Oligometastatic non small cell lung cancer without driver mutations: New developments, including immunotherapy

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- Stock Options: None

- I will not discuss off label use or promote non-registered drugs

Agenda

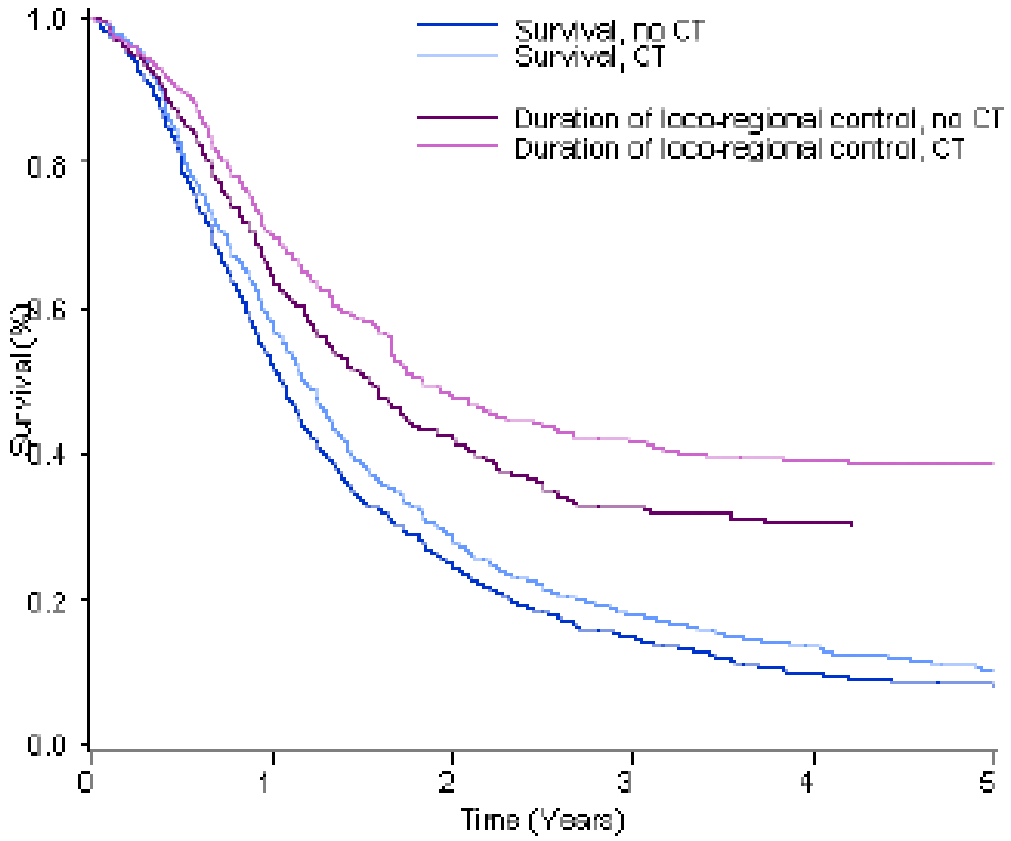
- Why systemic therapy?
- Which systemic therapy?
  - Chemotherapy
  - Immunotherapy
- Timing of systemic therapy
  - Chemotherapy
  - Immunotherapy

Why systemic therapy? Lessons from early disease

- Improve local-regional control
  - When used in conjuncture with radiotherapy

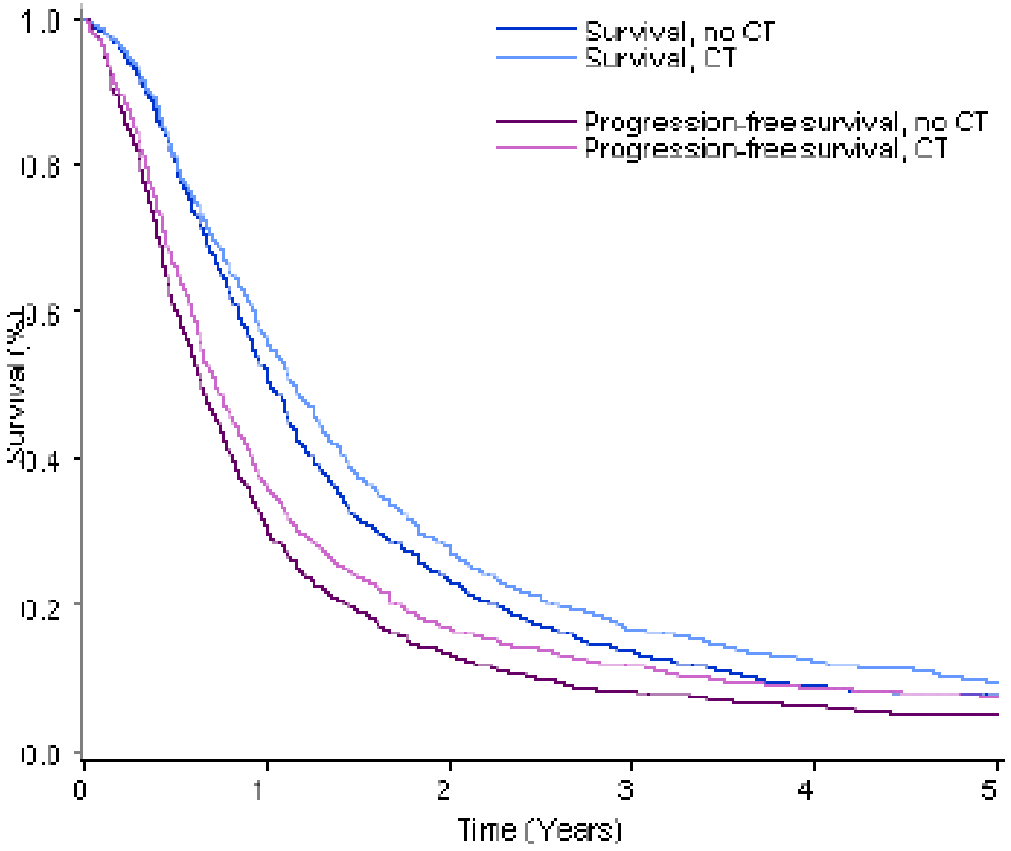
- Improve distant control
  - As adjuvant strategy to surgery

Improving loco-regional control in unresectable stage III NSCLC



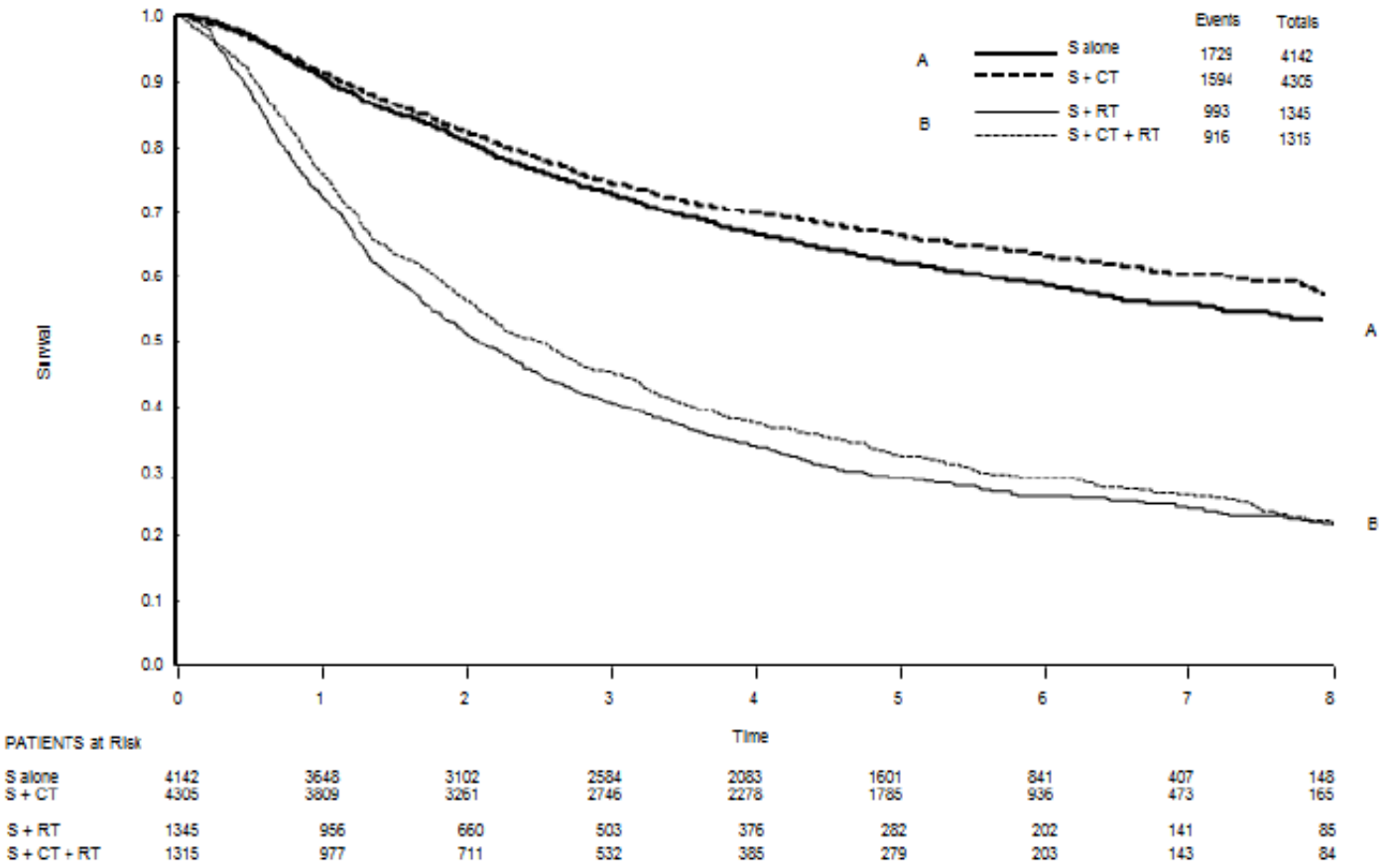
Mauguen et al. Lancet Oncology 2013

Improving distant control rates in unresectable stage III NSCLC



Mauguen et al. Lancet Oncol. 2013

Adjuvant chemotherapy in resectable disease



Cochrane review, 2015

Why systemic therapy?

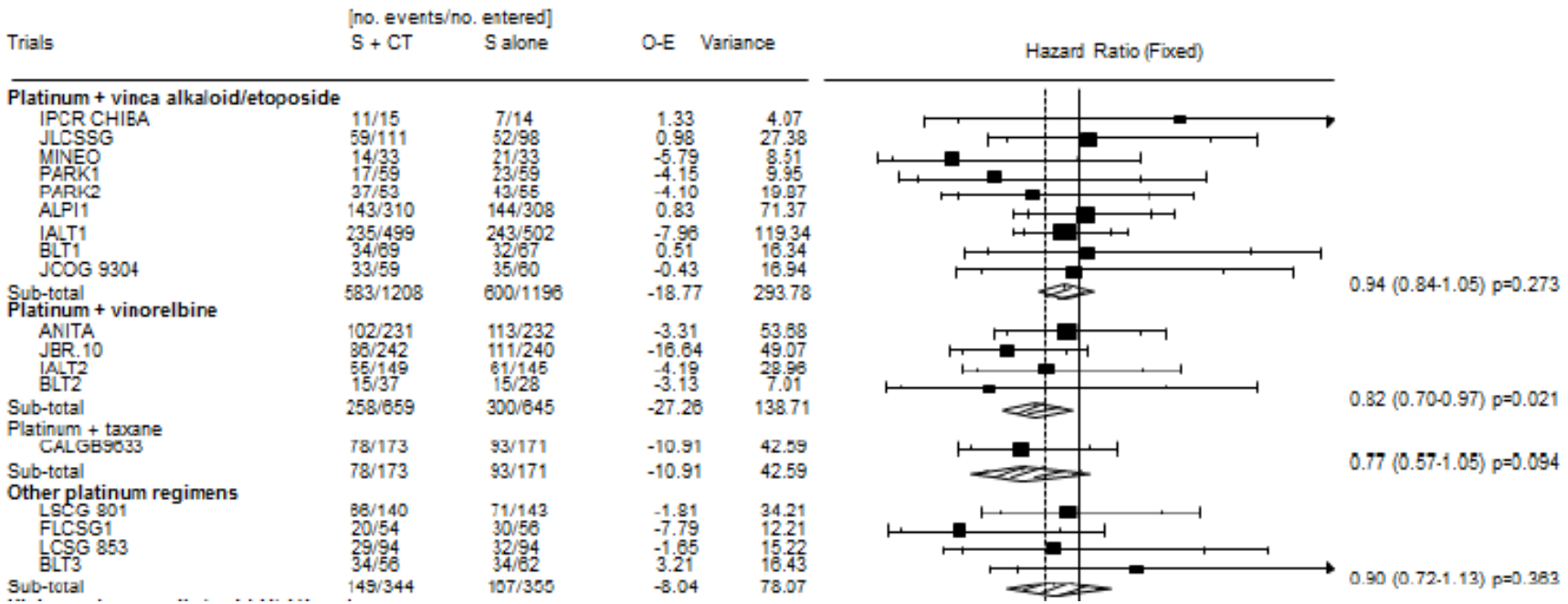
- Limited efficacy in stage IV
  - Palliative treatment
- Control possible by local therapies?
  - SBRT NCT01761929
- No randomised trials

Which systemic therapy?
Cytotoxic chemotherapy

- Depends on local treatment modality
  - Surgery
  - Radiotherapy (conventional)
  - SABR

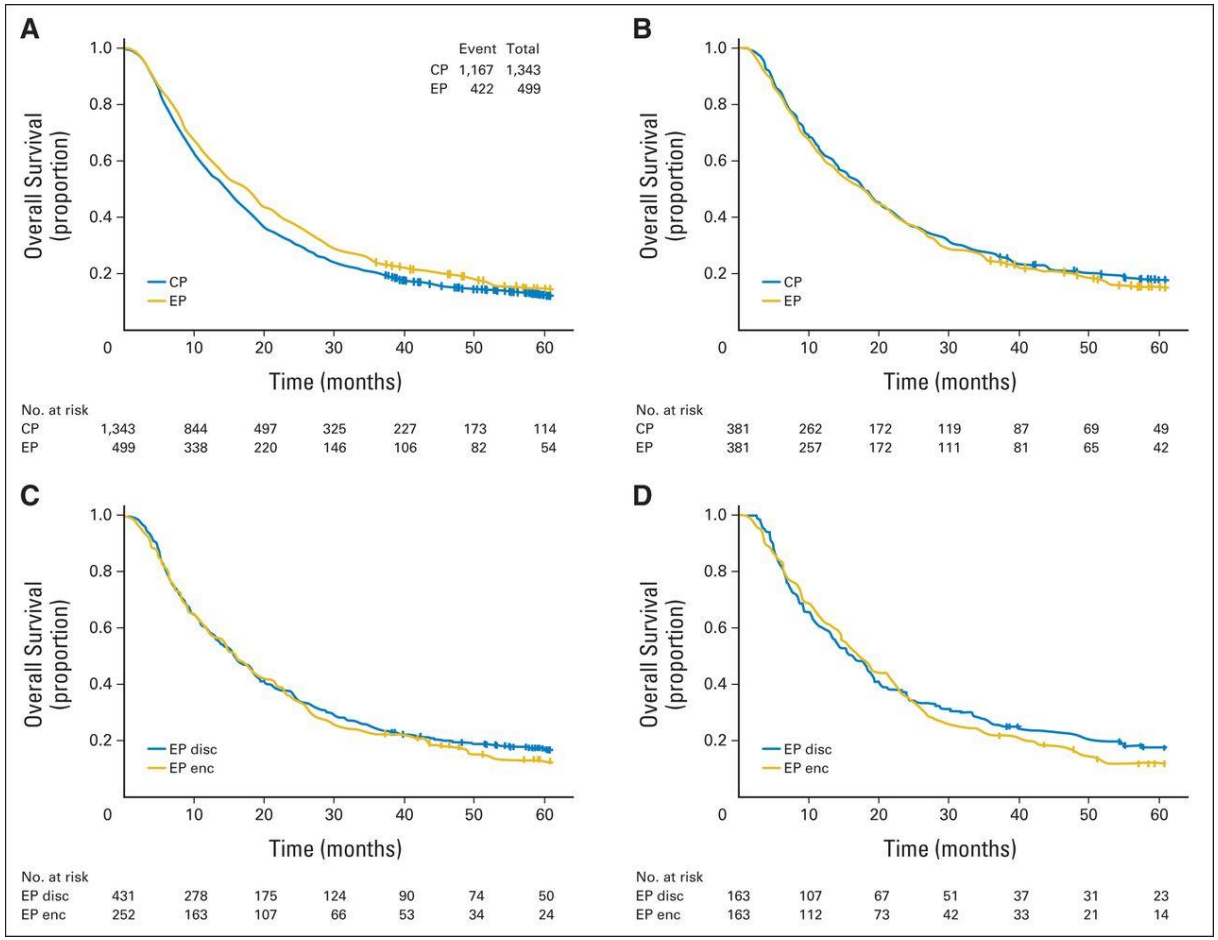
- Extrapolating from Stage IB-IV experience

Adjuvant chemotherapy



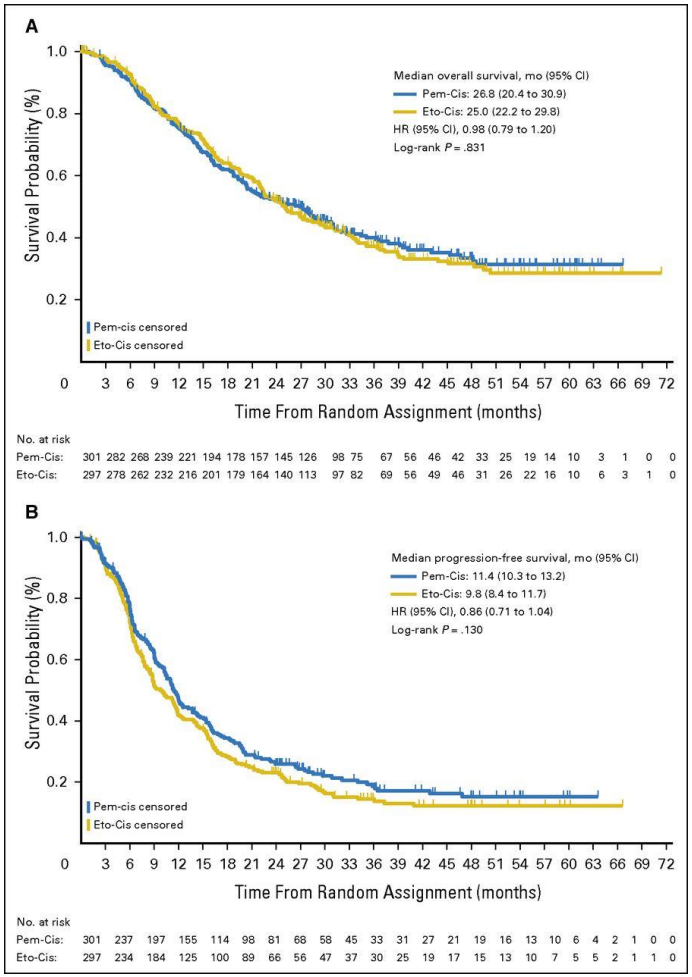
Cochrane review, 2015

Concurrent chemoradiation Retrospective analysis



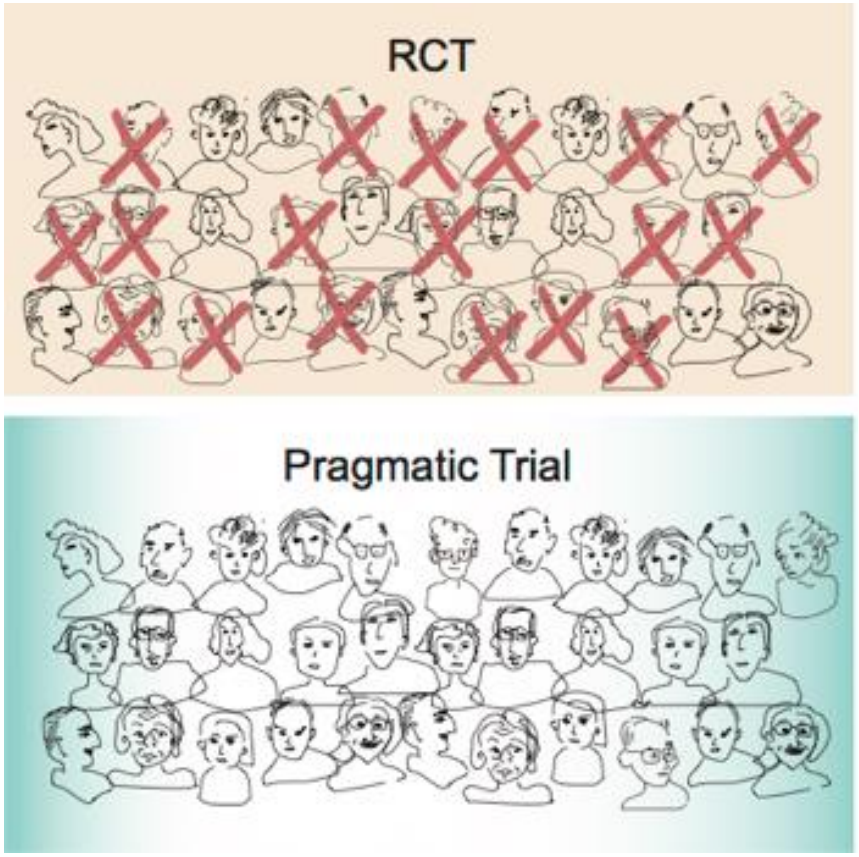
Santana-Davila, J. Clin. Oncol. 2015

Concurrent chemoradiation. Prospective phase III



Senan et al. J. Clin. Oncol. 2016

Daily practice in oligometastatic NSCLC



Radical treatment of non-small cell lung cancer (NSCLC) patients with synchronous oligometastases: Results of a prospective phase II trial (NCT01282450)

Main inclusion criteria:
Pathological proven NSCLC; UICC 6th edition stage IV; oligometastases (< 5) at primary diagnosis, which are amendable for radical local treatment (i.e. surgery or radiotherapy to a biological equivalent of at least 60 Gy/ 30 fractions), performance status 0-2.
Main exclusion criteria: stage I-III, except for T4 because of pleural metastases without effusion.
Primary endpoint: Overall survival (OS).
Secondary endpoints: Progression-Free survival (PFS), dyspnoea

de Ruysscher et al. J. Thor. Oncol. 2012

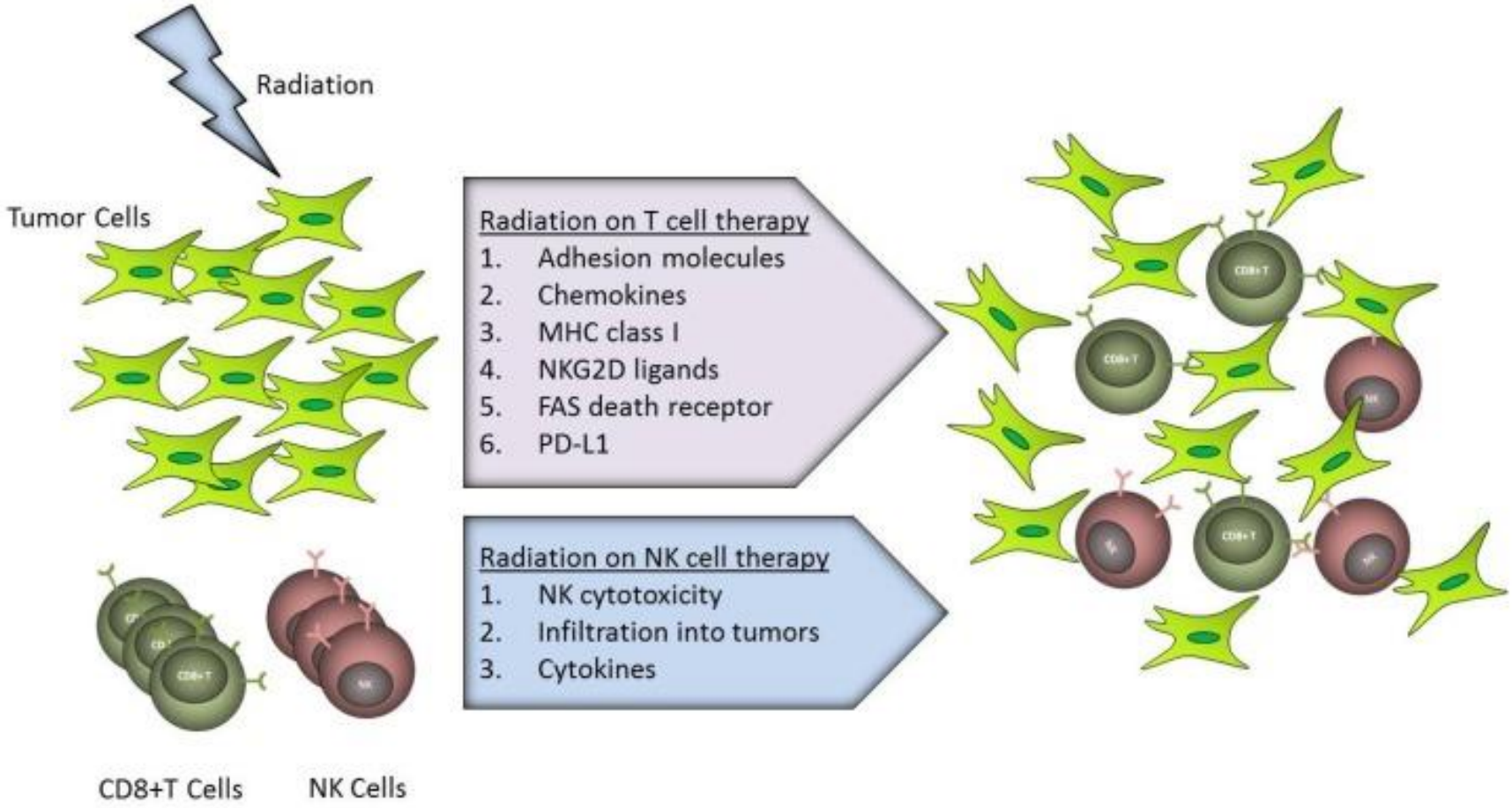
Chemotherapy regimens used

Chemotherapy	
No	2 (5.1 %)
Sequential chemo-radiotherapy	15 (38.5 %)
Cisplatin-gemcitabine	11
Carboplatin-gemcitabine	1
Cisplatin-pemetrexed	3
Concurrent chemo-radiotherapy	21 (53.8 %)
Cisplatin-etoposide	7
Cisplatin-vinorelbine	14
Adjuvant	1 (2.6 %)
Cisplatin-gemcitabine	
Radiotherapy dose (18-79.2)	62.3 ± 10.1 Gy
Number fractions	35.9 ± 8.4 (3-44)

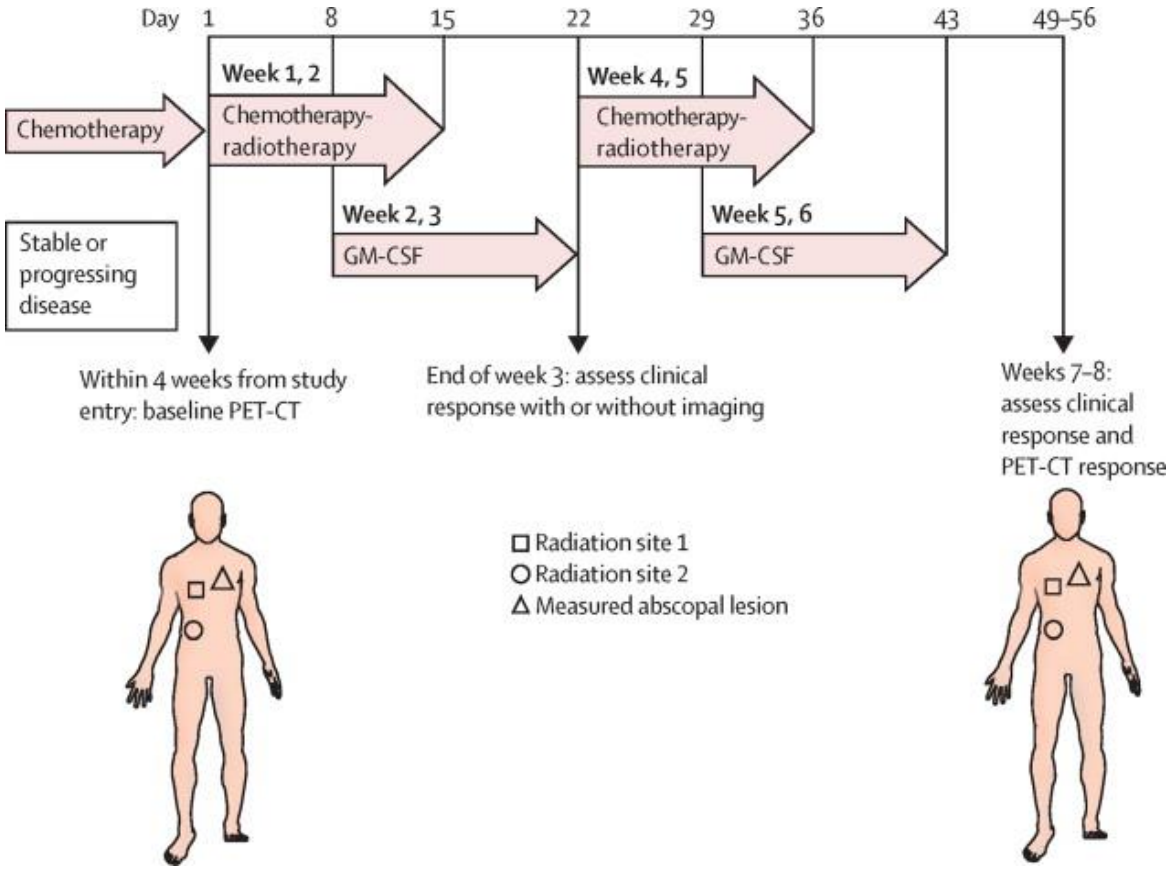
Immunotherapy why?

- No data in resectable disease
- Feasible in combination with radiotherapy?
  - Enhancement of abscopal effect?
- Promising data in stage IV disease

The abscopal effect

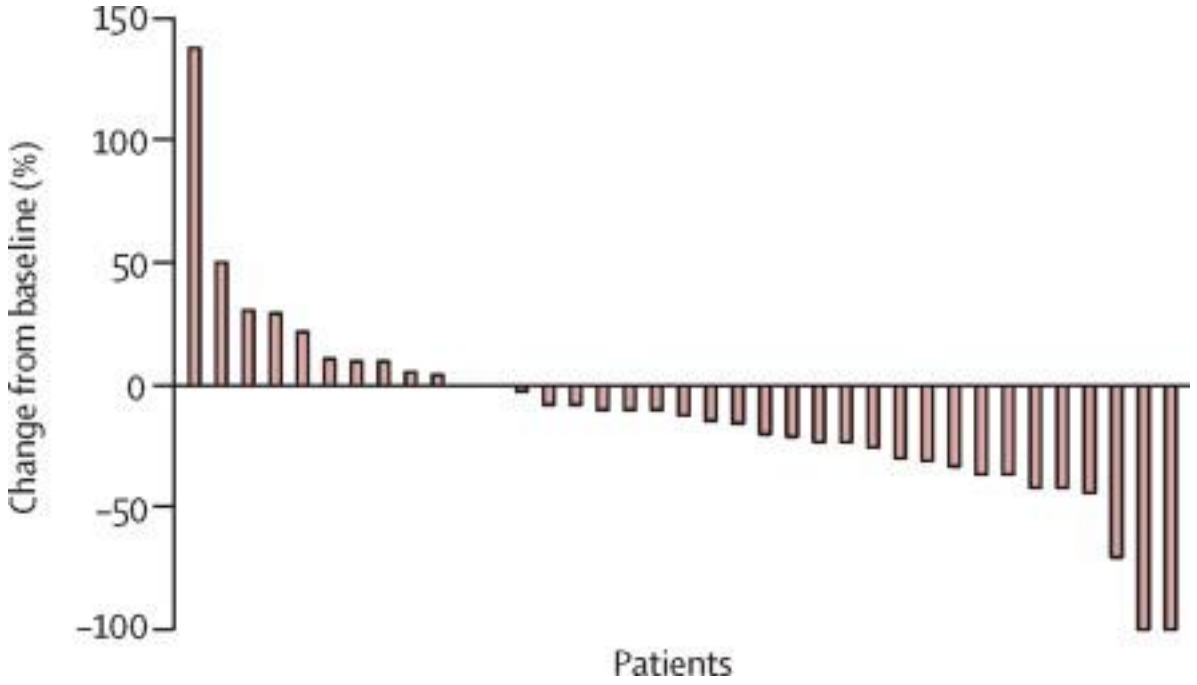


Does it exist in lung cancer?



Golden et al. Lancet Oncol. 2015

Best response



Goulden et al. Lancet Oncol. 2015

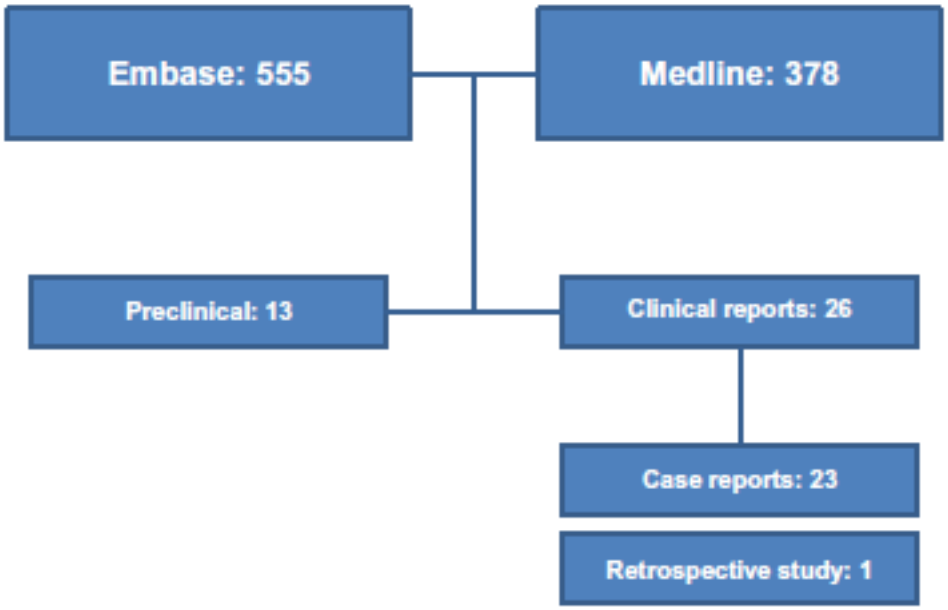
Efficacy

	Patients diagnosed	Patients completing scheduled therapy	Patients not assessable for best abscopal response	Patients assessable for best abscopal response				Patients assessable for best abscopal response who completed their scheduled therapy			
				PD	SD	PR	CR	PD	SD	PR	CR
Non-small-cell lung cancer	18 (44%)	13 (32%)	2 (5%)	2	10	2	2	1	7	2	2
Breast cancer	14 (34%)	11 (27%)	1 (2%)	2	6	5	0	2	4	4	0
Thymic cancer	2 (5%)	2 (5%)	--	0	0	2	0	0	0	2	0
Urothelial cancer	2 (5%)	0	--	0	2	0	0	0	0	0	0
Ovarian cancer	2 (5%)	0	1 (2%)	0	1	0	0	0	0	0	0
Eccrine cancer	1 (2%)	1 (2%)	--	0	1	0	0	0	1	0	0
Cervical cancer	1 (2%)	1 (2%)	--	0	1	0	0	0	1	0	0
Small-cell lung cancer	1 (2%)	1 (2%)	--	1	0	0	0	1	0	0	0
Total	41 (100%)	30 (73%)	4 (10%)	5	21	9	2	4	13	8	2

PD=progressive disease. SD=stable disease. PR=partial response. CR=complete disease.

Goulden et al. Lancet Oncol. 2015

Radiotherapy, abscopal effects and checkpoint inhibitors



Reynders et al. Cancer Treat. Rev. 2015

Few clinical data

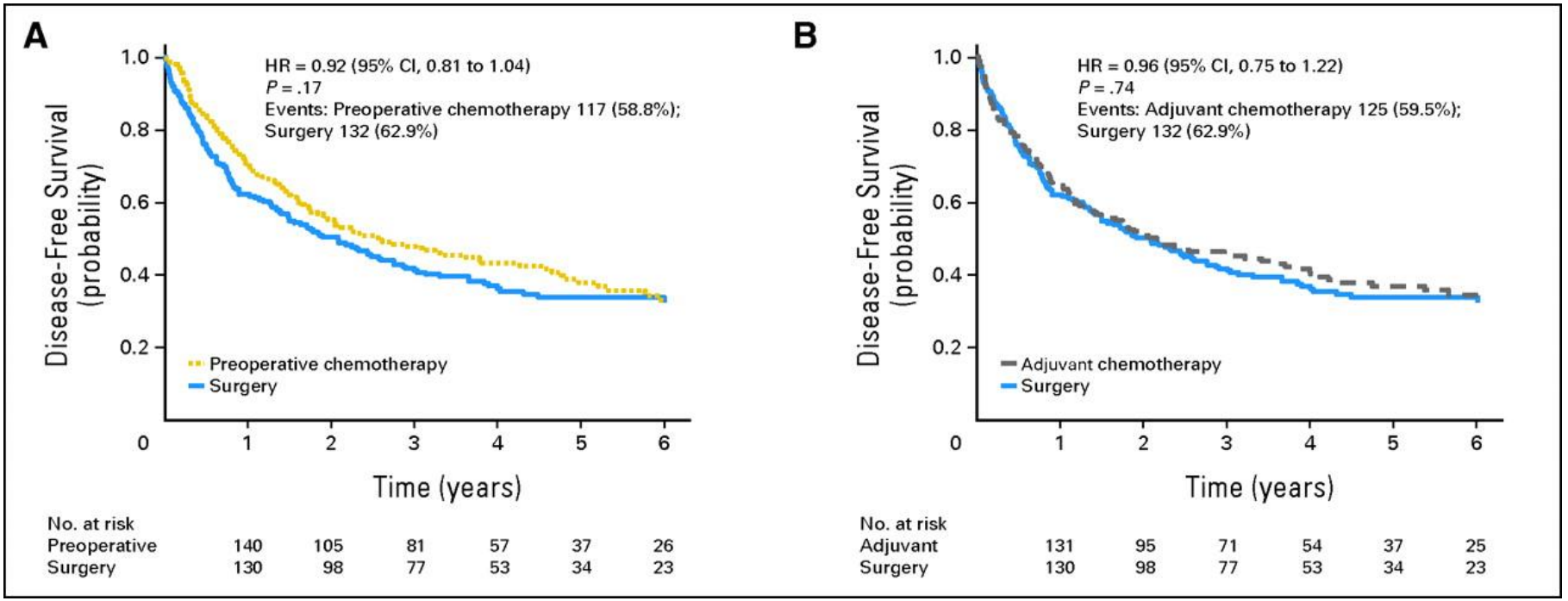
Clinical cases of abscopal effect after RT+ immune therapy.

Pub. year	Refs.	♂ ♀	Age	Histology	Primary site	Treatment of primary	RT treated sites	Treatment + RT Dose/ fractions	Non-irradiated abscopal regression	Time until abscopal response	PFS after response*
2014	[69]	M	74	Adenocarci-noma	Lung	Resection	Supraclavi-cular LN	BCG-vaccine 58 Gy/29×	Lung M+	6 m	47 m
2013	[33]	M	64	Adenocarci-noma	Lung	CT (PD)	Hepatic M+	Ipilimumab 30 Gy/5×	Liver M+/Bone M+/ Lung M+	3 m	5 m
2012	[34]	M	57	Melanoma	Arm	Wide excision/	Hepatic M+	Ipilimumab 54 Gy/3×	Cutaneous M+	6 m	6 m

Timing of systemic therapy

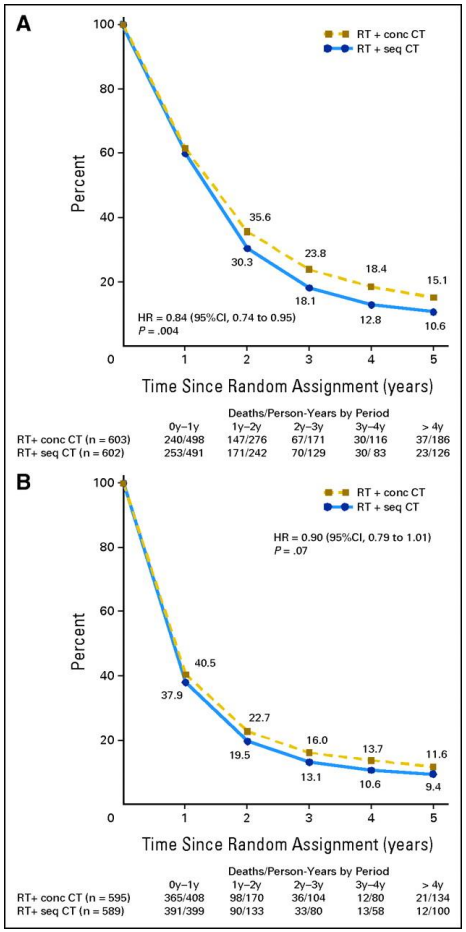
- Depends on local treatment modality
  - Surgery
  - Radiotherapy (conventional)
  - SABR

Timing of cytotoxic chemotherapy
Adjuvant or neo-adjuvant?



Felip et al. J. Clin. Oncol. 2010

Sequential vs Concurrent CRT in NSCLC



Auperin et al. J. Clin. Oncol. 2010

Timing of systemic therapy

- Depends on local treatment modality
  - Surgery
  - Radiotherapy (conventional)
  - SABR

Immunotherapy

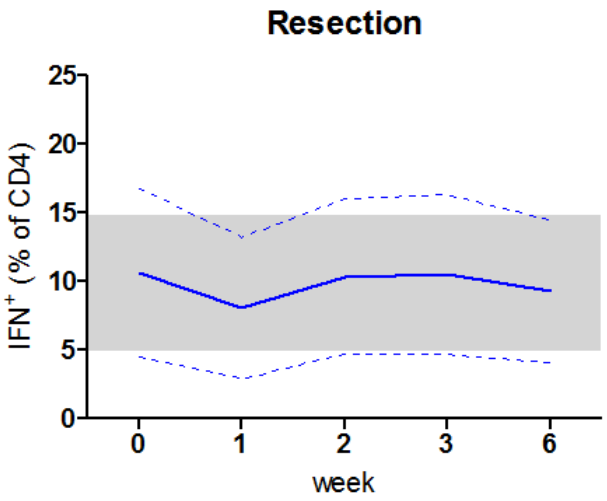
Determination of peripheral blood immune cells during SABRT and surgery for early stage NSCLC (Hamlet study)

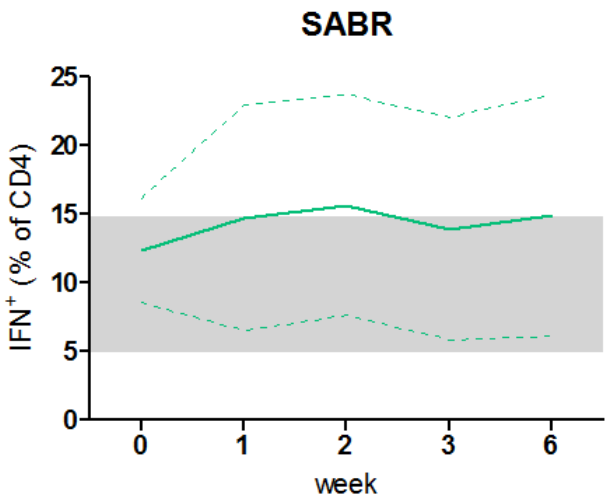
- Observational cohort study
- Stage I and IIa NSCLC, pathological proven
- Blood samples on week 1,2,3,4,5,6, after start of therapy
- Flowcytometric analysis of different immune cells,
  - Both fresh and frozen
  - Before and after stimulation

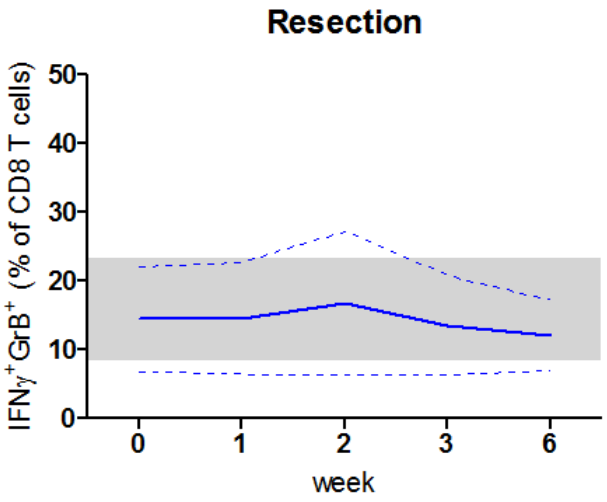
Patient Characteristics

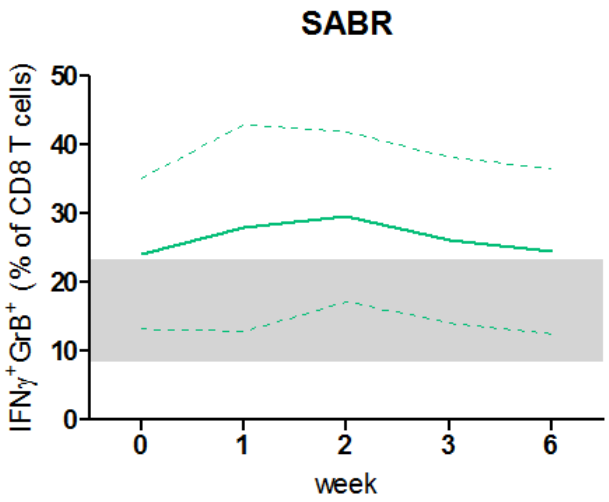
	Surgery	SABR
N	17	10
Age, mean (±SD)	64 (±8.8)	70 (±10.3)
Sex		
Male	7 (41%)	7 (70%)
Female	10 (59%)	3 (30%)
NSCLC type		
Adenocarcinoma	9 (53%)	4 (40%)
Squamous cell carcinoma	6 (35%)	5 (50%)
Large cell carcinoma	1 (6%)	
other	1 (6%)	1 (10%)
NSCLC stage (pre-ok, based on cTNM)	7 (41%)	7 (70%)
1A	5 (29%)	2 (20%)
1B	3 (18%)	
2A	1 (6%)	1 (10%)
2B	1 (6%)	
Unknown		
Comorbidities		
COPD	7 (41%)	3 (30%)
Other tumor	1 (6%)	3 (30%)
Diabetes	3 (18%)	2 (20%)
Other	7 (41%)	3 (30%)
Charlson comorbidity index		
Low (0 points)	5 (29%)	2 (20%)
Medium (1 to 2 points)	11 (65%)	3 (30%)
High (4 to 4 points)	1 (6%)	4 (40%)
Type of surgery		
Lobectomy	15 (88%)	
Segmentectomy	1 (6%)	
Bilobectomy	1 (6%)	
Surgery technique		
VATS	13 (76.5%)	
Open	4 (23.5%)	
SABR		
Total dosis, mean (range)		54 Gy (51-60)
Number of fractions		
3		6 (60%)
5		1 (10%)
8		3 (30%)

The fraction of IFNγ^{+} CD4 and IFNγ^{+}GranzymeB^{+} CD8 T cells increases after SABR

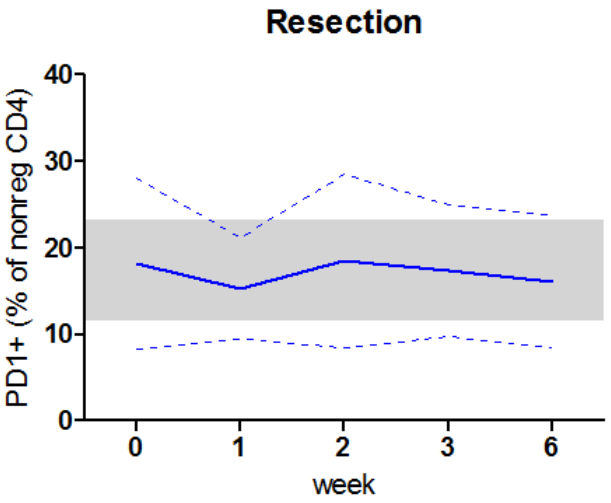


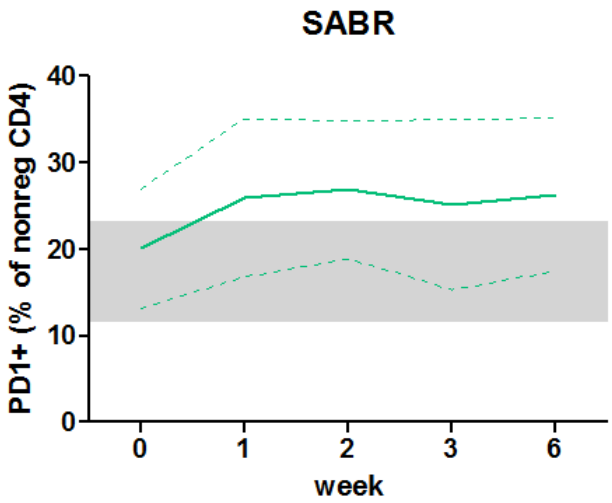


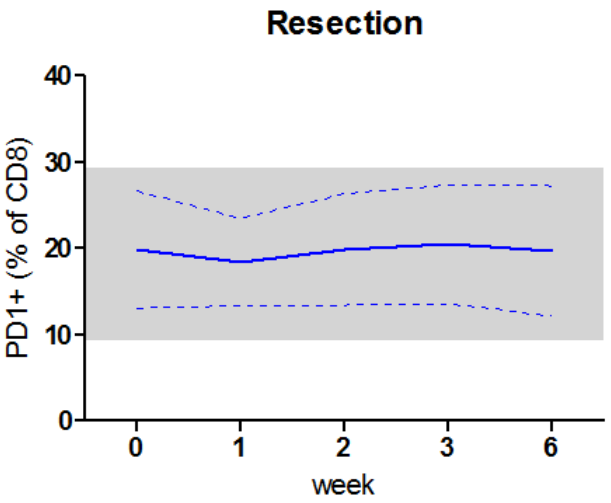


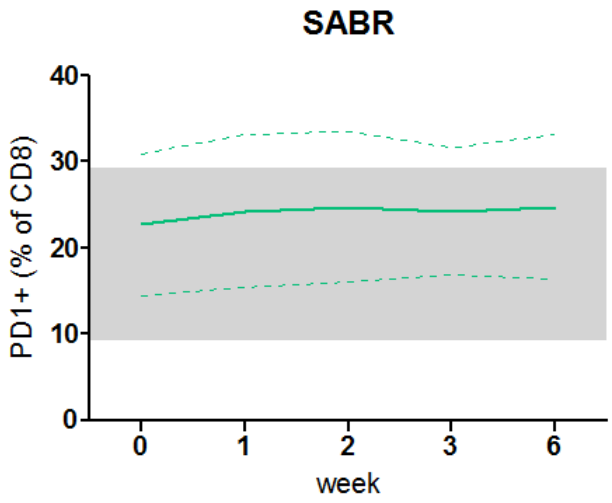


Fraction of PD1^{+} increases by SABR









Conclusions

- SABR but not surgery, stimulates T-cell activation .
- Our findings suggest that SABR may induce a specific anti-tumor response, and investigations to establish this finding are ongoing .
- The upregulation of PD-1 inherently accompanied with this activation of the immune system potentially warrants combination treatment with PD-(L)1 blockade.

Conclusions

- No new developments in cytotoxic chemotherapy.
- Immunotherapy has the potential of augmenting responses in patients treated with radiotherapy and trials are underway.
- Randomized trials are desperately needed