

Chemotherapy of malignant pleural mesothelioma does not preclude use of check-point blockade

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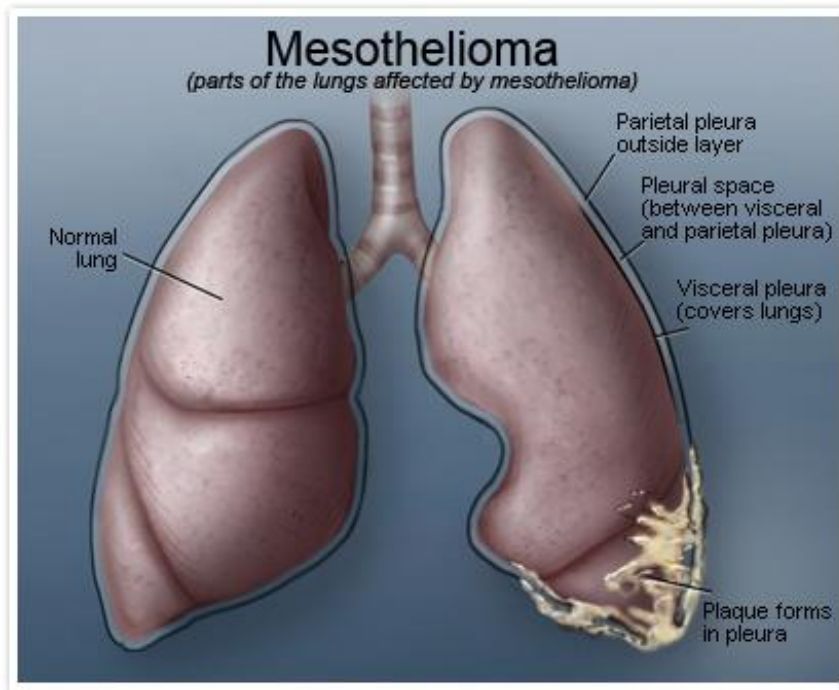


Disclosure

No conflicts of interest



Mesothelioma



- Epitheloid
- Biphasic
- Sarcomatoid

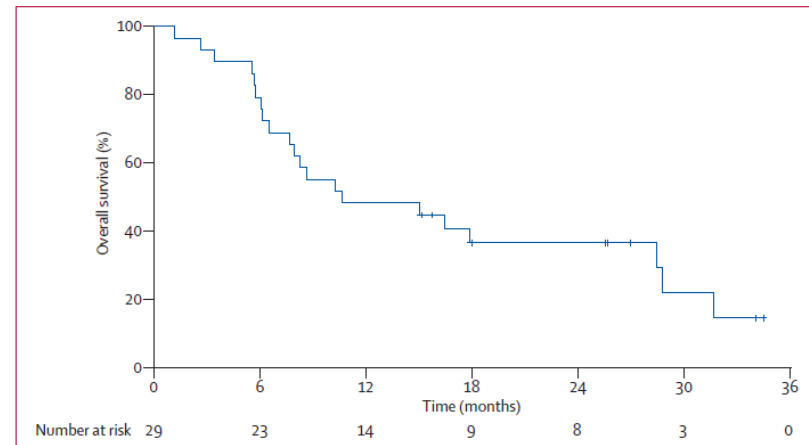
Systemic treatment of mesothelioma

- 1st line: platin-based and pemetrexed
- 2nd line: gemcitabine, vinorelbine
- Small molecules: no clinical benefit
- Checkpoint point inhibitors

Patients (N=29)	
Complete response	0
Partial response	2 (6.9%, 0.0-16.1)
Stable disease	7 (24.1%, 8.6-39.7)
Progressive disease	20 (69.0%, 52.1-85.8)
Disease control	9 (31.0%, 14.2-47.9)

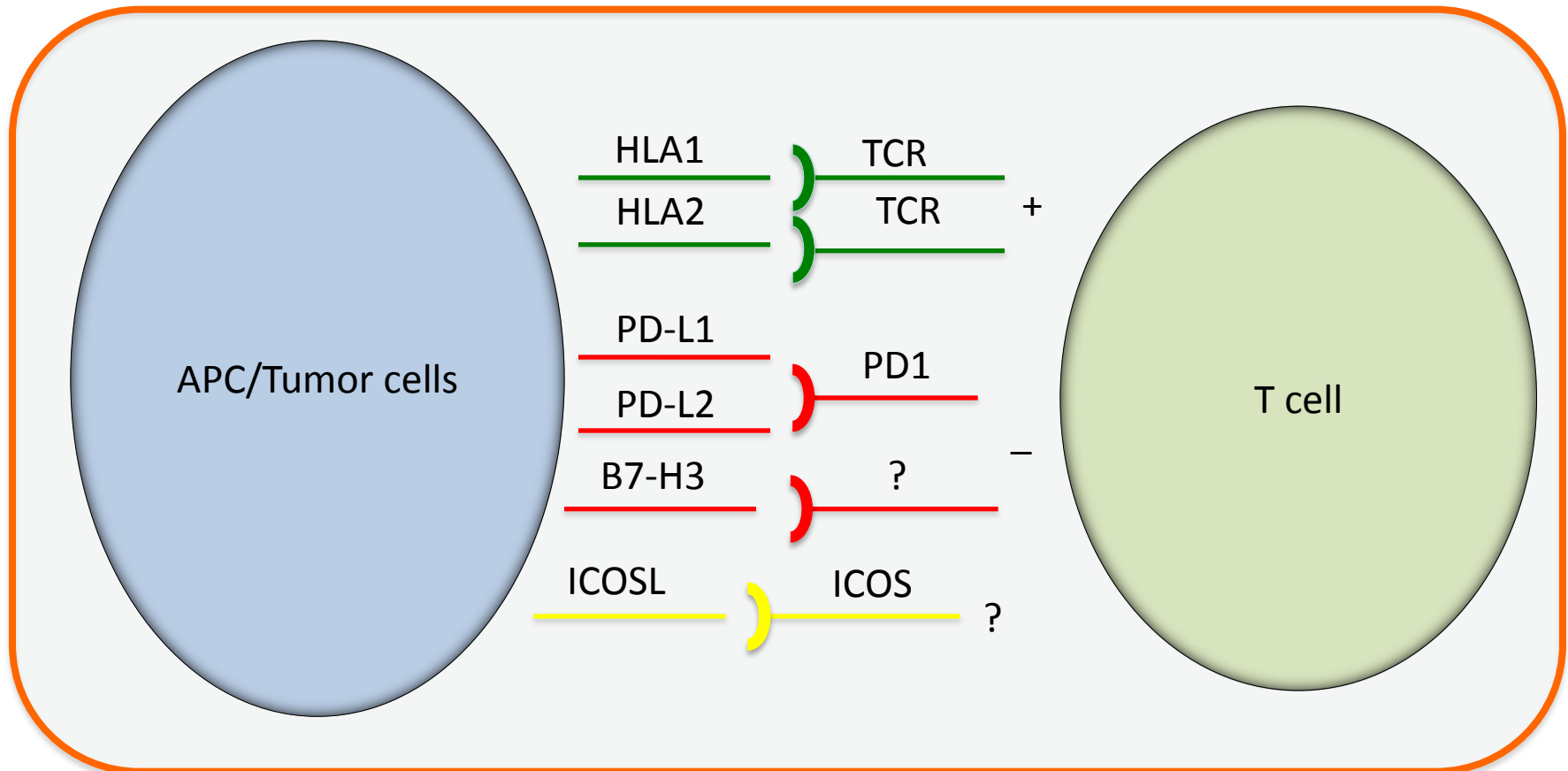
Data are n (%) or n (%; 95% CI). Tumours were assessed at 70-90 days (RECIST 1.0 for peritoneal or modified RECIST for pleural malignant mesothelioma).¹⁹
RECIST=Response Evaluation Criteria in Solid Tumors.

Table 2: Best tumour response and disease control

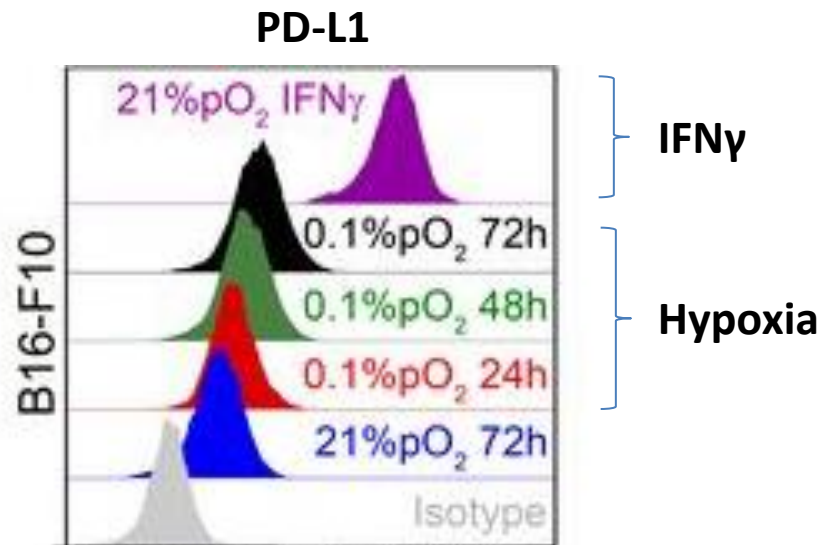


Calabro' et al Lancet Oncol 2013 Oct;14(11):1104-11

Molecules involved in co-inhibition and co-stimulation determine the quality of T cell responses



Modulation of expression through hypoxia and IFN-gamma



Muhammad Zaeem Noman et al. J Exp Med 2014;211:781-790

Does chemotherapy modulate targets of checkpoint blockade?

**Tumor
samples**

TMA (n=88)

before chemo

Whole tumor (n=10)

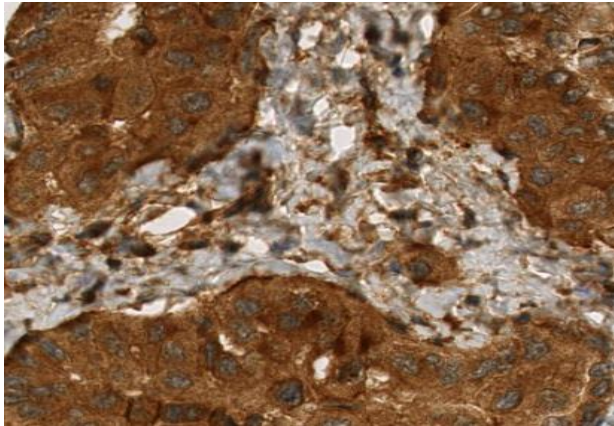
before - after chemotherapy

Cell lines

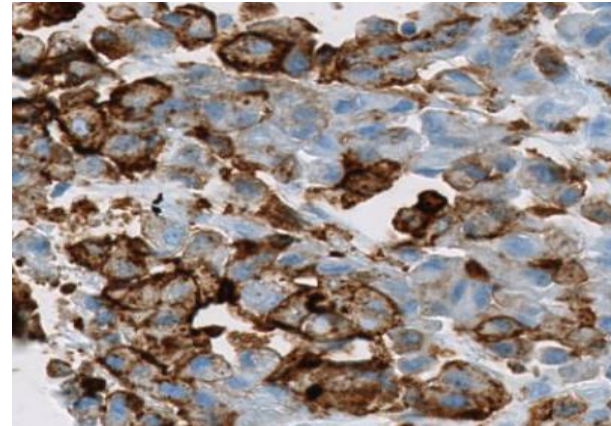
before - after
chemotherapy

TMA (n=88)

HLA I: 90% of cases positive

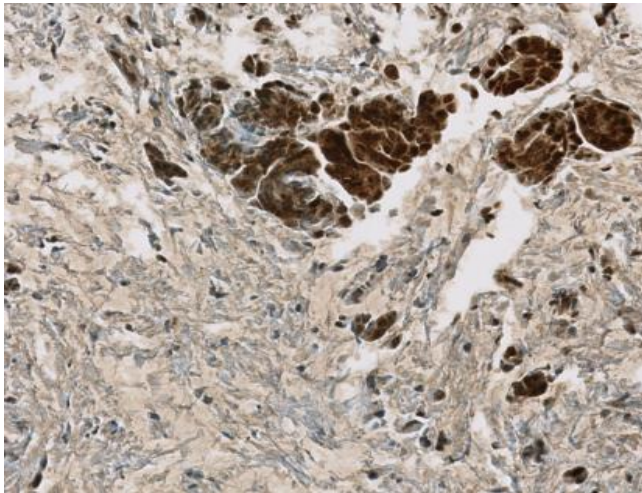


HLA II: 16% of cases positive

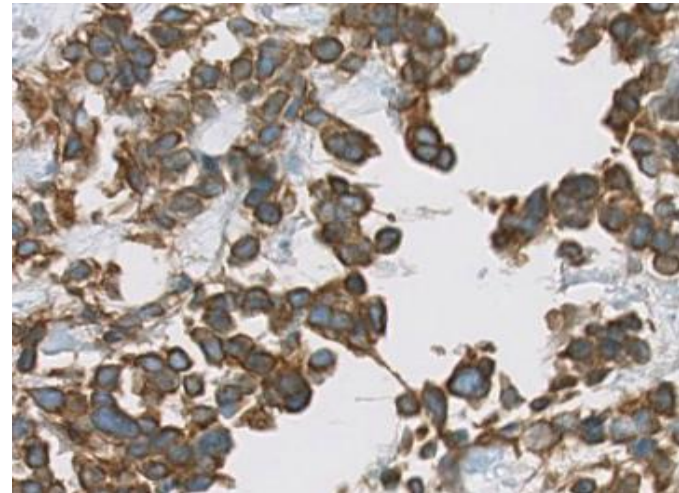


TMA (n=88)

ICOS-L: 90% of cases positive



B7-H3: 69% of cases positive

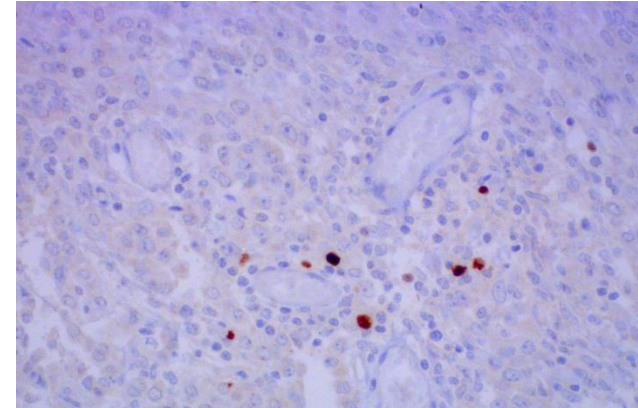
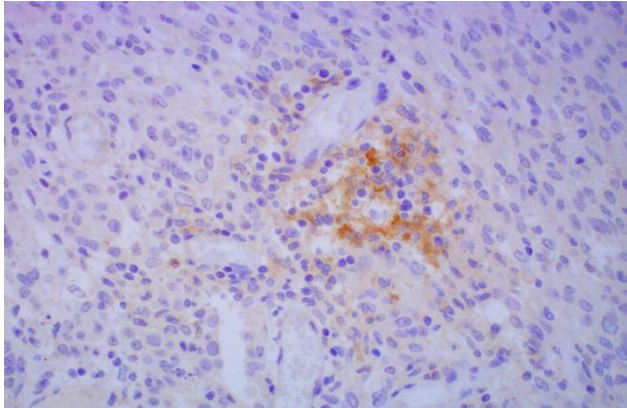


Whole tumor (n=10)

TUMOR

STROMA

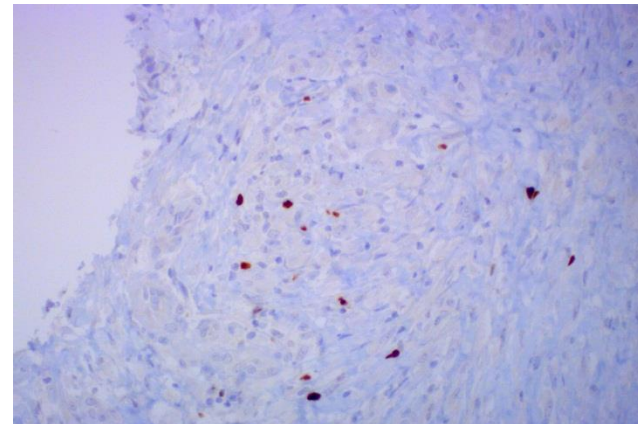
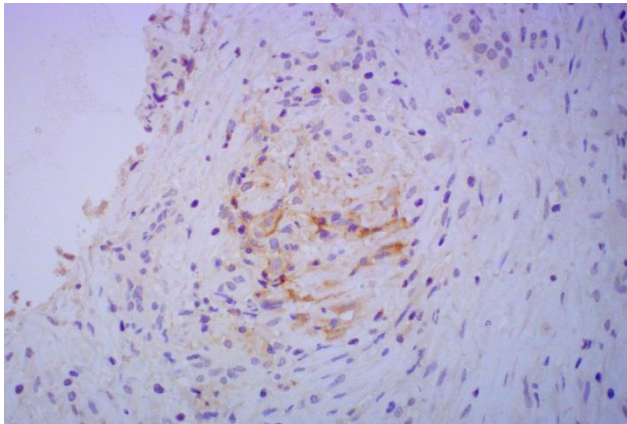
BEFORE



PD-L1

FoxP3

AFTER



Does chemotherapy modulate targets of checkpoint blockade?

Cell lines derived from the 3 histological subtypes
ZLT55, MSTO, SPC11

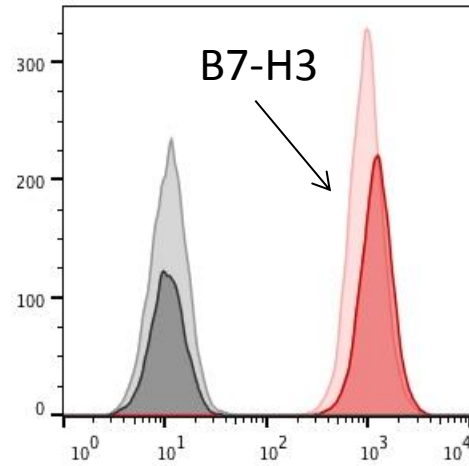
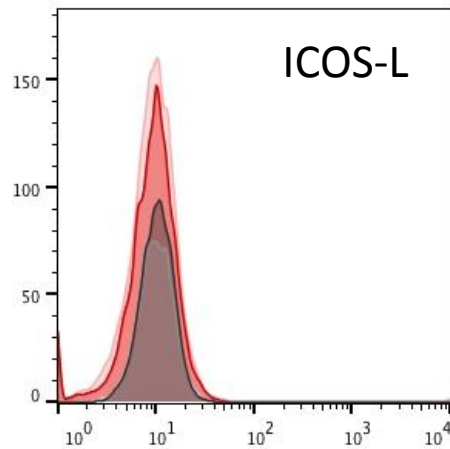
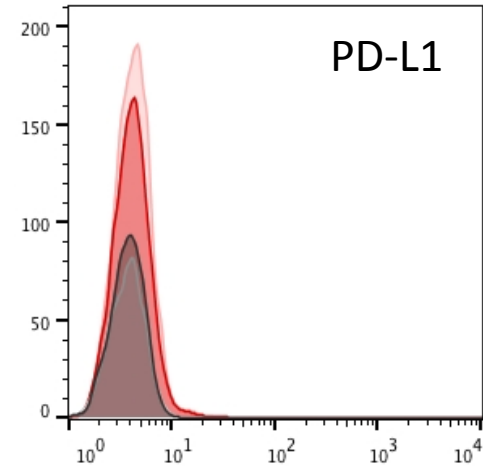
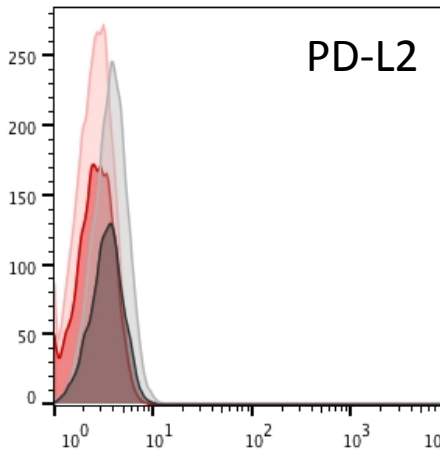
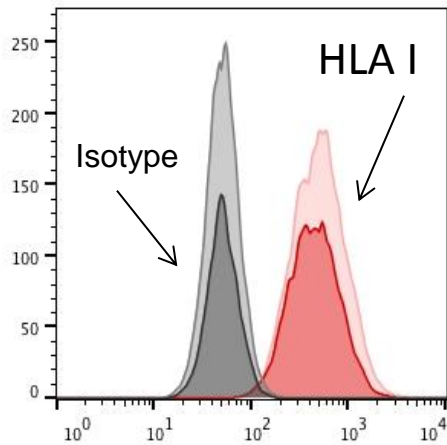
Chemotherapy:

Cisplatin /Pemetrexed

Gemcitabine

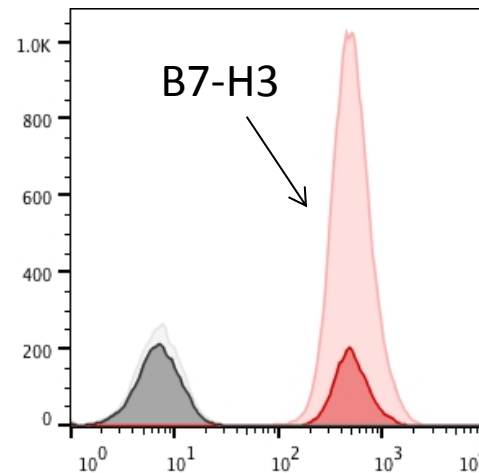
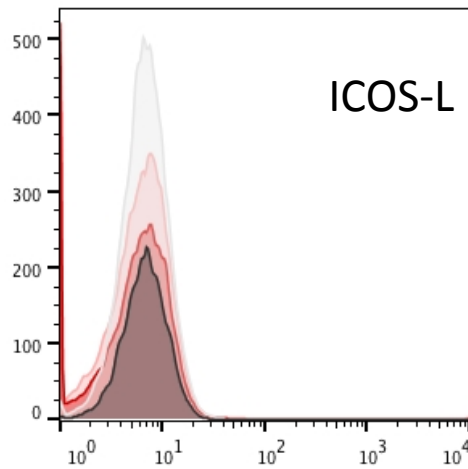
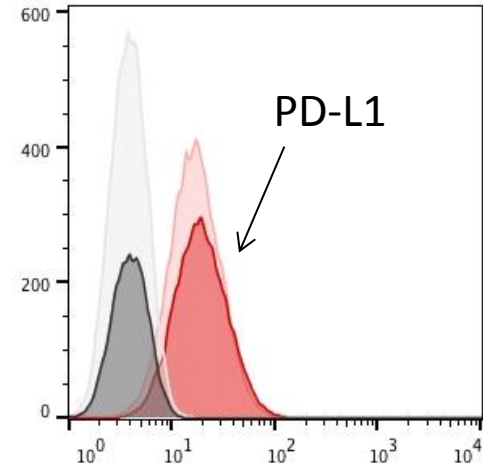
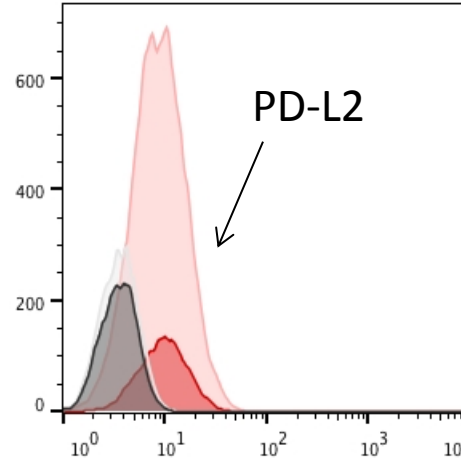
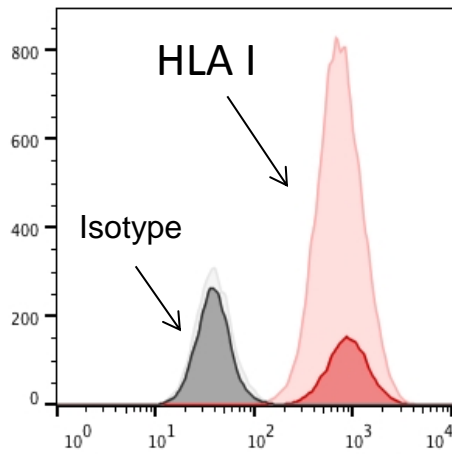


Stable expression upon treatment with gemcitabine ZLT55: derived from epitheloid subtype



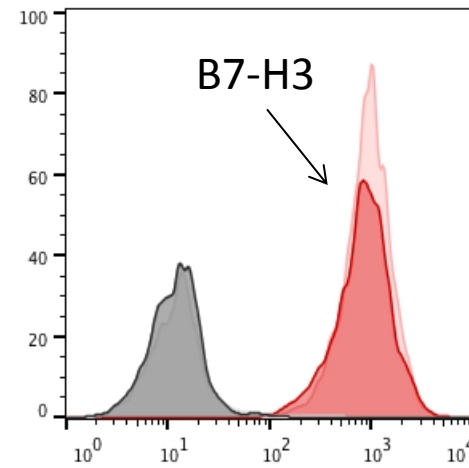
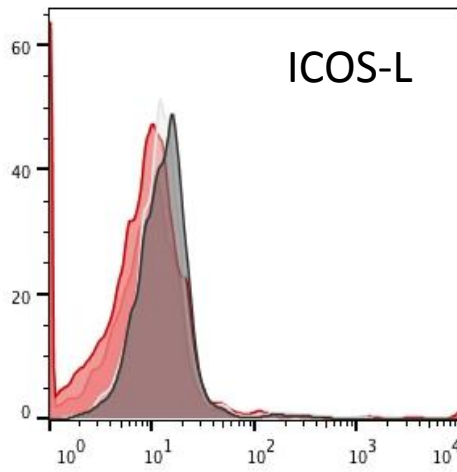
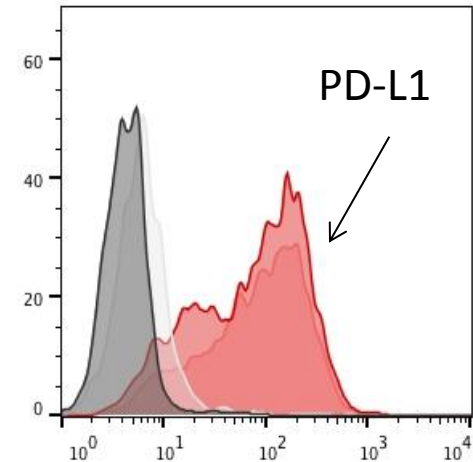
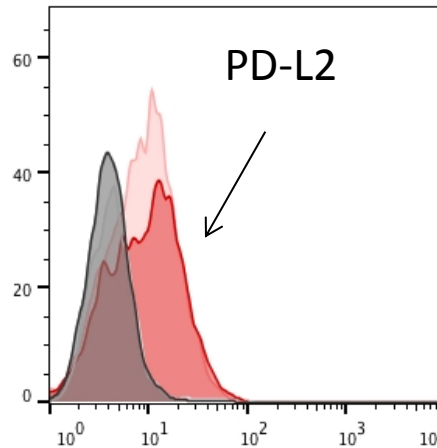
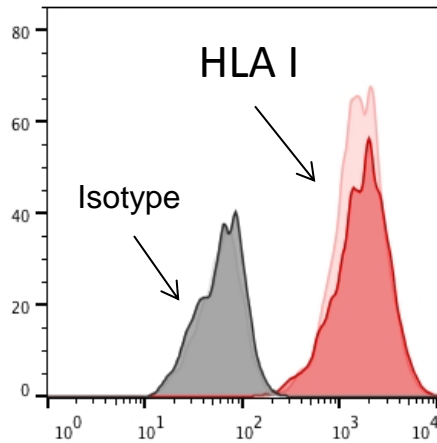
Stable expression upon treatment with gemcitabine

MSTO: derived from biphasic subtype



Stable expression upon treatment with gemcitabine

SPC11: derived from sarcomatoid subtype



Conclusions

- Frequent expression of HLA and immunomodulatory molecules
- The targets of immune checkpoint inhibitors are not downregulated by Gemcitabine or Cisplatin/Pemetrexed *in vivo* and *in vitro*
- Combining blockade of immune checkpoints with Gemcitabine or Cisplatin/Pemetrexed is rational

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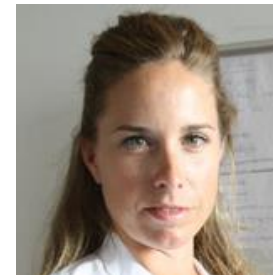
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Thank you!



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