# Characterization of the lung tumor microenvironment upon anti-PD-L1 therapy reveals an ambiguous role for TNF-α


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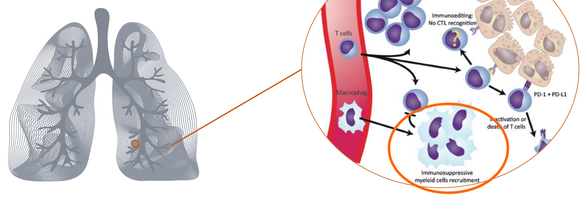
## Introduction






- **< 25%** of NSCLC patients don't respond to anti-PD-(L)1 immunotherapy
- **Myeloid cells**
  - Abundantly present in the lung tumor microenvironment (TME)
  - Linked to tumor progression and resistance to therapy
  - Can be PD-1$^+$, PD-L1$^+$ and Fc$\gamma$R$^+$

## Hypothesis

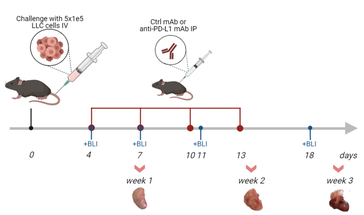
**Do PD-(L)1$^+$ myeloid cells hamper effective anti-PD-L1 therapy?**

## Conclusions

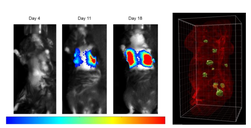
1. Upon anti-PD-L1 therapy, only the **lung TME infiltrated monocytes**:
   - produce and respond to increased **TNF-α levels**
   - **increase** their levels of **LAG-3, TIM-3, SIRP-α and VISTA**
2. **TNF-α** is involved in anti-PD-L1 therapy-mediated checkpoints
3. TNF-α and PD-L1 co-blockade **has no increased therapeutic benefit** *in vivo*
4. **Monocytes are crucial** for T cell stimulation via the **combination of anti-PD-L1 with anti-SIRP-α or anti-LAG3**

## Methods

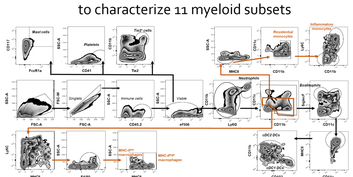
***In vivo* set-up**




***In vivo* BLI and 3D whole tissue imaging**
To follow tumor progression




**Multiplex flow cytometry**
to characterize 11 myeloid subsets



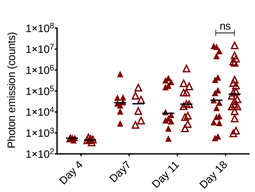
**FACS**
To isolate macrophages and monocytes

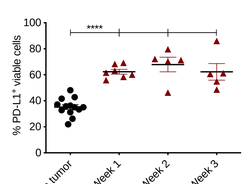
nanoString — Use in T cell killing assay

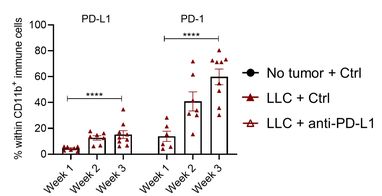
Monitor immune profile via flow cytometry

## Results

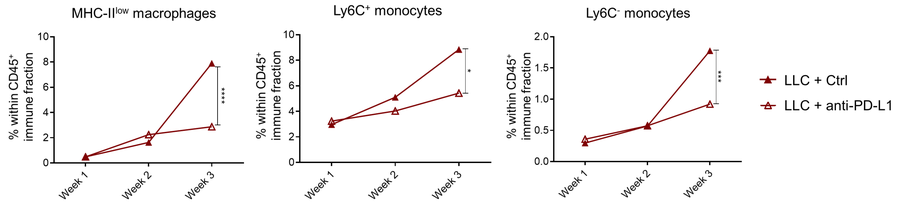
### 1. Anti-PD-L1 therapy has no therapeutic benefit despite elevated PD-L1 expression levels in lungTME



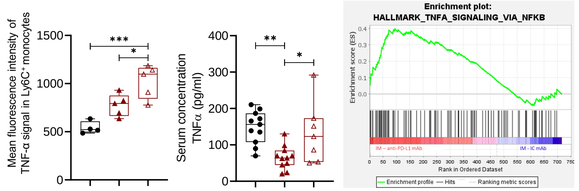



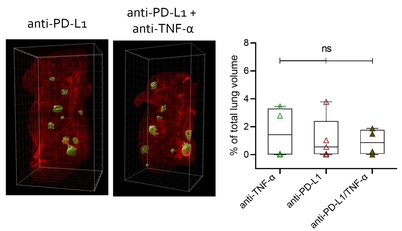

### 2. Anti-PD-L1 therapy abolishes the rise in MHC-II$^{low}$ TAMs and monocytes upon LLC progression



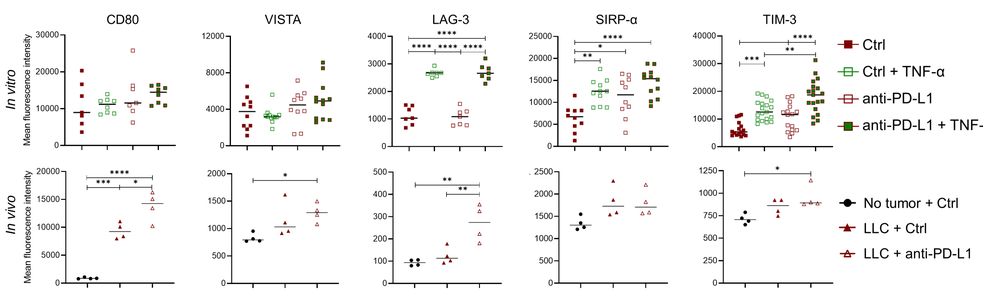

### 3. Anti-PD-L1 therapy results in a monocyte-specific TNF-α response



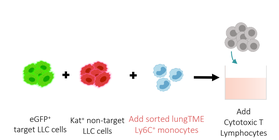

### 4. TNF-α - PD-L1 co-blockade has no increased therapeutical benefit

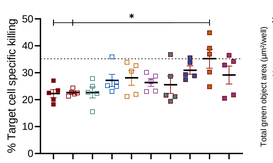


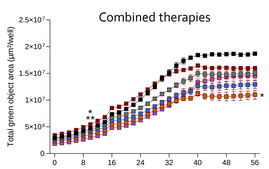

### 5. TNF-α fortifies the upregulation of checkpoint molecules on anti-PD-L1 treated monocytes

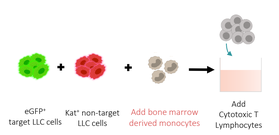


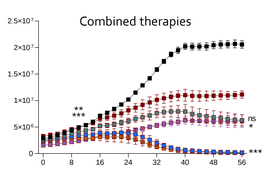

### 6. Monocytes play a key role in the CTL-stimulating potential of ICB combination therapy





Kom op tegen Kanker
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