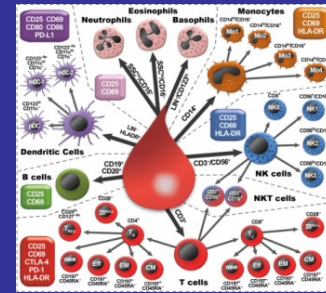




Foto: Strahlenklinik Erlangen



Zhou, Donaubaauer et al.,
J Immunother Cancer, 2021, Feb;9(2)

Precisely delivered high dose(s) of RT – role of immune system in thereby induced anti-tumor immune responses

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Deputy Head of Translational Radiobiology
(Prof. Dr. Udo Gaipl)
Department of Radiation Oncology, Universitätsklinikum Erlangen



ARBEITSGRUPPE RADIOCHIRURGIE/
STEREOTAXIE

Erlangen, 01.10.2022



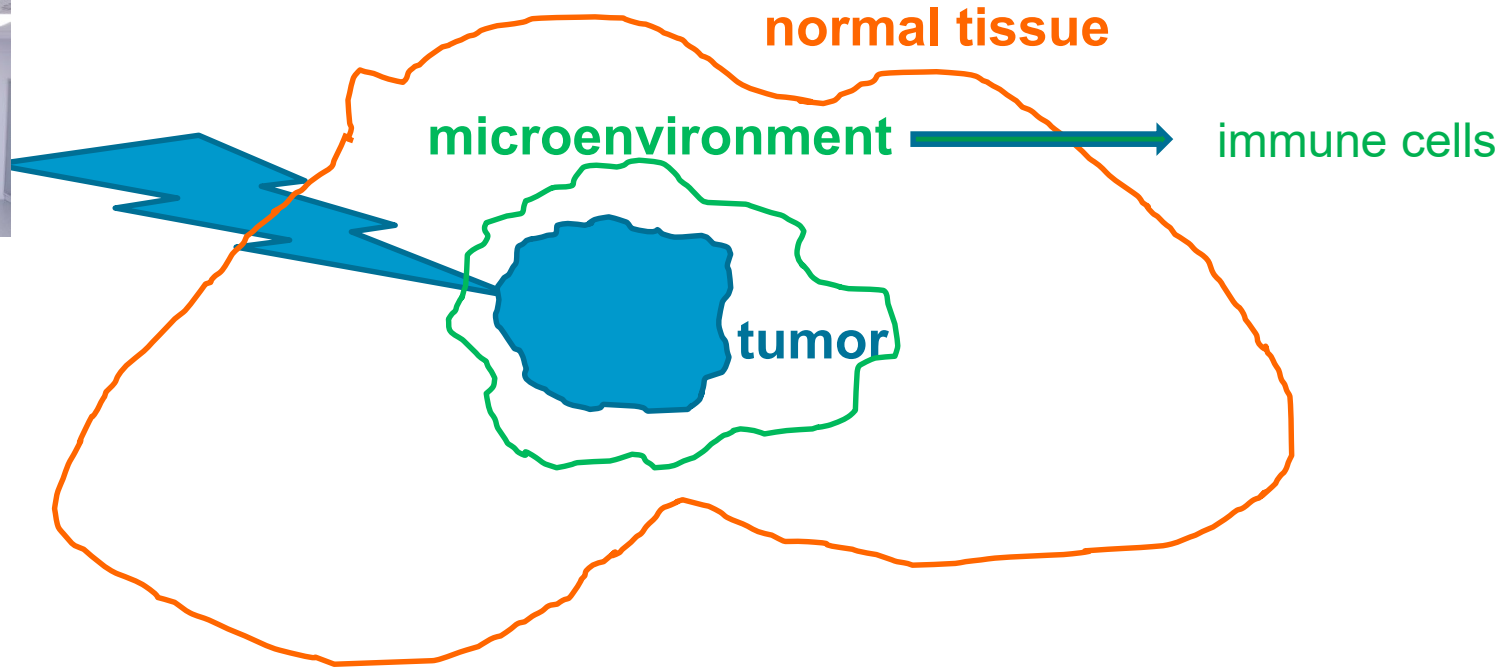
@translatraddio



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How biology Sees SBRT?



tumor control probability (TCP)

normal tissue complication probability (NTCP)

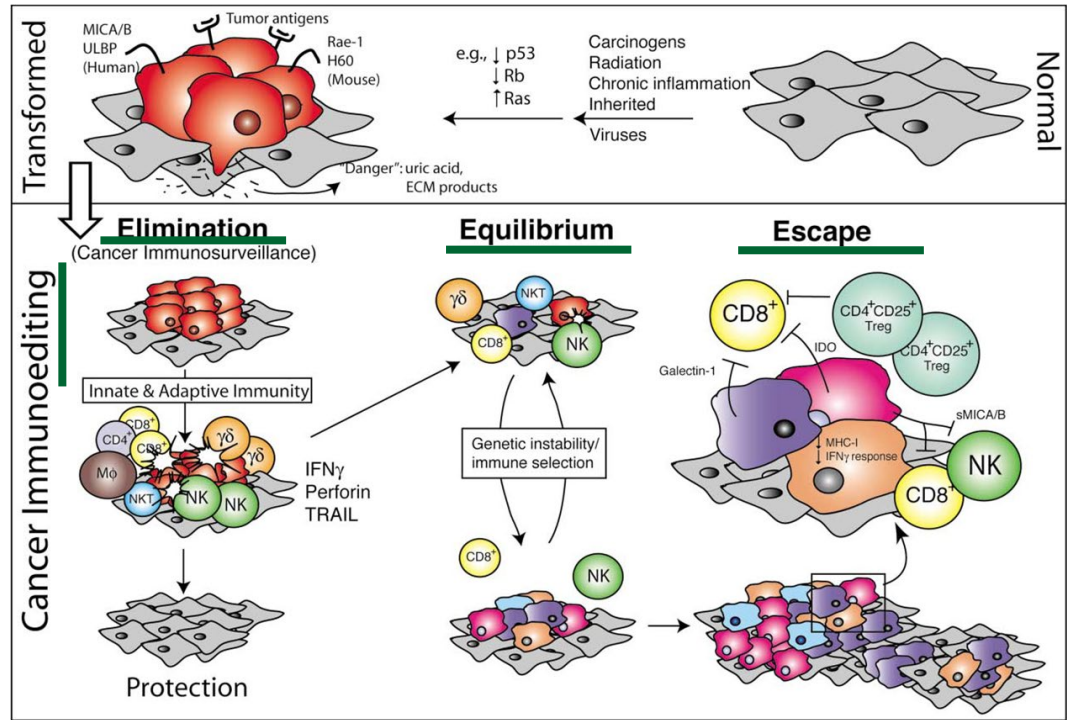
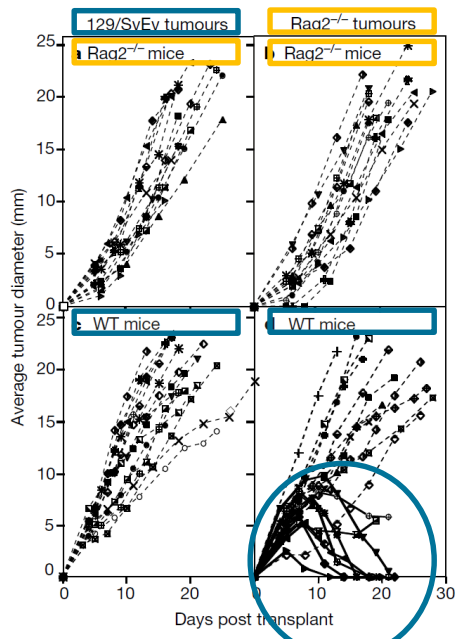




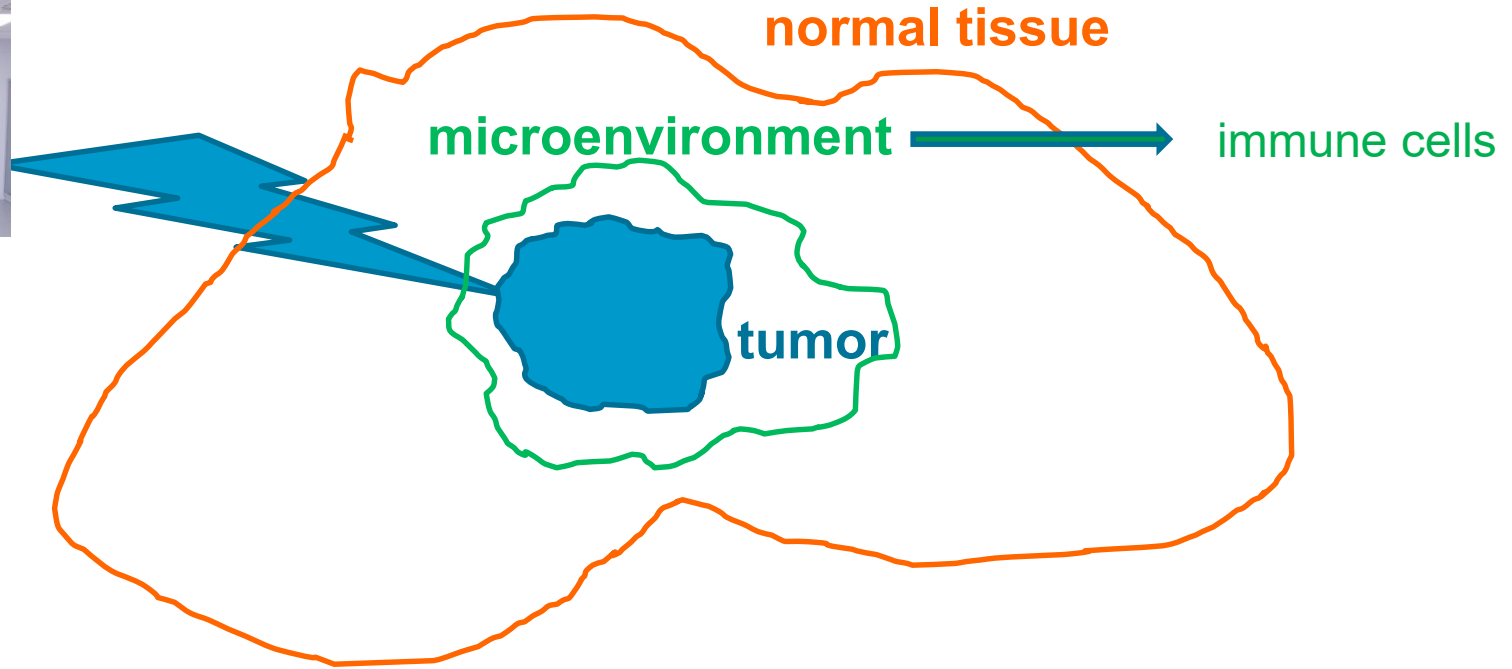
Tumor and immune system are in strong interconnection

→ Immunoediting of tumors: the prominent (four) E's

Increased immunogenicity of tumors developed in immune deficient mice



How biology Sees SBRT?



tumor control probability (TCP)

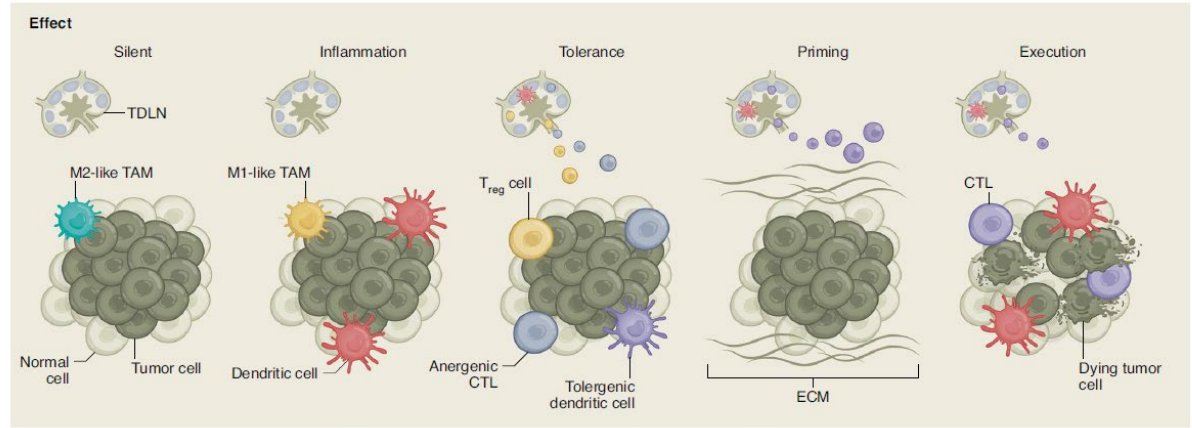
normal tissue complication probability (NTCP)





Tumor cell death (RCD) initiates anti-tumor immune responses: immune cells of TME and TDLN for priming

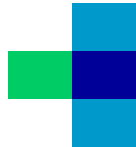
RCD	-	+	+	+	+
Antigenicity	-	-	+	+	+
Adjuvanticity	-	+	-	+	+
Microenvironment	+/-	+/-	+/-	-	+



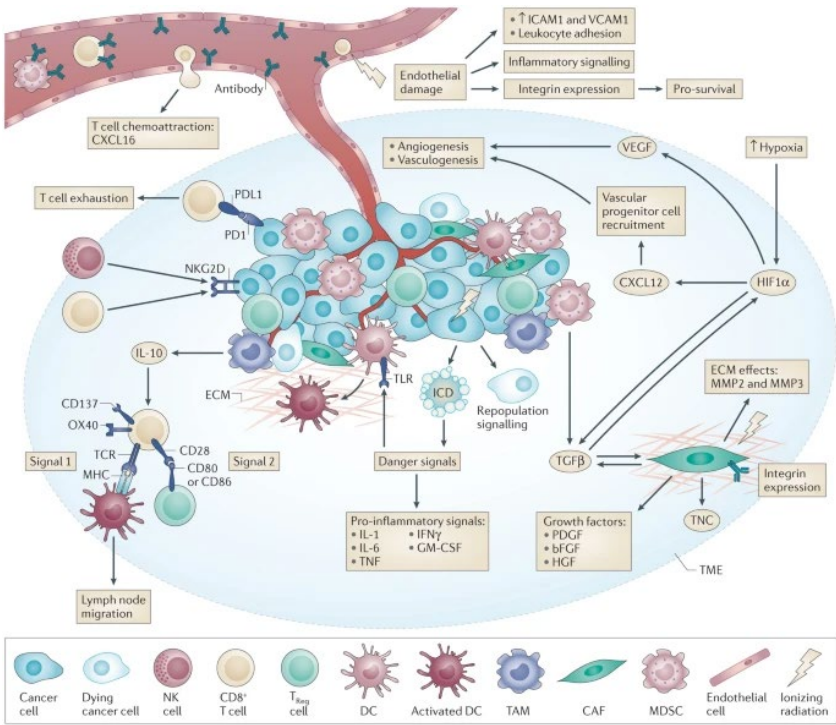
Immune competent tissues:

TME:
tumor micro-environment

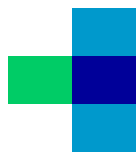
TDLN:
tumor draining lymph nodes



Tumor cells and immune cells are in close contact to and interaction with each other

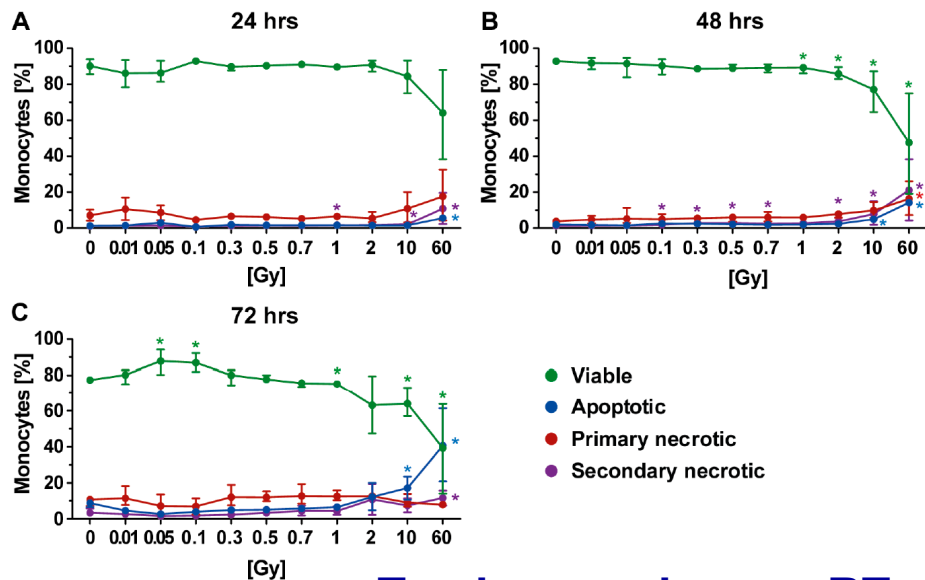


RT is capable of induction of anti-tumor immune responses!

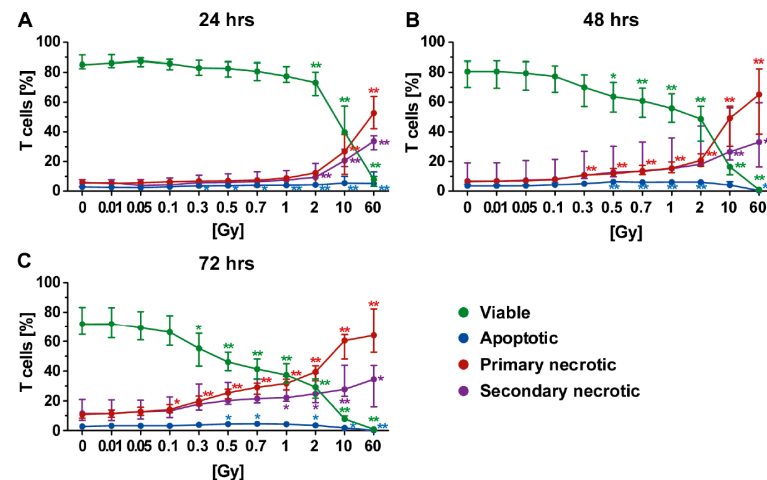


TME: immune cell types strongly differ in their radiosensitivity

monocytes



T cells



resistant

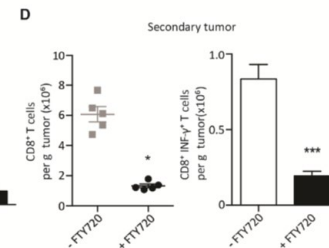
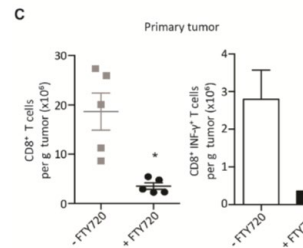
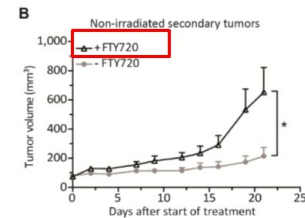
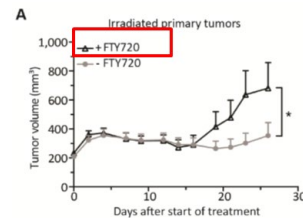
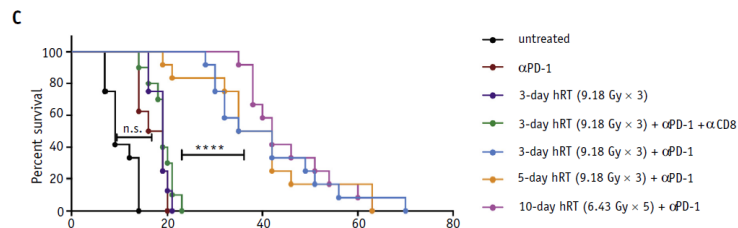
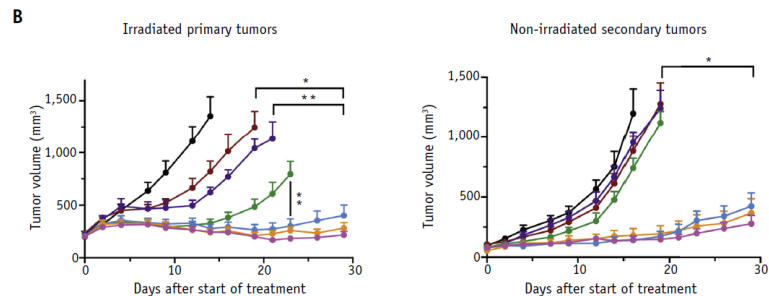
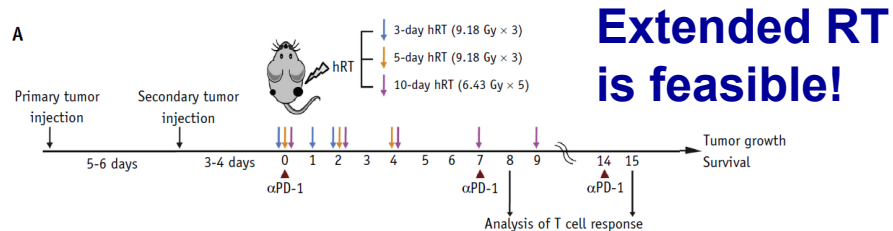
Too huge volumes: RT might
kill beneficial cytotoxic T cells!

sensitive

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T cell supply from lymph nodes is most important to exploit RT-induced anti-tumor immune responses



CAVE: LN!

B16-CD133 melanoma

3 x 9.18Gy plus anti-PD1

plus vs. w/o FTY720
(induces T cell
accumulation in LN)



Basics of radiotherapy versus radiotherapy-immunodose and volume of application



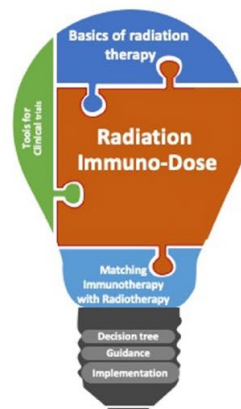
Box 1 Tumor microenvironment response to radiation: influence of radiation-induced immunomodulation in regulating response

Influence of radiation-induced immunomodulation on tumor microenvironment

- ▶ **Radiation:** Does the quality of radiation (high vs low linear energy transfer), dose, size, fractionation (low-dose fractionation vs high-dose fractionation) and dose rate (high-dose rate vs low-dose rate) and schedule (hypofractionation vs multifractionation) influence effective modulation of tumor immune microenvironment?
- ▶ **Tumor cell susceptibility:** Is the tumor cell susceptibility per se to immunotherapy impacted by the above radiation schedules?
- ▶ **Treatment volume:** Is irradiation of the complete tumor volume necessary? Or is irradiation of partial volume adequate for effective modulation of tumor immune microenvironment and minimize normal tissue injury? Should one treat gross tumor volume alone or including involved lymph nodes for effective immune modulation?
- ▶ **Abscopal effect:** Is distant effect (abscopal effect) a marker of effective modulation of tumor immune microenvironment?
- ▶ **Tumor cell immune characteristics:** Does human leukocyte antigen class I loss or low T-cell repertoire diversity or checkpoint expression influence radiation effects of immunomodulation? Does tumor immunogenicity predict radiation-induced tumor immune modulation?
- ▶ **Cytokines:** What dictates the balance between radio-induction of immunosuppressive cytokines and radio-induction of immune-activating cytokines?

Demaria et al

Management Idea Plan for Dose-Fraction



Radiation-Immuno-Dose

- Physical dose directly linked to biological perturbations
- Analysis of radiation-inducible immune perturbations to generate a radiation immuno-dose scale.



Tools for clinical trials

- Develop common critical elements of clinical trial design between radiation therapy and immunotherapy
- Trial concept should be based on robust pre-clinical data



Matching Immunotherapy with Radiotherapy

- Matching the mechanism of action of immunotherapeutic agents with radiation immune dose fractions
- Precision medicine approach in radiation and immunotherapy combinations

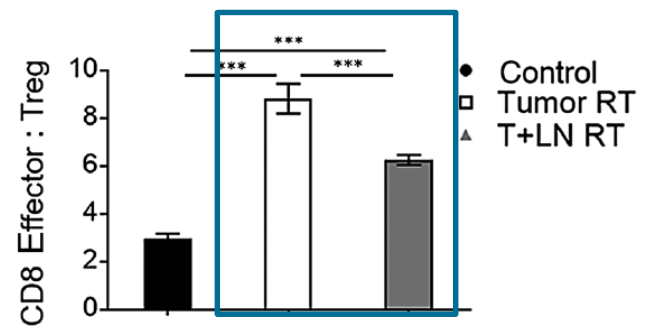
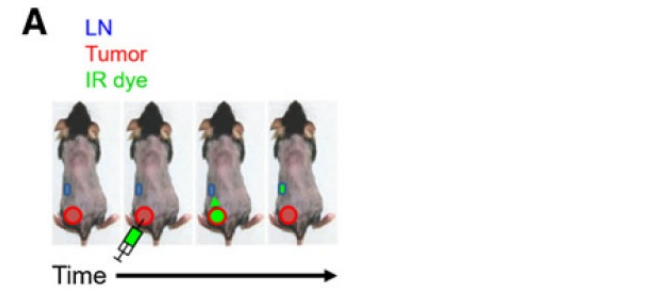


Basics of radiation therapy

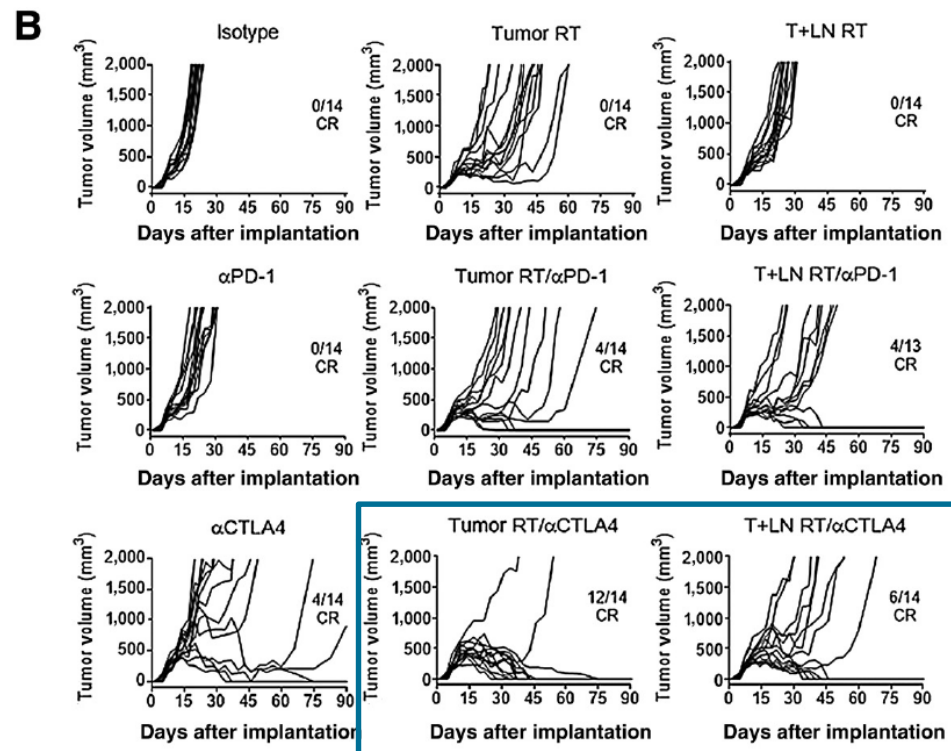
- Clinical applications of radiation therapy
- Delivery approaches of radiation therapy



Elective nodal irradiation attenuates efficacy of combination of radiotherapy with immune checkpoint inhibition

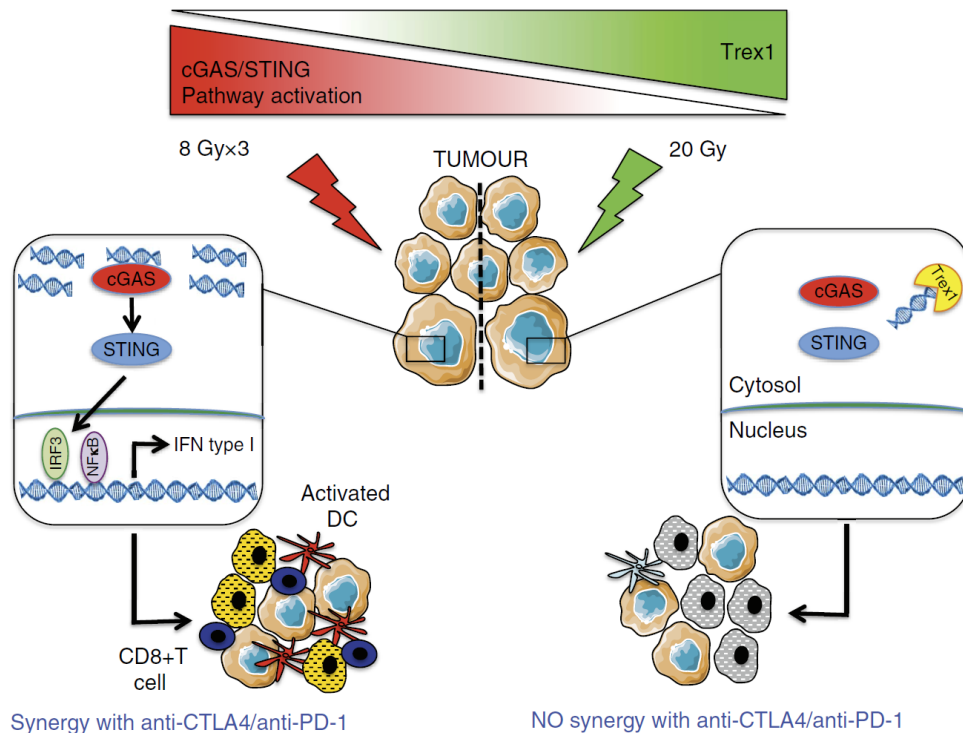


Sparing of lymph nodes should be envisaged!

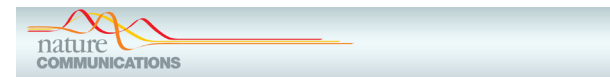


MC38: murine colon adenocarcinoma

But what is the optimum dose? Higher single dose, but not too high?!



Cave:



ARTICLE

Received 27 Mar 2017 | Accepted 12 Apr 2017 | Published 9 Jun 2017

DOI: 10.1038/ncomms15618 OPEN

DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity

Claire Vanpouille-Box¹, Amandine Alard^{2,3}, Molykutty J. Aryankalayil³, Yasmeen Sarfraz¹, Julie M. Diamond¹, Robert J. Schneider², Giorgio Inghirami², C. Norman Coleman³, Silvia C. Formenti¹ & Sandra Demaria^{1,4}

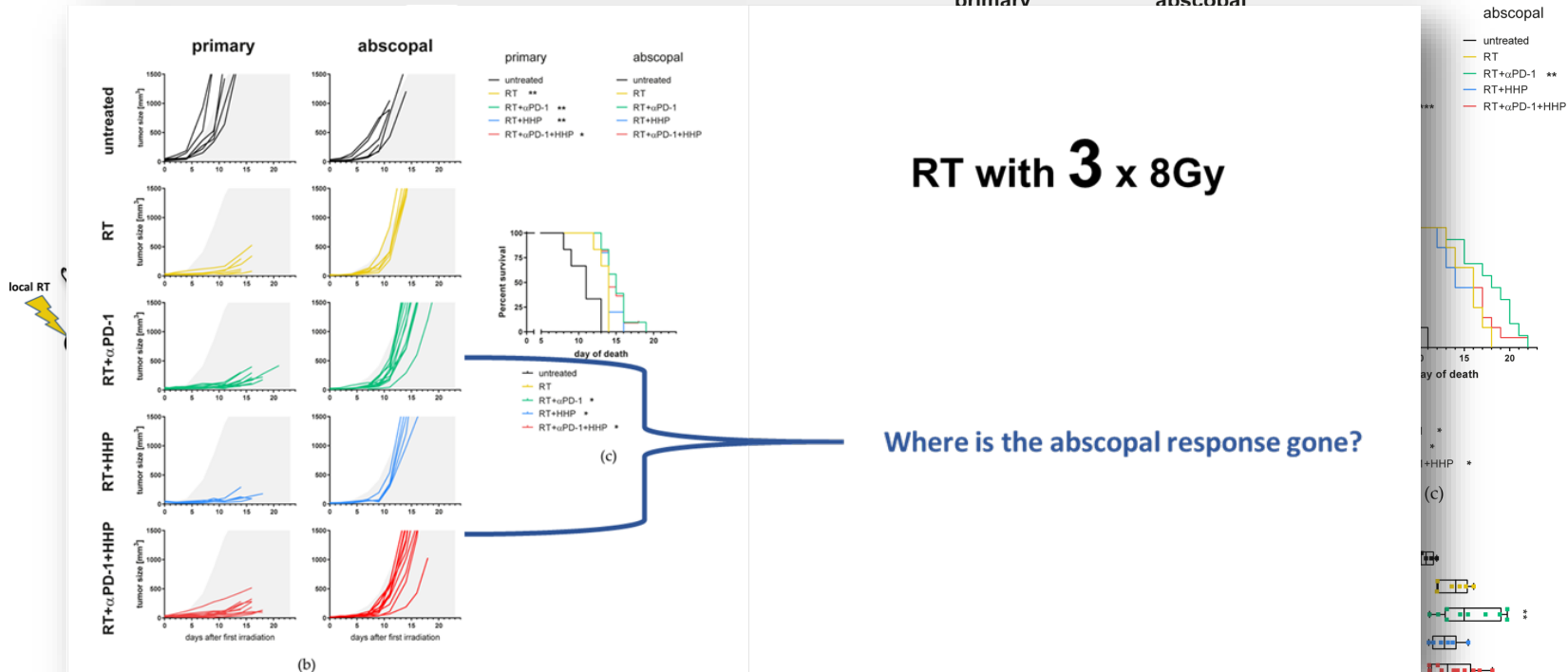




CAVE: Combi of RT with ICI and vaccination might differently affect primary and abscopal tumor growth

(a)

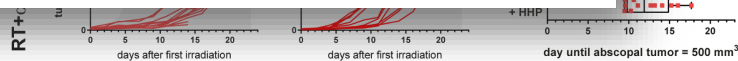
primary abscopal



RT with **3** x 8Gy

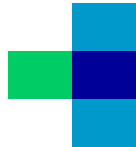
Where is the abscopal response gone?

(b)



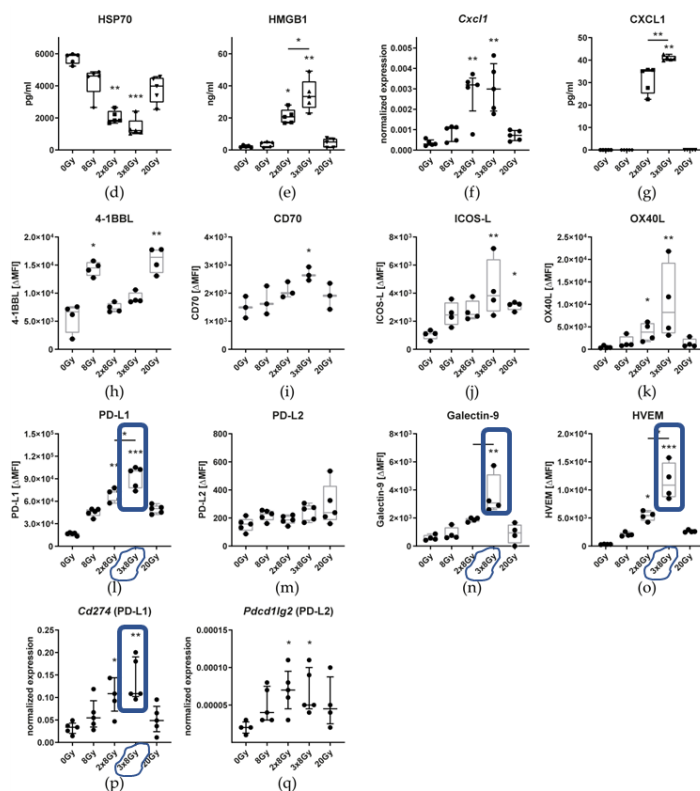
(b)

(d)





3x8Gy plus anti-PD-1 fails to induce abscopal responses - altered immune phenotype of TC



Need of individual assessment of immune properties in dependence of the applied therapies!

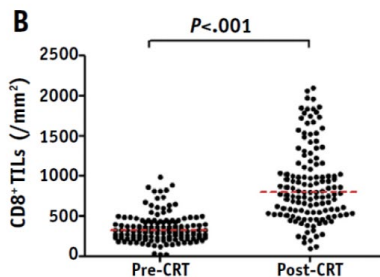
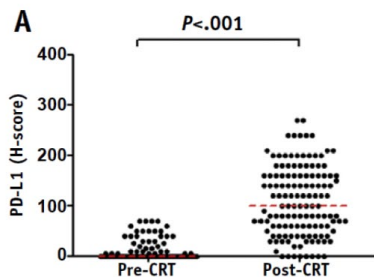


PACIFIC-trial: Durvalumab after RCT in stage III non-small-cell lung cancer

RT bis Randomisation	Hazard ratio (Tod)	95% CI
1-13 Tage	0.42	(0.27-0.67)
14-42 Tage	0.81	(0.62-1.06)



Better results when Durvalumab is applied early after RT



Chemoradiation impacts on PD-L1 expression and infiltration of CD8+ T cells

Lim et al, Int J Radiat Oncol Biol Phys, 2017
 Universitätsklinikum
 Erlangen

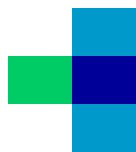
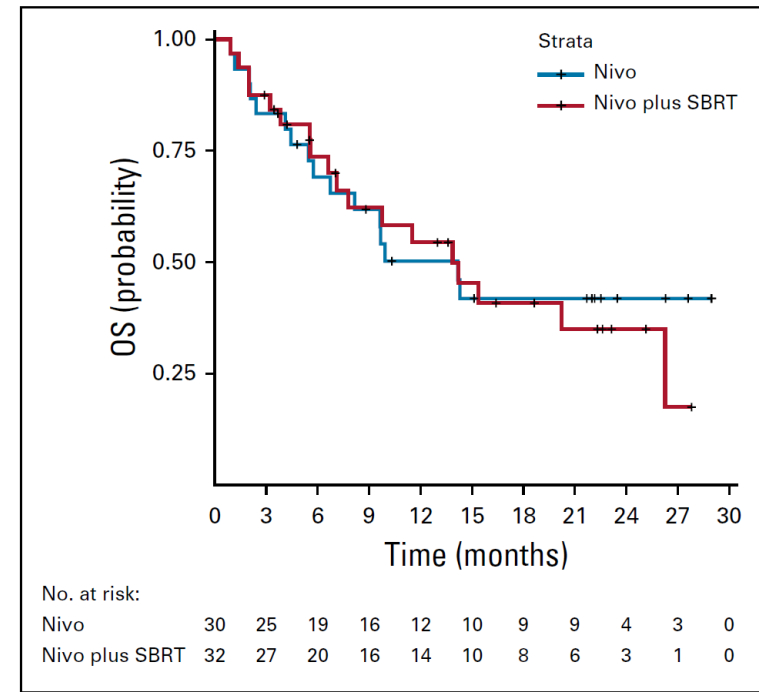




No improvement by addition of SBRT to nivolumab in unselected patients with metastatic HNSCC

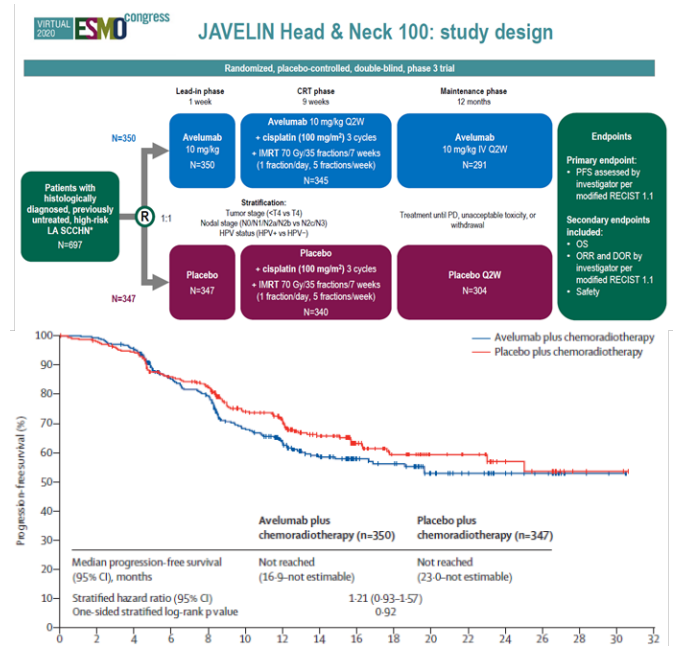
Randomized Phase II Trial of Nivolumab With Stereotactic Body Radiotherapy Versus Nivolumab Alone in Metastatic Head and Neck Squamous Cell Carcinoma

Sean McBride, MD, MPH¹; Eric Sherman, MD^{2,3}; C. Jillian Tsai, MD, PhD¹; Shrujal Baxi, MD, MPH²; Jahan Aghalar, MD¹; Juliana Eng, MD¹; Wanqing Iris Zhi, MD, PhD¹; Daniel McFarland, DO¹; Loren Scott Michel, MD¹; Robert Young, MD²; Robert Lefkowitz, MD⁴; Daniel Spielsinger, BS¹; Zhigang Zhang, PhD⁵; Jessica Flynn, BS⁵; Lara Dunn, MD^{2,3}; Alan Ho, MD, PhD^{2,3}; Nadeem Riaz, MD, MSc¹; David Pfister, MD^{2,3}; and Nancy Lee, MD¹

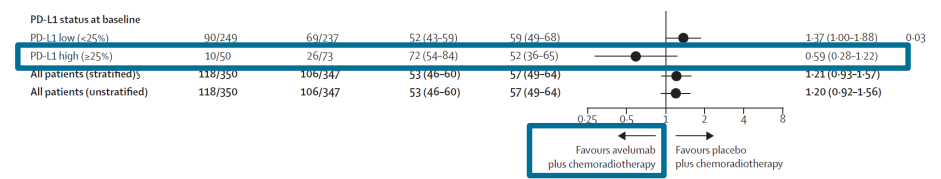




JAVELIN Head and Neck 100 trial: avelumab plus RCT vs placebo plus RCT



Need of patient selection

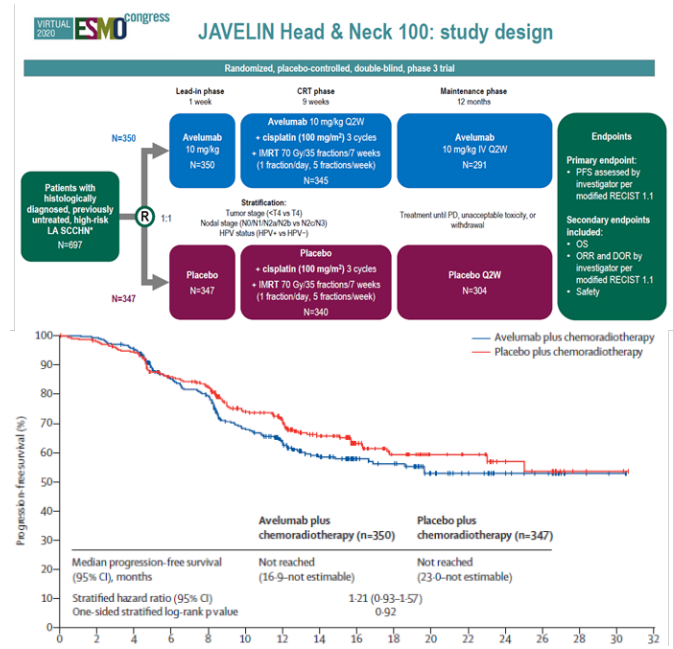


Interpretation The primary objective of prolonging progression-free survival with avelumab plus chemoradiotherapy followed by avelumab maintenance in patients with locally advanced squamous cell carcinoma of the head and neck was not met. These findings may help inform the design of future trials investigating the combination of immune checkpoint inhibitors plus CRT.

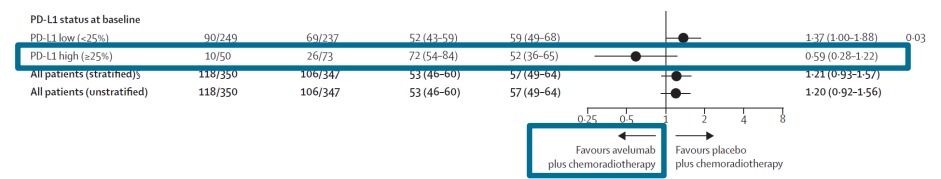
lymph nodes!



JAVELIN Head and Neck 100 trial: avelumab plus RCT vs placebo plus RCT



Need of patient selection



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lymph nodes!

Thank you for your attention!



Department of Radiation Oncology, Universitätsklinikum Erlangen

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