

442-J ANTI-AXL CAR-NK CELL IMMUNOTHERAPY TO TARGET BRAF INHIBITOR DRUG-RESISTANT AND METASTATIC MELANOMA

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**Background** Melanoma has a high mutational burden and is a highly metastatic and difficult-to-treat form of human cancer. The characteristics of more than 50% with BRAF mutation and immunogenicity have translated to targeted and immune therapies with remarkable responses and significantly improved patient survival. However, most patients will develop a tumor relapse and acquired resistance within several months. Understanding the molecular mechanism of recurrence and acquired resistance, as well as the potential of new therapeutic strategies in BRAF mutant melanoma, could be really important to improve patient outcomes. We previously have shown that resistance to BRAF kinase inhibitors (BRAFi) frequently occurs through the reactivation of AXL signaling. AXL was also shown to be expressed in the majority of metastatic melanoma, suggesting AXL is a viable target for treating patients with BRAFi-resistant and metastatic melanoma.

**Methods** We currently developed anti-AXL-specific CAR-NK cells for specifically targeting the BRAFi-resistant and metastatic melanomas with AXL expression.

**Results** We found that BRAFi-resistant melanomas could resist NK cell lysis while exhibiting significant sensitivity to anti-AXL CAR-NK cells. Moreover, the anti-AXL CAR-NK cells appeared a significantly higher ability of cytotoxicity to AXL-positive BRAFi-resistant melanoma compared to low AXL BRAFi-sensitive melanoma, suggesting that our CAR NK could specifically target the BRAFi-resistant melanoma with AXL expression. Notably, we found the anti-AXL CAR-NK cells could inhibit the BRAFi-resistant melanoma growth and metastasis in vivo preclinical mouse models.

**Conclusions** Our findings propose that Anti-AXL CAR-NK cell immunotherapy is a promising approach to target BRAF inhibitor drug-resistant and metastatic melanoma.

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