NBTXR3 nanoparticle with immunoradiation improves survival and generates long-term anti-tumor immune memory in an anti-PD1 resistant murine lung cancer model

Yun Hu[1], Sébastien Paris[2], Hampartsoum Barsoumian[1], Chike O. Abana[1], Sezen Duygu[1], Kewen He[1,3], Mark Wasley[1], Fatemeh Masrorpour[1], Dawei Chen[1,3], Liangpeng Yang[1], Joe D. Dunn[1], Saumil Gandhi[1], Quynh-Nhu Nguyen[1], Maria Angelica Cortez[1], James Welsh[1*]

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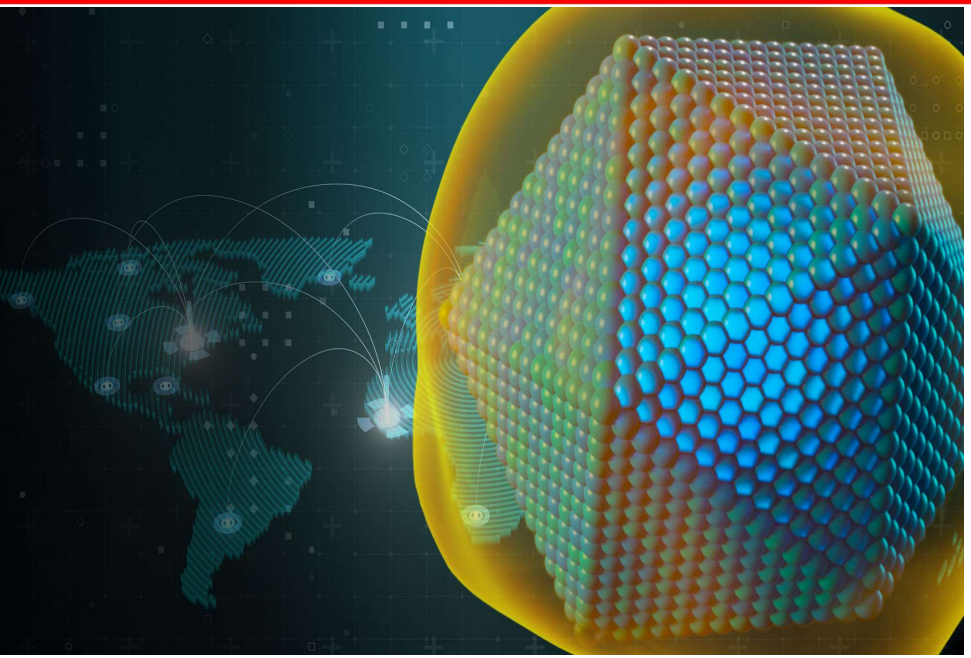
NBTXR3- A Novel Radioenhancer



- NBTXR3, a novel radioenhancer composed of functionalized hafnium oxide nanoparticles, is administered by a one-time ITI and activated by RT, such as SBRT/IMRT.
- NBTXR3 is designed to increase the radiotherapy energy deposit inside tumor cells and subsequently increases tumor cell death compared to radiotherapy alone.
- The physical and universal MoA of NBTXR3 is designed to trigger cellular destruction and prime an adaptive immune response.

Bonvalot S, Rutkowski PL, Thariat J, et al. *Lancet Oncol*. 2019;20:1148-59; Marill J, Mohamed Anesary N, Paris S. *Radiother Oncol.* 2019;141:262-266; Zhang P, Darmon A, Marill J, et al. *Int J Nanomedicine*. 2020;15:3843-3850.

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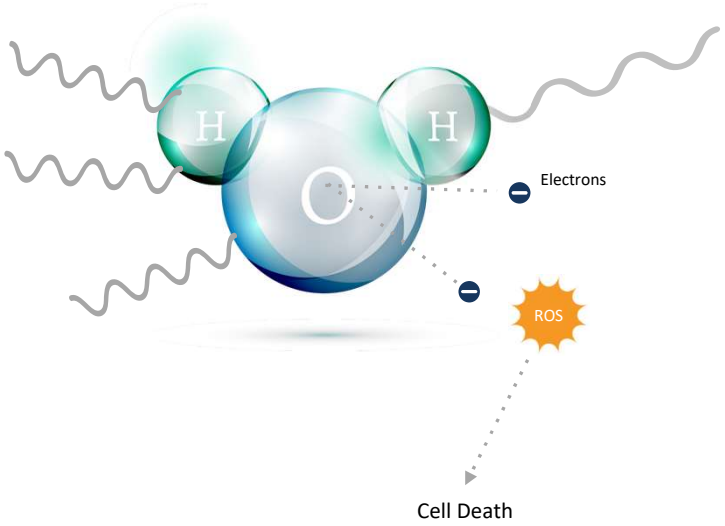
NBTXR3- Universal Mode of Action (MoA)

Radiotherapy (RT) Alone



Interaction of X-rays with water molecules in tumor cells generates electrons and secondary photons, generating reactive oxygen species (ROS; oxidative stress), DNA damage, leading to subsequent cell death.

Maggiorella L, et al. *Future Oncol.* 2012;8(9):1167-1181. In House Data.

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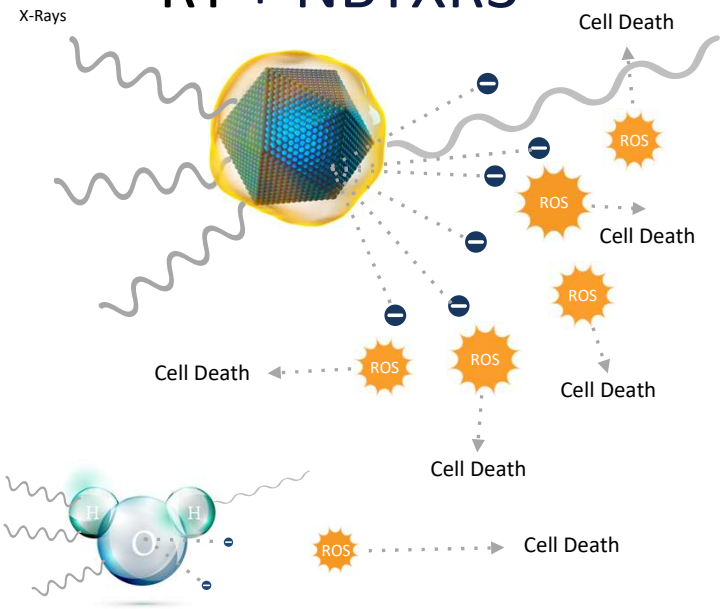
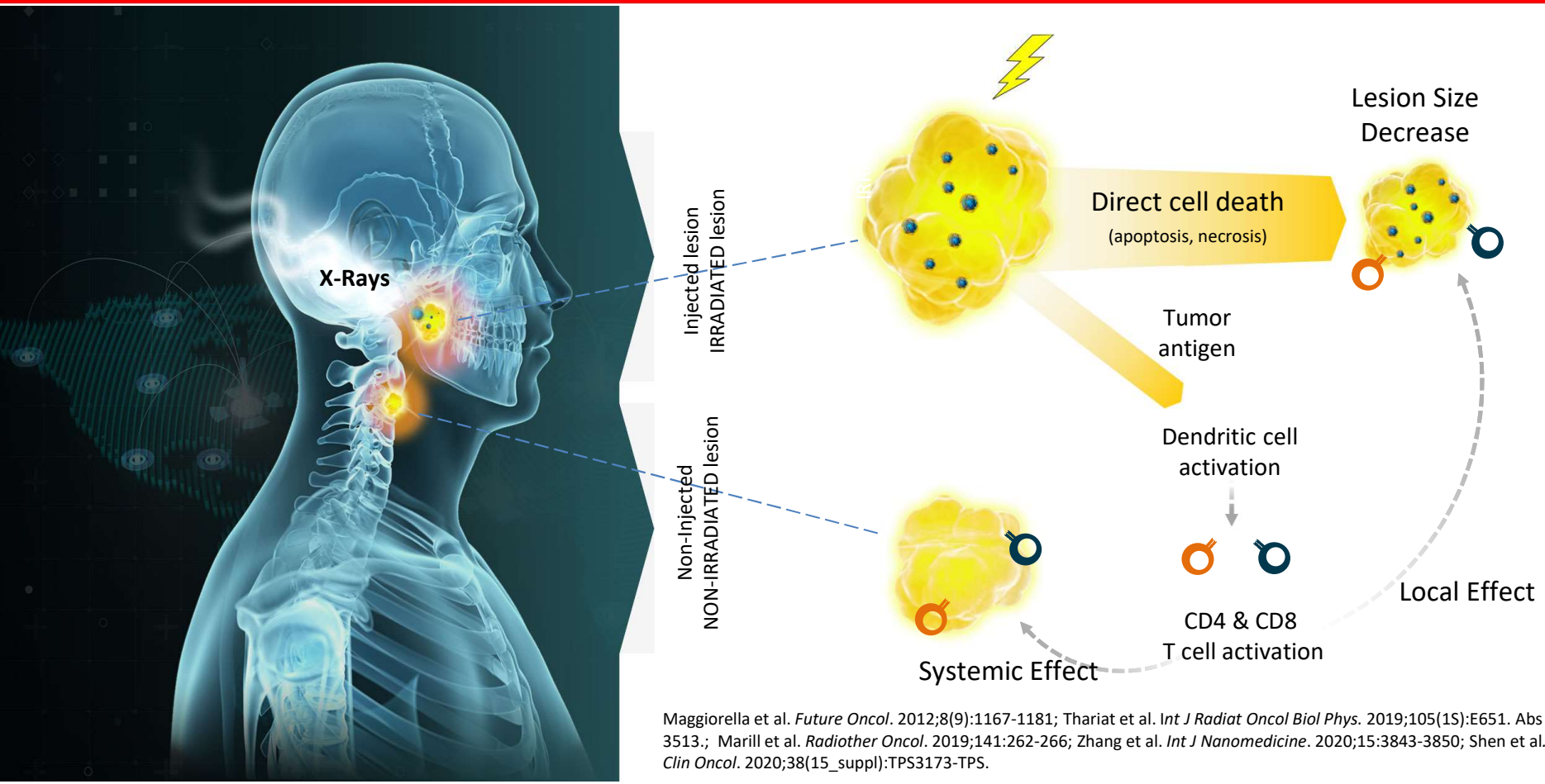
RT + NBTXR3



Interaction of X-rays with high electron density nanoparticles is higher and generates many more electrons and oxidative stress, and *in vitro* data suggests cells are killed more efficiently.

NBTXR3- Potential for Local and Systemic Control



Maggiorella et al. *Future Oncol*. 2012;8(9):1167-1181; Thariat et al. I*nt J Radiat Oncol Biol Phys.* 2019;105(1S):E651. Abs 3513.; Marill et al. *Radiother Oncol*. 2019;141:262-266; Zhang et al. *Int J Nanomedicine*. 2020;15:3843-3850; Shen et al. *J Clin Oncol*. 2020;38(15_suppl):TPS3173-TPS.

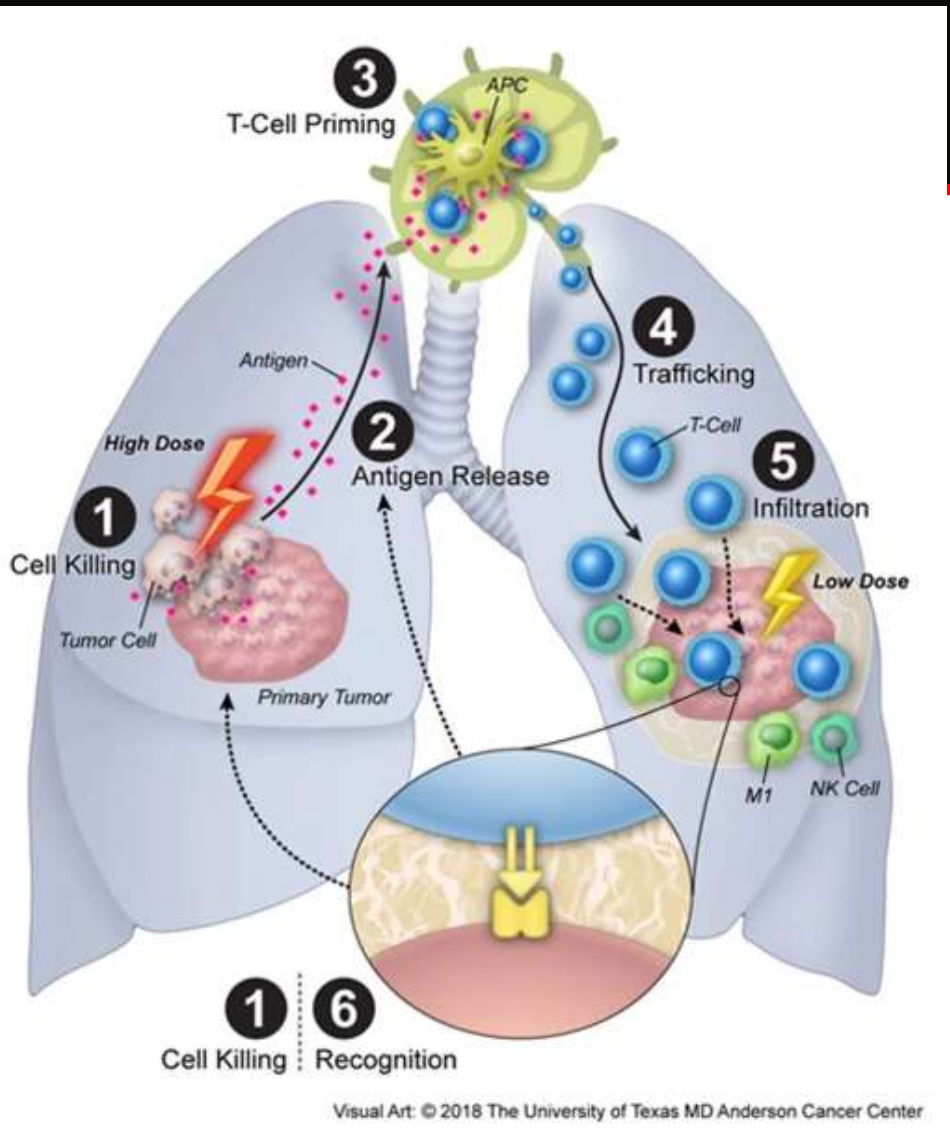
RadScopal™ Background

High-dose XRT

- Helps prime T-cells at primary tumor site
- Antigen release
- DAMPs release
- Upregulation of MHC-I
- Upregulation of Tregs, TGF-β, and MDSCs

Low-dose XRT

- Modulate the stroma of secondary tumors to increase the infiltration of T-cells and NK cells
- Polarize TAMs to M1
- Downregulate TGF-β



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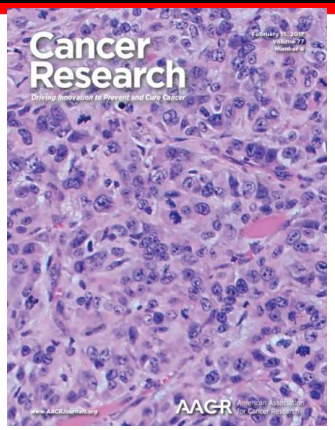
Menon and Welsh et al. J Immunother Cancer. 2019, Volume 7, Article number: 237
Barsoumian and Welsh et al. J Immunother Cancer. 2020, Oct;8(2):e000537

Development of anti-PD1 resistant metastatic lung cancer model in Welsh Lab



Published OnlineFirst November 7, 2016; DOI: 10.1158/0008-5472.CAN-15-3142

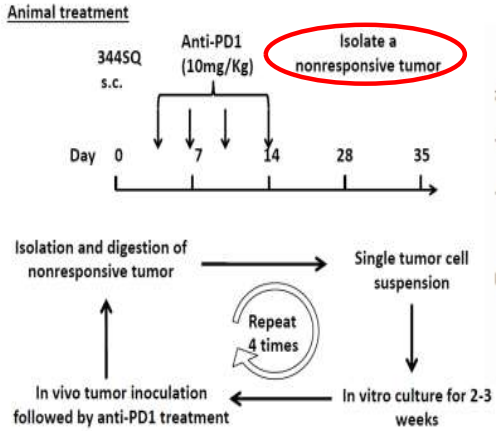
Microenvironment and Immunology

Cancer Research

Suppression of Type I IFN Signaling in Tumors Mediates Resistance to Anti-PD-1 Treatment That Can Be Overcome by Radiotherapy

Xiaohong Wang[1], Jonathan E. Schoenhals[1], Ailin Li[1], David R. Valdecanas[1], Huiping Ye[2], Fenglin Zang[3], Chad Tang[4], Ming Tang[5], Chang-Gong Liu[6], Xiuping Liu[6], Sunil Krishnan[4], James P. Allison[7], Padmanee Sharma[8], Patrick Hwu[9], Ritsuko Komaki[4], Willem W. Overwijk[10], Daniel R. Gomez[4], Joe Y. Chang[4], Stephen M. Hahn[4], Maria Angelica Cortez[1], and James W. Welsh[4]

A



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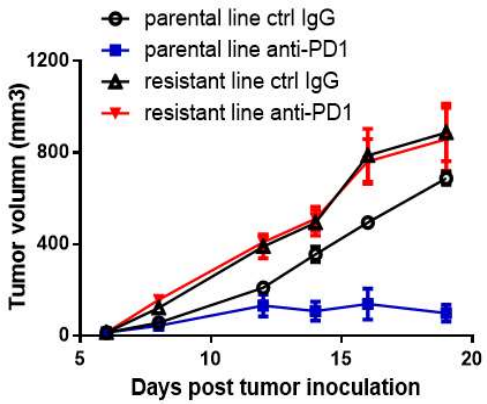

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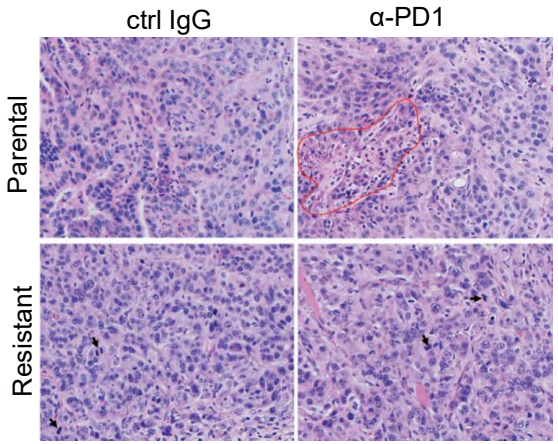

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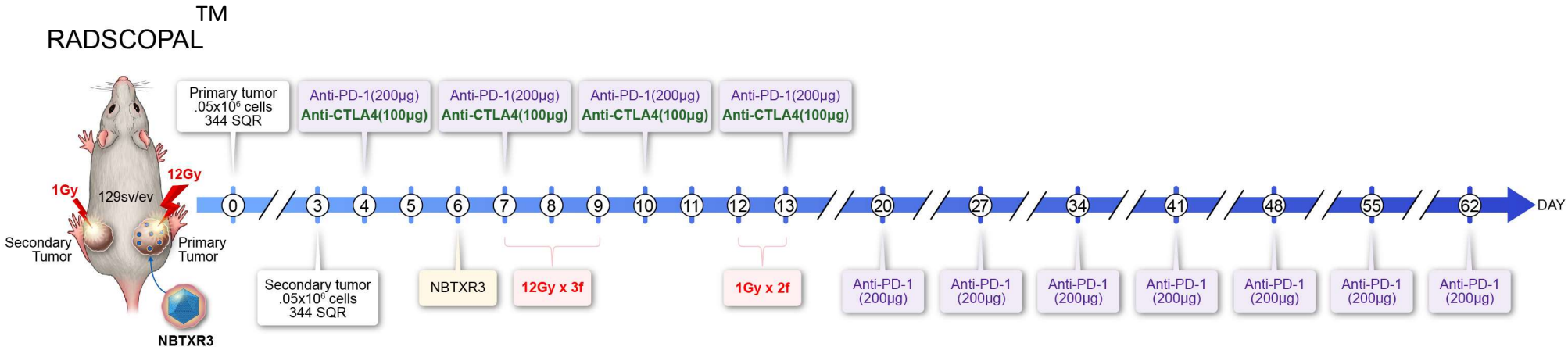
NBTXR3+RadScopal™ Radiation+checkpoint inhibition



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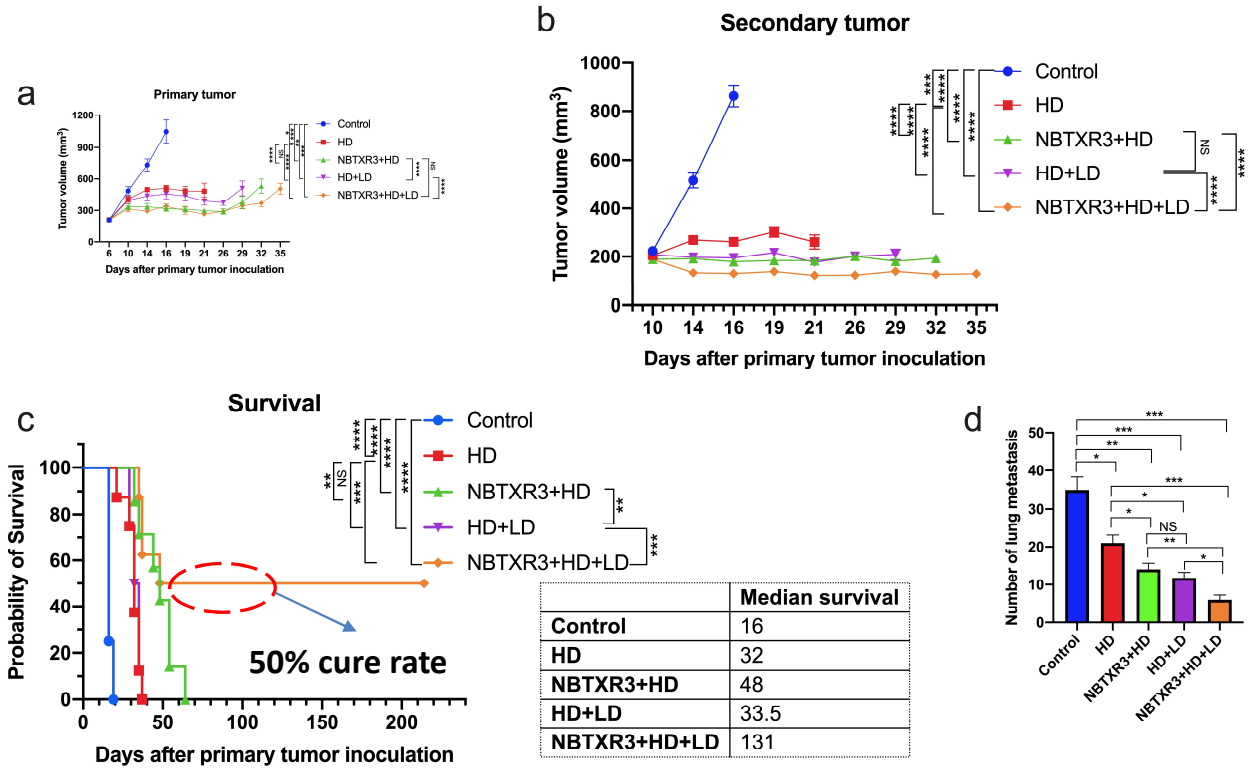
NBTXR3+RadScopal™+checkpoint inhibition improves treatment outcomes



	Median survival
Control	16
HD	32
NBTXR3+HD	48
HD+LD	33.5
NBTXR3+HD+LD	131

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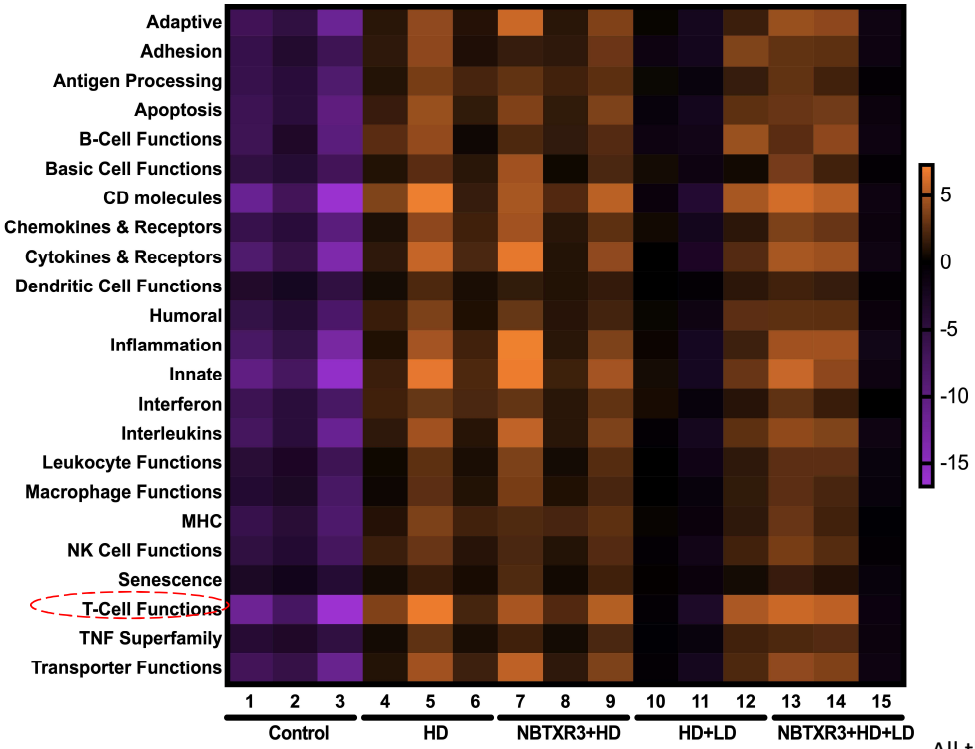
HD: High dose radiation
LD: Low dose radiation

All the treatment groups except the control group received both anti-PD1 and anti-CTLA-4

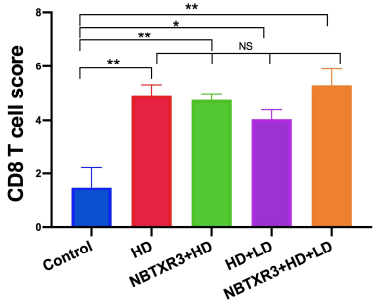
NBTXR3 upregulates activities of anti-tumor immune pathways in secondary tumors

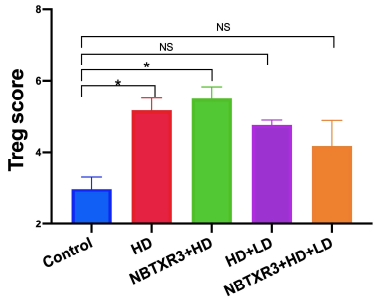
a



HD: High dose radiation
LD: Low dose radiation

b





All the treatment groups except the control group received both anti-PD1 and anti-CTLA-4

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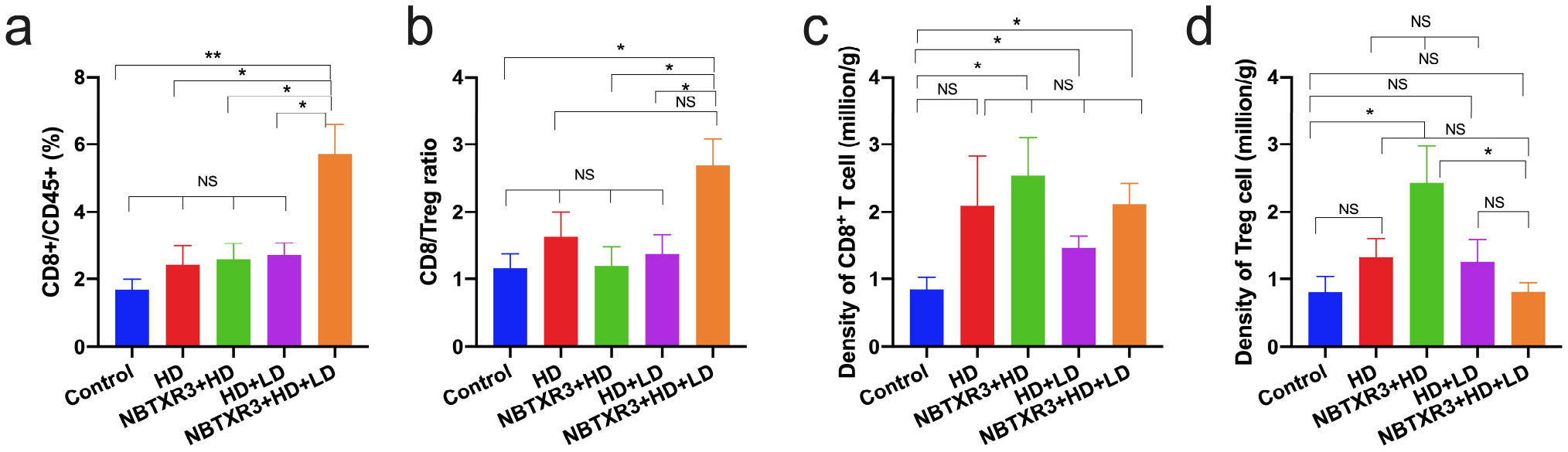
NBTXR3+RadScopal™+checkpoint inhibition upregulates CD8 T cells and downregulates Treg cells in secondary tumors



HD: High dose radiation
LD: Low dose radiation

All the treatment groups except the control group received both anti-PD1 and anti-CTLA-4

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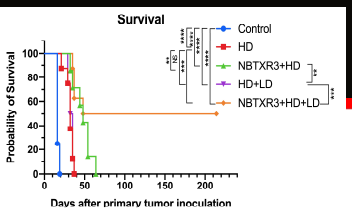
NBTXR3+RadScopal™+checkpoint inhibition maintains long-term anti-tumor memory response



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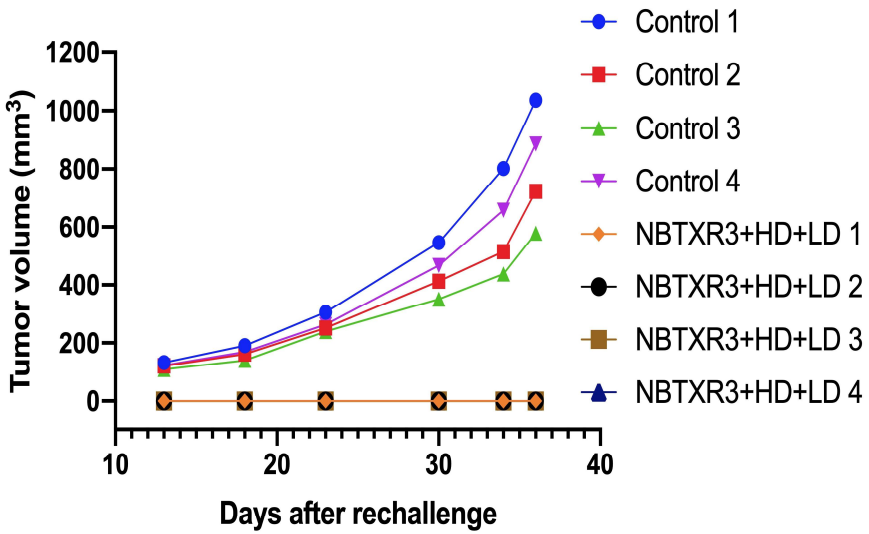

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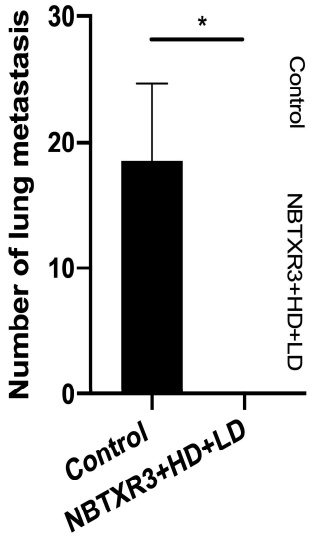

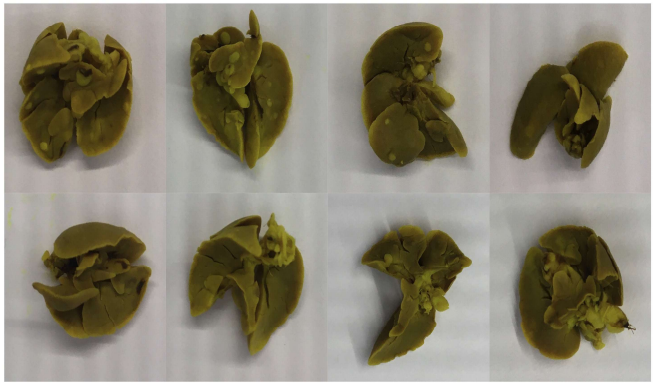

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The survivor mice in NBTXR3+HD+LD group were re-injected with 344SQR cells 165 days post radiotherapy.

HD: High dose radiation
LD: Low dose radiation

NBTXR3+RadScopal™+checkpoint inhibition produces potent immune memory

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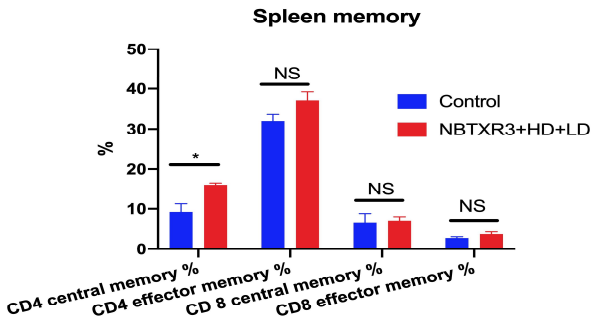

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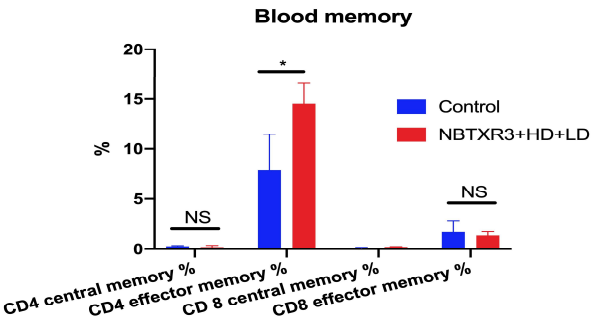

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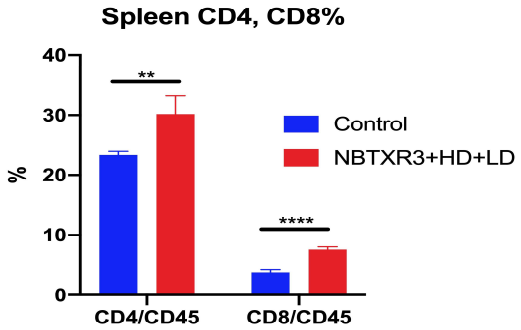

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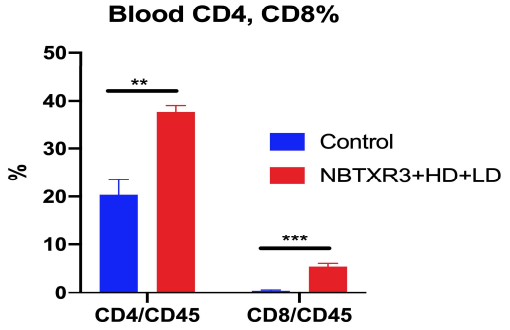

HD: High dose radiation
LD: Low dose radiation

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Conclusions

- NBTXR3+RadScopal™+checkpoint inhibition significantly improves the control of both the primary and secondary tumors, extends survival, and reduces lung metastases in an anti-PD1 resistant lung cancer model.

- NBTXR3+RadScopal™+checkpoint inhibition promotes anti-tumor response at both molecular and cellular levels.

- NBTXR3+RadScopal™+checkpoint inhibition produces long-term anti-tumor immune memory.

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Take home messages

- Timing and dose of radiation might be optimized to further improve the treatment efficacy.
- Other immunotherapies, including anti-Lag3, anti-TIGIT might be incorporated to the treatment.
- In-depth analysis of the genetic makeup of tumors in patients might be needed for selecting the tumor for receiving high dose and low dose radiation.

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