UTILIZZO E TIMING DEI FARMACI DI PRECISIONE IN CORSO DI RADIOTERAPIA: Razionale radiobiologico in termini di tossicità

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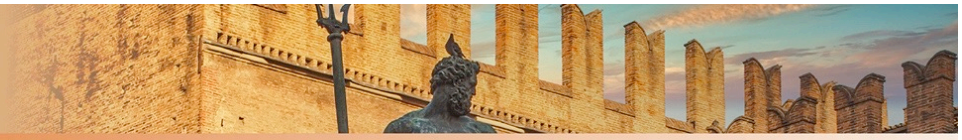
Società Italiana di Radiobiologia



DICHIARAZIONE

Relatore: Edy Ippolito

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(AstraZeneca, MSD)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Speaking fees **(Astrazeneca, Gentili)**

AIRO2022

XXXII CONGRESSO NAZIONALE AIRO
XXXIII CONGRESSO NAZIONALE AIRB
XII CONGRESSO NAZIONALE AIRO GIOVANI

Radioterapia di precisione per un'oncologia innovativa e sostenibile

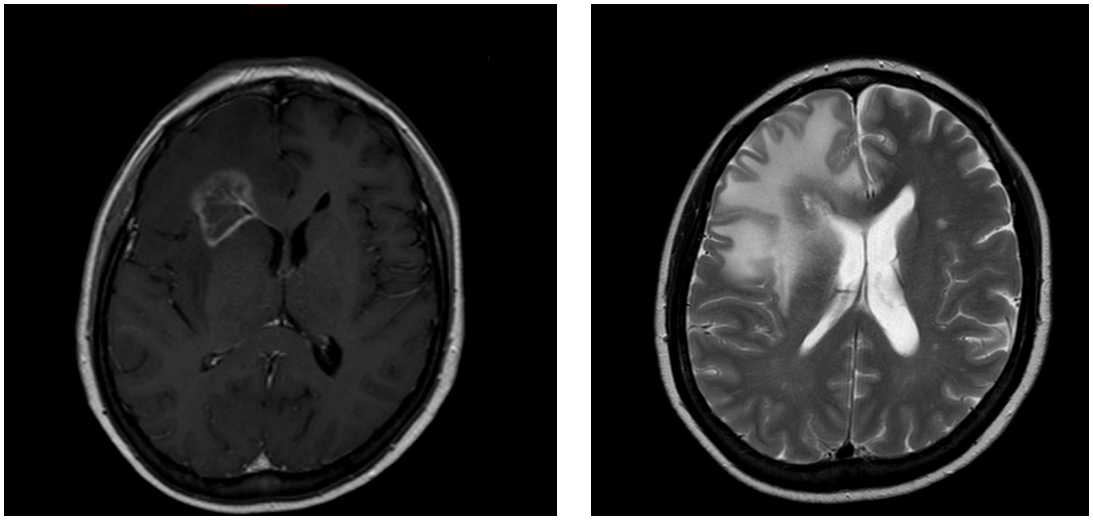
Radiation induced brain injury

Radiation induced lung injury

Radiation induced GI injury

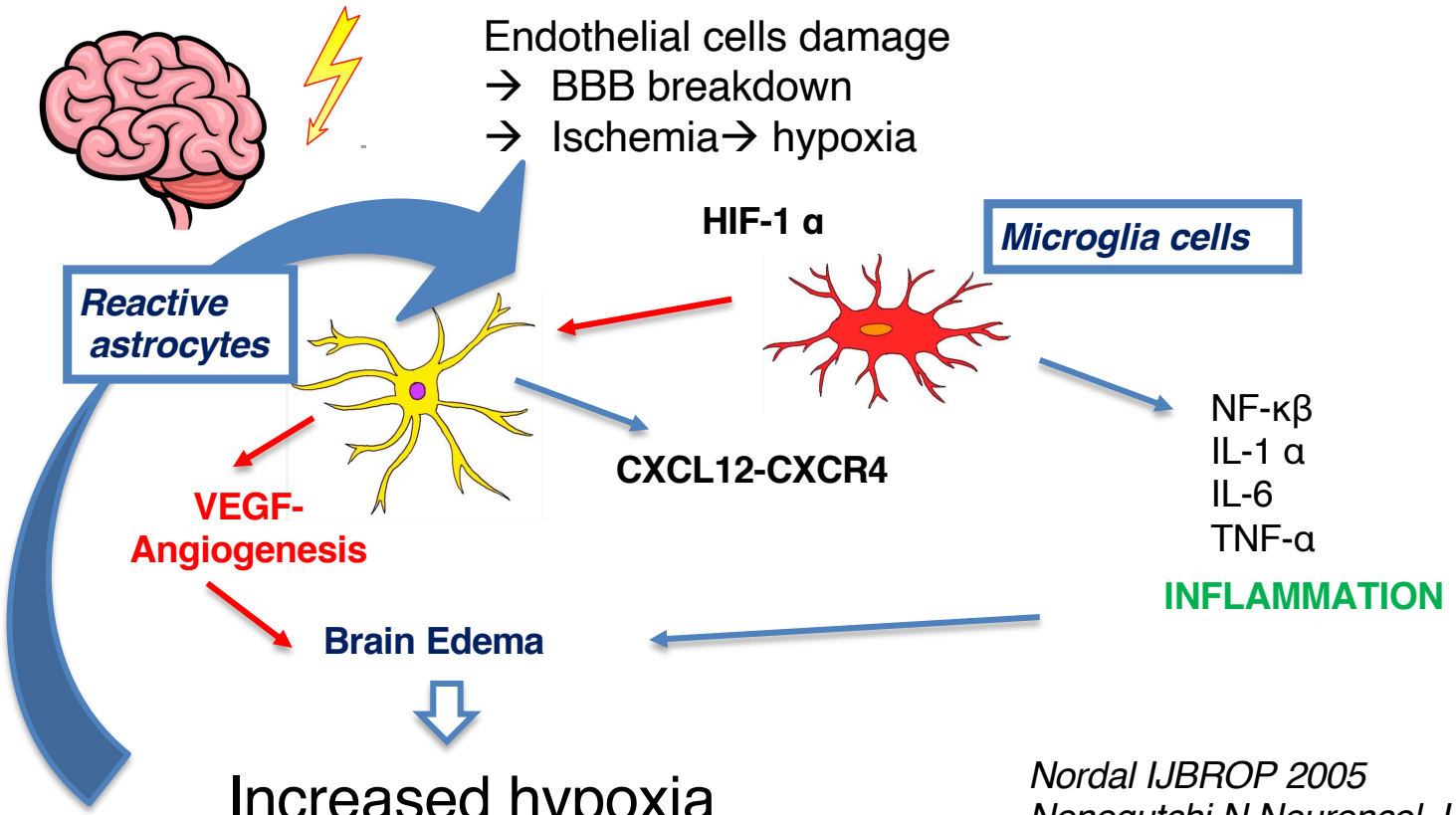
Cerebral Radionecrosis

- Incidence not well quantified, often under-reported
- Not gold-standard for DD between
  radiation necrosis and tumor progression



Lupattelli M, J Pers Med 2020

Radiation induced brain injury pathophysiology



Nordal IJBROP 2005
Nonogutchi N Neuroncol J 2012

Cerebral Radionecrosis: incidence and risk factors

Single fraction SRS

	S-RN
Minniti 2011 [28]	10%
Ohtakara 2012 [36]	6.9%
Blonigen 2010 [33]	10%
Kohutek 2015 [37]	17.3%
Korytko 2006 [32]	NA

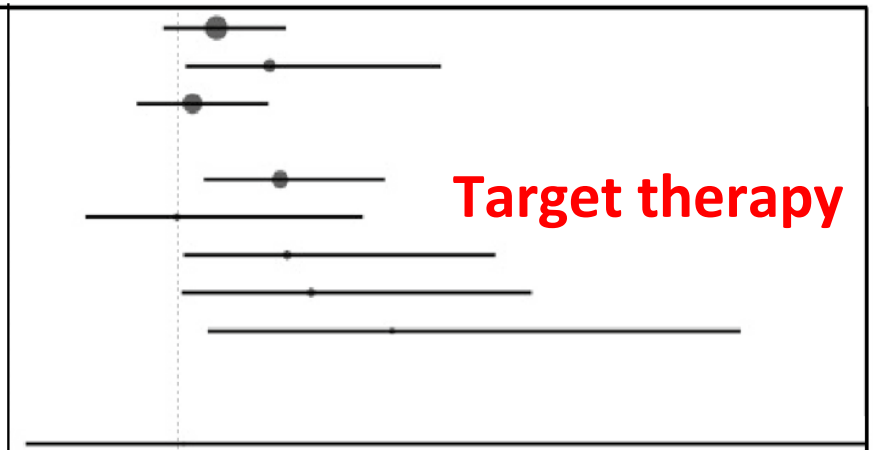
Multi fraction SRT

	S-RN
Minniti 2016 [48]	5%
Minniti 2014 [46]	NA
Doré 2016 [51]	NA
Ernst-Stecken 2006 [42]	NA

- ✓ Dose/volume interplay for irradiated lesions
- ✓ Uninvolved brain irradiated volume
- ✓ Previous WBRT
- ✓ Repeated treatment courses
- ✓ *Concurrent systemic therapy*

Vellayappen, Curr Tr Opt 2021
Lupattelli M, J Pers Med 2020

Agent	HR	95% CI	N*
Any Concurrent Therapy	1.23	0.93 - 1.62	854
Upfront WBRT	1.54	1.06 - 2.52	251
No Upfront WBRT	1.09	0.78 - 1.52	603
Cytokine Therapy	0.00	0.00 - 0.00	10
Targeted Therapy	1.60	1.17 - 2.20	451
VEGF Antibody	1.00	0.48 - 2.07	89
VEGFR TKI	**1.64**	**1.05 - 2.84**	**119**
HER2 Antibody	**1.78**	**1.04 - 3.05**	**111**
EGFR TKI	**2.25**	**1.19 - 4.26**	**60**
ALK TKI	0.00	0.00 - 0.00	2
BRAF Inhibitor	0.00	0.00 - 0.00	27
mTOR Inhibitor	1.04	0.13 - 8.01	12



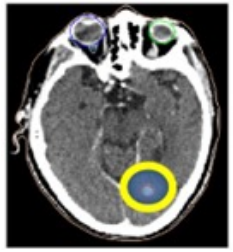
RN rate

SRT alone 5.3% [4.3–6.3%]
VEGFR TKI+ SRT – 13.0% p= 0.04
HER2 antibody – 9.0% p= 0.03
EGFR TKI – 14.0% p= 0.01
PD1-CTLA-4 inhibitors- 8% p= NS

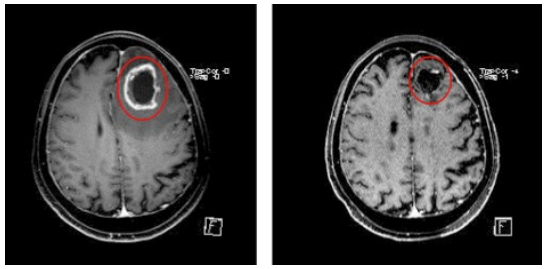
Kim JM et al,
J NeuroOncol 2016

In some disease such as NSCLC oncogene-addicted patients or HER2 + breast cancer patients THE NATURAL HISTORY AND PROGNOSIS of patients with brain metastases (BMs) can be measured in **YEARs**

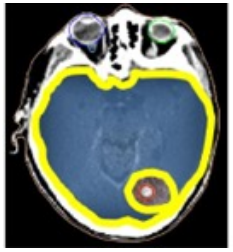
Intracranial Control



Freedom from brain injury

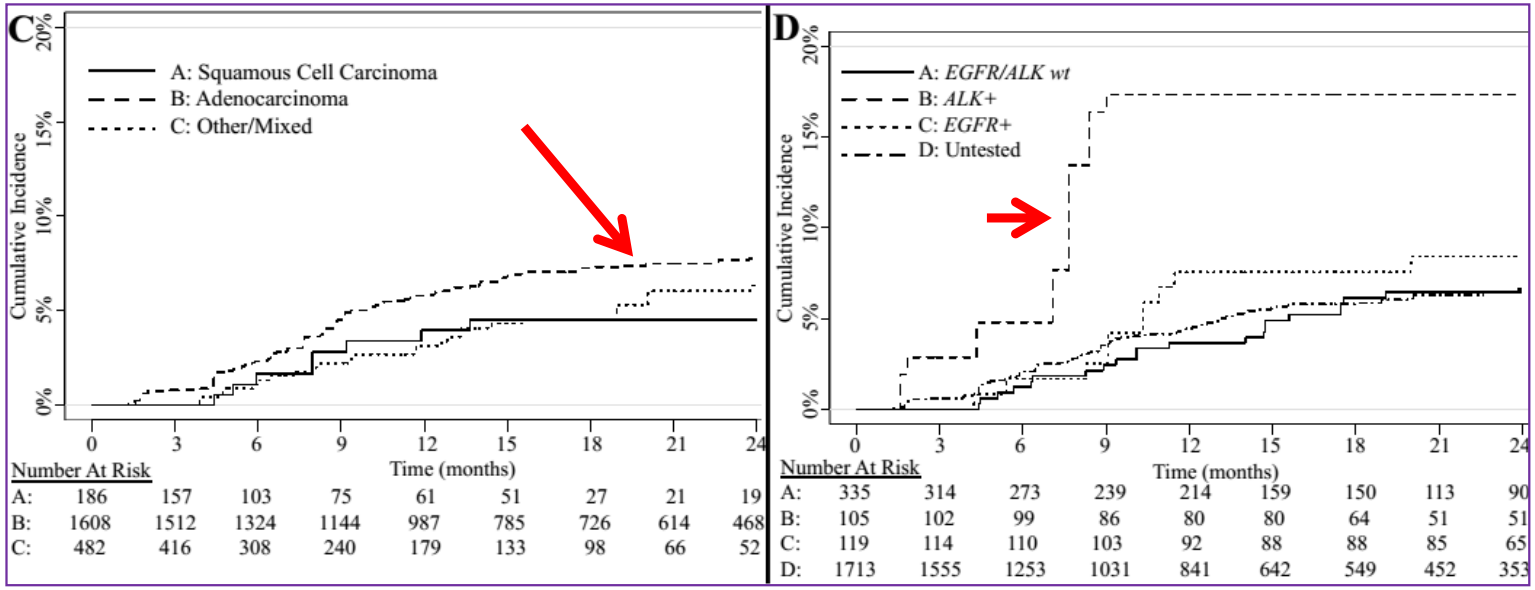


Freedom from new BMs



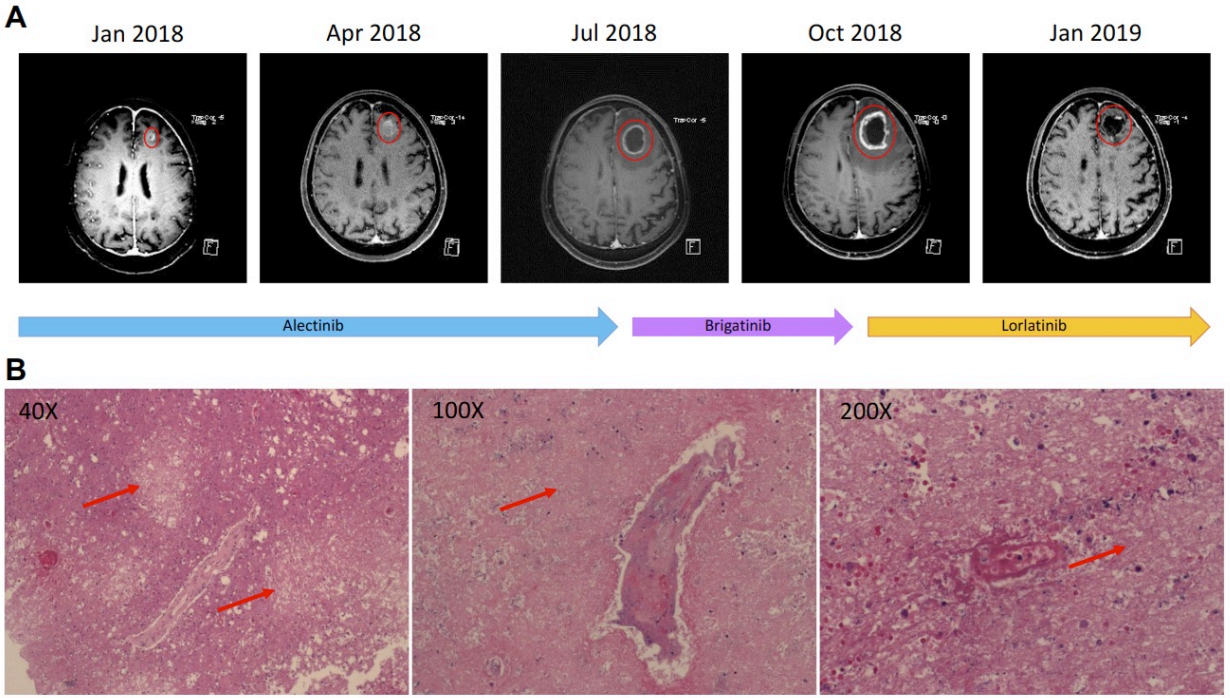
ALK TUMORS ARE MORE LIKELY TO DEVELOP RADIONECROSIS

RN incidence: 18% HR 5.77



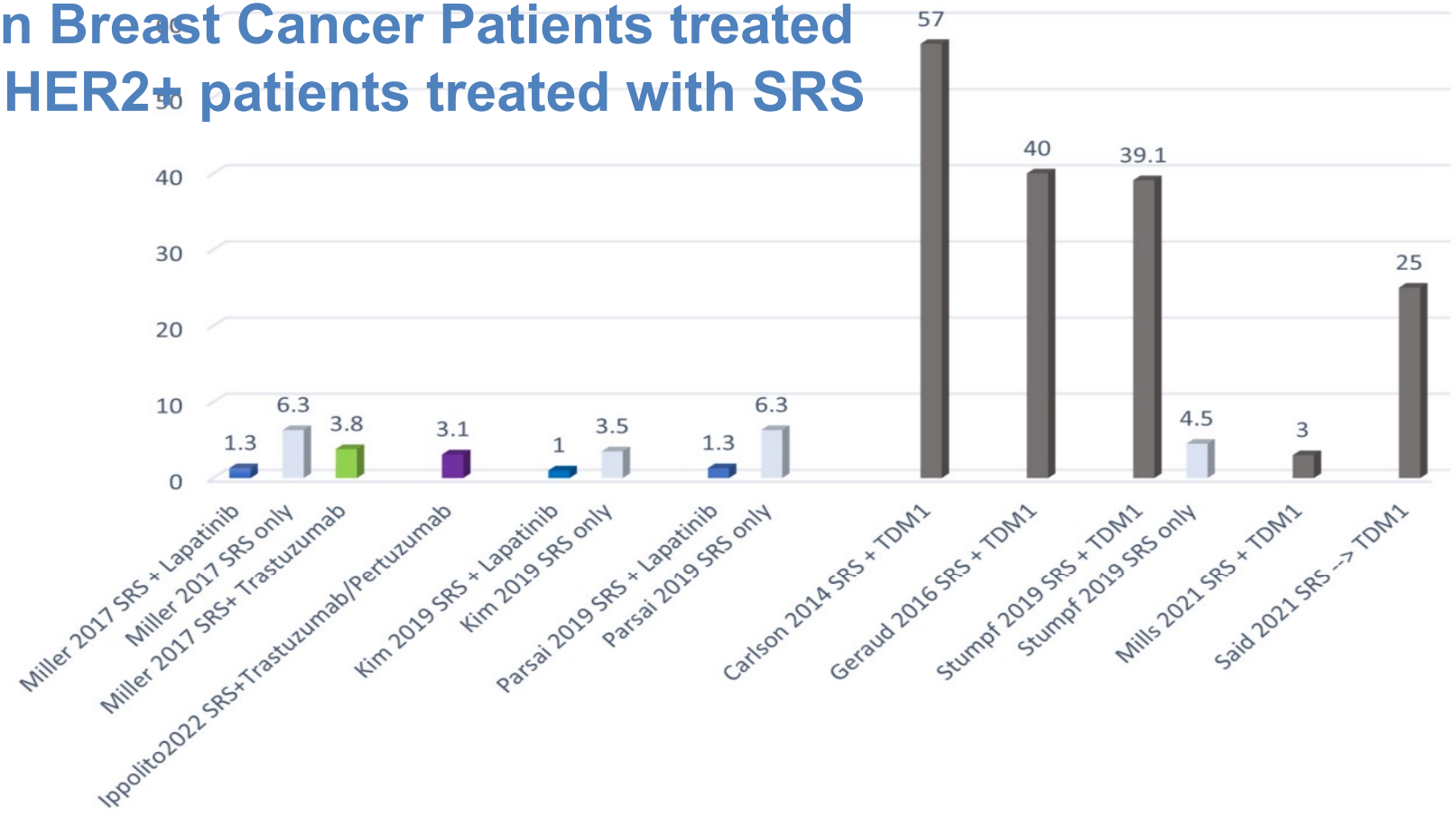
Miller et al. IntJ Radiation Oncol Biol Phys 2016, Singh Radiother Oncol 2020

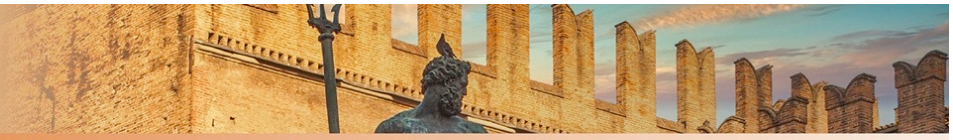
ALK TUMORS ARE MORE LIKELY TO DEVELOP RADIONECROSIS: PATHOPHYSIOLOGY?



- ✓ Disease history (high incidence of BM, need for multiple repeated treatment)
- ✓ Inherent tumor biology
- ✓ High Apoptosis induction → increase in hypoxia→ additive effect to RT

RN in Breast Cancer Patients treated with HER2+ patients treated with SRS





Translational Cancer Mechanisms and Therapy

Clinical Cancer Research

Combination of Trastuzumab Emtansine and Stereotactic Radiosurgery Results in High Rates of Clinically Significant Radionecrosis and Dysregulation of Aquaporin-4

Check for updates

45 patients identified:
10 patients (22.2%) developed **Clinically Significant RadioNecrosis** (CSRN), **9 of whom received T-DM1**.
CSRN was observed **in 39.1% of patients who received T-DM1 vs. 4.5% of patients who did not**.
Receipt of T-DM1 was associated with a **13.5-fold** ($p = 0.02$) increase in CSRN.

→ The combination of T-DM1 and SRS results in **alarming rates** of CSRN in patients with brain metastases from breast cancer

Stumpf et al, Trasl Cancer Mech and Therapy 2019

ASTROCYTE TARGETING

TDM1 acts on astrocyte disregulating cerebral edema mechanism

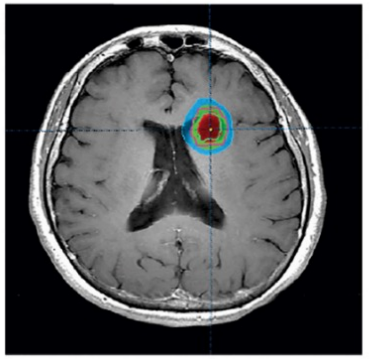
RN:

7/10 single fraction SRS

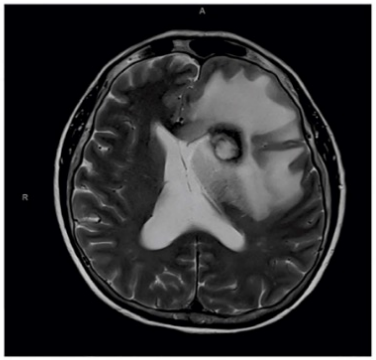
6/9 concurrent TDM1

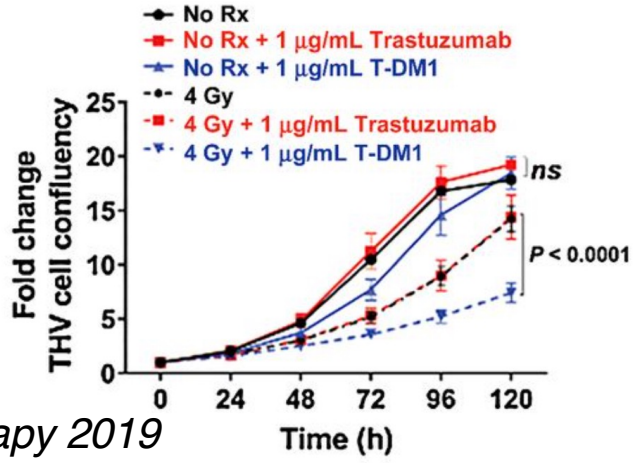
Interval from SRS to RN:
30 days-6.5 years

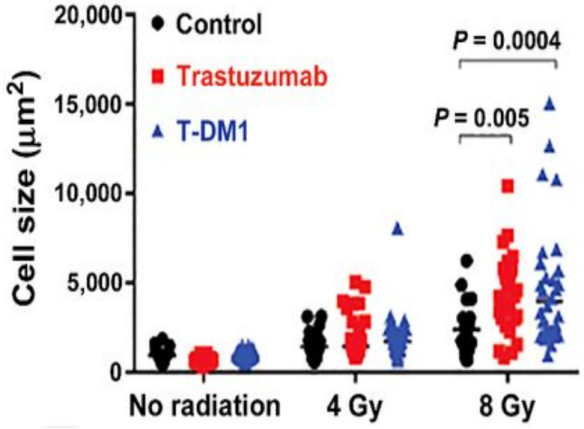
SRS Plan to 18Gy in a single fraction



MRI Brain: Axial T2 sequence 6 months after completion of SRS

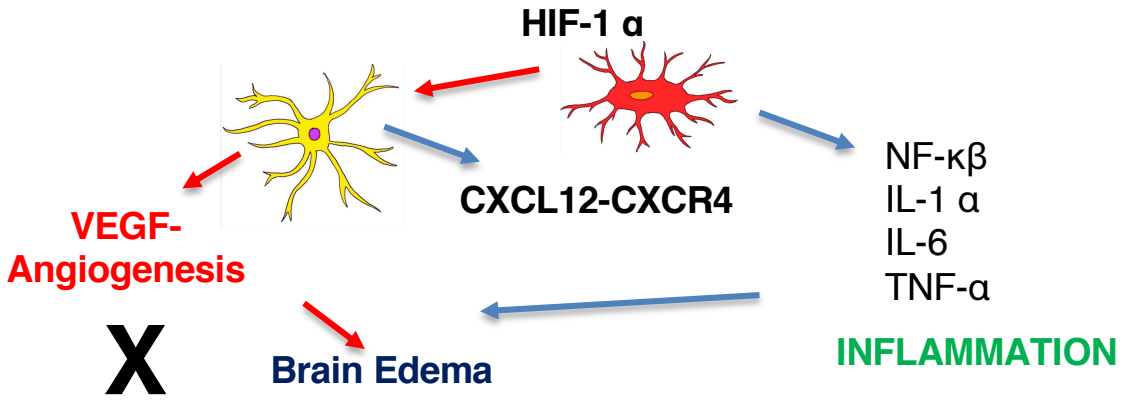






Stumpf et al, Trasl Cancer Mech and Therapy 2019

Anti-Vascular Endothelial Growth Factor Antibody to Reverse Radiation Necrosis



- ✓ **RN volume is decreased after anti-VEGF antibody treatment**
- ✓ **MRI ADC is reversed after the treatment**
- ✓ ***VEGF and HIF-1α remain upregulated after treatment***

Juan C J Neuroncol 2017

Conclusions

- The risk of radionecrosis may be enhanced by the type of drug and timing of administration

- Not all the drugs are the same!

- Mitigation strategies should be adopted if the risk is higher

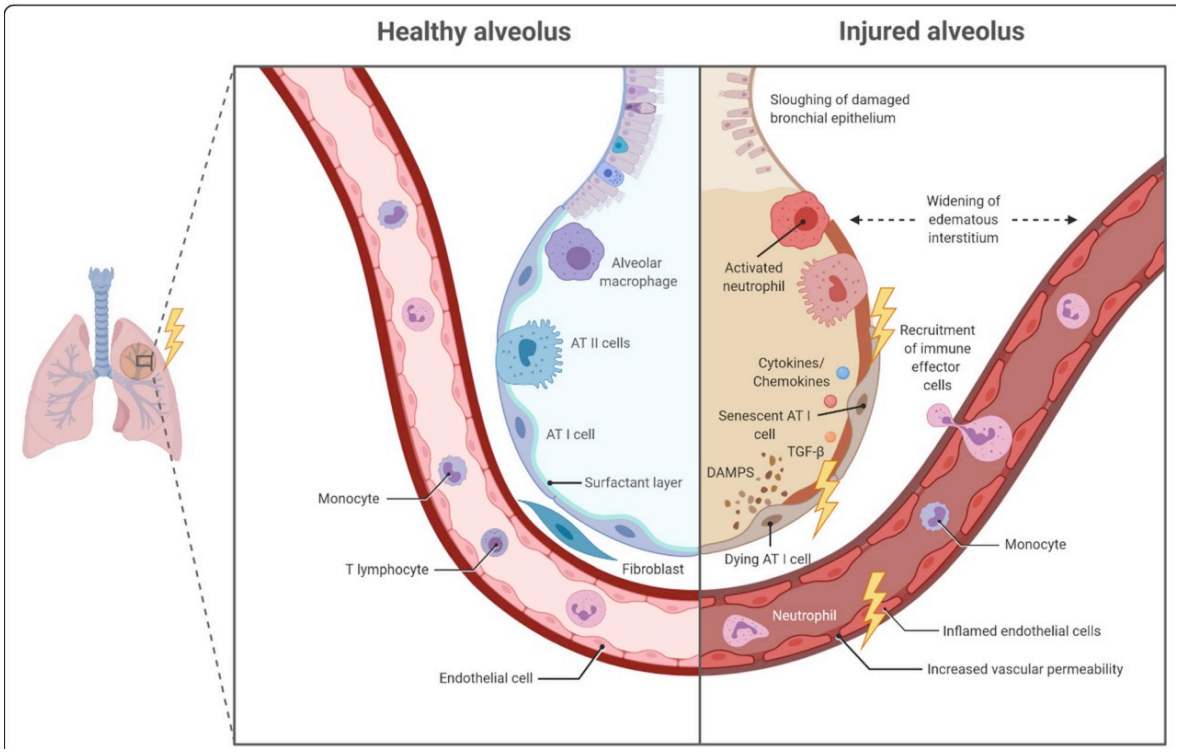
Lung Toxicity for Chemoradiation : the past

Endpoints	RTOG 0617 60Gy	PROCLAIM standard	PROCLAIM Pem/Plat
Median Follow-up	28.7 months	22.6 months	22.2 months
No	217	301	297
Grade 2		5.5%	11%
Grade 3-5	7%	2.6%	1.8%
Pulmonary events			
Grade 3-5	20%	Only dispnea and upper pulmonary 3.3%	Only dispnea and upper pulmonary 4.2%

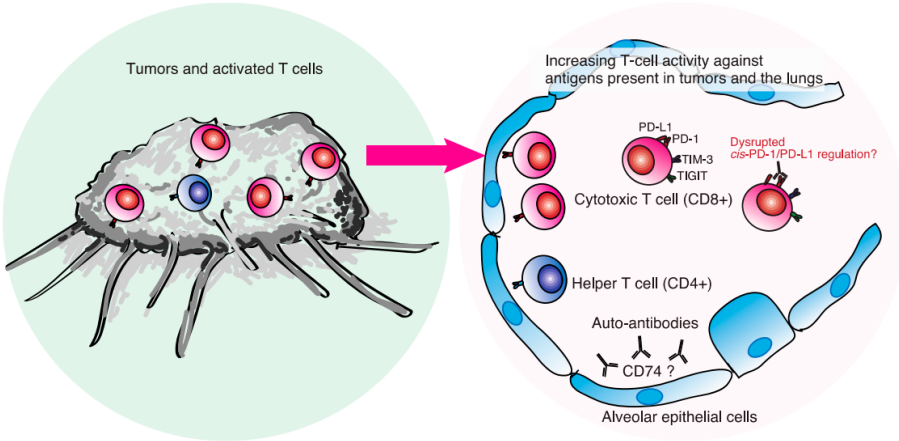
Lung Toxicity for Chemoradiation +/- Immunotherapy: present and next future

Endpoints	LUN 14-179[2] (Pembro)	PACIFIC[1] (Durva)	PACIFIC[1] (Placebo)	KEYNOTE 799 Pembro + Carbo Taxol RT	KEYNOTE 799 Pembro + Cisp Pem RT	NICOLAS TRIAL Nivo + CT+ RT
Median Follow-up	23.9 months	25.2 months	25.2 months			20 months
No	92	476	237	112	73	82 (79 evaluable)
Pneumonitis						
Grade 2	10.8%	any grade 33.9%	any grade 24.8%			
Grade 3-5	6.5%	3.6%*	3.0%*	**8%**	**5.5%**	**10.3%**
Pulmonary events		+	+			
Grade 3-5	Cough and dyspnea: 6.5% **=13%**	Pneumonia : 4.4% **=8%**	Pneumonia: 3.8% **=6.8%**			

RT pneumonitis



ICI pneumonitis



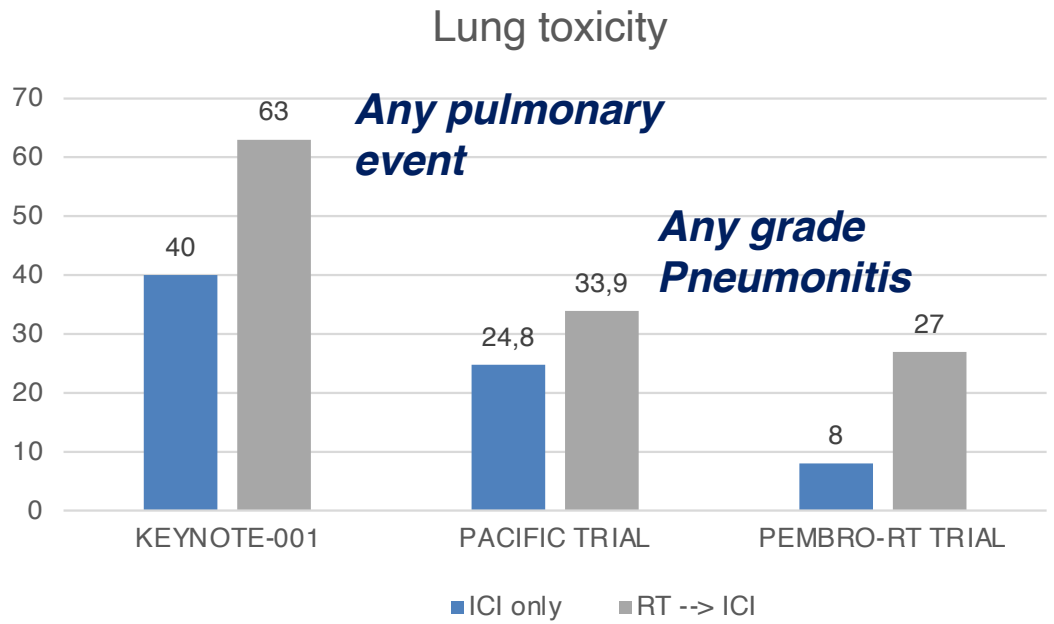
Kasman L Radiat Oncol 2020
Hando H Biomedicine 2021

Current Clinical SCENARIOS

1. Patients treated with ICI previously treated with radiotherapy

2. Patients with previous ICI adverse events undergoing RT

Patients treated with ICI previously treated with radiotherapy



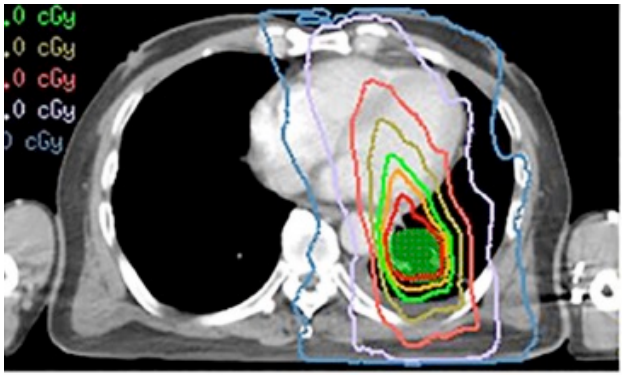
Radiation recall phenomenon!

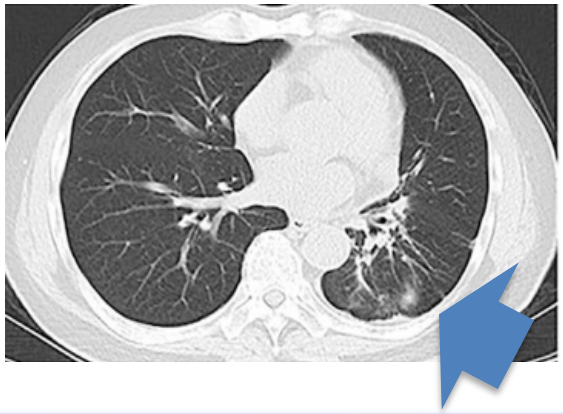
Shaverdian N, Lancet Oncology 2017
Theelen W, Jama Oncol 2010

Radiation Recall Phenomenon

***Unpredictable inflammatory reaction** within previously irradiated tissue, **triggered by pharmacological agents,** occurring even several years after irradiation*

- Anthracyclines and taxanes mostly responsible of RRP
- TKI→ 4.4% RRP





Radiation Recall Phenomenon with ICI

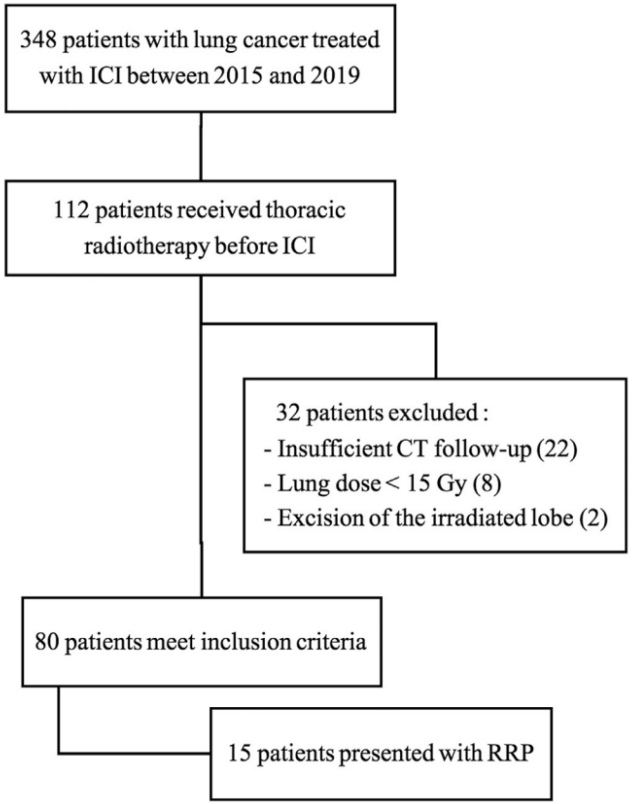
ELSEVIER
Contents lists available at ScienceDirect
Radiotherapy and Oncology
journal homepage: www.thegreenjournal.com

Original Article

Incidence, risk factors, and CT characteristics of radiation recall pneumonitis induced by immune checkpoint inhibitor in lung cancer

François Cousin [a,*], Colin Desir [b], Selma Ben Mustapha [c], Carole Mievis [c], Philippe Coucke [c], Roland Hustinx [a]

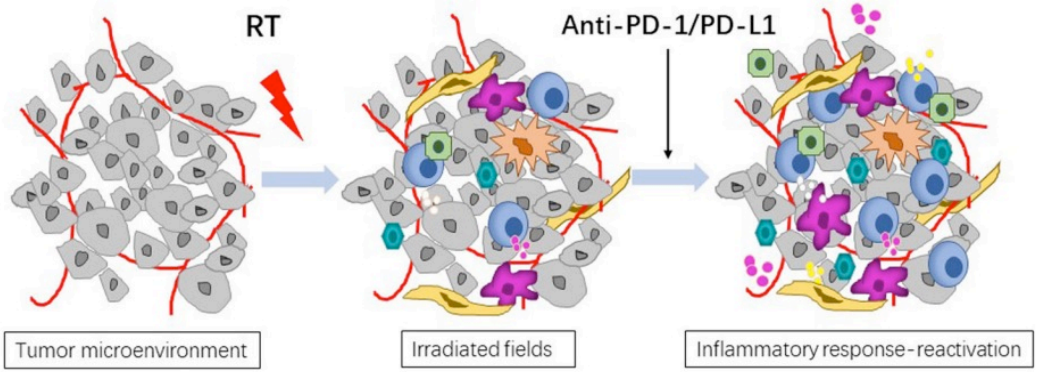
[a] Department of Nuclear Medicine and Oncological Imaging; [b] Department of Radiology; and [c] Department of Radiotherapy, University Hospital (CHU) of Liège, Liège, Belgium

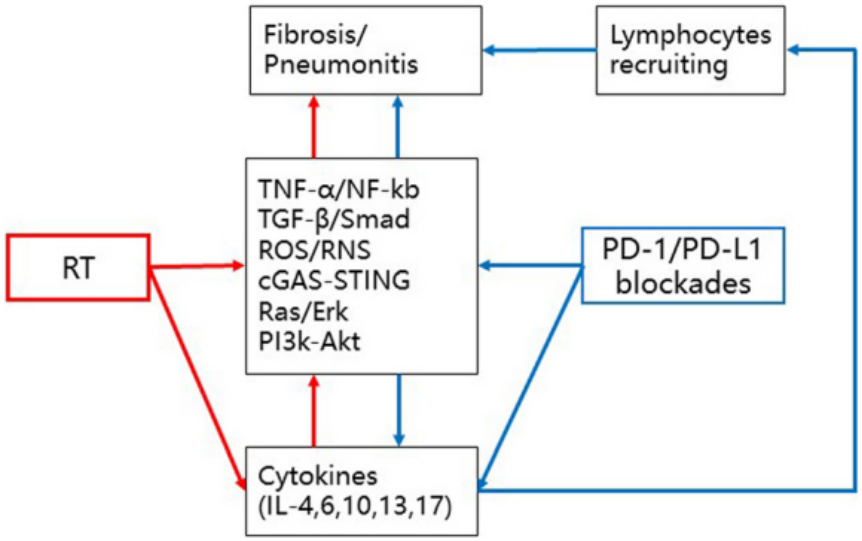


RRP: radiological changes of RT within RT field occurring >6 months after RT and more than 1 yrs after SBRT

- 18.8% incidence RRP (grade 3= 2%)
- Median time between RT and RRP= 450 days (231-1859 days)

Radiation Recall Phenomenon with ICI: mechanism





- Induced senescence of pulmonary stem cells making them unable to repair damage
- Long term modifications of T-cell population

→ LATENT PROINFLAMMATORY STATE

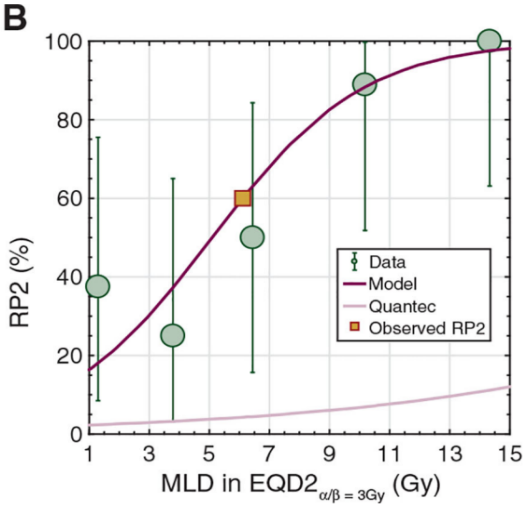
Teng F, BMC Medicine 2020

Current Clinical SCENARIOS

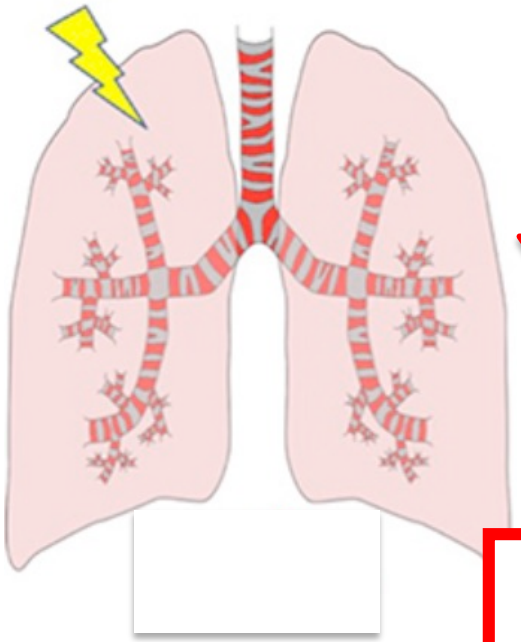
Patients with previous ICI adverse events undergoing RT

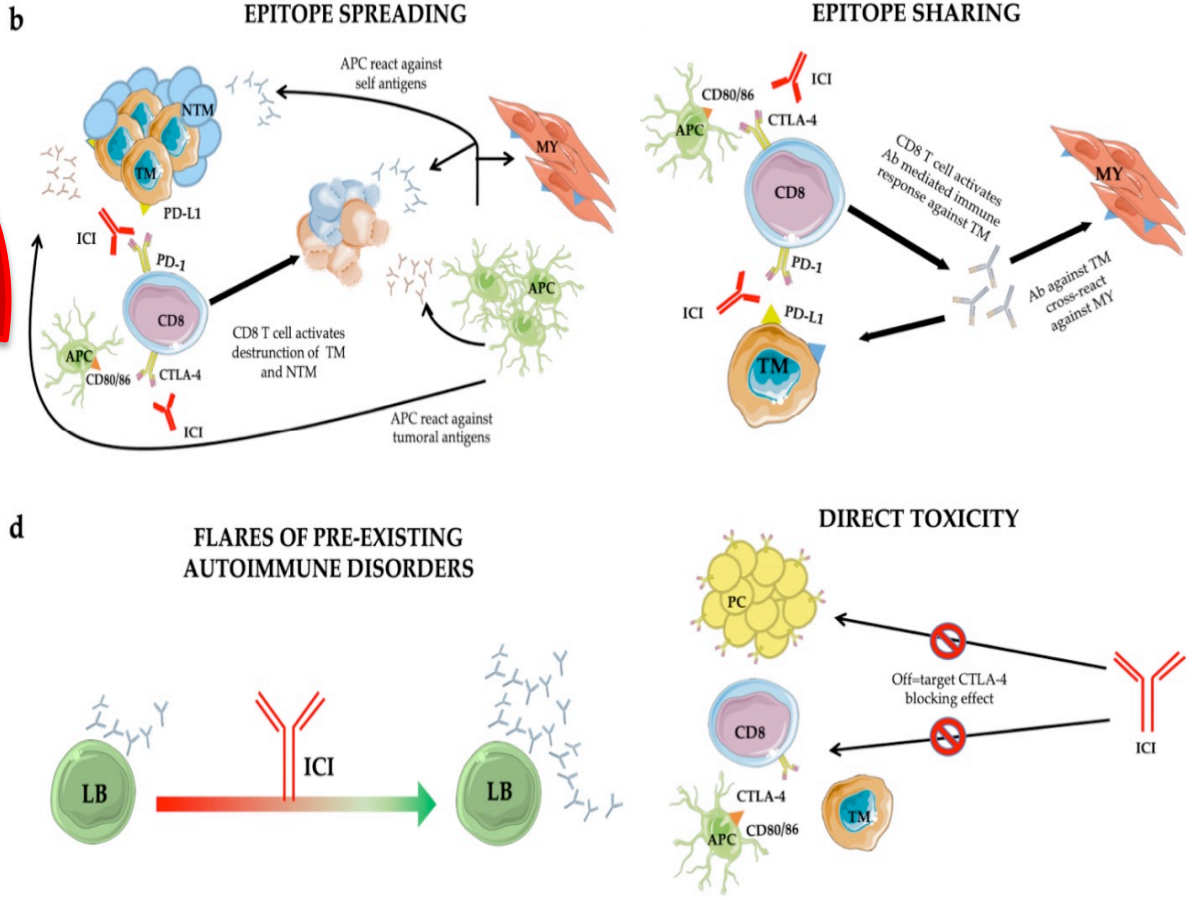
Safety of thoracic radiotherapy in patients with prior immune-related adverse events from immune checkpoint inhibitors

N. Shaverdian[#1,*], J. Beattie[#2], M. Thor[#3], M. Offin[4], A. F. Shepherd[1], D. Y. Gelblum[1], A. J. Wu[1], C. B. Simone II[1], M. D. Hellmann[4], J. E. Chaft[4], A. Rimner[1], D. R. Gomez[1]



- ✓ Patients who received thoracic radiation after symptomatic irAEs
- ✓ 61% of patients developed grade ≥2 RP
- ✓ Median time 8.1 months
- ✓ Exaggerated dose response (patients with MLD> 5Gy, 81% grade ≥2 RP)





Immunocellular infiltrates may enhance immunological reaction triggered by RT

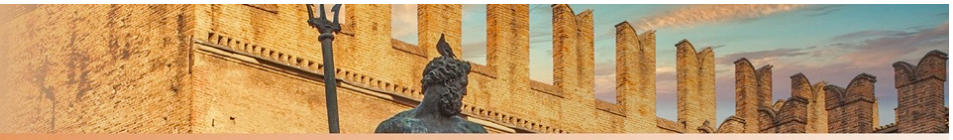
Senan S, Ann Oncol 2020
Solimando A. G., Int. J. Mol. Sci. 2020

Conclusions

- Combined immunotherapy and thoracic RT may increase the rate of symptomatic pneumonitis

- Due to the efficacy of combined treatment, mitigation strategies should be applied in RT treatment delivery (improve lung dosimetry, identify patients at higher risk)

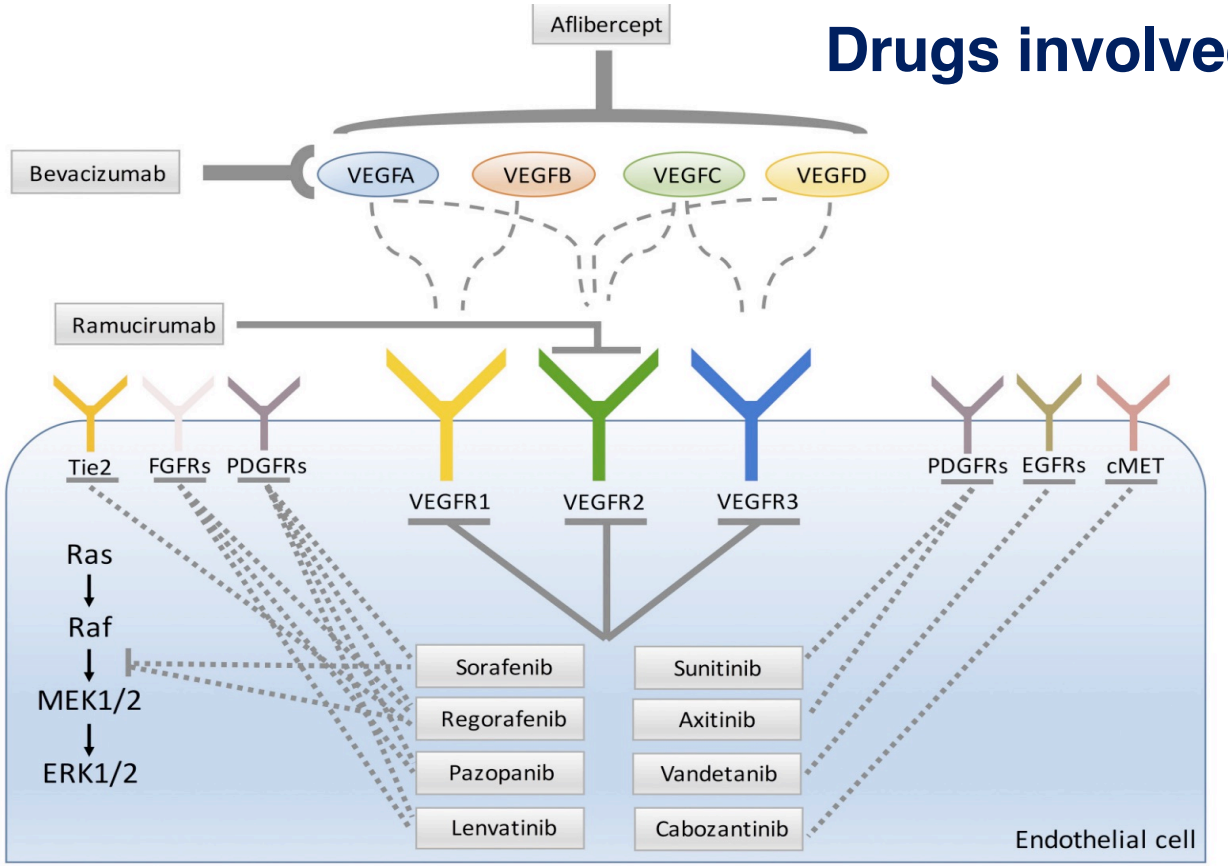
- Improve monitoring for pulmonary events



GI severe toxicity: perforation, bleeding

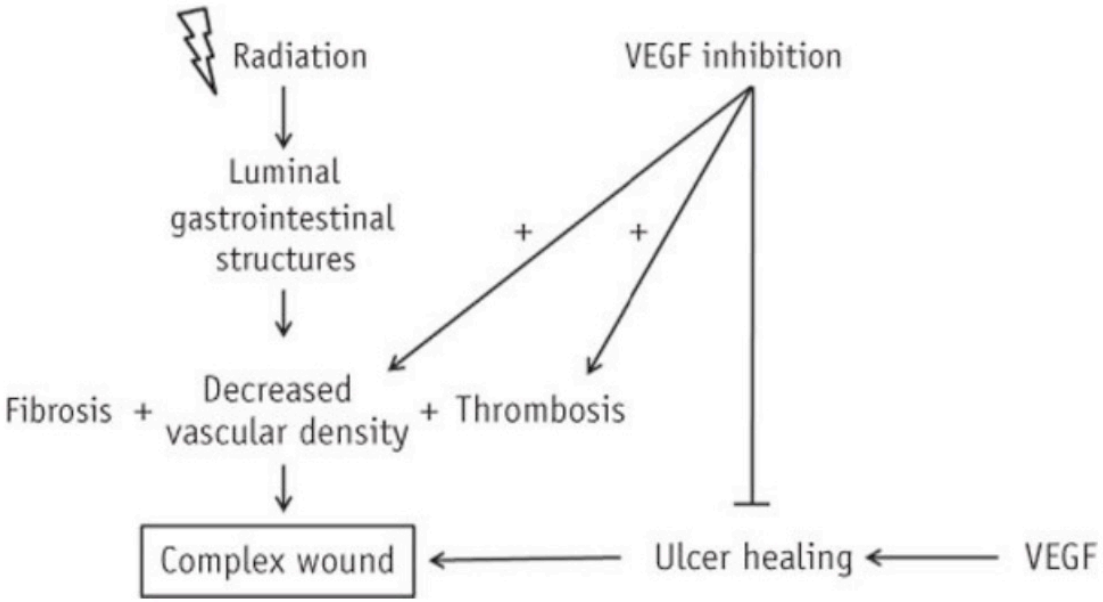
	DOSE (total/n fractions)	BED3 (Gy)	RT SITE	DRUGS	GI TOX
Peters 2008	8Gy/1 fr	29.3	Spine	Sorafenib	Grade 5 bowel perforation
Lordick 2006	28Gy/7 fr	65.3	Right ileum	Bevacizumab	Grade 5 bowel perforation
Stephans 2014	50Gy/5 fr	216.7	Lung metastases	NS	≥Grade 3 esophageal fistula
Barney 2013	30Gy/3 fr 60Gy/5 fr 42Gy/5 fr 60Gy/3 fr 40Gy/5 fr 60Gy/3 fr 60Gy/5 fr	130 300 162.9 460 146.7 460 300	Liver Liver Pancreas Liver Limphonode Liver Liver	Sorafenib Bevacizumab Bevacizumab Bevacizumab Bevacizumab Bevacizumab Bevacizumab	Grade 3 gastric ulcera Gastric perforation, grade 4 Duodenal perforation, grade 5 Small bowel perforation, grade 4 Duodenal ulcer, grade 3 Gastric ulcer, grade 3 Gastric ulcer, grade 4
Dawson 2012	36Gy/6 fr 30Gy/6 fr	108 90	Liver LIver	Sorafenib Sorafenib	Grade 4 bowel obstruction Grade 3 GI bleeding
Murray 2017	30Gy/10 fr 30Gy/10 fr	60 60	Lung	Sorafenib Sorafenib	Grade 3 esophagitis Grade 5 bowel perforation
Munoz Schuffenegger 2020	50Gy/5 fr OAR adapted	216.7	Liver	Sorafenib	5% Grade 3 GI bleeding No Grade 5

Drugs involved in VEGF pathways



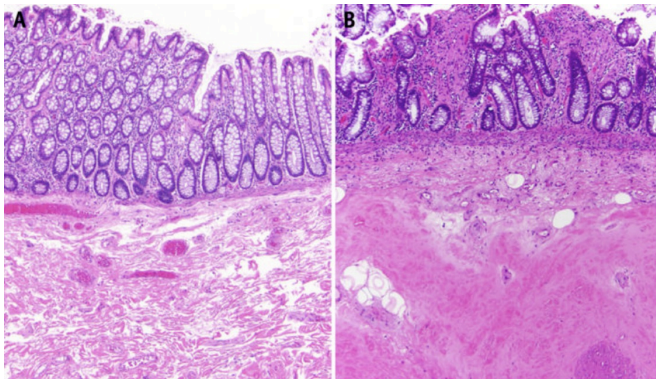
Kanthou C, Tozer G. Br J Radiol 2019

Mechanism of Radiation induced injury with anti VEGF



Anti VEGF drugs following RT:

- Delayed healing
- Worsen ischemic injury
- Increase thromboembolic events contribuiting to ischemia and perforation



Pollom, Tozer G. IJBROP 2015
Mangoni, Br J Radiology 2012

Conclusions

- Combined anti-VEGF and intra-abdominal RT may be associated to severe toxicity

- Anti-VEGF antibodies should not be given in combination with RT, unless GI structure are clearly out of treatment fields.

Kroeze Cancer Treat Reviews 2017
Guimond E, Advances in Radiation Oncology 2022