Updates on Radiation Therapy for Stage III NSCLC

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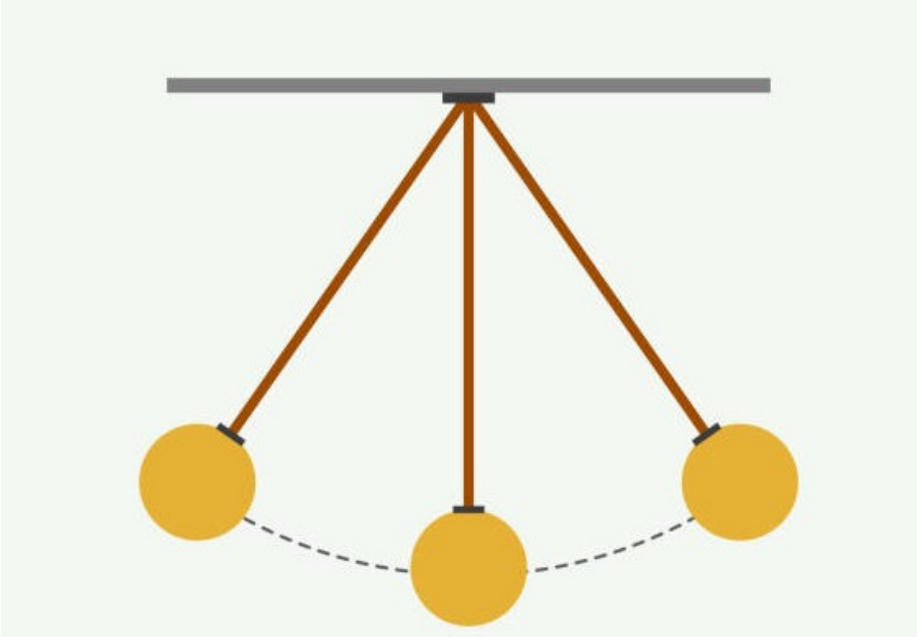
Locally Advanced NSCLC



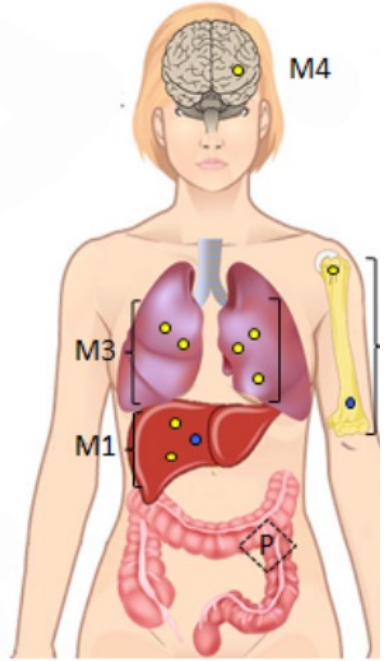
CRT + consolidative Immunotherapy

2017- First PACIFIC publication

Neoadj Chemo IO + Surgery

2022 – Checkmate 816

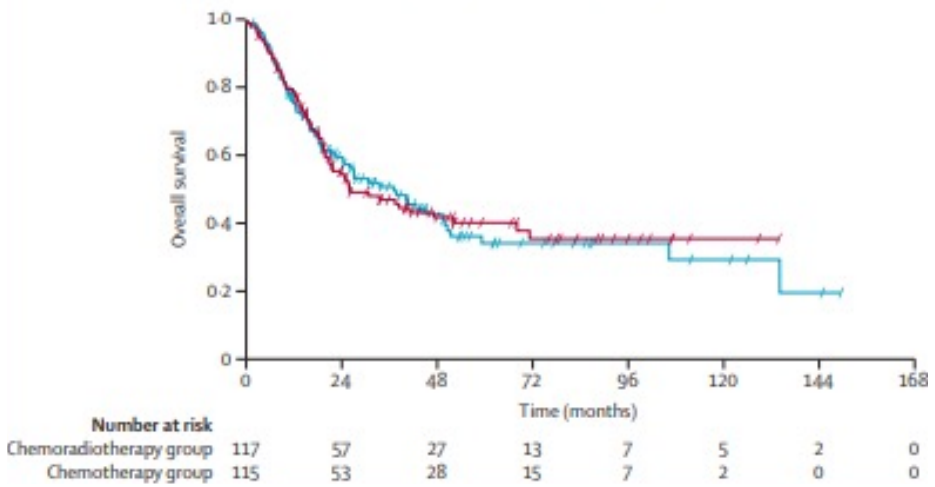
Local therapy in Stage IV disease



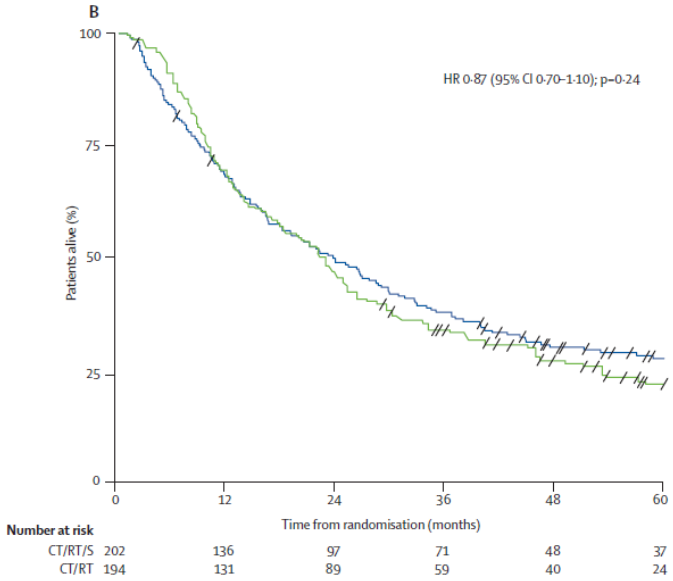
Presentations on RT in Advanced NSCLC

- **Stage III NSCLC**
  - **SAKK 16/18 - Patrick Dorn: Interim analysis of neoadjuvant chemo/ICI + immune stimulatory RT**
  - **INCREASE – Chris Dickhoff: Neoadjuvant ICI + CRT → Surgery**
- Stage IV NSCLC
  - COSINR – Juloori Aditya: Addition of multisite SBRT to Ipi/Nivo
  - BRIGHTSTAR – Aditya Juloori: Local Consolidative Therapy in patients treated with Brigatinib - Dr. Loo to present.

Prior studies evaluating 'Tri-Modality' therapy for stage III NSCLC



Chemo → RT → Surgery vs. Chemo → Surgery
SAKK *Pless et al. Lancet 2015*



Chemo/RT → Surgery vs. Chemo/RT
Int 0139 *Albain et al.* Lancet 2009

Quad-Modality?
The Fab Four of NSCLC?

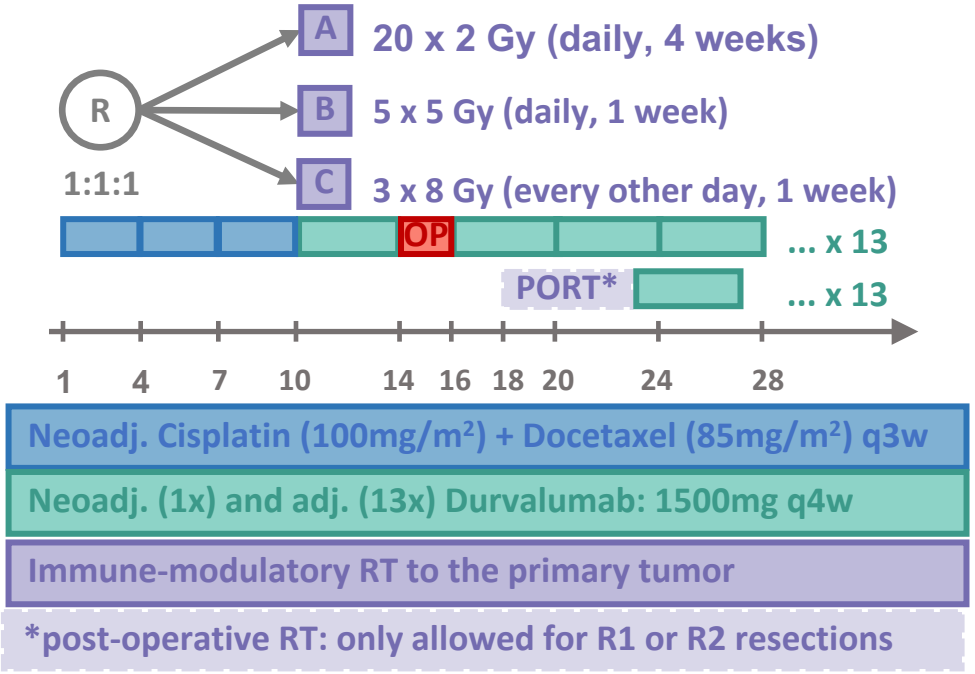
SAKK 16/18

Inclusion criteria:

- NSCLC, cT1-4$_{>7}$ N2 M0 (8th ed.)
- Primarily resectable and operable
- ECOG 0-1
- Adequate organ function (incl. eGFR ≥ 60 mL/min)

Exclusion criteria:

- Any previous treatment for NSCLC
- Previous checkpoint inhibitor or thoracic RT
- Active auto-immune disease, ≥ 10 mg/day of prednisone



- Primary endpoint: 1-yr EFS
- Interim safety analysis after 25 resections
- Unresected patients: safety F/U ≥ 90 days

SAKK 16/18

Durvalumab: N = 29 (94%) and

20x2Gy: N = 8	5x5Gy: N = 10	3x8Gy: N = 11

↓

Surgery: N = 25 (81%)

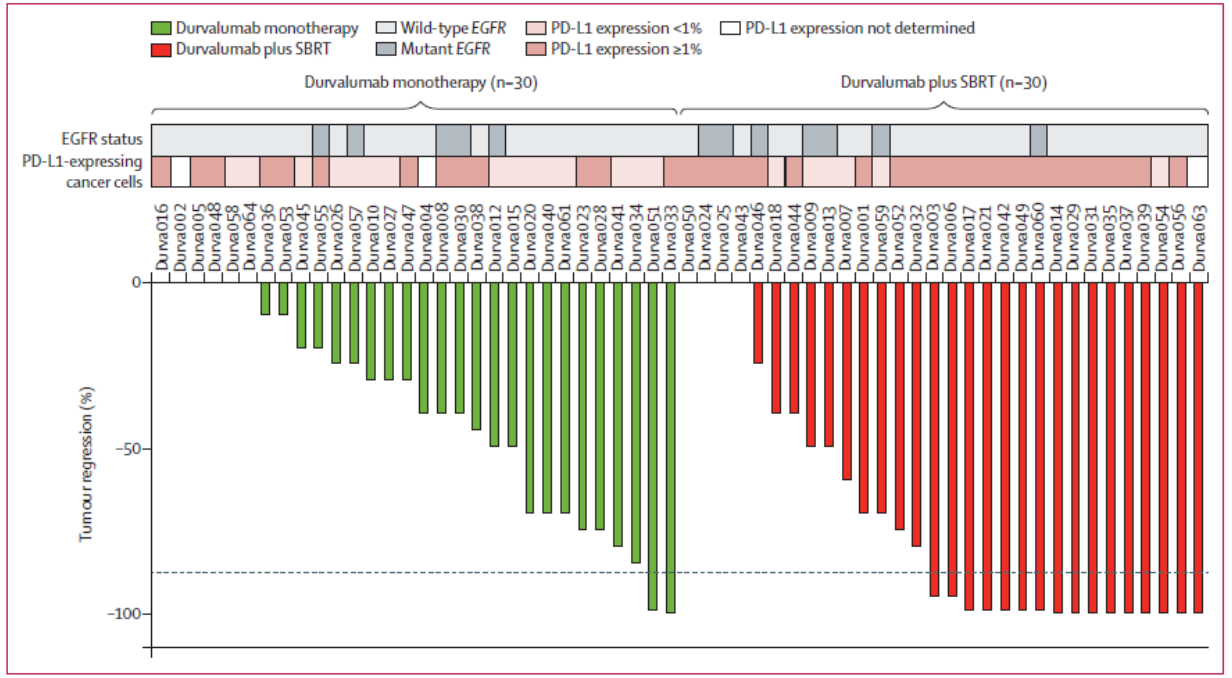
273 pre-/peri-operative TRAE occurred:

- 241 (88%) related to chemo
- 12 (4%) related to durvalumab
- 12 (4%) related to RT
- 23 (8%) related to surgery

Variable	Arm A N = 7	Arm B N = 9	Arm C N = 9	Total N = 25
MPR	4	8	7	19
pCR	0	3	2	5
<ypN2	3	6	6	15

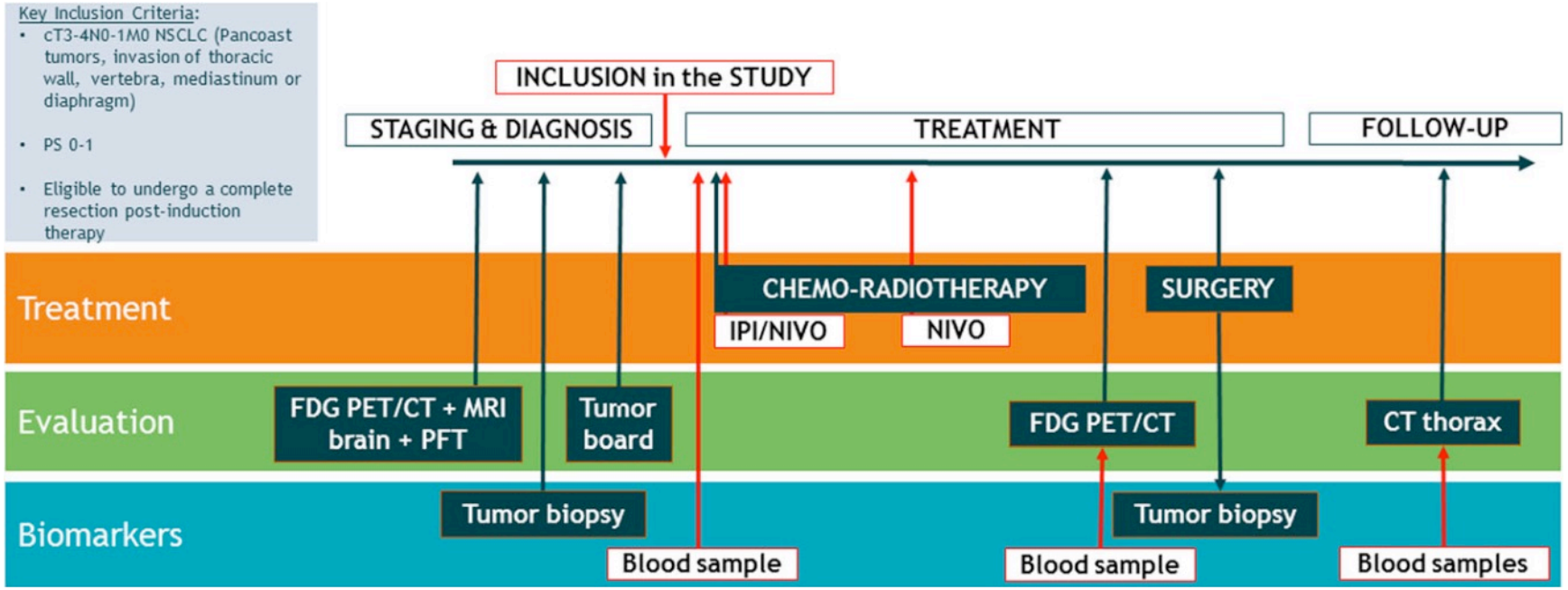
SAKK 16/18 Conclusions:

- Chemo → RT + Durva → Surgery
  - Safe and feasible on interim analysis. Accrue as planned (n=90)
- Too early to differentiate RT regimens
- No role off trial currently, interesting area of investigation



Cornell Durvalumab +/- SABR preop
8 Gy x 3
Altorki Lancet Oncol 2021

INCREASE Phase II Trial



- 1° endpoints – Safety, pCR rates
- RT to 50-60 Gy in 2 Gy / fx
- Chemo – Cis/Pem or Cis/Etop
- Surgery 3 weeks after CRT

		n (%)
Sex (male:female)		10:15
Age (years, median (IQR)))		64 (55-69)
Histology		
	Adenocarcinoma	12 (48%)
	Squamous cell carcinoma	7 (28%)
	Large-cell NOS	5 (20%)
	Large-cell neuroendocrine	1 (4%)
Tumor stage (8th TNM edition)		
Stage IIB	T3N0	5 (20%)
Stage IIIA	T3N1	4 (16%)
	T4N0	12 (48%)
	T4N1	3 (12%)
Stage IIIB	T3N2	1 (4%)
Chest wall invasion		11 (44%)
	Sulcus superior tumors	*7*
	Other	*4*
Radiotherapy dose		
	50Gy	22 (88%)
	60Gy	3 (12%)

	n (%)
Any TRAE	30 (100)
Grade 3-4	22 (73)
Grade 5	0 (0%)

Acceptable toxicity rates

No patients failed to undergo surgery due to TRAE's

Surgical Outcomes

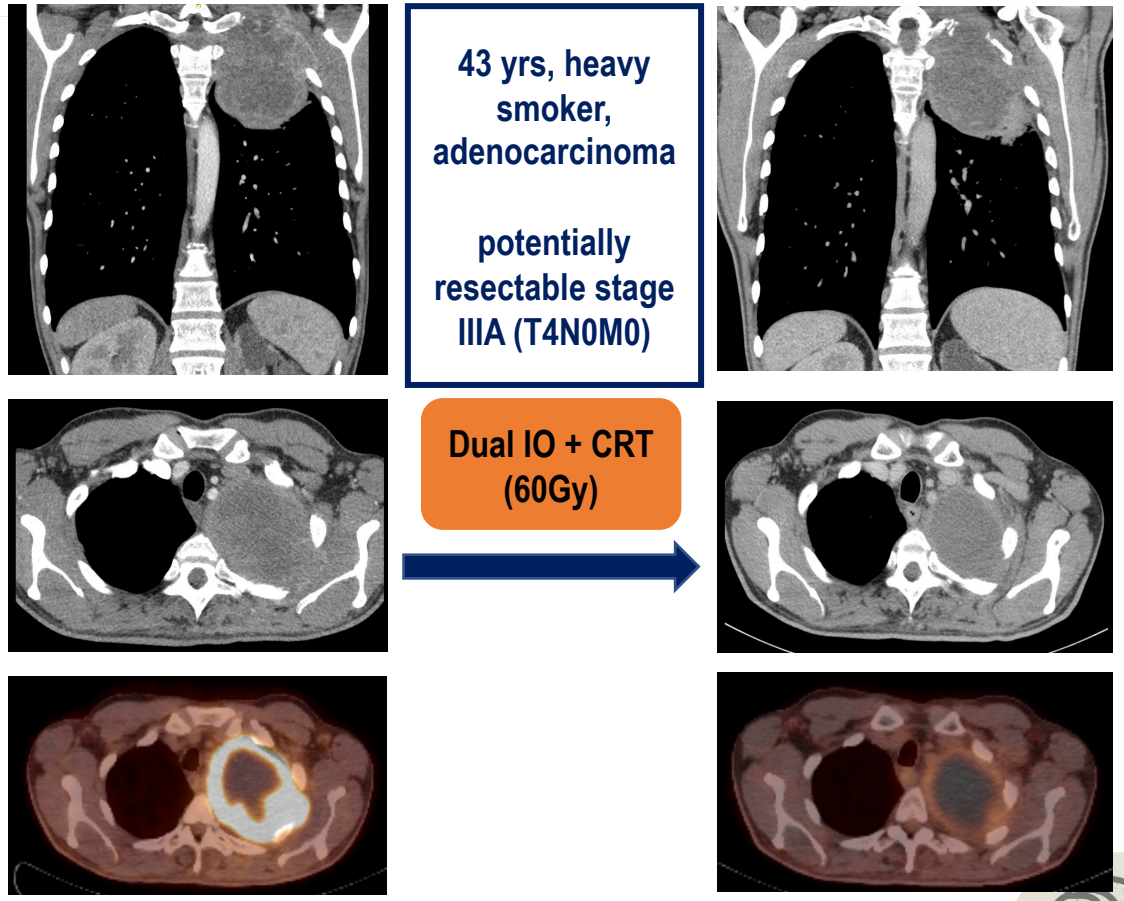
	n (%)
Time from last radiotherapy to surgery (days, median (IQR))	43 (41-44)
Pulmonary resection	
Lobectomy	13 (52%)
Lobectomy + chest wall	10 (40%)
Lobectomy + chest wall + partial vertebrectomy	1 (4%)
Pneumonectomy	1 (4%)
Resection margin	
R0	25 (100%)
Pathological response	
pCR	15 (60%)
MPR	19 (76%)
No MPR	6 (24%)
Hospital stay (days, median (IQR))	6 (5-9)

Surgical morbidity and mortality

Any grade		16 (64%)
Grade 1-2		11 (44%)
Grade 3-4		5 (20%)
	Wound dehiscence	*1 (readmission <30days)*
	Atelectasis	*2*
	Pancreatitis	*1*
	Empyema	*1 (readmission <30days)*
Grade 5		0 (0%)[#]

INCREASE Phase II Trial Conclusions:

- Dual ICI plus CRT resulted in pCR rates of 60% which compares favorably to CRT (33%) or ICI+Chemo (22%)
- Surgical morbidity and mortality are similar to prior trials of induction CRT
- Worthy of RCT evaluating 'Quad' modality therapy



Pathology showed complete response

[1]ESPATUE Trial Eberhardt 2015, Ann Oncol
[2]Keynote 816 Forde 2022, NEJM

	SAKK 16/18	INCREASE
Inclusion criteria	N2	N0-1
ICI	Durvalumab	Ipi/Nivo
Neoadj Sequence	Chemo→RT→ICI	Concurrent Cheom/RT/ICI
RT Dose	Immune stimulatory: 2 Gy x 20, 5 Gy x 5, 8 Gy x 3	Near definitive: 50-60 Gy
RT Target	Primary Disease	All sites of gross tumor
pCR	20% (5/25)	60% (15/25)

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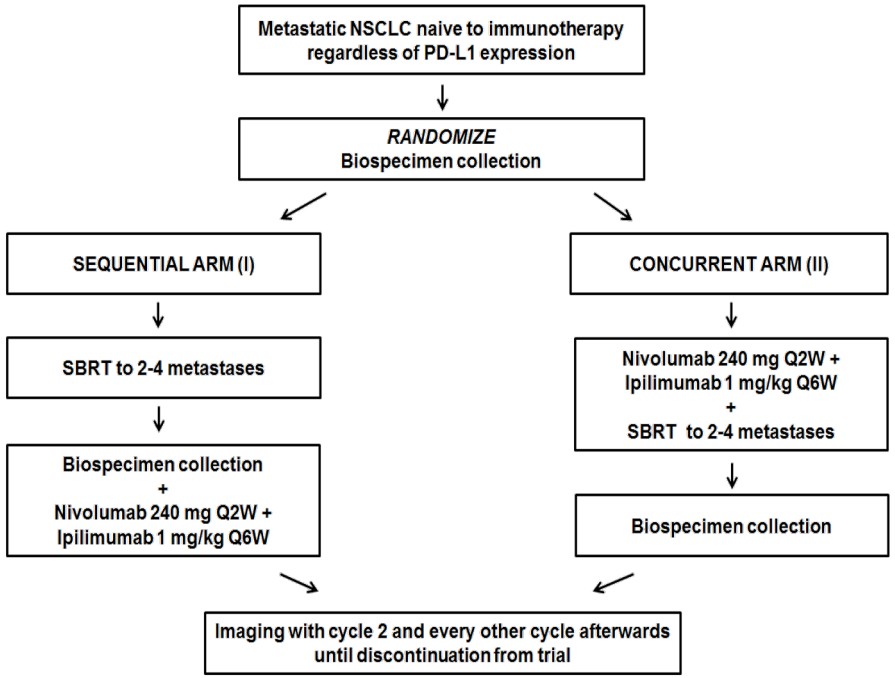
COSINR

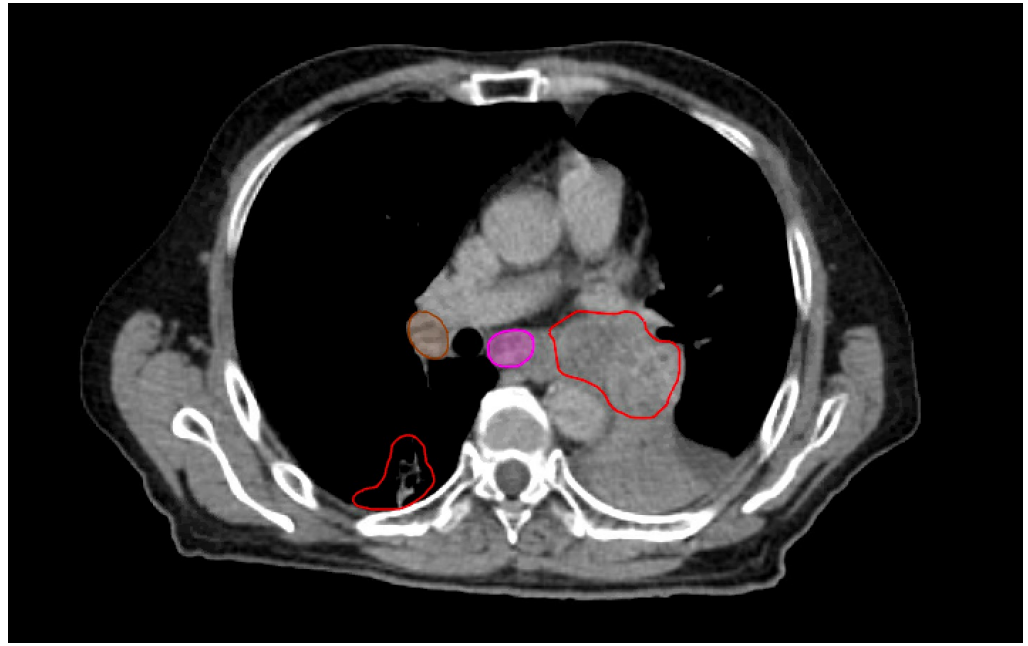


- Checkmate 227 ICI – Nivo q2 week, ipi q6 week
- N = 37 patients randomized to sequential or concurrent treatment
  - 19 sequential, 18 concurrent
- Lower DLTs in concurrent arm, accrued another n = 38 in concurrent arm

Concurrent arm had fewer DLTs (previously reported)

RT on COSINR

- Dosing and constraints modeled after NRG BR001
- Goal for RT to be safe, short, small fields and ablative
  - Prioritize OAR > Target coverage
  - Large tumors had central portion treated
  - Not all mets treated, up to 4 isos



PD-L1 status

- 0% in 35 patients (46.7%)
- 1 – 49% in 24 patients (32%)
- ≥50% in 14 patients (18.7%)
- Not evaluable in 2 patients

- Brain Metastasis was present in 32% of patients (10% in CM227)
- Liver Metastasis was present in 16% of patients (18% in CM227)

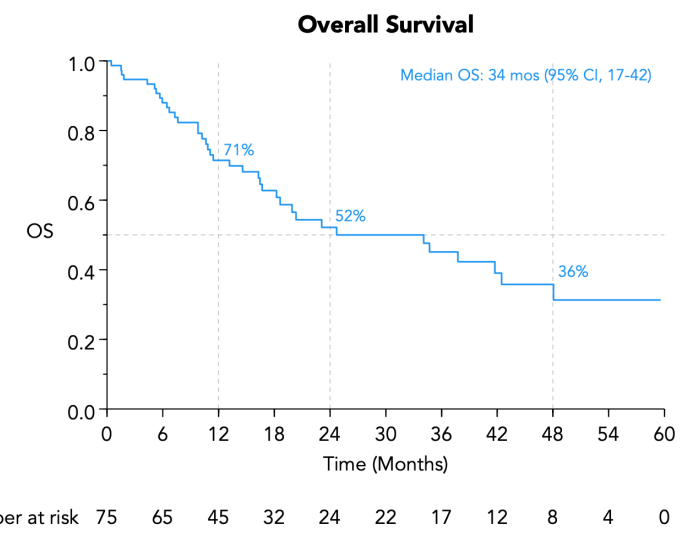
- Oligometastatic (3 or fewer metastases) = 30% of patients

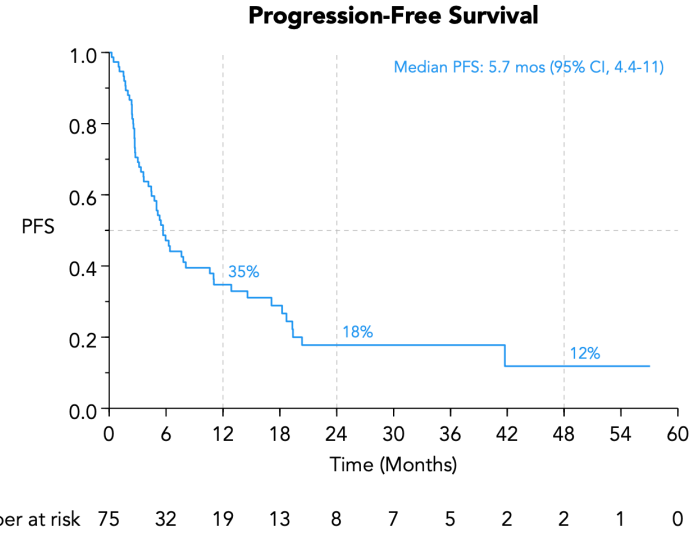
Results:

DLT = Grade 3 or higher adverse event that is either “probably” or “definitely” related to both immunotherapy and SBRT within 90 days of treatment

4 DLT events (5.3%) – all grade 3 pneumonitis events (oxygen requirement)

40 patients (81.6%) progressed with new intracranial or extracranial metastases

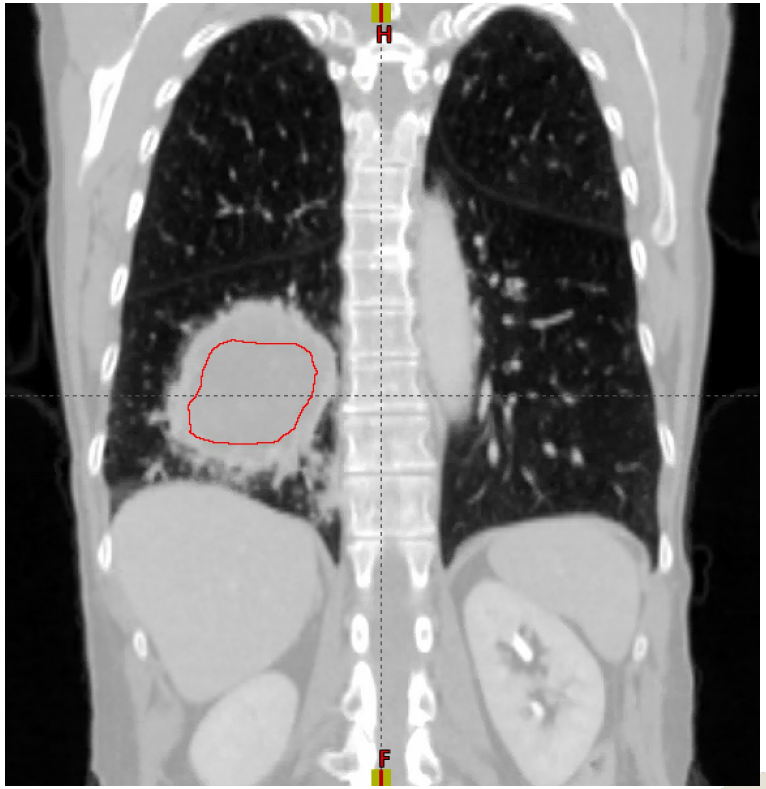




CM227 24mo. OS 40%, median PFS 17 months

COSINR Conclusions:

- IO + selective SABR appears safe
  - Prioritized OARs over coverage
- Promising median OS of 34 mo in population with high rate of PD-L1 0%
- Worth studying role of RT outside of oligometastatic setting
- No role off trial currently, interesting area of investigation



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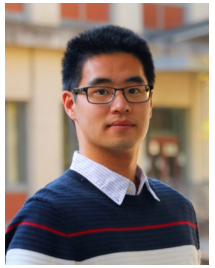

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