ImmunoScience Academy

Partnering for Education & Optimizing Treatment in ImmunoScience

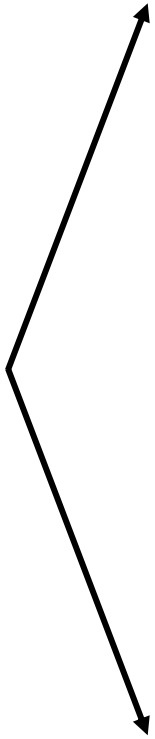
The immunology behind

long duration treatment with PD-1 blockade

Pierre Coulie
de Duve Institute
Universtity of Louvain

Comment on 'long duration'

Long duration of **response**



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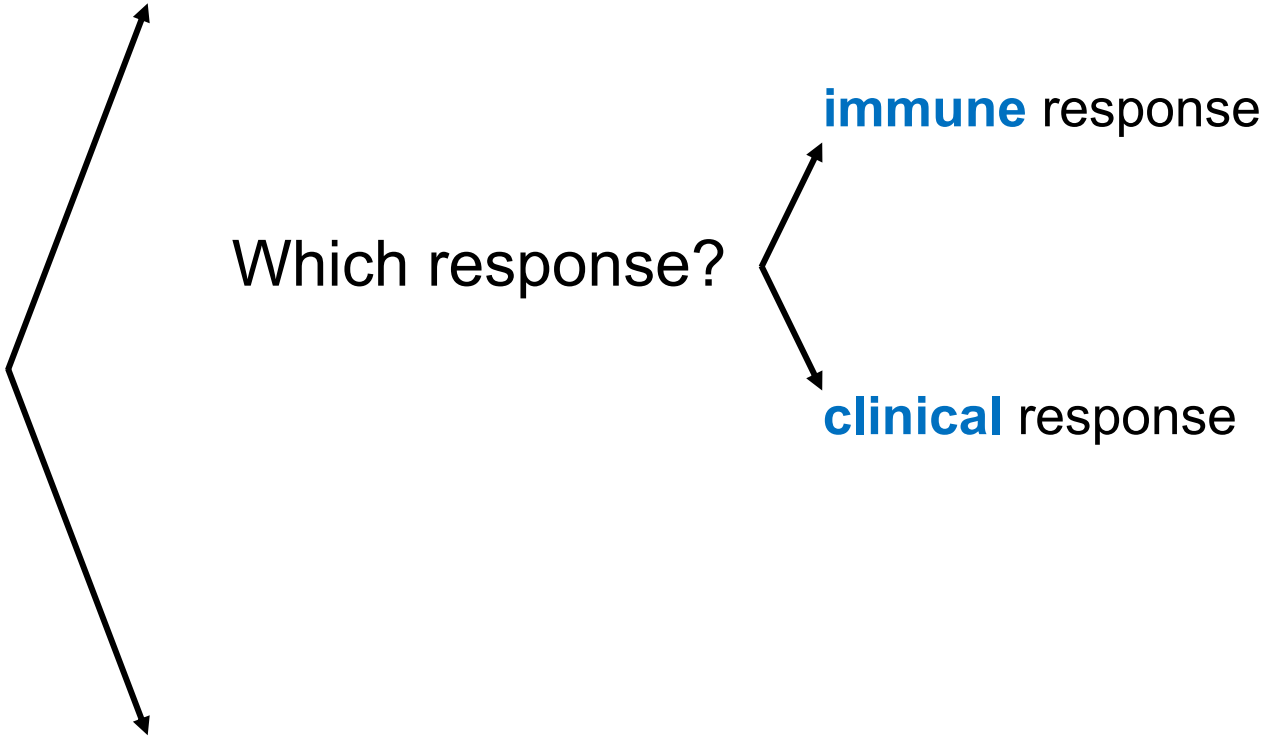

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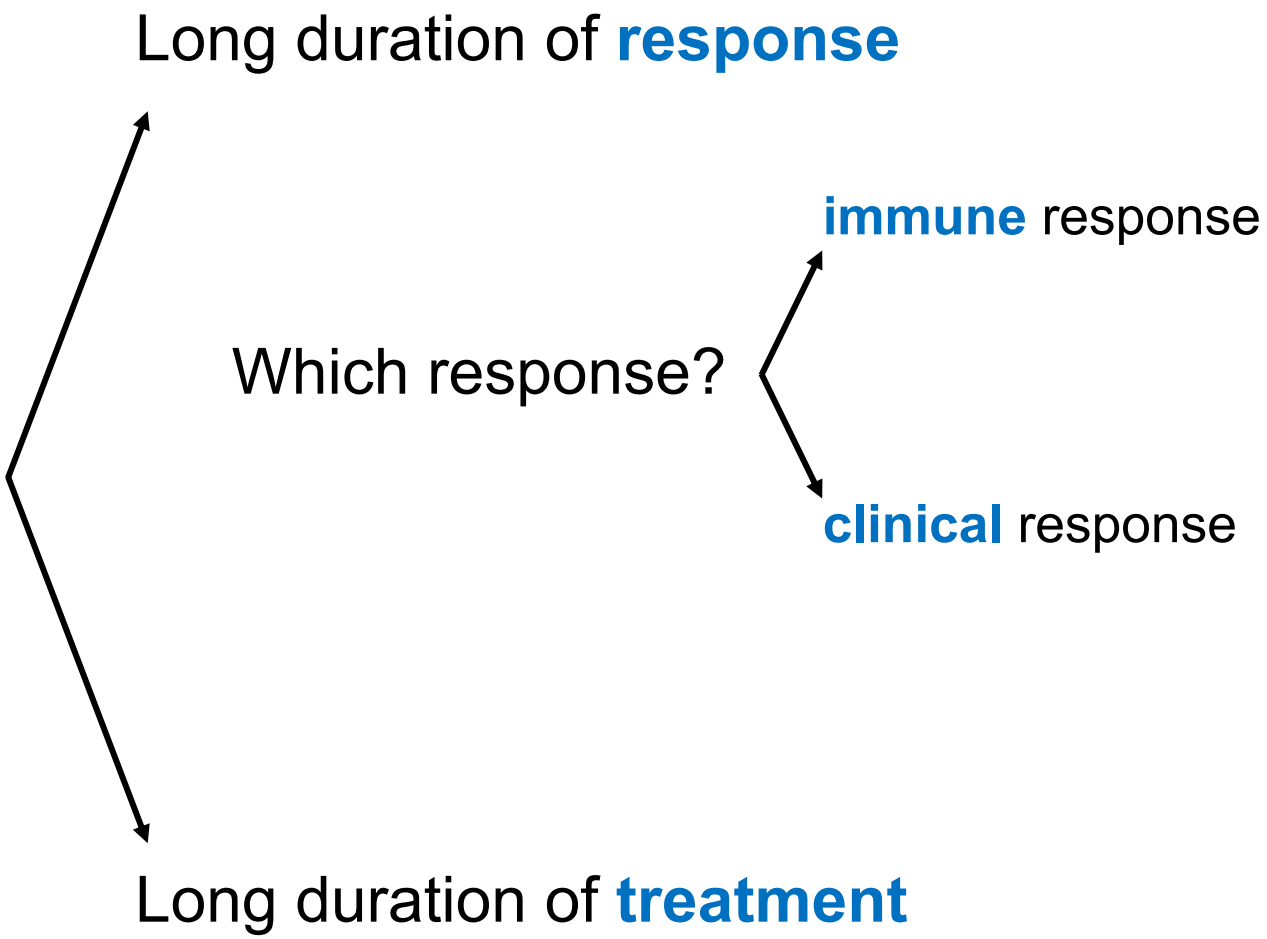

What is behind

- Immune memory: maintenance of a pool of memory T cells
  - (contrary to naive T cells, patrol in non-inflammed tissues and are easily restimulated)

Wei S, et al. *Cancer Discovery* 2018; 8; 1069–86; Chen D & Mellman I, *Immunity* 2013; 39:1–10.

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Which response?

- **immune** response
- **clinical** response

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- No or very few tumor cells left
- Less agressive tumor variant
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A long-acting CTLA-4 or PD-1 blockade is not required for a prolonged immune response

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- Concurrently: blocking Ab to CTLA-4, PD-1 or PD-L1

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Why do we need both?

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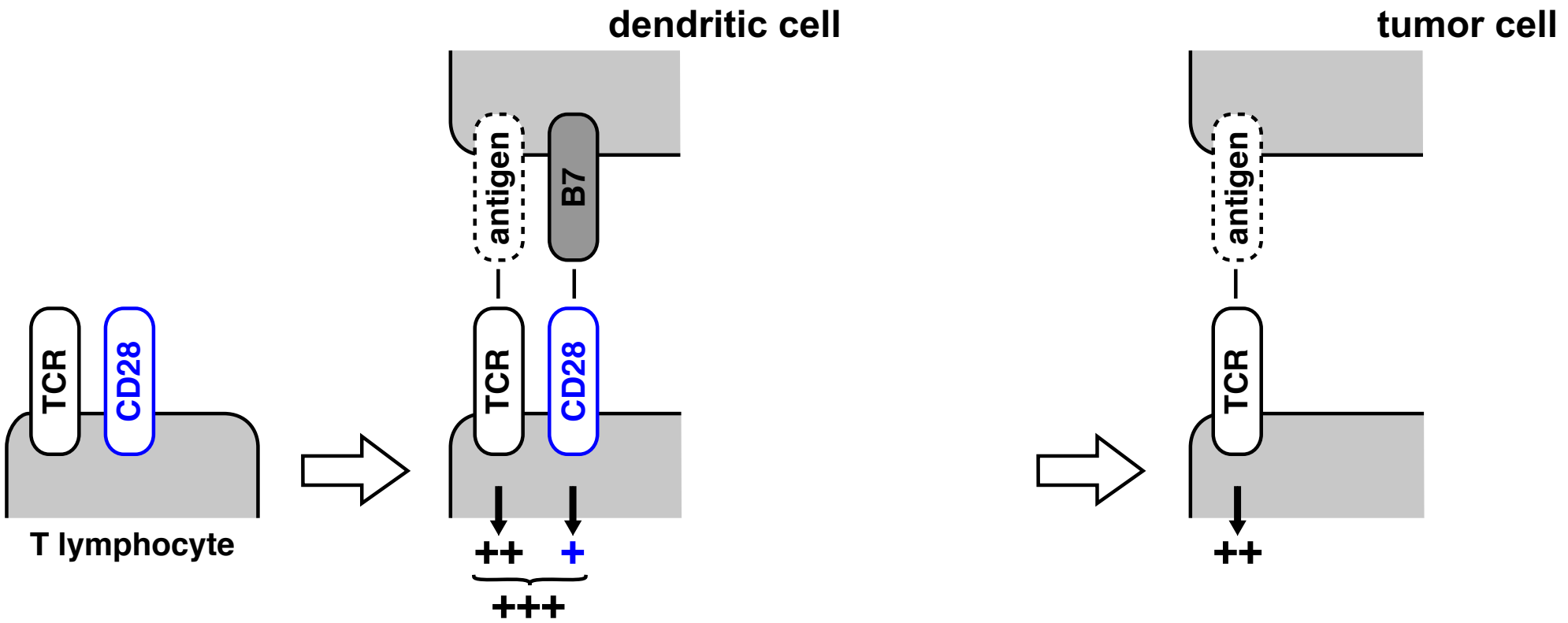
Antigenic stimulation and CTLA-4 or PD-1 blockade

naive T lymphocyte ⟹ **first activation** ⟹ (- proliferation, - differentiation) **subsequent activations**



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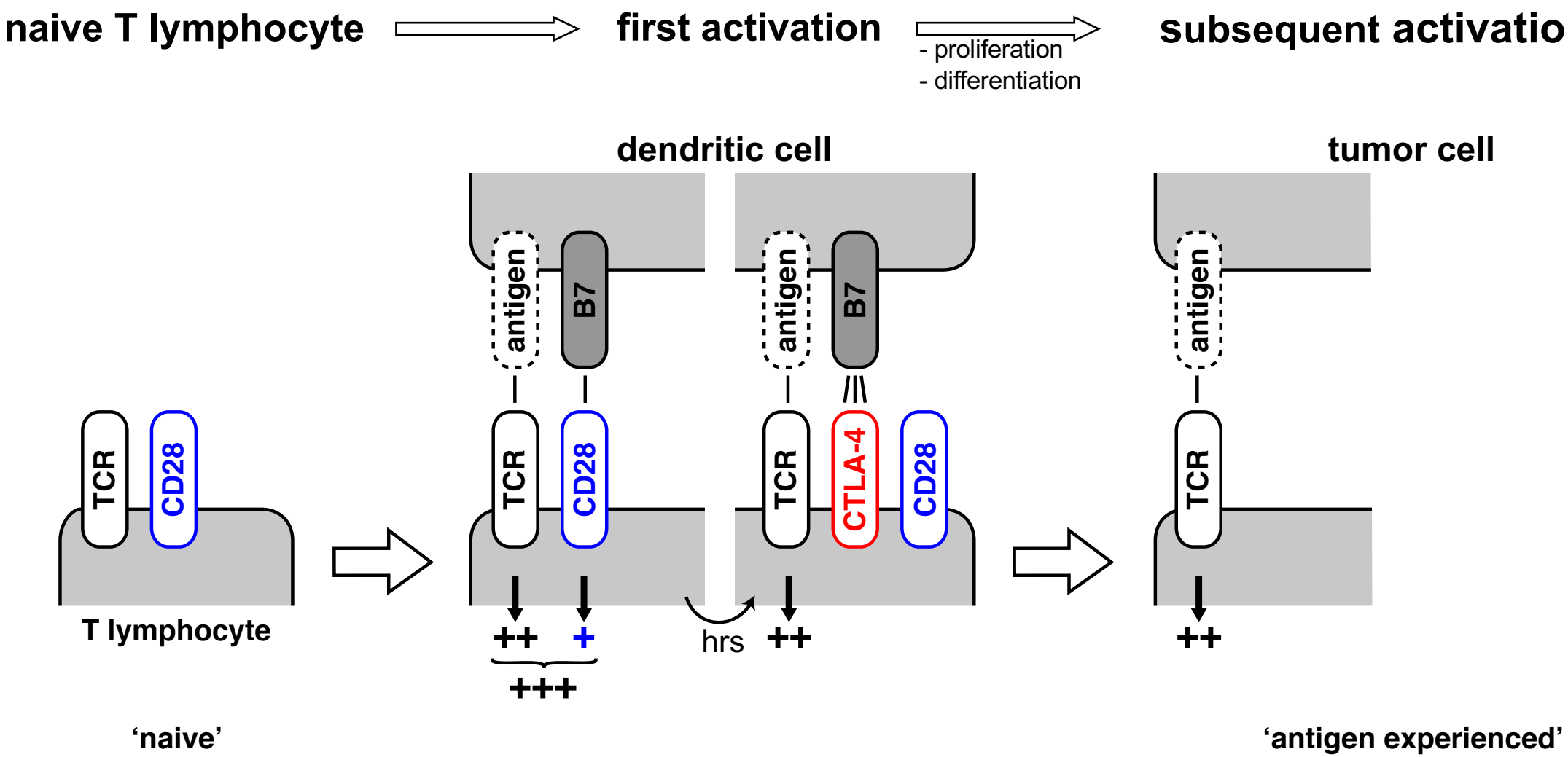

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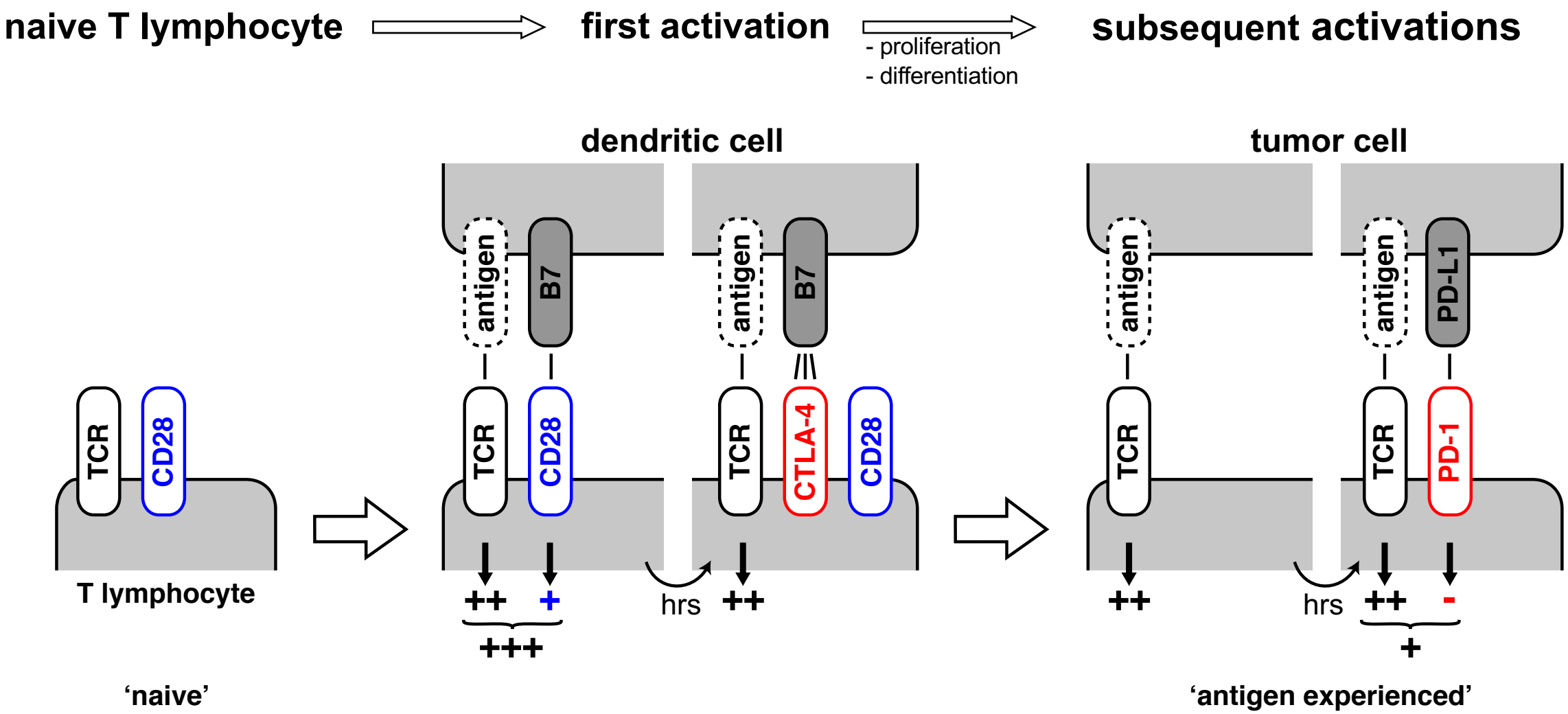

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- Both CTLA-4 and PD-1 come to the T cell surface only following TCR activation.
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- When T cells can be directly re-stimulated by the tumor cells themselves, it depends on their having access to the tumor and on a non-immunosuppressive microenvironment.

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- When T cells can be directly re-stimulated by the tumor cells themselves, it depends on their having access to the tumor and on a non-immunosuppressive microenvironment.
- It is therefore impossible to predict when exactly anti-tumor T cells will be activated in a given patient.
- It is expected that chemotherapy/radiotherapy/targeted therapy, which destroy tumor cells, increase the probability of activating anti-tumor T cells. Therapeutic anticancer vaccines even more so.

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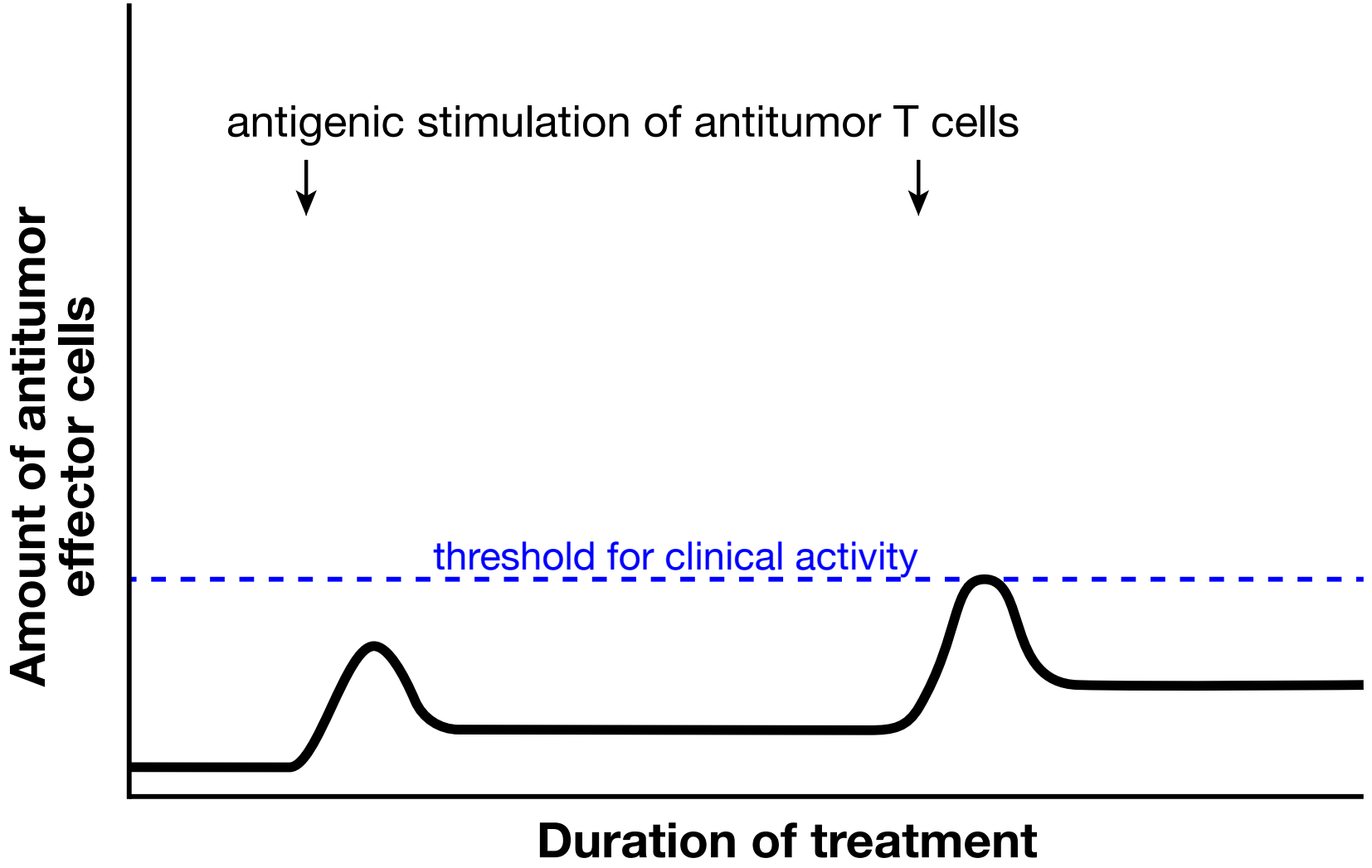
Delayed clinical response to immunostimulatory antibodies



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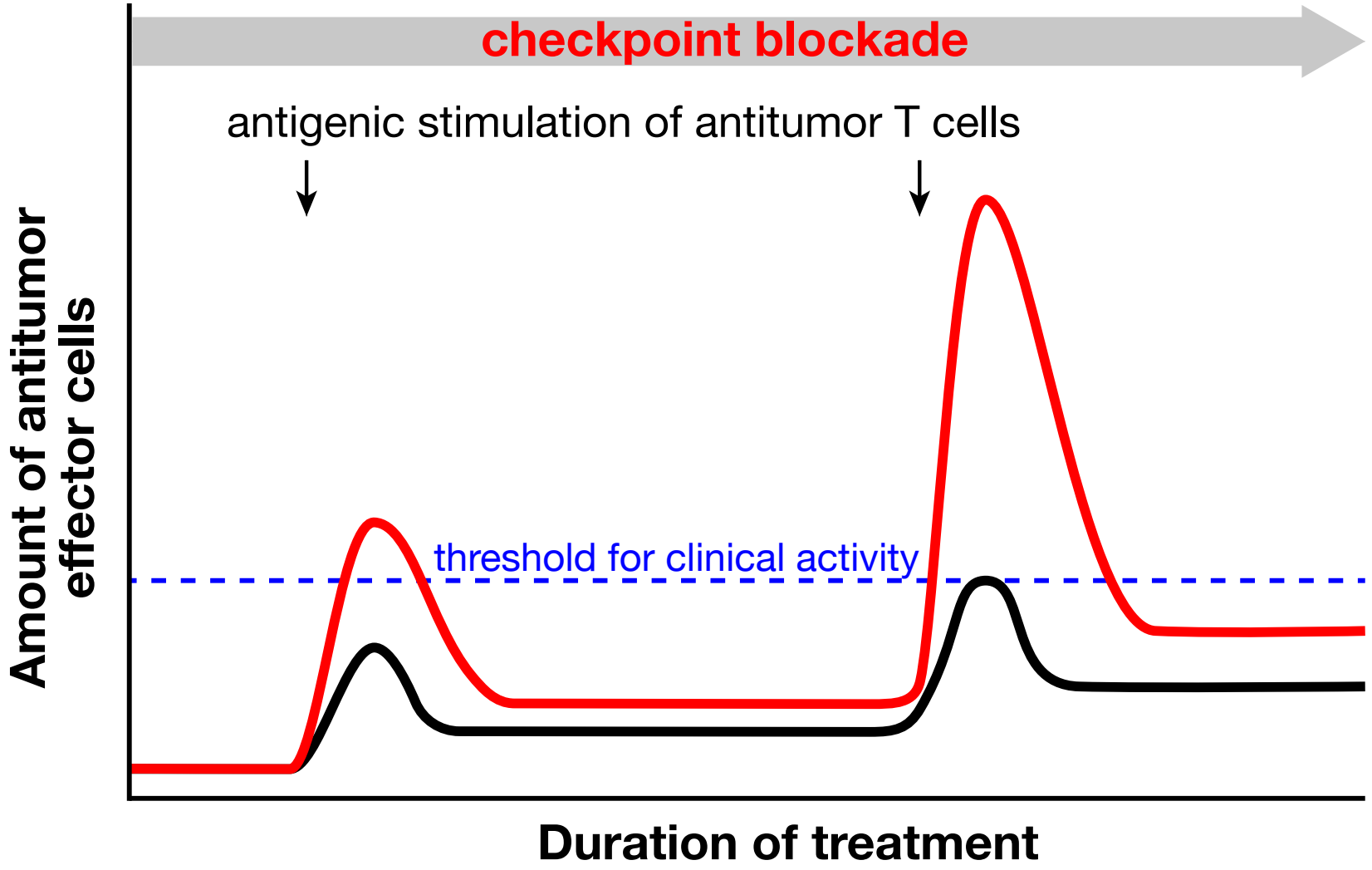

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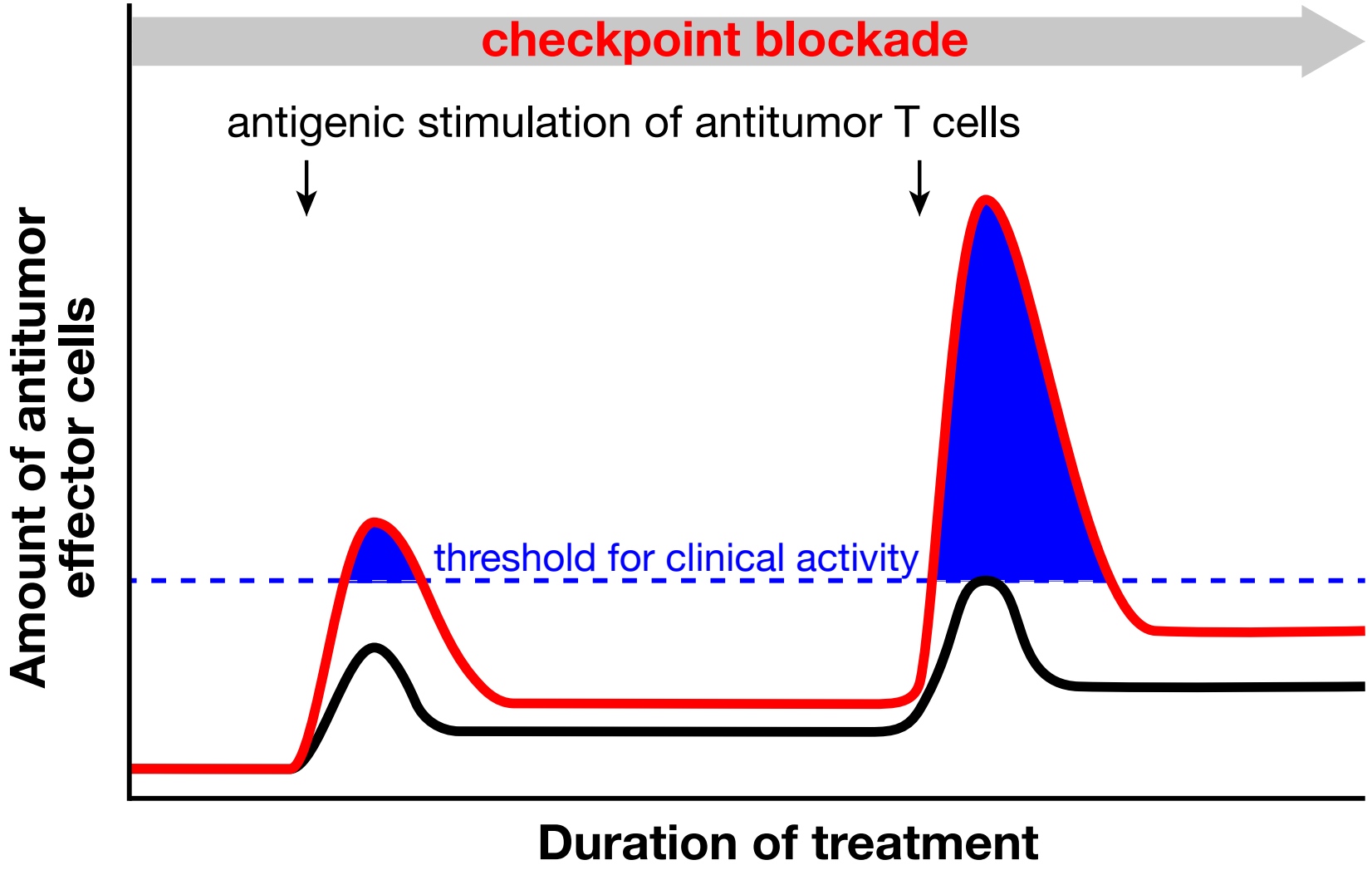

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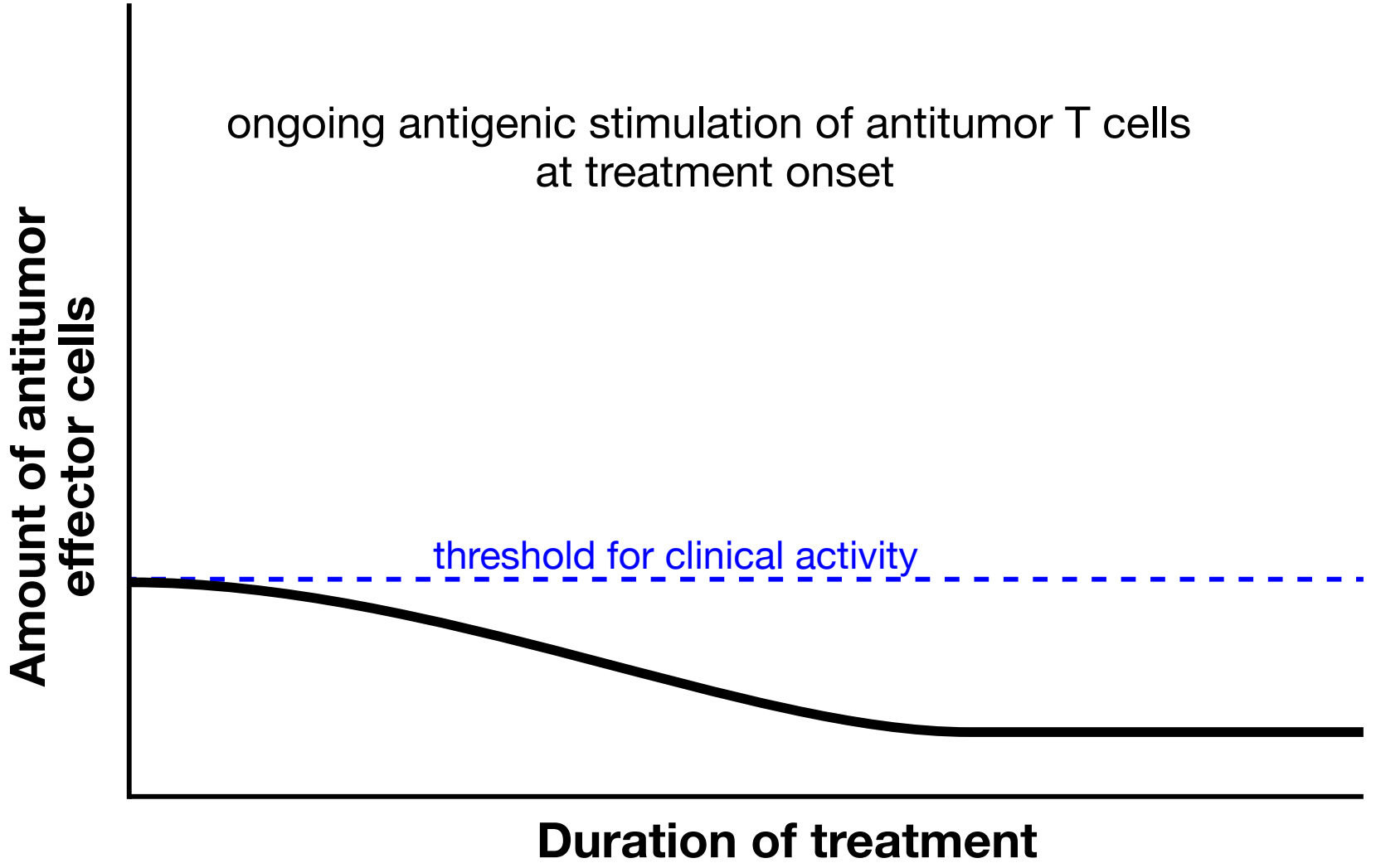

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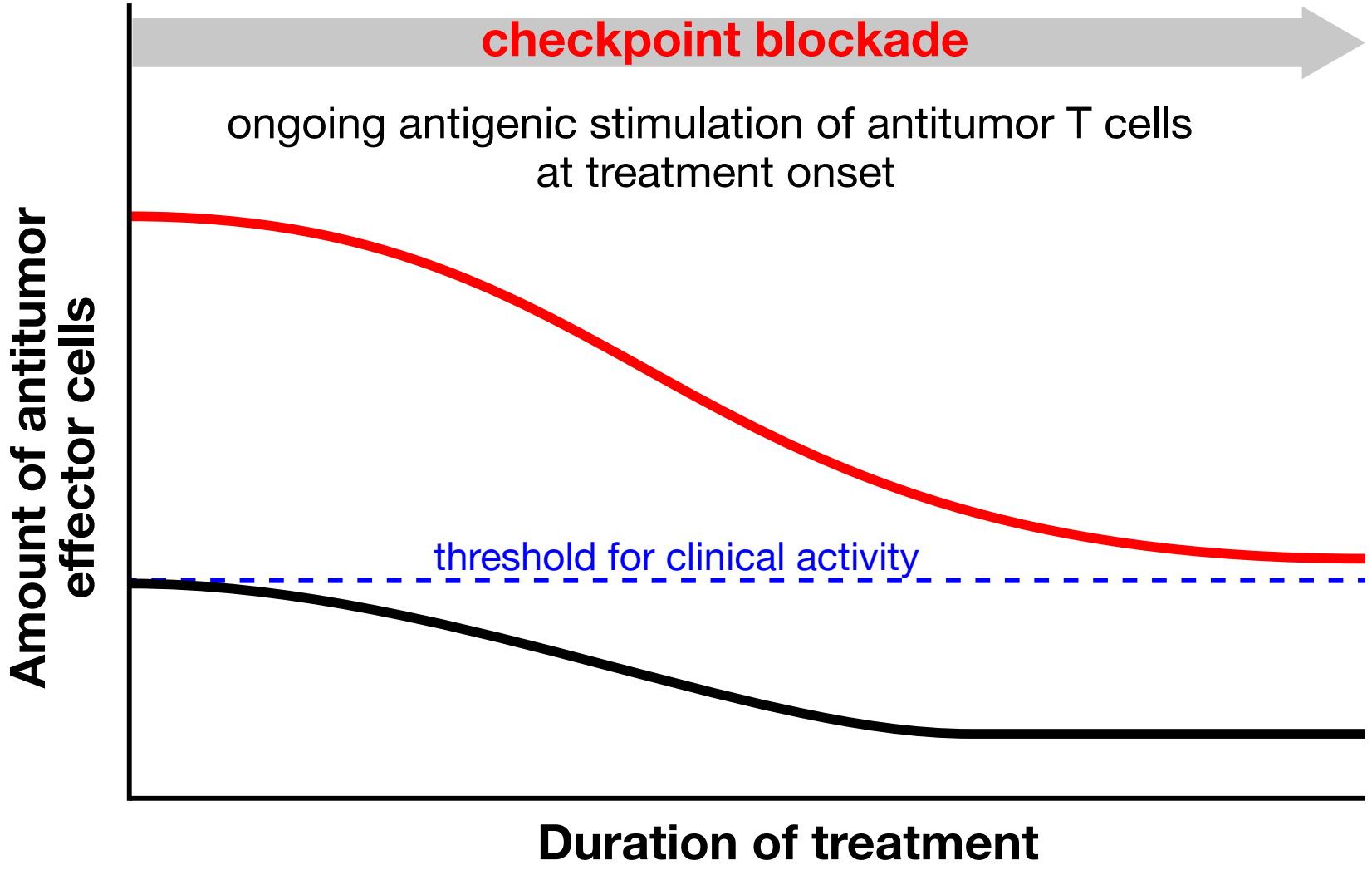

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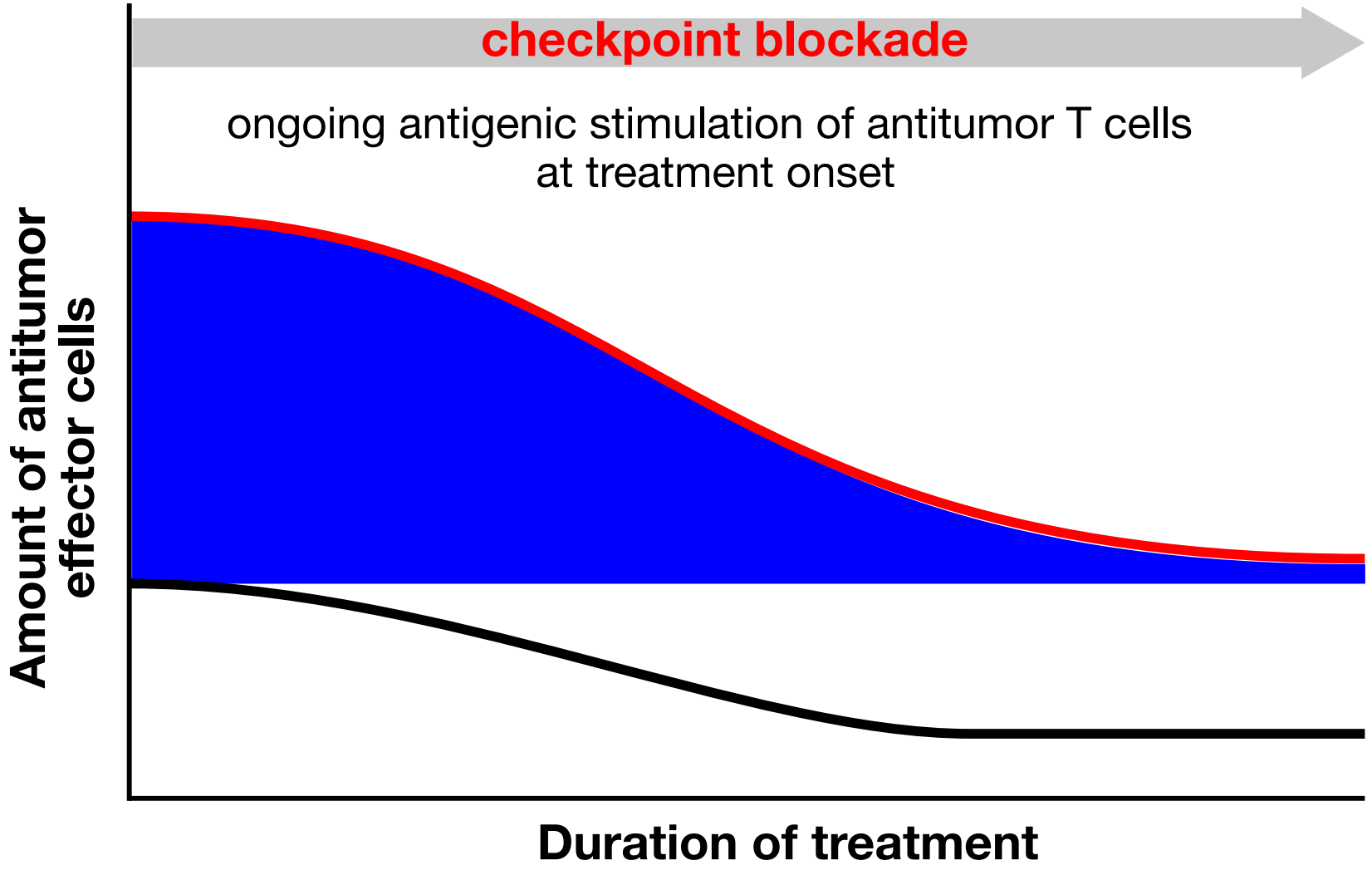

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Summary

- Under physiological conditions, CTLA-4 and PD-1 are present on the surface of activated T cells.
  - Cautionary note: regulatory T cells constitutively express high levels of surface CTLA-4, but we still do not know whether T-regs are important for the clinical responses to anti-CTLA-4 antibodies in humans
- Thus the main effects of CTLA-4 or PD-1 blockades in cancer immunotherapy are only expected following T cell activation, which implies tumor antigen release or presentation.
  - Cautionary note: tumors often contain so-called 'exhausted' T cells, which bear PD-1 and other inhibitory co-receptors. They are thought to be chronically activated and re-activated by PD-1 blockade

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  - Cautionary note: tumors often contain so-called 'exhausted' T cells, which bear PD-1 and other inhibitory co-receptors. They are thought to be chronically activated and re-activated by PD-1 blockade
- When and where anti-tumor T cells are activated in a given patient, is unpredictable, justifying long duration checkpoint blockade.
- This physiology of T cell activation increased or decreased, but never initiated, by co-receptors likely explains that the observed clinical effects of CTLA-4 or PD-1 blockades can be delayed.
- It supports the combination of CTLA-4/PD-1 blockades with other modalities of tumor cell destruction.

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