Anti-tumoral efficacy of therapeutic human anti-KIR antibody (lirilumab) in a preclinical xenograft tumor model

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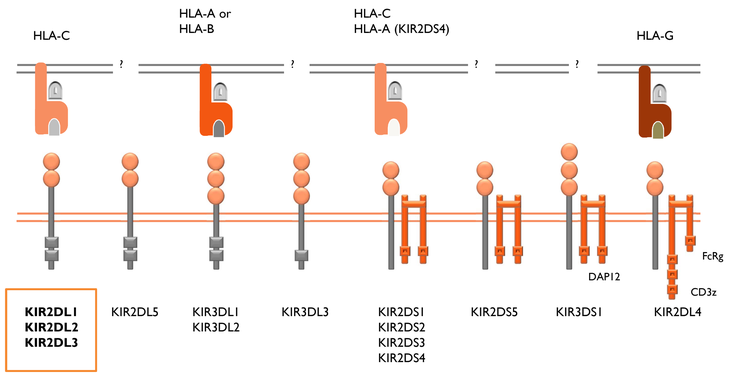
Introduction

- Natural Killer (NK) cells are lymphocytes able to recognize and kill tumors for which the expression of Major Histocompatibility Complex (MHC) class I molecules is altered. This "missing self" recognition is mediated by the lack of engagement of MHC class I molecules with NK cell inhibitory receptors that include lectin-like Ly49 molecules in mice and Killer Immunoglobulin-like Receptors (KIRs) in humans.
- Some tumors escape NK cell immune surveillance by increasing the expression of MHC class I molecules on their surface. Consequently, blocking interactions between KIR and MHC class I positive tumor cells constitutes an interesting therapeutic strategy.
- The anti-KIR2DL1/2/3-specific monoclonal antibody, **lirilumab/BMS-986015/IPH2102**, is a fully human IgG4 that is being developed for treating both hematologic malignancies and solid tumors.
- The objective of this study was to develop a preclinical model to assess the efficacy of the drug candidate used in clinical trials, lirilumab.

The KIR and their ligands

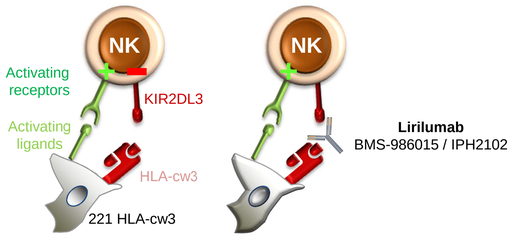


(Adapted from Thielens et al., *Curr Opin Immunol.* 2012; 24: 239-245)

Mat. & Meth.

- Rag1KO-Tg KIR2DL3 (Rag1KO-Tg KIR) mice express the human inhibitory KIR2DL3 molecule on the surface of NK cells (Romagne et al., *Blood*. 2009; 114: 2667-2677).
- Tumor challenge: 10^7 human B cells LCL 721.221 control (221) or transduced with lentiviral particules encoding a ligand of KIR2DL3, HLA-Cw3, (221 HLA-Cw3) were injected intravenously (i.v.) at day 0.
- Lirilumab, human IgG4 control (hIgG4) or vehicle were injected i.v.
- Mouse survival was monitored for 100 days after tumor challenge. Differences in median survival were analyzed statistically with Log-Rank (Mantel Cox) test.

Mechanism of action for lirilumab



Results

HLA-C-expressing tumor escapes NK cell control in Rag1KO-Tg KIR mice

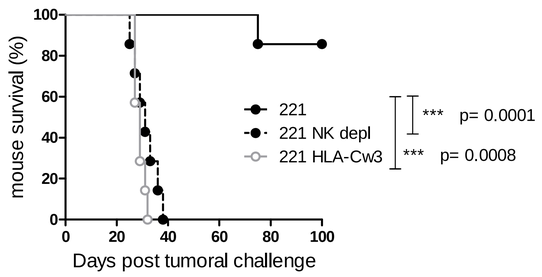


Figure 1. When indicated, NK cell depletion (NK depl) was achieved by i.v. injection of anti-NK1.1 mAb (100 µg/mouse) every 10 days, starting on the day of tumor challenge (results of one representative experiment, n= 6 or 7 mice per group).

Duration of KIR2DL3 saturation *in vivo* is lirilumab dose-dependent

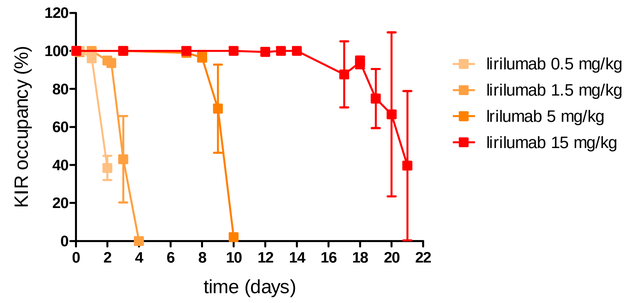
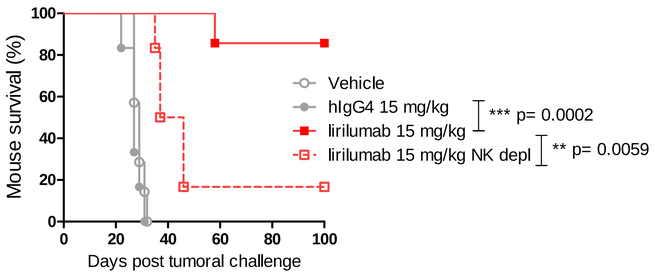


Figure 2. KIR2DL3 occupancy on peripheral blood NK cells (NKp46$^+$ lymphocytes) was assessed after single injection of lirilumab (4 doses) by detection of free KIR2DL3 with fluorochrome-conjugated lirilumab (mean ± SD, n= 3 to 8 mice per time-point).

Preventive lirilumab treatment improves mouse survival in a NK cell-dependent manner…



…and this effect is dependent on KIR saturation duration

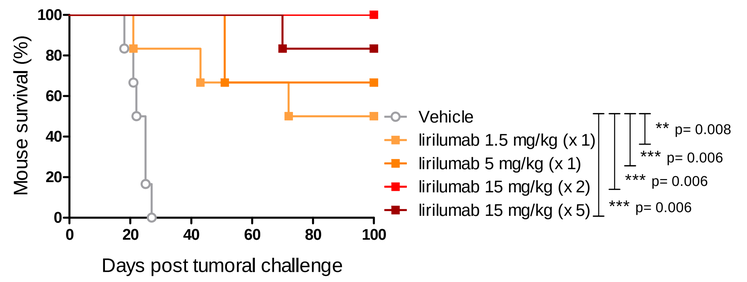
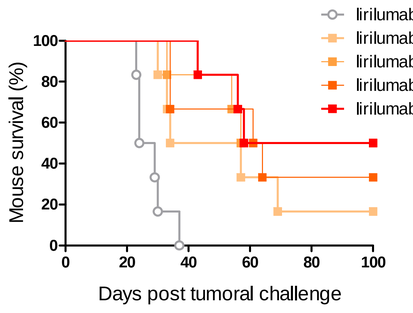


Figure 3. Lirilumab was injected once on the day of tumor challenge. When indicated, NK cell depletion was achieved as described in Fig.1, starting the day prior tumor challenge (results of one experiment, n= 6 mice per group).

Figure 4. Several doses of lirilumab were injected once (x 1) at day 0, twice (x 2) at days 0 and 7, or 5 times (x 5) i.e. every 7 days from day 0 (results of one experiment, n= 6 mice per group).

Therapeutic lirilumab treatment improves mouse survival



lirilumab (mg/kg)	MS (days)	ILS (%)	p
0	26.5	-	-
0.5	45.5	72	0.017*
1.5	57	115	0.0016**
5	61	130	0.0097**
15	64.5	143	0.0005***

Figure 5. Several doses of lirilumab were tested in single injection. Treatment was delayed 5 days after tumor challenge (results of one representative experiment, n= 6 mice per group).
Median survival (MS) and increase life span (ILS) are indicated.

Lirilumab therapeutic efficacy is mediated by NK cells

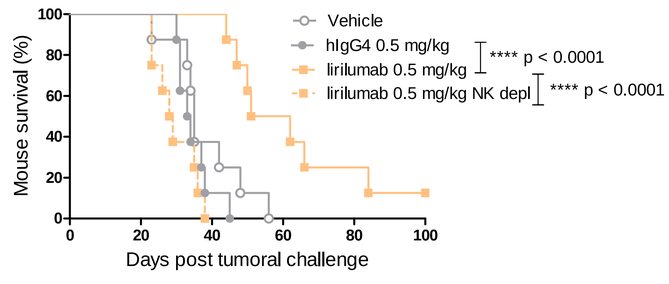


Figure 6. Lirilumab (0.5 mg/kg) or control mAb (hIgG4) were injected once 5 days after tumor challenge. When indicated, NK cell depletion was achieved as described in Fig.1 the day prior tumor challenge (results of one representative experiment, n= 6 or 7 mice per group).

Conclusions

- Lirilumab treatment increased mice survival in a dose-dependent manner when injected at the same time as the tumor challenge.
- This protective effect was NK cell-mediated and directly correlated with the duration of KIR2DL3 saturation.
- Lirilumab treatment improved survival in therapeutic conditions (i.e. when the antibody was injected 5 days after the tumor), also in a NK cell-dependent manner).
- This study showed efficacy of lirilumab, as single agent in a HLA-Cw3-expressing tumor model and this xenogenic pre-clinical model will be an excellent tool to investigate the therapeutic benefits of combination treatments.

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