Combining Immunotherapy With Radiation Therapy In Thoracic Oncology

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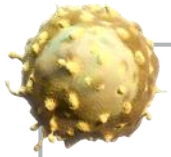
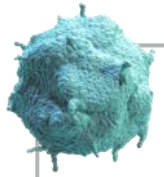
Empowering the immune system: innate and adaptive immunity



Innate immune response

The first line of defense, it identifies and attacks tumor cells without antigen specificity. **Natural killer (NK) cells** are the main effector cells of innate immunity.



Adaptive immune response

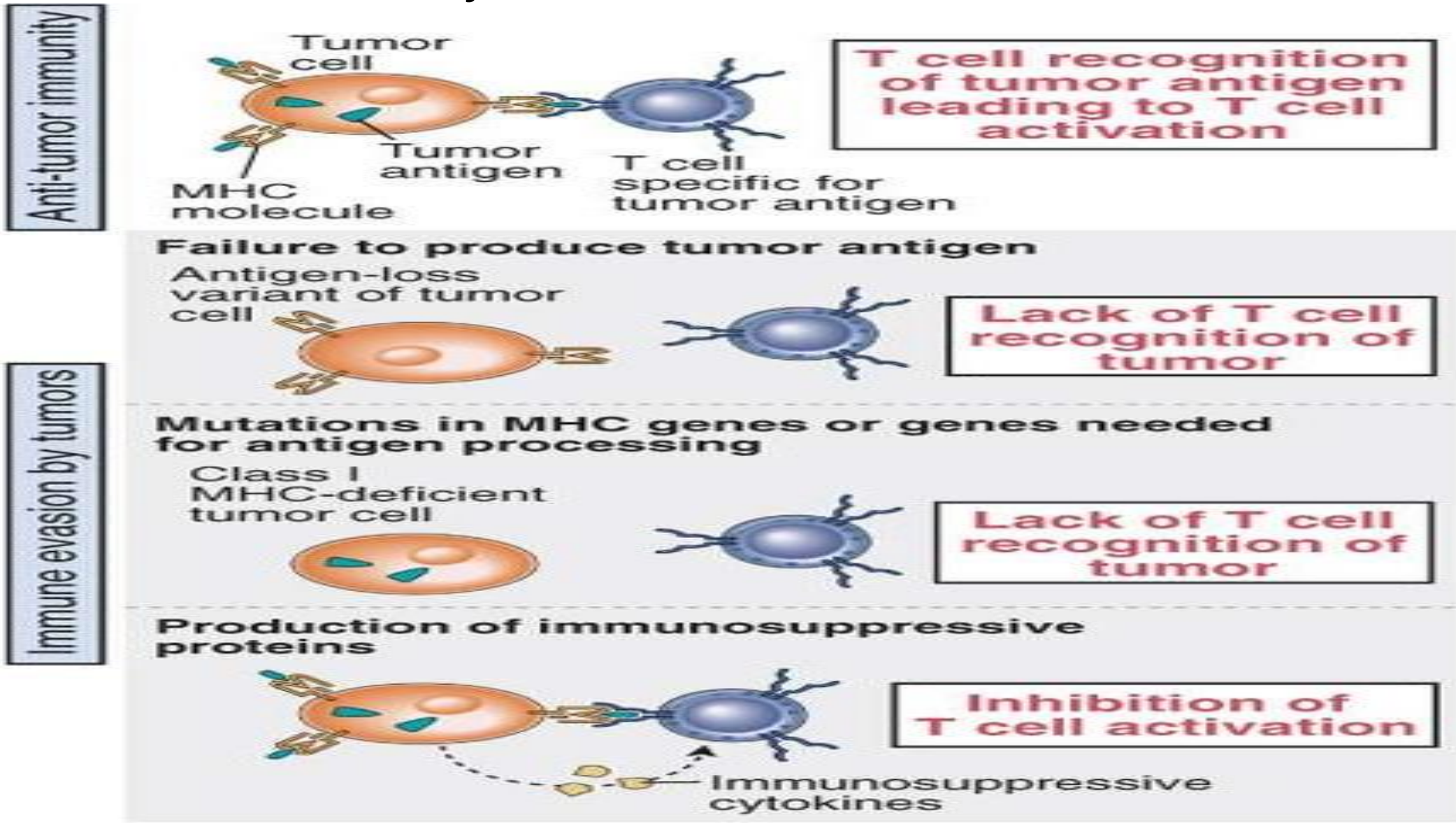
A durable response that attacks tumor antigens. Once activated, it can be sustained through a memory response. **Cytotoxic T cells** are the main effector cells of adaptive immunity.

The antitumor activity of NK cells and cytotoxic T cells is regulated through a network of **activating** and **inhibitory** signaling pathways:

⊕ ACTIVATING
Stimulating pathways trigger immune responses

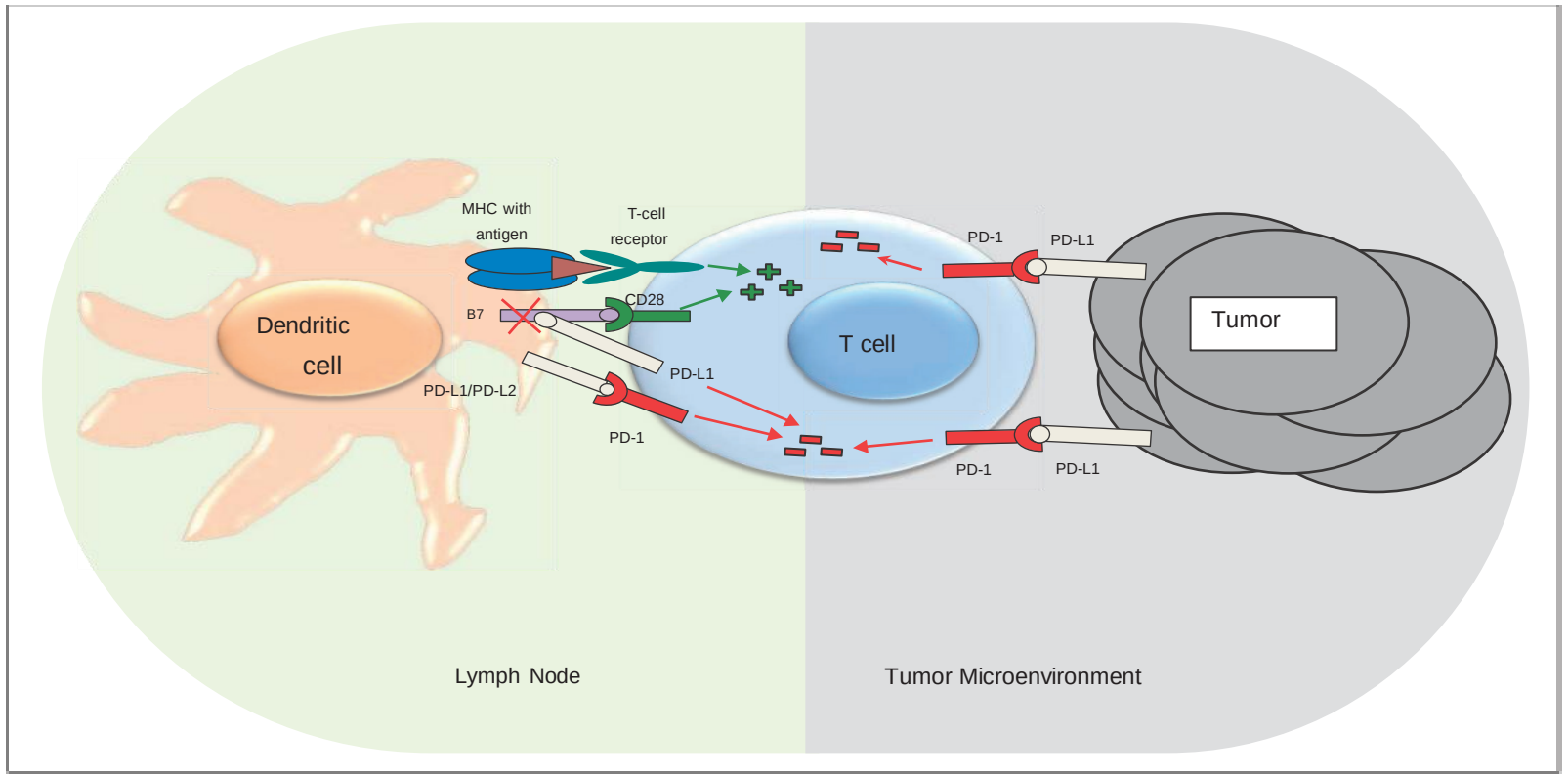
⊖ INHIBITORY
Pathways that counterbalance immune activation such as checkpoints

Evasion Of Immune System



Elsevier. Abbas et al: Cellular and Molecular Immunology 6e - www.studentconsult.c

The programmed cell death protein1 (PD-1) immunologic checkpoint



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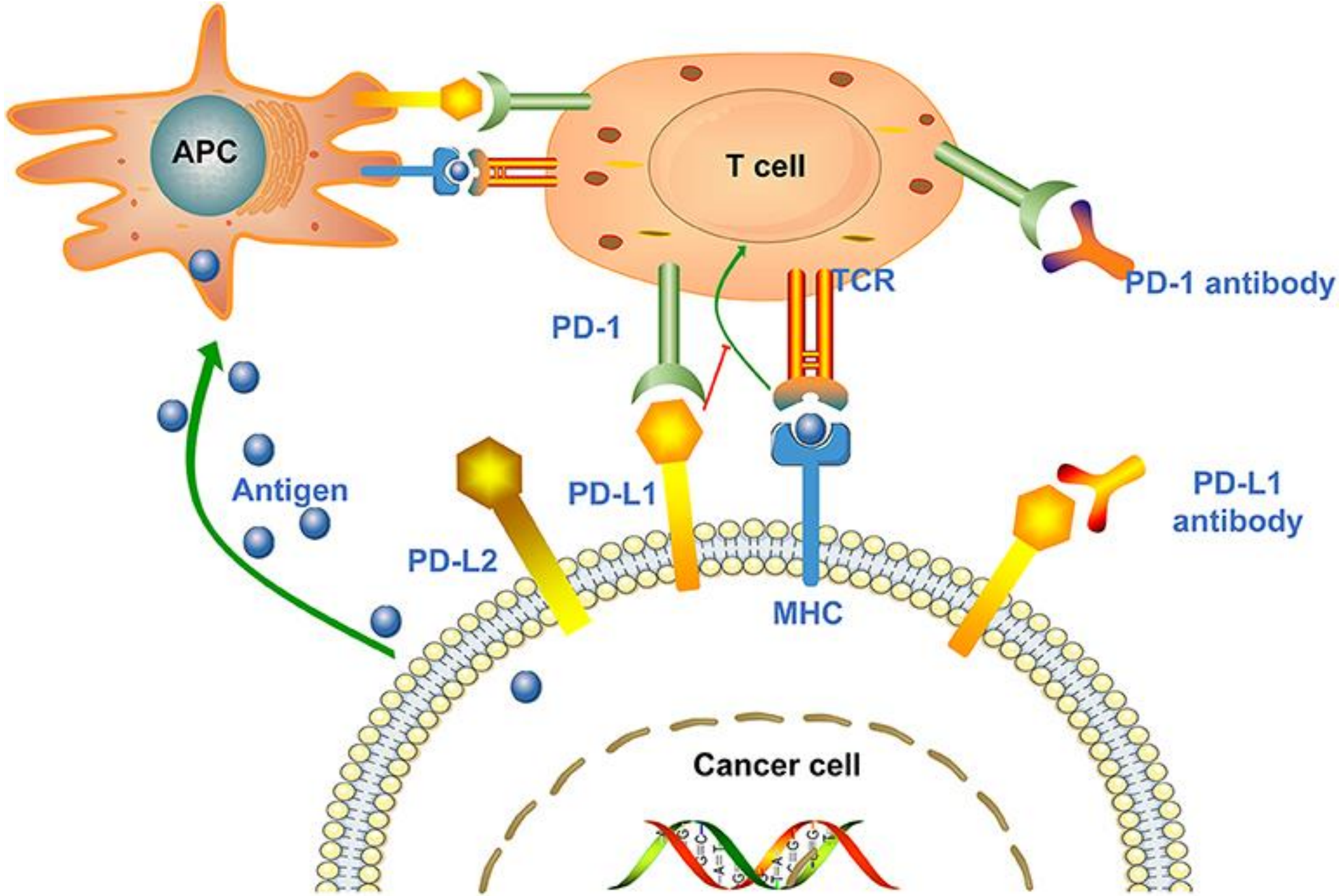
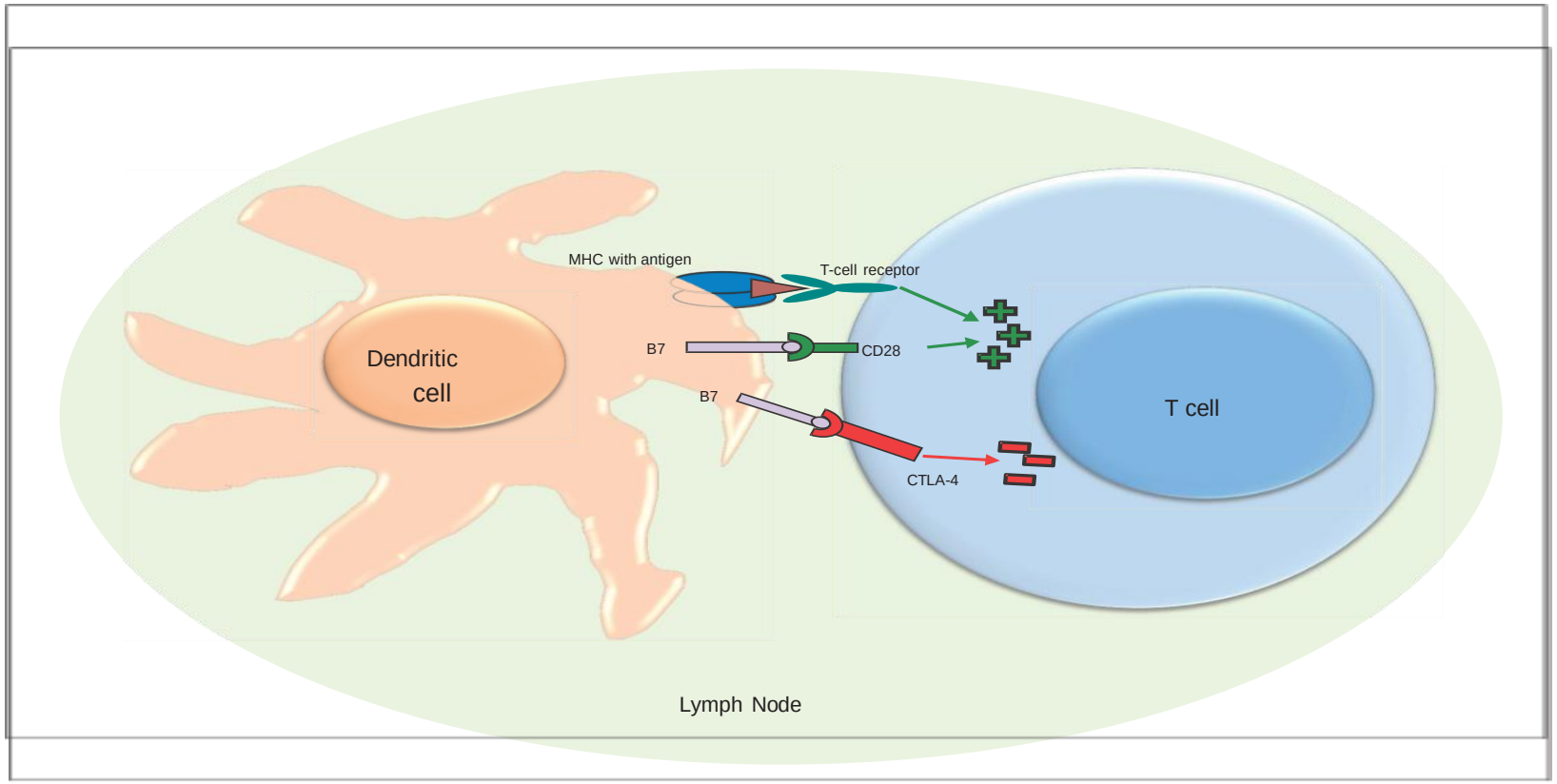
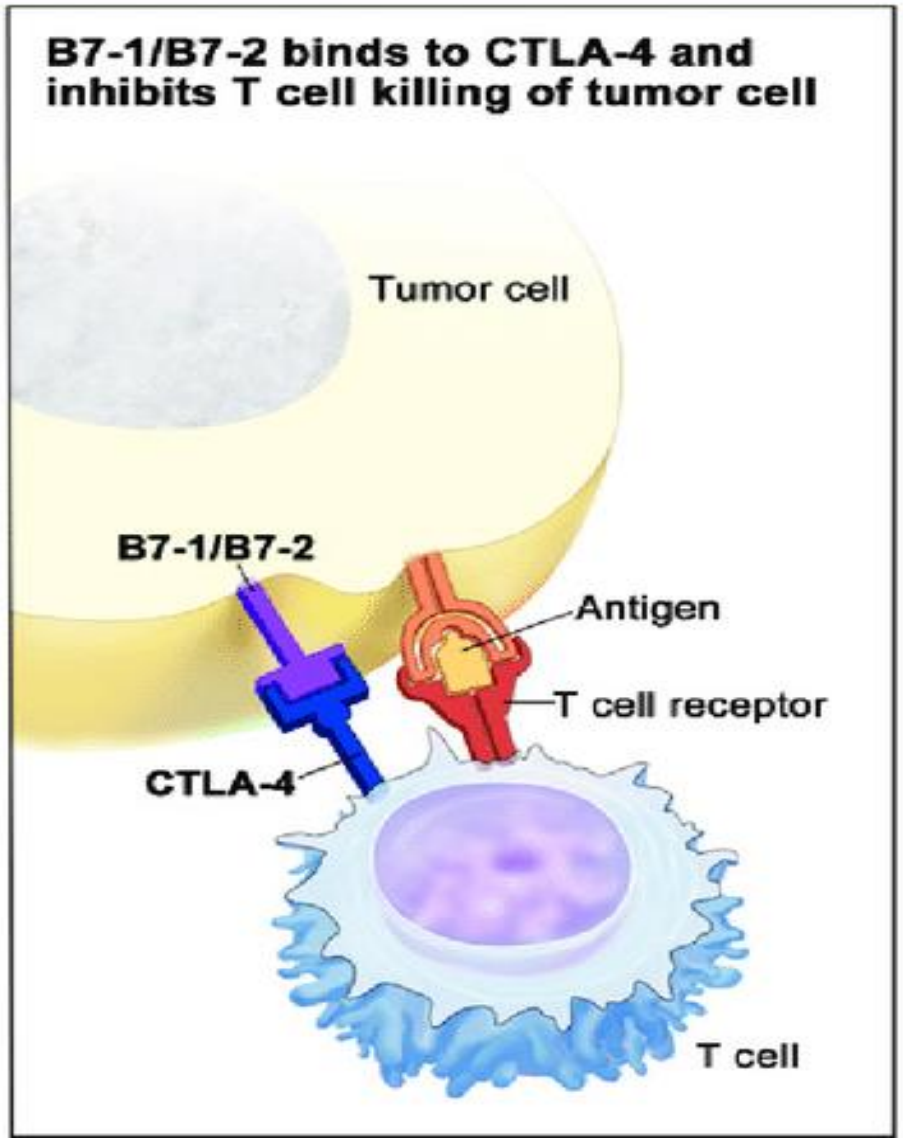
PD-1 is expressed on activated T cells. Interactions between PD-1 and its ligands,PD-L1 and PD-L2, are complex and occur at multiple steps of an immune response. Early after activation in the lymph node where PD-L1/PD-L2 on an antigen presenting cell (dendritic cell shown) negatively regulates T-cell activity throughPD-1 and through an interaction betweenB7 and PD-L1. The PD-1 pathway is also likely important in the tumour microenvironment where PD-L1 expressed by tumours interacts with PD-1 on T cells to suppress T-cell effector function. MHC, major histocompatibility complex.

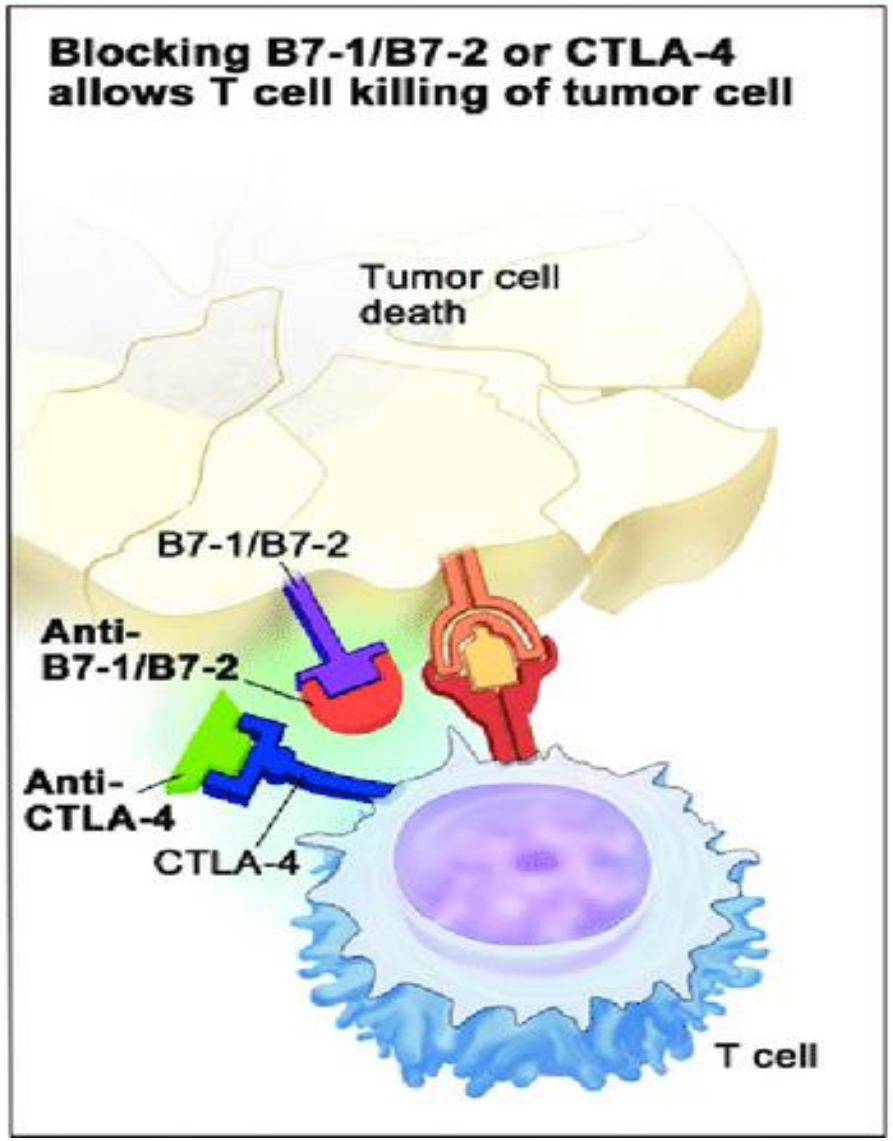

APC
T cell
PD-1 antibody
TCR
PD-1
Antigen
PD-L1
PD-L2
PD-L1
antibody
MHC
Cancer cell

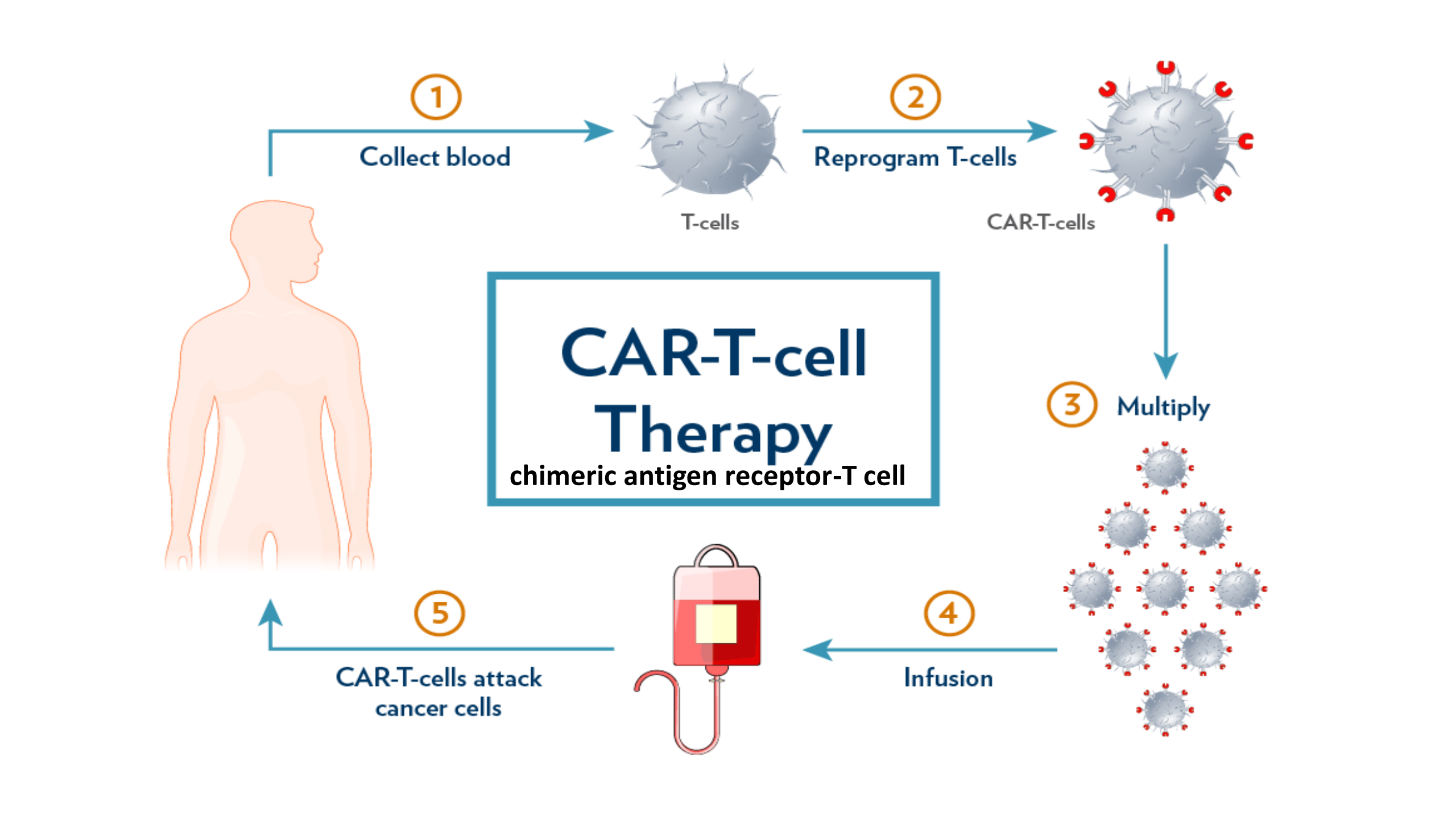
The cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) immunologic check point.



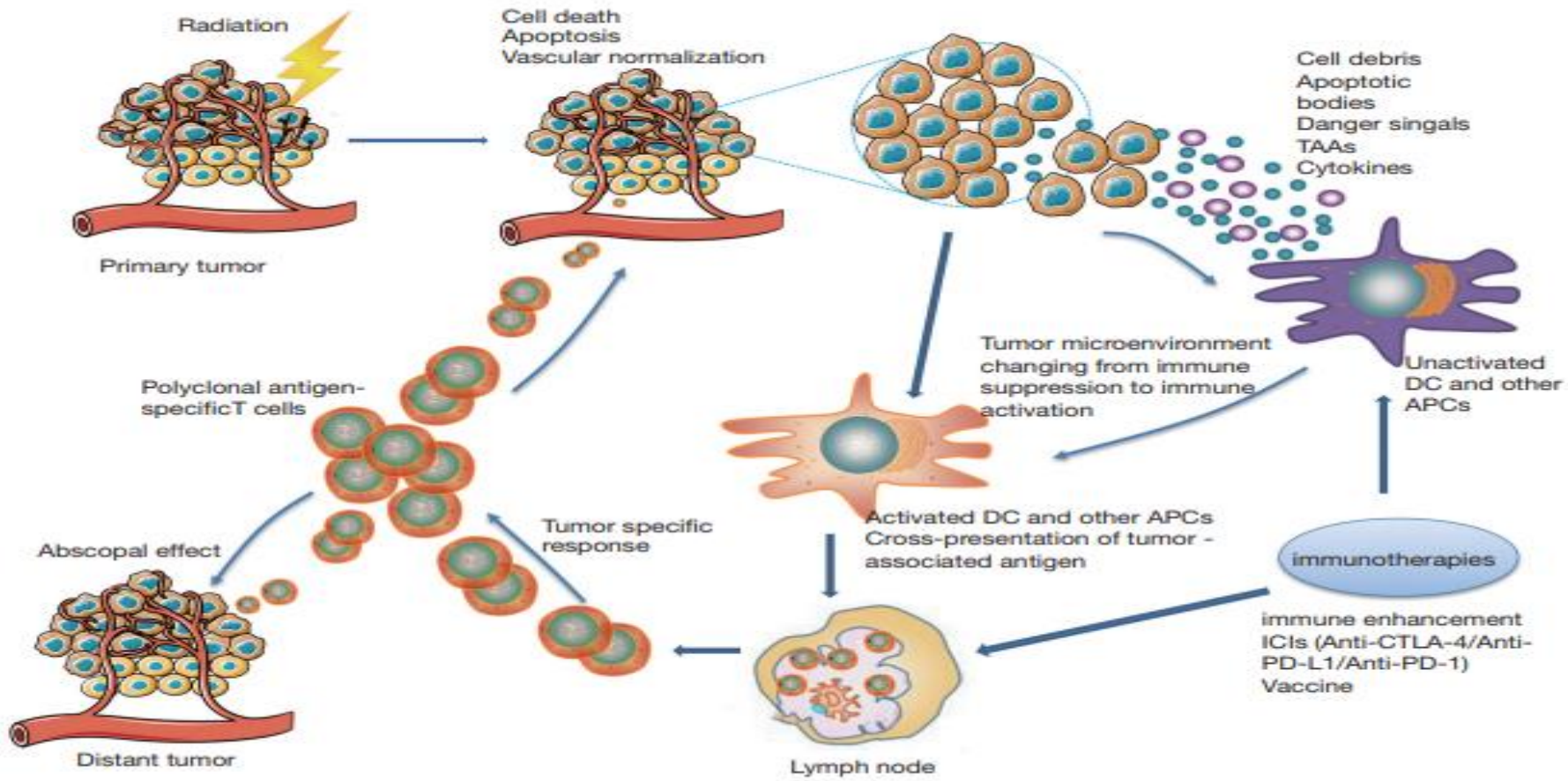
T-cell activation requiers antigen presentation in the context of a major histocompatibility complex (MHC) molecule in addition to the costimulatory signal achieved when B7 on an antigen-presenting cell (dendritic cell shown) interacts with CD28 on a T cell. Early after activation, to maintain immunologic homeostasis, CTLA-4 is translocated to the plasma membrane where it down regulates the function of T cells.






1
Collect blood
T-cells
2
Reprogram T-cells
CAR-T-cells
CAR-T-cell Therapy
chimeric antigen receptor-T cell
3
Multiply
4
Infusion
5
CAR-T-cells attack cancer cells

IMMUNOLOGIC EFFECTS OF RADIOTHERAPY



- INDUCTION OF DNA DAMAGE AND APOPTOSIS AFTER RADIOTHERAPY
- GENERATION OF IMMUNOGENIC CELL DEATH AFTER RADIOTHERAPY
- ENHANCING ABSCOPAL RESPONSES: SINGLE OR MULTISITE RADIOTHERAPY?
- EFFECTS OF RADIOTHERAPY ON THE TUMOR IMMUNE MICROENVIRONMENT
  - Polarizing macrophages and enhancing their function
  - Enhancing dendritic cell maturation and antigen presentation
  - Promoting and inhibiting myeloid-derived suppressor cells
  - Increased activation and infiltration of tumor-specific CD8+ T cells
  - Increasing natural killer cytotoxicity
  - Increased regulatory T cells with a highly suppressive function
- INCREASED CYTOKINES, ADHESION PROTEINS AND UPREGULATED INHIBITORY MOLECULES
- NORMALISATION OF TUMOR VASCULATURE AND REDUCTION IN TUMOR HYPOXIA
- TISSUE-RESIDENT MEMORY CELLS IN THE CONTEXT OF IMMUNE CHECKPOINT BLOCKADE AND RADIOTHERAPY

MECHANISTIC RATIONALE FOR COMBINING RADIATION WITH IMMUNOTHERAPY

- Radiation Increases Antigen Visibility
- Radiation Activates the cGAS-STING Pathway to Trigger Immune Responses
- Radiation Modifies Tumor Stromal Microenvironments

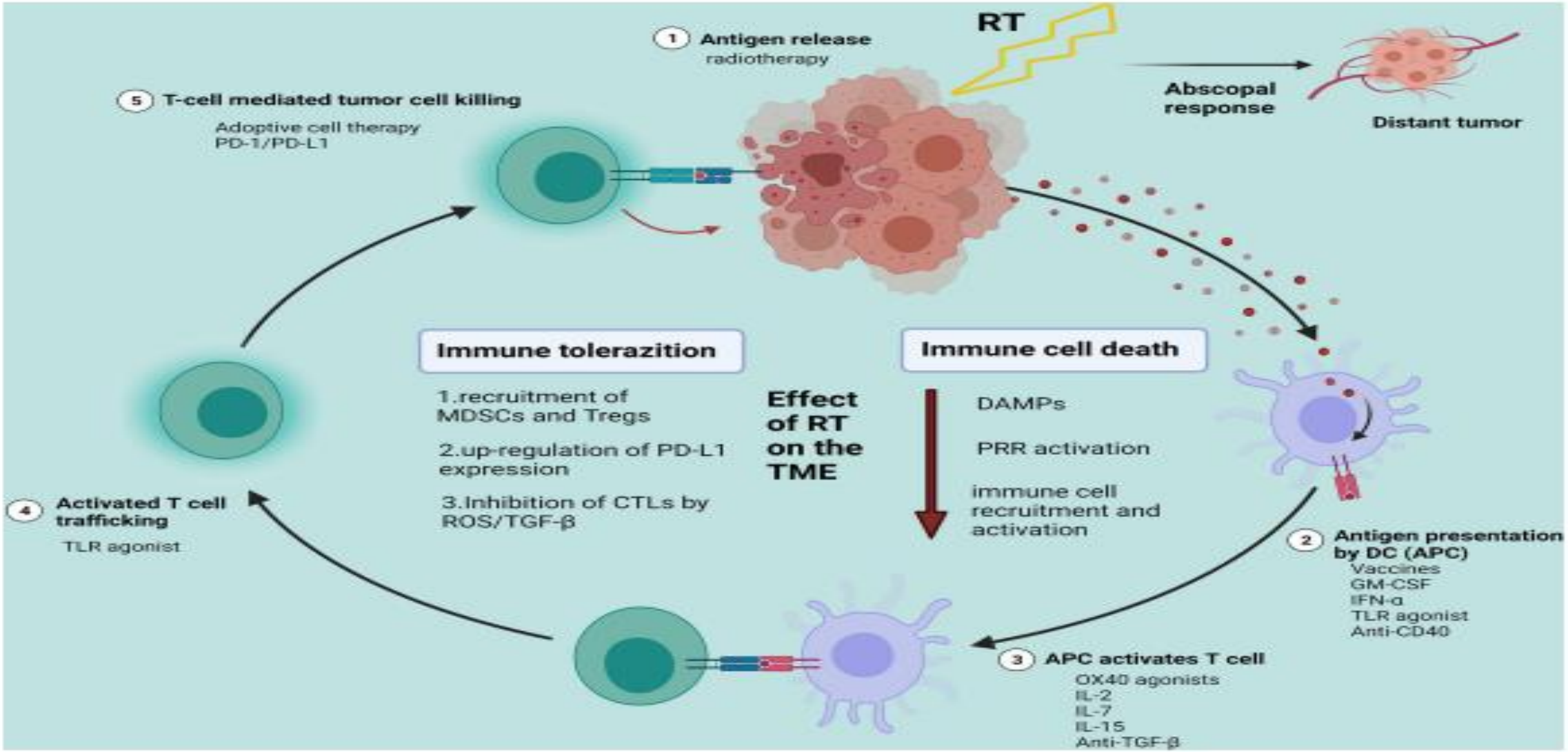
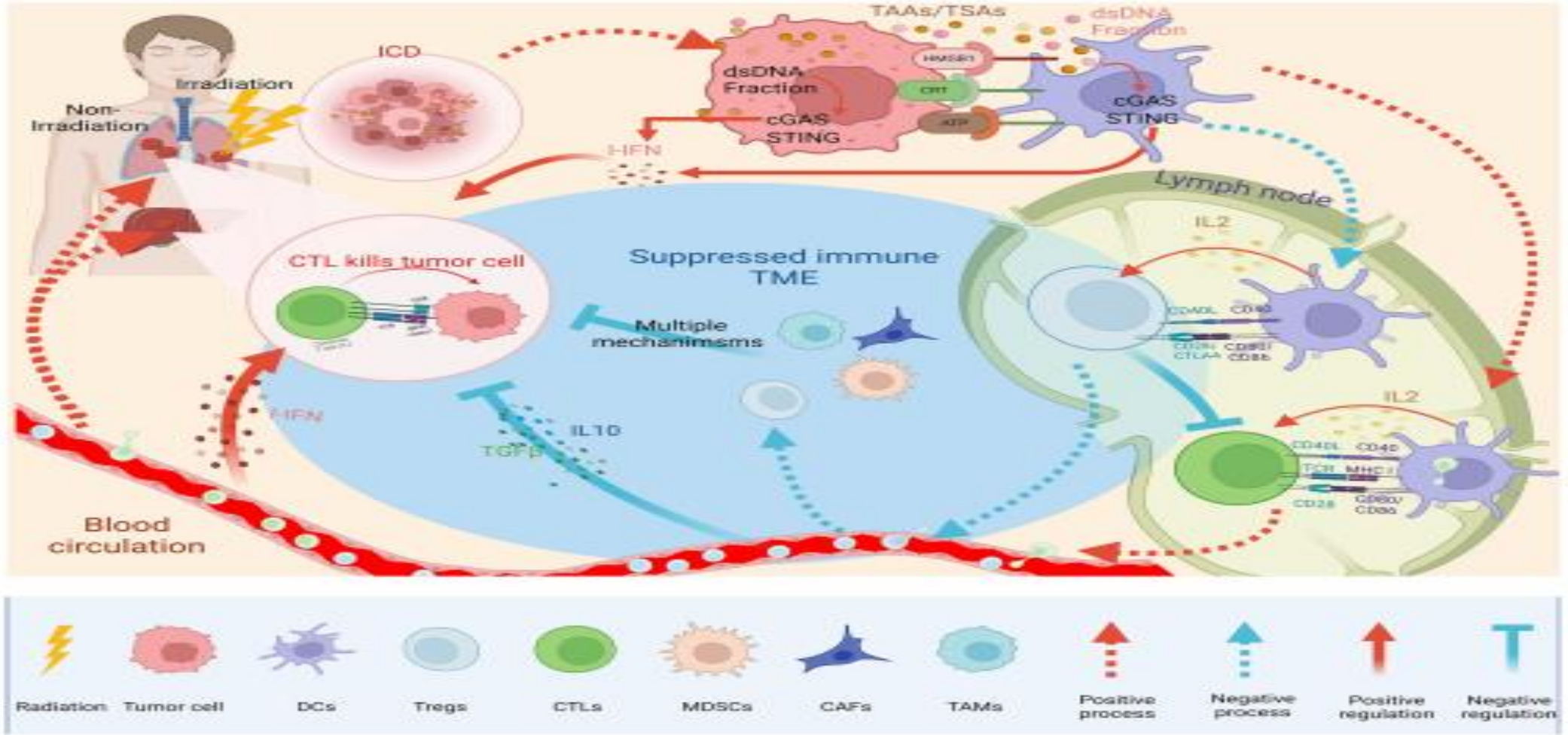


FIGURE 2 | Effects of radiotherapy on the tumor microenvironment and potential strategies for the combination of radiotherapy with different immunotherapies. Created with BioRender.com. RT, radiotherapy; DAMPs, damage-associated molecular patterns; PRR, pattern recognition receptor; TME, tumor microenvironment; MDSCs, myeloid-derived suppressor cells; Tregs, T-regulatory cells.

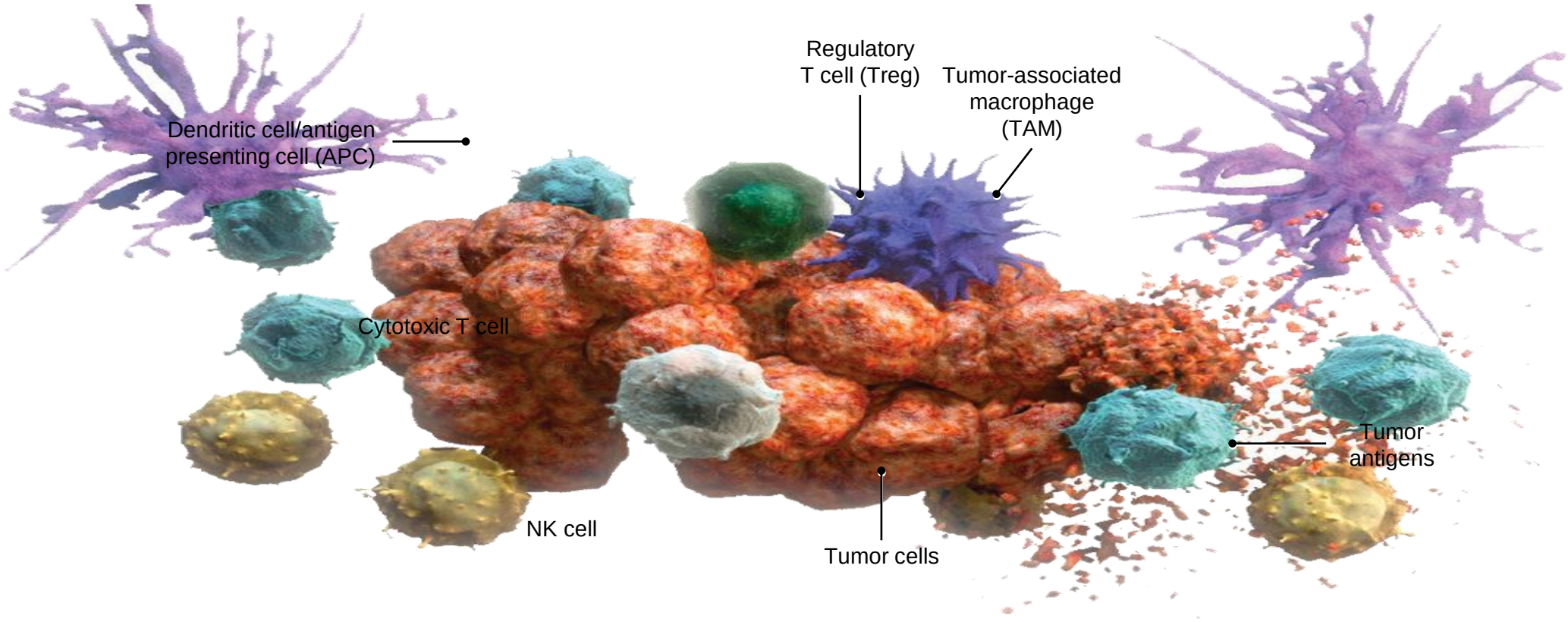
Double-edged sword function of RT on immunity



Preclinical rationale for combining radiation with ICIs

- As ICPB does not result in tumor regression in more than half of patients for the majority of solid tumor types, finding strategies to enhance the likelihood of response is critically important. Many studies are therefore investigating multimodal approaches by combining ICPB with conventional cancer therapies to increase response rates.
- Radiotherapy is considered a key candidate - because of its ability to release DAMPs, activate immune responses, potentially turning ‘cold’ tumors into ‘hot’ tumors. Being a local treatment, radiotherapy also allows the avoidance of many unwanted systemic side effects and toxicities

tumor assisted macrophages (TAMs), neutrophils, MDSCs, and Tregs all play a role in the TME, with increased T-cell infiltration into tumor, mature dendritic cells, and B cells correlating with favorable prognosis



Tumors can use various mechanisms to escape detection and enable growth.

Preclinical rationale for combining radiation with ICIs

- The TME is a complex interplay of- neutrophils, T-regulatory cells (Tregs), and myeloid-derived suppressor cells (MDSCs).

There are pattern recognition receptors expressed by epithelial cells that can recognize and respond to pathogens through various pathways, as well as kill pathogens via these mechanisms

- tumor assisted macrophages (TAMs), neutrophils, MDSCs, and Tregs all play a role in the TME, with increased T-cell infiltration into tumor, mature dendritic cells, and B cells correlating with favorable prognosis

- Studies have indicated that this synergy may be the result of RT overcoming PD-1inhibitor resistance via induction of type I interferon (IFN) production leading to enhanced MHC class 1 expression.
- Preclinical studies have also demonstrated potential synergetic effects when combining RT with ICIs.
- PD-1 blockade enhances T-cells, driving immune response and increasing effector cell activity, while CTLA-4 blockade depletes inhibitory Tregs .Additionally, RT alone can influence the immune system in a multitude of ways, some of which enhance tumor response while others render further RT less effective.

Rationale for the combination of ICIs and RT

- The two most actively studied immune-checkpoint receptors are both inhibitory receptors: cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1). In general, inhibitory ligands and receptors that regulate T-cell effector functions are overexpressed on tumor cells.
- Based on the promising preclinical data combining RT and immune checkpoint blockers for non-thoracic malignancies, a number of investigators have explored the efficacy of the combination in preclinical NSCLC models.

Preclinical rationale for combining radiation with immunotherapy beyond checkpoint inhibitors

- The crux of CAR T-cell therapy is based on genetically engineering a T-cell with a CAR that can recognize cancer cells independent of MHC proteins.
- Constructing these modified T-cells requires attention to two major components: an intracellular transmembrane component and an extracellular, tumor-recognition component.
- Challenges to effective CAR T-cell therapy

CHALLENGES IN COMBINING RADIATION AND IMMUNOTHERAPY

- Optimizing the Timing of Radiotherapy and Immunotherapy
- Optimizing the Dose of Radiotherapy: Conventional Fractionation or Hypofractionation
- Minimizing the Direct Effects of Radiation on T Cells

Optimal Scheduling Of Radio-immunotherapy

- Still unclear.
- To obtain the full potential -ICPB be administered before, concurrent with, or after radiotherapy?
- The most accepted sequence and mechanism are to deliver radiotherapy before ICPB as, in cold tumors, radiotherapy could theoretically facilitate antigen and neoantigen release activating DCs and tumor-specific T cells.
- However, some in vivo studies have shown that delivering radiotherapy after or concurrent with ICPB was superior to pre-treatment.

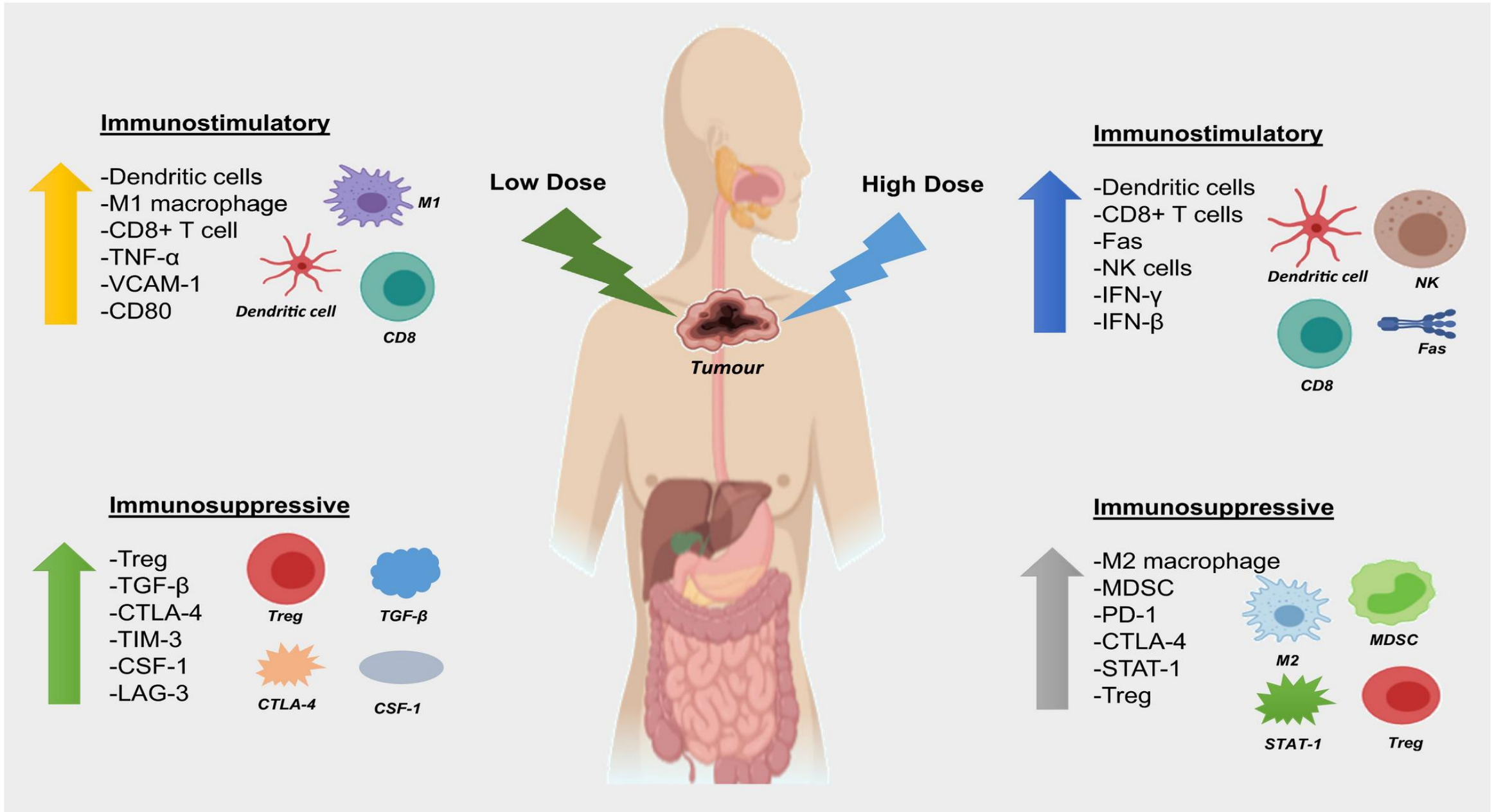
Table 2. Selected clinical studies of scheduling between radiotherapy and ICPB

Cancer	Radiotherapy dose	Sequence	Outcomes	Study
Prostate cancer	8 Gy (single fraction)	Radiotherapy before ipilimumab	Clinical antitumor activities with disease control in a proportion of patients and generally controllable safety profile	Slovin *et al.*[142]
Melanoma brain metastasis	30–37 Gy (10–13 fractions)	Ipilimumab before radiotherapy vs. ipilimumab after radiotherapy	Overall survival was 18.4 months for patients taking ipilimumab after radiotherapy vs. 8.1 months patients receiving ipilimumab before radiotherapy	Silk *et al.*[143]
Melanoma	21 Gy	Comparison among three time points	Patients received radiotherapy during or before ICPB had better overall survival than radiotherapy after ICPB	Kiess *et al.*[122]
Melanoma brain metastasis	NA	Comparison between ipilimumab before and after radiotherapy	No significant differences in overall survival	Knisely *et al.*[144]
Metastatic melanoma	8–30 Gy (1–10 fractions) and one patient received 48 Gy	Concurrent therapy of radiotherapy with anti-PD-1 compared to sequential treatments	Concurrent administration of radiotherapy with anti-PD-1 had higher response rates than patients receiving sequential treatment	Liniker *et al.*[145]

- The underlying mechanism for efficacy of later scheduling remains unclear. One possible explanation is that delivery of radiotherapy after or concurrent with ICPB occurs in the context of pre-blockade of inhibitory receptor expression; hence, cellular infiltrates after radiotherapy all express inhibitory receptors, which may be harder to achieve with delivery of radiotherapy before ICPB.
- each checkpoint inhibitor has a different mechanism of action and will interact uniquely with radiotherapy, underline the importance of careful study and emphasise that radiotherapy and checkpoint blockade will not be **‘one size fits all’**

Fraction schedule?

- Other preclinical work focusing on the immune response of varying RT fractionation schemes shows a difference in immune cell recruitment with fractionation, noting more CD8+ recruitment in higher dose-per-fraction (30 Gy in 1 fraction) schemes compared to more MDSC recruitment with more fractionated approaches (3 Gy ×10 fractions)
- As a result of the varying ways that RT can influence the immune system, clinical responses have been mixed.


Immunostimulatory
-Dendritic cells
-M1 macrophage
-CD8+ T cell
-TNF-α
-VCAM-1
-CD80
M1
Dendritic cell
CD8
Low Dose
High Dose
Tumour
Immunostimulatory
-Dendritic cells
-CD8+ T cells
-Fas
-NK cells
-IFN-γ
-IFN-β
Dendritic cell
NK
Fas
CD8
Immunosuppressive
-Treg
-TGF-β
-CTLA-4
-TIM-3
-CSF-1
-LAG-3
Treg
TGF-β
CTLA-4
CSF-1
Immunosuppressive
-M2 macrophage
-MDSC
-PD-1
-CTLA-4
-STAT-1
-Treg
M2
MDSC
STAT-1
Treg

BIOMARKERS PREDICTING RESPONSE TO RADIO-IMMUNOTHERAPY COMBINATIONS

- may help clarify mechanisms of benefit.
- Each of tumor characteristics, immune infiltrate characteristics and changes in either tumor or immune cells after radiotherapy or ICPB may be potential biomarkers of clinical response to radioimmunotherapy.
- In some cancers, most notably NSCLC, the increased tumor expression of PD-L1 predicts clinical responses to anti-PD-L1/anti-PD-1 monoclonal antibodies

BIOMARKERS

- **increased PD-L1 expression**
- **high CD8+ T-cell and PD-L1 expression in tumor**
- **MDSC and eosinophils as biomarkers**
- **higher circulating IL-6 and IL-8 levels**
- **expression of the cGAS-STING IFN type I synthesis pathway**
- **increased HIF-1a and vascular endothelial growth factor-A**
- Overall, although these biomarkers may provide some indication of the likelihood of response, they have low specificity, and more research is warranted to validate candidate biomarkers, to broaden our understanding of the impacts of radiotherapy on the immune system – and thus optimise combinations of radiotherapy and ICPB.

Preclinical data supporting the use of RT with immunotherapy

- Beyond the benefits of direct cytotoxicity, radiotherapy is associated with immunomodulatory effects that can be leveraged in combination with immunotherapy
- Specific examples of radiotherapy-inducing tumor associated antigens were demonstrated in carcinoembryonic antigen (CEA)- and mesothelin-expressing tumors. radiotherapy enhanced Fas gene expression leading to improved antitumor activity in the setting of CEA-based vaccine therapy where T-cell killing proceeds through the Fas/FasL pathway.

- Mesothelin is a cell surface protein overexpressed in mesotheliomas, pancreatic, and ovarian tumors.
- Hassan et al. demonstrated the dose-dependent response of irradiated A4310K5 carcinoma cells resulting in elevated extracellular mesothelin expression and enhanced antitumor activity of an anti-mesothelin immunotoxin against mesothelin-expressing tumor xenografts.
- Additional examples of increased tumor associated antigens following radiotherapy include c-met and HER2.
- Beyond enhancing tumor-associated antigens, radiotherapy also has been shown to address some of the barriers to effective T-cell therapy related to trafficking and chemotaxis.
- The combination CAR T-cell therapy and radiation is likely to be explored in future clinical trials that promise to enhance our understanding of this treatment paradigm.

PRECLINICAL STUDIES COMBINING RADIOTHERAPY AND CHECKPOINTBLOCKADE

Table 1. Selected preclinical studies combining radiotherapy with ICPB

Type of cancer	Radiotherapy dose	ICPB agent	Outcomes	Study
Melanoma	8 Gy (4 fractions)	Anti-PD-1	Reduced tumor growth; large number of activated $CD8^+$ T cells even in non-irradiated areas suggesting abscopal effects	Pfannenstiel *et al.*[136]
Head and neck squamous cell carcinoma	10 Gy	Anti-PD-L1	Enhanced tumor growth control and improved survival compared to either radiotherapy or anti-PD-L1 alone	Oweida *et al.*[137]
Hepatocellular carcinoma	10 Gy (single fraction)	Anti-PD-L1	Greatly suppressed tumor growth compared with PD-L1 or radiotherapy alone; increased $CD8^+$ T cells and restored its function	Kim *et al.*[138]
Pancreas tumor	12 Gy (3 fractions, daily)	Anti-PD-L1	Delivered radiotherapy booster shot after ICPB to second tumor significantly reduced tumor growth at third non-irradiated area. This was associated with transient increase in $CD4^+$, $CD8^+$ T cells, MDSC and TAM	Chuong *et al.*[139]
Glioma	10 Gy (single fraction)	Anti-CTLA-4	Induced at least 50% long-term tumor-free survival with high $CD4^+$ and $CD8^+$ tumor-infiltrating T cells	Belcaid *et al.*[140]
Colon cancer	10 Gy (single fraction)	Anti-CTLA-4 Immature DC	Inhibition of distant tumor by IR/iDC and this effect was enhanced by the addition of anti-CTLA-4; survival rate has also been improved with tumor-specific interferon-γ-producing T cells and cytotoxic T-cell activity	Son *et al.*[141]
Non-small cell lung cancer	24 Gy (3 fractions)	Anti-PD-1	Increased inflammation in treated group evidenced by higher neutrophil, CD4, CD8, IFN-γ, TNF and IL-5 in combined treatment group compared to other groups	Wang *et al.*[88]

COMBINING RADIOTHERAPY AND CHECKPOINT BLOCKADE-

Thoracic cancers

- predominantly of nonsmall cell lung cancer (NSCLC)
- small cell lung cancer (SCLC)
- malignant pleural mesothelioma (MPM)
- advanced esophageal cancers
- advanced stage thymoma, and thymic carcinoma

have a predilection for distant metastasis and are associated with a poor prognosis

In recent years the benefit of immunotherapy, which harnesses the body's ability to eliminate cancer cells, has emerged for some patients with thoracic malignancies

fourth pillar of cancer care .

The spotlight has focused especially on immune checkpoint inhibitors (ICIs) although other types of immunotherapies including tumor vaccines and chimeric antigen receptor (CAR) T-cell therapy are also promising

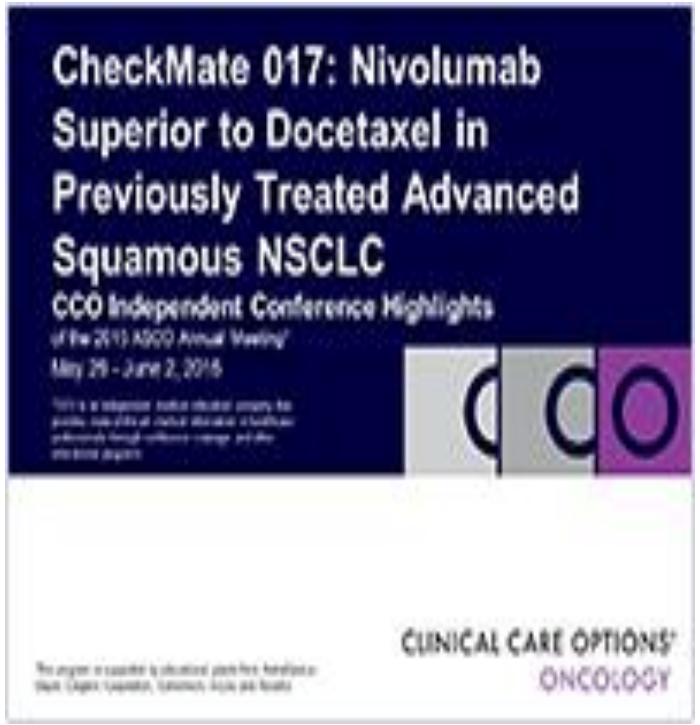
PRECLINICAL STUDIES COMBINING RADIOTHERAPY AND CHECKPOINT BLOCKADE-Thoracic cancers

potential immunogenic effects of ICPB, whether focal radiotherapy enhances the efficacy of this systemic treatment?

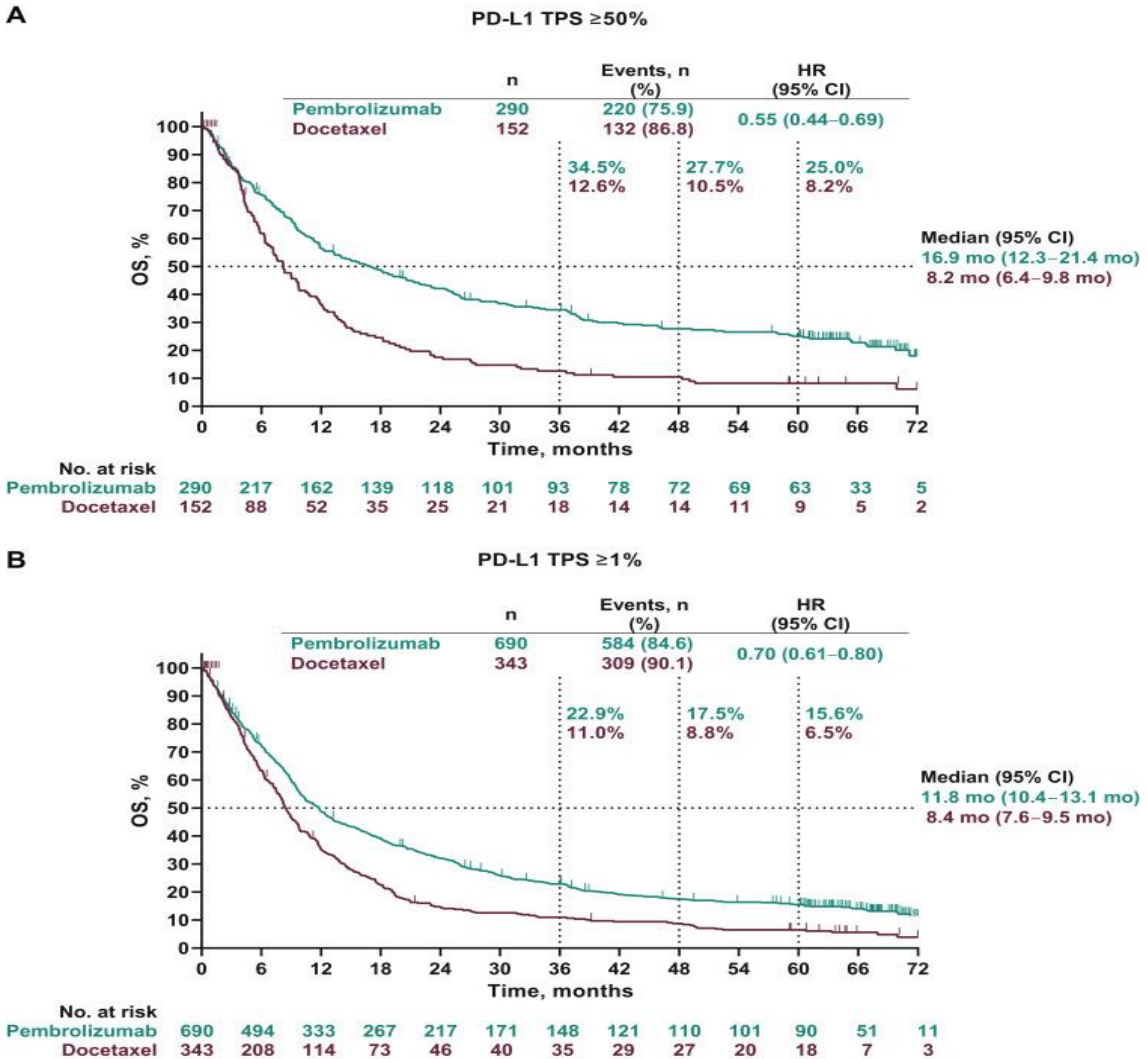
- **In a C57BL/6 tumor xenograft** mouse model of lung cancer - addition of local 6 Gy in three daily fractions to anti-PD-L1 treatment effectively inhibited tumor progression compared to either anti-PD-L1 or radiotherapy alone-synergy between RT and anti-PD-L1, ↑ intratumoral CD8+ T cells and ↓ MDSC and iTregs
- In **another NSCLC mouse model**, the combination of precise target IGRT -8.5 Gy in two fractions with anti-PD-1 showed a significant (70%) reduction in tumor volume compared with baseline, and durable tumor regression for up to 12 weeks.
- **In a dual murine model of mesothelioma**, left (primary tumor) and right flanks (secondary tumor), combining 5 Gy local c-irradiation with anti-CTLA-4 antibody, increased antitumor effects over either single agent. This study also showed that radiotherapy alone increased both Treg and cytotoxic T-cell infiltration into primary and secondary tumors. **However, the proportion of Tregs to effector T cells was reversed by** the addition of anti-CTLA-4 with increased CD8+ T-cell activation.
- Notably, each of these studies used different doses, schedules and methodologies, with no detailed optimization of the radiotherapy component of the investigation

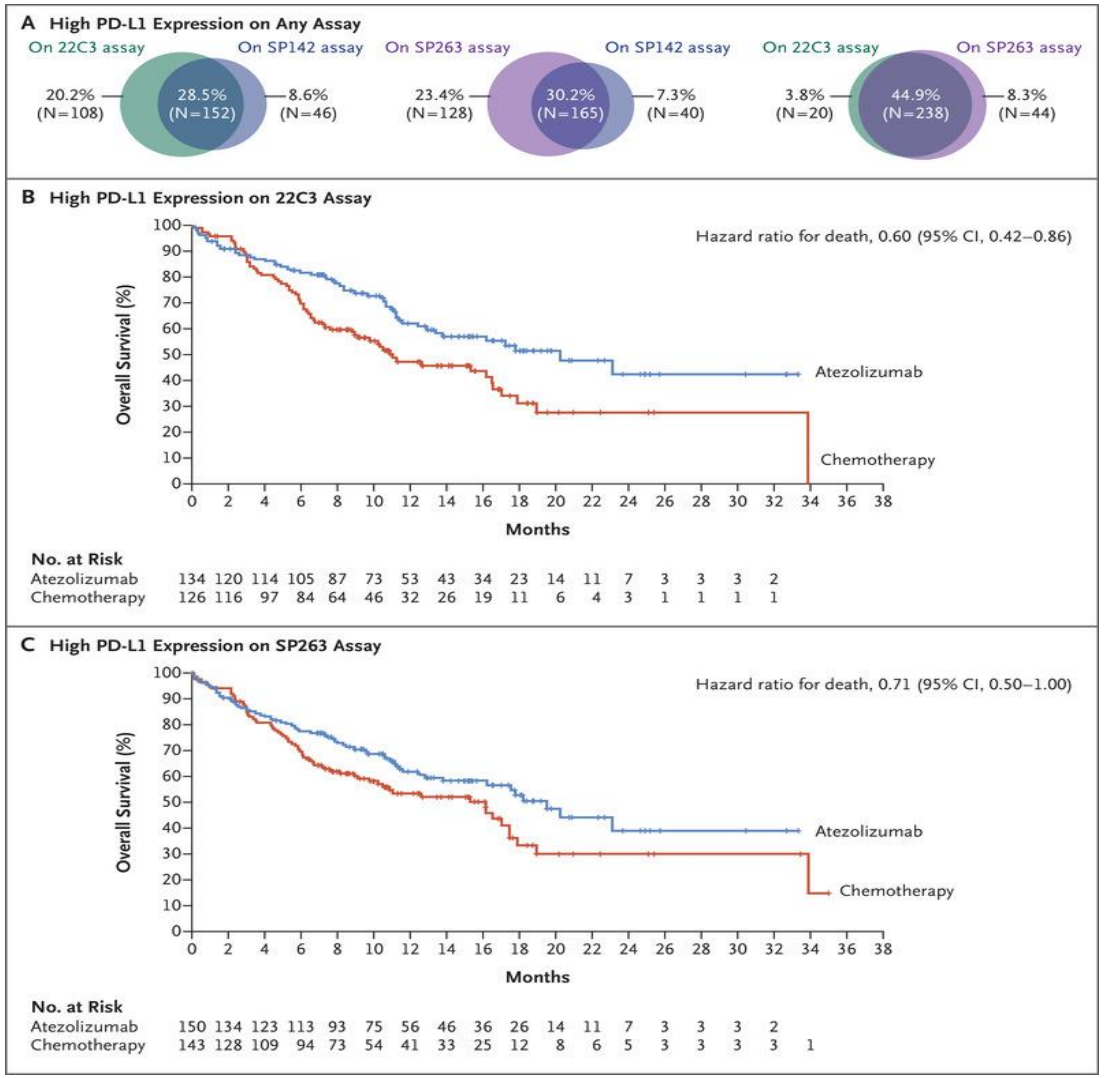
Immunotherapy for NSCLC

- In 2015, results of the Checkmate 017 trial revolutionized systemic therapy for NSCLC. Among patients with advanced, previously treated squamous-cell NSCLC, overall survival, response rate, and progression-free survival were significantly better with nivolumab than with docetaxel, regardless of PD-L1 expression level along with significantly fewer serious treatment-related adverse events.

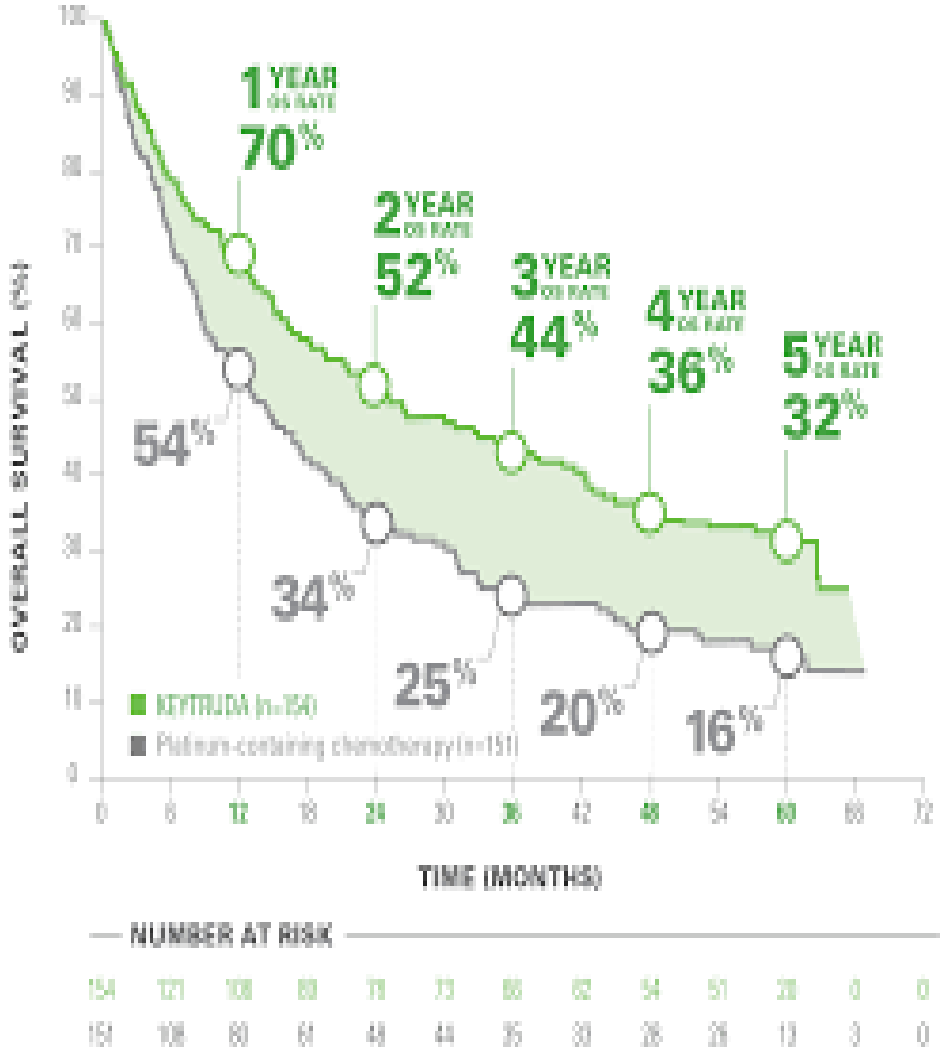


KEYNOTE-010(pembrolizumab vrs docetaxel) **and POPLAR trials(**atezolizumab b vrs docetaxel **found significant improvements in OS and fewer serious AEs.**the FDA approved nivolumab, pembrolizumab, and atezolizumab for second-line treatment of metastatic NSCLC.

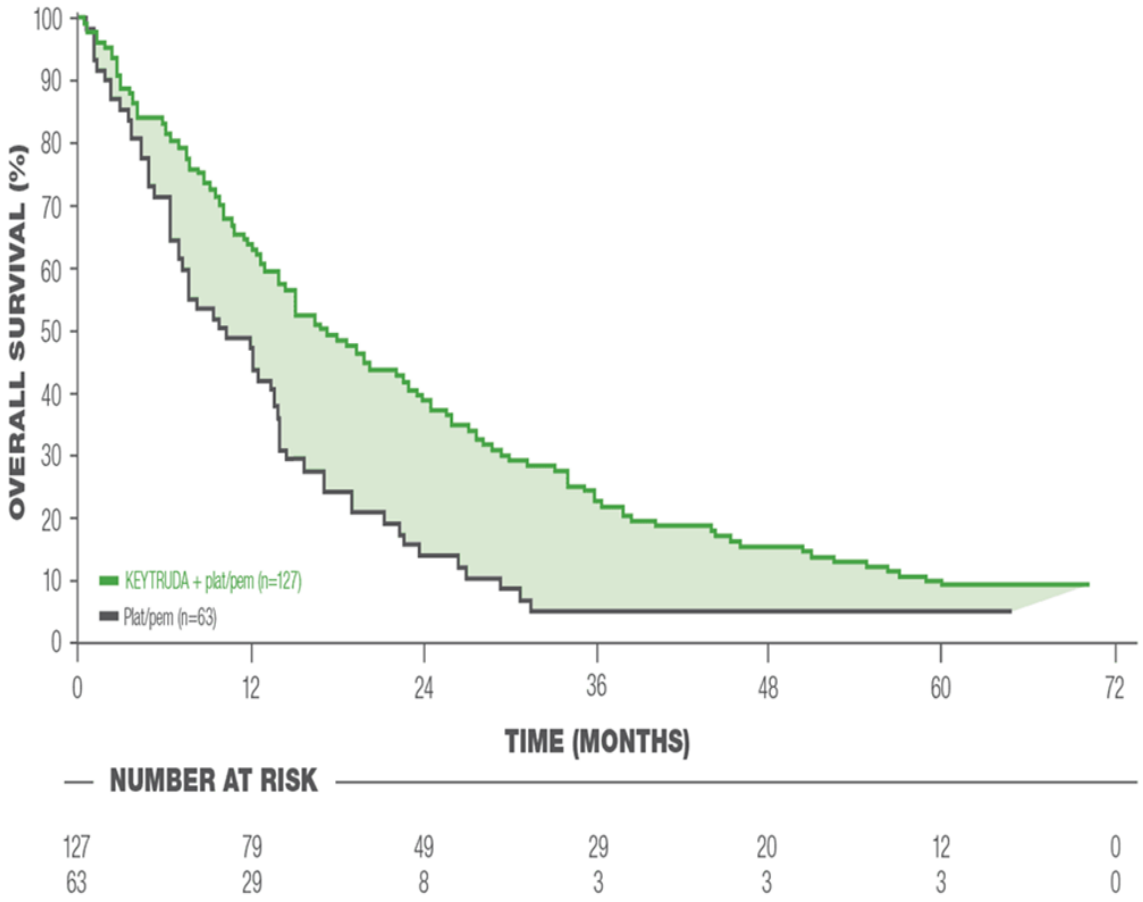




KEYNOTE-024 trial -Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non–Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater



KEYNOTE-189 trial- . Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer-Based on the results of this trial, the FDA approved pembrolizumab for first-line treatment of patients with metastatic NSCLC whose tumors express PD-L1 on ≥50% of tumor cells



Radiation plus immunotherapy for metastatic NSCLC

- RT has historically been used only for palliative purposes and has not been thought to improve survival over chemotherapy alone.
- two recent randomized clinical trials have demonstrated that in appropriately selected NSCLC patients with a low burden of metastatic disease to a limited number of distant sites(oligometastatic), RT can improve progression-free survival (PFS) and potentially OS.
- This revelation, along with the preclinical findings of the potential synergy of RT with immunotherapies has opened up an exciting new indication for RT in patients with metastatic NSCLC. The rapid adoption of ICIs for metastatic NSCLC and the frequent need for palliative RT for this patient population have resulted in a number of retrospective analyses reporting the safety and efficacy of combining ICIs with RT.
- Hubbeling et al. (2018) reported no significant difference in RT-related AEs in patients with metastatic NSCLC receiving cranial RT that previously or concurrently received PD-1/PD-L1 inhibitors compared to patients receiving cranial RT who were PD-1/PD-L1 inhibitor naïve.

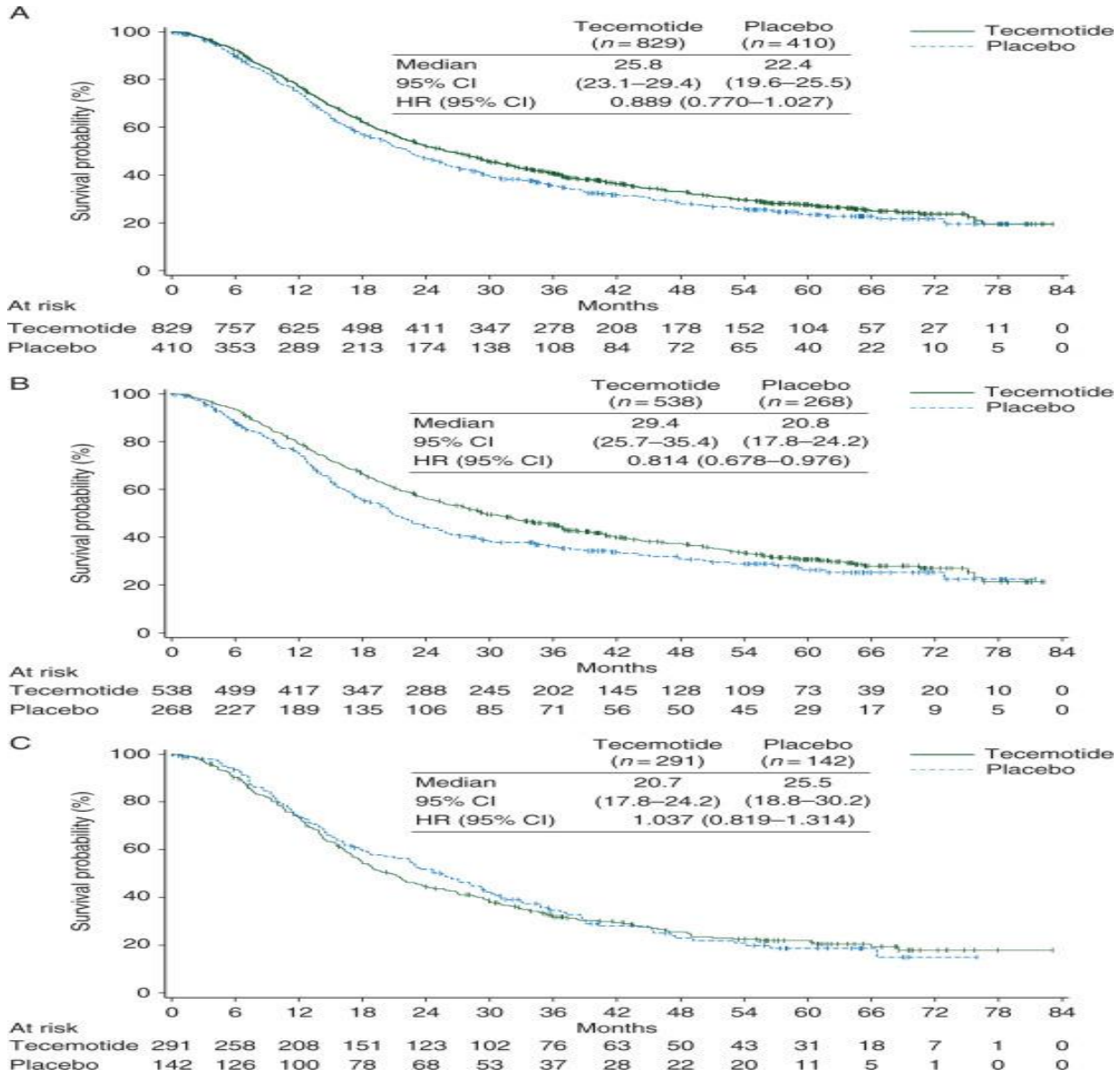
Author (year)	Number of cases	Means of intervention	Radiotherapy plan	Immunotherapy plan	Outcome
Patruni et al (2019)[25]	13,998	RT + IO (545) vs. RT (13,545)	/	/	Median OS:13.1 vs. 9.7 months 3-year OS: 17% vs. 12%
Shaverdian et al (2017)[26]	97	Extracranial RT + IO (38) vs. IO (59)	/	Pembrolizumab (2 mg/kg or 10 mg/kg, q3w, iv; or 10 mg/kg, q2w, po)	Median PFS: 6.3 months vs. 2.0 months; 6-month PFS: 54% vs. 21%
Ahmed et al (2017)[27]	17	RT + IO	SRS or FSRT, 18–24 Gy/F or 25 Gy/5F	Nivolumab or Durvalumab	OS KM rates (6/12 months): 48%/81% (from the date of SRS); 81%/51% (from the date of cranial metastases diagnosis)
Chen et al (2018)[28]	260 (157 NSCLC)	SRS/SRT (181) vs. non-concurrent SRS/SRT + IO (51) vs. concurrent SRS/SRT + IO (28)	SRS/SRT, 15–24 Gy/1F, 18–24 Gy/3F or 25 Gy/5F	Ipilimumab, Nivolumab, or Pembrolizumab	Median OS: 12.9 months (SRS/SRT) vs. 14.5 months (non-concurrent SRS/SRT + IO) vs. 24.7 months (concurrent SRS/SRT + IO)
Pike et al (2017)[29]	85 (39 NSCLC)	SRS/WBRT + IO	WBRT (12–39 Gy)/SRS (15–30 Gy)	Pembrolizumab, Nivolumab or both (3 mg/kg)	Median OS: 192 days

The optimal timing for radiotherapy combined with ICIs

Author (year)	Number of cases	Intervention time	Radiotherapy plan	Immunotherapy plan	Outcome
Li et al (2020) [30]	13	Concurrent RT + IO (SRS within 7 days of IO)	SRS	(Nivolumab, 3 mg/kg, q2w + Ipilimumab, 1 mg/kg, q6w) × 4 cycles + Nivolumab, 450 mg, q4w.	Intracranial mPFS: 9.7 months; 4-month PFS rate: 75% Extracranial ORR: 33%
Porte et al (2021)[31]	51	"SRT before IO" vs. "concurrent SRT + IO" (IO within 1 month of SRT) vs. "SRT after IO"	SRT (15–21 Gy/F, 56.0% or 18–27 Gy/3F, 41.8%)	Nivolumab (47.1%), Pembrolizumab (33.3%), Durvalumab (15.7%), or Atezolizumab (3.9%) (for a median duration of 4.9 months)	1 year R-PFI: 24.1% vs. 49.6% vs. 34.2%; 1 year OS: 67.5% vs. 70.2% vs. 69.2%; 1-year L-PFI: 70.1% vs. 78.9% vs. 77.8%
Srivastava et al (2017)[34]	50 (24 NSCLC)	RT + adjuvant IO (applying PD-1 inhibitors more than 3 weeks after SRS) (23) vs. Concurrent RT + IO (applying PD-1 inhibitors at or <3 weeks before SRS) (27)	SRS	Nivolumab/Pembrolizumab	6-month LC (76% vs. 100%) 6-month DBC (41% vs. 71%)
Imber et al (2017)[36]	45	Sequential IO + brain RT (RT >2 months after last IO) (36%) vs. Concurrent brain RT + IO (64%)	SRS (2100 cGy)/hRT (3000 cGy/5F)	Anti PD-(L)1	Median DBF:4.9 months vs. 3.9 months

Radiation plus immunotherapy locally advanced NSCLC

- Approximately one-quarter of patients with NSCLC present with locally advanced disease with regional lymph node involvement.
- Traditionally treated with concurrent platinum-based doublet chemotherapy and daily RT over 6 to 7 weeks. However, long-term disease control rates with this approach are limited.
- Two years after chemoradiation, nearly half of patients develop distant metastases, and only 30% will be alive without progressive disease



The START trial

is the first phase III trial of immunotherapy maintenance in patients with stage III NSCLC. Although the results did not show a survival improvement with tecemotide (consisting of the MUC1-derived 25-aminoacid BLP25 lipopeptide, the immunoadjuvant monophosphoryl lipid A, and three liposome-forming lipids) in all assigned patients, their data suggest that the subgroup of patients who received previous concurrent chemoradiotherapy might benefit from maintenance tecemotide.

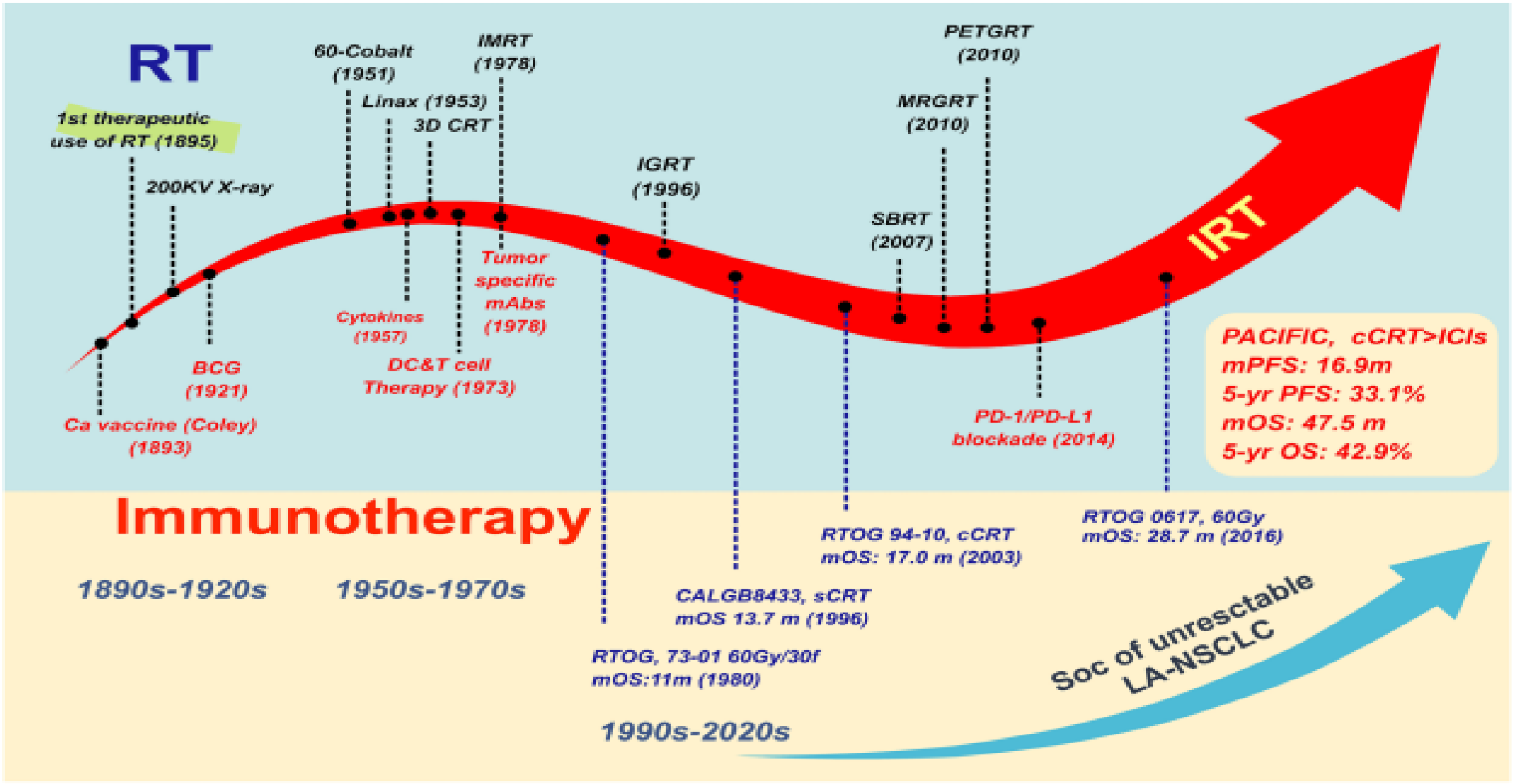


Fig. 1 The history and development of iRT, along with shifts in SoC of unresectable LA-NSCLC. RT has experienced several technological revolutions

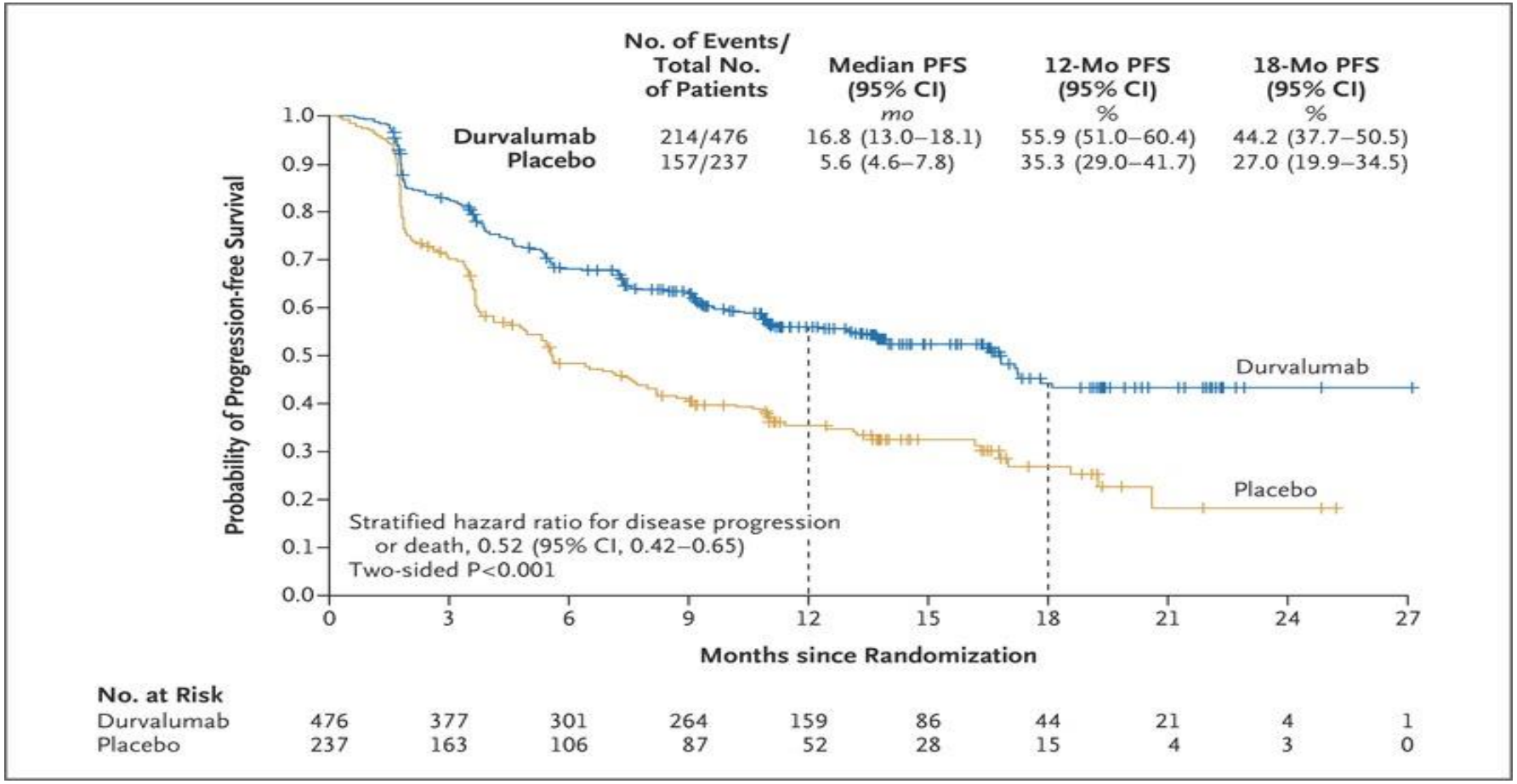
ORIGINAL ARTICLE

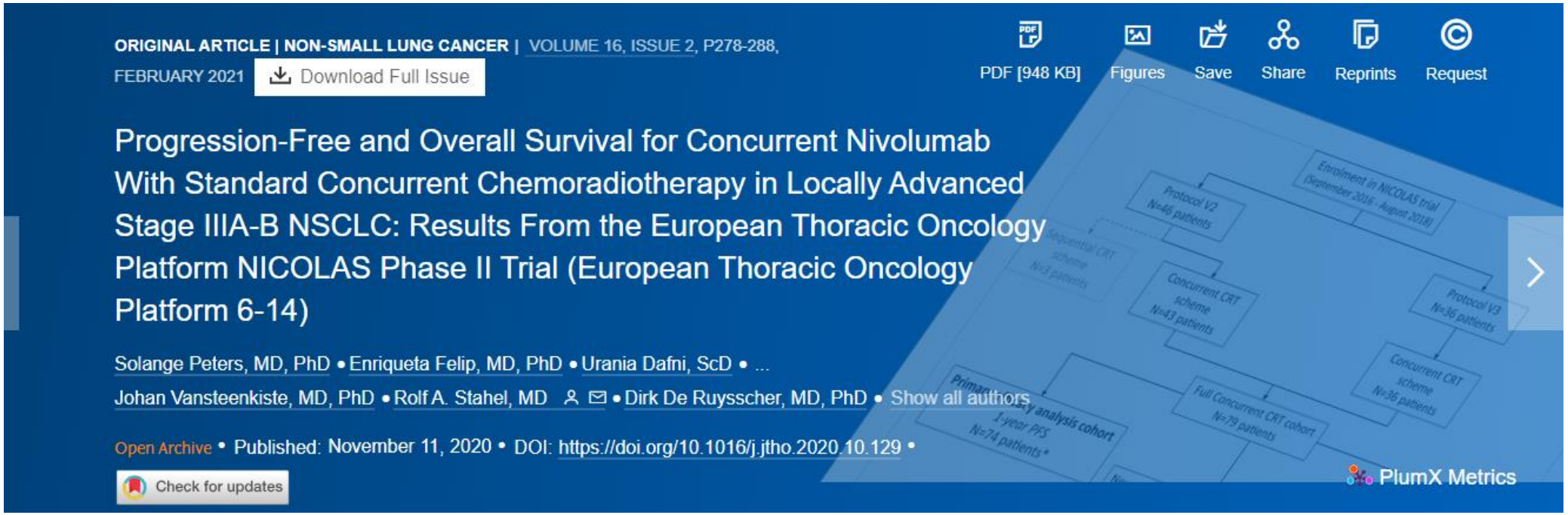
Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

Scott J. Antonia, M.D., Ph.D., Augusto Villegas, M.D., Davey Daniel, M.D., David Vicente, M.D., Shuji Murakami, M.D., Rina Hui, Ph.D., Takashi Yokoi, M.D., Ph.D., Alberto Chiappori, M.D., Ki H. Lee, M.D., Ph.D., Maike de Wit, M.D., Ph.D., Byoung C. Cho, M.D., Ph.D., Maryam Bourhaba, M.D., et al., for the PACIFIC Investigators*

November 16, 2017
N Engl J Med 2017; 377:1919-1929
DOI: 10.1056/NEJMoa1709937

PACIFIC randomized- patients to receive consolidation with the antiPD-L1 antibody durvalumab (at a dose of 10 mg given intravenously per kilogram of body weight) or placebo every 2 weeks until disease progression or 12 months, whichever occurred first .Durvalumab was given 1–42 days after the conclusion of chemotherapy and RT. In a report from a planned interim analysis, the median PFS from randomization was 16.8 months with immunotherapy versus 5.6 months with placebo





- Conclusions: PFS and OS are arithmetically higher in studies involving the same population. However, on the basis of the formal hierarchical efficacy analysis, the 1-year PFS rate is at least 45%.
- Both radiation and immunotherapy can cause a similar presentation of pneumonitis, and to date, there are little prospective data on the potential synergistic toxicity of the combination.
- This combination is, therefore, being approached with caution, at the present time, the use of checkpoint inhibitors given concurrently with CCRT remains experimental, but this strategy is promising enough to warrant further investigation.

Clinical trials testing addition of PD-1/PD-L1 inhibitors to concurrent chemoradiation in LA-NSCLC.

Trial Name	Drug	Phase	Patient No.	Results/Comments
PD-1/PD-L1 inhibitors as consolidation after chemoradiation				
PACIFIC[2, 3]	Durvalumab	3	713	18-month PFS=44.2% with durvalumab, 27% with placebo
LUN 14–179[50]	Pembrolizumab	2	93	18-month PFS=49.5%
BIG10CRC LUN 16–081[51]	Nivolumab +/− ipilimumab	2	20, ongoing	No unexpected safety signals in the first 20 patients
PACIFIC 6	Durvalumab	2	Ongoing	For patients receiving sequential chemotherapy and radiation, testing 2 years of consolidation durvalumab
PD-1/PD-L1 inhibitors concurrent with chemoradiation				
PACIFIC 2	Durvalumab	3	Ongoing	Comparing concurrent chemoradiation alone (without consolidation durvalumab) versus chemoradiation plus durvalumab during and after chemoradiation
ECOG EA5181	Durvalumab	3	Ongoing	All patients receive concurrent chemoradiation plus consolidation durvalumab (i.e. PACIFIC regimen), randomizing between concurrent durvalumab or not during chemoradiation
DETERRED[52]	Atezolizumab	2	40, ongoing	No increase in toxicity for first 40 patients.
NICOLAS[53]	Nivolumab	2	82, ongoing	No unexpected adverse events or increased toxicities were observed.
CheckMate73L	Nivolumab +/− ipilimumab	3	Ongoing	Compares the current standard of care treatment (chemoradiation then durvalumab) against nivolumab given concurrent with chemoradiation, then either nivolumab alone or with ipilimumab as consolidation therapy.
KEYNOTE-799	Pembrolizumab	2	Ongoing	1 cycle of pembrolizumab and chemotherapy prior to starting radiation with cycle 2 of systemic therapy (chemotherapy and pembrolizumab every 3 weeks). Patients also receive 14 additional cycles of consolidation pembrolizumab every 3 weeks.

Radiation plus immunotherapy for Early stage NSCLC

- either undergo a resection or be treated with RT.
- SBRT has emerged over the past decade as an effective treatment with improved disease control and patient quality of life when compared to conventionally fractionated radiation
- While primary tumor control is high with SBRT, systemic recurrence remains problematic, and the predominant method of failure.
- However, SBRT has been shown anecdotally to cause an abscopal effect in patients receiving immunotherapy for a variety of solid tumors.

Table 4. Emerging clinical evidence supporting combining SBRT with ICIs in high-risk N0 ES NSCLC.

Study	N	Stage	Treatment	Response	Toxicity	Survival
Pembro-RT trial (phase II)/ MDACC phase I/II trial [58,59,62]	Pembro: 76 Pembro + SBRT: 72	IV	Pembro vs. SBRT + Adj. Pembro (Pembro-RT)/Concurrent Pembro + SBRT/HypoFrx-RT (MDACC trial)	ARR: 19.7% vs. 41.7% ($p = 0.0039$) ACR: 43.4% vs. 85.3% ($p = 0.0071$)	Grade 3–5 irAEs: Pembro-RT: 17% MDACC trial: 19% after concurrent Pembro-SBRT	Median PFS: 4.4 vs. 9.0 months ($p = 0.045$). Prognostic factor for PFS: SBRT with 50 Gy/4 Frx Median OS: 8.7 vs. 19.2 months ($p = 0.0004$)
Cornell randomized phase II trial [61]	Dur: 30 Dur + SBRT: 30	I-IIIA	Neoadj. Dur × 2 cycles vs. Dur × 2 cycles + SBRT (8 Gy × 3 Frx)	MPR: 6.7% vs. 53.3% ($p < 0.0001$) CR after Dur + SABR: 50%	Grade 3–4 AEs: 17% vs. 20%	

MDACC: MD Anderson Cancer Center; Pembro: Pembrolizumab; Adj.: adjuvant; ARR: abscopal response rate; ACR: abscopal control rate; PFS: progression-free survival; OS: overall survival; Dur: Durvalumab; Neoadj.: neoadjuvant; MPR: major pathological response; pCR: pathological complete response; AE: adverse effect.

Table 5. Clinical trials investigating SBRT and ICI combinations for N0 ES NSCLC.

	Phase	Tumor Stage	Study Drug	Drug Schedule and Duration	Primary End Point
NCT02599454 (active, not recruiting)	I	cT1-2N0M0: ≥2 cm, or SUV_{max} ≥ 6.2, or Mod-poorly diff/undifferentiated	Atezolizumab	Neoadj, concurrent, and adj. × 6 cycles combined with SBRT (4–5 frx)	MTD
NCT03050554 (terminated)	I/II	cT1-T2aN0M0	Avelumab	Concurrent and adj. 6 cycles with SBRT (4–5 frx)	Safety and RFS
NCT03148327 (active, not recruiting)	I/II	cT1-3N0M0	Durvalumab	Phase II: SBRT vs. SBRT (3, 4, 10 frx) + neoadj. (5 days before), concurrent, and adj. ICI × 5 cycles	Safety and median PFS
NCT03383302 (was recruiting between 2017–2020)	Ib/II	cT1-3N0M0 (≤5 cm, AJCC 7th ed.)	Nivolumab	Adj. starting within 24 h from last frx of SBRT (3–5 frx) for 12 months	≥grade 3 pneumonitis at 6 months after SBRT
NCT04271384 (recruiting)	II	cT1-2aN0M0 (≤4 cm)	Nivolumab	Concurrent × 3 doses with SBRT (3, 5, or 8 frx) before surgery	pCR rate
NCT03110978 (recruiting)	II	cT1-3N0M0; Isolated recurrence	Nivolumab	Concurrent and adj. × 12 weeks (4 cycles) with SBRT (4 or 10 frx)	EFS
NCT04944173 (not yet recruiting)	II	cT1-2N0M0	Durvalumab	4 cycles of ICI, SBRT (4 frx) concurrent with 2nd cycle	Overall recurrence rate at 18 months
NCT03446547 (recruiting)	II	cT1-2N0M0	Durvalumab	SBRT (3–4 frx) vs. SBRT + adj. ICI × 12 months	TTP
NCT03833154 (recruiting)	III	cT1-3N0M0	Durvalumab	SBRT (3–5, 8 frx) vs. SBRT + adj. ICI × 24 months	PFS
NCT04214262 (recruiting)	III	cT1-T3N0M0	Atezolizumab	SBRT (3–5 frx) vs. SBRT + neoadj., concurrent, and adj. ICI for 8 cycles	OS
NCT03924869 (recruiting)	III	cT1-T3N0M0	Pembrolizumab	SBRT (3–5, 8 frx) vs. SBRT + concurrent and adj. ICI × 12 months	EFS, OS

Mod-poorly diff: moderately to poorly differentiated; Neoadj.: neoadjuvant; Adj.: adjuvant; frx: fraction; MTD: maximum tolerated dose; RFS: recurrence-free survival; PFS: progression-free survival; CR: complete response; EFS: event-free survival; TTP: time to progression; OS: overall survival.

Open Access Review

Rationale for Combing Stereotactic Body Radiation Therapy with Immune Checkpoint Inhibitors in Medically Inoperable Early-Stage Non-Small Cell Lung Cancer

by Alexander Chi [1,2,*] and Nam P. Nguyen [3]

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Cancers **2022**, *14*(13), 3144; https://doi.org/10.3390/cancers14133144

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(This article belongs to the Special Issue Immunotherapy for Non-small Cell Lung Cancer)

. SBRT may induce immunogenic effects on cancer, which are augmented by immune checkpoint inhibitors, leading to a strong systemic effect, known as the "abscopal effect". This occurs along with enhanced antitumor activity locally. Such effects are most prominent when an ICI is delivered concurrently with irradiation. Early clinical evidence has been consistent with preclinical findings, which supports combining SBRT with ICIs when treating N0 ES NSCLC with high-risk features, such as larger tumor size. Clinical investigations in this area are currently ongoing..

Radiation plus immunotherapy for SCLC

- Although very responsive to first-line chemotherapy, SCLC frequently relapses, and response to second-line agents is extremely poor.
- Immunotherapy -an exciting development - has the potential to overcome the limitations of chemotherapy.
- Numerous preclinical and clinical studies have demonstrated that tumors with a high mutagenic burden, and thus high expression of neoantigens, have high response rates to ICIs, irrespective of levels of PD-L1 tumor expression .SCLC has long been known to have a high tumor mutation burden .This has been found to be correlated with response to checkpoint inhibitors due to re-awakening of pre-existing strong anti-tumor CD8+ cytotoxic T-cell responses

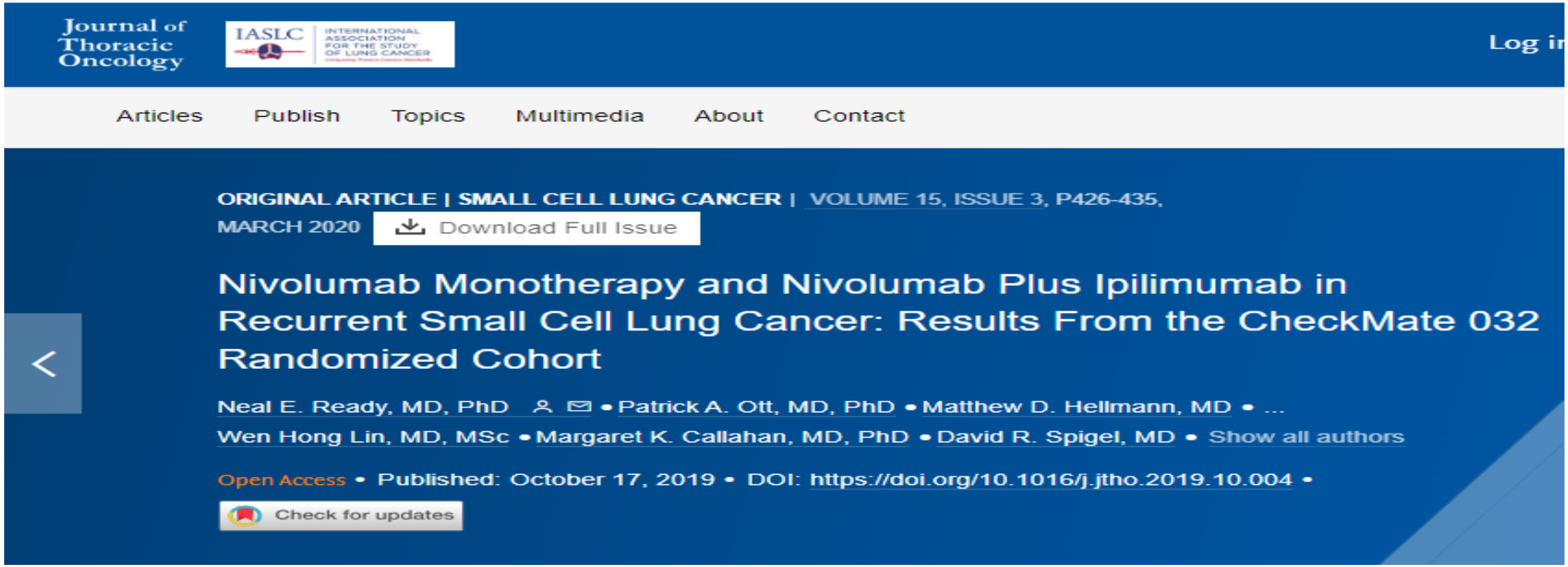
Journal of Thoracic Oncology
Volume 15, Issue 4, April 2020, Pages 618-627

Original Article
Non–Small Cell Lung Cancer

Pembrolizumab After Two or More Lines of Previous Therapy in Patients With Recurrent or Metastatic SCLC: Results From the KEYNOTE-028 and KEYNOTE-158 Studies

Hyun Cheol Chung MD, PhD [a], Sarina A. Piha-Paul MD [b], Jose Lopez-Martin MD, PhD [c], Jan H.M. Schellens MD, PhD [d], Steven Kao MBChB, PhD, FRACP [e], Wilson H. Miller Jr. MD, PhD [f g h], Jean-Pierre Delord MD, PhD [i], Bo Gao MD, PhD [j], David Planchard MD, PhD [k], Maya Gottfried MD [l], Alona Zer MD [m], Shadia I. Jalal MD [n], Nicolas Penel MD, PhD [o], Janice M. Mehnert MD [p], Ignacio Matos MD [q], Jaafar Bennouna MD, PhD [r], Dong-Wan Kim MD, PhD [s], Lei Xu PhD [t], Suba Krishnan MD [t], Kevin Norwood MD [t], ... Patrick A. Ott MD, PhD [u]

Patients with recurrent or metastatic SCLC that progressed after two or more previous lines of therapy, pembrolizumab had promising antitumor activity with durable clinical benefit, and no new safety signals were identified. This pooled analysis supports the use of pembrolizumab monotherapy for patients with SCLC as a third-line or later therapy.



Whereas ORR (primary endpoint) was higher with nivolumab plus ipilimumab versus nivolumab, OS was similar between groups. In each group, OS remained encouraging with long-term follow-up. Toxicities were more common with combination therapy versus nivolumab monotherapy.

ACTIVE, NOT RECRUITING

Pembrolizumab and Concurrent Chemoradiotherapy or Radiation Therapy in Treating Patients With Small Cell Lung Cancer

ClinicalTrials.gov ID NCT02402920

Sponsor M.D. Anderson Cancer Center

Information provided by M.D. Anderson Cancer Center (Responsible Party)

Last Update Posted 2022-02-14

Study record dates

Phase I trial

PRIMARY OBJECTIVES:

I. Safety of pembrolizumab (MK 3475) plus chemotherapy (chemo)/radiation for limited-stage small-cell lung cancer (LS-SCLC).

II. Safety of MK-3475 plus radiation for extensive-stage small-cell lung cancer (ES-SCLC).

SECONDARY OBJECTIVES:

I. MK-3475 will improve progression free survival (PFS) compared to historical controls for LS-SCLC and ES-SCLC.

Clinical Trial > Ann Oncol. 2022 Jan;33(1):67-79. doi: 10.1016/j.annonc.2021.09.011.
Epub 2021 Sep 23.

Consolidation nivolumab and ipilimumab versus observation in limited-disease small-cell lung cancer after chemo-radiotherapy - results from the randomised phase II ETOP/IFCT 4-12 STIMULI trial

S Peters [1], J-L Pujol [2], U Dafni [3], M Dómine [4], S Popat [5], M Reck [6], J Andrade [7], A Becker [8], D Moro-Sibilot [9], A Curioni-Fontecedro [10], O Molinier [11], K Nackaerts [12], A Insa Mollá [13], R Gervais [14], G López Vivanco [15], J Madelaine [16], J Mazieres [17], M Faehling [18], F Griesinger [19], M Majem [20], J L González Larriba [21], M Provencio Pulla [22], K Vervita [23], H Roschitzki-Voser [24], B Ruepp [24], P Mitchell [25], R A Stahel [26], C Le Pechoux [27], D De Ruysscher [28]; ETOP/IFCT 4-12 STIMULI Collaborators

Collaborators, Affiliations + expand

PMID: 34562610 DOI: 10.1016/j.annonc.2021.09.011

The STIMULI trial did not meet its primary endpoint of improving PFS with nivolumab-ipilimumab consolidation after chemo-radiotherapy in LD-SCLC. A short period on active treatment related to toxicity and treatment discontinuation likely affected the efficacy results.

Clinical Trial > J Immunother Cancer. 2020 Dec;8(2):e001302. doi: 10.1136/jitc-2020-001302.

Durvalumab and tremelimumab with or without stereotactic body radiation therapy in relapsed small cell lung cancer: a randomized phase II study

Suchita Pakkala [1], Kristin Higgins [2], Zhengjia Chen [1], Gabriel Sica [3], Conor Steuer [1], Chao Zhang [4], Guojing Zhang [1], Shuhua Wang [1], Mohammad S Hossain [1], Bassel Nazha [1], Tyler Beardslee [1], Fadlo R Khuri [1], Walter Curran [2], Sagar Lonial [1], Edmund K Waller [1], Suresh Ramalingam [1], Taofeek K Owonikoko [5]

Affiliations + expand

PMID: 33428583 PMCID: PMC7754662 DOI: 10.1136/jitc-2020-001302

Free PMC article

Conclusions The D/T combination with and without SBRT was safe but did not show sufficient efficacy signal in relapsed SCLC. Changes in peripheral blood lymphocyte and TILs were consistent with an immunologic response.

Radiation plus immunotherapy for mesothelioma

- rare disease with poor OS and limited effective treatment options. The development of metastatic disease is common, and there have not been significant strides in cytotoxic chemotherapies in recent years.
- Patients with MPM often have a large burden of disease and poor performance status, thus the discovery of effective immunotherapies has long been of interest. IL-2, IFN-alfa 2a and IFN-alfa 2b have been evaluated with mixed results.

Table 1 Single Arm Studies of immunotherapy in Mesothelioma

Study	Drugs & Schedule	N	Phase	Line of Treatment	Response Rate	PFS (mon)	OS (mon)
KEYNOTE028[51]	Pembrolizumab 10mg/kg q2 weekly	25	1b	2+	20%	5.4	18
IRB14-1381[52]	Pembrolizumab 200mg q3 weekly	65	2	2	19%	4.5	11.5
KEYNOTE158[53]	Pembrolizumab 200mg q3 weekly	118	2	2+	8%	2.1	10.0
MERIT[54]	Nivolumab 240mg q2 weekly	34	2	2	29%	6.1	17.3
INITIATE[55]	Nivolumab 240mg q 2weekly + ipilimumab 1mg/kg q 6weekly	38	2	2+	29%	6.2	NR
NIBIT-MESO-1[56]	Tremelimumab 1mg/kg + durvalumab 20mg/kg q4 weekly	40	2	1-2	28%	5.7	16.6
DREAM[57]	Cisplatin 75mg/m2 + pemetrexed 500mg/m2 + durvalumab 1125mg q3weekly	54	2	1	48%	6.9	18.4
PrE0505[58]	Cisplatin 75mg/m2 + pemetrexed 500mg/m2 + durvalumab 1120mg q3 weekly	55	2	1	56%	6.7	21.1

Table 2 Randomised Studies of immunotherapy in Mesothelioma

Study	Drugs & Schedule	N	Phase	Line of Treatment	Response Rate	PFS (mon)	OS (mon)
PROMISE-Meso[59]	Pembrolizumab 200mg q3 weekly versus chemotherapy	144	3	2	22% versus 6%*	2.5 versus 3.4	10.7 versus 12.4
CONFIRM[60]	Nivolumab 3mg/kg q2 weekly versus placebo	332	3	2	NA	3.0 versus 1.8*	9.2 versus 6.6*
MAPS2[61]	Nivolumab 3mg/kg q2 weekly + Ipilimumab 1mg/kg q6weekly versus Nivolumab 3mg/kg q2weekly	125	2	2-3	28% versus 19%	5.6 versus 4.0	15.9 versus 11.9
CHECKMATE743[14]	Nivolumab 3mg/kg q 2weekly + ipilimumab 1mg/kg q6 weekly versus platinum + pemetrexed chemotherapy	605	3	1	40% versus 43%	6.8 versus 7.2	18.1 versus 14.1*
DETERMINE[62]	Tremelimumab 10mg/kg q3weekly versus placebo	571	2b	2+	4.5% versus 1.1%	2.8 versus 2.7*	7.7 versus 7.3 months

JTO Clin Res Rep. 2022 Dec 1;4(1):100440. doi: 10.1016/j.jtocrr.2022.100440. eCollection 2023 Jan.

A Phase 1 Safety Study of Avelumab Plus Stereotactic Body Radiation Therapy in Malignant Pleural Mesothelioma

Andreas Rimner [1], Prasad S Adusumilli [2], Michael D Offin [3], Stephen B Solomon [4], Etay Ziv [4], Sara A Hayes [4], Michelle S Ginsberg [4], Jennifer L Sauter [5], Daphna Y Gelblum [1], Annemarie F Shepherd [1], David M Guttmann [1], Jordan E Eichholz [3], Zhigang Zhang [6], Erika Ritter [7], Phillip Wong [7], Afsheen N Iqbal [3], Robert M Daly [3], Azadeh Namakydoust [3], Henry Li [1], Megan McCune [1], Emily H Gelb [1], Neil K Taunk [1], Donata von Reibnitz [1], Neelam Tyagi [8], Ellen D Yorke [8], Valerie W Rusch [2], Marjorie G Zauderer [3]

Affiliations + expand

PMID: 36590015 PMCID: PMC9801123 DOI: 10.1016/j.jtocrr.2022.100440

Free PMC article

- This was a single-arm, investigator-initiated trial in patients who progressed on prior chemotherapy. Avelumab was delivered every other week, and SBRT was delivered to one lesion in three to five fractions (minimum of 30 Gy) followed by continuation of avelumab up to 24 months or until disease progression
- Combination avelumab plus SBRT seems tolerable on the basis of the prespecified toxicity end points of the first stage of this Simon two-stage design phase 1 study.

Radiation plus immunotherapy for esophageal cancer

- Trimodalitytherapyconsistingofconcurrent chemoradiation followed by surgical resection is the standard of care for locally advanced esophageal cancer patients who are surgical candidates
- PD-L1 expression is present in 45% of esophageal cancer tissues and is associated with more locally aggressive disease and decreased survival.
- Irradiated tumors have been associated with an increased expression of PDL1 leading to suppression of anti-tumoral activity of T-cells .

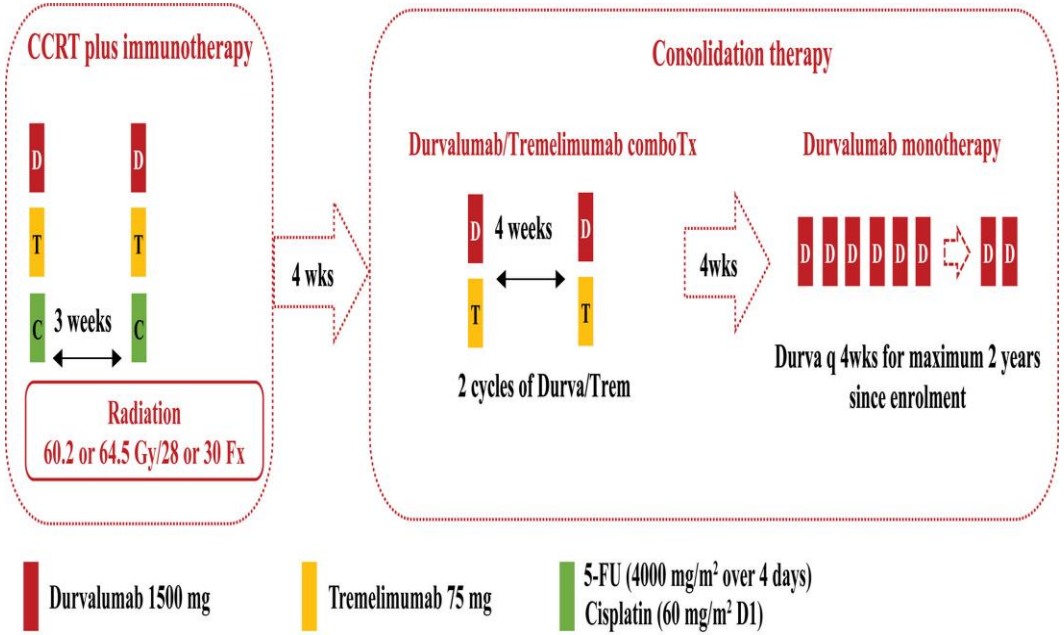
Cancer

Original Article | Free Access

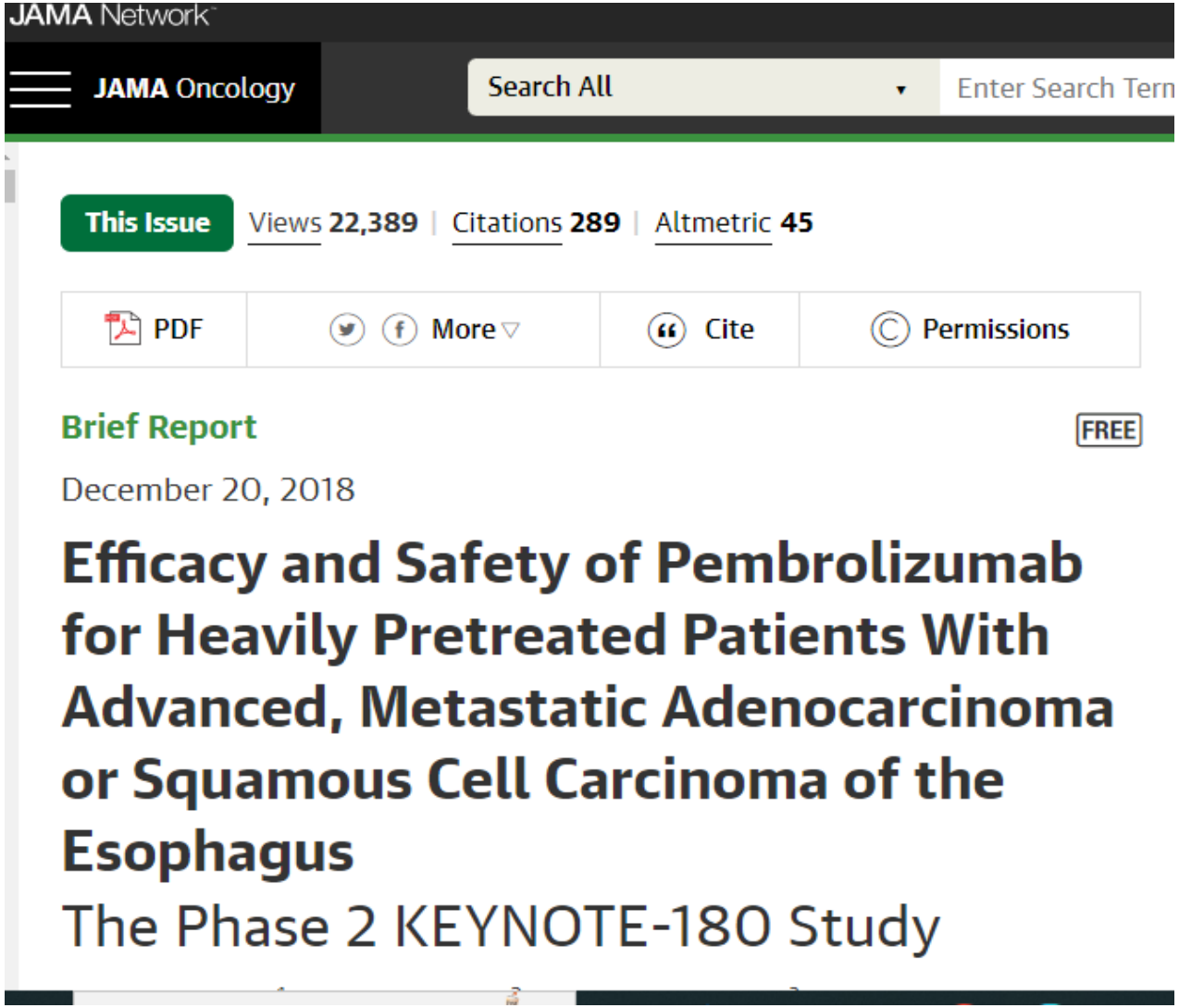
Durvalumab and tremelimumab with definitive chemoradiotherapy for locally advanced esophageal squamous cell carcinoma

Sehhoon Park MD, PhD, Dongryul Oh MD, PhD, Yoon-La Choi MD, PhD, Sang Ah Chi BS, Kyunga Kim PhD, Myung-Ju Ahn MD, PhD, Jong-Mu Sun MD, PhD

First published: 23 March 2022 | https://doi.org/10.1002/cncr.34176 | Citations: 8



In conclusion, the current results suggest a promising efficacy and safety profile for durvalumab plus tremelimumab with definitive CCRT in patients who have locally advanced ESCC. Furthermore, PD-L1 expression may have a strong predictive role when ICIs are incorporated with definitive CCRT.



These data support pembrolizumab as a valuable treatment option with durable benefit for heavily pretreated patients with advanced, metastatic esophageal cancer whose disease progressed after 2 or more lines of therapy

European Journal of Cancer
Volume 144, February 2021, Pages 232-241

Original Research

Preoperative pembrolizumab combined with chemoradiotherapy for oesophageal squamous cell carcinoma (PALACE-1)

Chengqiang Li [a 1], Shengguang Zhao [b 1], Yuyan Zheng [a 1], Yichao Han [a 1], Xiaoyan Chen [c], Zenghui Cheng [d], Yuquan Wu [a], Xijia Feng [a], Weixiang Qi [b], Kai Chen [a], Jie Xiang [a], Jian Li [e], Toni Lerut [f], Hecheng Li [a]

PPCT was safe, did not delay surgery, and induced a pCR in 55.6% of resected tumours. A phase II multicentre study is undergoing for further confirmation of efficacy (NCT04435197).

Journal of Clinical Oncology > List of Issues > Volume 41, Issue 4_suppl >

Meeting Abstract | 2023 ASCO Gastrointestinal Cancers Symposium

ESOPHAGEAL AND GASTRIC CANCER

Long-term outcomes from adding durvalumab to neoadjuvant treatment of operable gastroesophageal cancers: Results from a multicenter study LUD2015-005.

Mark R. Middleton, Ioannis Karydis, Xin Lu, Aileen Ryan, Ralph Rudolph Venhaus, Kristen Auferio Ramirez, ...

Conclusions: Adding D to standard neo-adjuvant regimens for GEC is well tolerated. Survival times and response rates exceeded those expected for the regimens used (2 year survivals with FLOT 68% and CROSS 67%) in this non-randomised multi-centre trial.

ELSEVIER

Advances in Radiation Oncology

Volume 7, Issue 1, January–February 2022, 100807

Scientific Article

A Phase 2 Trial Combining Pembrolizumab and Palliative Radiation Therapy in Gastroesophageal Cancer to Augment Abscopal Immune Responses

Joseph Chao MD [a], Ting-Fang He PhD [b], Massimo D'Apuzzo MD, PhD [c], Yi-Jen Chen MD, PhD [d], Paul Frankel PhD [e], Michael Tajon PhD [a], Helen Chen MD [d], Shawn Solomon BS [b], Samuel J. Klempner MD [f g], Marwan Fakih MD [a], Peter Lee MD [b]

Conclusions

Combining palliative radiation therapy and pembrolizumab provided promising durable responses in this patient population but we were unable to definitively distinguish abscopal biologic changes. Biomarker analyses beyond PD-L1 expression are needed to better understand putative mechanisms and identify patients who will benefit from this approach

Radiation plus immunotherapy for thymoma

- While survival outcomes are generally good, intrathoracic failures after definitive treatment for thymoma can occur in approximately up to one-quarter of patients .
- Due to its rarity, there is a dearth of understanding of the molecular

biology of these tumors, and immunotherapy approaches are limited to small patient cohorts.

There are some studies suggesting PD-L1 expression has higher prevalence in more aggressive histologies (i.e., B1-3 thymomas and thymic carcinomas) and in higher Masaoka stages

TET Immunotherapy clinical trials

	TET in trial	Trial drug	No. of patients	ORR	mPFS (months)	mOS (months)
Giaccone *et al.* (28)	Thymic carcinoma	Pembrolizumab	40	22.5%	4.2	24.9
Rajan *et al.* (29)	Thymoma	Avelumab	7	29%	N/A	N/A
Cho *et al.* (30)	Thymic carcinoma	Pembrolizumab	26	19.2%	9.7	14.5
Cho *et al.* (30)	Thymoma	Pembrolizumab	7	28.6%	N/R	N/R

TET Immunotherapy trials in progress

Trial	Trial drug	TET	No. of patients currently enrolled
NCT03076554	Avelumab	Thymoma, TC	8
NCT03134118	Nivolumab	Thymoma, TC	N/A
NCT03295227	Pembrolizumab	Thymoma, TC	N/A
NCT03463460	Pembrolizumab + Sunitinib	Thymoma, TC	N/A
NCT02364076	Pembrolizumab + Epacadostat	Thymoma, TC	45

Pembrolizumab in Treating Patients With Rare Tumors That Cannot Be Removed by Surgery or Are Metastatic

ClinicalTrials.gov Identifier: NCT02721732

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

Recruitment Status : Active, not recruiting
First Posted : March 29, 2016
Last Update Posted : May 19, 2023

View this study on the modernized ClinicalTrials.gov

Sponsor:
M.D. Anderson Cancer Center

Collaborator:
National Cancer Institute (NCI)

Information provided by (Responsible Party):
M.D. Anderson Cancer Center

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Pembrolizumab for Patients With Refractory or Relapsed Thymic Epithelial Tumor: An Open-Label Phase II Trial

Jinhyun Cho, Hae Su Kim, Bo Mi Ku, Yoon-La Choi, Razvan Cristescu, Joungho Han, Jong-Mu Sun, Se-Hoon Lee, Jin Seok Ahn, Keunchil Park, and Myung-Ju Ahn

Pembrolizumab showed encouraging antitumor activity in patients with advanced TET. Given the high incidence of autoimmunity, additional studies are needed to identify those who can benefit from pembrolizumab without immune-related adverse events.

Conclusions

- The combination of immunotherapy and RT has the potential to revolutionize treatments for thoracic malignancies.
- Preclinical data have demonstrated impressive synergy between the two therapies that appears to extend beyond the irradiated target. For patients with advanced NSCLC, recent clinical trials incorporating ICIs have exhibited dramatic improvements in outcomes compared to conventional chemotherapies.
- results are awaited from ongoing and future preclinical research and clinical trials to better define the optimal approaches to combining these two pillars of cancer care.(immunosensitizer)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