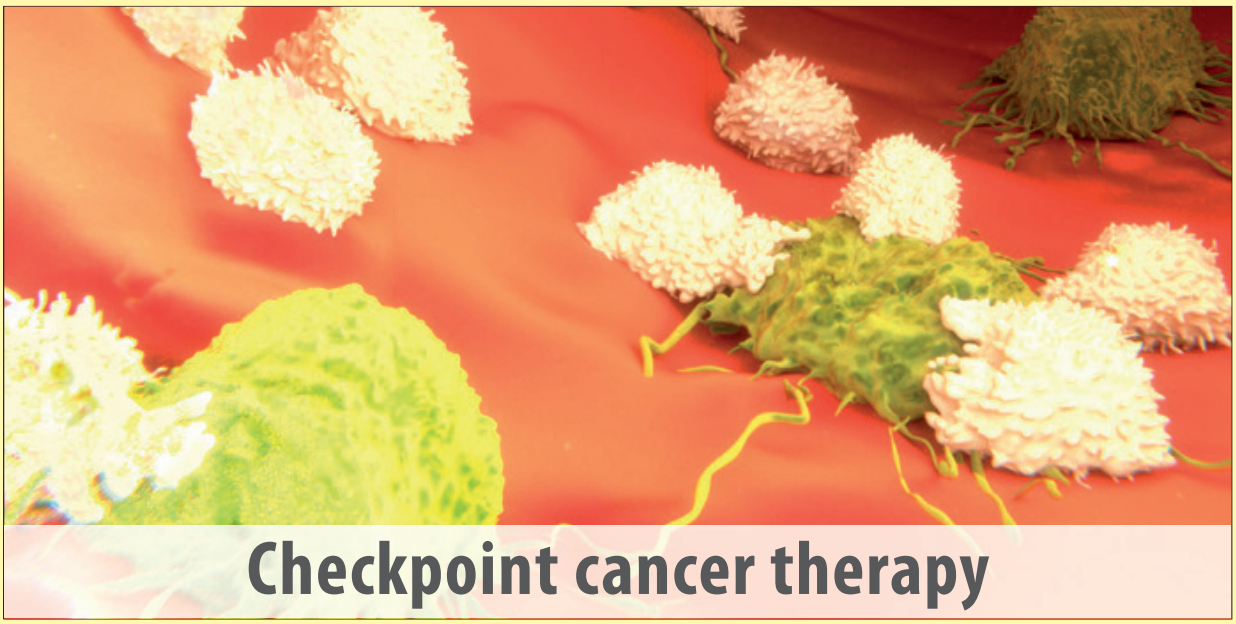
Cancer, Immunotherapy
and the role of kynurenine



IDK® Kynurenine

Portfolio for human serum, plasma, urine and dried blood

- Basis: **kynurenine as a biomarker for tumor escape**
- Research: **biomarker for immunotherapies**
- Clinic: **kynurenine in serum and the prognosis for the patient**
- Therapy: **combination of checkpoint and IDO inhibition**

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Cancer, Immunotherapy and the role of kynurenine

Immunotherapy is the new hope for the treatment of cancer. One target for such a therapy are so-called **immune checkpoints**. Immune checkpoints function by modulating the immune activity to prevent the body from autoimmune diseases and allow for self-tolerance. Tumours may take advantage from these checkpoints by manipulating them.

One example is the PD-1 – PDL-1 signalling: most tumours produce the "programmed death ligand" PD-L1. This PD-L1 can interact with the receptors PD-1 and B7.1 on T cells, which is like a hand shaking with T cells, leading to less T killer cells and more T regulatory cells. This leads to a comfortable micro-environment for the tumour.

CTLA4 (cytotoxic T-lymphocyte-associated protein 4), is a protein receptor, functioning as an immune checkpoint. CTLA4 acts as an „off" switch when bound to CD80 or CD86 on the surface of antigen-presenting cells. With CTLA4 APCs are inhibited and the immune response is less strong. Tumour cells induce the formation of CTLA4 and are so able to switch off the immune system.

In recent years, **therapeutic antibodies** are developed inhibiting the **interaction of the tumour cells with the checkpoint molecules**. Anti-PD-1 and PD-L1 antibodies (nivolumab, pembrolizumab, atezolimab or durvalumab) inhibit the interaction between checkpoint and tumour and thus the inhibition of T cell attack on cancer cells. The anti-CTLA4 antibody (ipilimumab or tremelimumab) prevents the inhibition of the CTLA4 system and thus activates the T cell attack of the cancer cells (Xia et al., 2016).

In recent years, these therapeutic antibodies are increasingly used in cancer therapy. The concept was rewarded with the Nobel Prize for Medicine in 2018.

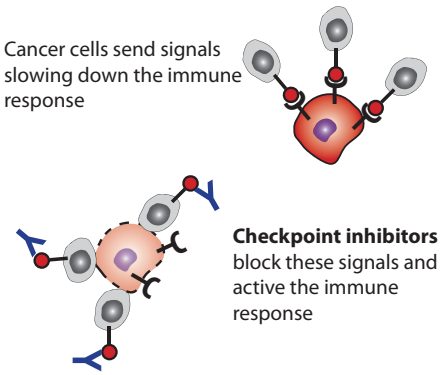

Fig. 1: **Checkpoint inhibition** (according to www.wissensschau.de)

Checkpoint inhibitor:
Blocking of either PD-1 (with Nivolumab or Pembrolizumab) or PD-L1 (with Atezolimab or Durvalumab) or blocking of another checkpoint, CTLA4 (with Ipilimumab) can inhibit the tumour escape and camouflage.

An important checkpoint molecule is **indolamin-2, 3-dioxygenase (IDO)**. IDO inhibits the proliferation of T cells by forming the endogenous immunosuppressive molecule kynurenine and so depleting tryptophan. This creates a tumour-friendly environment via the proliferation of T regs.

- High IDO activity leads to high kynurenine levels and immune suppression (less active T cells and NK cells; more T regs; angiogenesis in the tumour and tumour development)
- Inhibition of IDO activity leads to lower kynurenine levels and activation of the immune system (proliferation of T cells, suppression of T regs)
- Komiya et al. sum up: IDO inhibitors show an increased efficacy in combination with checkpoint inhibitors

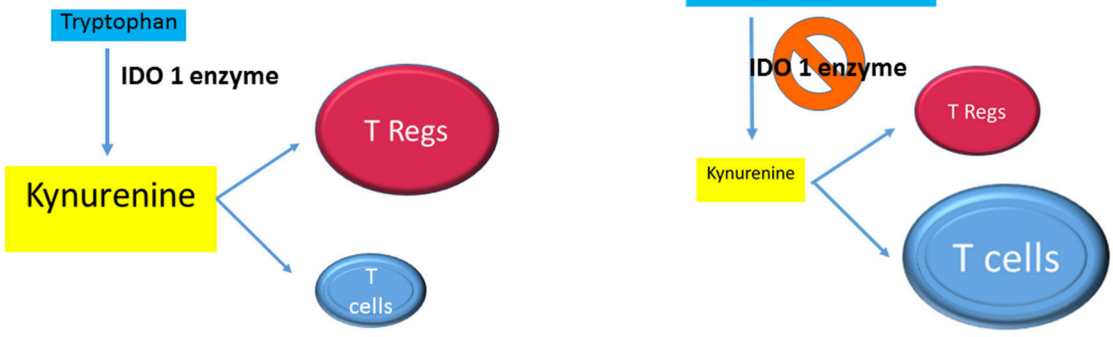

Fig. 2: **IDO activity and IDO inhibition** (according to Komiya et al., 2018)

Presently, several IDO inhibitors with different functional approach undergo clinical trials.

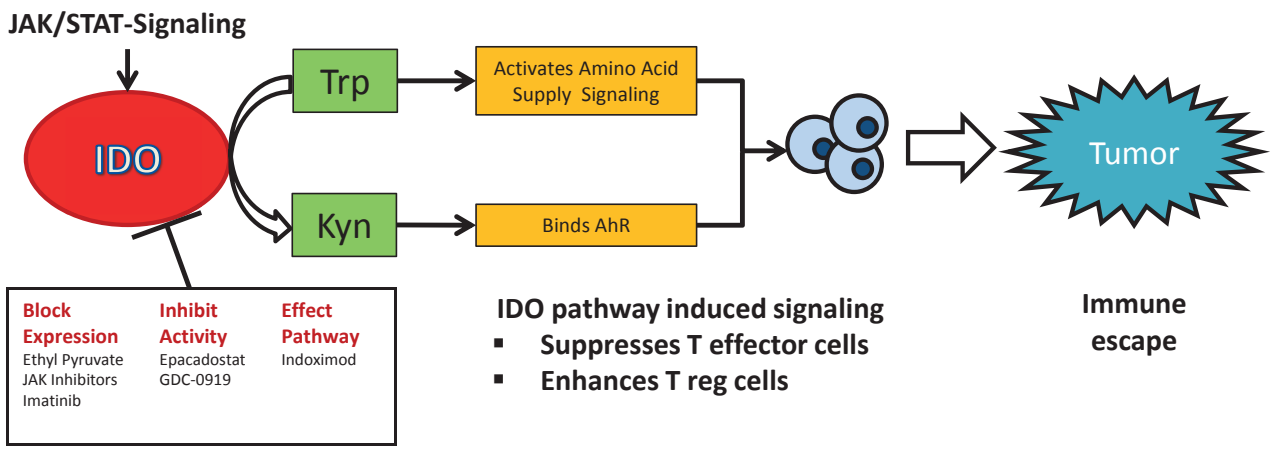

***Fig. 3:* IDO inhibition** (according to Shan Qian et al. (2016) RSC Adv. 6: 7575-81.)

During the last years, it became more and more obvious that tumours manipulate in parallel PD-1 / PD-L1 ***and*** the IDO system.

Having this in mind, a study by Botticelli et al. (published in 2018) is to be understood, in which a large portion of the PD-1 treatment failures showed a high IDO activity (measured as the ratio of kynurenine to tryptophan).

Patients with high IDO activity showed therapy failure (group „YES", early progression of disease). Patients with a ratio of more than 65 µmol/mmol have a significantly worse prognosis (see *Fig 4b*: Kaplan-Meier-curve).

A high ratio of Kynurenine/Tryptophan is therefore a predictive biomarker for therapy resistance during treatment with PD-1 blocker.

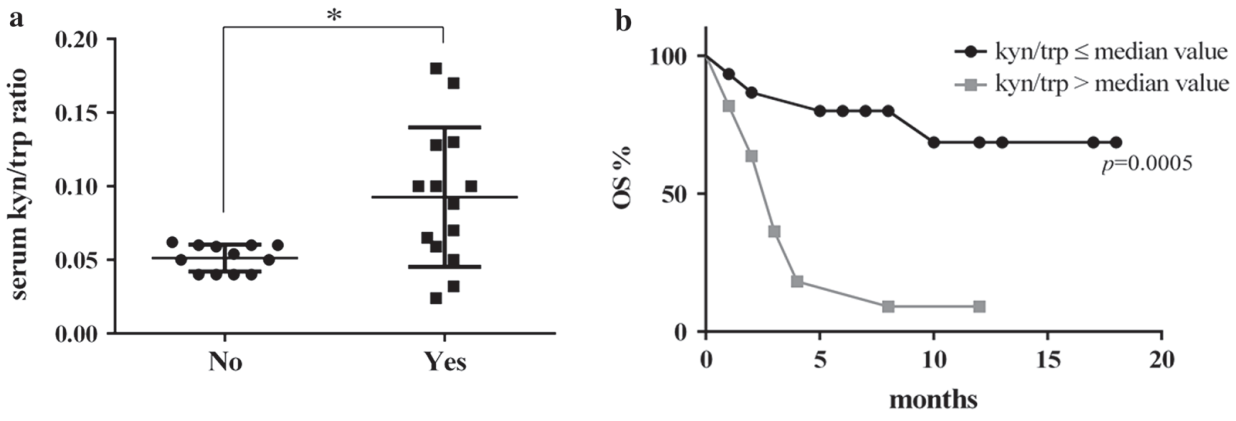

Fig. 4: according to Botticelli et al. (2018) J Transl Med 16:219, Fig. 1 and Fig. 2

- IDO activity is a valuable biomarker to identify patients benefitting from a combined therapy of anti-PD-1 plus anti-IDO
- IDO activity can be used to stratify patients receiving checkpoint-inhibitors
- Further studies with potentially synergistic agents are necessary to improve immunotherapies

IDK® Kynurenine Portfolio:

IDK® IDO activity ELISA (K 7726)

IDK® IDO ELISA (KR7727) *(for research use only)*

IDK® Kynurenine ELISA (K 7728)

IDK® Kynurenine high sensitive ELISA (KR3728) *(for research use only)*

IDK® Tryptophan ELISA) (K 7730)

IDK® Tryptophan high sensitive ELISA (KR3730) *(for research use only)*

IDK® Kynurenic acid (KynA) ELISA (K 7735)

IDK® Quinolinic acid (Quin A) ELISA (K 7736)

Literature:

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