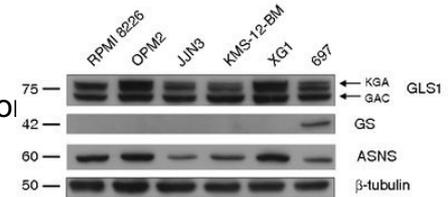
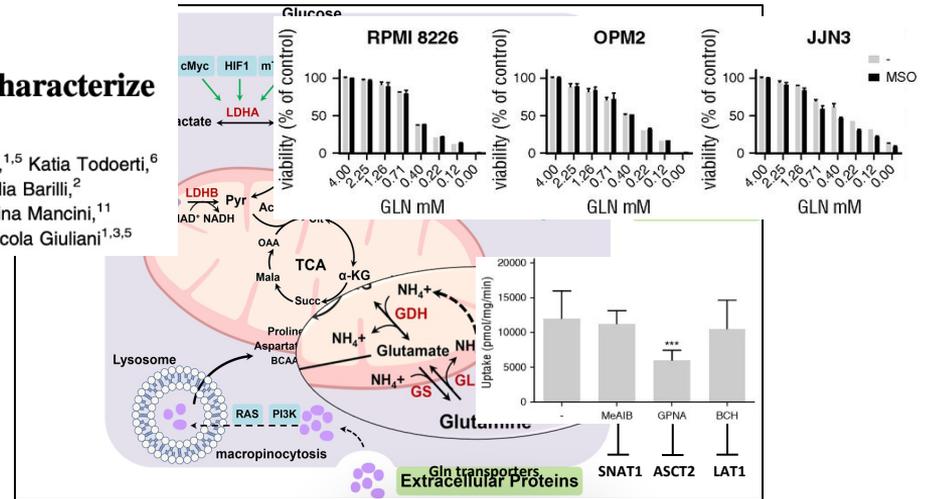
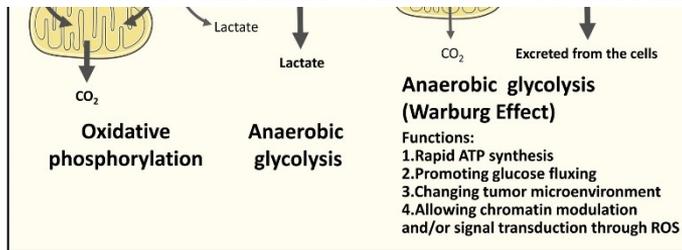
Regular Article



LYMPHOID NEOPLASIA

Dependence on glutamine uptake and glutamine addiction characterize myeloma cells: a new attractive target

Marina Bolzoni,^{1,*} Martina Chiu,^{2,*} Fabrizio Accardi,^{1,3,*} Rosanna Vescovini,¹ Irma Airoidi,⁴ Paola Storti,^{1,5} Katia Todoerti,⁶ Luca Agnelli,⁷ Gabriele Missale,⁸ Roberta Andreoli,⁹ Massimiliano G. Bianchi,^{2,9} Manfredi Allegri,² Amelia Barilli,² Francesco Nicolini,¹⁰ Albertina Cavalli,⁸ Federica Costa,¹ Valentina Marchica,^{1,5} Denise Toscani,¹ Cristina Mancini,¹¹ Eugenia Martella,¹¹ Valeria Dall'Asta,² Gaetano Donofrio,¹² Franco Aversa,^{1,3} Ovidio Bussolati,² and Nicola Giuliani^{1,3,5}



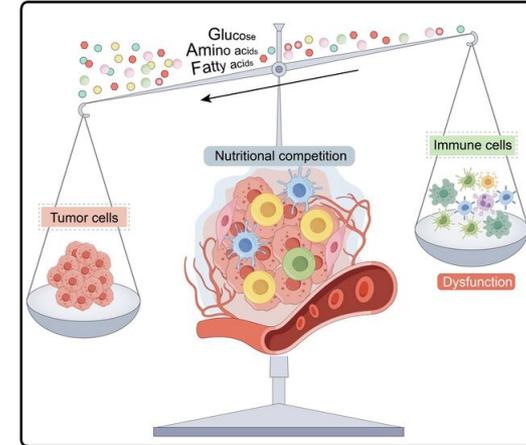
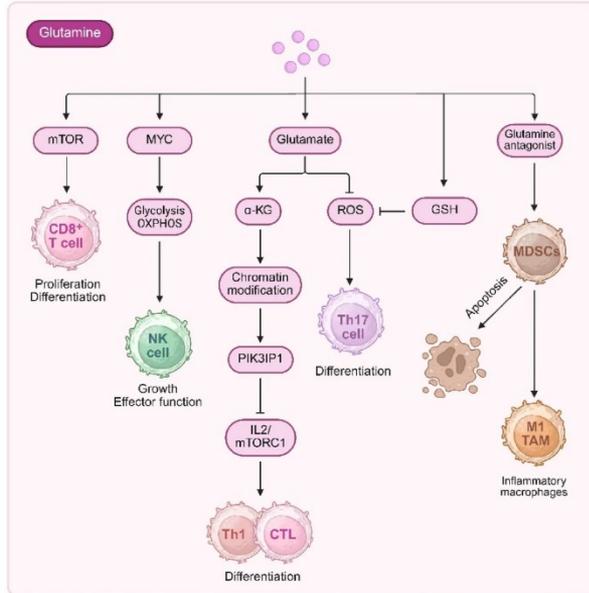
GLS: Glutaminase
 GS: Glutamine synthetase

¹Hanahan D. and Weinberg R.A. Cell 2011

²Vander Heiden M. G. et al. Science 2009

METABOLIC COMPETITION FOR GLUTAMINE IN THE TUMOR MICROENVIRONMENT (TME)

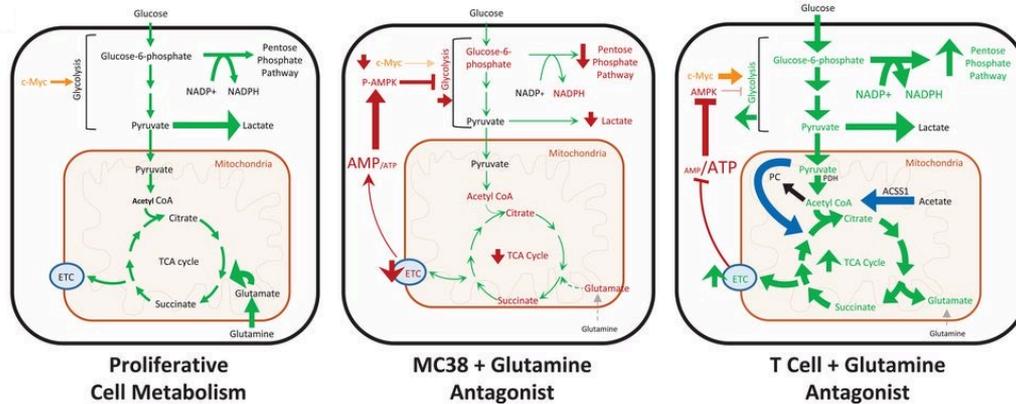
MM cells reprogram glutamine (Gln, Q) metabolism, generating competition in the TME that limits its availability for T cells.¹



Excessive glutamine uptake by cancer cells may interfere with optimal T cell responses, as T cells require glutamine-derived carbon and nitrogen to sustain anabolic metabolism upon activation.²

¹Dang, Q., et al. *Molecular Cancer* 23.1 (2024): 72.
²Zhang, H., et al. *Molecular Cancer* 24.1 (2025): 249.

REWIRING GLN METABOLISM CAN ENHANCE ANTI-TUMOR T-CELL FUNCTION



Cancer cells are highly sensitive to glutamine (Gln) blockade, whereas T cells exhibit metabolic plasticity and can shift between Gln and glucose metabolism to retain anti-tumor function.^{1,2}

In other tumor models, inhibition of Gln metabolism (e.g., with the glutaminase inhibitor CB-839) has been shown to enhance CD8⁺ T-cell activity and improve immunotherapy responses.³⁻⁵

In MM, metabolic reprogramming of CAR T cells via ASCT2 overexpression enhanced anti-MM activity.⁶

This evidence highlights a potentially important immunoregulatory metabolic axis in the TME.

¹Nan D., et al. *Cell Communication and Signaling* 23.1 (2025): 45.

²Giles, J.R., et al. *Immunity* 56.10 (2023): 2231-2253.

³Edwards D.N., et al. *The Journal of Clinical Investigation* 131.4 (2021).

⁴Leone R.D., et al. *Science* 366.6468 (2019): 1013-1021.

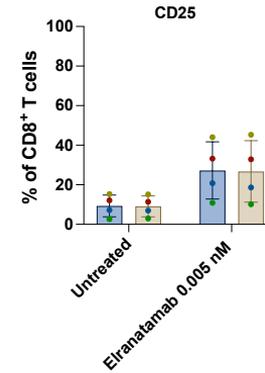
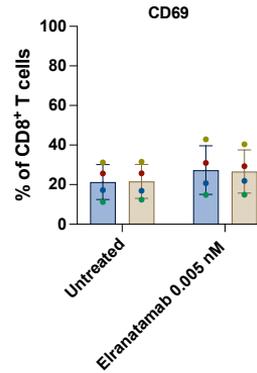
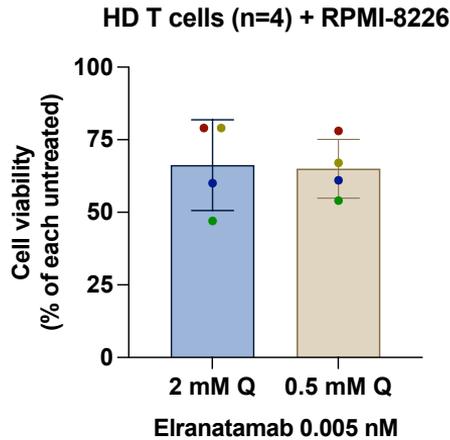
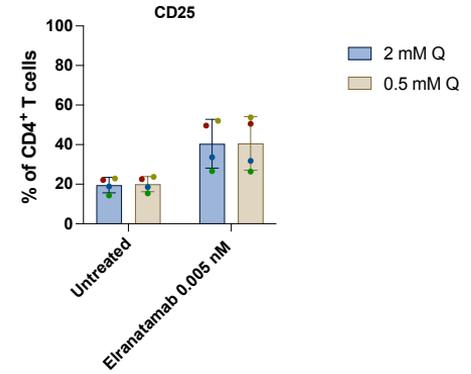
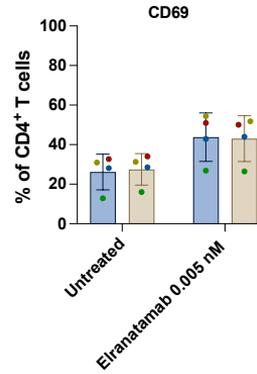
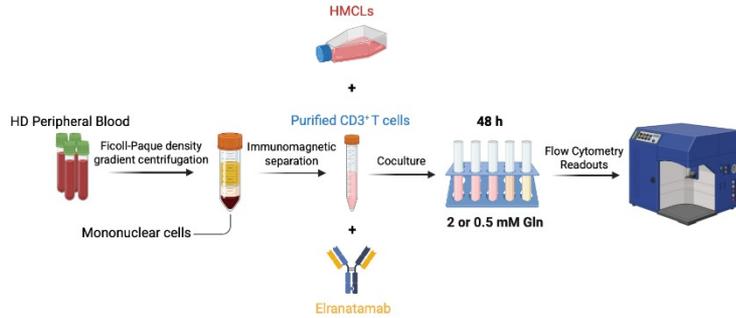
⁵Varghese S., et al. *Molecular cancer therapeutics* 20.3 (2021): 500-511.

⁶Navarro, Flor, et al. *Blood* 146.24 (2025): 2931-2944.

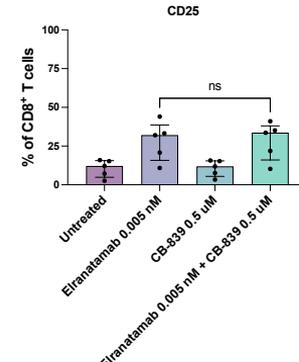
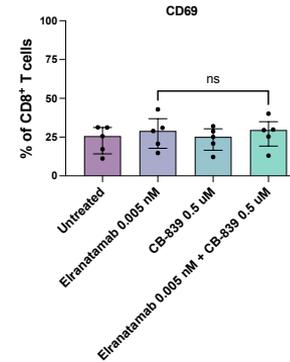
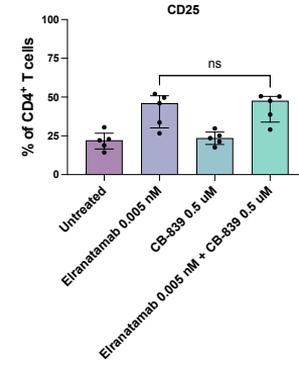
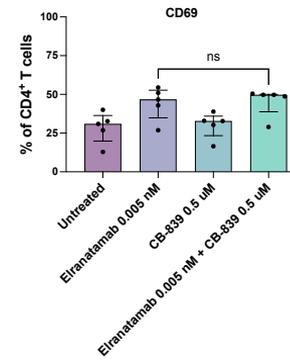
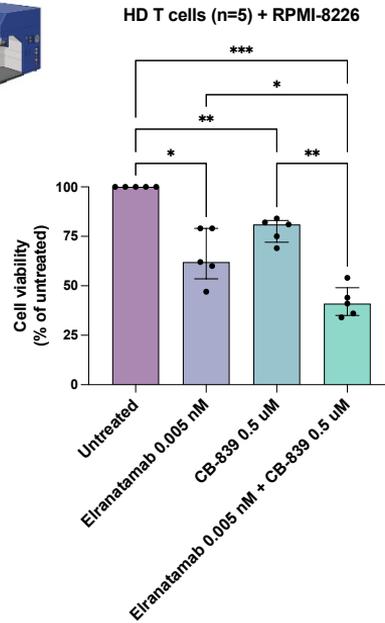
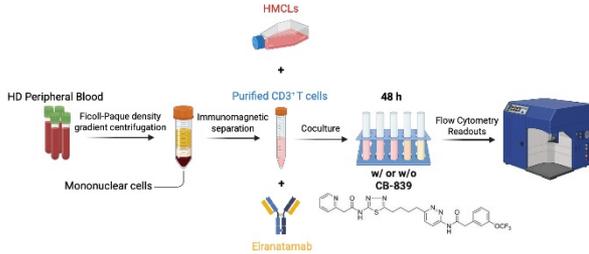
AIM OF THE STUDY

To determine whether metabolic intervention, via glutamine restriction or glutaminase inhibition with CB-839, enhances the activity of elranatamab, a BCMA \times CD3 bispecific T-cell engager, in MM.

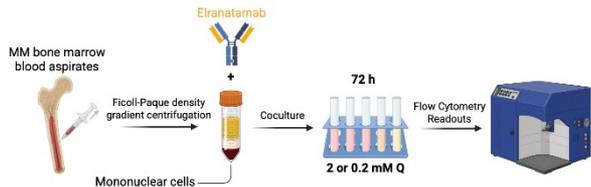
GLN RESTRICTION DOES NOT COMPROMISE ELRANATAMAB ACTIVITY OR T-CELL FUNCTION IN VITRO USING HEALTHY DONOR (HD) T CELLS



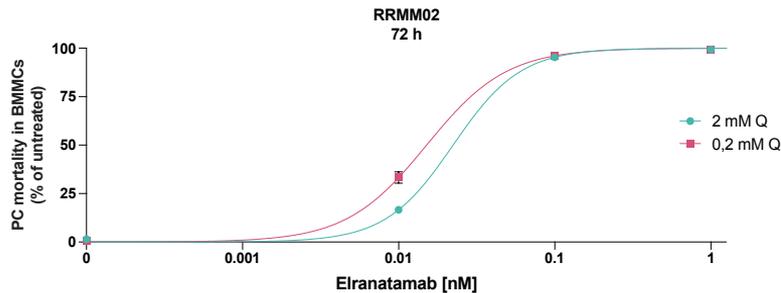
COMBINED ELRANATAMAB AND CB-839 BOOSTS ANTI-MM RESPONSE WITHOUT AFFECTING HD T CELLS



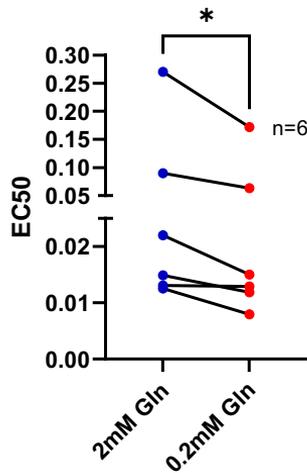
GLN RESTRICTION ENHANCES ELRANATAMAB EFFICACY IN PATIENT-DERIVED MONONUCLEAR CELLS EX VIVO



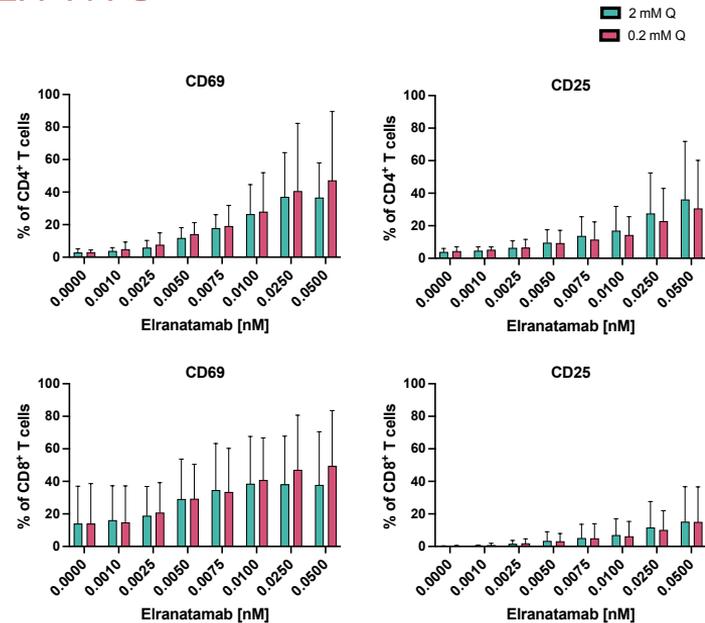
Representative patient-derived drug-induced PC cytotoxicity in BMNCs under glutamine restriction



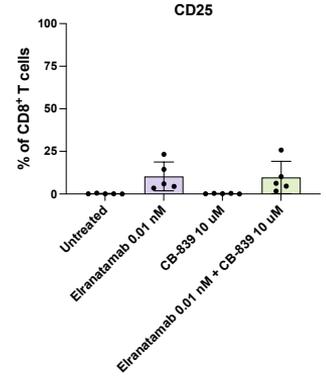
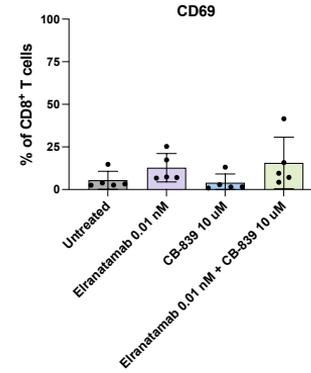
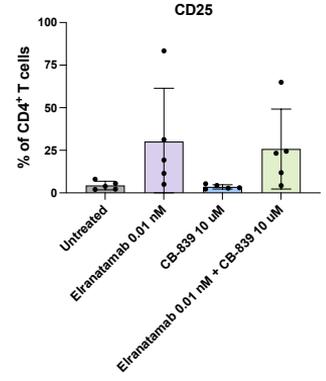
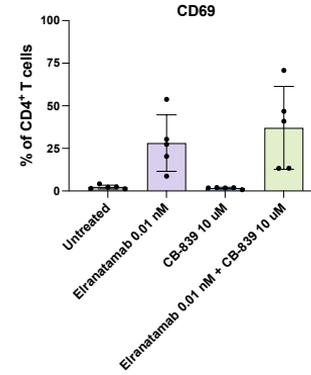
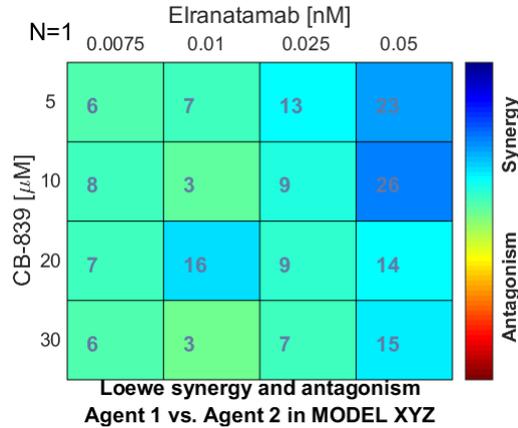
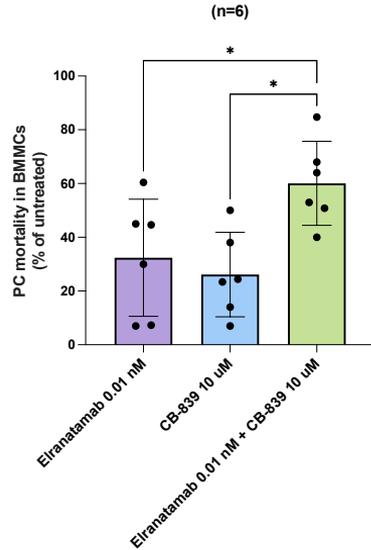
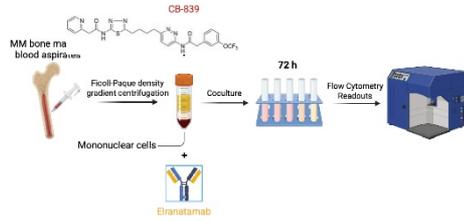
	2 mM Q	0.2 mM Q
EC50	0.02232	0.01510



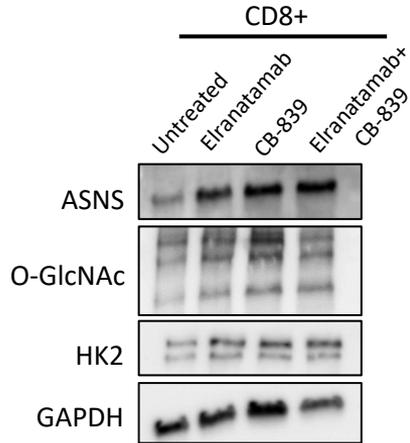
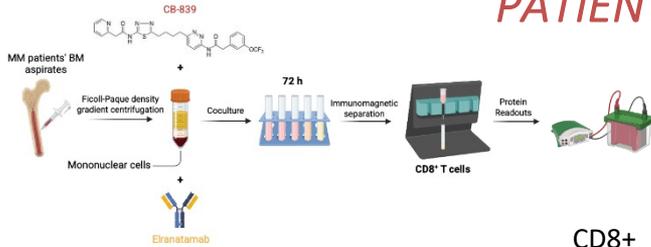
	2 mM Gln	0.2 mM Gln
Median EC50	0.01845	0.01396



GLS INHIBITION SYNERGIZES WITH ELRANATAMAB TO ENHANCE ANTI-MM ACTIVITY IN EX VIVO PATIENT-DERIVED MONONUCLEAR CELLS

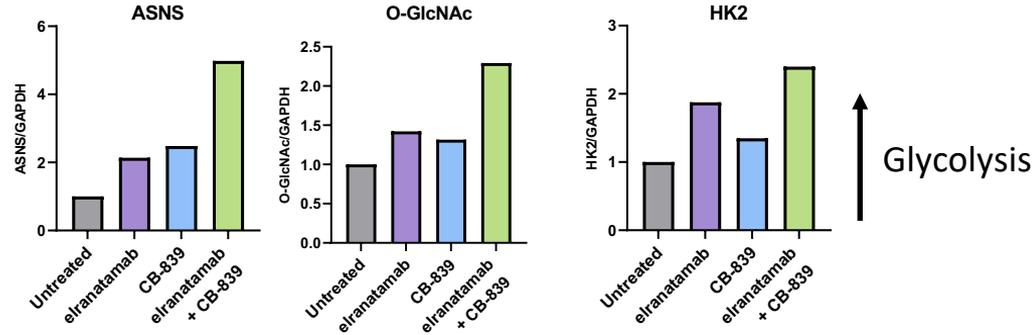


COMBINATION THERAPY DRIVES METABOLIC REWIRING IN CD8⁺ T CELLS FROM MM PATIENTS UNDER GLUTAMINE BLOCKADE



Elranatamab: 0.01 nM
 CB-839: 10 μM

ASNS: asparagine synthetase
 O-GlcNAc: O-linked N-acetylglucosamine
 HK2: hexokinase 2



Under GLS blockade, cytosolic glutamine is redirected into alternative biosynthetic pathways, including asparagine and hexosamine synthesis.

SUMMARY AND CONCLUSIONS

- ❖ Gln restriction or pharmacological GLS inhibition preserves T-cell effector function during T-cell engager treatment.
- ❖ GLS inhibition (CB-839) synergistically enhances elranatamab-mediated killing of MM cells.
- ❖ Elranatamab-activated CD8⁺ T cells exhibit metabolic plasticity under GLS blockade by upregulating alternative metabolic pathways.

Targeting glutamine metabolism selectively sensitizes MM cells while preserving T-cell effector function, providing a rationale for combining metabolic intervention with T-cell-based immunotherapies in MM.

ACKNOWLEDGEMENTS

**Hematology Laboratory
Department of Medicine and Surgery
University of Parma**

**Multiple myeloma and monoclonal
gammopathies program
Hematology AOU Parma**

Prof. Nicola Giuliani

Denise Toscani
Rosanna Vescovini
Oxana Lungu
Paola Storti
Mattia Dessena
Camilla Sitzia
Nicolas Thomas Iannozzi
Gabriella Sammarelli
Giannalisa Todaro

Benedetta Dalla Palma
Matteo Scita
Stefania Ricci



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