

Investigating the association between genetically proxied immune checkpoint protein inhibition and cancer survival using Mendelian randomisation.

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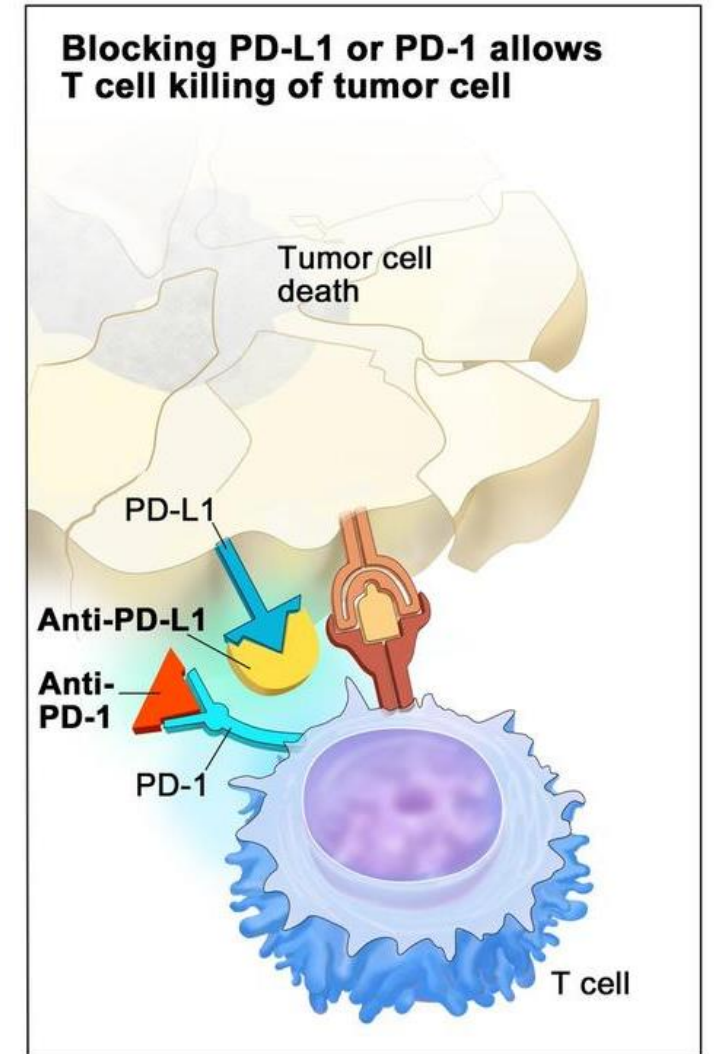
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Background

- Immune checkpoint proteins: PD-1, PD-L1
- Suppression of T cell activation
 - Evade anti-cancer immune responses
- **PD-1 inhibitors**, e.g. cemiplimab, dostarlimab, nivolumab, pembrolizumab
- **PD-L1 inhibitors**, e.g. atezolizumab, avelumab, durvalumab

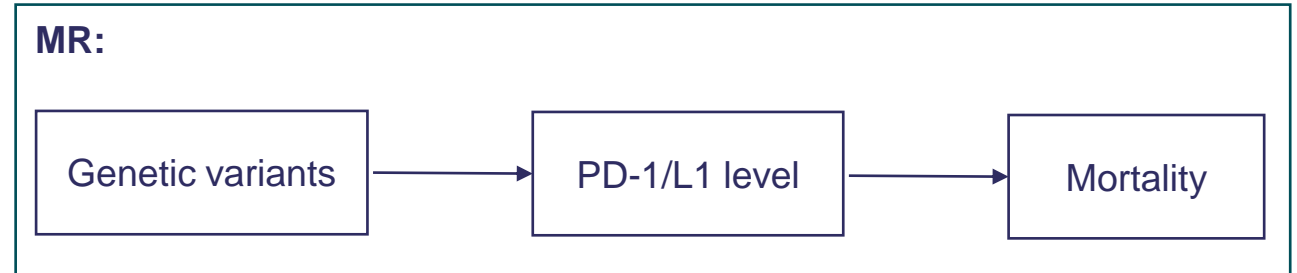


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Aims

Aim 1: Investigate repurposing potential of ICIs in cancer treatment using MR

| Cancer site | Current MHRA approvals [1] | |
|-------------|----------------------------|------------------|
| | PD-1 inhibitors | PD-L1 inhibitors |
| Breast | Yes | Yes |
| Lung | Yes | Yes |
| Melanoma | Yes | No |
| Ovary | No | No |
| Prostate | No | No |



- Broader populations than current indications (breast, lung, melanoma)
- New indications (ovarian, prostate)

Aim 2: Investigate applicability of MR in cancer survival settings



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1. Medicines & Healthcare products Regulatory Agency. *MHRA Products*. Available from: <https://products.mhra.gov.uk/>.

Methods - data

1. Exposure data

- UK Biobank serum protein expression GWAS (N = 54,219) [2]

2. Outcome data

| Cancer site | Consortium | N participants | N events | Survival outcome |
|-------------|---|----------------|----------|--------------------------|
| Breast | BCAC [3] | 91,686 | 7,531 | Breast cancer-specific |
| Lung | ILCCO, DFCI, Genomics England meta-analysis (unpublished) | 7,352 | 4,598 | All-cause |
| Melanoma | Melanoma Institute Australia, UK Biobank [4] | 10,982 | 1,041 | Melanoma-specific |
| Ovary | OCAC [5] | 2,901 | 1,656 | All-cause |
| Prostate | PRACTICAL [6] | 67,758 | 7,914 | Prostate cancer-specific |

Methods overview

1. Main analysis

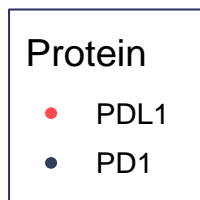
- Summary-level MR (IVW) with survival outcome

2. Collider bias assessment

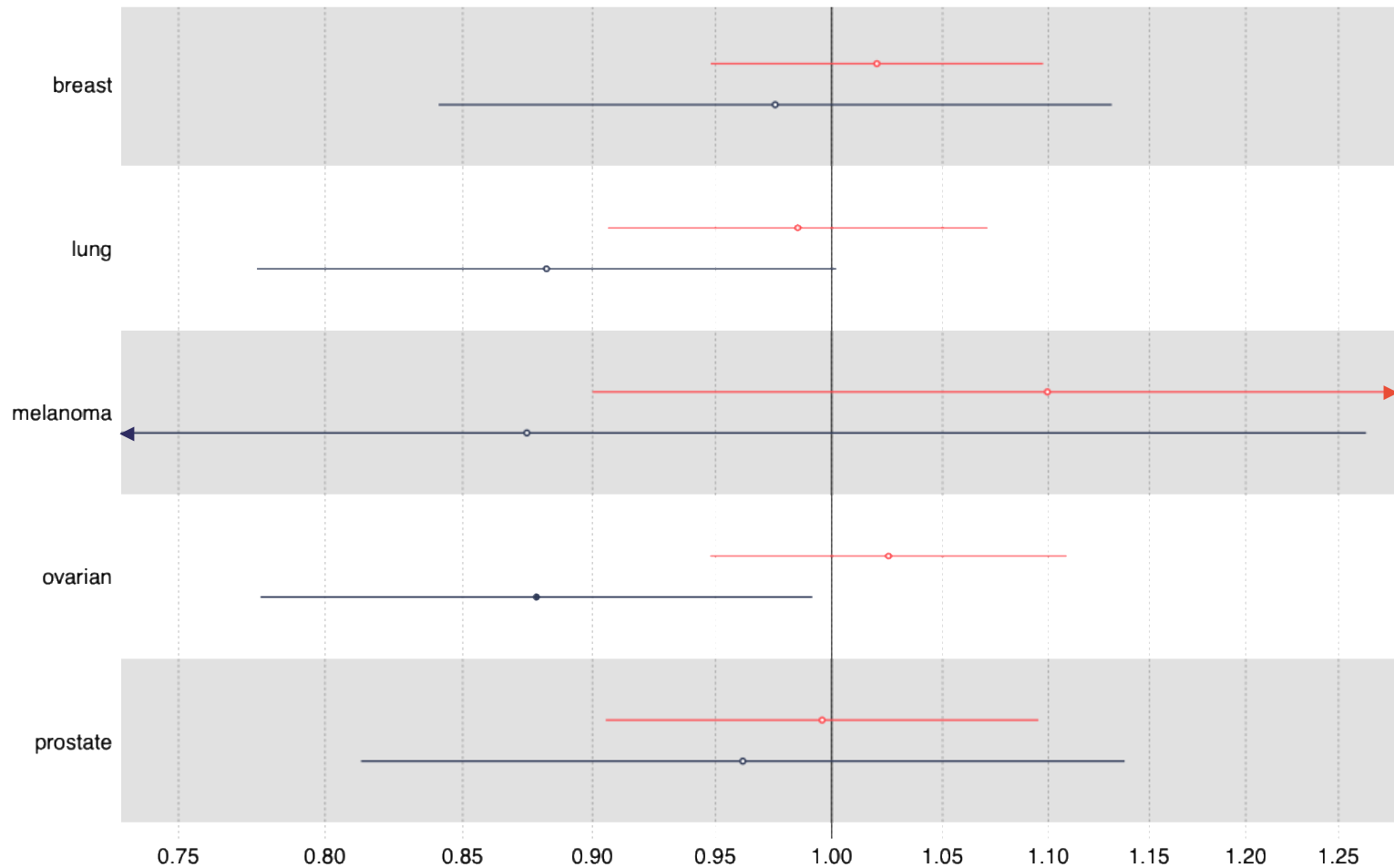
- Summary-level MR (IVW) with risk outcome

3. Sensitivity analyses (ongoing)

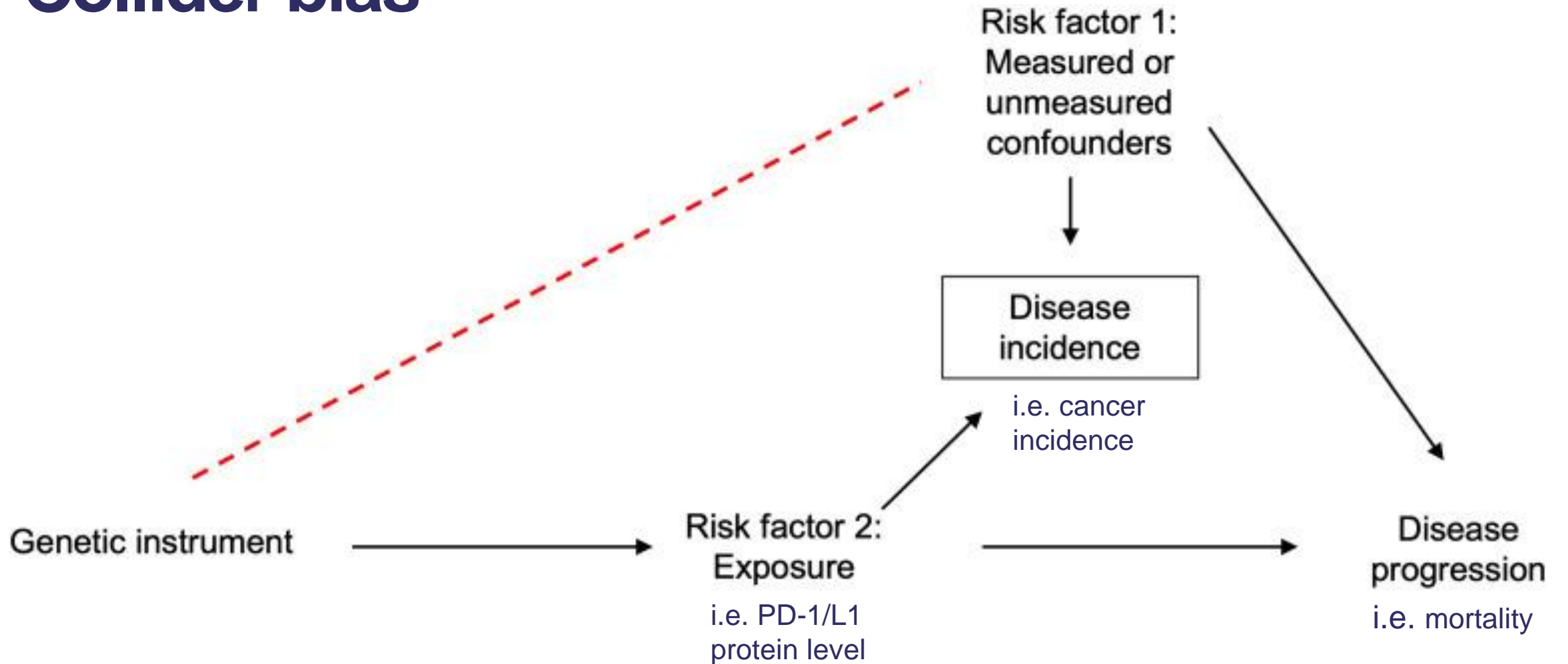
Risk of mortality



Hazard ratio (95% CI) for death per SD unit decrease in genetically proxied PD-1 or PD-L1

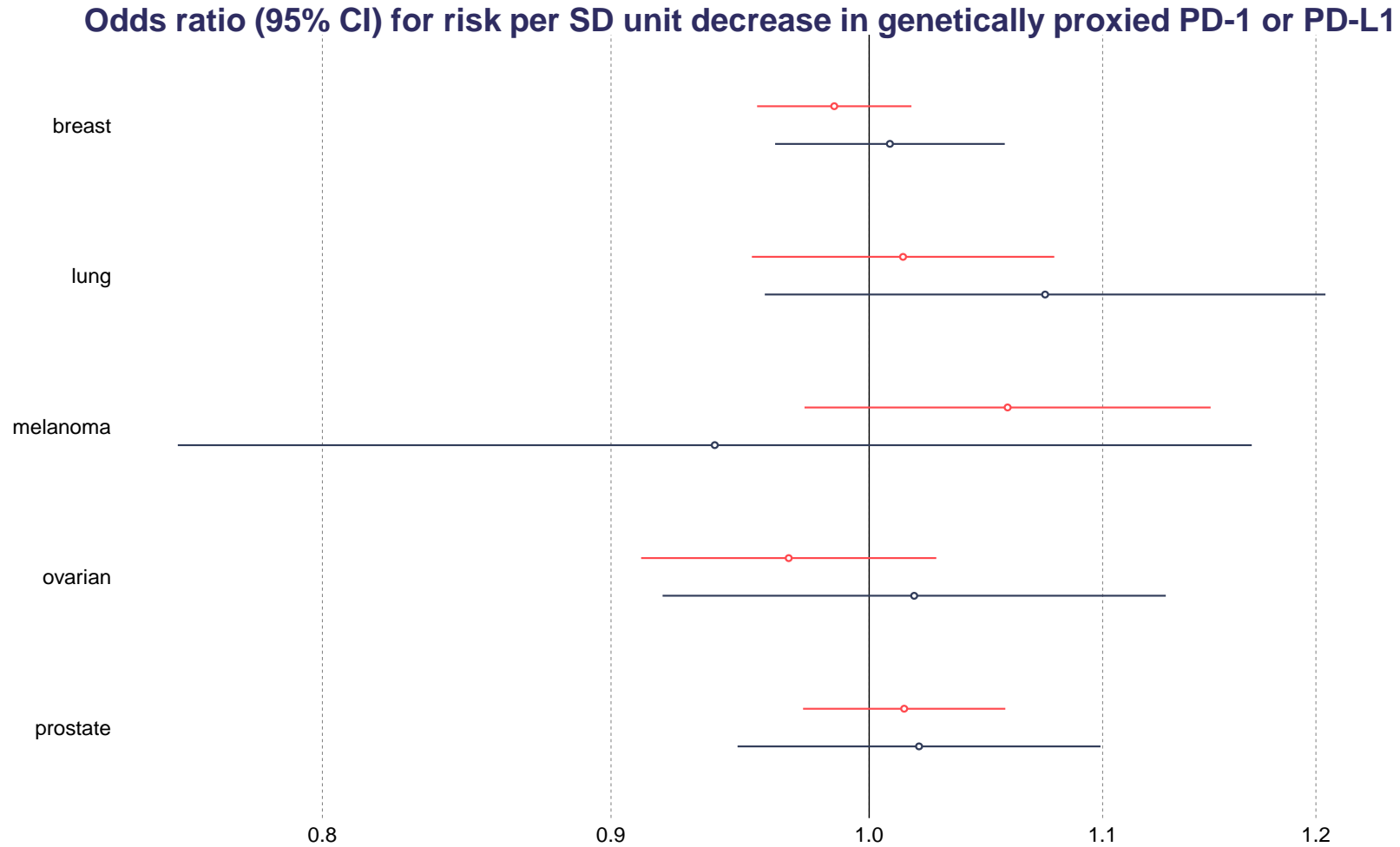
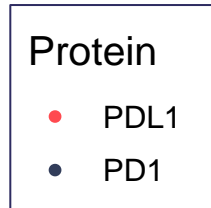


Collider bias



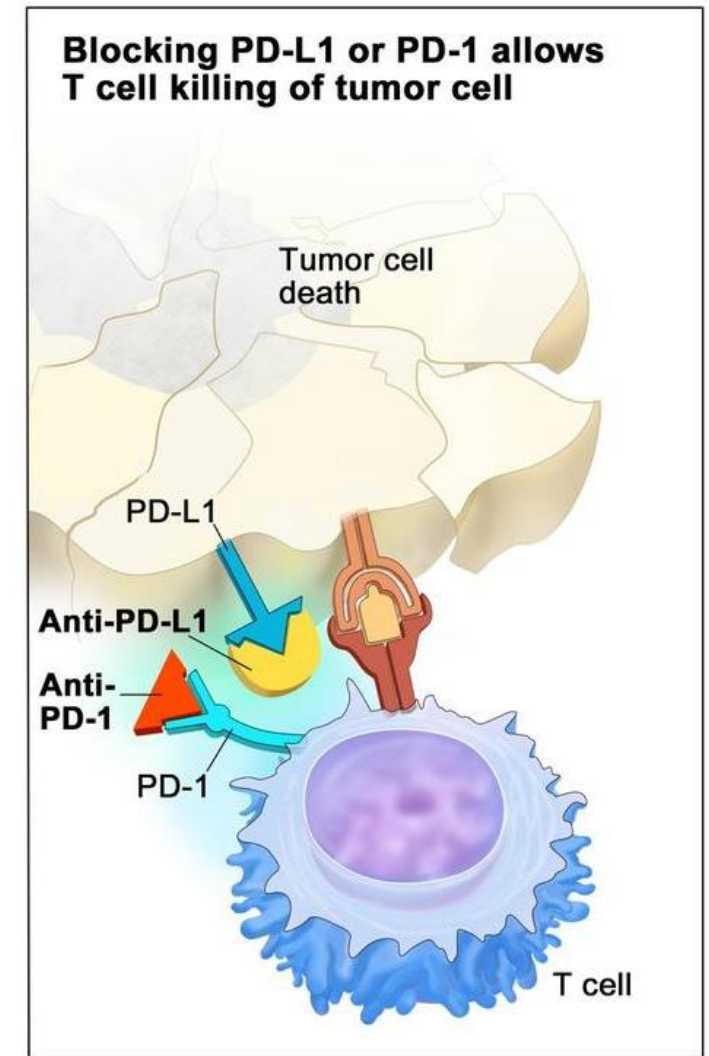
Obtained from: [7]

Cancer risk



Lack of clear associations for PD-L1

- Poor instrument validity
 - Biologically relevant tissue?
 - General vs cancer population
- Limitations of prognosis MR:
 - Power
 - Heritability
 - Treatment effects



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Conclusions

Aim 1: Investigate repurposing potential of ICIs in cancer treatment using MR

- No strong evidence for PD-L1 inhibitor repurposing
- Some evidence for PD-1 inhibitor repurposing

Aim 2: Investigate applicability of MR in cancer survival settings

- Remaining challenges: power, instrument validity
- Potential host (PD-1) vs tumour (PD-L1) difference in applicability



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TCGA (lung)

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Mei Dong

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ILCCO consortium

Patients and families



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Thank you

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