FLT3 Ligand (CDX-301) and Stereotactic Radiotherapy for Advanced Non-Small Cell Lung Cancer

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Disclosures

- **N. Ohri:** None
- **B. Halmos:** None
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- **C. Guha:** None

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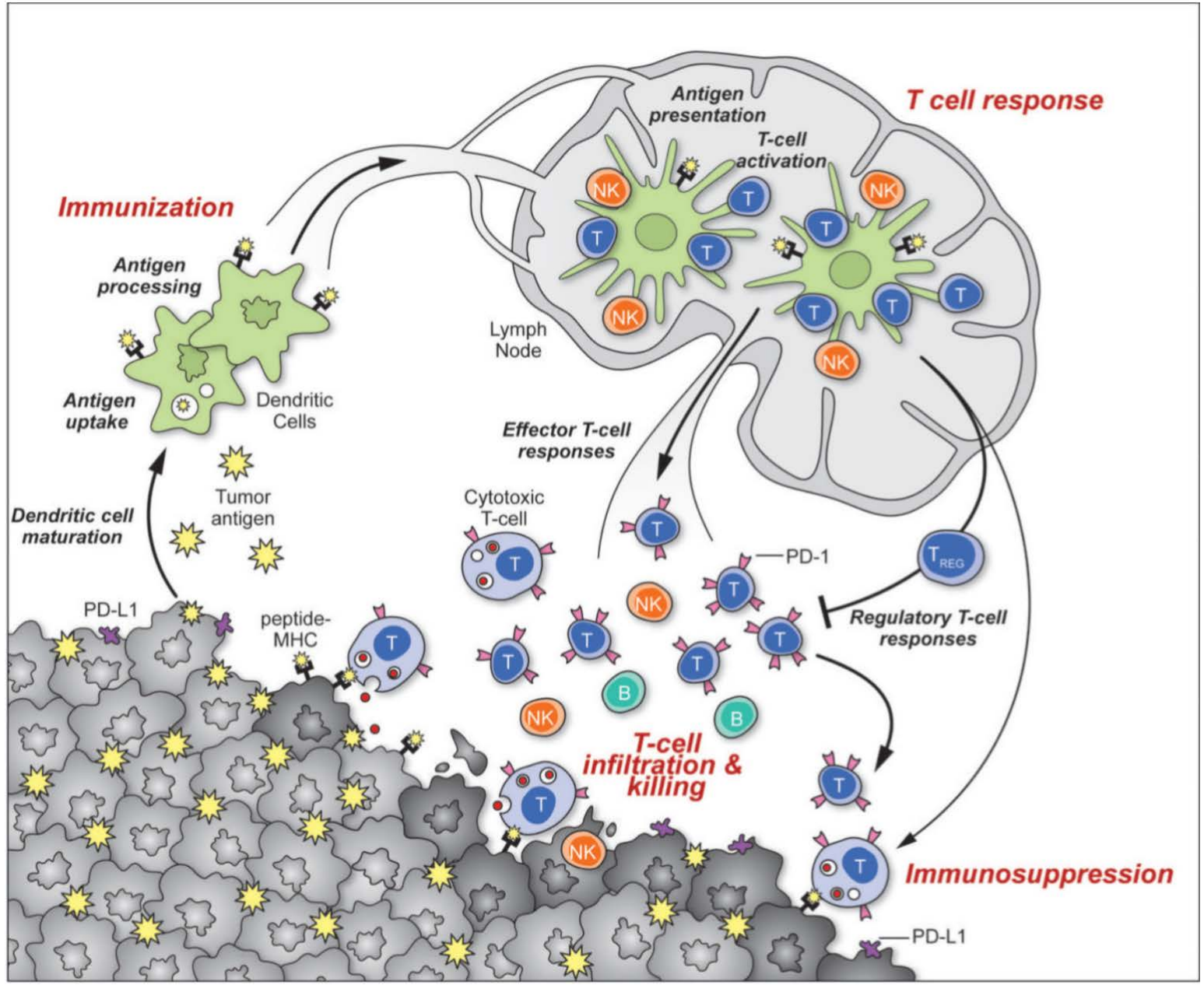
T cell response
Antigen presentation
T-cell activation
Immunization
Antigen processing
Antigen uptake
Dendritic Cells
Lymph Node
Effector T-cell responses
Dendritic cell maturation
Tumor antigen
Cytotoxic T-cell
PD-1
Regulatory T-cell responses
PD-L1
peptide-MHC
T-cell infiltration & killing
Immunosuppression
PD-L1

Flt3-Ligand Administration after Radiation Therapy Prolongs Survival in a Murine Model of Metastatic Lung Cancer

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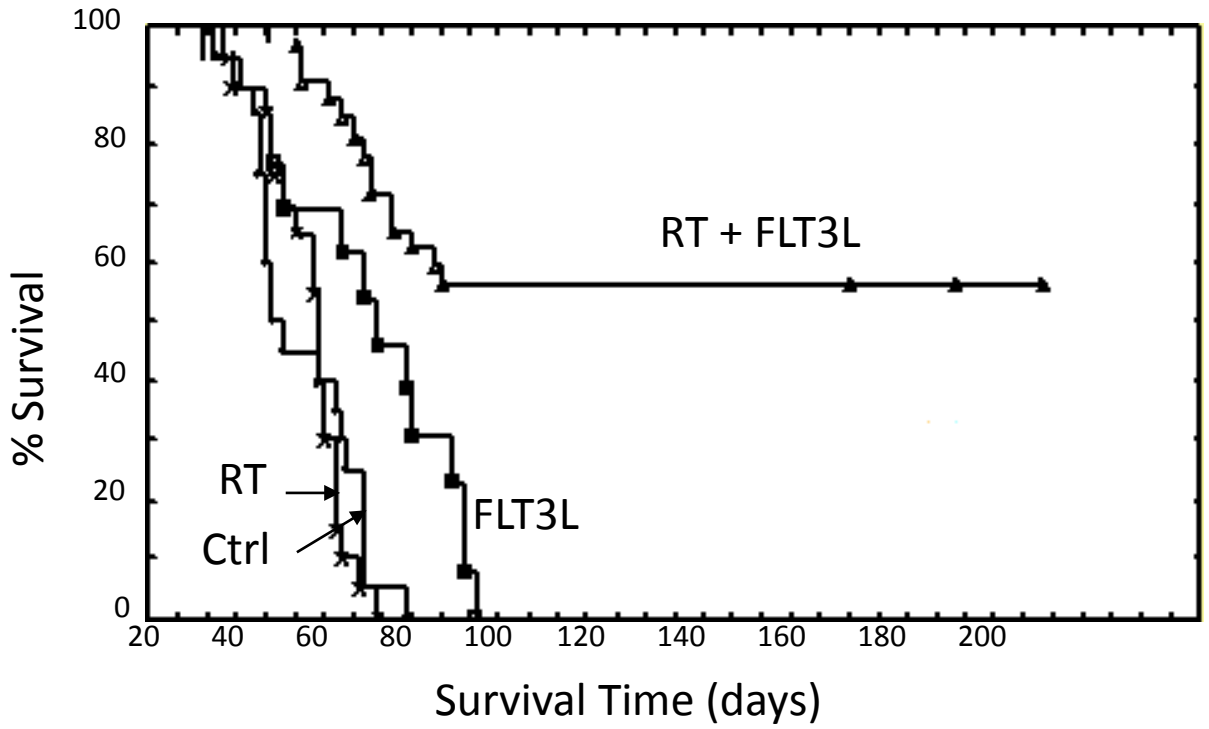
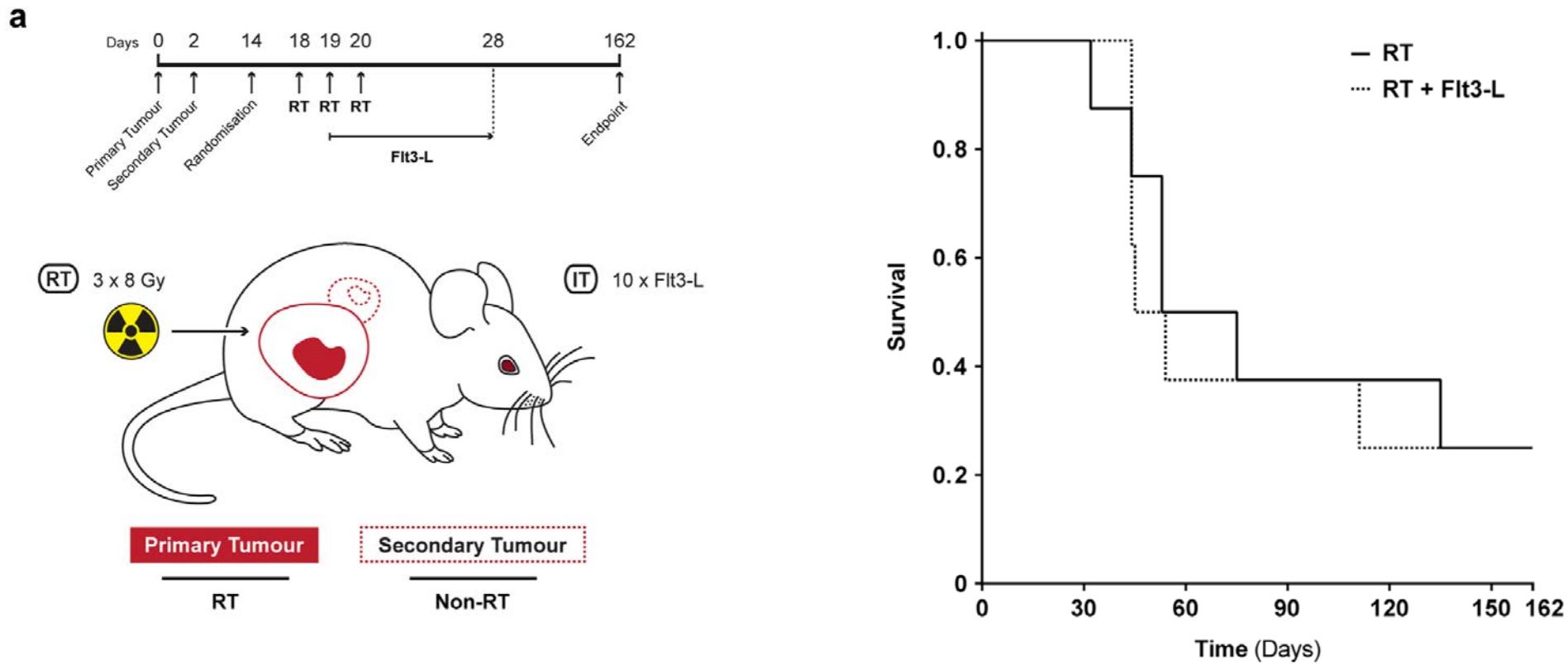
- Established 3-week-old Lewis lung tumors
- RT: **60 Gy** to primary tumor
- FLT3L: 500 μg/kg/day × 10 days, initiated one day after RT
- Combined treatment
  - induced primary and memory tumor-specific immune response
  - prevented lung metastasis
  - prolonged survival



CANCER RESEARCH 59, 6028–6032, December 15, 1999

Fractionated Radiotherapy with 3 x 8 Gy Induces Systemic Anti-Tumour Responses and Abscopal Tumour Inhibition without Modulating the Humoral Anti-Tumour Response

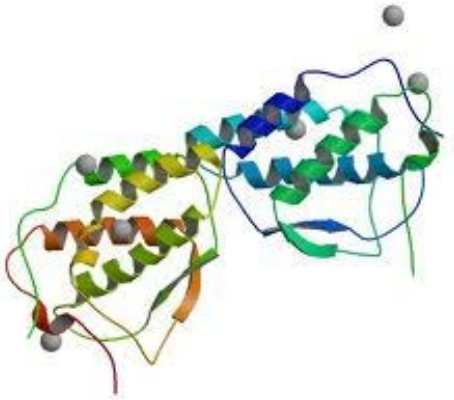
Thomas H. P. M. Habets[1,2], Tammy Oth[1], Ans W. Houben[1,3], Mirelle J. A. J. Huijskens[1], Birgit L. M. G. Senden-Gijsbers[1], Melanie C. A. Schnijderberg[1], Boudewijn Brans[3], Ludwig J. Dubois[4], Philippe Lambin[4], Marijke De Saint-Hubert[3], Wilfred T. V. Germeraad[1,5], Marcel G. J. Tilanus[2], Felix M. Mottaghy[3], Gerard M. J. Bos[1,5☯], Joris Vanderlocht[2☯*]



Sub-ablative radiation with FLT3L did not improve survival.

PLoS One. 2016 Jul 18;11(7):e0159515.

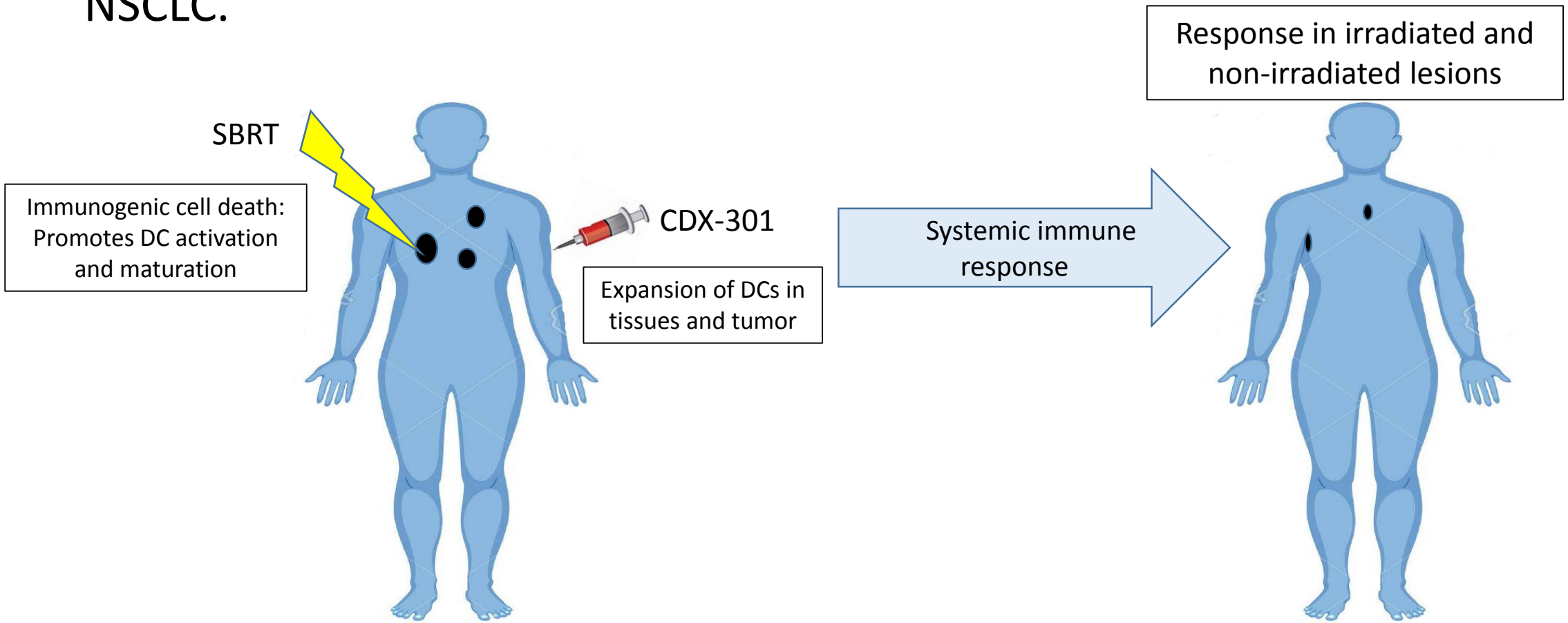
CDX-301 (FLT3 ligand) Background



- Fms-like tyrosine kinase-3 ligand (FLT3L) uniquely binds CD135 (FLT3 receptor) and induces proliferation, differentiation, and mobilization of hematopoietic stem cells, early progenitor cells, and dendritic cells (DCs)
  - Key regulator of DCs inducing marked increases in both myeloid and plasmacytoid DCs
- CDX-301 is the soluble recombinant human protein form of FLT3L.
- Clinical experience (studies by Immunex and Celldex)
  - >500 subjects treated, including >300 cancer patients
    - No significant safety issues
    - 10 to 100+ fold increase in DCs (including CD141+ DCs)
    - Augments humoral and T cell response to NY-ESO-1 vaccine
    - No clear activity as monotherapy in advanced cancer patients

Study Hypothesis

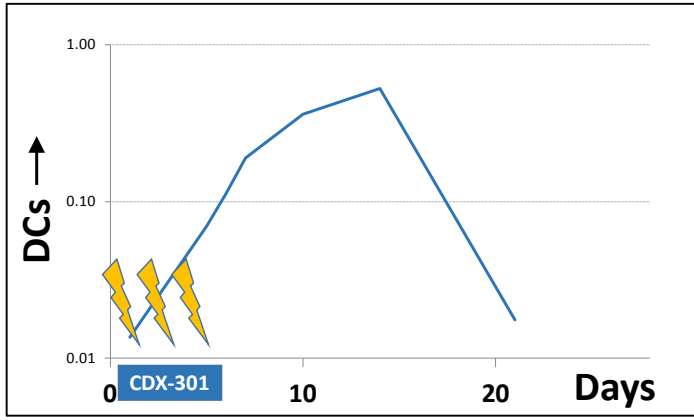
- The combination of stereotactic body radiotherapy (SBRT) to a single pulmonary lesion and CDX-301 will have clinical activity in advanced NSCLC.



Key Eligibility Criteria

- AJCC stage 3 or 4 histologically proven NSCLC not amenable to curative therapy
- Prior treatment with at least one standard chemotherapy regimen or targeted agent prior to enrollment
- Measurable disease that includes:
  - at least one pulmonary lesion ≥ 1 cm in greatest dimension that would be amenable to SBRT
  - at least one measurable lesion that would be outside of the SBRT treatment fields
- ECOG performance status 0-2
- No untreated central nervous system metastases.
- No ongoing or recent use of high dose oral corticosteroids.
- No history of allogeneic organ transplant or autoimmune disease.

Study Design



- One-week treatment course:
  - 5 daily subcutaneous injections of CDX-301 (75 µg/kg)
  - Stereotactic body radiotherapy (SBRT) to a single thoracic lesion
    - Peripheral tumor ≤ 2 cm and > 1 cm from chest wall — **34 Gy x 1 fraction = 34 Gy**
    - Peripheral tumor ≤ 5 cm and not eligible for 34 Gy x 1 — **18 Gy x 3 fractions = 54 Gy**
    - Other thoracic lesions — **10 Gy x 5 fractions = 50 Gy**
- Sample size: 29 patients

	Pre-tx	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Weeks 16, 24, 31
Stereotactic Radiotherapy (SBRT)		XXX								
CDX-301		XXXXX								
History and Physical Examination	X	X	X	X	X		X		X	X
CBC, CMP	X	X	X	X	X		X		X	X
Whole body PET/CT	X								X	X
Immune Correlates	X		X		X				X	

No additional treatment until disease progression

Endpoints

- Primary endpoint: Progression-free survival 4 months after treatment initiation (PFS4)
  - Scored using Immune-related response criteria (irRC)[1]
  - H0: PFS4 ≤ 20%[2,3] H1: PFS4 ≥ 40.5%
  - Accept H1 if PFS4 is achieved in 10/29 subjects
- Secondary endpoints:
  - Adverse events / Dose-limiting toxicities
  - Overall Survival
  - Radiographic responses in lesions <u>not treated with SBRT</u>
    - CT: irRC[1]
    - PET: PERCIST[4]
      - Total Glycolytic Activity (TGA): volumetric sum of activity in all hypermetabolic lesions
      - Partial Metabolic Response (PMR): Decrease in TGA of at least 45%

1 - Clin Cancer Res 2009;15(23):7412-20
2 - J Clin Oncol 2010;28(13):2167
3 - BMC cancer 2010;10(1):633
4 - J Nucl Med 2009;50:122S-150S

Patient Characteristics (n=9)

- 9 subjects enrolled between October 2016 and September 2017
- 7/9 previously treated with anti-PD-(L)1 therapy
  - 5 with documented progression on anti-PD-(L)1 therapy
  - Median interval from anti-PD-(L)1 therapy termination to study enrollment: 3 months

Gender, n	
Male	4
Female	5
Age, mean (range)	70 (54-81)
ECOG Performance Status, n	
0	0
1	3
2	6
Histology, n	
Adenocarcinoma	6
Squamous cell carcinoma	2
Mixed	1
PD-L1 expression	
0%	4
60%	1
75%	1
unknown	3
Previous lines of systemic therapy for advanced NSCLC, n	
1	1
2	4
3	4
Prior anti-PD-(L)1 therapy, n	7
SBRT schedule, n	
1 fraction	1
3 fractions	1
5 fractions	7

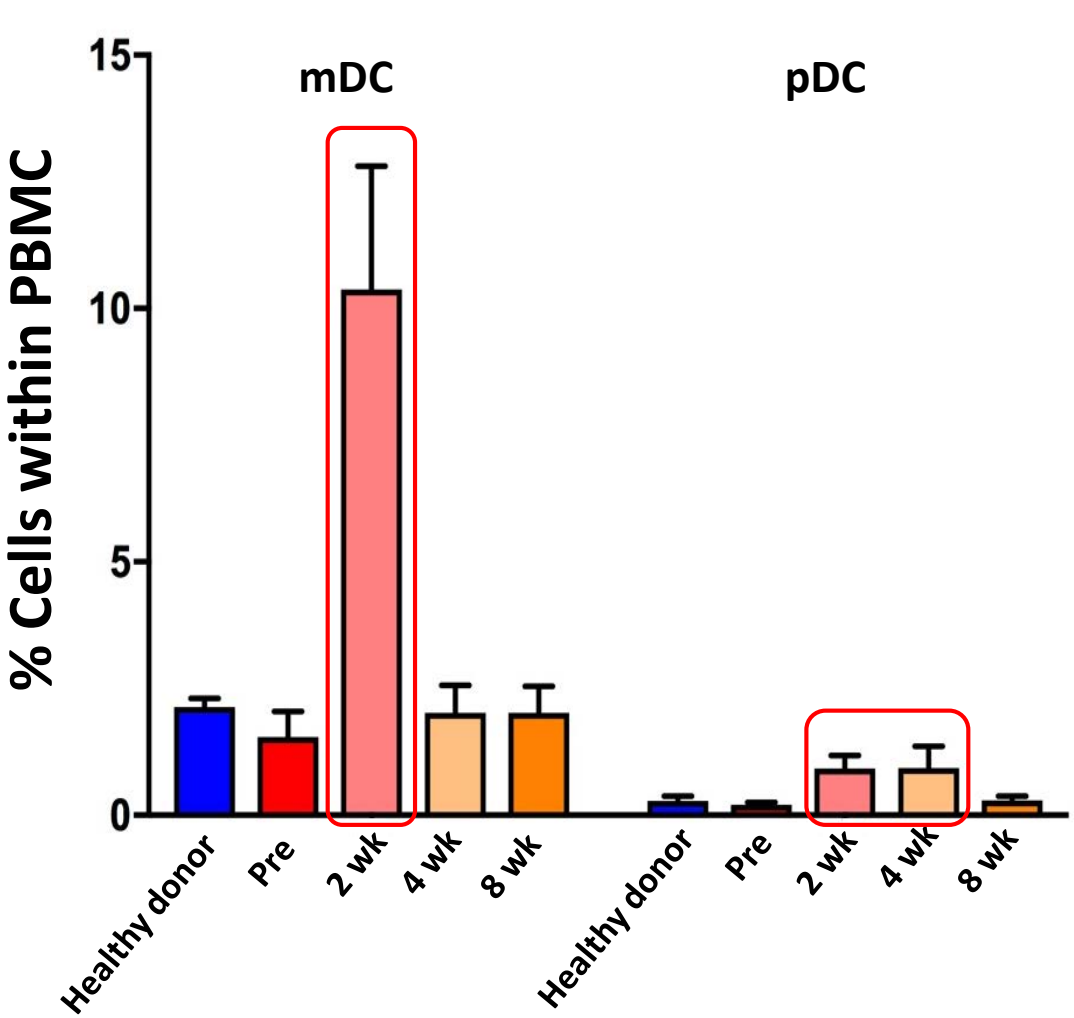
Adverse Events

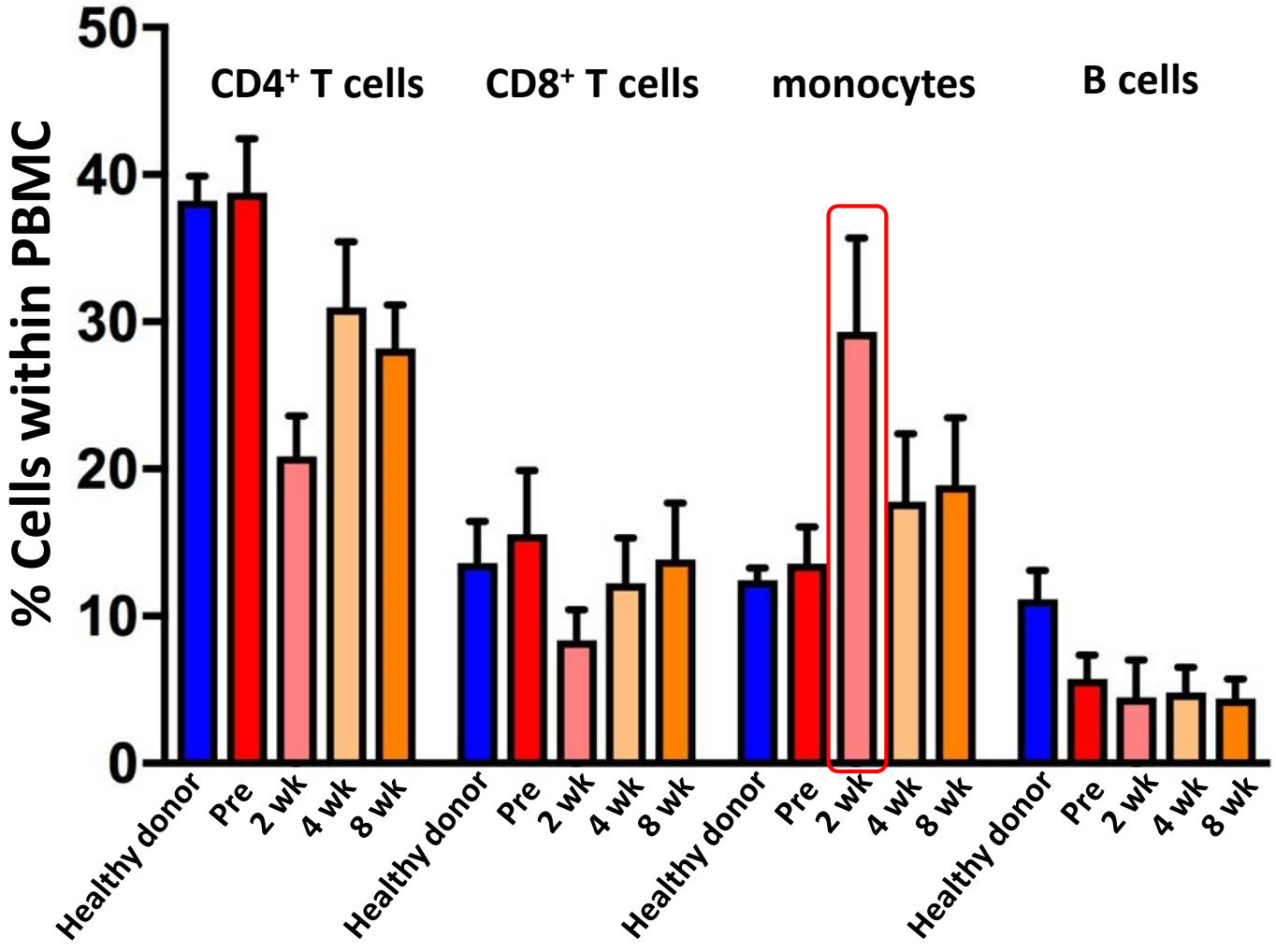
Possibly/probably related to study therapy, scored using CTCAE v 4.0

	Grade 1	Grade 2	Grade 3+
Cough	6	1	0
Dyspnea	0	1	0
Esophagitis	0	1	0
Fatigue	3	1	0

- No dose-limiting toxicities observed
- One case of delayed pneumonitis attributed to prior immune checkpoint inhibitor therapy

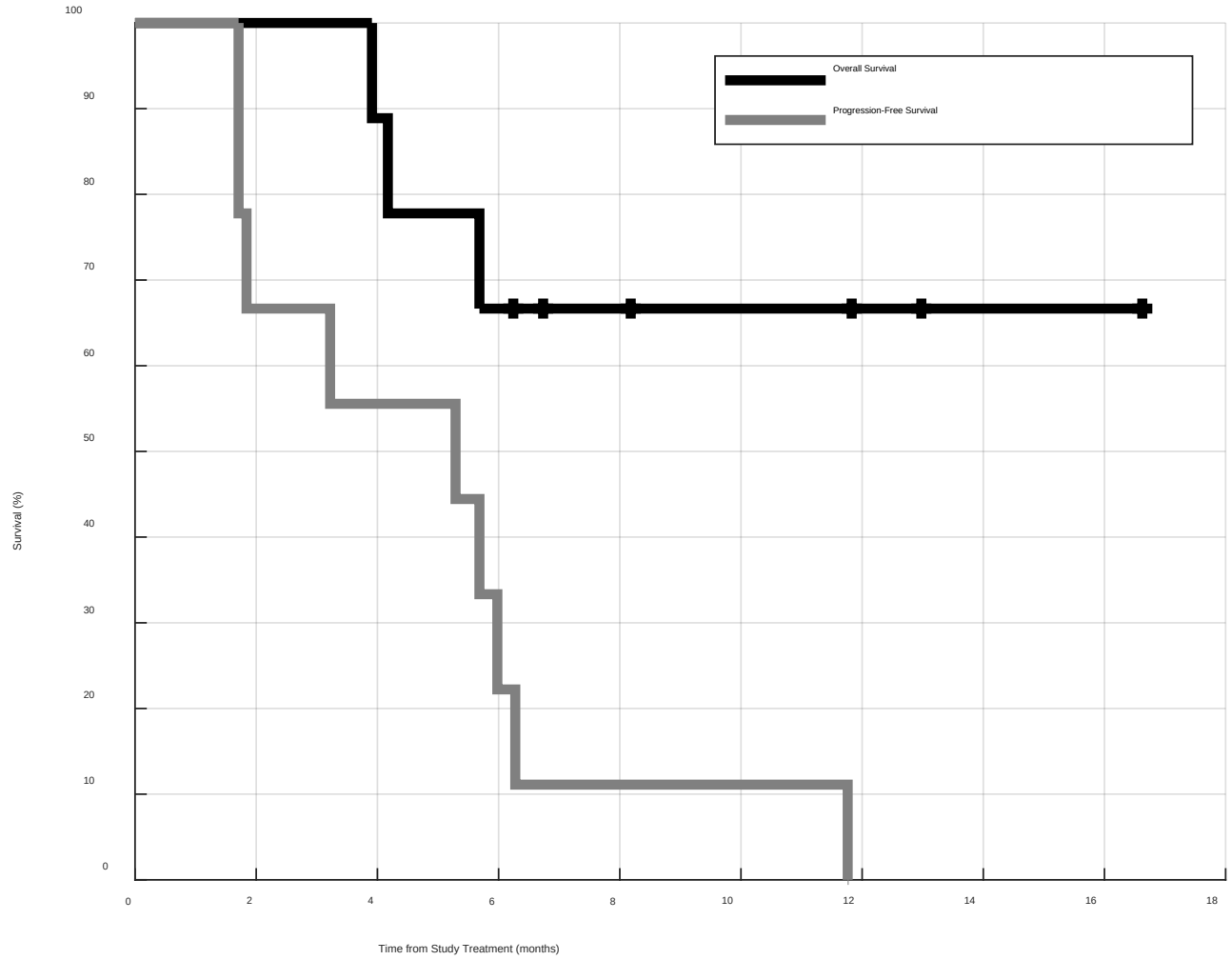
CDX-301 Increases DCs and Monocytes





Clinical Outcomes (n=9)

- PFS4 achieved in 5 subjects (based on CT/irRC)
- 6 subjects currently alive with disease
- 10 month median follow-up duration for surviving patients



Best Responses (excluding SBRT target): CT/irRC v. PET/PERCIST

	CT/irRC	PET/PERCIST
Partial Response	3	5
Stable Disease	3	1
Progressive Disease	3	3

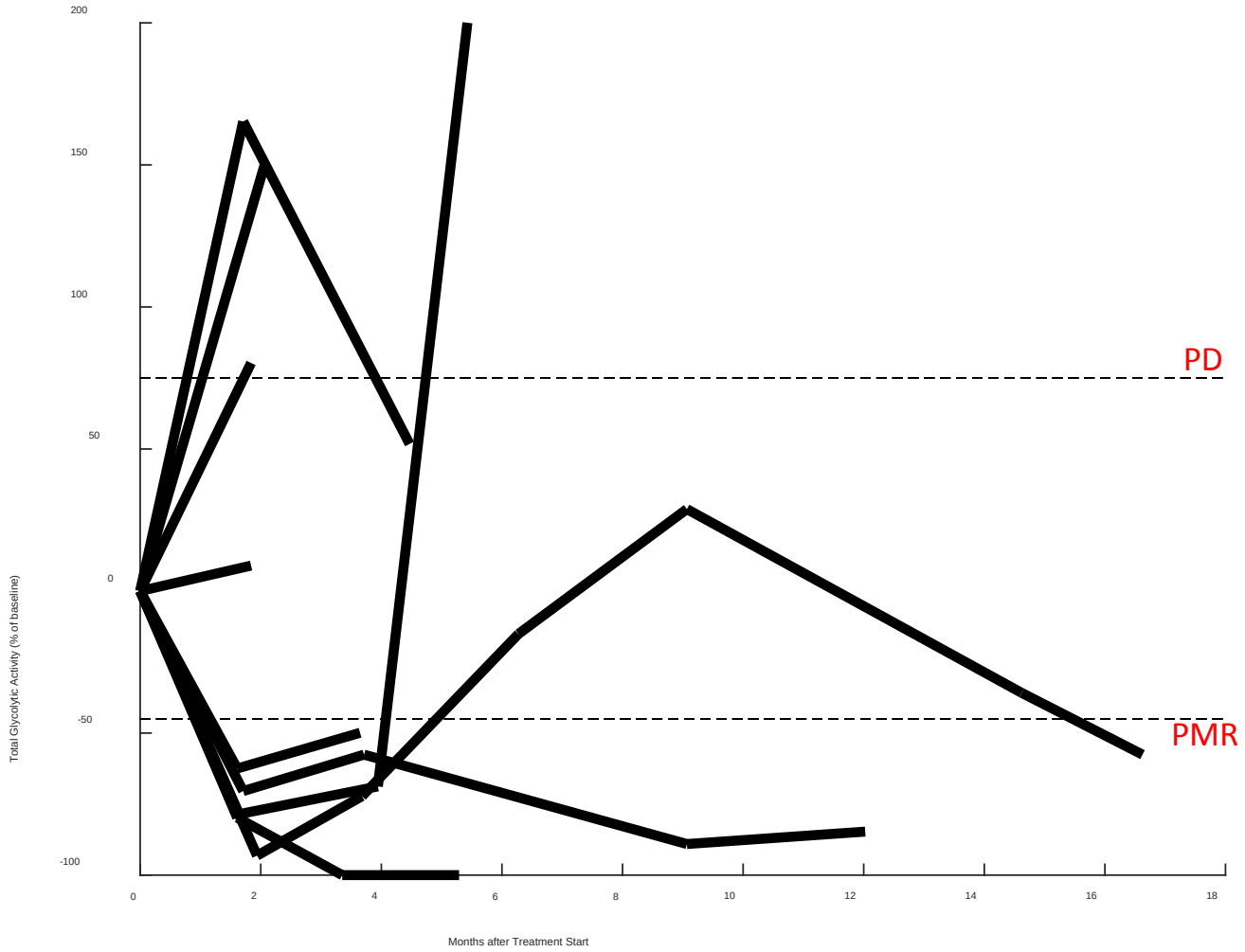
Kappa = 0.481

Weighted Kappa = 0.667

(moderate to good agreement)

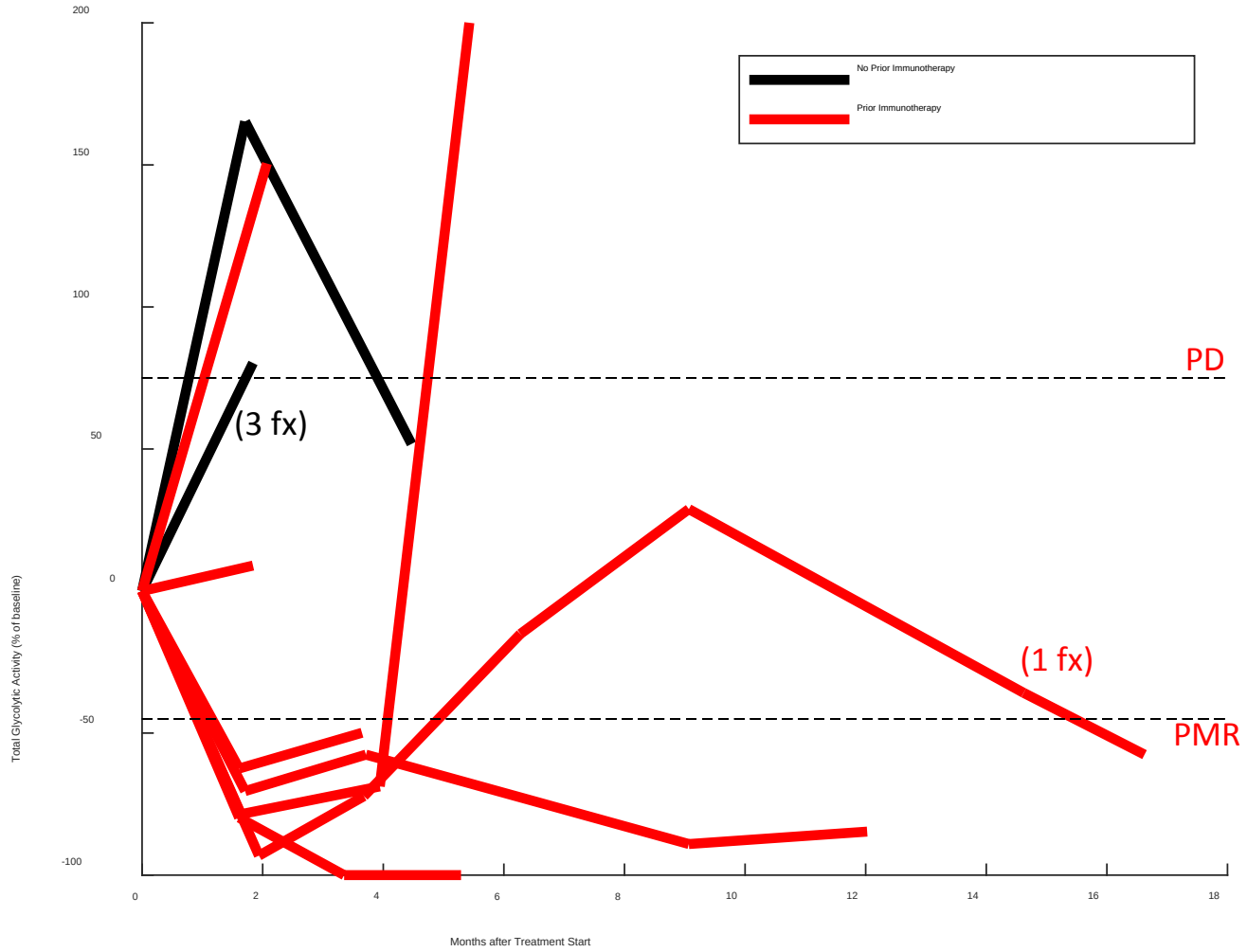
Responses on PET (excluding SBRT Targets)

- 9 subjects
  - 5 demonstrated Partial Metabolic Response on Week 8 PET



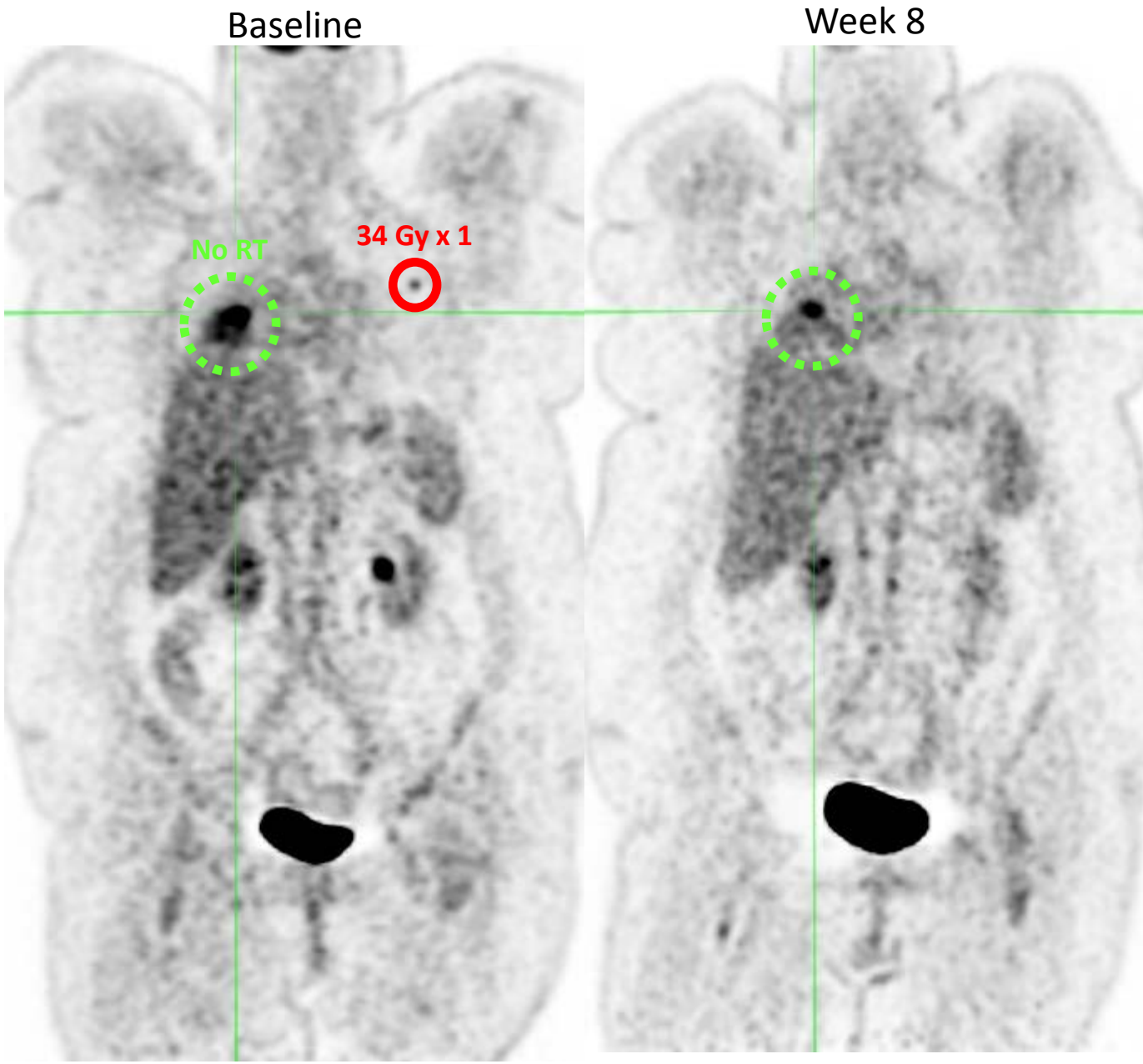
Responses on PET (excluding SBRT Targets)

- 9 subjects
  - 5 demonstrated Partial Metabolic Response on Week 8 PET
    - All 5 previously received immunotherapy



Patient 2

- 55 year-old female with right lung adenocarcinoma, left lung nodules
  - 1st line: carboplatin, pemetrexed (PD)
  - 2nd line: nivolumab (arthralgias), discontinued June 2016
  - Nov 2016: SBRT + CDX-301



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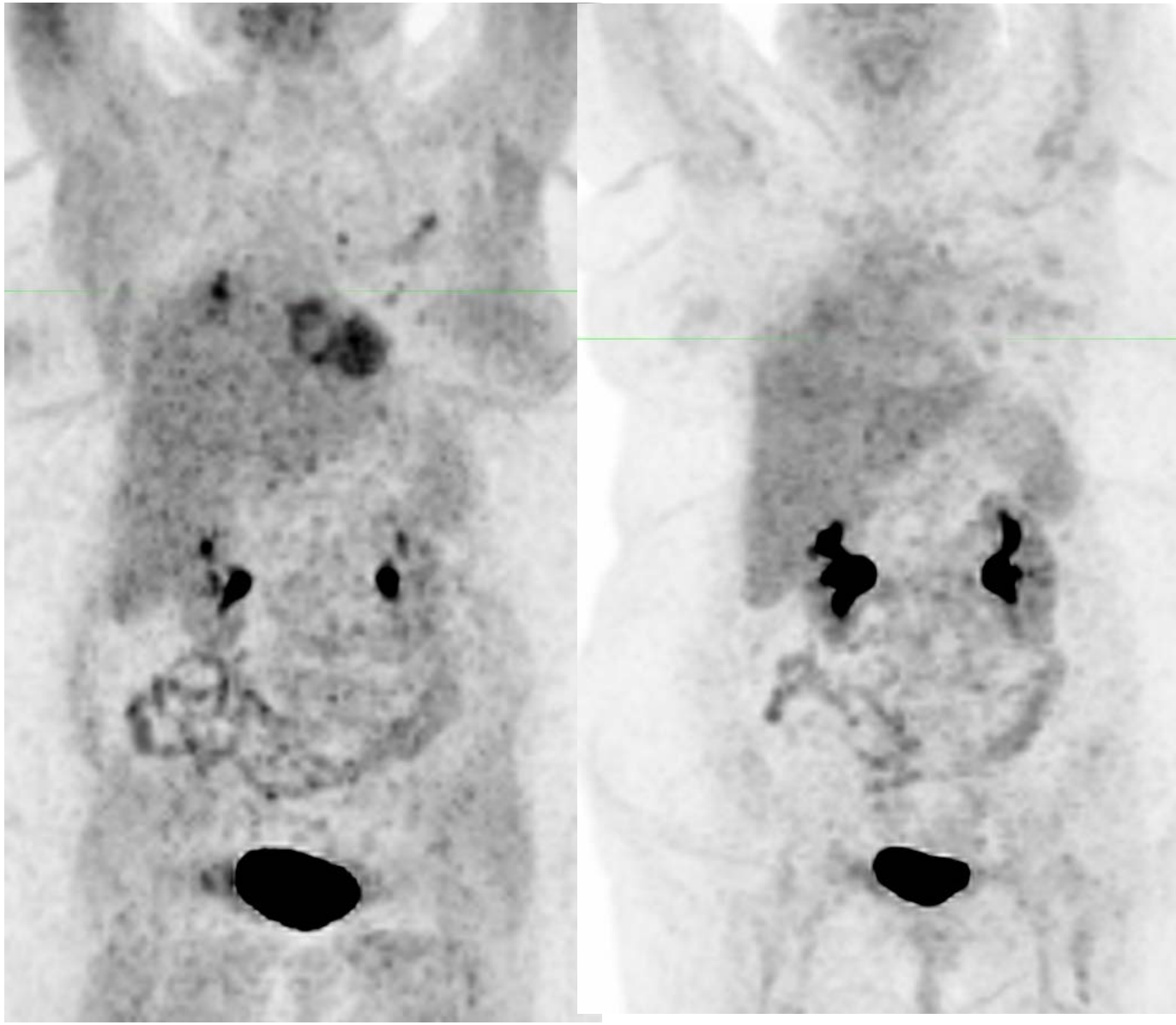
  - 1st line: carboplatin, pemetrexed (PD)
  - 2nd line: nivolumab (arthralgias), discontinued June 2016
  - Nov 2016: SBRT + CDX-301
  - May 2017: PD in left lung
  - April 2018: clinically well **without additional treatment**

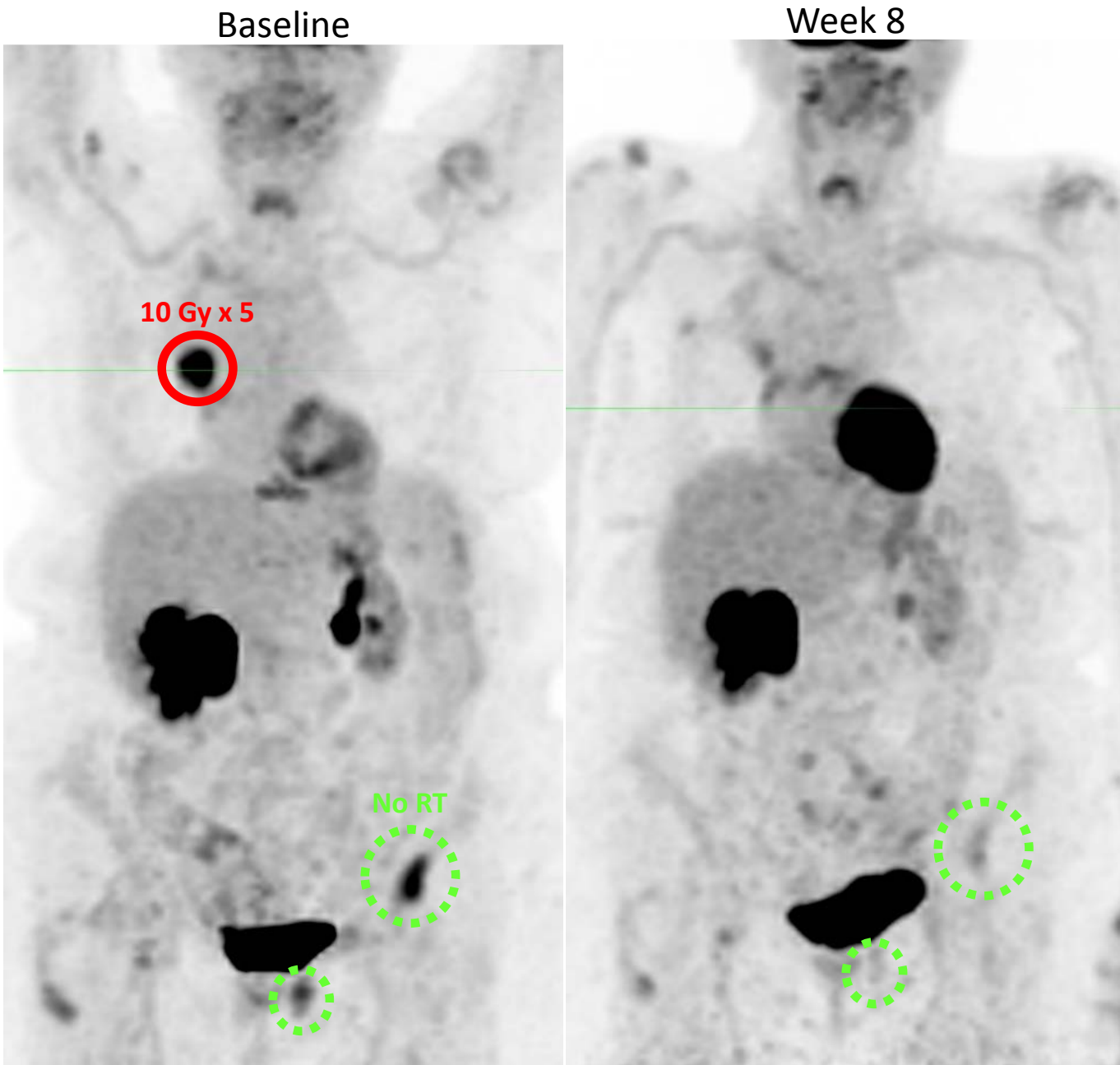
PD at 6 months

17 months



Patient 3

- 80 year-old female with right lung squamous cell carcinoma, bone metastases
  - 1st line: carboplatin, gemcitabine (SD, then PD)
  - 2nd line: nivolumab (PR, then PD), discontinued Dec 2016
  - Feb 2017: SBRT + CDX-301



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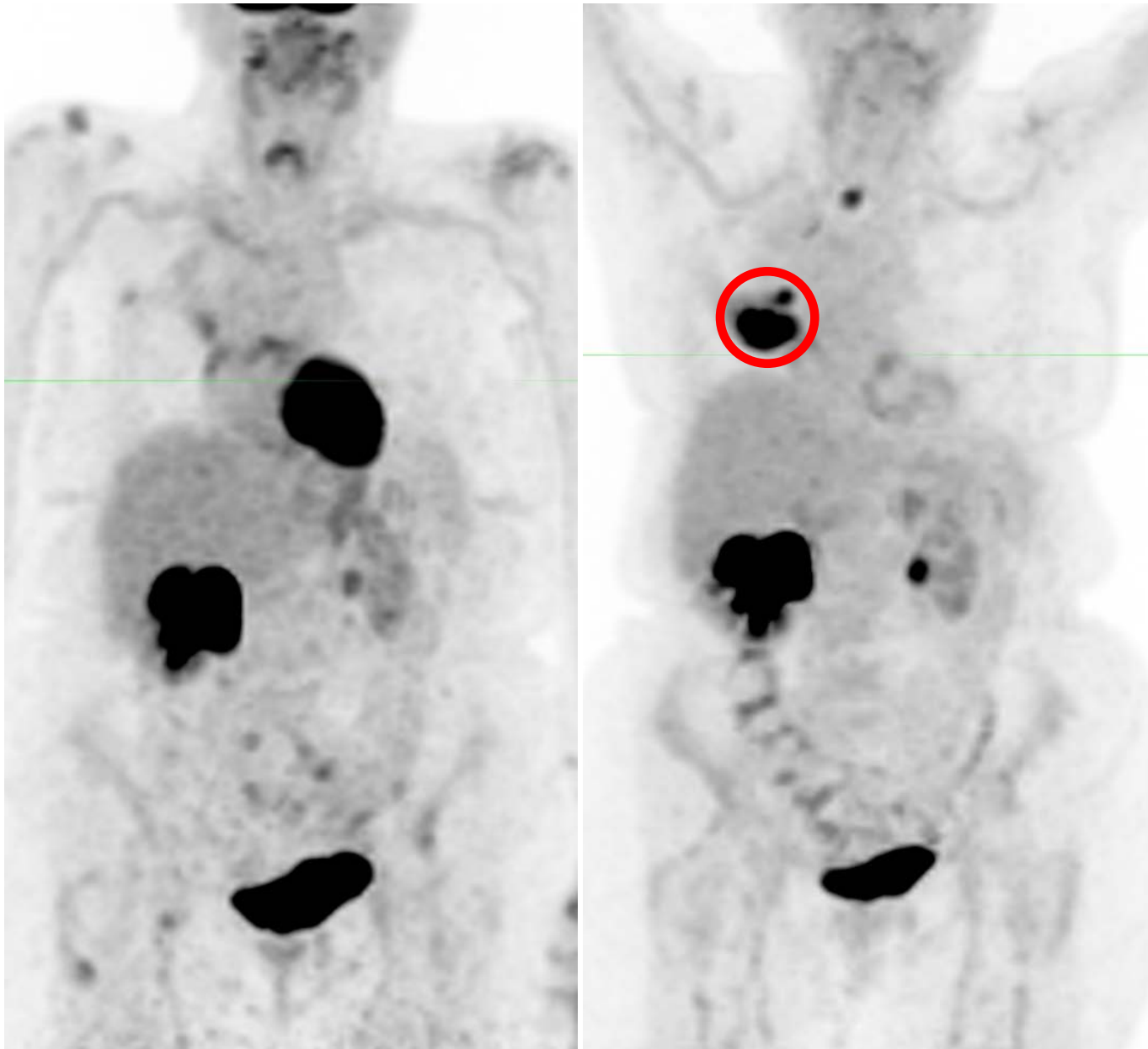
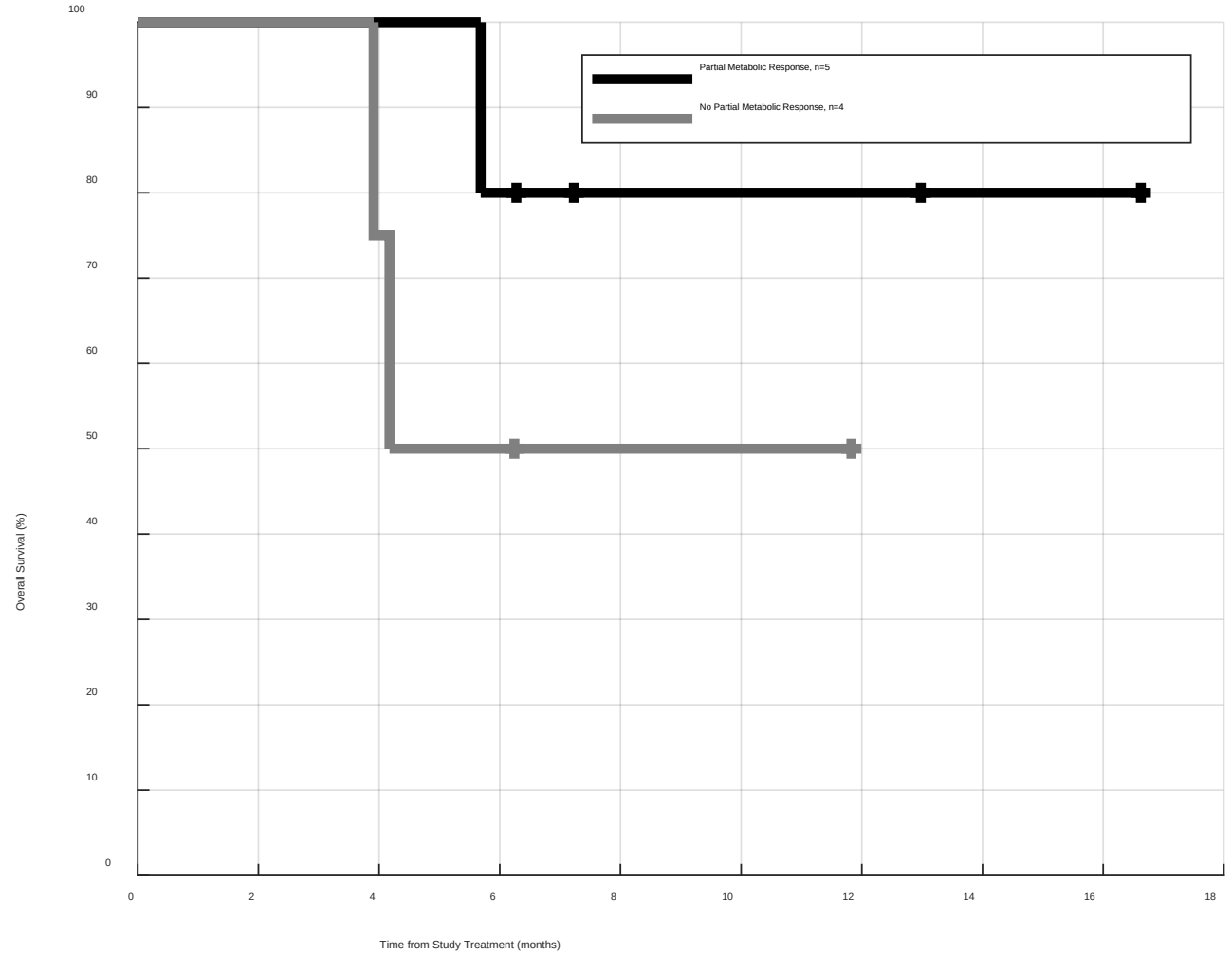
- 80 year-old female with right lung squamous cell carcinoma, bone metastases
  - 1st line: carboplatin, gemcitabine (SD, then PD)
  - 2nd line: nivolumab (PR, then PD), discontinued Dec 2016
  - Feb 2017: SBRT + CDX-301
  - Feb 2018: PD in right lung
  - April 2018: On pembrolizumab

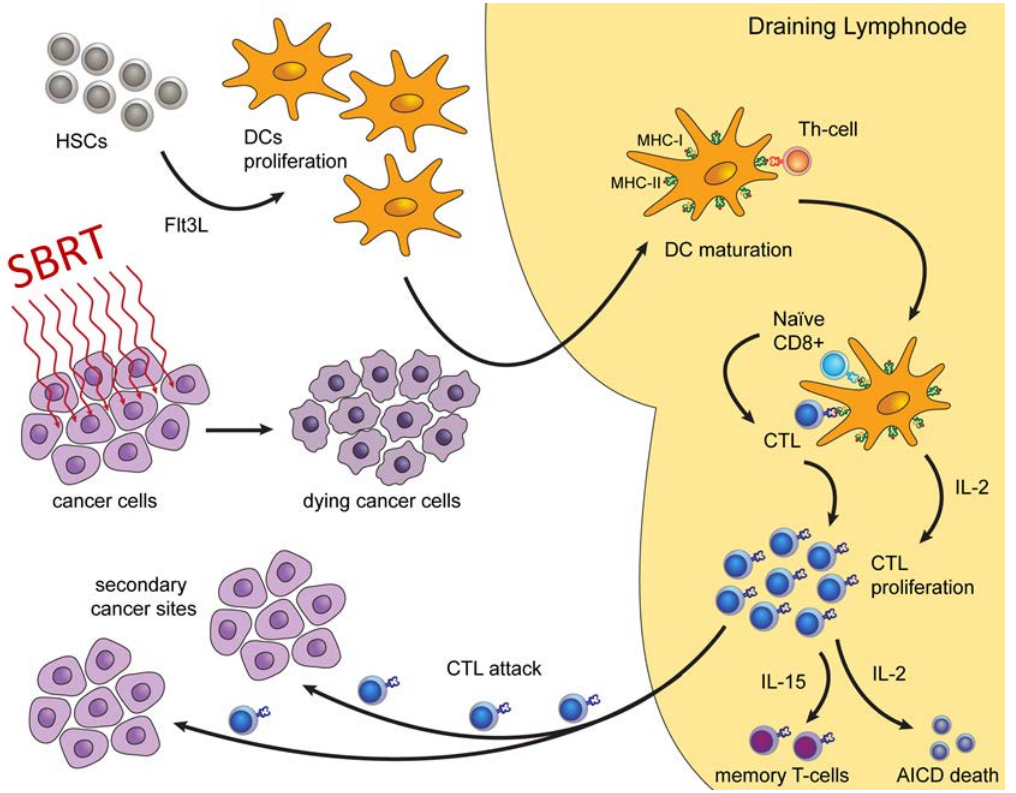


Response on Week 8 PET and Overall Survival



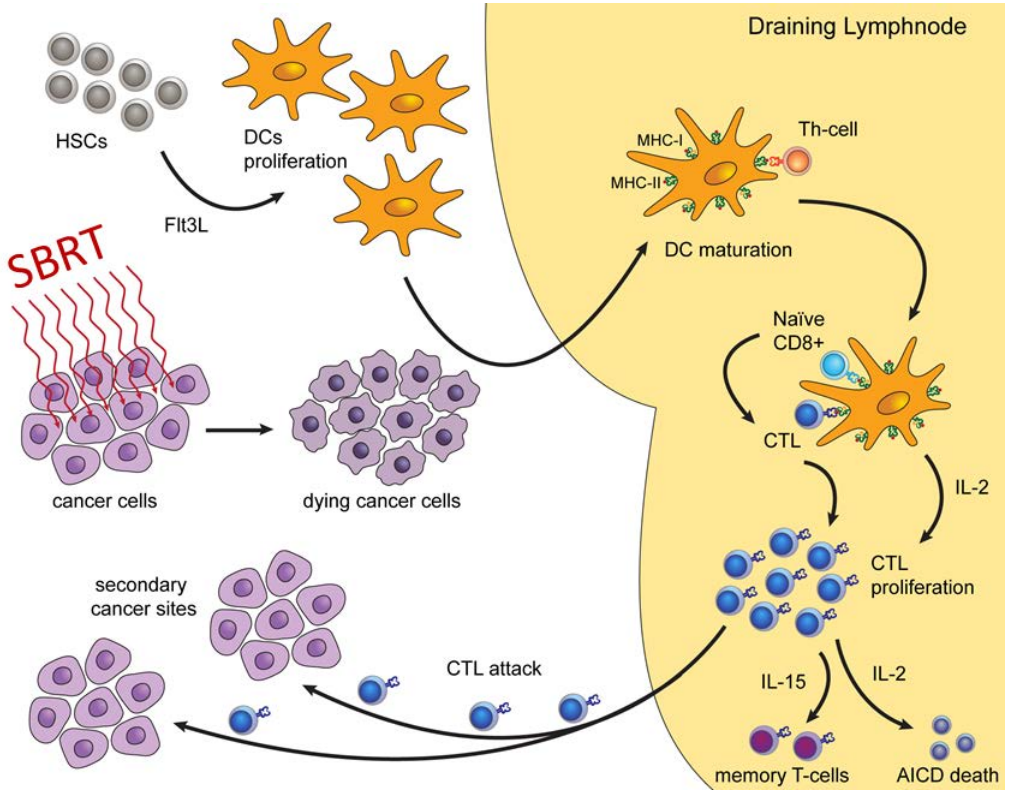
Study Conclusions

- This “bench to bedside” trial explores the combination of ablative radiotherapy and FLT3L as an *in situ* vaccine.
- The combination of SBRT and CDX-301 is well tolerated in patients with advanced NSCLC.
- SBRT + CDX-301 has clinical activity (“abscopal effects”) in advanced NSCLC
  - rapid and durable responses



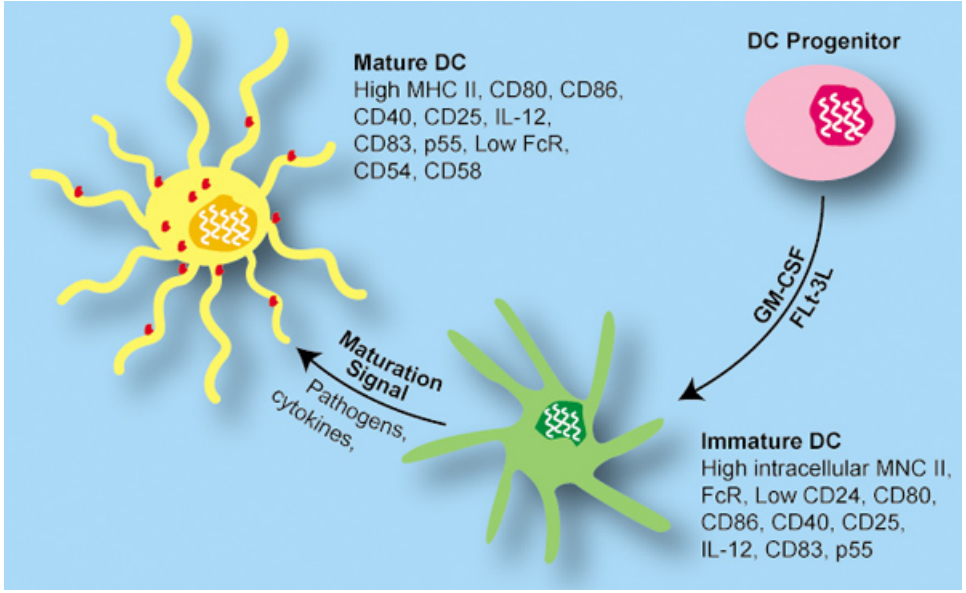
Study Conclusions (cont.)

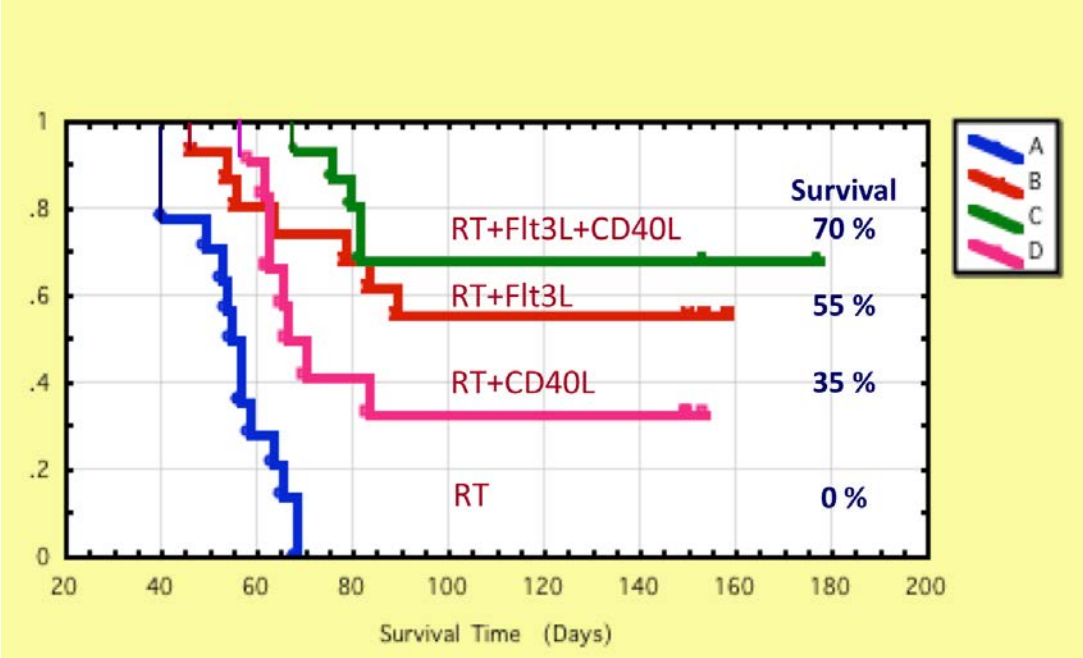
- SBRT + CDX-301 may be particularly effective in patients who have previously received anti-PD(L)1 therapy.
  - Including patients who have progressed
- Early PET findings after treatment may predict long-term clinical outcomes.
- Enrollment to further characterize the safety and efficacy of this regimen is ongoing.



Future Directions

- Optimize treatment regimen
  - Add “Booster” doses of SBRT + CDX-301
  - Add activating anti-CD40 antibody
    - CDX-1140, currently in phase I trials
- Explore combinations with immune checkpoint inhibitors
  - anti-PD(L)1 → SBRT+CDX-301 → anti-PD(L)1





http://dendritic-cells-research.com
Guha Laboratory