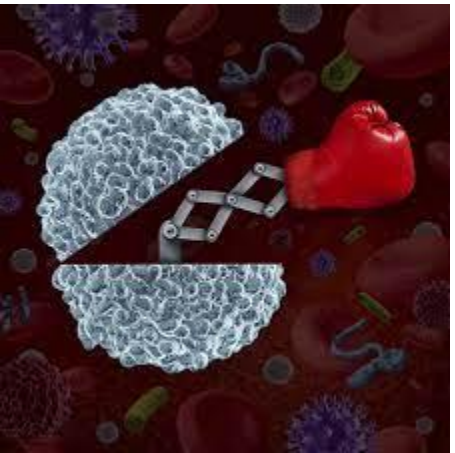
KASTURBA MEDICAL COLLEGE
MANIPAL
(A constituent unit of MAHE, Manipal)

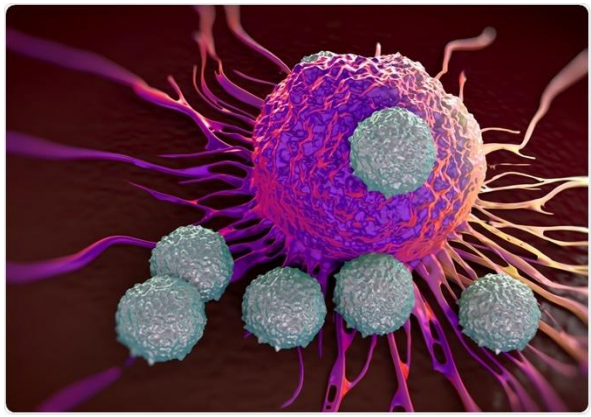
Manipal Comprehensive Cancer Care Centre
Precise. Precision. Person-Centred. Population.

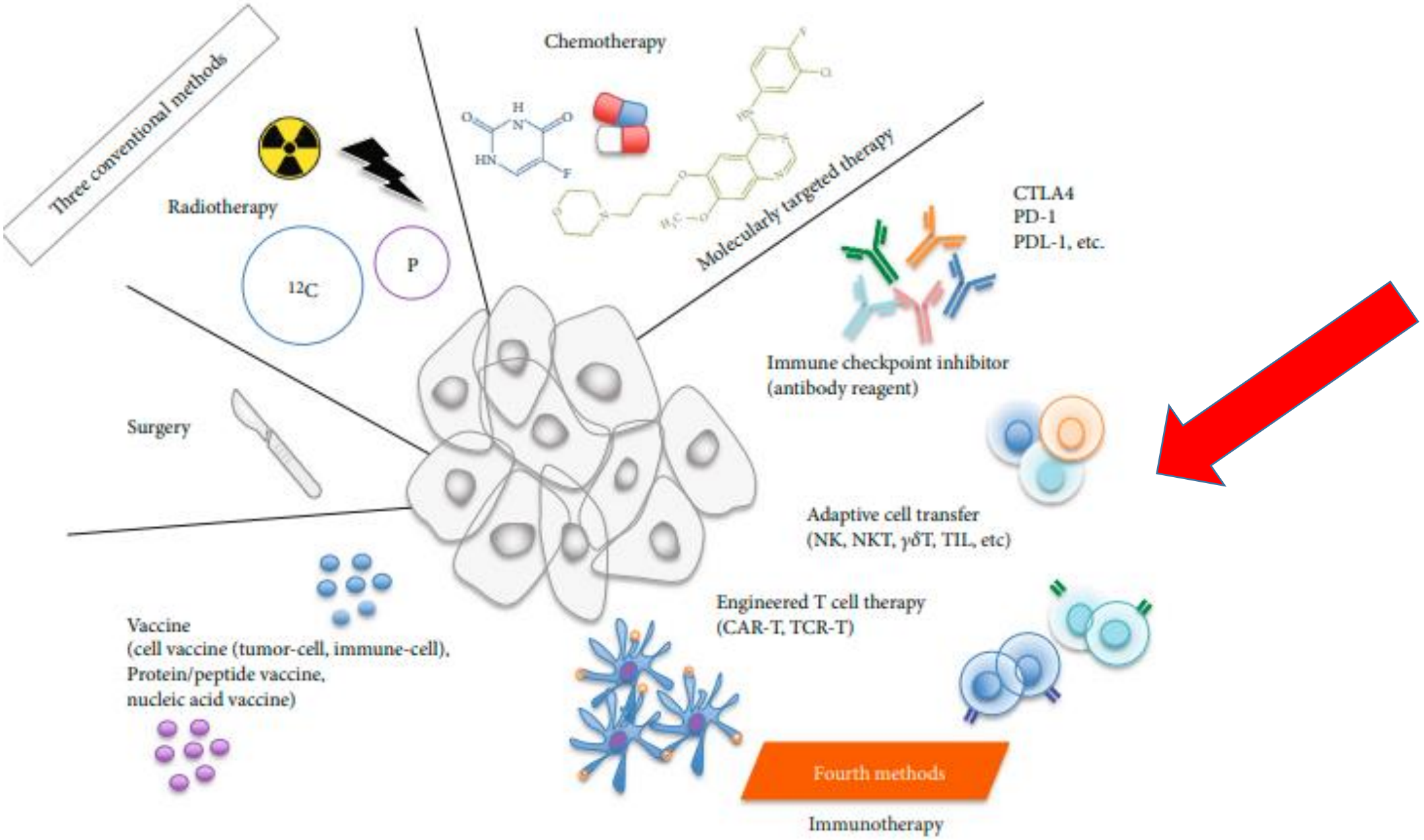
Introduction to Immunotherapy and Interaction with Radiation

Dr Shirley Lewis MD, DNB, FRCR
Fellowship in GI and Lung cancer- Princess Margaret Cancer centre, Toronto

Associate Professor and Head
Department of Radiation Oncology
Manipal comprehensive Cancer Care Centre
Kasturba Medical College, Manipal







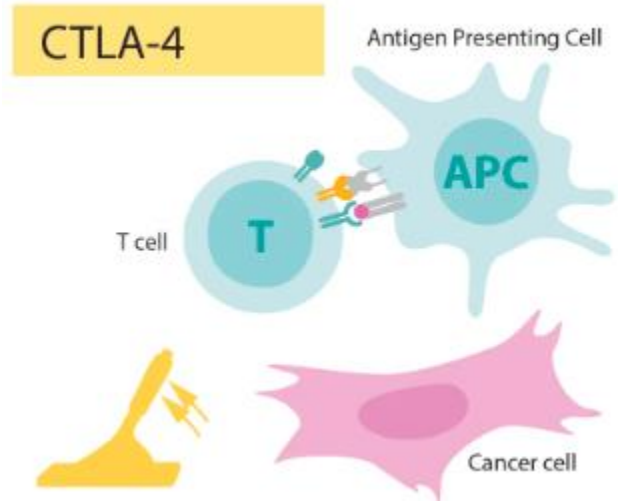
Journal of Immunology Research Volume 2020, Article ID 5825401

Immunotherapy timeline

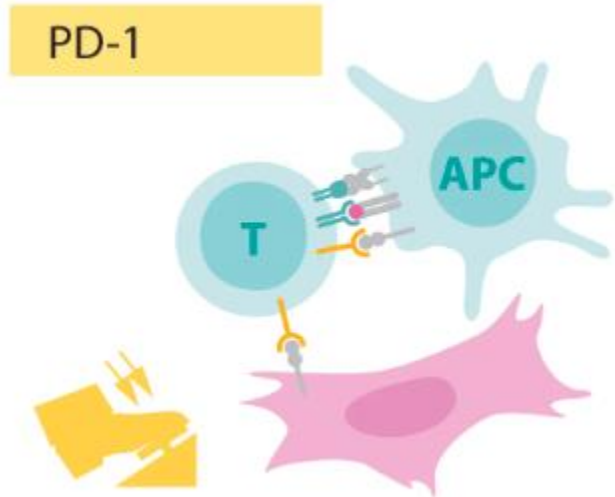
- Wilhelm Busch and Friedrich Fehleisen- immune status and cancer.
- 1890's William Coley-'Father of Cancer Immunotherapy'- extracts of heat-inactivated S. pyogenes and Serratia marcescens- 'Coley's toxins'.
- 1909- Paul Ehrlich- immune system eradicates cancer antigens.
- Lewis Thomas and Sir Frank Macfarlane- Cancer immune surveillance.

Nobel 2018
Immune Brakes

Dr James P Allison



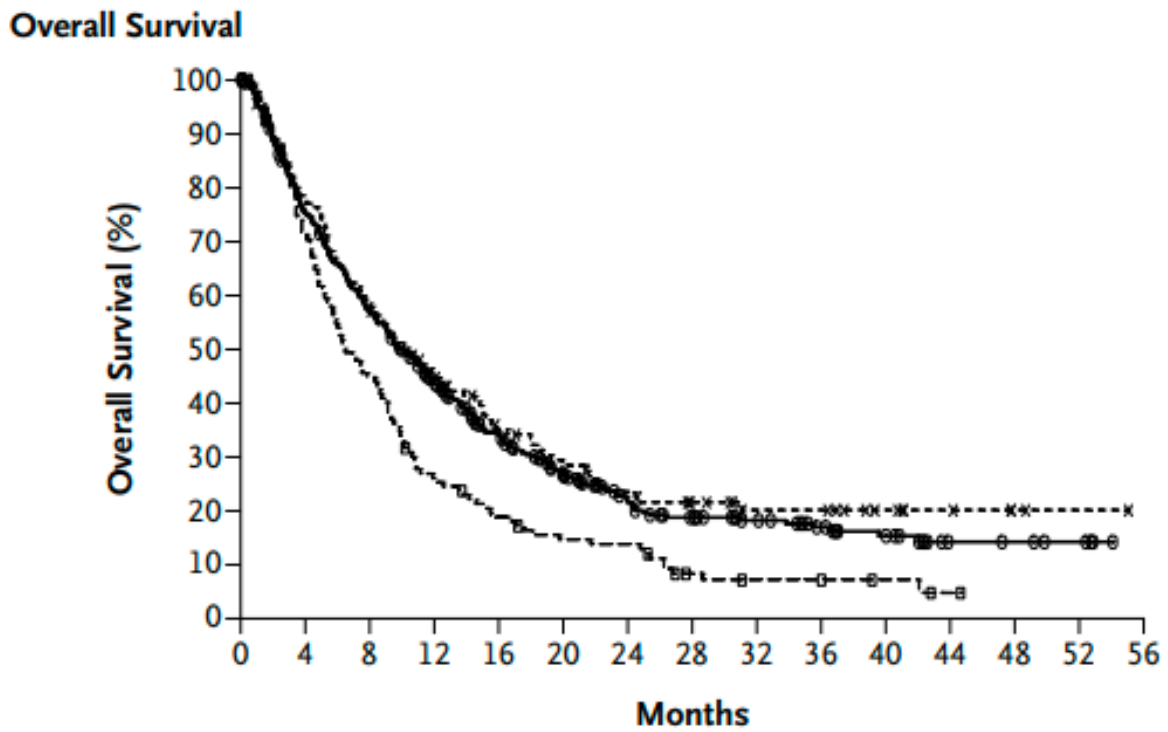
Dr Tasuku Honjo



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 19, 2010 VOL. 363 NO. 8

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

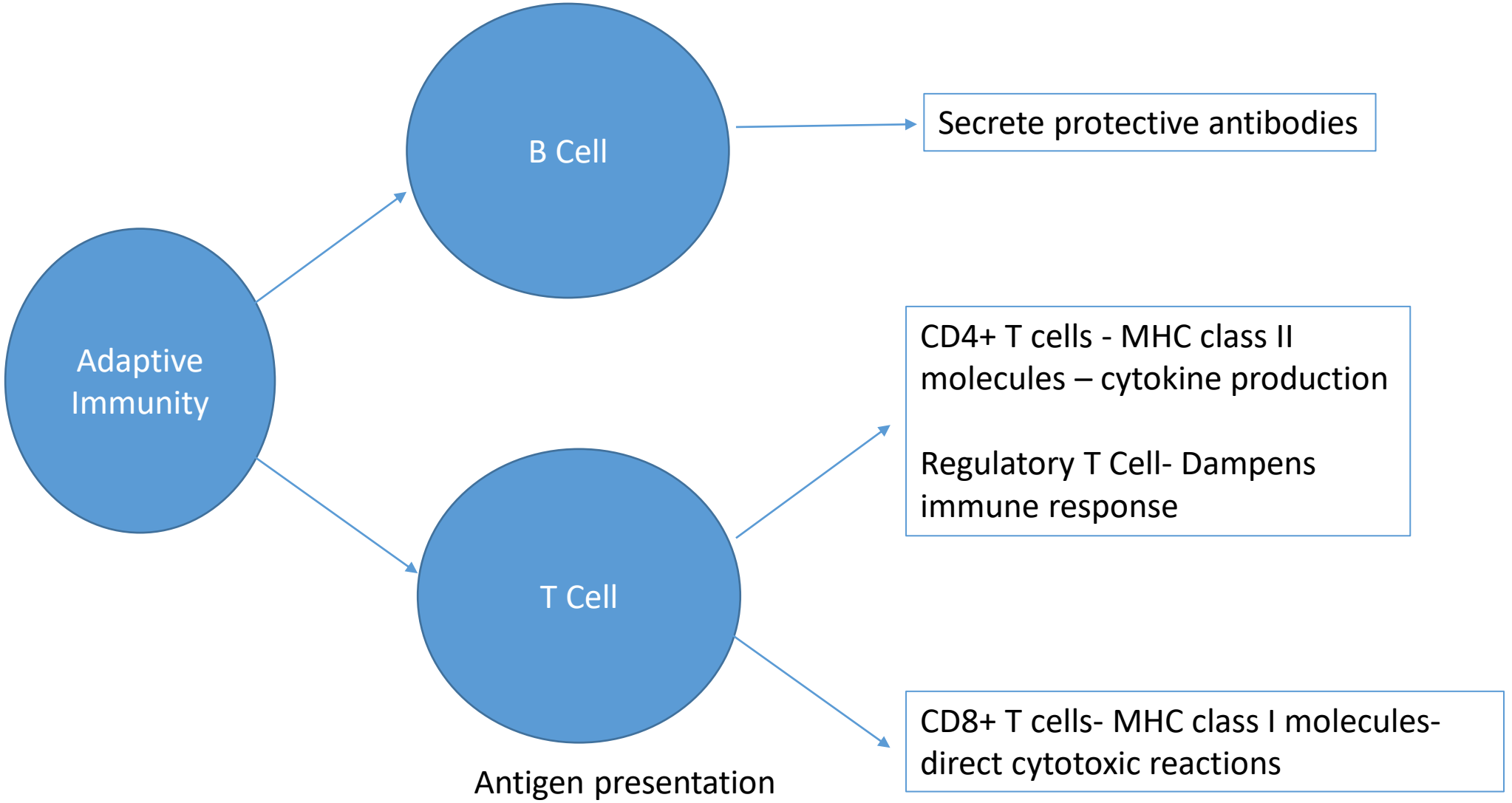


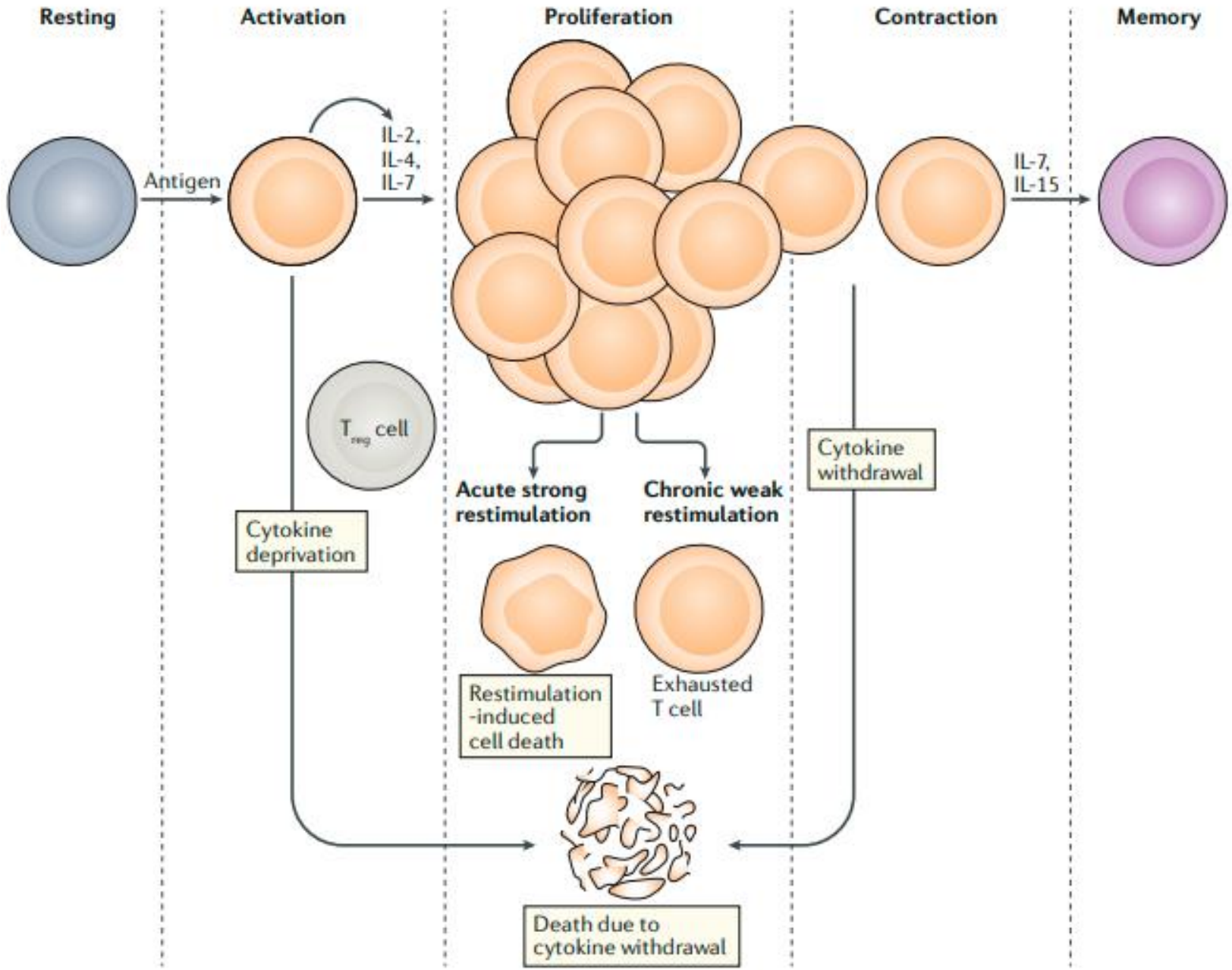
Hodi et al N Engl J Med 2010;363:711-23

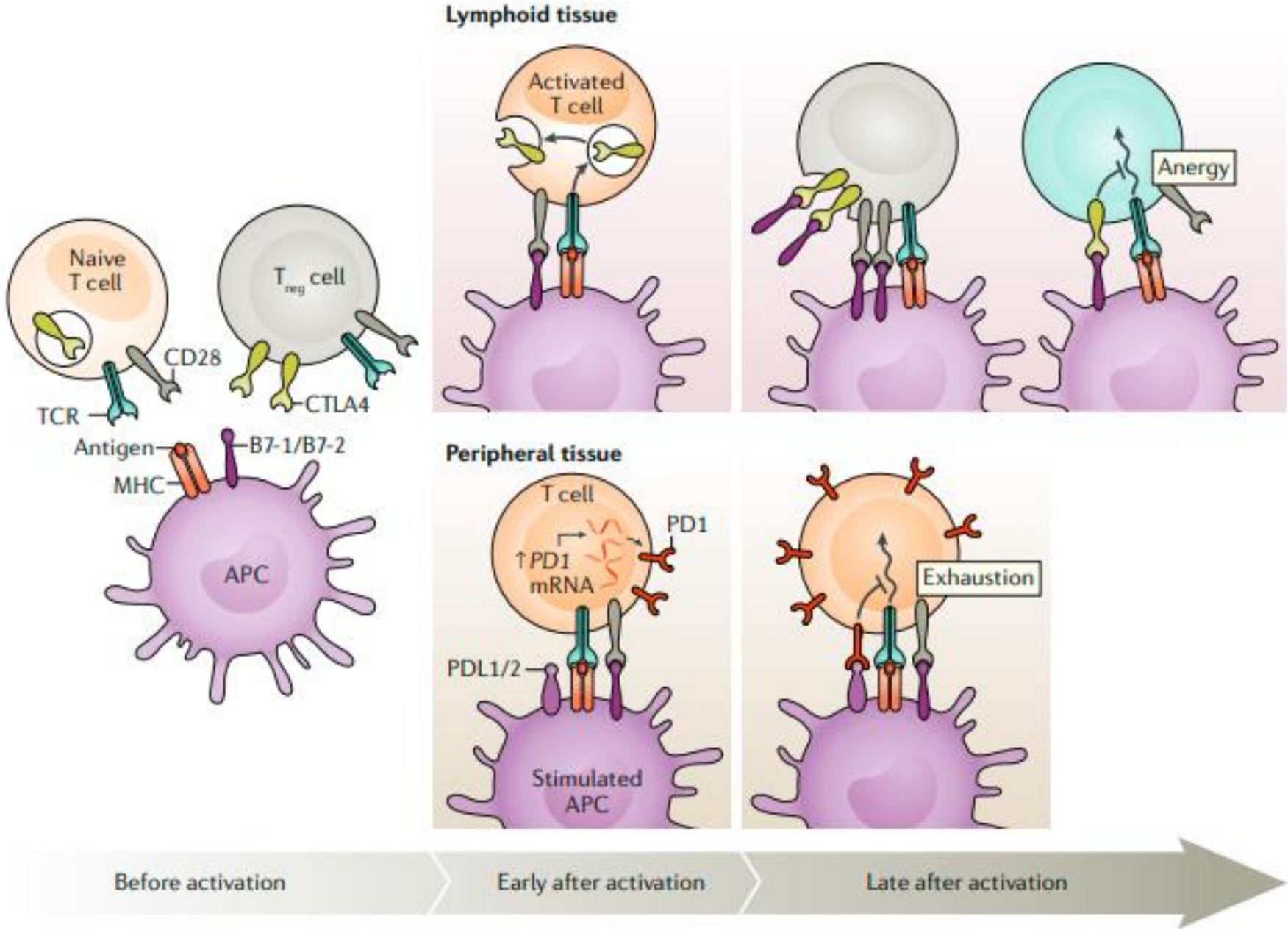
2013 Breakthrough of the Year

CANCER IMMUNOTHERAPY: harnessing the immune system to battle tumors

Immune surveillance

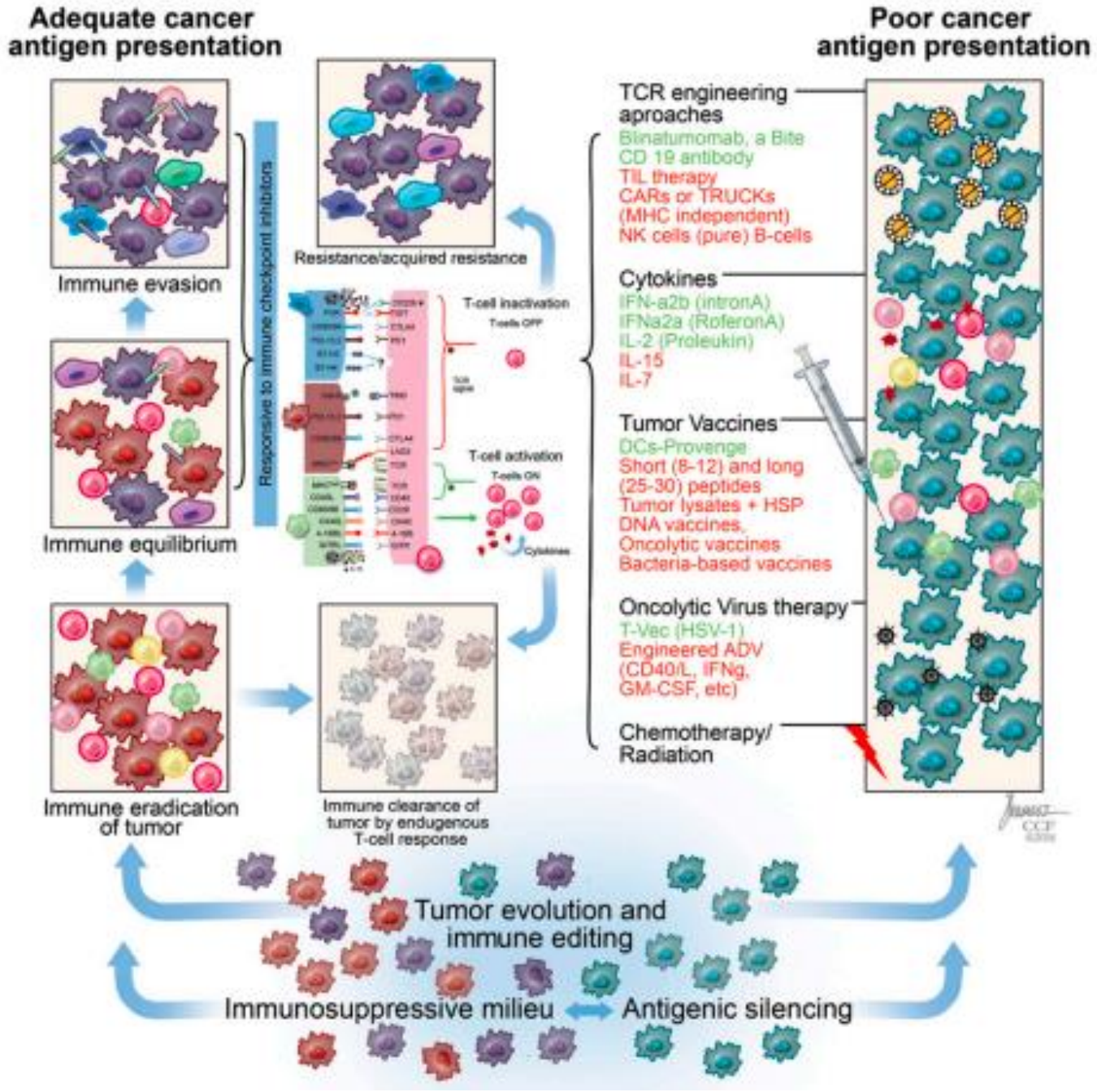



Resting
Activation
Proliferation
Contraction
Memory
Antigen
IL-2,
IL-4,
IL-7
IL-7,
IL-15
T_{reg} cell
Cytokine deprivation
Cytokine withdrawal
Acute strong restimulation
Chronic weak restimulation
Restimulation -induced cell death
Exhausted T cell
Death due to cytokine withdrawal

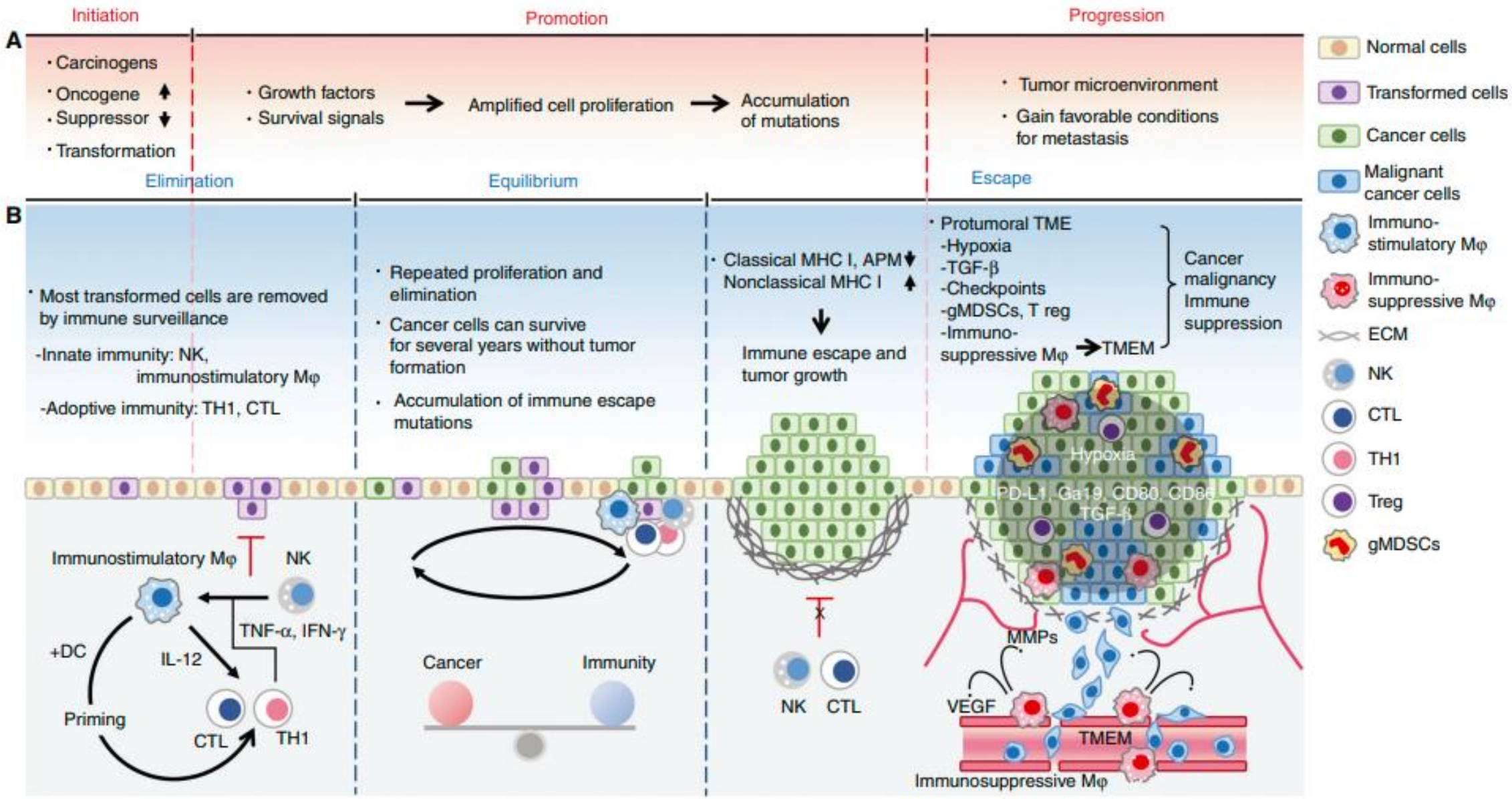

Lymphoid tissue
Naive T cell
T_{reg} cell
CD28
TCR
CTLA4
Antigen
B7-1/B7-2
MHC
APC
Activated T cell
Anergy
Peripheral tissue
T cell
PD1
↑PD1 mRNA
PDL1/2
Stimulated APC
Exhaustion
Before activation
Early after activation
Late after activation

Immune-evasion

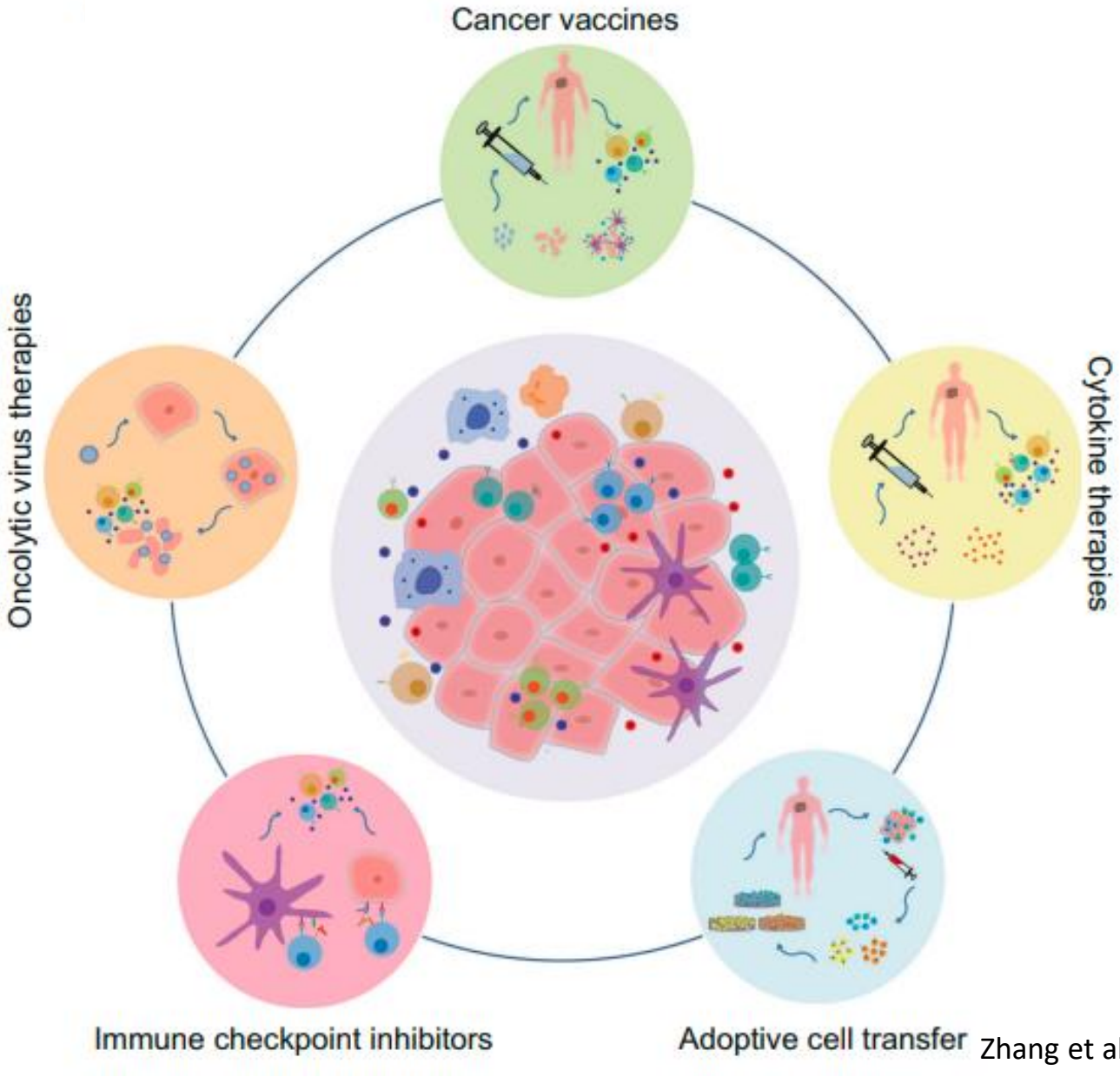
Tumors overcome the prolonged dormancy/latency phase through a process of immune editing, resulting in selective pressure eradicating or diminishing the most immunogenic clones.



Immuno-editing



Types of Immunotherapy



Zhang et al Cellular & Molecular Immunology (2020)

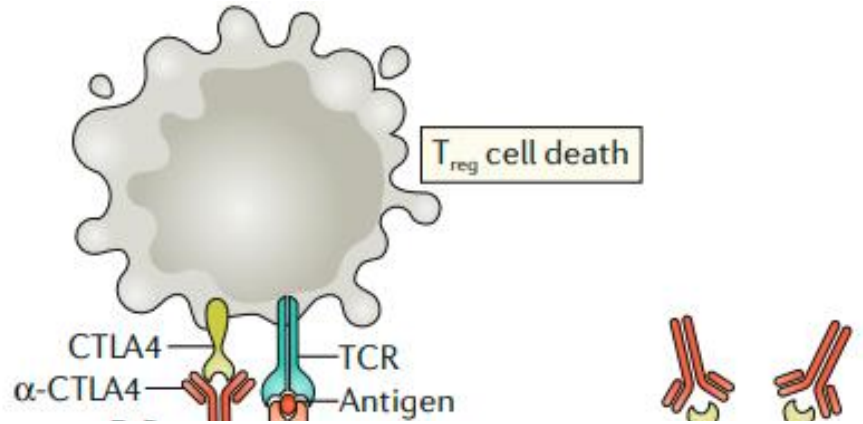
Immune check point Inhibitors

- T cell immune checkpoint molecules:
- **Cytotoxic T lymphocyte antigen 4 (CTLA4)**
- **Programmed cell death 1 (PD1)**
- Lymphocyte-activation gene 3 (LAG-3)
- T cell immunoglobulin and mucin domain 3 (TIM-3)
- V-domain immunoglobulin suppressor of T cell activation (VISTA)

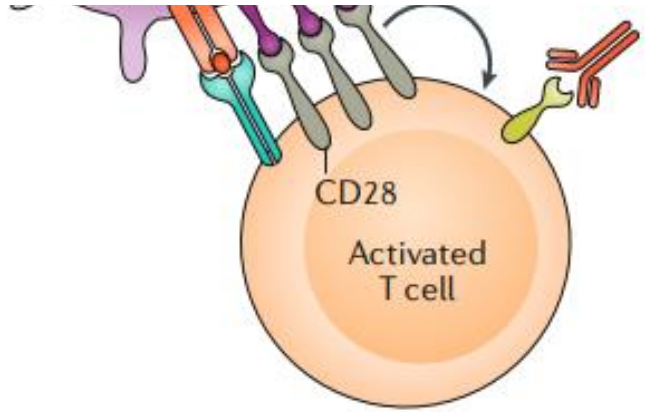
- Inhibit T cell activation and proliferation- prevent antitumor response.

- Upregulation of these molecules in tumor

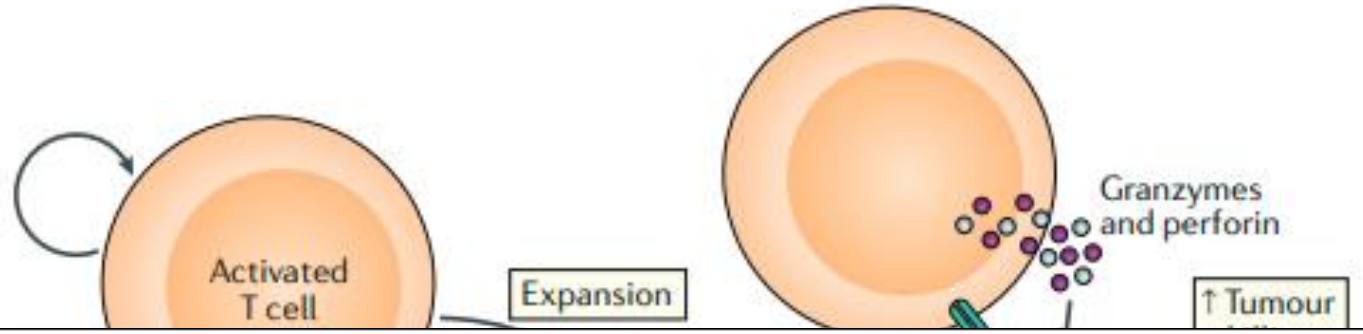
CTLA4 Blockade



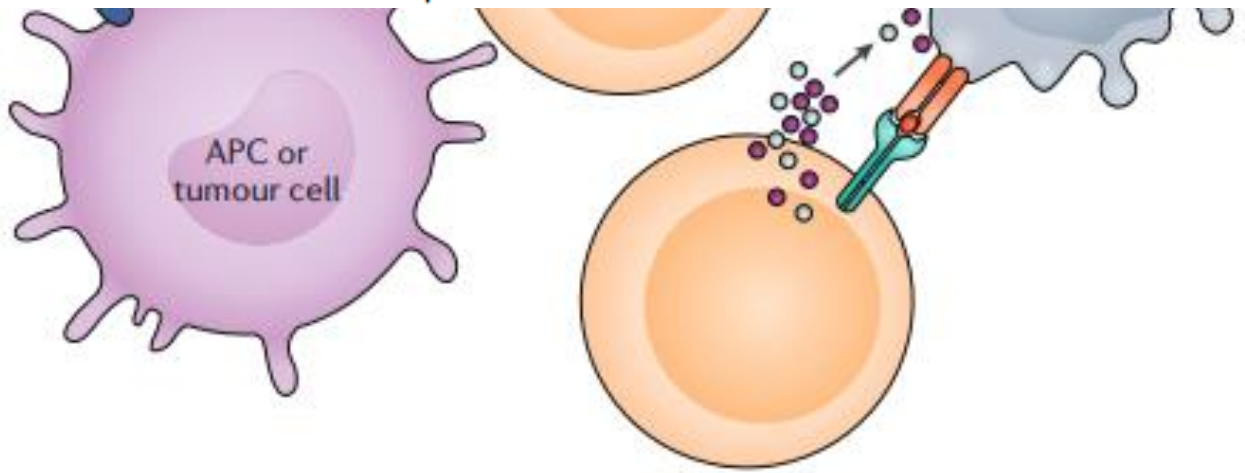
Co-inhibitory Checkpoint	Receptor Distribution	Ligand	Mechanism of Immune Evasion	Drugs Targeting	Tumor Type
CTLA-4	Activated CD8 T-cells, regulatory T cells	CD80, CD86	Cytoplasmic tail interacts with protein kinase C-Л (PKC-Л) and recruitment of SHP-2; ectodomain competition with counter receptor (CD28)	Ipilimumab, tremelimumab	Melanoma, lung cancer



PD 1/PDL1



PD-1	Activated CD8 T cells, regulatory T cells, DCs, NK cells, Macrophages	PD-L1, PD-L2	Recruitment of SH2-domain containing protein tyrosine phosphatases to the ITSM cytoplasmic region of PD-1 then inhibits downstream signals of the T-cell receptor	Anti–PD-1s: nivolumab, pembrolizumab, pidilizumab; anti–PD-L1s: avelumab, atezolizumab, durvalumab	Multiple solid tumors



Target	Name	Isotype
Anti-CTLA-4	Ipilimumab	IgG1
	Tremelimumab	IgG2
Anti-PD-1	Nivolumab	IgG4
	Pembrolizumab	IgG4
	PDR001	IgG4
Anti-PD-L1	Atezolizumab	Fc mut* IgG1
	Durvalumab	Fc mut IgG1
	Avelumab	IgG1

- Trigger autoimmune and inflammatory toxicities- immune-related adverse events (irAEs).

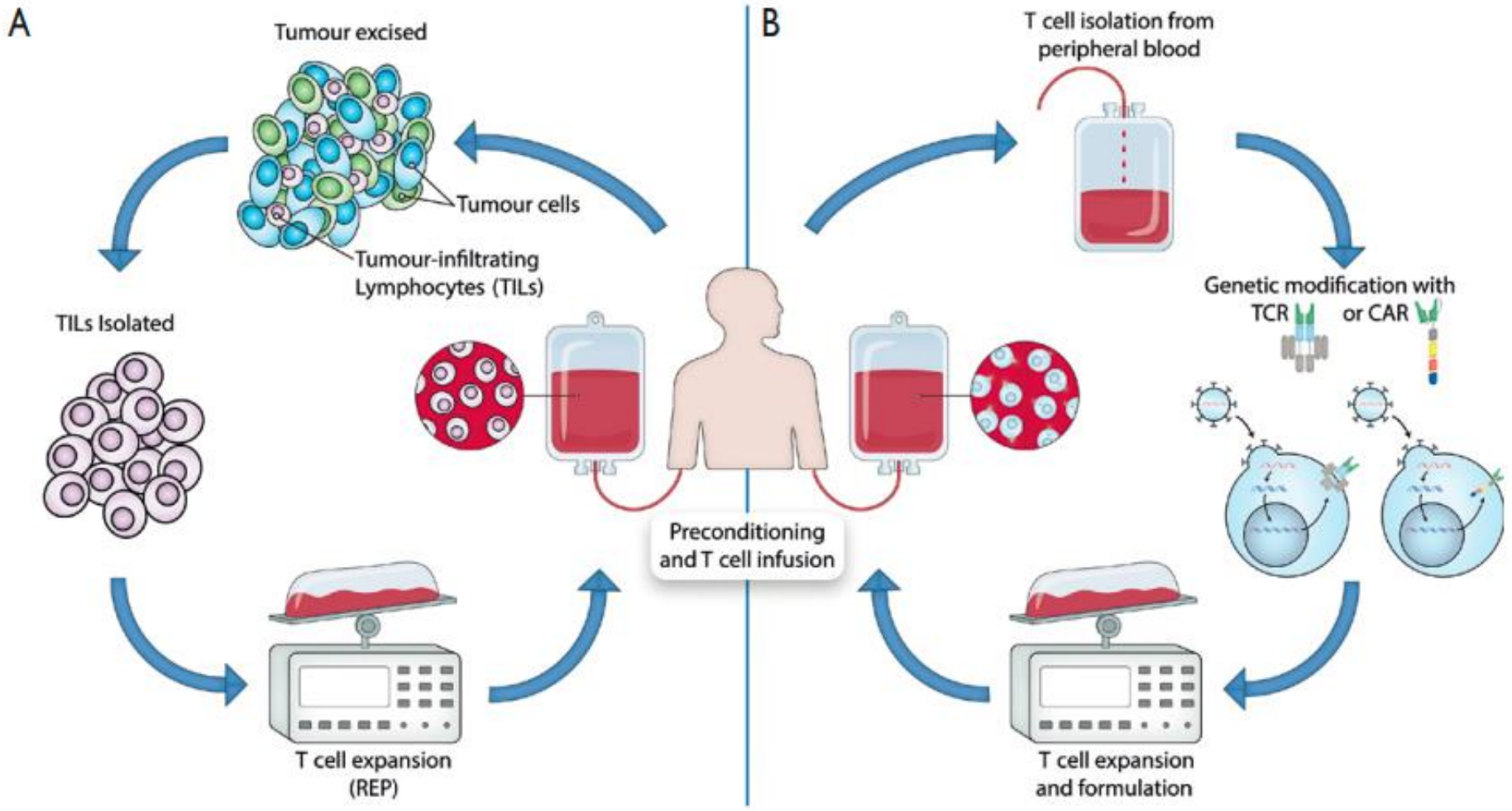
Biomarkers for response

- PDL1 on IHC
- Mutational load or burden
- MSI-H/MMR status

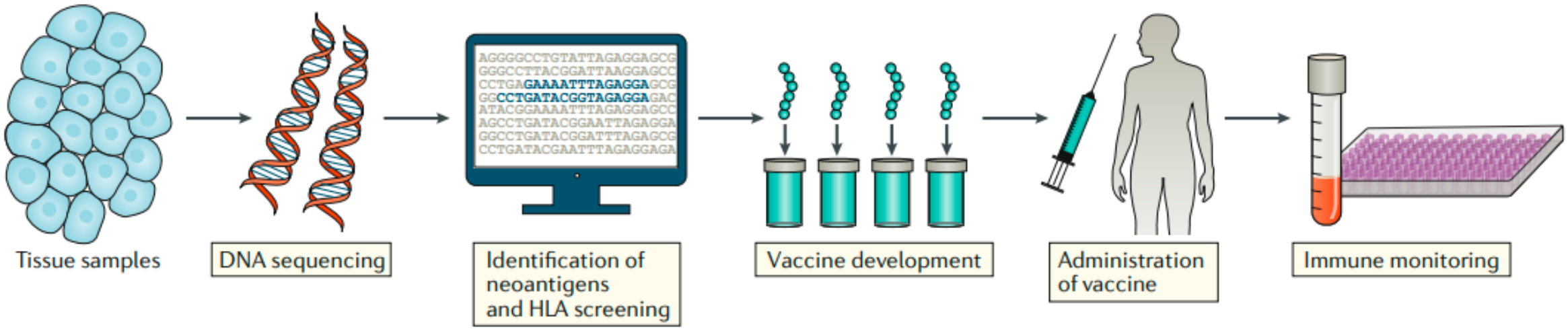
Adoptive T cell therapy (ACT)

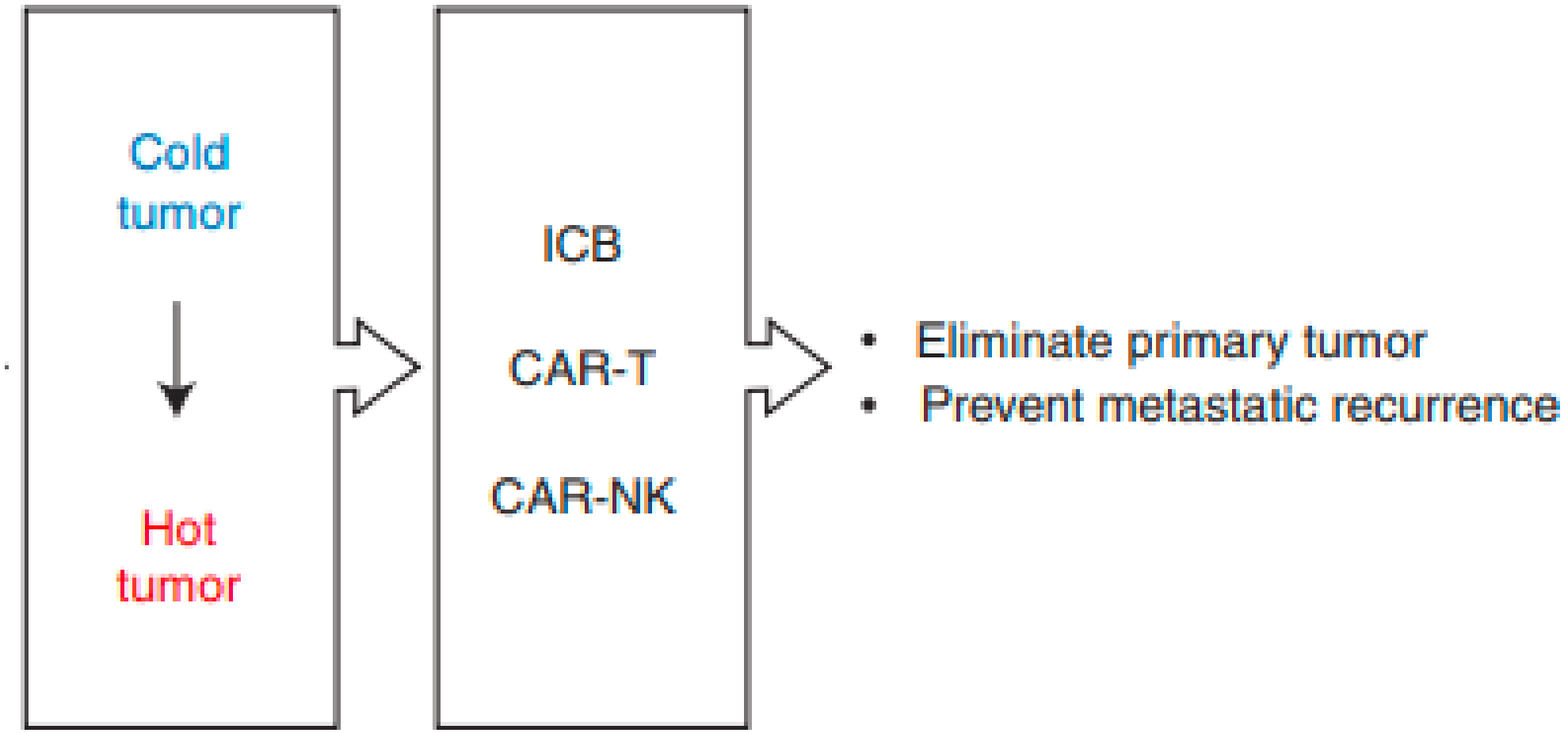
(1) Isolation
occurrin
specific
existing

(2) Genetic
blood-de
allow
recognit
cells.



Vaccines


Tissue samples
DNA sequencing
Identification of neoantigens and HLA screening
Vaccine development
Administration of vaccine
Immune monitoring

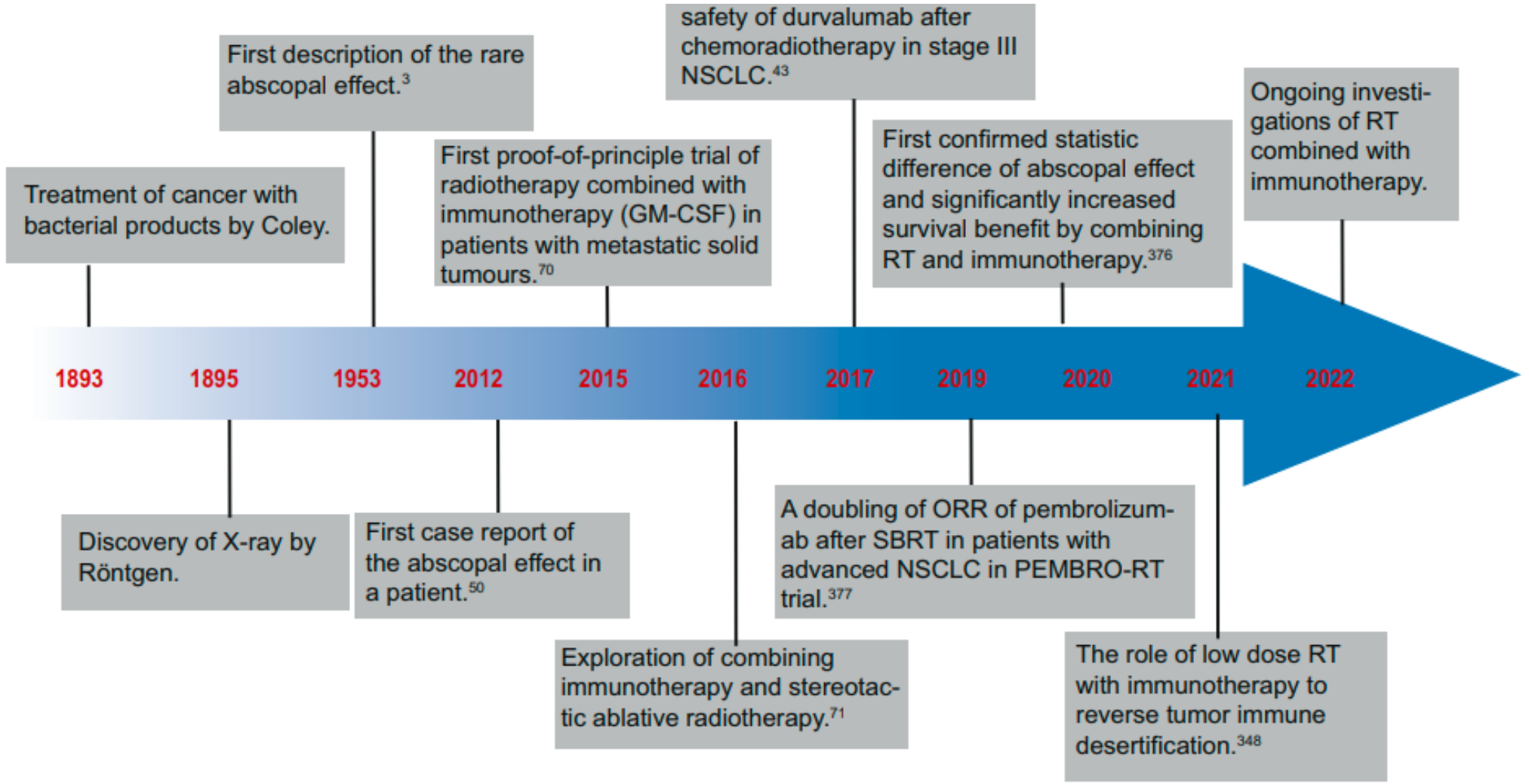


Cold Spring Harb Perspect Med 2020;10:a036863

Interaction of Immunotherapy with Radiation

- Preclinical studies- 1979- Radio resistance in immunosuppressed.
- RT can deeply reshape the tumor environment by modulating the immune response.
- RT induces in situ vaccination by killing tumor cells and triggering a systemic immune response.

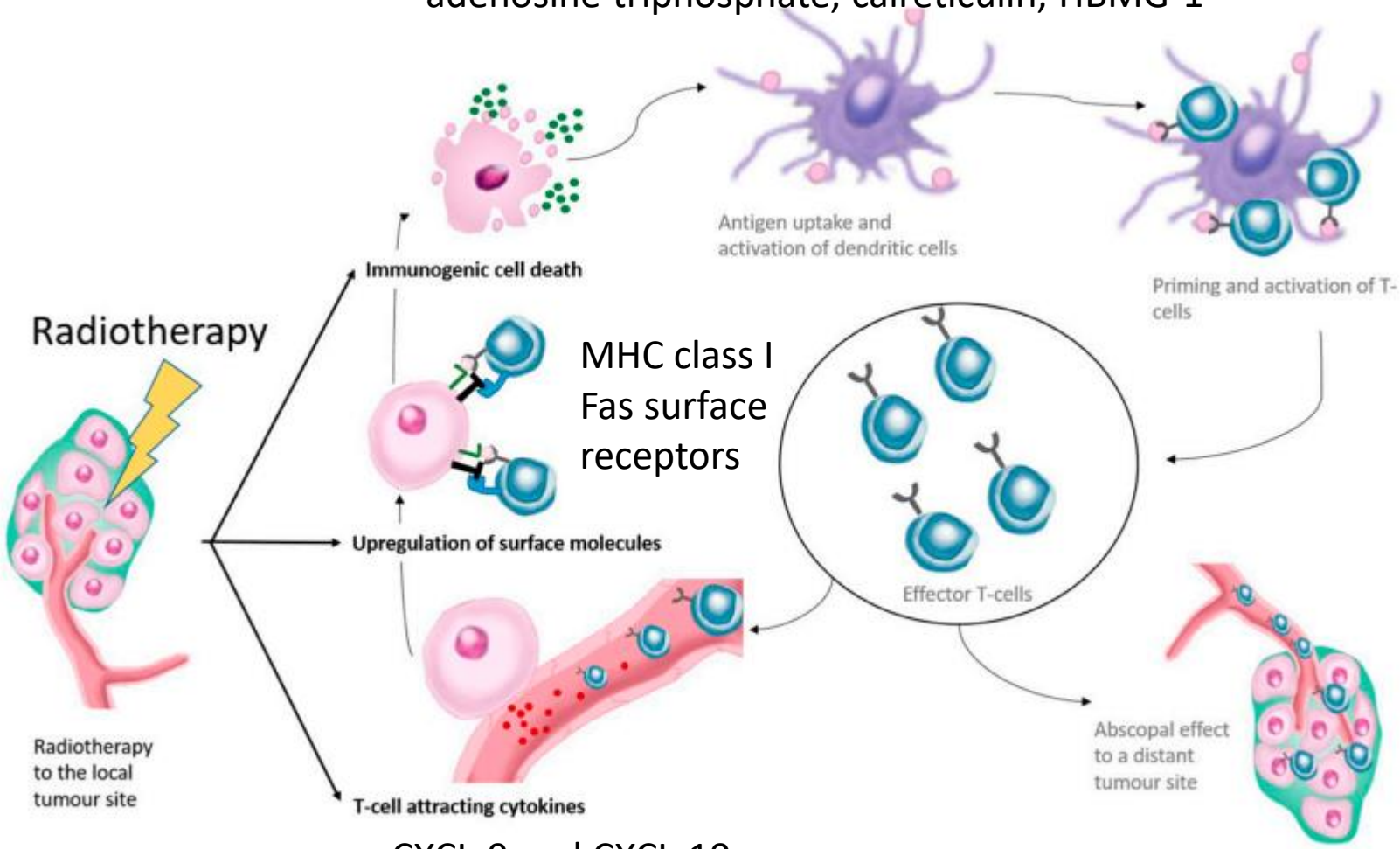
Immuno-RT (iRT)



Zhang et al Signal Transduction and Targeted Therapy (2022) 7:258

Mechanism of action

adenosine triphosphate, calreticulin, HBMG-1



CXCL-9 and CXCL-10

(1) Induction of immunogenic cell death (ICD) broadening up the immune repertoire of T cells
(2) Increasing vulnerability towards T-cell-mediated cell killing
(3) Recruitment of T cells towards the irradiated tumour

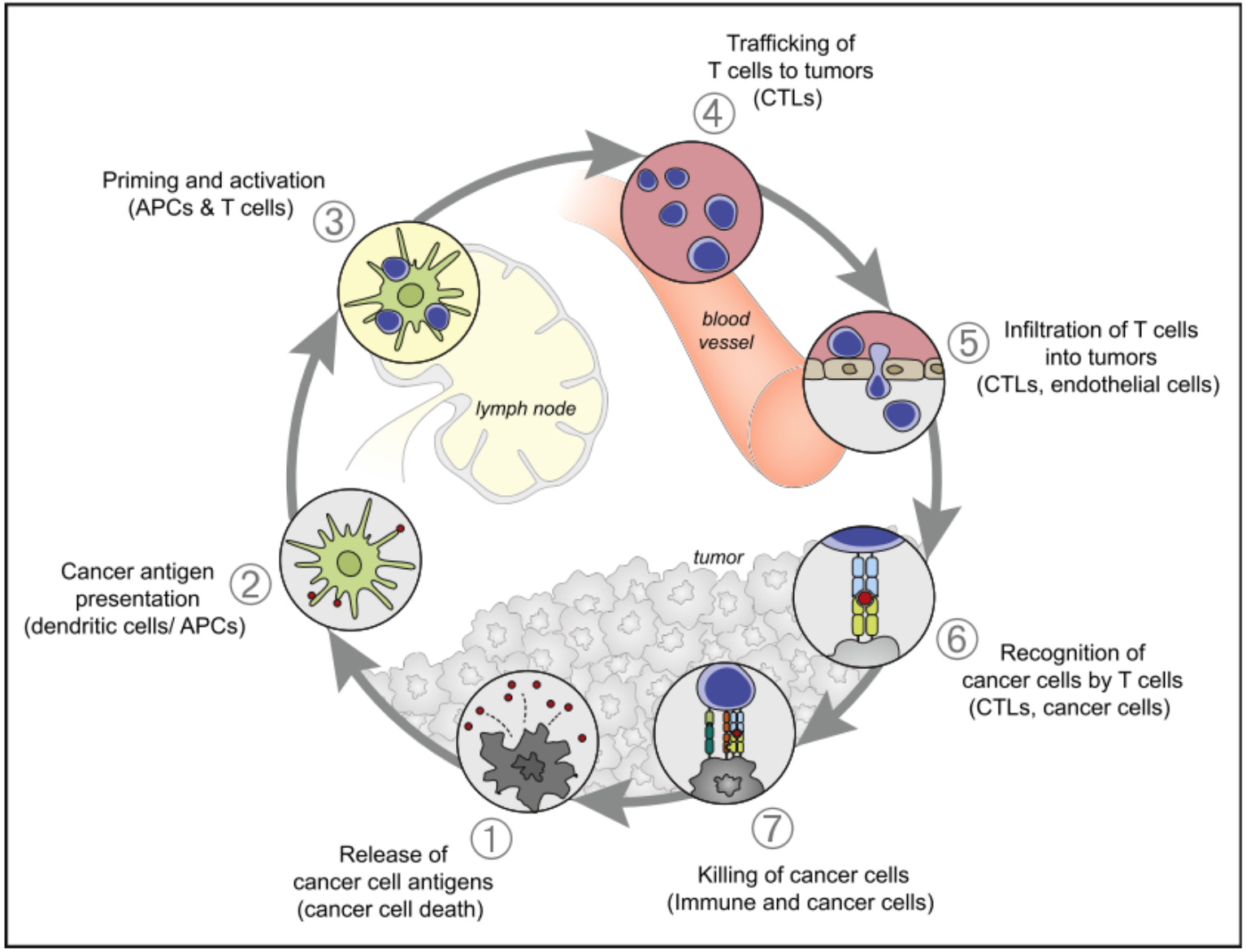
Limbergen et al Br J Radiol 2017; 90: 20170157

Biological rationale for iRT

RT exerts potent antitumor immune response influences almost all steps in the cancer-immunity cycle.

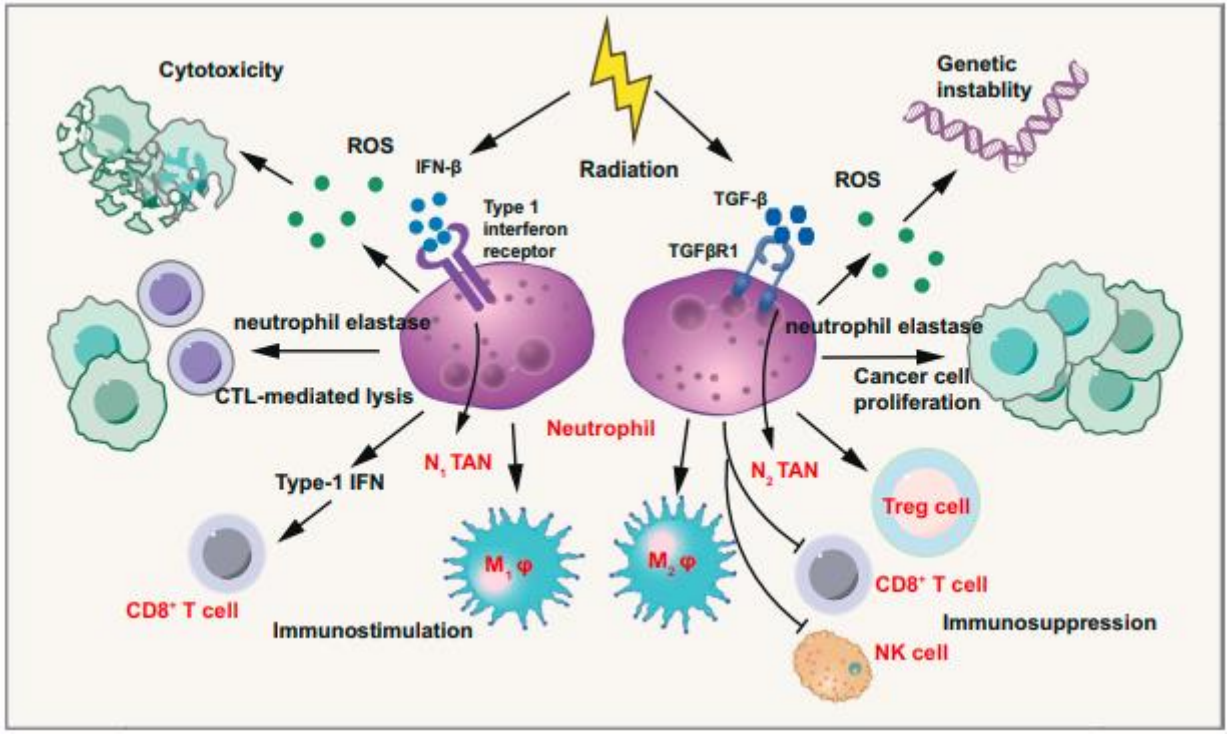
Stress response induced by RT – Release of DAMPs- cellular response driven by DNA damage changes the immunogenicity of the irradiated cancer cells.

Reprogrammed tumor microenvironment(TME) induced by RT plays a role as a “game changer” to transform “cold” tumors into “hot” tumors - a pre-requisite for response to IC

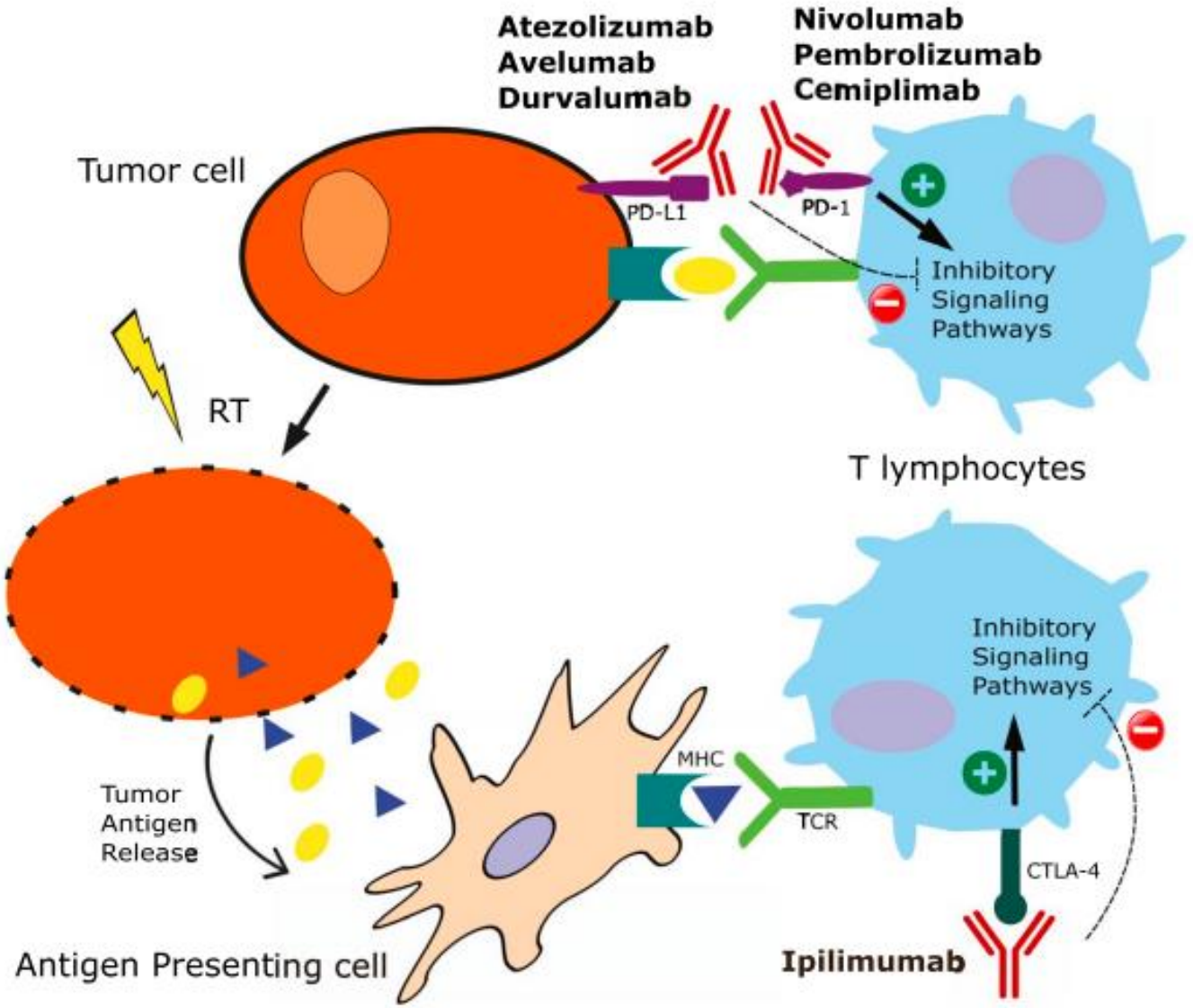


Immunomodulatory effect induced by RT is a double edge sword that not only enhances systemic antitumor immune response but also promotes immunosuppression to some extent.

RT influences tumor microenvironment: by increasing Treg cells and myeloid derived suppressor cells (MDSCs) and elevation in immunosuppressive cytokines.



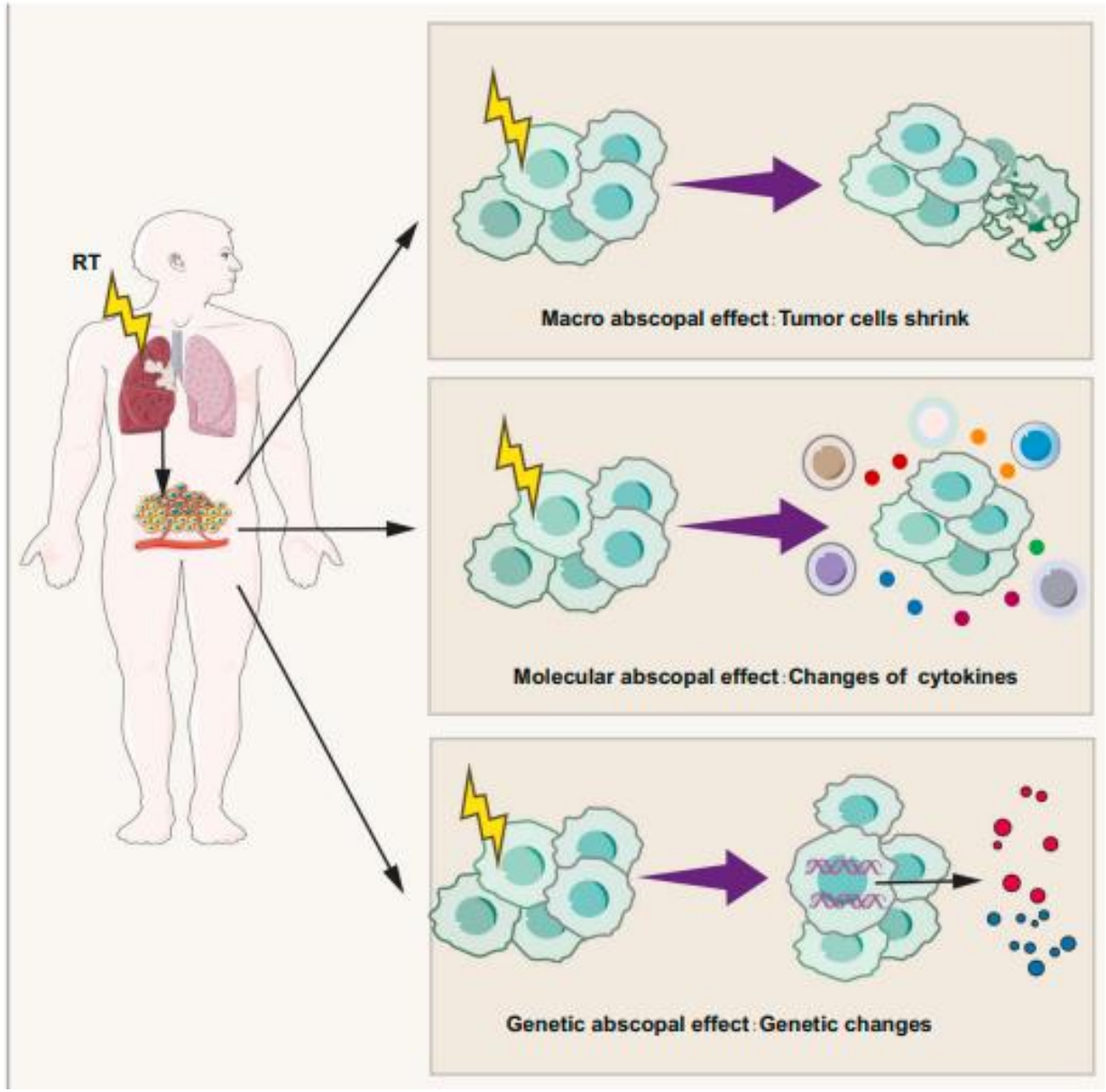
Zhang et al Signal Transduction and Targeted Therapy (2022) 7:258


Atezolizumab
Avelumab
Durvalumab
Nivolumab
Pembrolizumab
Cemiplimab
Tumor cell
PD-L1
PD-1
Inhibitory
Signaling
Pathways
RT
T lymphocytes
Inhibitory
Signaling
Pathways
MHC
TCR
Tumor
Antigen
Release
CTLA-4
Antigen Presenting cell
Ipilimumab

Just a local therapy? Abscopal Effect

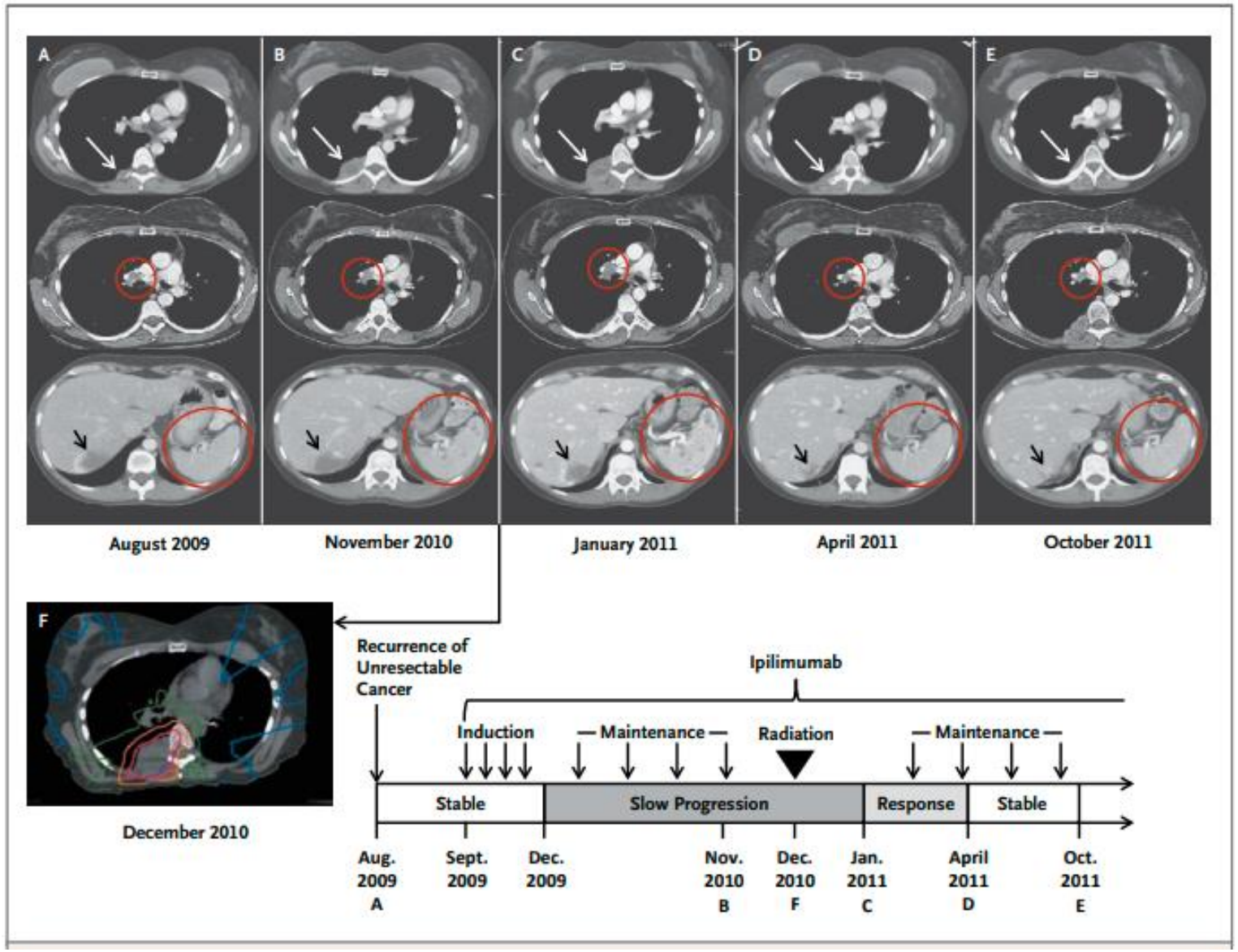
- Latin- ab scopus meaning on a distant site (away from target)
- Also termed “invivo vaccination effect” or “accelerant”
- >20 case reports
- “The abscopal effect is a phenomenon in which local radiotherapy is associated with the regression of metastatic cancer at a distance from the irradiated site.”

Mechanism



Zhang et al Signal Transduction and Targeted Therapy (2022) 7:258

Immunologic Correlates of the Abscopal Effect in a Patient with Melanoma



Palliative radiation to
Para spinal mass
28.5Gy/3 fractions

Postow et al N Engl J Med 2012;366:925-31.

iSABR

Study details	SABR dose (Gy)/fractions	SABR Target	Immunotherapy agent	Sequence of treatments	Location of response
Postow *et al.*, (2012)[36]	28.5/3	Paraspinal	Ipilimumab	immunotherapy, then SABR, then immunotherapy	IF and OF
Hiniker *et al.*, (2012)[38]	54/3	Liver	Ipilimumab	immunotherapy, then SABR, then immunotherapy	IF and OF
Golden *et al.*, (2013)[39]	30/5	Liver	Ipilimumab	Concurrent	IF and OF
Silk *et al.*, (2013)[40]	14–24/1–5	Brain	Ipilimumab	immunotherapy then SABR, or SABR then immunotherapy	IF
Stamell *et al.*, (2014)[41]	NR	Brain	Ipilimumab	Concurrent	IF and OF
Karbach *et al.*, (2014)[42]	45/1	Brain	Autologous tumor-lysate-loaded dendritic cells	SABR then immunotherapy	IF and OF
Kiess *et al.*, (2014)[43]	15–24/1	Brain	Ipilimumab	SABR then immunotherapy, or Concurrent treatment, or Immunotherapy then SABR	IF
Kwon *et al.*, (2015)[44]	8/1	Bone	Ipilimumab	SABR then immunotherapy	IF
Seung *et al.*, (2012)[45]	20/1	Any	IL-2	SABR then immunotherapy	IF and OF

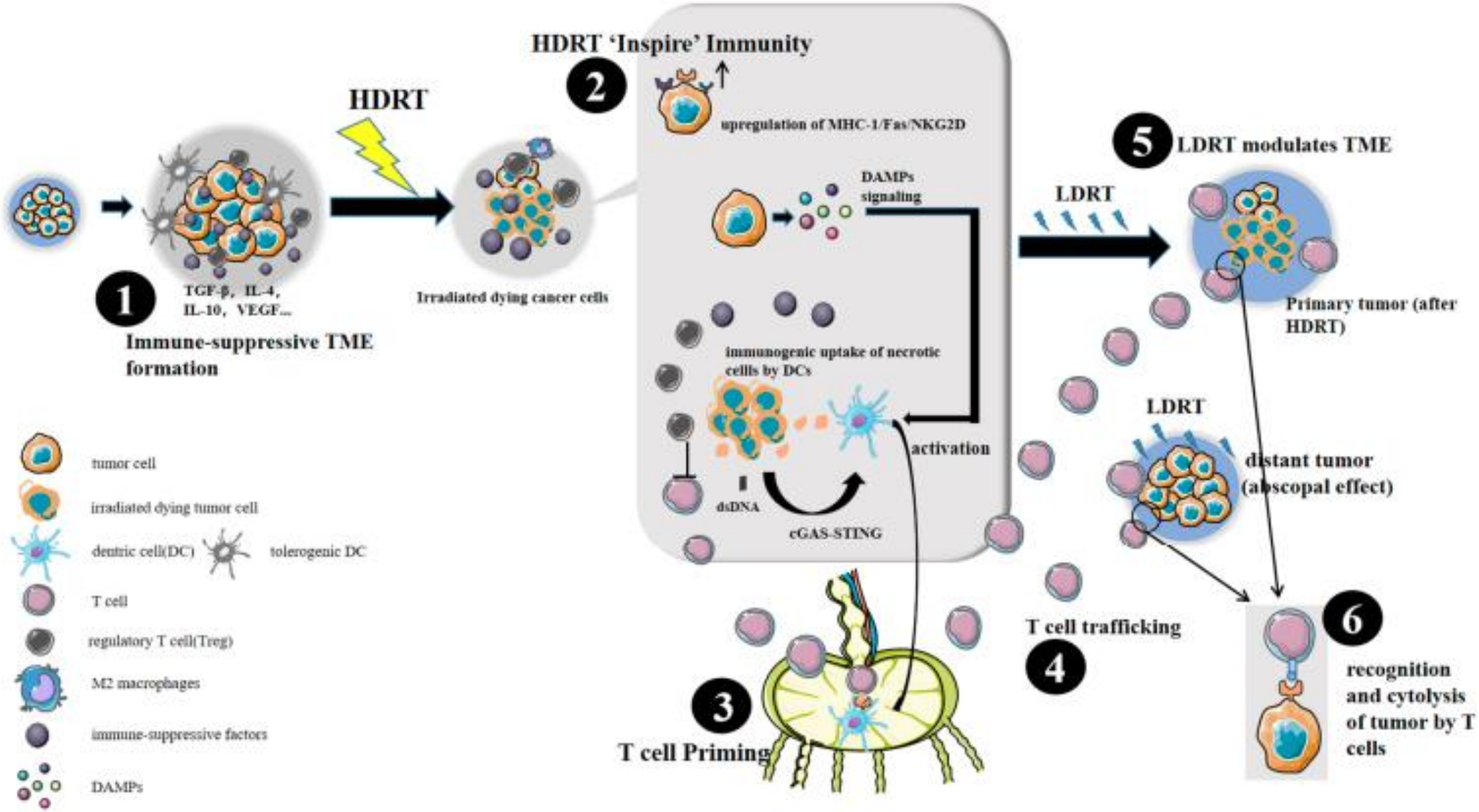
Low dose radiation and Radscopal effect

- The technique of combining HDRT to the primary tumor, LDRT to the secondary tumor, and an ICI was coined the “RadScopal” concept
- Stereotactic RT and low-dose RT was proposed by James Welsh - strategy as “RadScopal” technique.

- Low-dose RT can increase secretion of chemokines involved in the attraction of T cells.
- Increasing T cells, NK cells, polarizing M1 macrophage, upregulating immunostimulatory factors and downregulating inhibitory factors.

Ji et al Cancers 2022, 14, 3505.

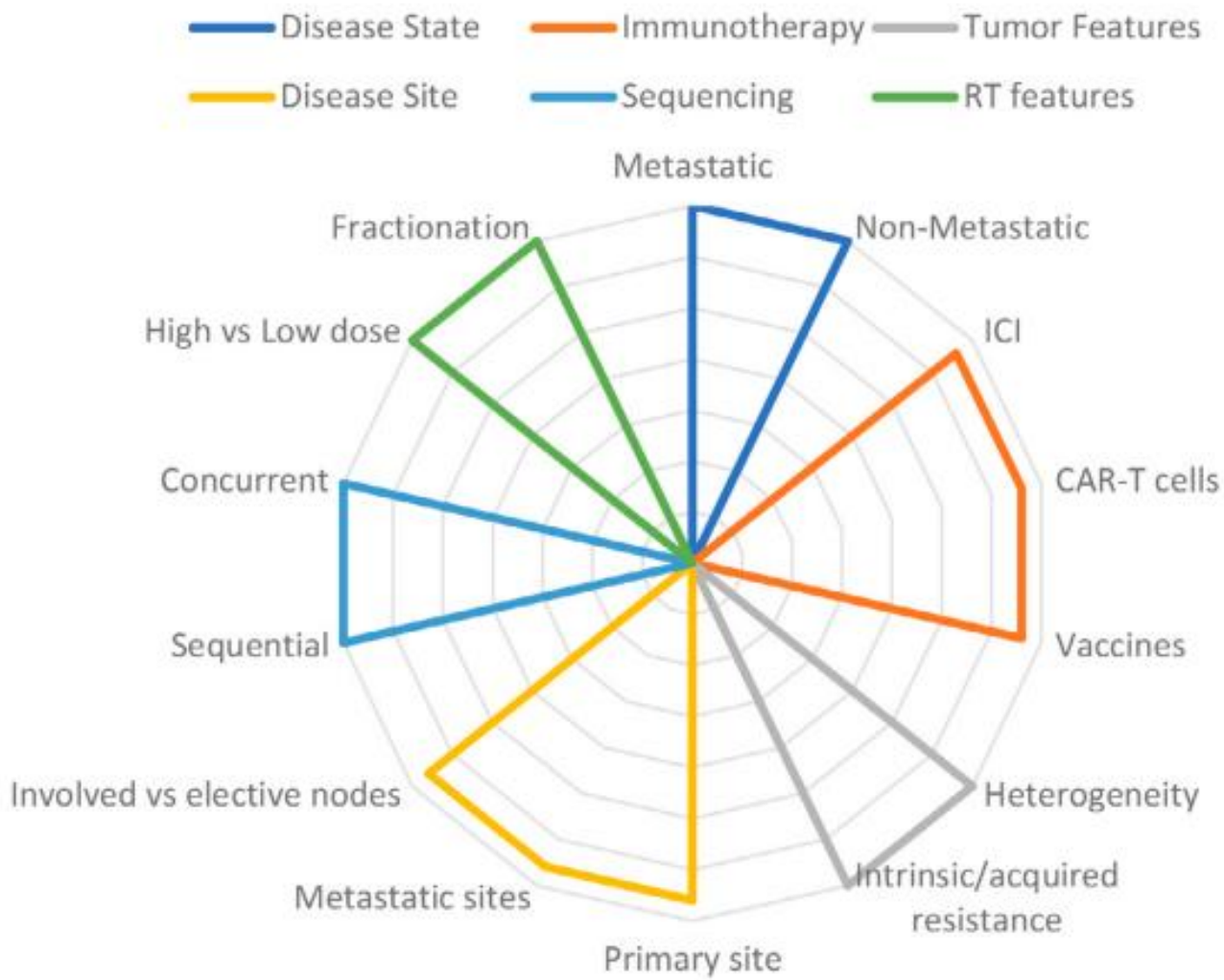
Authors	Mice and Cell Line	Number of Tumor Sites	RT Regimen	Immunotherapy	Results
H Barsoumian et al. [19]	129Sv/Ev mice 344SQ parental lung adenocarcinoma cell line	2	12 Gy*3 HDRT to the primary tumor + 1 Gy*2 LDRT to the secondary tumor (3 days after HDRT)	anti-CTLA-4 anti-PD1	Delayed growth in both primary and secondary tumors. Enhanced natural killer cell activation, increased M1 macrophages and CD4 + T-cells, and decreased TGF-β in secondary tumors.
H Barsoumian et al. [20]	129Sv/Ev mice 344SQ parental lung adenocarcinoma cell line	2	12 Gy*3 HDRT to the primary tumor + 1 Gy*2 LDRT to the secondary tumor (3 days after HDRT)	anti-TIGIT anti-PD1	Delayed growth in both primary and secondary tumors, reduced the exhaustion of T-cells, generated effector immune memory, and prolonged survival.



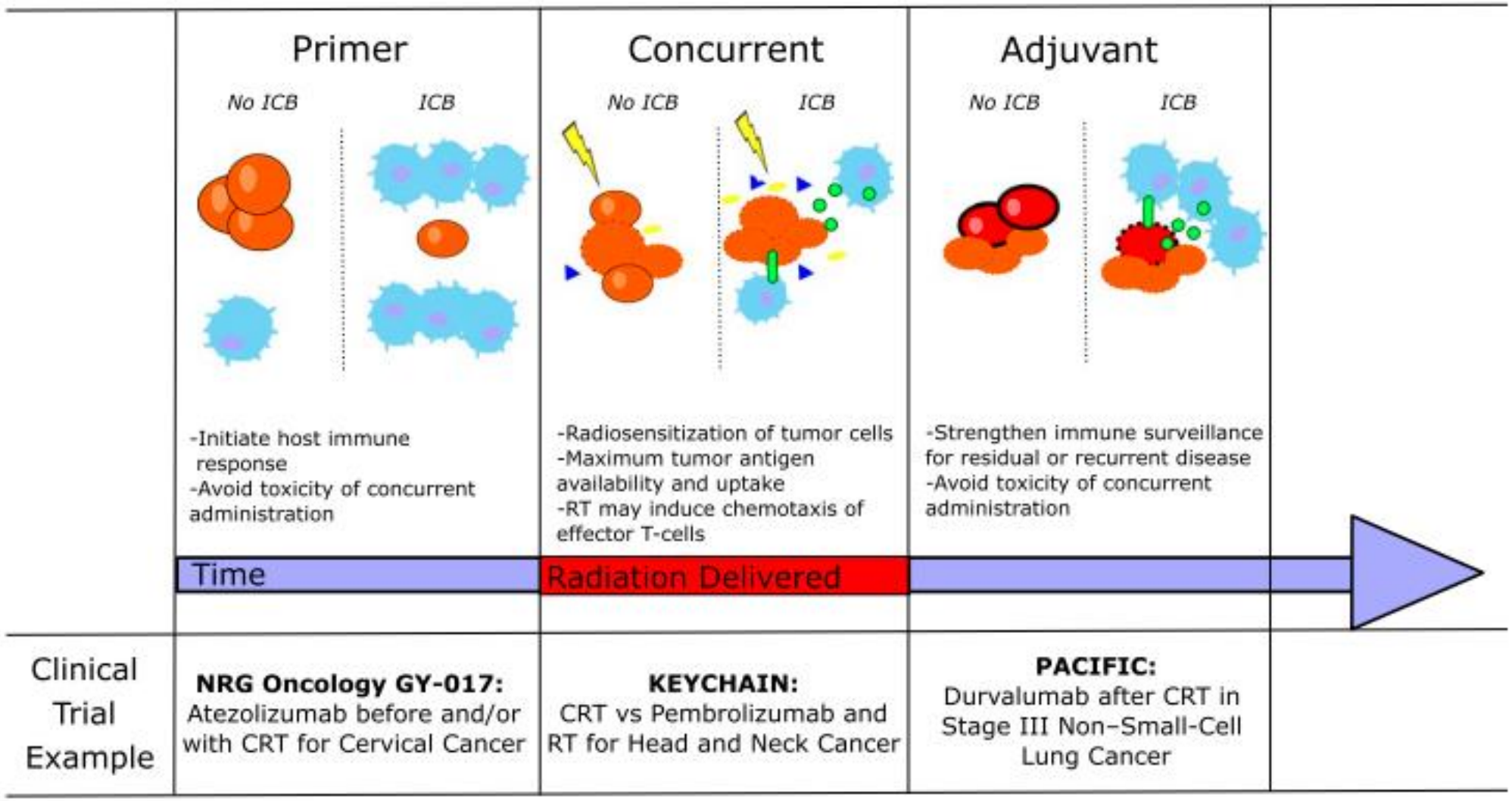
Ji et al Cancers 2022, 14, 3505. https://doi.org/10.3390/cancers14143505

Factors for iRT

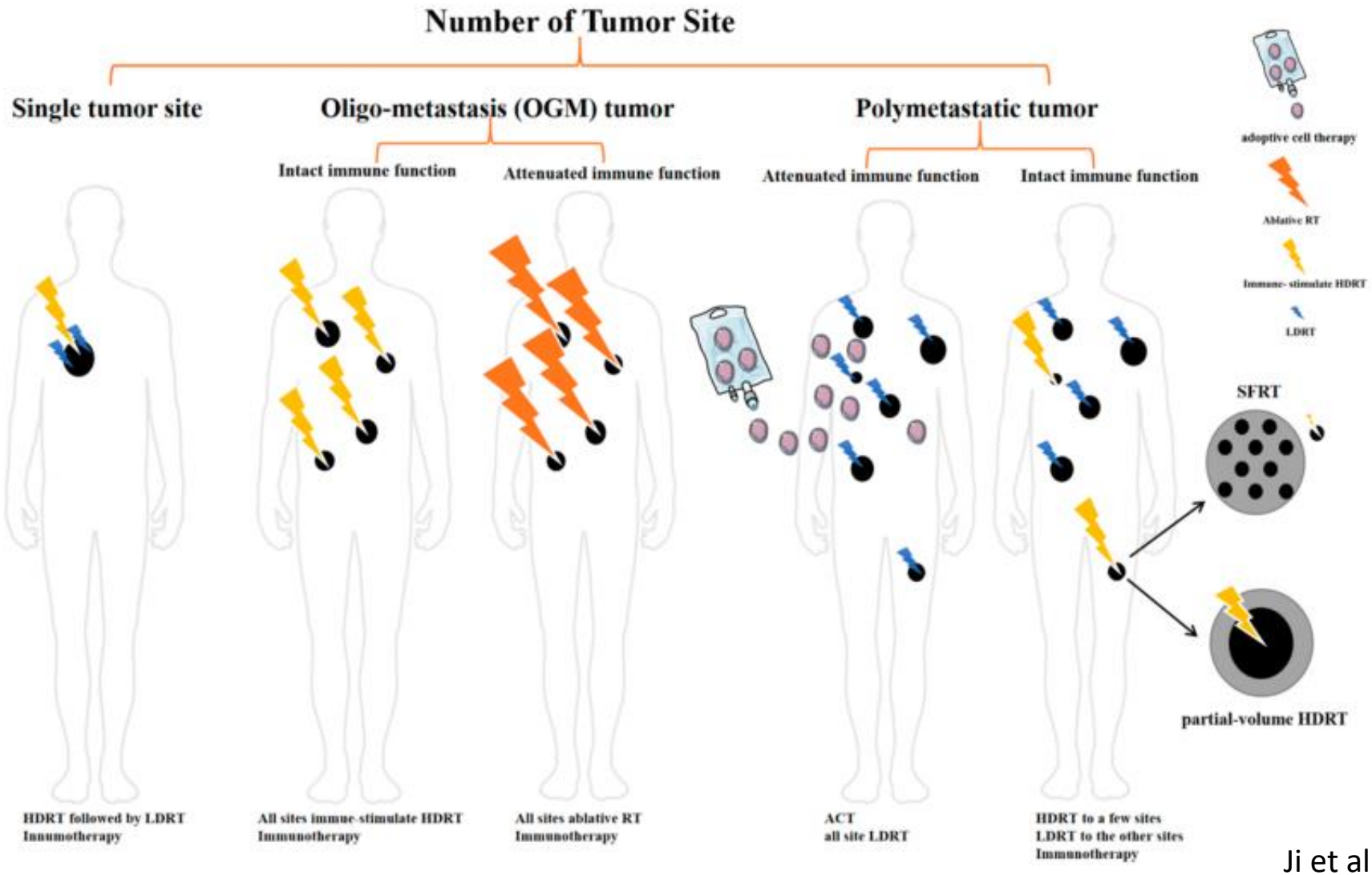
- The agents
- Sequence
- Timing
- Dose
- Fractionation
- Irradiated sites



Sequencing

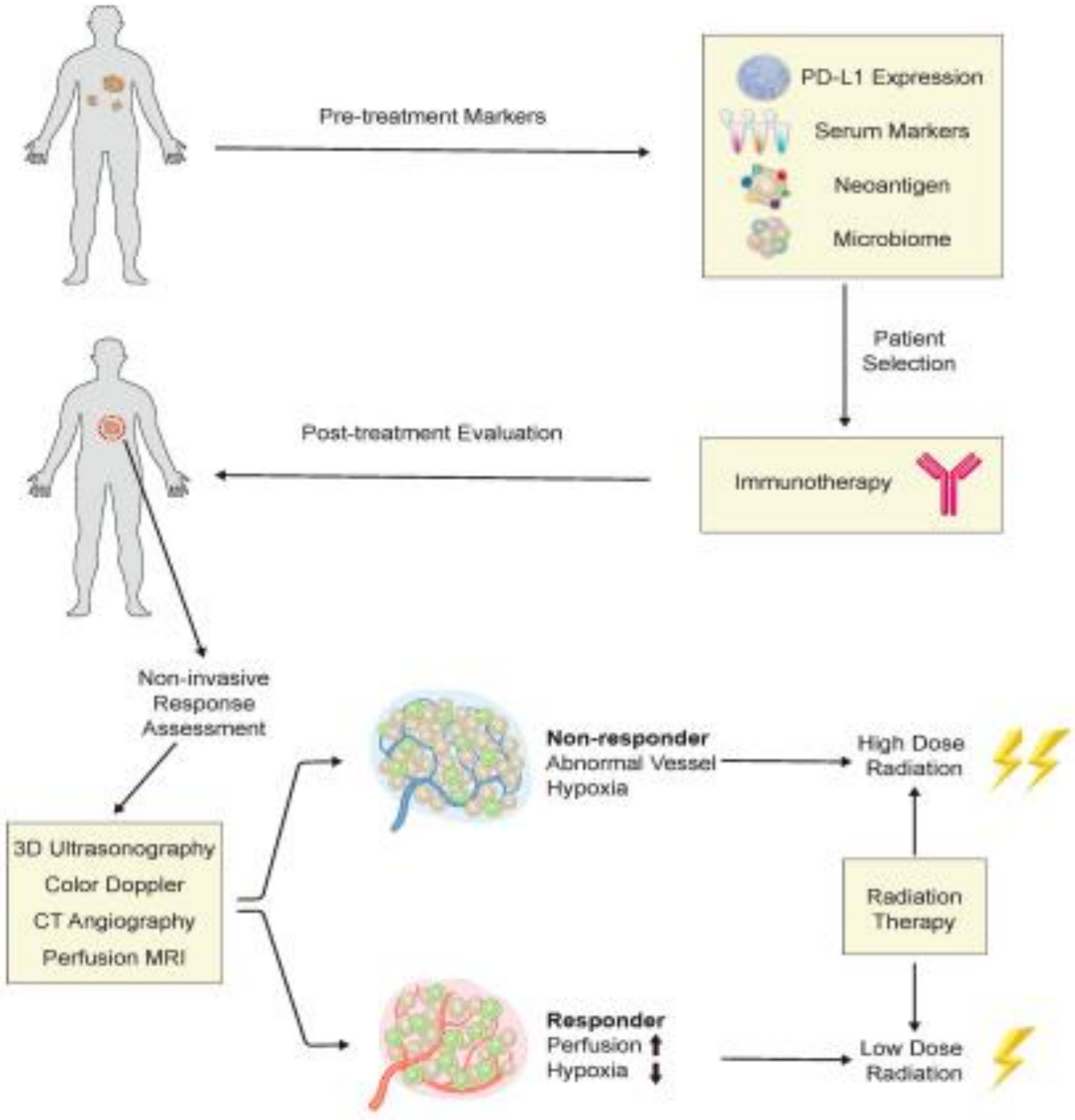

Primer
No ICB
ICB
-Initiate host immune response
-Avoid toxicity of concurrent administration
Concurrent
No ICB
ICB
-Radiosensitization of tumor cells
-Maximum tumor antigen availability and uptake
-RT may induce chemotaxis of effector T-cells
Adjuvant
No ICB
ICB
-Strengthen immune surveillance for residual or recurrent disease
-Avoid toxicity of concurrent administration
Time
Radiation Delivered
Clinical Trial Example
NRG Oncology GY-017: Atezolizumab before and/or with CRT for Cervical Cancer
KEYCHAIN: CRT vs Pembrolizumab and RT for Head and Neck Cancer
PACIFIC: Durvalumab after CRT in Stage III Non–Small-Cell Lung Cancer

Sites to Irradiate



Ji et al Cancers 2022, 14, 3505.

Type of Radiation



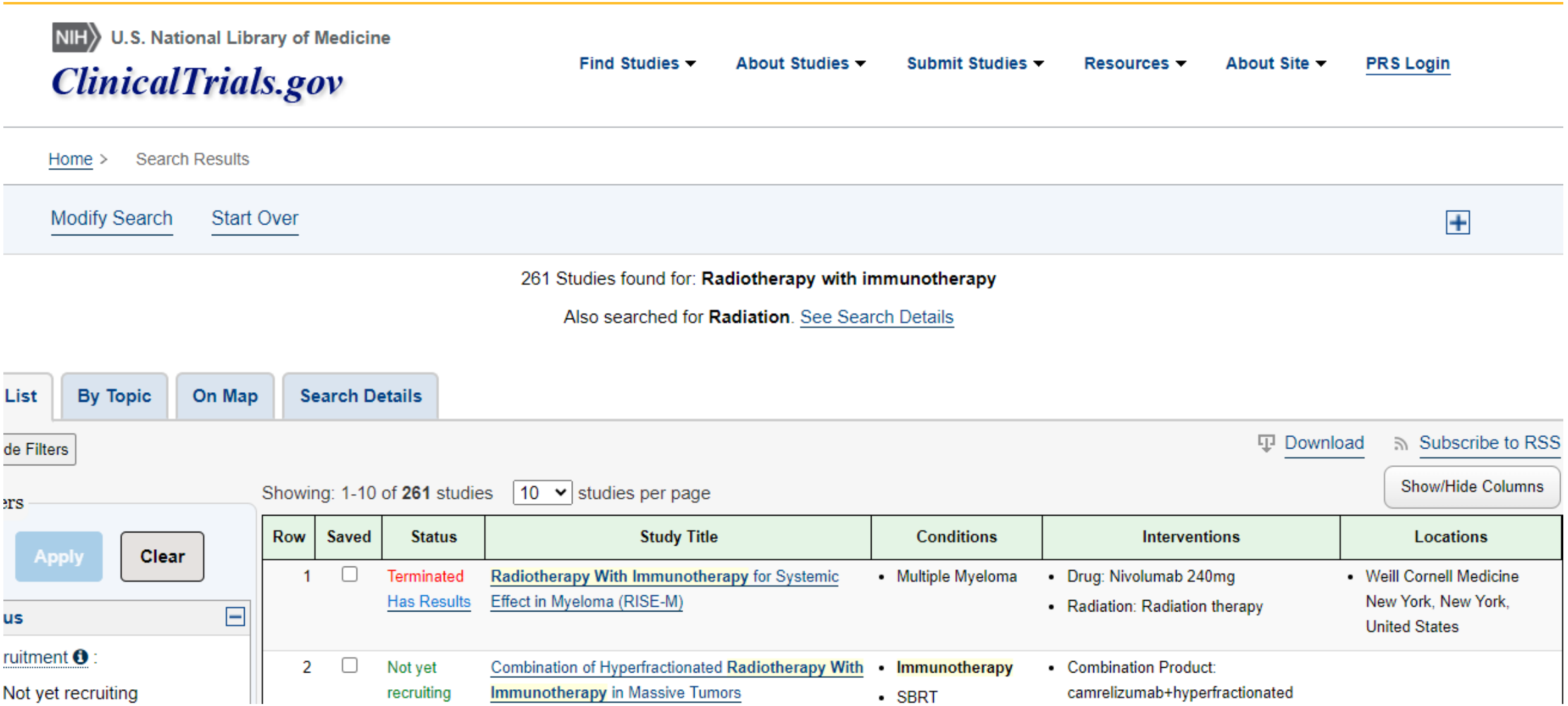
Wang et al Clin Cancer Res. 2019 March 15; 25(6): 1709–1717

ClinicalTrials.gov identifier	Trial Phase	Condition or disease	Sequence	RT	IO	Results	Sponsors	Estimated/actual study completion date
NCT02474186	Phase 1 Phase 2	Various	Concurrent	35 Gy in 10 fractions	GM-CSF	Abscopal responses in 27.6% of patients	NYU Langone Health	July 2015
NCT02125461	Phase 3	NSCLC	RT, IO	54 to 66 Gy	Durvalumab	Durable PFS and sustained OS benefit with durvalumab after chemoradiotherapy	AstraZeneca	December 30, 2022
NCT02608385	Phase 1	Solid tumors	SBRT, IO	SBRT dosing varied by site and ranged from 30 to 50 Gy in three to five fractions	Pembrolizumab	Well tolerated with acceptable toxicity	University of Chicago	July 2022
NCT02221739	Phase 1 Phase 2	NSCLC	Concurrent	6 Gy x5, later changed to 9.5 Gy x3	Ipilimumab	Objective responses were observed in 18%, and 31% had disease control	NYU Langone Health	October 27, 2015
NCT02434081	Phase 2	NSCLC	Concurrent	66 Gy in 33 fractions	Nivolumab	The addition of nivolumab to concurrent CRT is safe and tolerable	European Thoracic Oncology Platform	March 31, 2020
NCT02492568	Phase 2	NSCLC	RT, IO	SBRT 3 doses of 8 Gy	Pembrolizumab	Well tolerated and a doubling of ORR	The Netherlands Cancer Institute	June 2018
NCT02444741	Phase 1 Phase 2	NSCLC	Concurrent	Various	Pembrolizumab	Safe and more beneficial for patients with low PD-L1 expression	M.D. Anderson Cancer Center	September 17, 2022
NCT02343952	Phase 2	Carcinoma, NSCLC	RT, IO	59.4 to 66.6 Gy	Pembrolizumab	PFS and OS improvement with consolidation pembrolizumab	Nasser Hanna, M.D.	September 2022
NCT03631784	Phase 2	NSCLC	Concurrent	60 Gy in 30 daily fractions	Pembrolizumab	Promising antitumor activity and manageable safety	Merck Sharp & Dohme Corp.	May 15, 2023

Title (Reference)	ClinicalTrials.Gov Identifier	Setting	Phase/Type	Treatment	Endpoint	Toxicity	Status
Durvalumab after chemoradiotherapy in stage III non–small-cell lung cancer (Antonia 2017[65])	NCT02125461	Stage III NSCLC	3	Chemoradiation with or without consolidative durvalumab	PFS and OS	Grade 3/4 events in 29.9% of patients in durvalumab arm and 26.1% of placebo arm; most common was pneumonia	Published
Concurrent irradiation with the anti-programmed cell death ligand-1 immune checkpoint blocker durvalumab: single centre subset analysis from a phase 1/2 trial (Levy 2016[67])	NCT01693562	Advanced head and neck (palliative intent)	1/2	Palliative RT plus durvalumab	Safety and efficacy	Five patients reported grade 1-2 AEs; no grade ≥3; most common was transient mucositis	Published
Durvalumab and Radiation Therapy Followed by Adjuvant Durvalumab in Patients With Urothelial Cancer (T2-4 N0-2 M0) of the Bladder (DUART)	NCT02891161	Urothelial cancer	1/2	RT with concurrent durvalumab followed by adjuvant durvalumab	Safety/PFS	Pending report	Active
Prostate Cancer With OligometaSTatic Relapse: Combining Stereotactic Ablative Radiotherapy and Durvalumab (MEDI4736) (POSTCARD)	NCT03795207	Oligometastatic prostate cancer	2	SBRT with or without durvalumab (to be started 1 mo before SBRT and then given for 12 mo total)	PFS	Pending report	Active
Avelumab With Chemoradiation in Locally Advanced Rectal Cancer	NCT03299660	Locally advanced rectal cancer	2	Standard long-course chemoradiation followed by 4 cycles of avelumab followed by resection	Pathologic response rate	Pending report	Open
A Study Evaluating the Association of Hypofractionated Stereotactic Radiation Therapy and Durvalumab for Patients With Recurrent Glioblastoma (STERIMGLI)	NCT02866747	Recurrent glioblastoma	1/2	Hypofractionated RT with durvalumab starting on the last d of RT	DLT/OS	Pending report	Open
CALLA: efficacy and safety of durvalumab with and following concurrent chemoradiotherapy (CCRT) versus CCRT alone in women with locally advanced cervical cancer: a phase III, randomized, double-blind, multicenter study (Monk 2019[68])	NCT03830866	Cervix (FIGO IB2-IIB with positive lymph nodes or IIIA-IVA with any lymph node status)	3	Durvalumab + chemoradiation or placebo + chemoradiation followed by durvalumab or placebo maintenance for 24 mo	PFS	Pending report	Open

Study	Cancer Type (n)	Disease Stage	Treatment Setting	ICI Agent	Radiation Details (Gy / fractions)	Trial Design	Selected Results
Spigel et al. (PACIFIC)	NSCLC ($n = 709$)	III	Adjuvant	Durvalumab	60-66 Gy in 30-33 fractions to primary tumor and involved nodes	Durvalumab following no PD[1] after definitive CRT[2]	mOS[3] 47.5 ICI vs. 29.1 mo placebo mPFS 16.9 mo vs. 5.6 mo placebo 5OS[4] 42.9% vs. 33.4% placebo 5PFS[4] 33% vs. 19% placebo
Kelly et al. (Checkmate-577)	Esophageal/GEJ ($n = 794$)	II/III	Adjuvant	Nivolumab	Definitive RT dose (not specified) to primary tumor and nodes (involved and elective)	Neoadjuvant CRT with PR followed by R0 resection of stage II/III cancer	mPFS 22.4 mo ICI vs. 11.0 mo placebo
Lee et al. (JAVELIN)	HNSCC ($n = 697$)	HPV-/Non-Opx[8] HPV+: III/IVA/IVB OPx HPV+: T4/N2c/N3	Definitive	Avelumab	70 Gy in 35 fractions to primary tumor and nodes (involved and elective)	Locally advanced SCC[5] treated with CRT with concurrent ICI vs placebo	mPFS not reached (95% CI 16.9 mo – not reached for ICI vs. 23.0 mo – not reached for placebo)
Bourhis et al. (PembroRad)	HNSCC ($n = 131$)	III/IVA/IVB	Definitive	Pembrolizumab	69.96 Gy in 33 fractions to primary tumor and nodes (involved and elective)	Non-operable SCC receiving CRT (cetuximab) vs. ICI + RT	15mo LRC 59% CRT vs. 60% ICI-RT (NS) 2PFS[7] 40% CRT vs. 42% ICI-RT (NS) 2OS[7] 55% CRT vs. 62% ICI-RT (NS)
Lim et al. (Checkmate-548)	MGMT methylated GBM ($n = 320$)	-	Definitive	Nivolumab	60 Gy in 30 fractions to primary tumor	RT + TMZ + placebo vs. RT + TMZ + ICI	mPFS 10.6 mo ICI vs. 10.3 mo placebo mOS 28.9 mo ICI vs. 32.1 mo placebo

Ongoing trials



Conclusion

- Immunotherapy and Radiation are a powerful combo
- Potential Game changer for metastatic disease.
- Biomarkers needed for selection of iRT strategies.
- Understanding of underlying biology to harness the potential.
- Large studies needed to demonstrate clinical benefit for various tumors.

Acknowledgements

Thank you

Any question?