"SESSIONE 4 - Volumi di trattamento e frazionamento della dose nelle combinazioni radio-immunoterapiche: evidenze attuali e sfide future"

Polmone

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Background

Oligometastatic NSCLC (SRS+IO)

JAMA Oncology | Original Investigation

Effect of Pembrolizumab After Stereotactic Body Radiotherapy vs Pembrolizumab Alone on Tumor Response in Patients With Advanced Non-Small Cell Lung Cancer
Results of the PEMBRO-RT Phase 2 Randomized Clinical Trial

Willemijn S. M. E. Theelen, MD; Heike M. U. Peulen, MD, PhD; Ferry Lalezari, MD; Vincent van der Noort, PhD; Jeltje F. de Vries, PhD; Joachim G. J. V. Aerts, MD, PhD; Daphne W. Dumoulin, MD; Idris Bahce, MD, PhD; Anna-Larissa N. Niemeijer, MD; Adrianus J. de Langen, MD, PhD; Kim Monkhorst, MD, PhD; Paul Baas, MD, PhD

	Pembrolizumab (40 pts)	SRT+Pembrolizumab (36 pts)	p
ORR 12 weeks (%)	18	36	0,07
Median PFS (months)	1,9	6,6	0,19
Median OS (months)	7,6	15,9	0,16

Unresectable Stage III NSCLC (CCRT+IO)

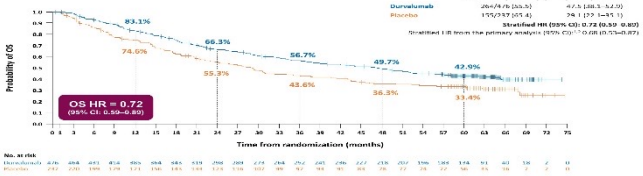
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC

S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Kurata, A. Chiappori, K.H. Lee, M. de Wit, B.C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.-C. Kim, C.S. Karapetis, S. Hiret, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. de Castro Carpeño, C. Faivre-Finn, M. Reck, J. Vansteenkiste, D.R. Spigel, C. Wadsworth, G. Melillo, M. Taboada, P.A. Dennis, and M. Özgüroğlu, for the PACIFIC Investigators*

Updated OS (ITT)

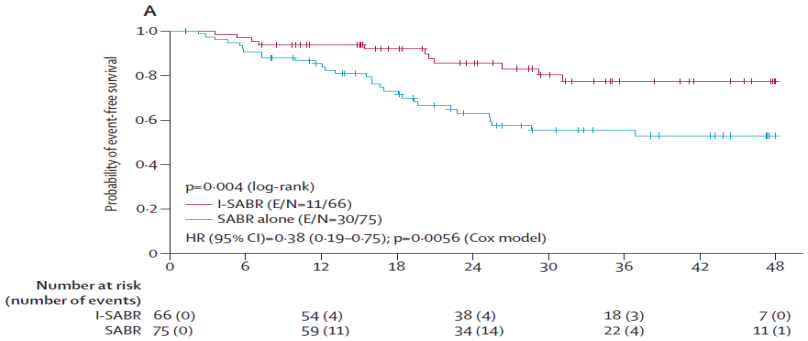


Background

Early-stage NSCLC (SBRT+IO)

Stereotactic ablative radiotherapy with or without immunotherapy for early-stage or isolated lung parenchymal recurrent node-negative non-small-cell lung cancer: an open-label, randomised, phase 2 trial

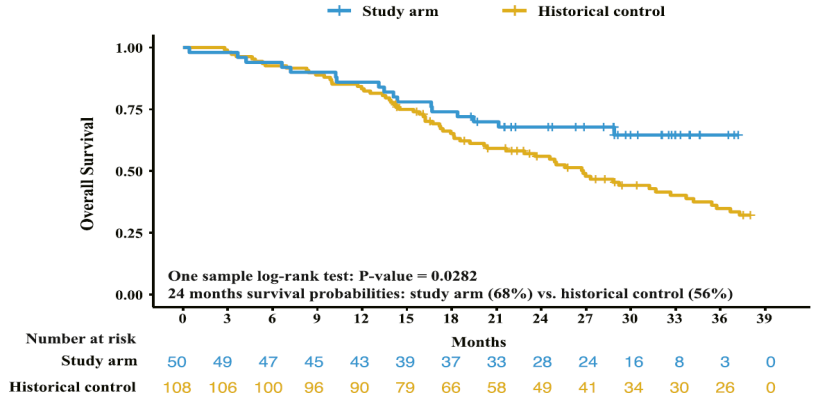
Joe Y Chang, Steven H Lin, Wenli Dong, Zhongxing Liao, Saumil J Gandhi, Carl M Gay, Jianjun Zhang, Stephen G Chun, Yasir Y Elamin, Frank V Fossella, George Blumenschein, Tina Cascone, Xiuning Le, Jenny V Pozadzides, Anne Tsao, Vivek Verma, James W Welsh, Aileen B Chen, Mehmet Altan, Reza J Mehran, Ara A Vaporciyan, Stephen G Swisher, Peter A Balter, Junya Fujimoto, Ignacio I Wistuba, Lei Feng, J Jack Lee, John V Heymach



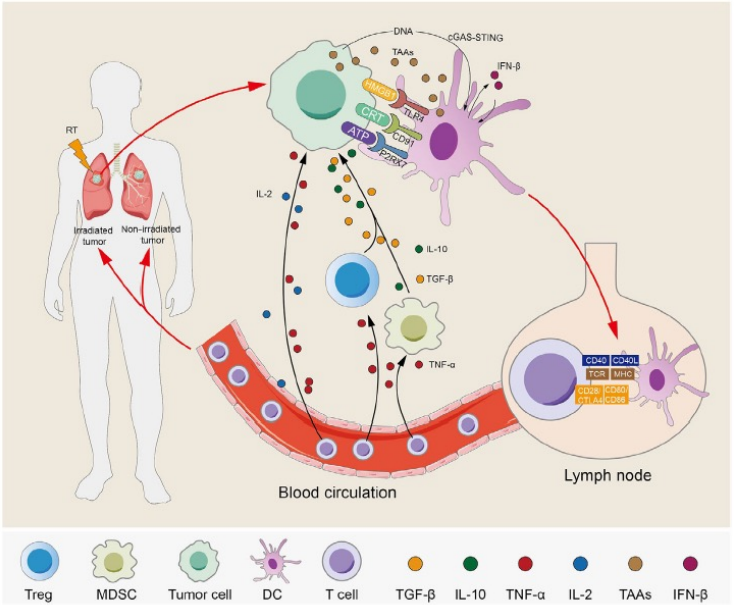
LS-SCLC (CCRT + IO)

Durvalumab with chemoradiotherapy for limited-stage small-cell lung cancer

Sehhoon Park [a,1], Jae Myoung Noh [b,1], Yoon-La Choi [c], Sang Ah Chi [d], Kyunga Kim [e], Hyun Ae Jung [a], Se-Hoon Lee [a], Jin Seok Ahn [a], Myung-Ju Ahn [a], Jong-Mu Sun [a,*]



Radiotherapy-induced effects on tumor cells



- In-situ vaccination effect
- Abscopal effect
- Bystander effect
- Immunosoppressive effect
  - PD-L1 upregulation
  - T cells exhaustion
  - Lymphocytes depletion
  - Myeloid-derived suppressor cells
  - T-reg proliferation

Shang S, Canc Comm, 2021

Doses and fractionations

HDFI (High dose per fraction irradiation)

- Usually, for early-stage and oligometastatic NSCLC, ablative doses are preferred
- Tumoral antigens releasing and priming T cells is dose-dependent (8 Gy better than 2 Gy for single fraction)
- SRT 3 x 8 Gy better than 5 x 6 Gy or 1 x 20 Gy for inducing abscopal effect

1° challenge: Is tumoricidal irradiation absolutely required for localized disease when HDFI and IO are combined?

Golden BE, Oncoimmunology 2017
Morisada M, Oral Oncol, 2017
Dewan MZ, Clin Cancer Res, 2009

Doses and fractionations

Conventional fractionation

- IO as consolidative agent after CHT-RT for unresectable LA-NSCLC (1.8-2 Gy x 30-33)
- 2.5-4 Gy per fraction could reduce the amount of blood passing through the beam and thus the duration and severity of lymphopenia and T-cells suppression
  - Increasing toxicity
  - Low synergistic effect by mild hypofractionation and IO

2° challenge: Could de-escalated hypofractionated RT in combination to IO represent a new approach for stage III NSCLC?

Tang C, IJROBP, 2014
Zhao Q, Radiat Onco, 2019
Fenwick JD, IJROBP, 2020
Jeong J, Clin Cancer Res, 2017

Doses and fractionations

LDI (Low Dose Irradiation)

- 0.5-2 Gy for 1 o few fractions potentially increase the immunogenicity (Klug F, Cancer Cell, 2013)
  - Induction T-reg apoptosis
  - Promotion of M1 macrophages phenotype (iNOS+) able to normalize tumor vasculature and to induce TILs
- Preclinical data (Yin L, IJOBP, 2020)
  - HDFI of the primary tumor + LDI of the abscopal effect + anti-PD-L1 achieves the best response, compared to HDFI + anti PD-L1, HDFI +LDI or LDI + anti-PD-L1 (mouse model)
- Clinical data (Menon H, J Immunother Canc, 2019 – Welsh JW, Cancer Immunol Res, 2019)
  - response of non-target lesions that received LDI (mainly scatter dose) compared to no dose lesions (<1 Gy)
  - Intentional LDI (range 2-8 Gy/2 fr to 1 lesion) +ICI + HDFI →28,2% shrinking on the low dose treated lesion

3° challenge: Would a combined approach of LDI and HDFI be feasible in the context of a RT - IO combination?

Volumes

Reduction of irradiated tissue volume

- Sparing of tumor-associated lymphocytes from peri-tumoral TME could lead a pro-immunogenic effect by sparing effector TILs (highly radiosensitive) and suppression of intra-tumoral T-reg
- IGRT or gating/tracking strategies to reduce PTV

4° challenge: Could CTV be omitted in the context of RT-IO?

Boivin G, Front Oncol, 2018
Muroyama Y, Cancer Immunol Res, 2017
Arina A, Nat Commun, 2019
Wilkins RC, Mutat Res, 2002
Grayson JM, J immunol, 2002

Volumes

Partial Tumor Volume Irradiation (PTVI)

- Deliberate exclusion of a part of tumor from the irradiation (i.e. large tumor close to OAR)
- Preclinical data (Markovsky E, IJROBP, 2019)
  - In 2 murine models, doses of 10 Gy, 15 Gy or 20 Gy delivered to 50% to PTVI or to full volume led the similar response
- Clinical data (Lemons JM, IJROBP, 2017)
  - NRG-BR001 phase 1 trial of SRT (3x15Gy, 5x10 Gy, 3x10 Gy) + Anti-PD-L1, similar local control in partially irradiated large tumors an fully irradiated small tumors
- However, the "non-irradiated" portion receives non-tumoricidal but scattered doses that could be sufficient to elicit an immune response.

5° challenge: Does Adscopal effect or bystander effect depend on LDI or PTVI?

Volumes

Multi-target irradiation

- Radiation-mediated immunogenicity differs according to the target/organ due to the differences TME (antigenic load, abundance of innate immune cells and lymphocytes)
- Liver and lung sites are better than bone and brain ones to enhance peripheral T-cell activation (McGee HM, IJROBP, 2018)
- Multi-target irradiation can potentiate the distruction of subclonal population and act through the differences in immunogenicity
- A high tumor burden is a source of persistent antigen exposure, so the maximal reduction in tumor burden would lead to a decrease in T-cell exhaustion due to persistent antigen exposure (Wherry WJ, Nat Rev Immunol, 2015)

6° challenge: Is multi-target irradiation a possible strategy to increase "reinvigoration-to-tumor burden» ratio?

Organs at risk

Radiation-induced lymphopenia (RILP)

- Lethal doses to reduce the surviving fraction of circulating CD4+ and CD8+ T lymphocytes by 90%, 50% and 10% are only 3Gy, 2 Gy and 0.5 Gy, respectively (96)
- All factors leading to prolonged RT duration will increase the amount of blood passing through the beam and could potentially increase the severity of RILP (43 116 117)
  - hyperfractionation with twice-daily fractions
  - a low-dose rate
  - irradiation of organs containing large blood volumes and/or with high blood flow velocity (heart, lungs spleen, large vessels, non-involved draining lymph nodes, bone marrow within spine)

7° challenge: Could RT techniques (FFF RT, stereotactic RT, proton RT, FLASH RT) reduce RILP?

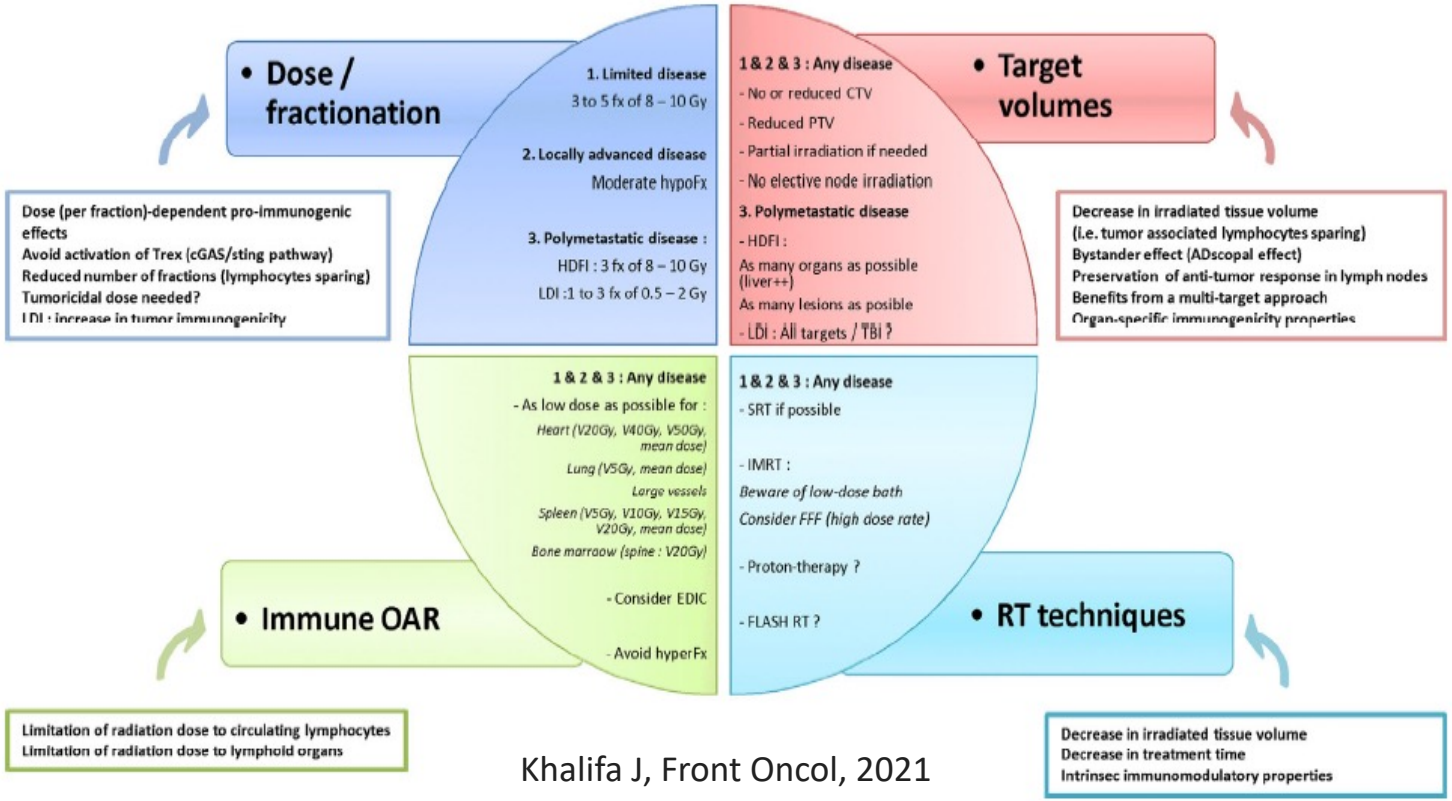
Nakamura N, Radiat Res, 1990
Saito T, Radiol Oncol, 2017
Yuan C, Clin Transl Oncol, 2018

Timing and Sequences

RT and IO combinations

- Anti-PD-L1 therapy seems to be more effective when administered concurrently with RT because act on newly activated and exhausted T cells
- Anti-CTLA-4 appears to have better synergy if administered before RT because act on naïve T cells
- Deliver RT every other day rather than consecutively could be better, based on the idea that it takes 48 h to replenish lymphocytes
- ***8° challenge: When are RT and IO really synergic?***

Buchbinder EI, Am J Clin Oncol Cancer Clin Trials 2016
Spranger S, Annu Rev Cancer Bio, 2018
Demaatria S, JAMA oncol, 2015



Khalifa J, Front Oncol, 2021

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- Xia WY, Feng W, Zhang CC, Shen YJ, Zhang Q, Yu W, Cai XW, Fu XL. Radiotherapy for non-small cell lung cancer in the immunotherapy era: the opportunity and challenge-a narrative review. Transl Lung Cancer Res. 2020 Oct;9(5):2120-2136. doi: 10.21037/tlcr-20-827. PMID: 33209631; PMCID: PMC7653139.
- Luna J, Zafra J, Areses Manrique MC, Rodríguez A, Sotoca A, Fírvida JL, Chicas-Sett R, Mielgo X, Reyes JCT, Couñago F. New challenges in the combination of radiotherapy and immunotherapy in non-small cell lung cancer. World J Clin Oncol. 2021 Nov 24;12(11):983-999. doi: 10.5306/wjco.v12.i11.983. PMID: 34909394; PMCID: PMC8641011.
- Khalifa J, Mazieres J, Gomez-Roca C, Ayyoub M, Moyal EC. Radiotherapy in the Era of Immunotherapy With a Focus on Non-Small-Cell Lung Cancer: Time to Revisit Ancient Dogmas? Front Oncol. 2021 Apr 21;11:662236. doi: 10.3389/fonc.2021.662236. PMID: 33968769; PMCID: PMC8097090.
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