MaTOS™
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Role of Radiation Therapy in TIMEs: Good, Bad, Don't Know

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Would make the argument that each of these characters had a little bit of good, bad, and ugly in them…dependent on the context and their position.

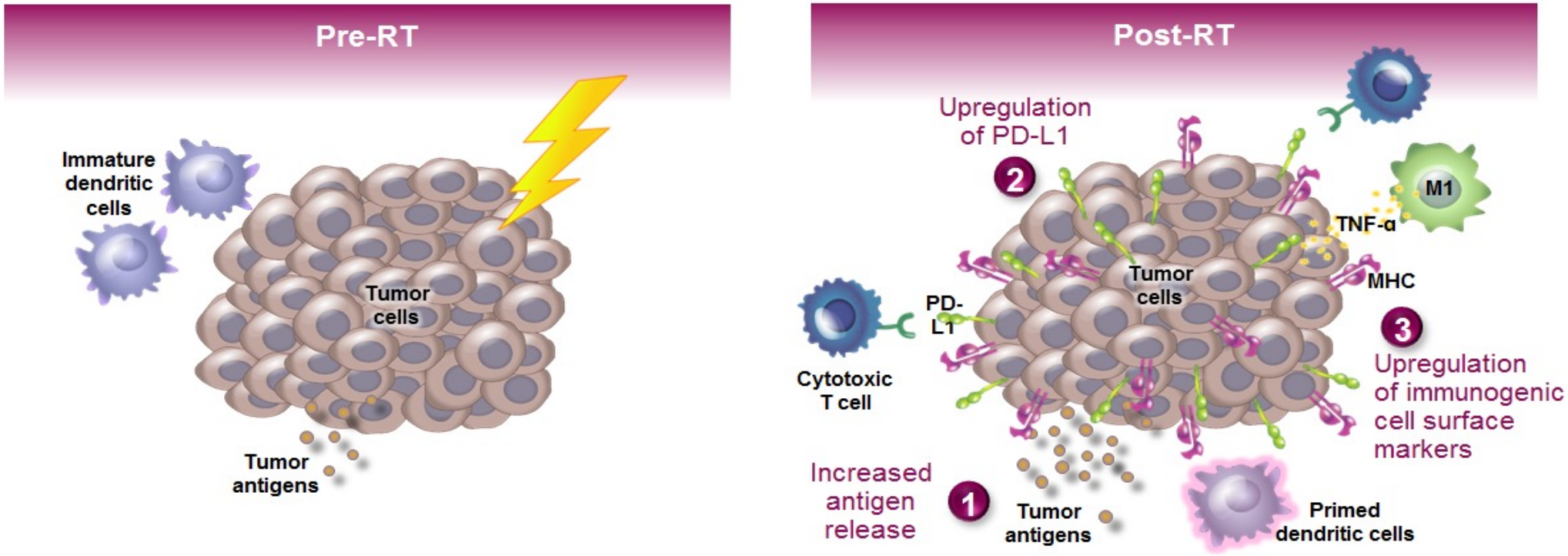
Same applies for radiation and its effect on TIMEs.

How to integrate radiotherapy in the modern and rapidly-changing era?

- Emphasis on multimodality therapy
- **Sequence and timing of radiation therapy may be critically important**
- Variation may depend on heterogeneity in NSCLC
- Molecular considerations may impact response
- Importance of clinical trials to tease all of this out

Immunotherapy biomarkers are upregulated following RT

RT Induces Multiple Immunomodulatory Changes That May Influence the Effectiveness of Immunotherapy[1-3]



M1, tumor-associated macrophage; MHC I, major histocompatibility complex I; PD-L1, programmed cell death-ligand 1; TNF-α, tumor necrosis factor alpha.

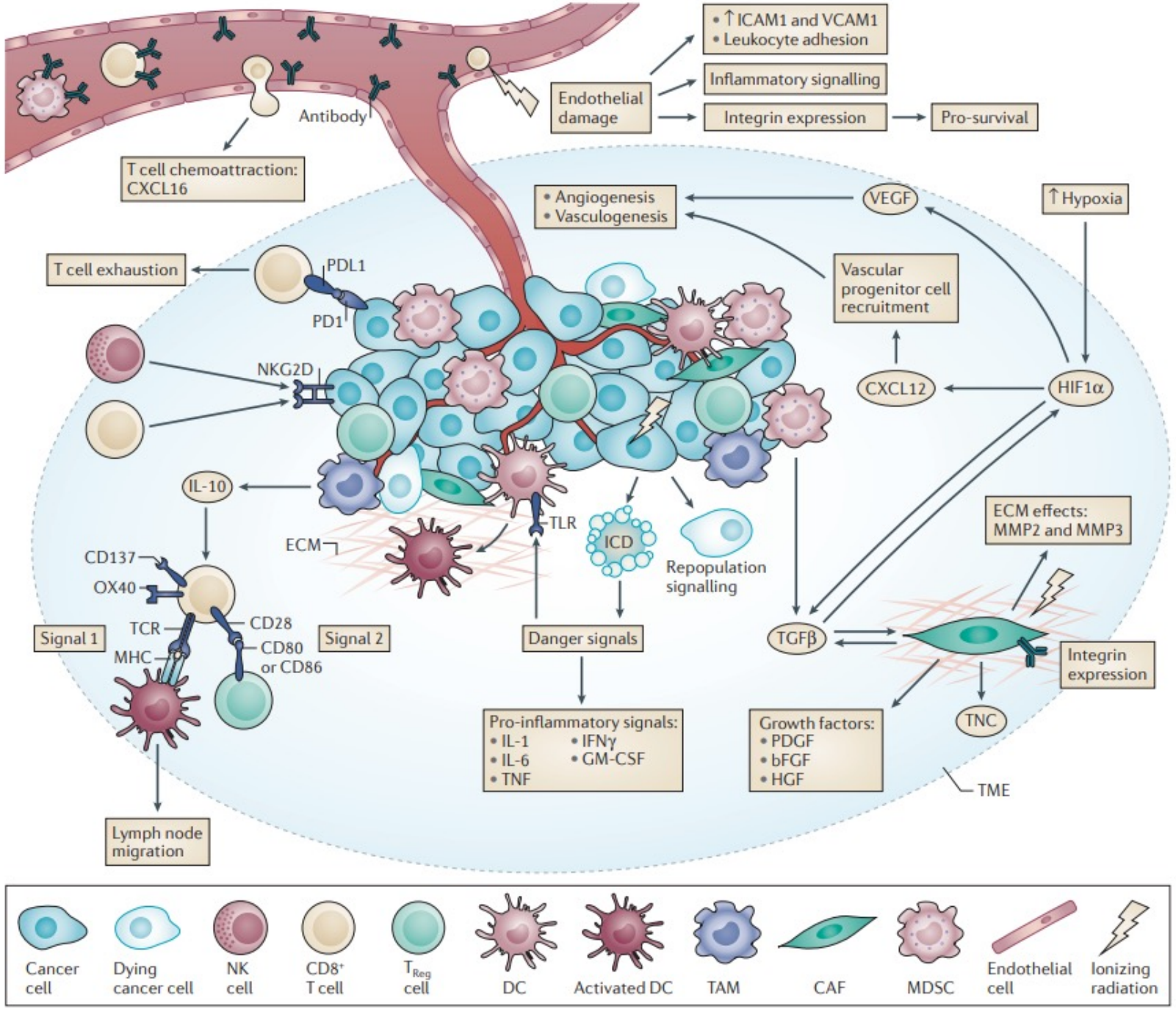
1. Daly ME, et al. *J Thorac Oncol*. 2015;10(12):1685-1693. 2. Kaur P, Asea A. *Frontiers Oncol*. 2012;2:191. 3. Deng L, et al. *J Clin Invest*. 2014;124(2):687-695.

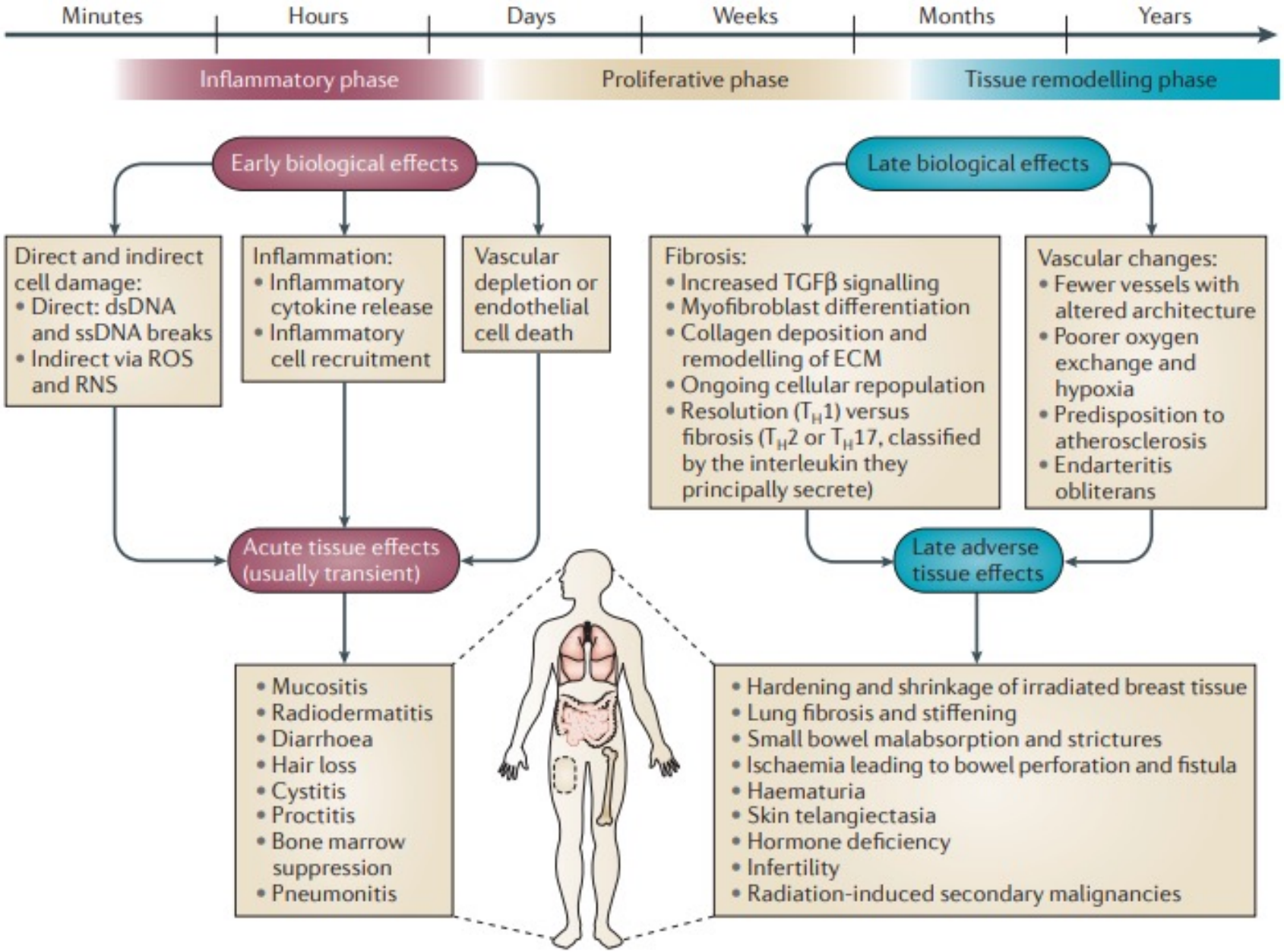
Published: 24 June 2015

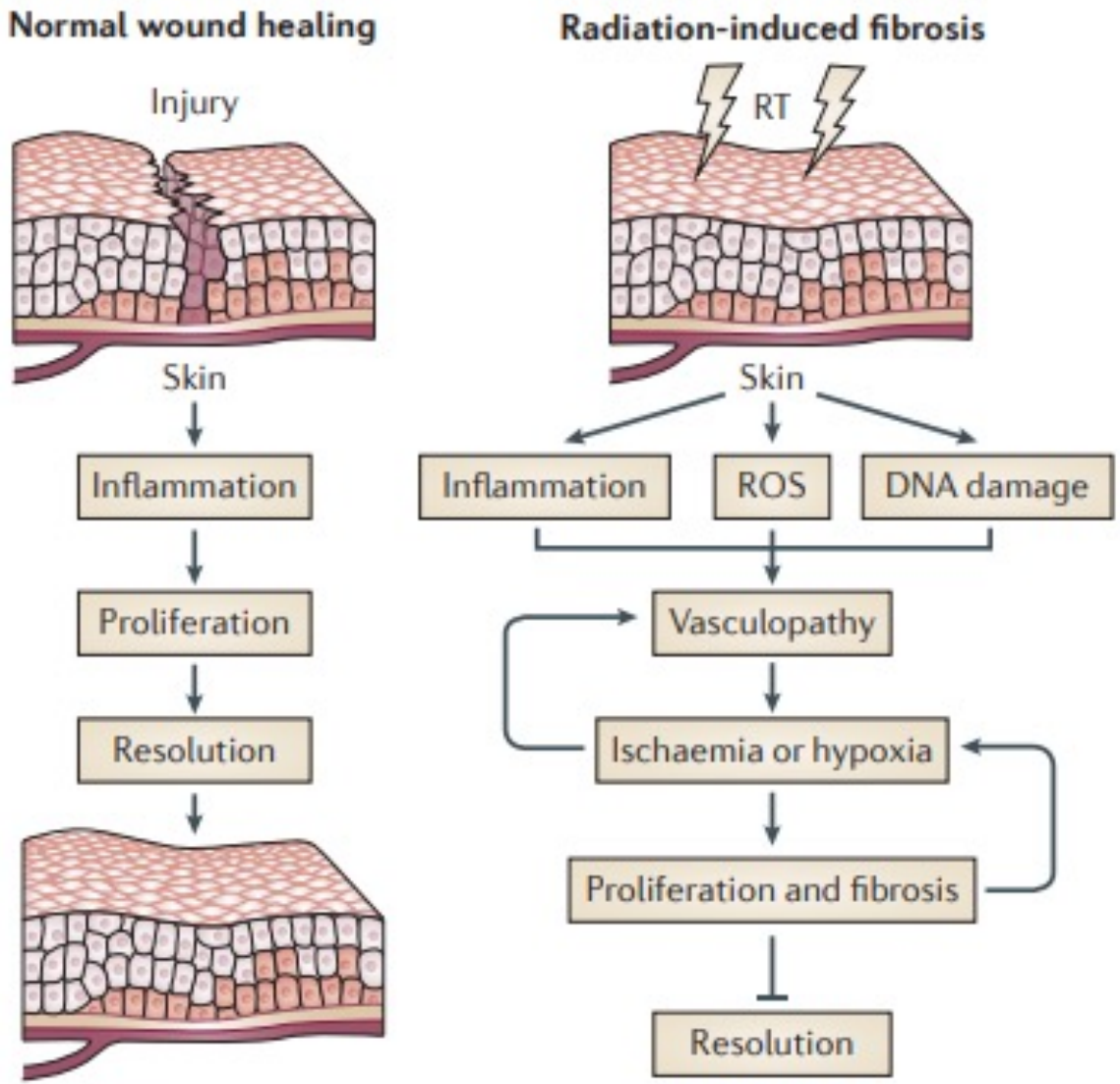
The tumour microenvironment after radiotherapy: mechanisms of resistance and recurrence

Holly E. Barker, James T. E. Paget, Aadil A. Khan & Kevin J. Harrington

Nature Reviews Cancer **15**, 409–425 (2015) | Cite this article







Please add cGAS/STING pathways to this mix.

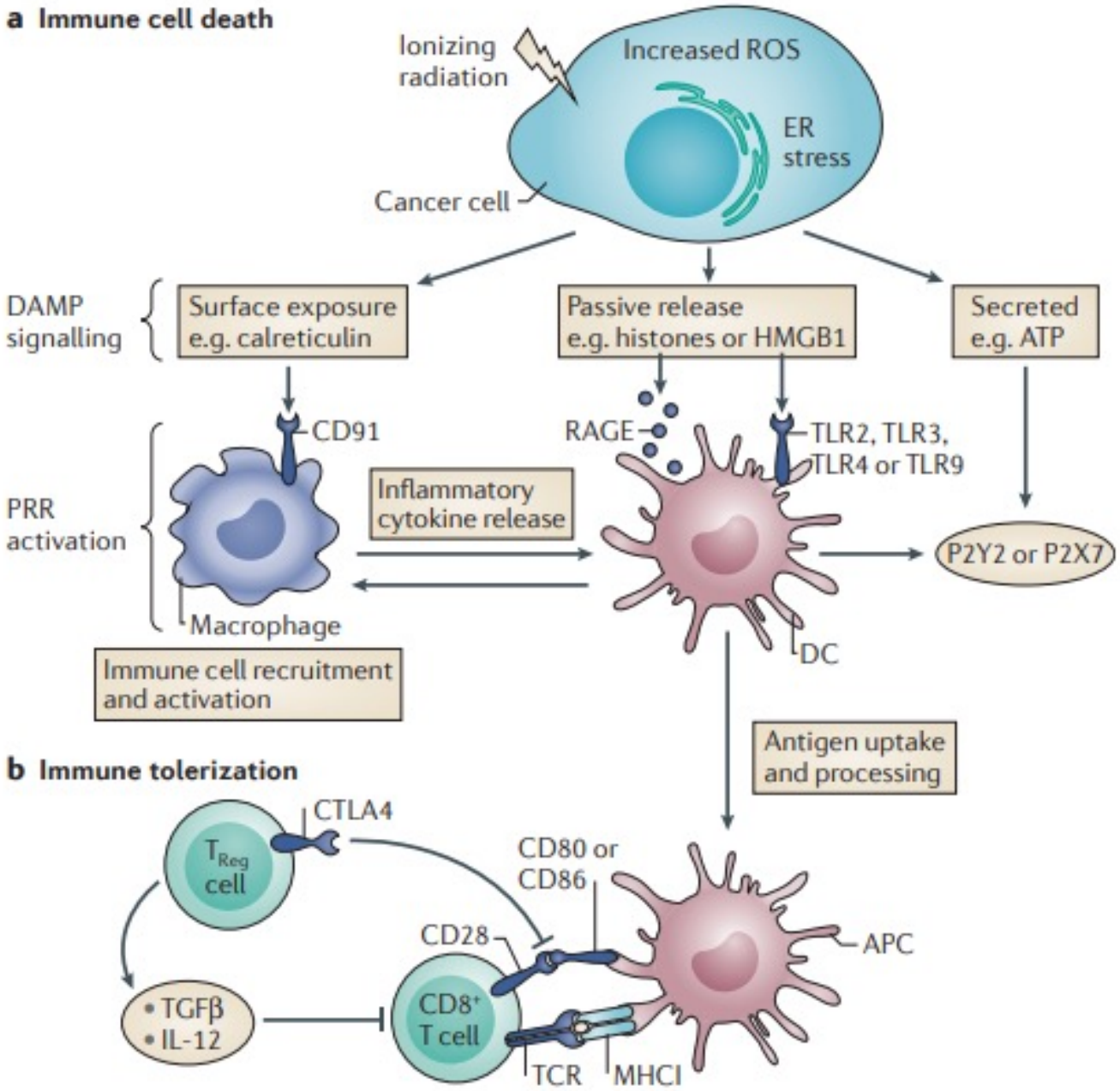


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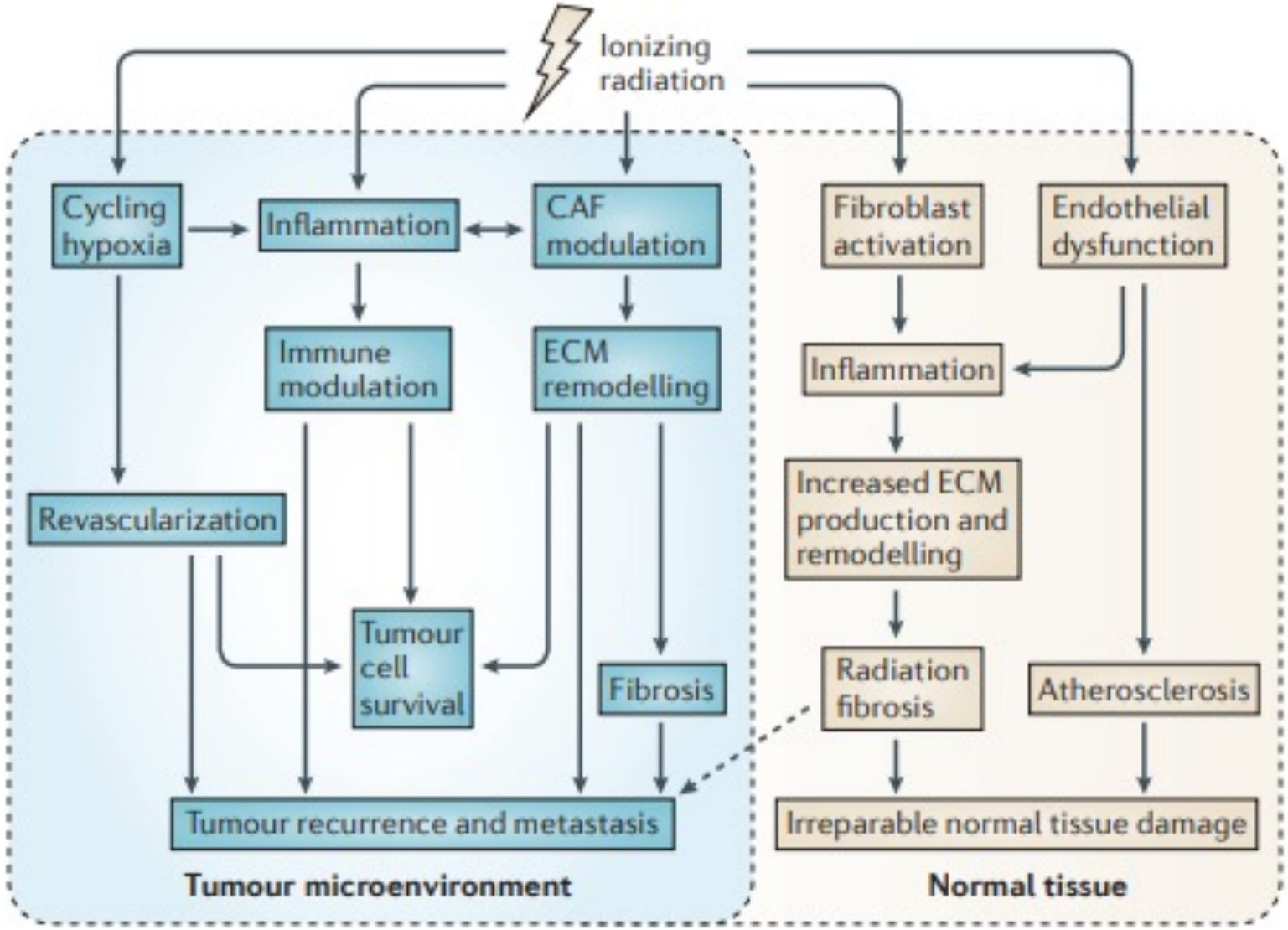
Table 1 | **Current and future TME targets for radiosensitization**

Resistance mechanism	Drugs	Targets	Mode of action
Immune response	Ipilimumab	CTLA4	T cell activation
	Nivolumab and pembrolizumab	PD1	T cell exhaustion
	Imiquimod	TLR7	DC activation
	Oncolytic viruses	Tumour cells	Activate immune response
	Future inhibitors	IL-6 and IL-10	T cell activation
		PDL1, TIM3 and LAG3	Prevent T cell exhaustion
	Future agonists	GM-CSF, CXCL16, OX40, CD40L, CD80 and CD137	T cell recruitment and activation
		CCL3, CCL5, IL-2, IL-4, IL-12 and IRX-2	Activate immune response
Hypoxia	Nitroimidazole derivatives (that is, nimorazole)	Hypoxic cells	Reduce tumour hypoxia
	Bioreactive albumin–MnO_2 nanoparticles	Hypoxic cells	Reduce tumour hypoxia
	Acriflavine and YC-1	HIF1α	Reduce hypoxia response pathway activity
	Aflibercept	All VEGF molecules and PlGF	Vessel normalization
	AMG386	ANG1 and ANG2	Inhibit pBMDC recruitment
	Endostar	VEGF, TGFβ, HIF1α and bFGF	Inhibit angiogenesis
	AMD3100	CXCL12 and CXCR4	Inhibit BMDC recruitment and vasculogenesis
	Integrin inhibitors (cilengitide, vitaxin and volociximab)	Integrins αvβ3, αvβ5 and α5β1	Inhibit angiogenesis
	Future inhibitors	Integrins α6β1 and α6β4	Reduce endothelial cell survival and inhibit angiogenesis
	Future inhibitors	PlGF and ANG2	Vessel normalization and overcome resistance to anti-VEGF therapies
Fibrotic processes	BIBF1000 and BIBF1120	PDGF, VEGF and bFGF receptors	Reduce GF signalling and TME remodelling; fibrosis
	Imatinib, nilotinib and dasatinib	TGFβ and PDGF	GF signalling; collagen synthesis
	Vismodegib, saridegib and sonidegib	SMO	Reduce HH signalling; fibrosis
	Suramin	PDGF, EGF, TGFβ, FGF2 and IGF receptors and heparanase enzymes	Reduce GF signalling and TME remodelling; fibrosis
	ST0001, PG545, M402 and PI-88	Heparanase	Inhibit TME remodelling
	SD-208	TGFβR1	Inhibit TGFβ signalling
	Simtuzumab	LOXL2	Reduce TME remodelling; liver fibrosis
	81C6 and F16SIP	TNC	Reduce CAF-mediated TME remodelling
	Future inhibitors	HGF, CTGF, MMP2, MMP3, and integrins α11β1, αvβ6 and α3β1	TME activation and remodelling; radiation-mediated fibrosis

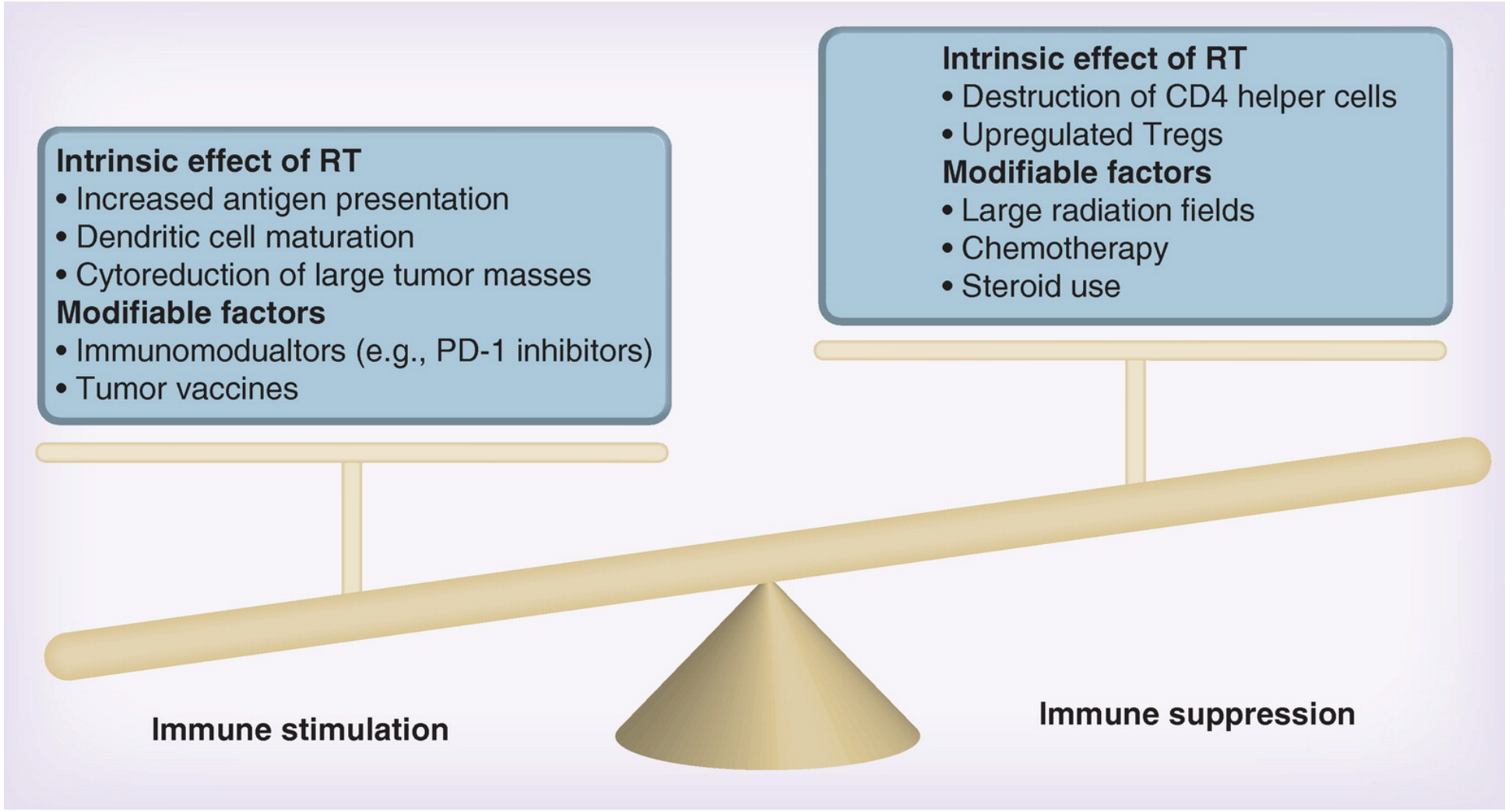
Table 2 | **Fractionation of radiotherapy and timing of immunomodulation**

Study type	Cancer type	Intervention	Outcome	Refs
Fractionation				
Preclinical	Murine glioma	• RT: 10 Gy in one fraction • Immunomodulation: anti-PD1	Longer survival seen (53 days (RT and anti-PD1) versus 25 days (control), 27 days (anti-PD1) or 28 days (RT))	190
Preclinical	Murine breast cancer	• RT: 20 Gy in one fraction, 24 Gy in three fractions or 30 Gy in five fractions • Immunomodulation: anti-CTLA4	Best response seen in 24 Gy in three fractions	171
Preclinical	Murine breast cancer	• RT: 12 Gy in one fraction, 24 Gy in two fractions • Immunomodulation: anti-CTLA4	$CD8^+$ T cell antitumour immunity demonstrated	191
Clinical	Patients with hepatoma	• RT: 8 Gy in one fraction • Immunomodulation: DC vaccine	Two partial responses, four minor ones	192
Clinical	Prostate cancer	• RT: 70 Gy in 30 fractions • Immunomodulation: IL-2 and GM-CSF	Increased levels of PSA-specific T cells	193
Clinical	MF	• RT: 9–18 Gy in nine fractions • Immunomodulation: injected TLR9 agonist	5 out of 15 responses	194
Timing				
Clinical	MM or RCC	• RT: 60 Gy in three fractions • Immunomodulation: IL-2	8 out of 12 responses	195
Preclinical	Murine prostate cancer expressing HA	• RT: 15 Gy in one fraction • Immunomodulation: $CD4^+$ T cells primed against HA (given at points on a time course after RT)	Tolerance seen between days 3 and 16. Normal T cell response by day 33	55
Clinical case report	MM	• RT: 28.5 Gy in three fractions • Immunomodulation: ipilimumab (anti-CTLA4) at 1 month after RT	Complete response	74
Clinical case report	MM	• RT: 54 Gy in three fractions • Immunomodulation: ipilimumab	Complete response	54

CTLA4, cytotoxic T lymphocyte antigen 4; DC, dendritic cell; HA, haemagglutinin antigen; MF, mycosis fungoides; MM, malignant melanoma; PD1, programmed cell death protein 1; PSA, prostate-specific antigen; RCC, renal cell carcinoma; RT, radiotherapy; TLR, Toll-like receptor.



Balance immune-stimulatory effects and suppressive effects of RT



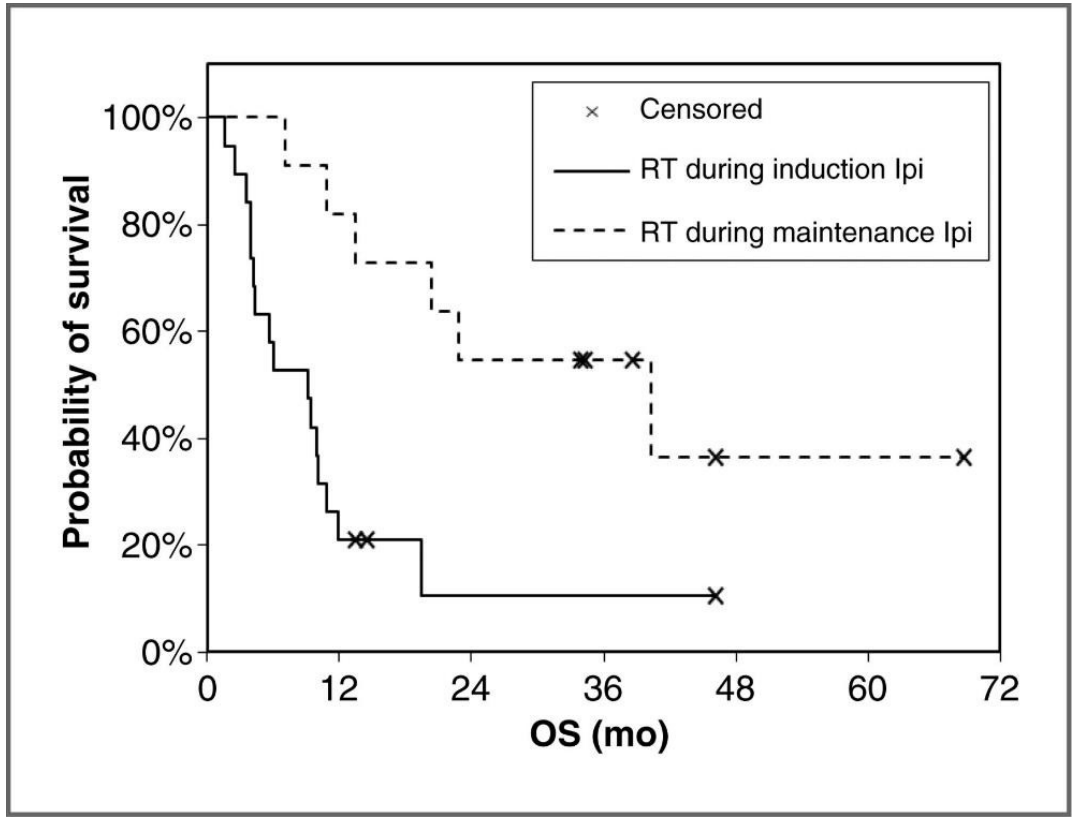
Lawrence, Future Medicine 2014

Potential Benefits of Combining RT and Immunotherapy

- SBRT is less immunosuppressive than conventionally fractionated RT or sx
  - SBRT specifically can even be immunostimulatory and deplete immunosuppressive cells
- RT can improve antigen presentation by antigen presenting cells
  - SBRT specifically can release high levels of tumor antigens
- SBRT upregulates immunogenic cell surface markers (ie. MHC-1)
- SBRT can induce immunogenic cell death
- RT and especially SBRT can increase homing of immune cells to tumor
- RT can recruit regulatory T cells (Tregs)
- RT can shift tumor-associated macrophages polarization from M2 to M1
- RT can induce secretion of danger signals and cytokines (ie. TNFalpha)
- RT can upregulate cell-surface expression of PD-L1

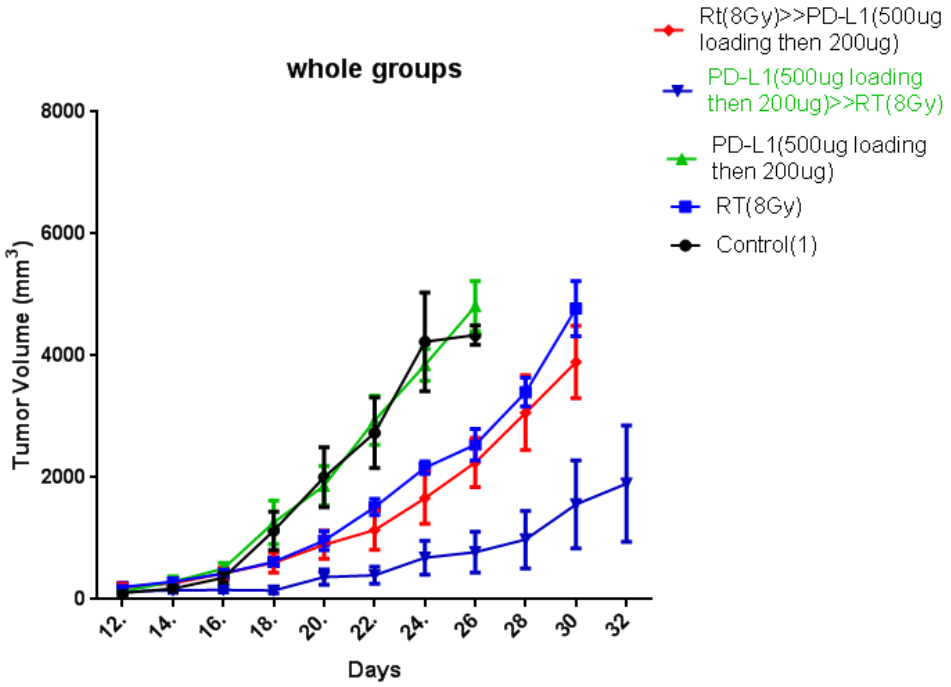
RT + Immunotherapy: The Importance of Timing

- MSKCC retrospective study of melanoma patients treated with ipilimumab and extracranial RT
- Median OS: 9 months when RT given during induction vs. 39 months when RT given during maintenance



Barker CA, et al. *Cancer Immunol Res*. 2013;1(2):92-98.

Timing of Immunotherapy and SBRT



Significantly superior tumor control was achieved in Balb/c mice when the PD-L1 blockade was delivered prior to radiotherapy to 8 Gy

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PACIFIC: Study Design

Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter, International Study

- Unresectable, Stage III NSCLC without progression after definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- If available, archived pre-cCRT tumor tissue for PD-L1 testing*

All-comers population (i.e. irrespective of PD-L1 status)

N=713 randomized

1–42 days post-cCRT

R

2:1 randomization, stratified by age, sex, and smoking history

Durvalumab
10 mg/kg q2w for up to 12 months
N=476

Placebo
10 mg/kg q2w for up to 12 months
N=237

Primary endpoints

- PFS by BICR using RECIST v1.1†
- OS

Key secondary endpoints

- ORR, DoR and TTDM by BICR
- PFS2 by investigator
- Safety
- PROs

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PACIFIC: Prognostic baseline factors for OS (ITT)

	Comparator		Reference		
Baseline Variable	Group	No. of Events/Total No. of Patients (%)	Group	No. of Events/Total No. of Patients (%)	HR (95% CI)
Treatment arm	Durvalumab	264/476 (55.5)	Placebo	155/237 (65.4)	0.71 (0.58 to 0.87)[a]
Age, years	≥ 65	210/322 (65.2)	< 65	209/391 (53.5)	1.30 (1.06 to 1.59)[a]
Disease stage[b]	IIIB	182/319 (57.1)	IIIA	227/377 (60.2)	1.03 (0.84 to 1.26)
Best response to prior treatment[c]	CR/PR	195/365 (53.4)	SD	216/338 (63.9)	0.88 (0.72 to 1.08)
Tumor histologic type	Squamous	205/326 (62.9)	Nonsquamous	214/387 (55.3)	1.28 (1.04 to 1.58)[a]
WHO PS	1[d]	233/365 (63.8)	0	186/348 (53.4)	1.23 (1.01 to 1.50)[a]
Prior platinum CT agent[e]	Cisplatin	215/395 (54.4)	Carboplatin	190/301 (63.1)	0.84 (0.69 to 1.03)
Race	Asian	95/192 (49.5)	White	310/494 (62.8)	0.63 (0.49 to 0.81)[a]
	Black or African American	7/14 (50.0)			0.81 (0.38 to 1.73)
	Other[f]	7/13 (53.8)			0.91 (0.41 to 1.99)
Sex	Male	304/500 (60.8)	Female	115/213 (54.0)	1.27 (1.01 to 1.61)[a]
Smoking status	Smoker	384/649 (59.2)	Nonsmoker	35/64 (54.7)	0.83 (0.56 to 1.22)
Time from CRT to random assignment, days	≥ 14	312/531 (58.8)	< 14	107/182 (58.8)	0.97 (0.77 to 1.22)
EGFR or *ALK* aberration status	Positive[g]	25/43 (58.1)	Negative	275/482 (57.1)	1.06 (0.69 to 1.64)
	Unknown	119/188 (63.3)			0.95 (0.73 to 1.23)
PD-L1 expression level	TC ≥ 25%	78/159 (49.1)	TC < 25%	175/292 (59.9)	0.82 (0.62 to 1.07)
	Unknown	166/262 (63.4)			1.19 (0.92 to 1.54)

Spigel, D JCO, December 2021.

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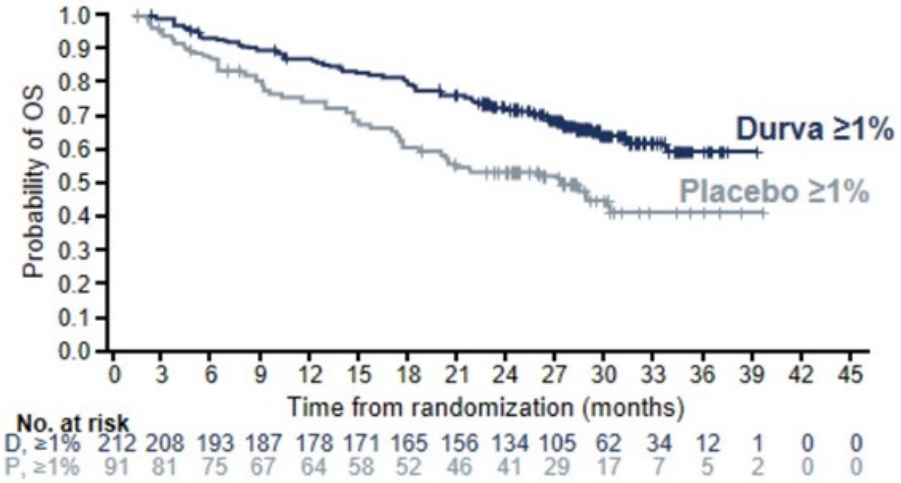
Conclusions on Outcomes by PD-L1 Status is not definitive due to limitations

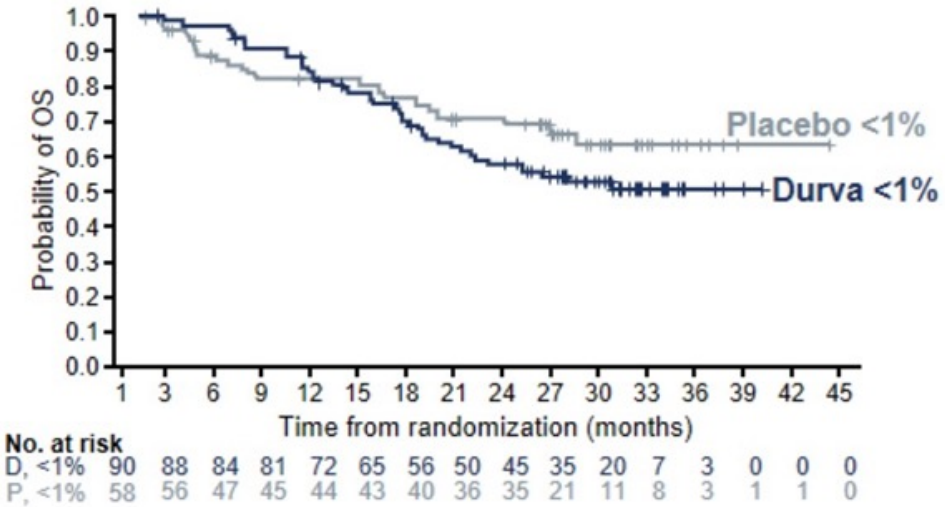
OS (BICR) by PD-L1 TC ≥1%

	No. events / no. patients (%)	Median OS (95% CI), mo
Durvalumab, ≥1%	70/212 (33.0)	NR (NR, NR)
Placebo, ≥1%	45/91 (49.5)	29.1 (17.7, NR)
	≥1% OS HR 0.53 (95% CI 0.36, 0.77)	



OS (BICR) by PD-L1 TC <1%

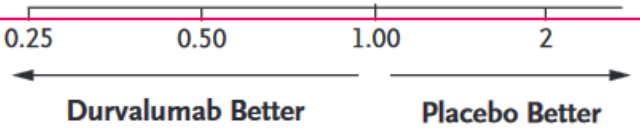
	No. events / no. patients (%)	Median OS (95% CI), mo
Durvalumab, <1%	41/90 (45.6)	NR (20.8, NR)
Placebo, <1%	19/58 (32.8)	NR (27.3, NR)
	≥1% OS HR 1.36 (95% CI 0.79, 2.34)	



- In the PD-L1 TC <1% subgroup, imbalances exist in baseline characteristics.
- Placebo arm: > more males, SQCLC, and Stage IIIB.

DFS by EGFR status

Subgroup	Durvalumab	Placebo	Unstratified Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients		
All patients	476	237	0.55 (0.45–0.68)
Sex			
Male	334	166	0.56 (0.44–0.71)
Female	142	71	0.54 (0.37–0.79)
Age at randomization			
<65 yr	261	130	0.43 (0.32–0.57)
≥65 yr	215	107	0.74 (0.54–1.01)
Smoking status			
Smoker	433	216	0.59 (0.47–0.73)
Nonsmoker	43	21	0.29 (0.15–0.57)
NSCLC disease stage			
IIIA	252	125	0.53 (0.40–0.71)
IIIB	212	107	0.59 (0.44–0.80)
Tumor histologic type			
Squamous	224	102	0.68 (0.50–0.92)
Nonsquamous	252	135	0.45 (0.33–0.59)
Best response			
Complete response	9	7	—
Partial response	232	111	0.55 (0.41–0.75)
Stable disease	222	114	0.55 (0.41–0.74)
PD-L1 status			
≥25%	115	44	0.41 (0.26–0.65)
<25%	187	105	0.59 (0.43–0.82)
Unknown	174	88	0.59 (0.42–0.83)
EGFR mutation			
Positive	29	14	0.76 (0.35–1.64)
Negative	315	165	0.47 (0.36–0.60)
Unknown	132	58	0.79 (0.52–1.20)



Antonia SJ et al. N Engl J Med 2017.

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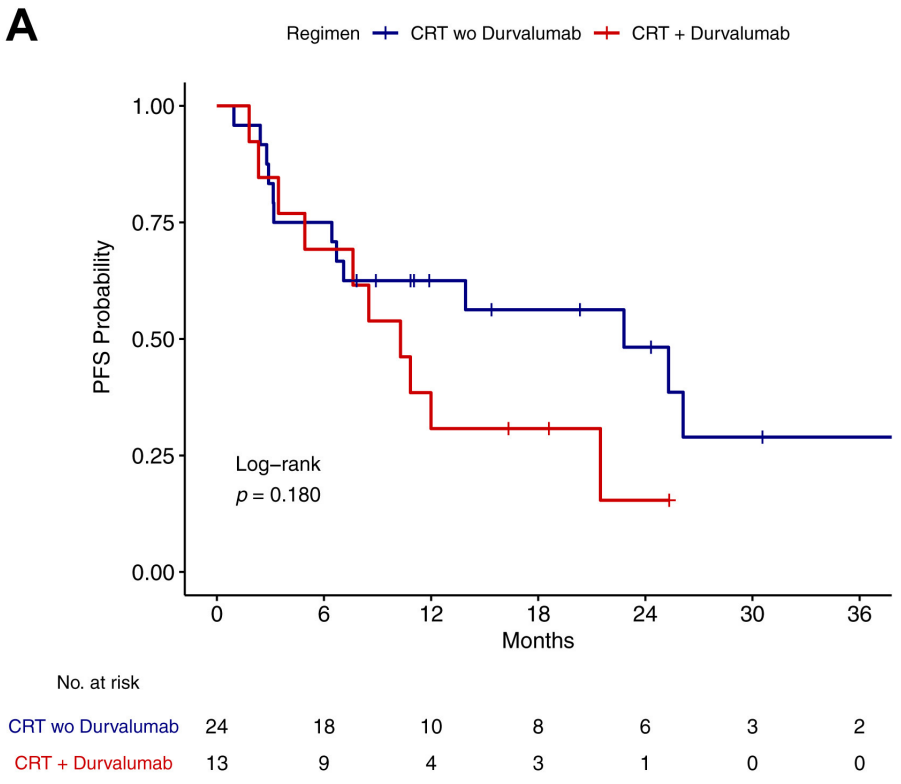
Consolidation Durvalumab for Stage III EGFRmut NSCLC – Stanford, City of Hope, UCSF, UC Davis



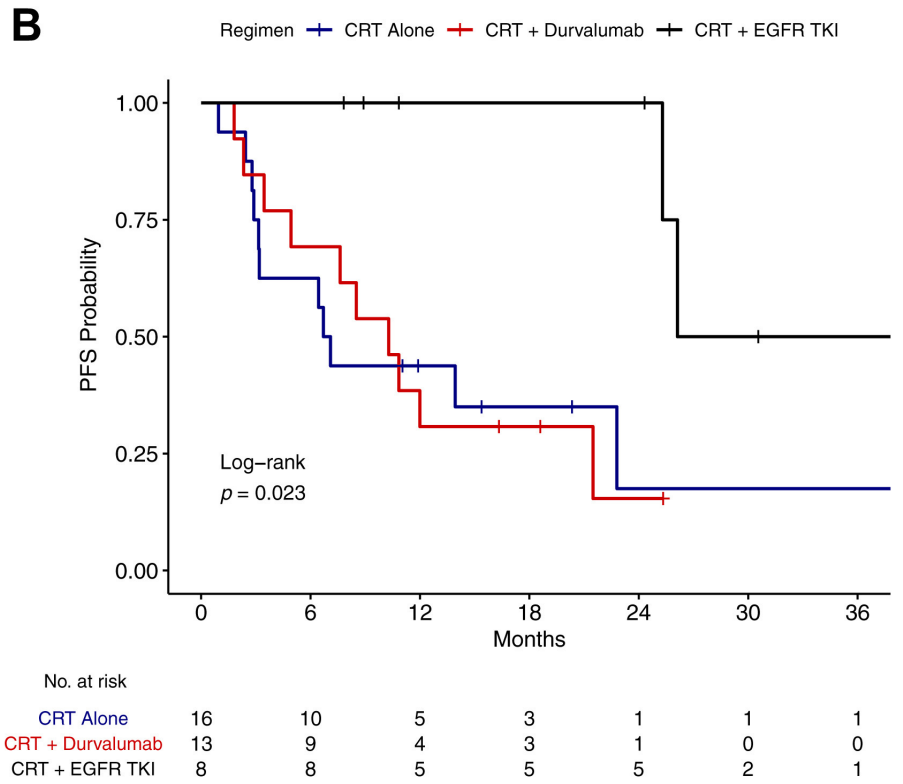


Figure 3: PFS after chemoXRT +/- Durva
(*A*) Median PFS CRT + durvalumab versus CRT wo durvalumab
10.3 months versus 22.8 months (log-rank $p = 0.180$).
(*B*) Median PFS CRT alone versus CRT durvalumab versus CRT + EGFR TKI :
6.9 mo vs 10.3 mo vs 26.1 mon (log-rank $p = 0.023$).

Aredo JTO 2021

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Conclusions

Radiation therapy effects on TIMEs and, as a consequence, tumor control can be influenced by:

1. Sequencing of systemic therapy and local therapy

2. Type of systemic therapy and type of radiation

3. Dose of radiation

4. The understudied variation in host immune and systemic biology responses to tumor and therapy (systemic therapy and/or radiation)