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Selection of PD-L1 escape variants in microsatellite stable metastatic colorectal cancer on avelumab treatment

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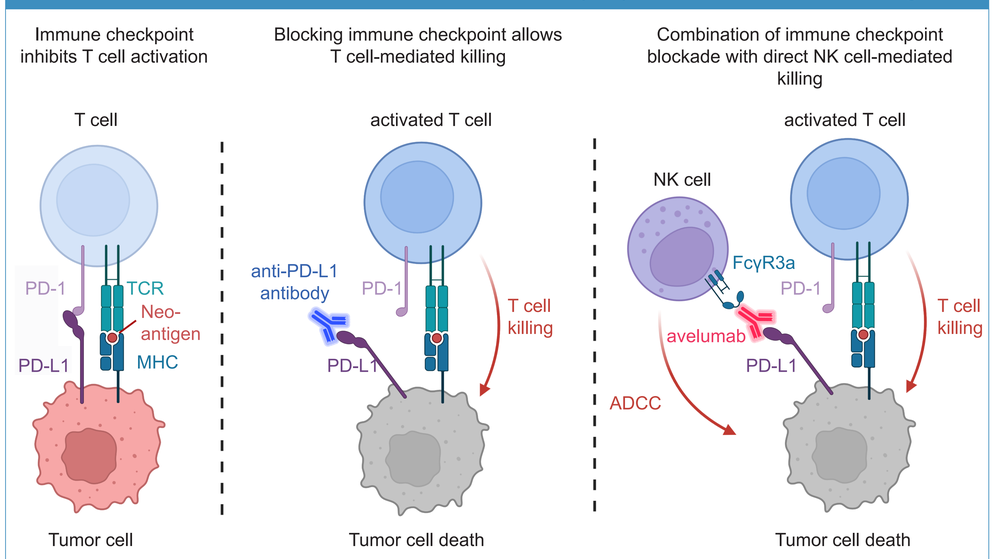
Avelumab combines immune checkpoint blockade (ICB) with direct tumor cell killing



ICB in microsatellite stable (MSS) metastatic colorectal cancer

Current state
ICB is considered uneffective in metastatic MSS colorectal cancer and combinatorial approaches enhancing immunogenicity need exploration.

Rationale
Combination of immunomodulatory chemotherapy (e.g. 5-FU and oxaliplatin), immunogenic cell death inducing targeted therapy (e.g. cetuximab) and ICB may be synergistic.

Methods
Investigate feasibility and safety in single arm multicenter phase-II trials AVETUX and FIRE6:

AVETUX
mFOLFOX6/cetuximab + avelumab from the second cycle onwards.

FIRE-6
4 cycles FOLFIRI/cetuximab
→ 4 cycles FOLFIRI/cetuximab + avelumab
→ avelumab maintenance for 10 weeks until EOT

Funding statement , conflict of interest and references

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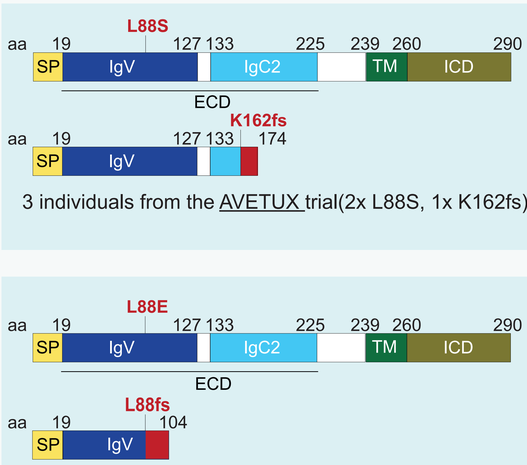
References:

1. Stein A*, Simnica D*, Schultheiß C*, Scholz R, Tintelnot J, et al. PD-L1 targeting and subclonal immune escape mediated by PD-L1 mutations in metastatic colorectal cancer. Journal for Immunotherapy of Cancer. 2021 Jul;9(7):e002844. doi: 10.1136/jitc-2021-002844.

2. Claaß LV*, Schultheiß C*, Scholz R*, Paschold L, Simnica D, Heinemann V, Stintzing S, Binder M. PD-L1 amino acid position 88 represents a hotspot for PD-L1 stability with relevance for PD-L1 inhibition. Frontiers in Oncology. 2022 Jul 22;12:941666. doi: 10.3389/fonc.2022.941666.

Liquid biopsy (ddPCR/NGS) identifies PD-L1 escape variants under avelumab treament in individuals with high affinity SNP of FcγR3a (rs396991)

A Schematic representation of PD-L1 mutations

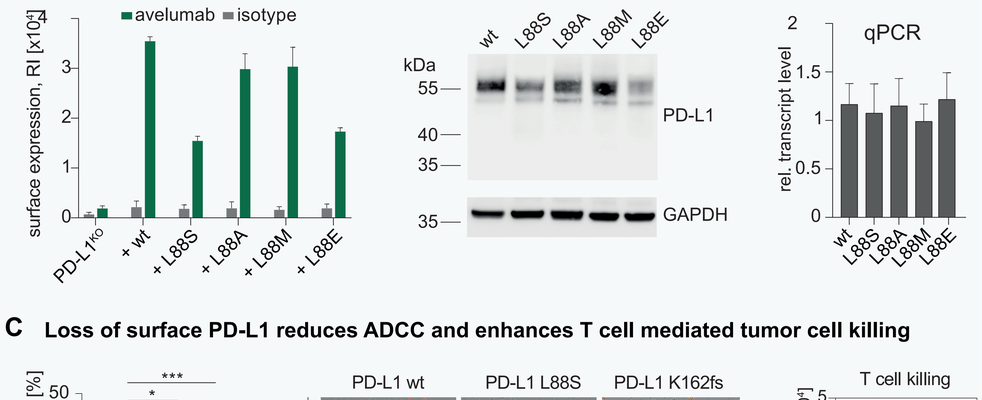


Published in:

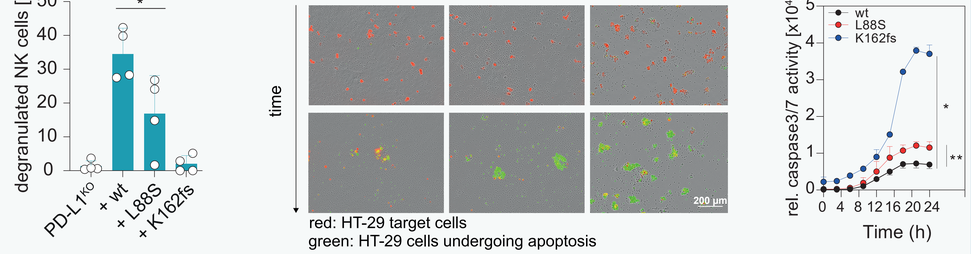
1 Avetux: Stein et al 2021, JITC

2 FIRE-6: Claaß et al 2022, Front Oncol

B PD-L1 mutations result in reduced surface expression and total protein abundancy independent of transcription in cell models

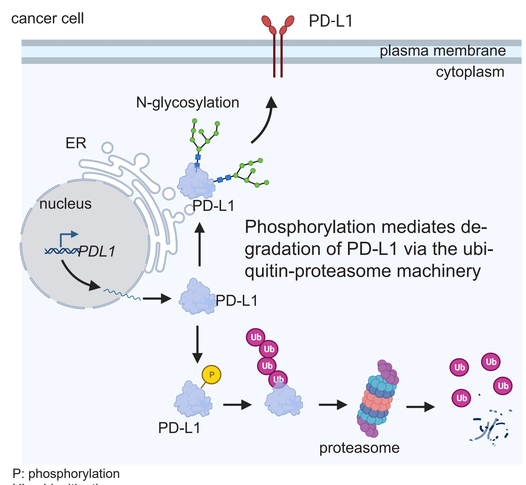


C Loss of surface PD-L1 reduces ADCC and enhances T cell mediated tumor cell killing

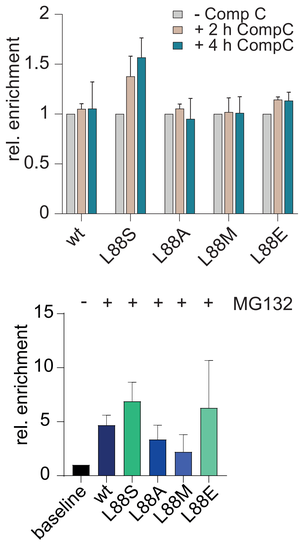


Generation of a new phospho (or phosphomimetic) site enhances proteasomal degradation

PD-L1 stability after synthesis is mediated by N-glycosylation



P: phosphorylation
Ub: ubiquitination



- AMPK phosphorylates ECD of PD-L1
- AMPK blockade with CompC enriches L88S variant
- Blocking of the proteasome with MG132 enriches L88S and L88E variants

Conclusion

- The addition of avelumab to cetuximab and chemotherapy is feasible and safe
- PD-L1 mutations at position 88 mediates subclonal immune escape to avelumab in some patients with expressing high-affinity FcγR3a (SNP rs396991)
- Together with the emergence of truncated PD-L1 variants, regulation of PD-L1 availabilty but not epitope disruption appears to be the key mechanistic principle towards PD-L1 escape
- Patients with MSS metastatic colorectal cancer expressing high affinity FcγR3a may represent a subgroup that benefits from avelumab

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