IMUNOTERAPIA CONTRA TUMORES

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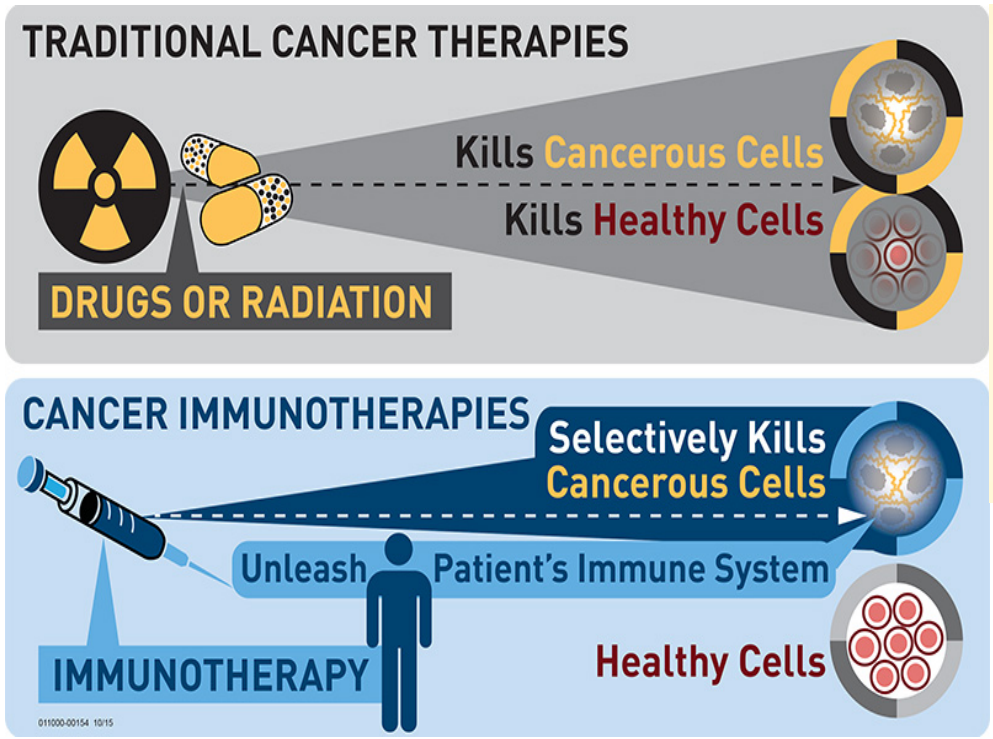
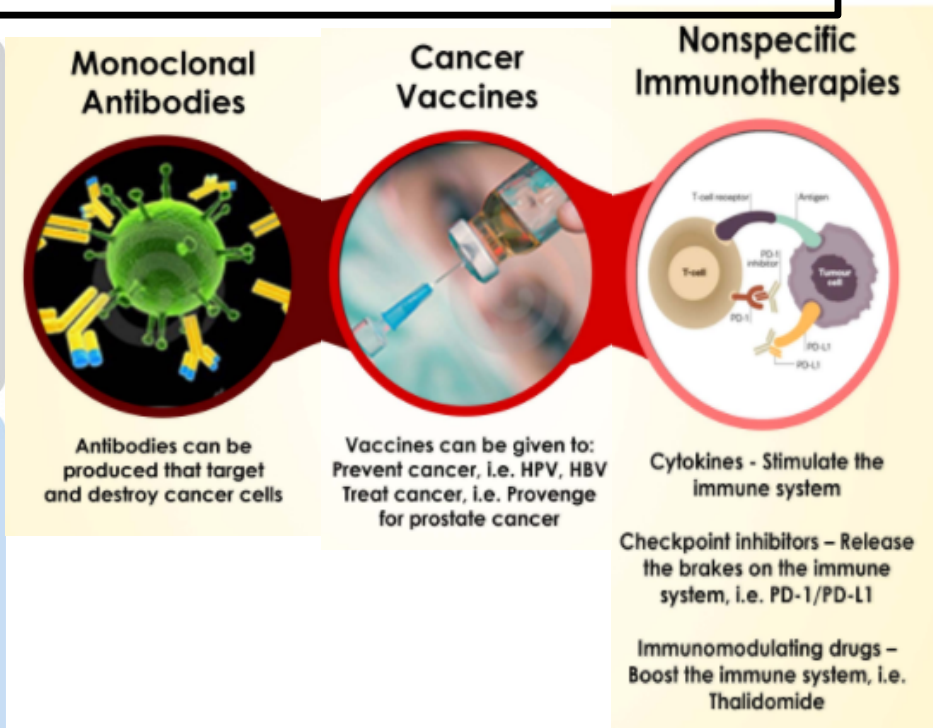
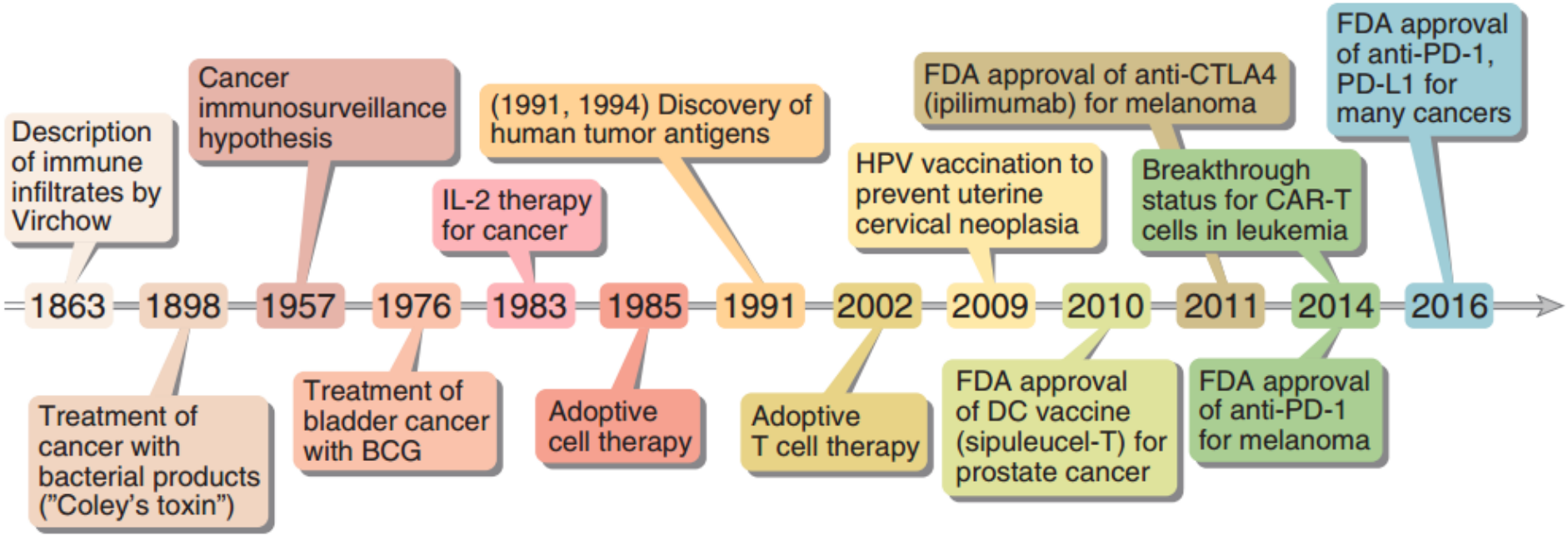
IMUNOTERAPIA DO CANCER

Immune responses to tumors can theoretically be highly specifc for tumor cells and will not injure most normal cells.





IMUNOTERAPIA DO CANCER

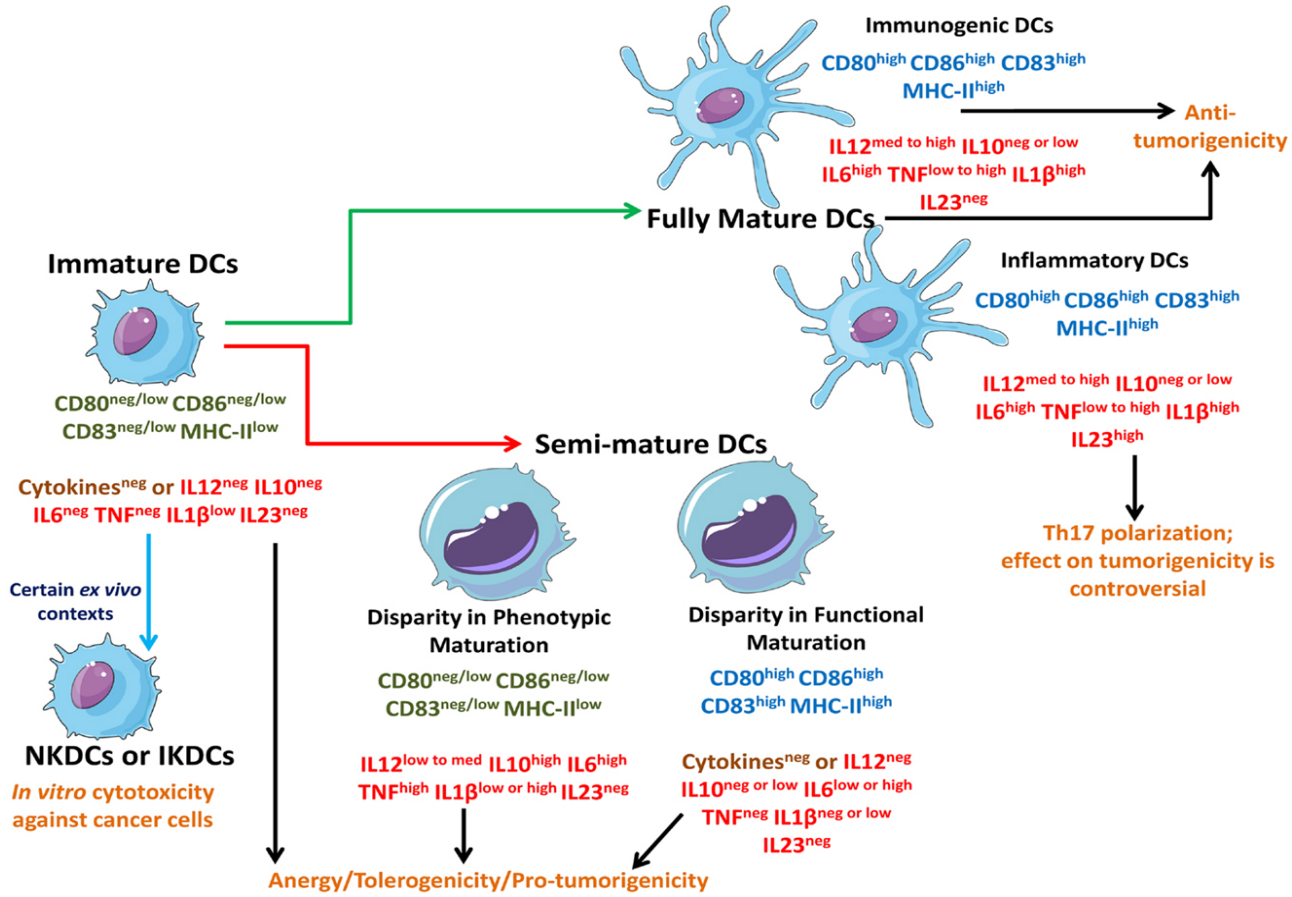


IMUNOTERAPIA DO CANCER

Strategy	Basic mechanism and major advantages	Major disadvantages	Reference
Cytokines			
IL-2	-Stimulates the host's immune system	-Low response rates -Significant risk of serious systemic inflammation	[1]
IFN-α	-Stimulates the host's immune system -Durable responses (from a small subset of melanoma patients)	-Low response rates -High-dose toxicity	[1]
Cell-based therapies			
Vaccines	-Stimulates the host's immune system -Minimal toxicity (e.g., sipuleucel-T) -Administered in the outpatient clinic	-Lack of universal antigens and ideal immunization protocols lead to poor efficacy and response	[6]
Adoptive cellular therapy	-Omits the task of breaking tolerance to tumor antigens -Produces a high avidity in effector T cells -Lymphodepleting conditioning regimen prior to TIL infusion enhances efficacy -Genetic T cell engineering broadens TIL to malignancies other than melanoma	-Restricted to melanoma -Safety issues, serious adverse effects, and lack of long lasting responses in many patients -Requires time to develop the desired cell populations -Expensive	[5, 27, 60, 62–64, 68–70]
Immune checkpoint blockade			
Anti-CTLA-4 monoclonal antibodies	-Unleashes pre-existing anticancer T cell responses and possibly triggers new -Exhibits potent antitumor properties -Prolongation of overall survival	-Only a relatively small fraction of patients obtain clinical benefit -Severe immune-related adverse events have been observed in up to 35 % of patients	[5, 13, 76, 77]
Anti-PD1 and anti-PD-L1 antibodies	-Sufficient clinical responses which are often long-lasting -Therapeutic responses in patients within a broad range of human cancers -Reduced toxicity compared to anti-CTLA-4 antibodies	-Only a relatively small fraction of patients obtain clinical benefit	[2, 84, 90]
Combination immunotherapy (immune checkpoint blockade as the backbone)	-Improvement of anti-tumor responses/ immunity	-May lead to increases in the magnitude, frequency, and onset of side effects	[9, 10]

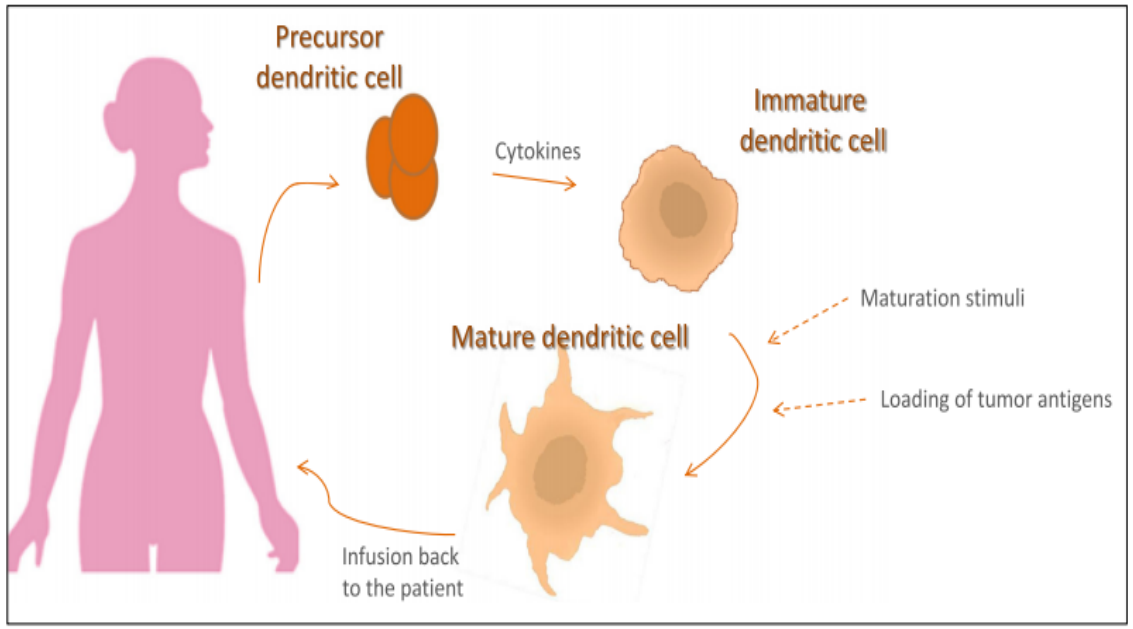
IL-2, Interleukin 2; IFN-α, Interferon-alpha; CTLA-4, Cytotoxic T lymphocyte-associated protein 4; PD1, Programmed cell death protein 1; TIL, Tumor infiltrating antibodies

IMUNOTERAPIA DO CANCER: DC VACINAS



IMUNOTERAPIA DO CANCER: DC VACINAS

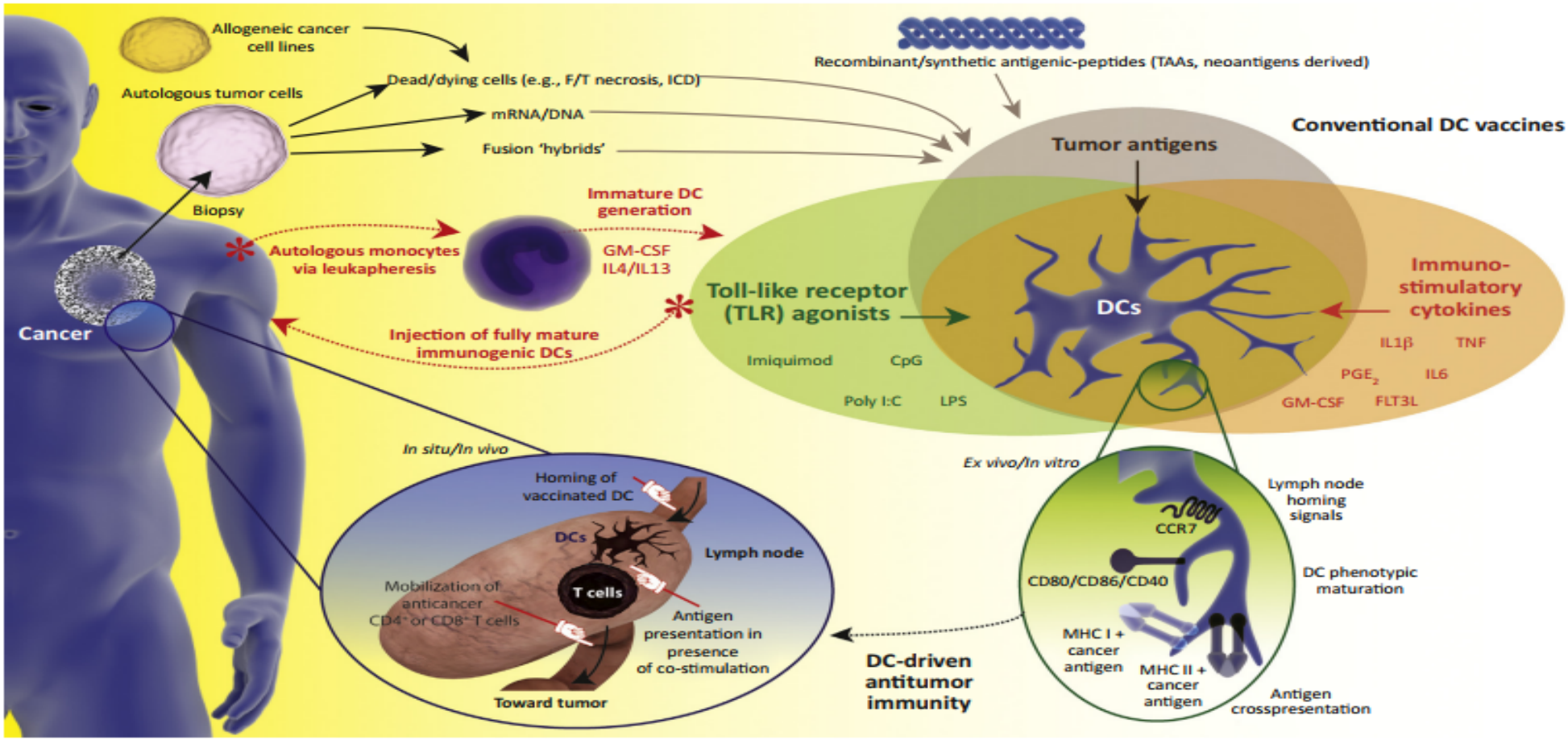
Tumor **environment disables the immune response** and therefore could **induce tolerance**. In contrast to conventional prophylactic vaccines for infectious agents, **cancer vaccination must break the tolerance acquired by the tumor cells.**



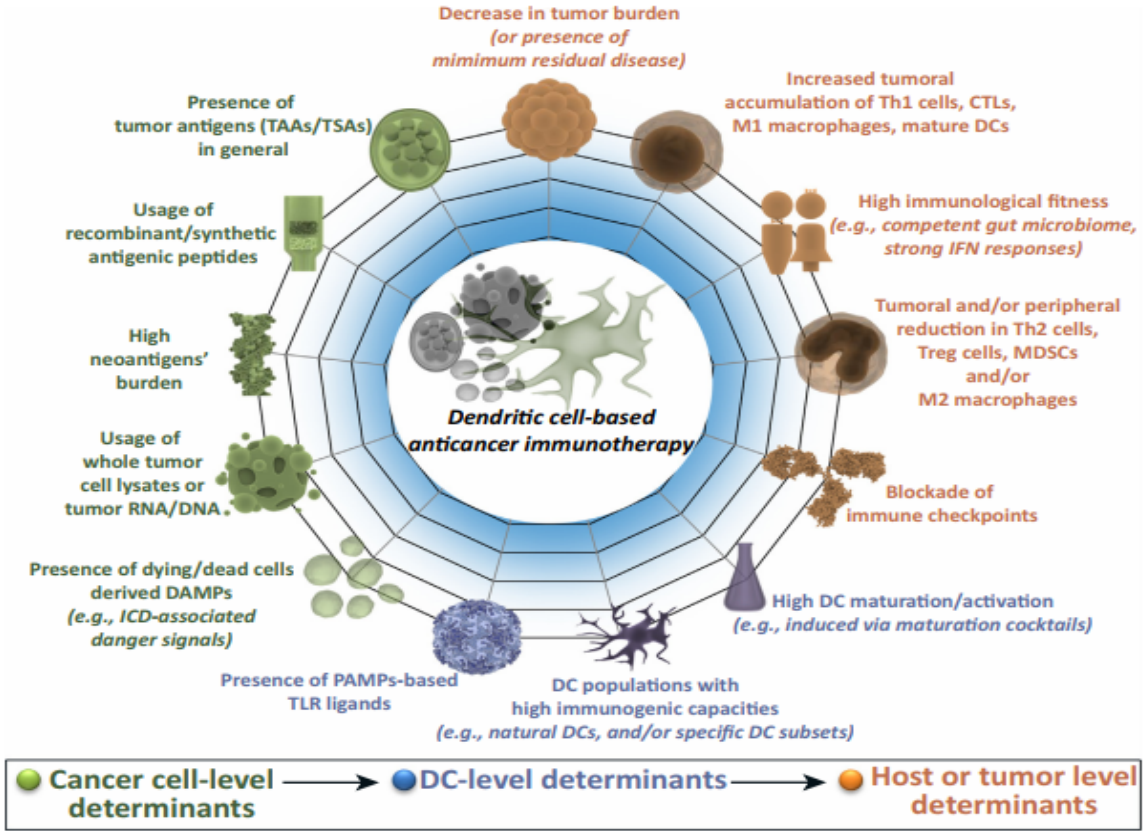
- DCs -> Professional APCs
- Antigens must be targeted to DCs.
- Short peptides?
- Long peptides?
- Tumoral Lysate?

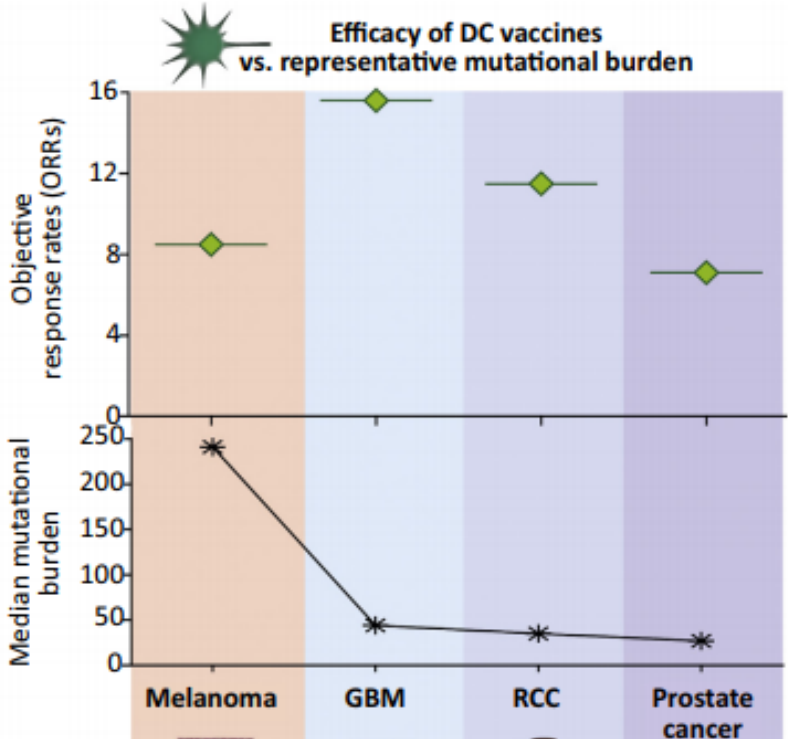
Basic principle behind DC vaccines entails the **isolation of autologous DCs** from a patient followed by their **in vitro 'loading' with appropriate source of tumor antigens** (i.e., **signal 1)** and s**ubsequent activation by defined 'maturation cocktails' (required to generate signals 2–3).**

IMUNOTERAPIA DO CANCER: DC VACINAS



IMUNOTERAPIA DO CANCER: VACINAS DC





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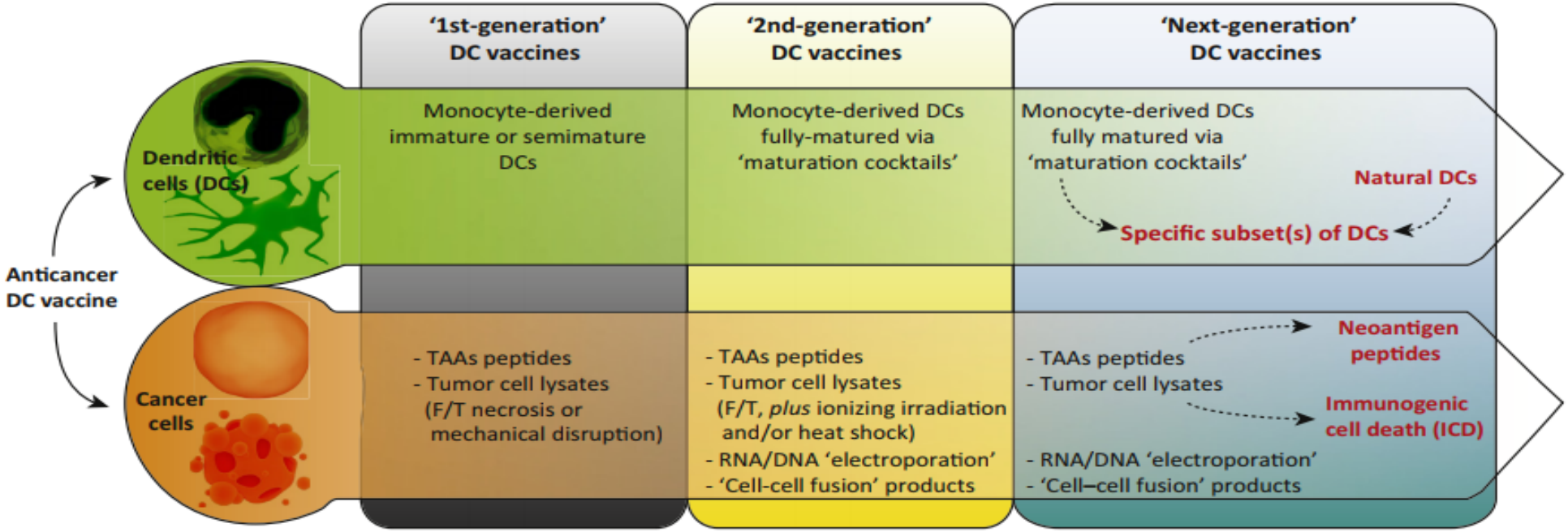
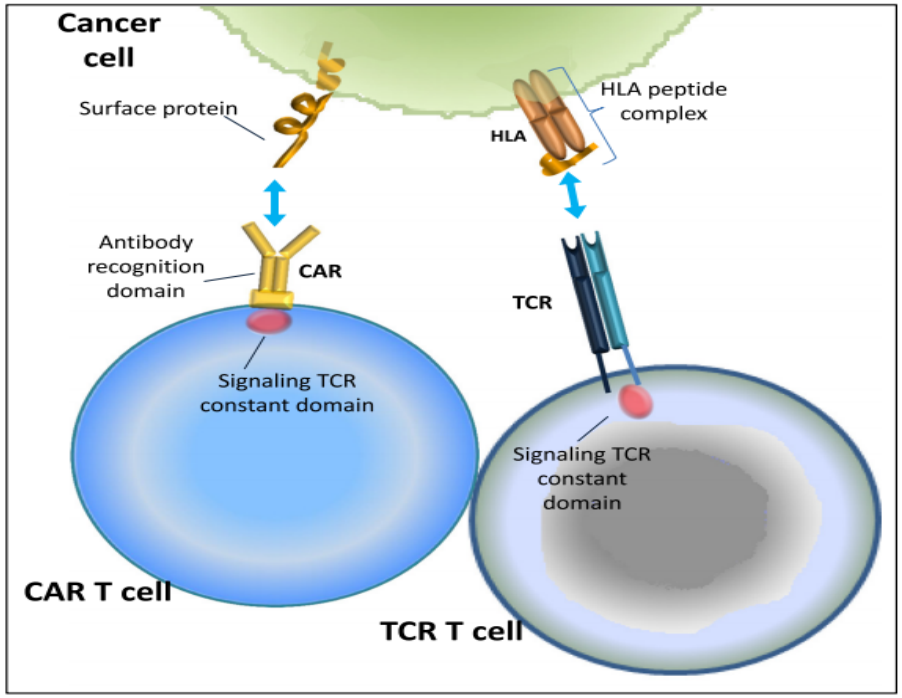


IMUNOTERAPIA DO CANCER: TERAPIA CELULAR ADOPTIVA

Adoptive cellular immunotherapy is the **transfer of cultured immune cells** that **have antitumor reactivity into a tumor-bearing host**. The immune cells are derived from a cancer patient's blood or solid tumor, and then are treated in various ways in vitro to expand their numbers and enhance their antitumor activity, before reinfusion back into the patient.

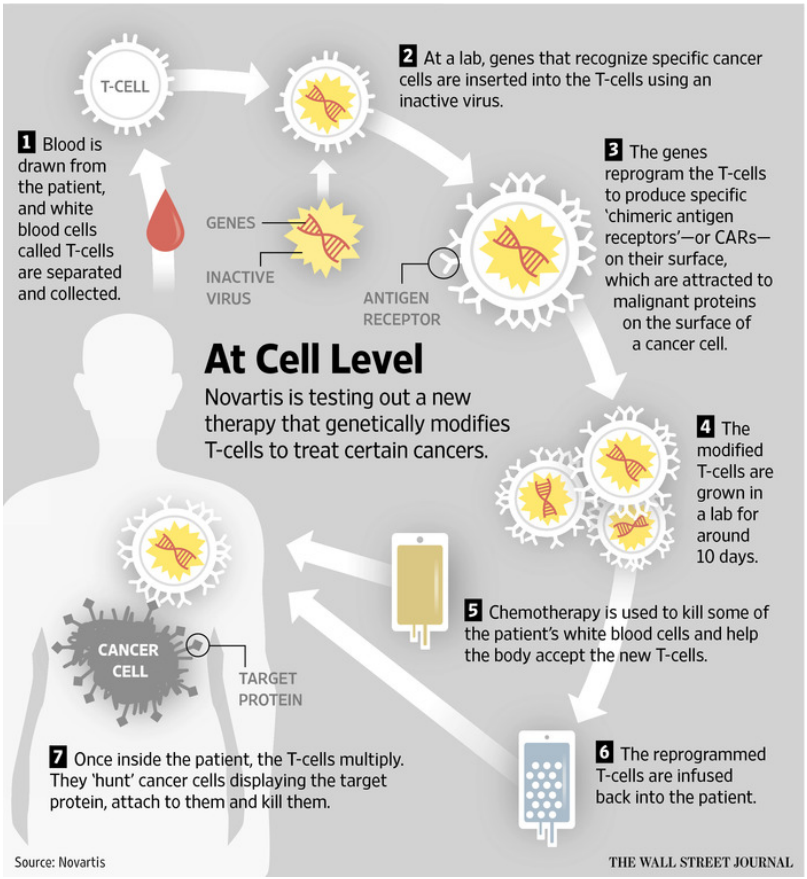


Tumor-infiltrating lymphocytes (TILs): T cells, generally mixtures of CD8+ and CD_4+ T cells grown from resected metastatic tumor deposits, are harvested and expanded ex vivo with a cocktail of cytokines, prior to adoptive transfer

CAR T - > Genetically engineered receptors : Tumor antigen–specific binding sites (recombinant immunoglobulin variable genes) + and cytoplasmic tails with signaling domains (TCR and coestimulatory receptors).

- Avoids the problem of the MHC restriction of TCR

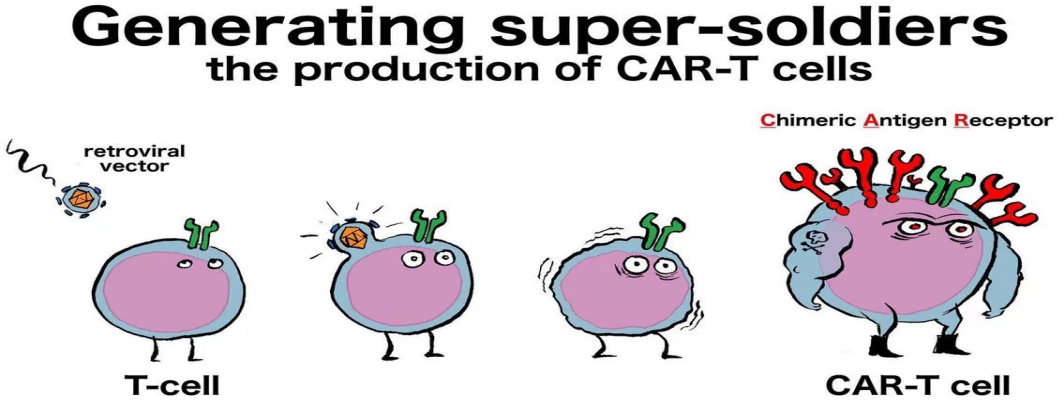
IMUNOTERAPIA DO CANCER: TERAPIA CELULAR ADOPTIVA



NOVARTIS

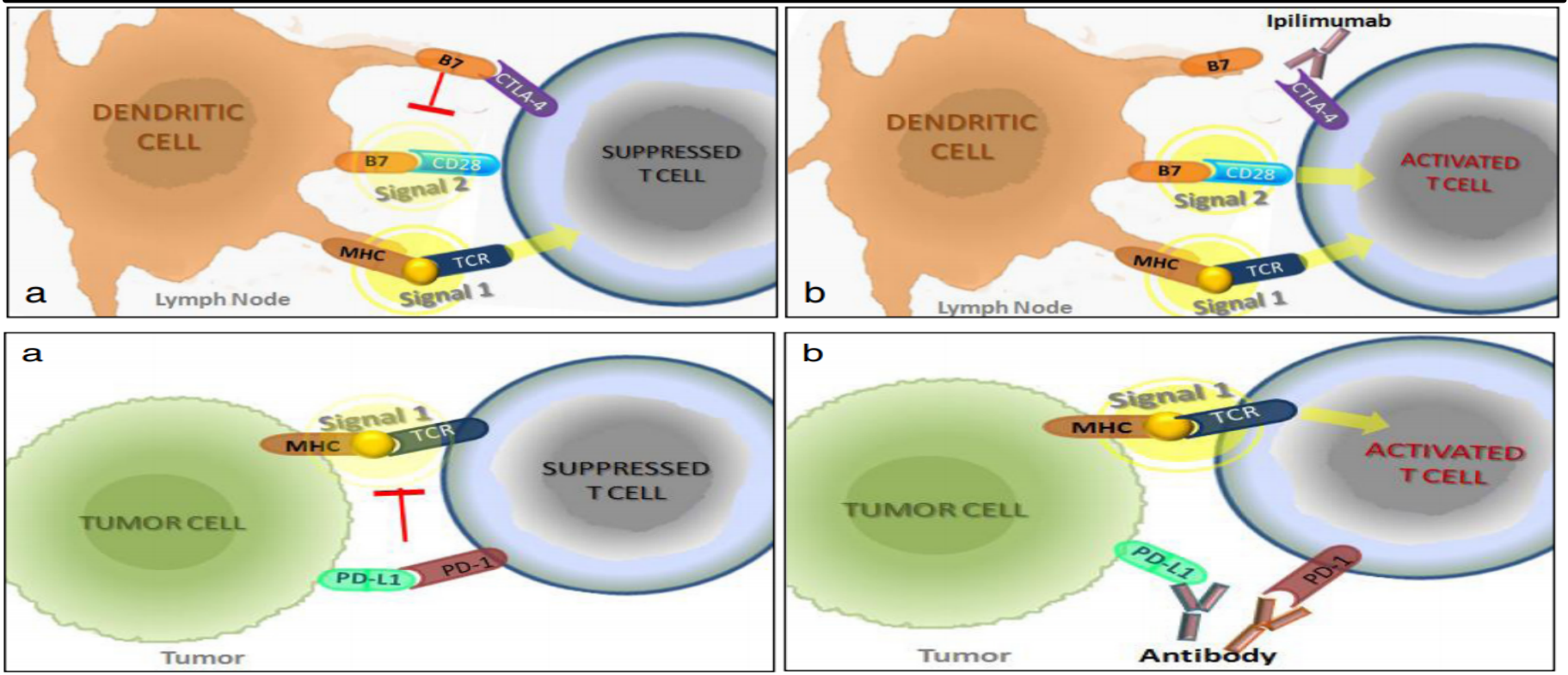
Novartis receives first ever FDA approval for a CAR-T cell therapy, Kymriah™ (tisagenlecleucel, CTL019), for children and young adults with B-cell ALL that is refractory or has relapsed at least twice

AUG 30, 2017



IMUNOTERAPIA DO CANCER: BLOQUEIO DOS CHECKPOINTS

Blockade of T cell inhibitory molecules has emerged as one of the most promising methods for effectively enhancing patients' immune responses to their tumors.



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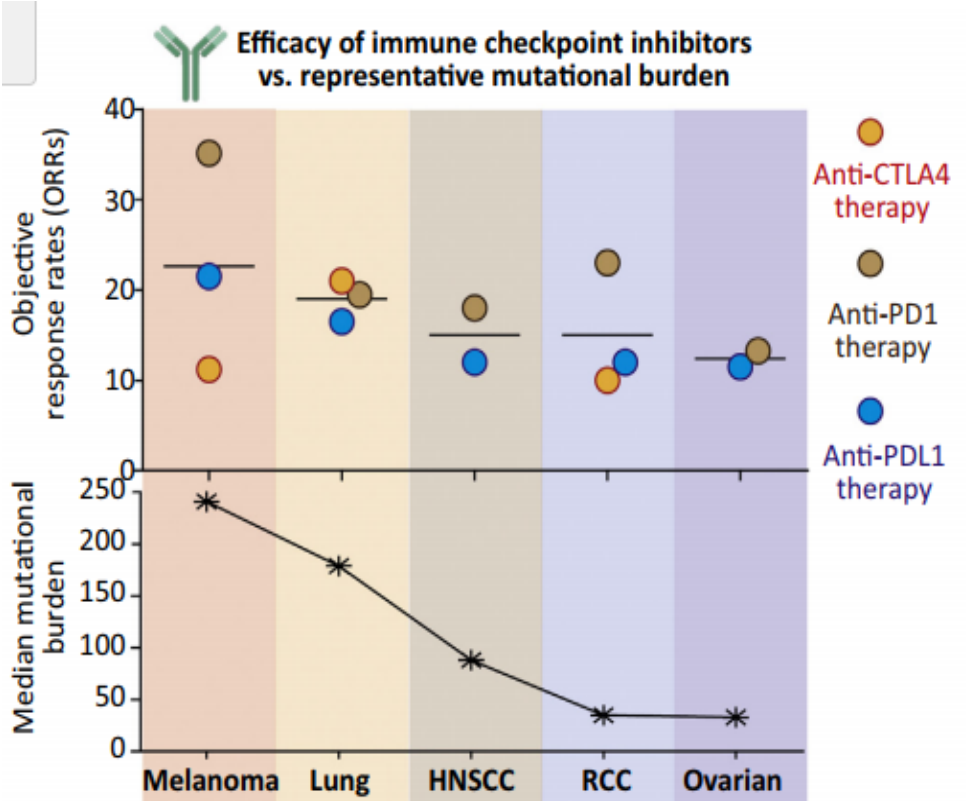
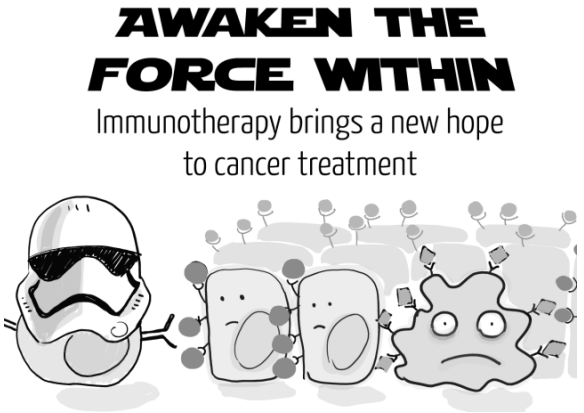
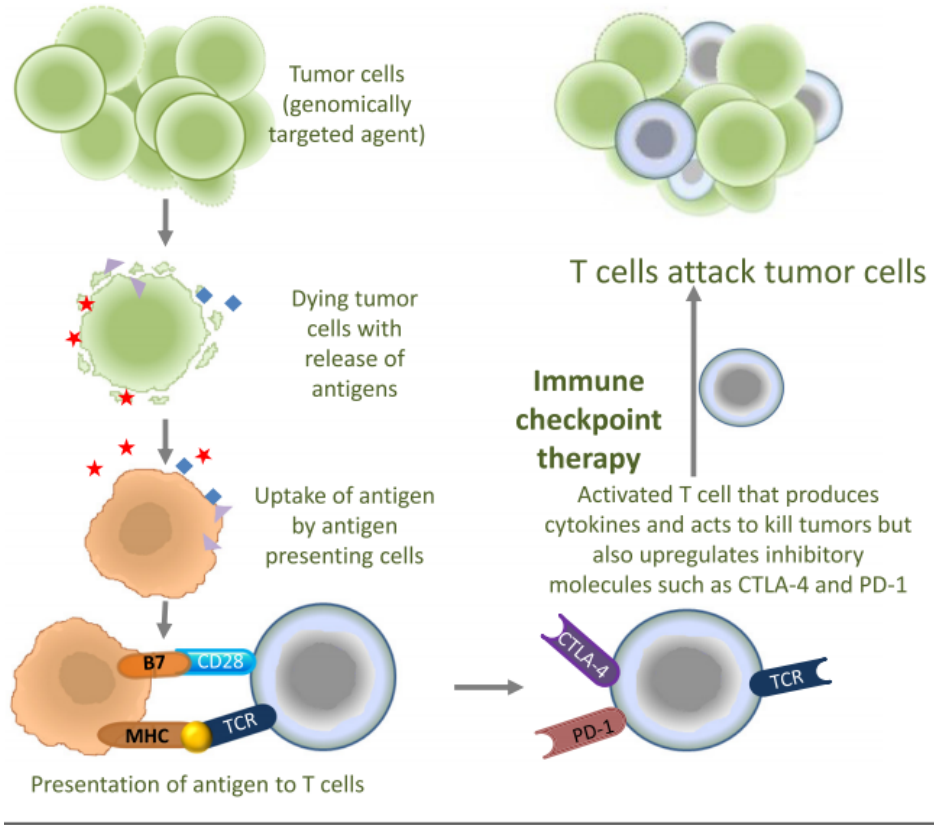


These antibodies are now considered **first-line therapy** for some tumors that have **metastasized**. A combined blockade of both PD-1 and CTLA-4 appears to be more effective against certain cancers than either alone and is already approved for several cancers.



IMUNOTERAPIA DO CANCER: TERAPIAS COMBINADAS



CTLA-4 checkpoint plays a major role in **dampening T cell priming and activation**, whereas **PD1 blocks effector T cell responses within tissues**. Thus, the **combination** of anti-CTLA-4 and anti-PD1 therapies has been anticipated to demonstrate **synergy**.

Combining immune checkpoint inhibitors with chemotherapy may take advantage of the **reduction of tumor burden** caused by chemotherapy.

Immune checkpoint + molecularly targeted therapies (by attack cancer cells with specific genetic characteristics) = restrict the response generated by immunotherapy agents to tumor antigens

Immune checkpoint + anti VEGF

Immune checkpoint + immunostimulatory antibodies

IMUNOTERAPIA DO CANCER: TERAPIAS COMBINADAS

Agents	Indication	Regimen or design	n	Overall response (CR and PR)	Survival
Ipilimumab and nivolumab	Advanced-stage untreated melanoma	Nivolumab or ipilimumab alone versus nivolumab plus ipilimumab	945	-44 % nivolumab -19 % ipilimumab -58 % ipilimumab plus nivolumab	Median PFS: -2.9 months for ipilimumab* -6.9 months for nivolumab† -11.5 months for nivolumab plus ipilimumab*,†
Ipilimumab and nivolumab	Advanced-stage melanoma	Concurrent or sequential combination with dose escalation	53	42 % (concurrent combination)	OS rate: -85 % 1-year -79 % 2-year
Ipilimumab and nivolumab	Advanced-stage untreated melanoma	Ipilimumab alone versus Ipilimumab plus nivolumab	142	-11 % ipilimumab* -61 % ipilimumab plus nivolumab*	Median PFS: -4.4 months for ipilimumab -Not reached for ipilimumab plus nivolumab
Ipilimumab and GP100 vaccine	Previously treated advanced-stage melanoma	Ipilimumab or vaccine alone versus ipilimumab plus vaccine	676	-10.9 % ipilimumab alone* -1.5 % vaccine alone† -5.7 % ipilimumab with vaccine*,†	Median OS: -10.1 months for ipilimumab alone -6.4 months for vaccine alone* -10.0 months for ipilimumab plus vaccine*
Ipilimumab and dacarbazine	Advanced-stage untreated melanoma	Dacarbazine alone versus Ipilimumab plus dacarbazine	502	-10.3 % dacarbazine alone -15.2 % ipilimumab with dacarbazine	Median OS: -9.1 months for dacarbazine alone* -11.2 months for ipilimumab plus dacarbazine*
Ipilimumab and radiotherapy	Post-docetaxel CRPC	Radiotherapy followed by placebo versus radiotherapy followed by ipilimumab	799	NA	Median OS: -10.0 months for radiotherapy followed by placebo -11.2 months for radiotherapy followed by ipilimumab
Carboplatin plus paclitaxel with placebo or ipilimumab	NSCLC	Placebo control versus phased or concurrent schedule	204	-18 % chemotherapy control -32 % irBORR ipilimumab	Median irPFS: -4.6 months chemotherapy control* -5.7 months for phased ipilimumab*
Carboplatin plus paclitaxel with placebo or ipilimumab	ED-SCLC	Placebo control versus phased or concurrent schedule	130	-53 % chemotherapy control -71 % irBORR ipilimumab	Median irPFS: -5.3 months chemotherapy control* -6.4 months for phased

IMUNOTERAPIA DO CANCER: TERAPIAS COMBINADAS