Associazione Italiana Radioterapia e Oncologia clinica

Società Italiana di Radiobiologia

STereotactic Ablative RadioTherapy in NEWly diagnosed and recurrent locally advanced non-small cell lung cancer patients unfit for concurrEnt chemo-Radiotherapy: early analysis of the START-NEW-ERA non randomised phase II trial

Fabio Arcidiacono
Radiotherapy Oncology Centre - Terni

Associazione Italiana Radioterapia e Oncologia clinica
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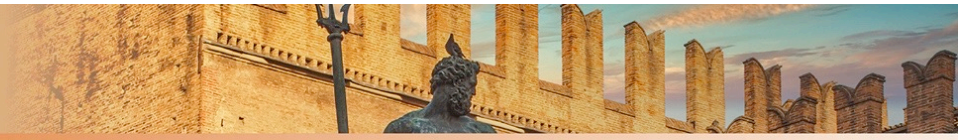


DICHIARAZIONE

Relatore: FABIO ARCIDIACONO

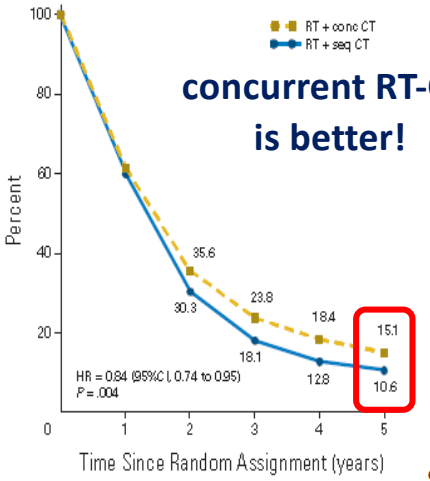
Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**

Locally advanced non-small cell lung cancer

OS before and after PACIFIC trial

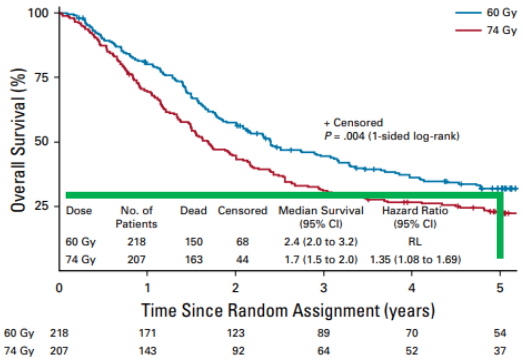
The past…



concurrent RT-CT is better!

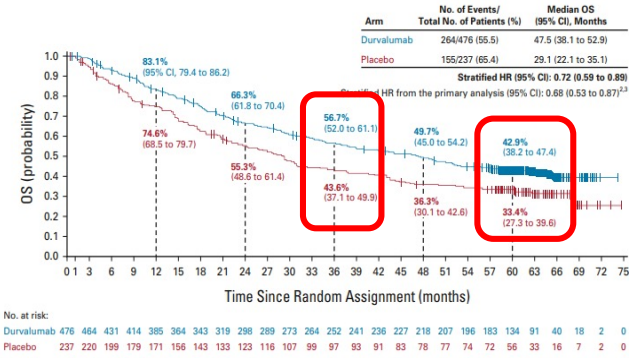
Auperin,JCO 2010

standard RT dose is 60 Gv!



RTOG 0617,JCO 2019

The present!



PACIFIC,JCO 2022

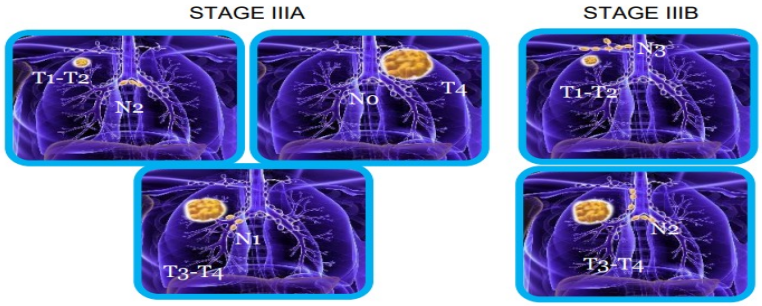
Durvalumab after concurrent RT-CT is the best!

Heterogeneity in Patient Population

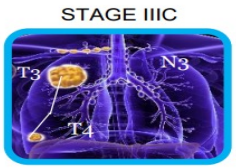
Fit vs unfit (Frail) Patient

- Age (i.e. elderly patients)
- Co-morbidities
- Cardio-pulmonary reserve
- organ damage from persistent smoking
- Cisplatin-based chemotherapy tolerability

Heterogeneity in Disease Location and Extent



De Leyn et al JTO 2009



T/M	Label	N0	N1	N2	N3
T1	T1a ≤1	IA1	IIB	IIIA	IIIB
	T1b >1-2	IA2	IIB	IIIA	IIIB
	T1c >2-3	IA3	IIB	IIIA	IIIB
T2	T2a >3-4	IB	IIB	IIIA	IIIB
	T2a >3-4	IB	IIB	IIIA	IIIB
	T2b >4-5	IIA	IIB	IIIA	IIIB
T3	T3 >5-7	IIB	IIIA	IIIB	IIIC
	T3 Invc	IIB	IIIA	IIIB	IIIC
	T3 Satell	IIB	IIIA	IIIB	IIIC
T4	T4 >7	IIIA	IIIA	IIIB	IIIC
	T4 Invc	IIIA	IIIA	IIIB	IIIC
	T4 Ipsi Nod	IIIA	IIIA	IIIB	IIIC

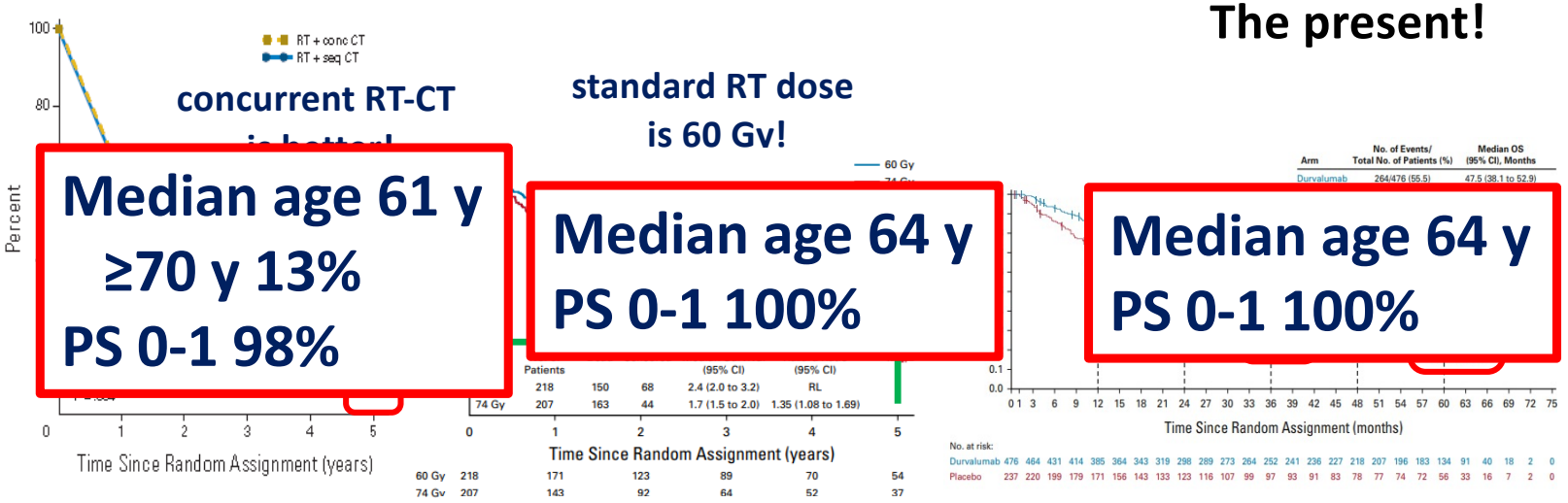
- Large tumor volume
- Location primary tumor
- Bulky nodal involvement
- Multiple nodal involvement
- Bilateral nodal involvement
- Supraclavicular nodal involvement

Locally advanced non-small cell lung cancer

OS before and after PACIFIC trial

The past…

The present!



concurrent RT-CT is better!

Median age 61 y
≥70 y 13%
PS 0-1 98%

standard RT dose is 60 Gv!

Median age 64 y
PS 0-1 100%

Median age 64 y
PS 0-1 100%

Auperin,JCO 2010

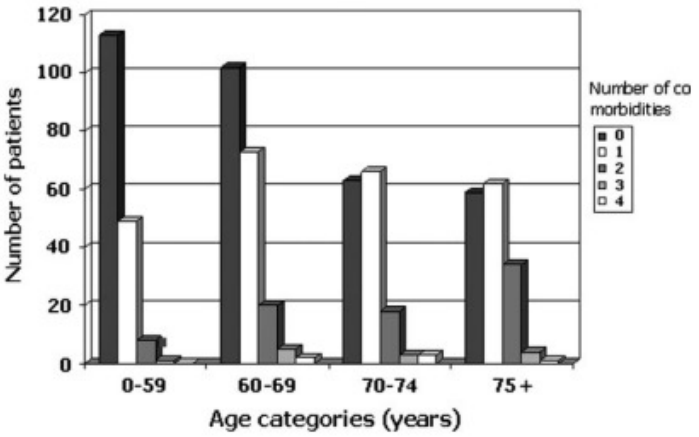
only fit patients

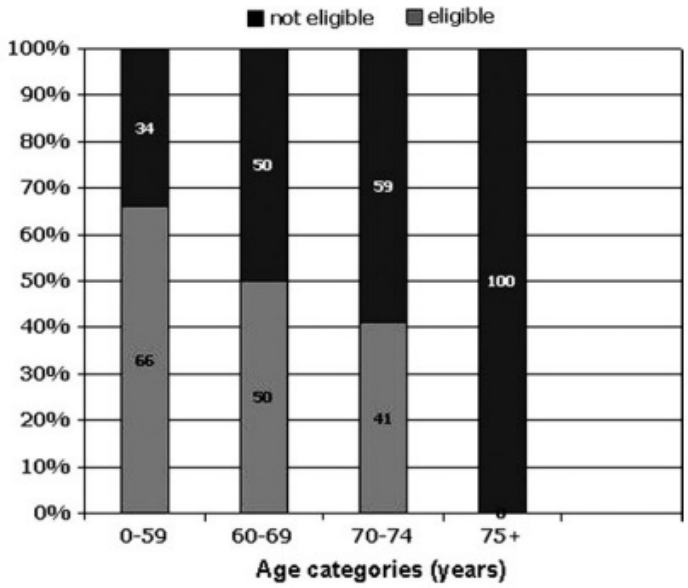
PACIFIC,JCO 2022

Durvalumab after concurrent RT-CT is the best!

De Ruysscher, Annals of Oncology 2009

Eligibility for concurrent chemotherapy and radiotherapy of locally advanced lung cancer patients: a prospective, population-based study





Garassino, JTO 2022

Durvalumab After Sequential Chemoradiotherapy in Stage III, Unresectable NSCLC: The Phase 2 PACIFIC-6 Trial

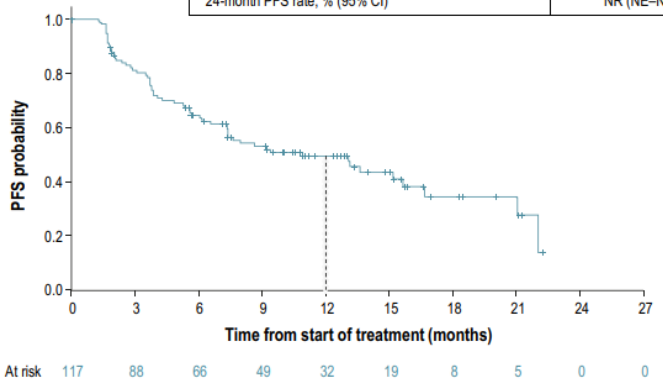
66% ≥65 y
18% ≥75 y

40% ECOG PS 0
57% ECOG PS 1

96% started Durvalumab
≥ 14 days after completion RT

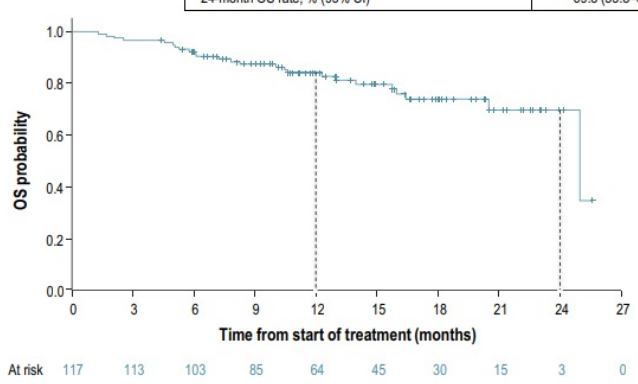
A

	All patients (N = 117)
Total progression events, n (%)	61 (52.1)
Median PFS, months (95% CI)	10.9 (7.3–15.6)
12-month PFS rate, % (95% CI)	49.6 (39.5–58.9)
24-month PFS rate, % (95% CI)	NR (NE–NE)



B

	All patients (N = 117)
Deaths, n (%)	25 (21.4)
Median OS, months (95% CI)	25.0 (25.0–NE)
12-month OS rate, % (95% CI)	84.1 (75.6–89.9)
24-month OS rate, % (95% CI)	69.8 (55.8–80.2)



Start DURVALUMAB as soon as possible is better!

PACIFIC

CT CT (CT) Durvalumab

Radiotherapy

day 1 40 ≤ 54

OTT

PACIFIC 6

CT CT CT Radiotherapy Durvalumab

day 1 22 43 64 104 ≤118

OTT

Kaster, Clin Lung Cancer 2015

Radical-Intent Hypofractionated Radiotherapy for Locally Advanced Non–Small-Cell Lung Cancer: A Systematic Review of the Literature

Table 1 Studies With Concurrent Chemoradiotherapy

Study	Dose	Fraction	Dose/fx	Acute BED	Late BED	3 Year OS (%)	1 Year OS (%)	AE (%)	AP (%)	LE (%)	LP (%)
Machtay (2005)[21]	60	20	3	78.0	120.0			0	0	0	25
Belderbos (2007)[22]	66	24	2.75	84.2	126.5	29	56	17	9	5	18
Uitterhoeve (2007)[23]	66	24	2.75	84.2	126.5	31	57	NR	NR	5[a]	18[a]
Tsoutsou (2008)[24]	52.5	15	3.5	7							
Bral (2010)[25]	67.2	30	2.24	8							
Mat											
Cas											
Carr											
Mag											
Lin (2013)	69	22-24	3								
Liu (2013)[30]	75	25	3	7							
Chen (2013)[31]	55	20	2.75	7							
Donato (2013)[32]	68.4	30	2.28	8							
van Den H											
Bearz (20											

Table 2 Studies With Nonconcurrent Chemoradiotherapy

Bernier (1999)[37]	55	20	2.75	70.1	105.4			6	9	3	6
Nguyen (1999)[38]	45	15	3	58.5	90.0			NR	NR	NR	NR
Sun (2000)[39]	65	26	2.5	81.3	119.2			0	0	NR	NR
Hallqvist (2004)[40]	84	35	2.4	104.2	151.2			NR	NR	NR	NR
										0	0
										0	0
										0	6
										NR	NR
Bral (2010)[44]	70.5	30	2.35	87.1	125.7	18	65	NR	NR	0	16
	65-68	25-26	2.6	81.9-85.8	121.3-127.3	32	68	6	3	NR	NR
	67.5	30	2.25	82.7	118.1			0	0	NR	NR
	45	15	3	58.5	90.0	12	53	NR	NR	NR	NR
	55	20	2.75	70.1	105.4			0	0	NR	NR
	55	20	2.75	70.1	105.4			NR	NR	NR	NR
	60	20	3	78.0	120.0		75	7	3	3	7
	77-85.5	25	2.28-3.42	70.0-114.7	100.3-183.0	29		0	0	0	0
	66	24	2.75	84.2	126.5	22	69	5	8	4	13
	66	24	2.75	84.2	126.5	19	53	NR	NR	5[a]	18[a]
Donato (2013)[32,b]	68.4	30	2.28	82.7	118.1		77[a]	0	10[a]	0[a]	5[a]
Maguire (2012)[17,b]	55	20	2.75	70.1	105.4	27	83	NR	NR	NR	NR

OS was found to be associated with tumor BED

positive relationship between OS and OTT

Table 3 Reported Weighted Toxicity for Studies With Concurrent Chemoradiotherapy

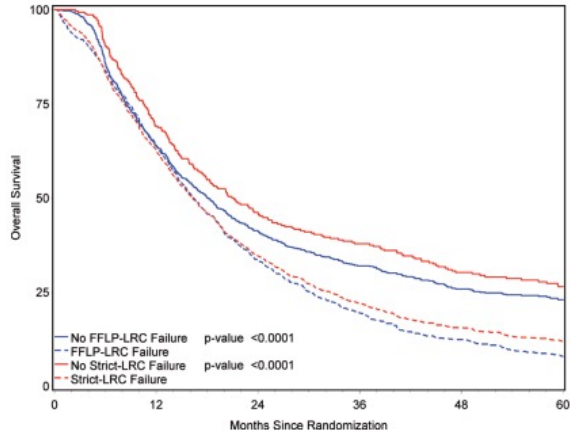
Site	Acute, Mean (95% CI)	Late, Mean (95% CI)
Esophagus	14.9% (0.7%, 29.1%)	6.6% (−1.9%, 4.0%)
Lung	7.9% (−9.8%, 20.9%)	12.2% (−3.8%, 8.1%)

Machtay, JTO 2012

Defining Local-Regional Control and Its Importance in Locally Advanced Non-small Cell Lung Carcinoma

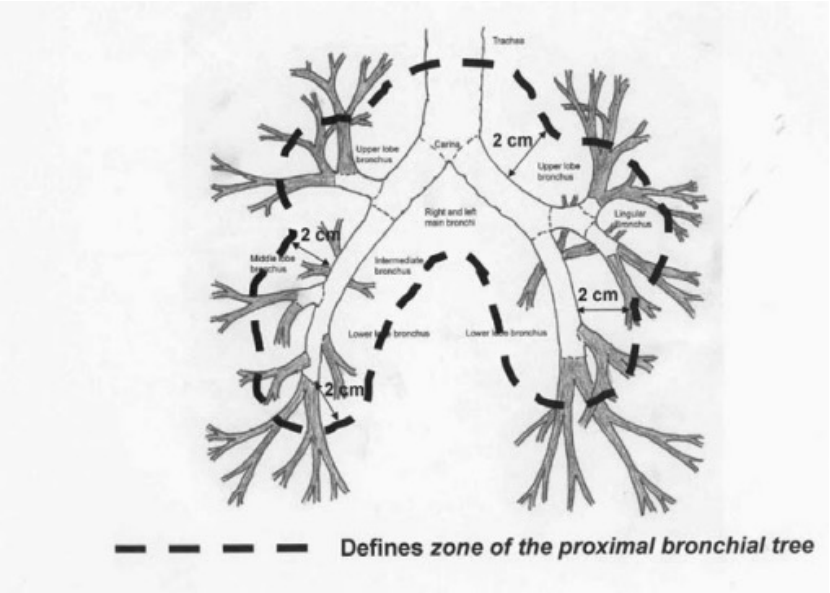
A Radiation Therapy Oncology Group Analysis

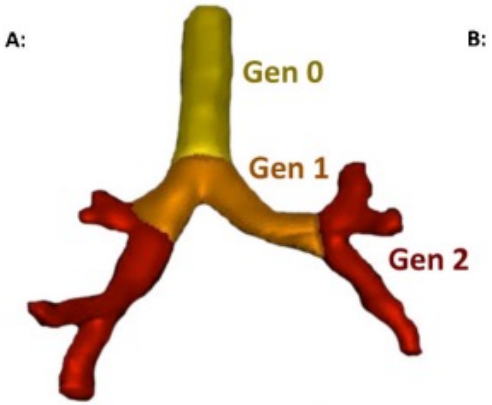
It is axiomatic that **cure of cancer cannot be achieved without control** of primary tumor



In LA-NSCLC there is a **strong association** between **loco-regional control and survival**

ULTRACENTRAL Tumors





tumors in cases in which the **GTV directly abuts the major airways**

Chang, Int J Radiat Oncol Biol Phys 2014

Stereotactic Ablative Radiation Therapy for Centrally Located Early Stage or Isolated Parenchymal Recurrences of Non-Small Cell Lung Cancer: How to Fly in a "No Fly Zone"

AIRO2022
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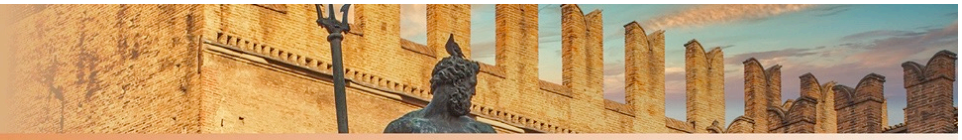
Radioterapia di precisione per un'oncologia innovativa e sostenibile



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FULL LENGTH ARTICLE | ARTICLES IN PRESS

STereotactic Ablative RadioTherapy in NEWly diagnosed and recurrent locally advanced non-small cell lung cancer patients unfit for concurrEnt RAdio-chemotherapy: early analysis of the START-NEW-ERA non-randomised phase II trial

Fabio Arcidiacono, MD • Paola Anselmo, MD • Michelina Casale, PhD • Cristina Zannori, MD • Mark Ragusa, MD • Francesco Mancioli, MD • Giovanni Marchetti, MD • Fabio Loreti, MD • Marco Italiani, PhD • Sergio Bracarda, MD • Ernesto Maranzano, MD • Fabio Trippa, MD • Show less

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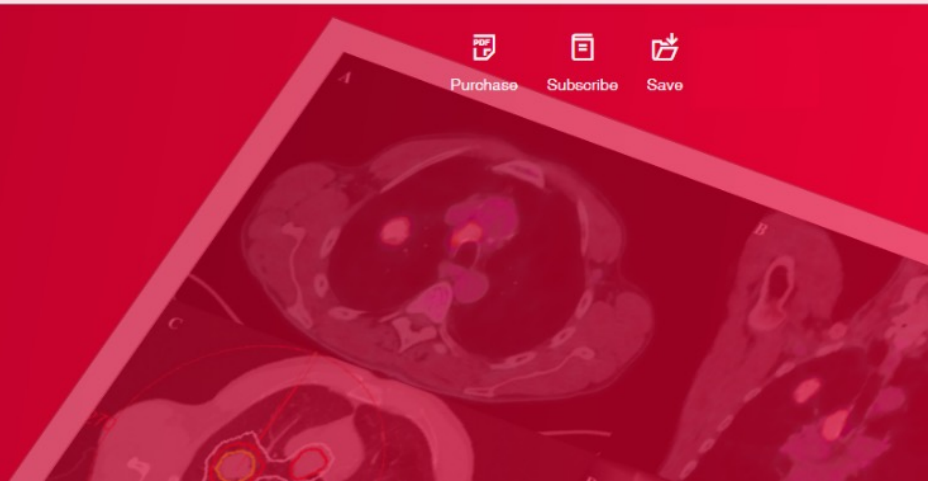


Clinical trials.gov NCT05291780

Enrollment

- Patients firstly discussed within the **multidisciplinary lung cancer group** and judged **unfit** for surgery and concurrent CT-RT
- ECOG **PS ≤2**
- De-novo or recurrent LA-NSCLC
- **PET/CT** and brain **MRI** (CT)

Enrollment

- Neoadjuvant CT (**CDDP and Vinorelbine** x3-4) in fit patients
- After PACIFIC trial results patients who had no progression after CT and SAbR received **Durvalumab**

Radiation Planning

- **GTV-T** and **GTV-N** → residual disease on PET-CT after CT and pre-SAbR
- SAbR delivered by **V-MAT**

- **SIB** was optimized to differentiate the dose for T and N

Treatment Planning

- Treatment schedule based on target volume and closeness to **OAR**
- Total prescribed dose biologically equivalent to 54-60 Gy in 27-30 fractions (**BED_{10} = 59,5Gy-72Gy**)
- PTV Dmax no more than 107% of the prescription dose

- OAR dose constraints:

❑ **normal lungs - GTV**, V_{20Gy} <10%

❑ **heart**: $D_{0.5cc}$ <27-29 Gy

❑ **esophagus**: $D_{0.5cc}$ <32-34 Gy

❑ **trachea, proximal bronchial tree and ipsilateral bronchus**: $D_{0.5cc}$ <35 Gy

❑ **aorta and others great vessels**: $D_{0.5cc}$ <53 Gy

❑ **spinal cord**: $D_{0.5cc}$ 30 Gy

Endpoints

Primary

- **LOCAL CONTROL**: lack of progression of the treated volume.
- **SAFETY**: absence of ≥G3 toxicity according CTCAE v4.0

Endpoints

Secondary

- Regional (N) recurrence free-survival
- Distant progression free-survival
- Overall survival

Results

- **80 LA-NSCLC** patients enrolled (2015/12→until now)

- **50 LA-NSCLC** patients (early analysis)

Results

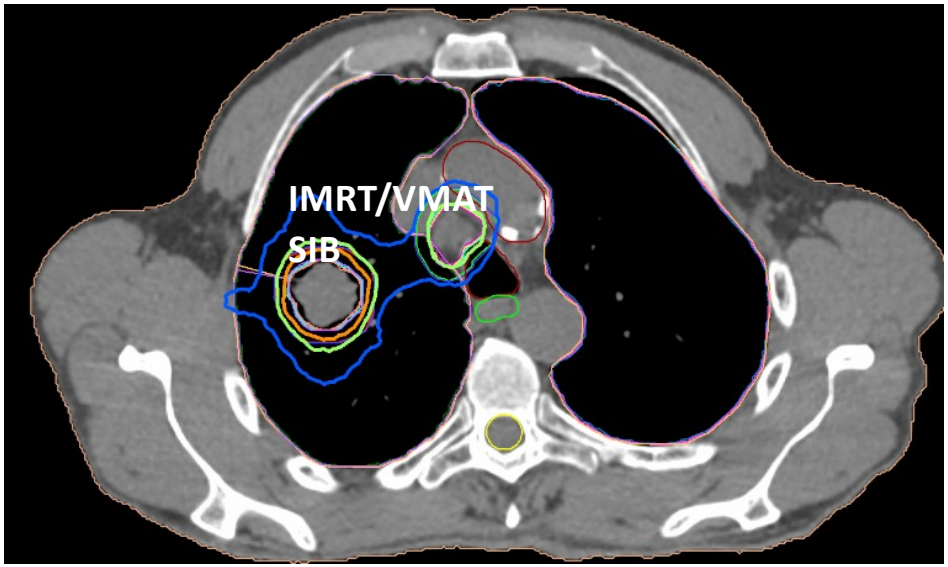
	Number of patients	%
Total patients	50	100
Median age	73 (45-88)	
EGOG PS		
0-1	43	86
2	7	14
Histology		
Adenocarcinoma	26	52
Squamous Cell C	24	48
Stage (TNM 8th)		
IIB	9	18
IIIA	20	40
IIIB	17	34
IIIC	4	8
Other treatments		
Neoadjuvant CT	27	54
Durvalumab	7	14

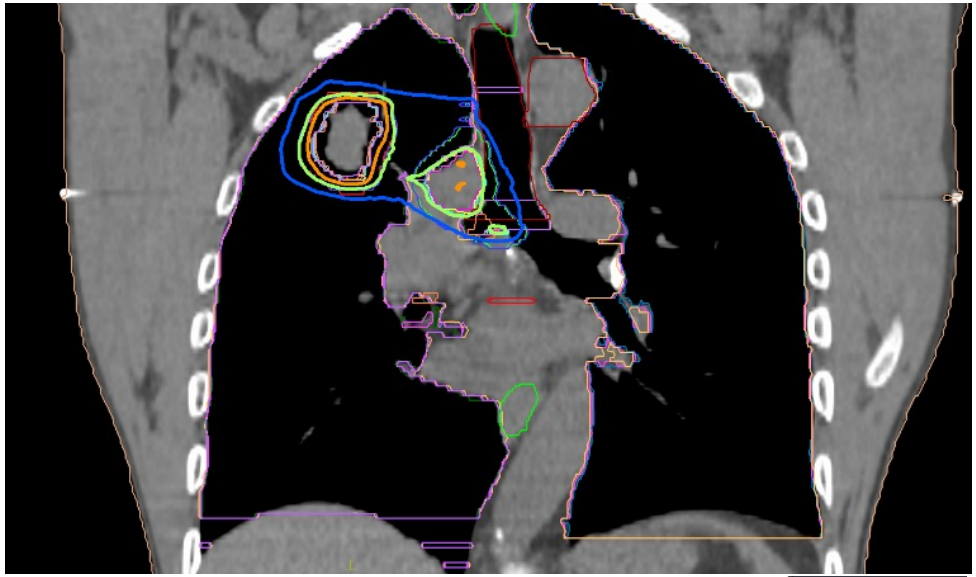
median FU 38 months (12-80)

median prescribed dose

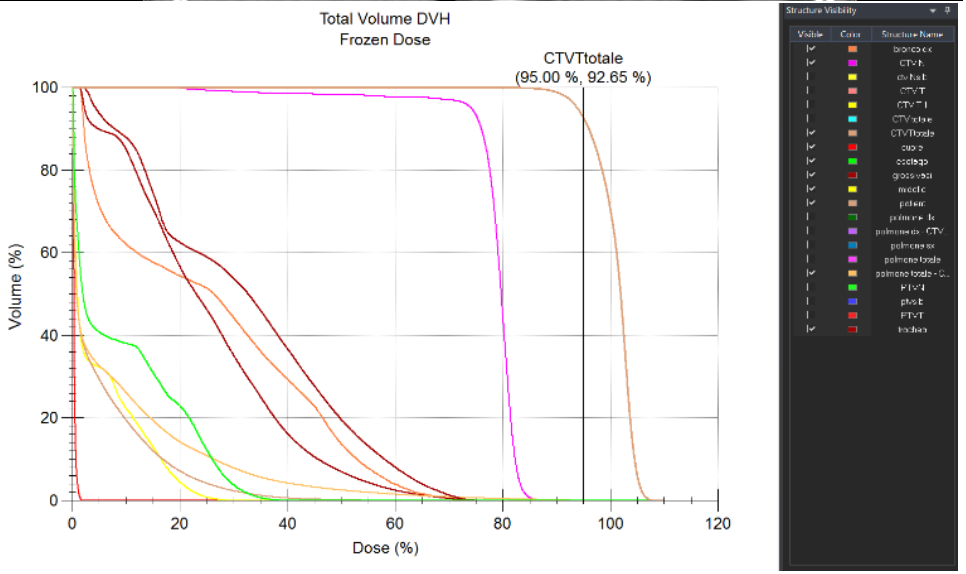
T → 45 Gy/5 fx (35-55)
N → 40 Gy/5 fx (35-45)

46% SAbR alone





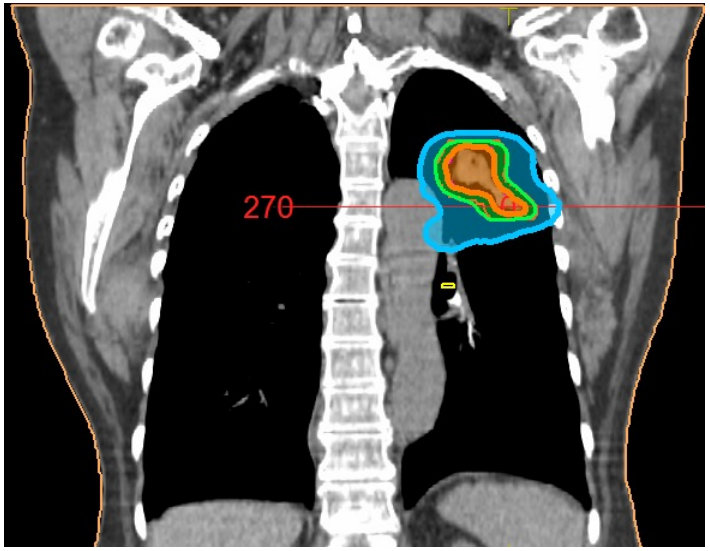
50 Gy/5 fx → T
40 Gy/5 fx → N

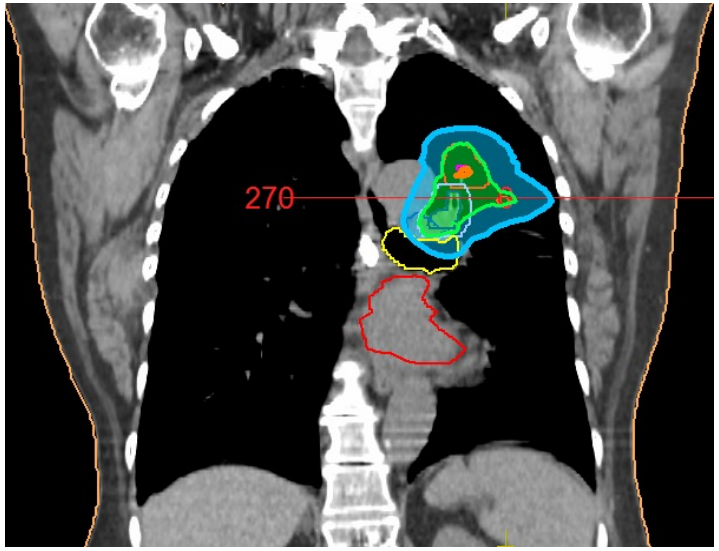


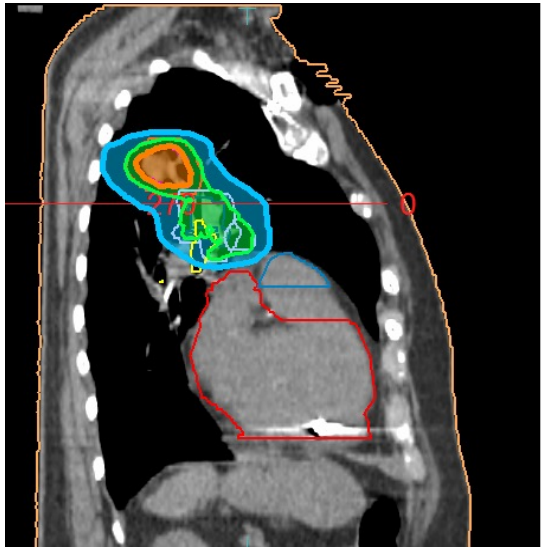
50 Gy

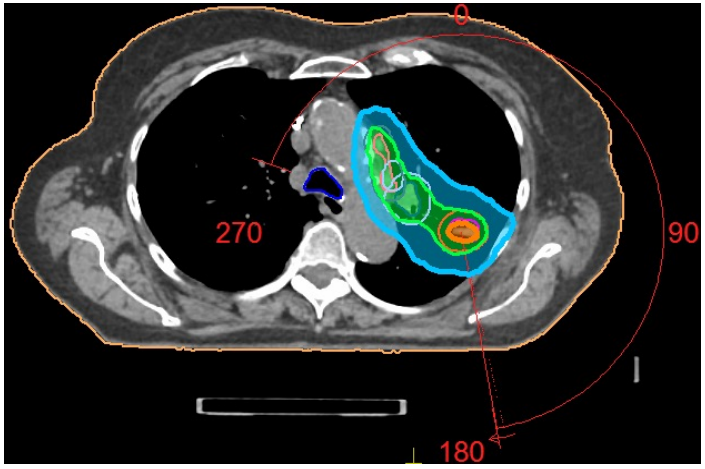
40 Gy

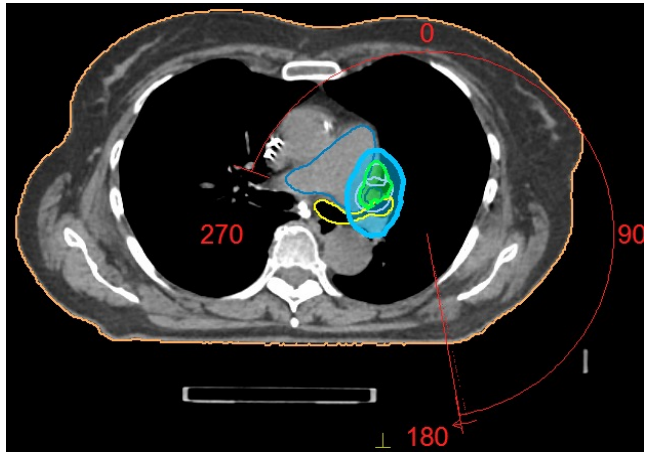
35 Gy

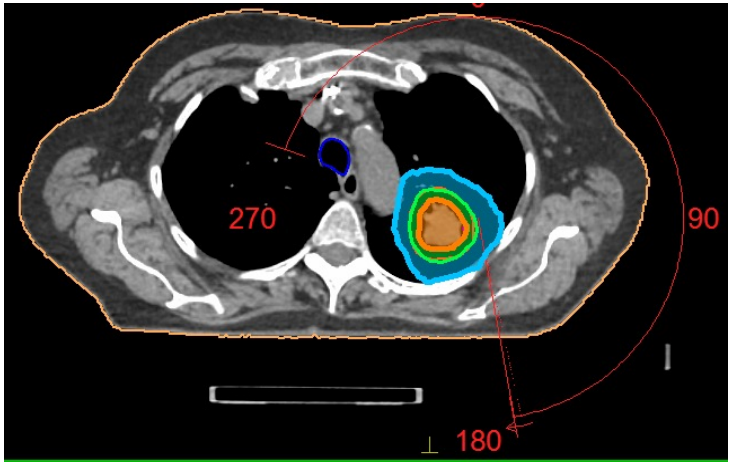




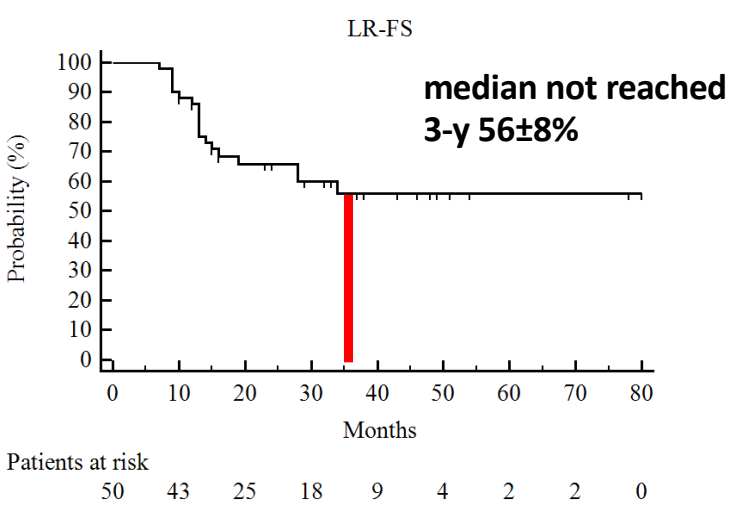


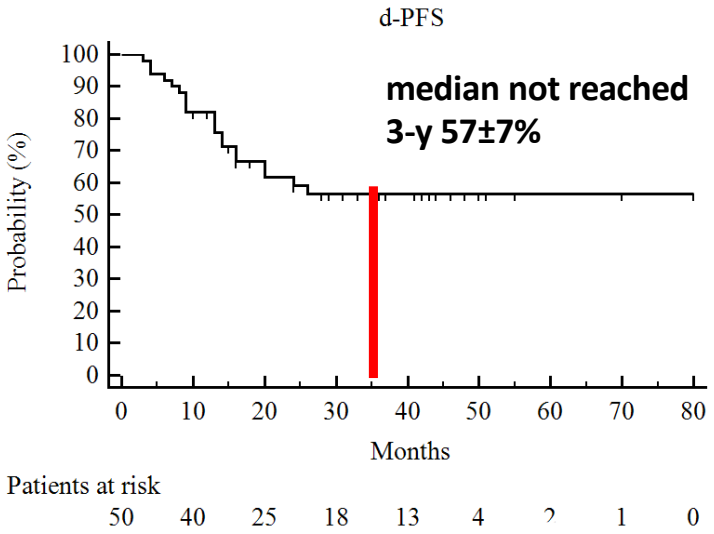


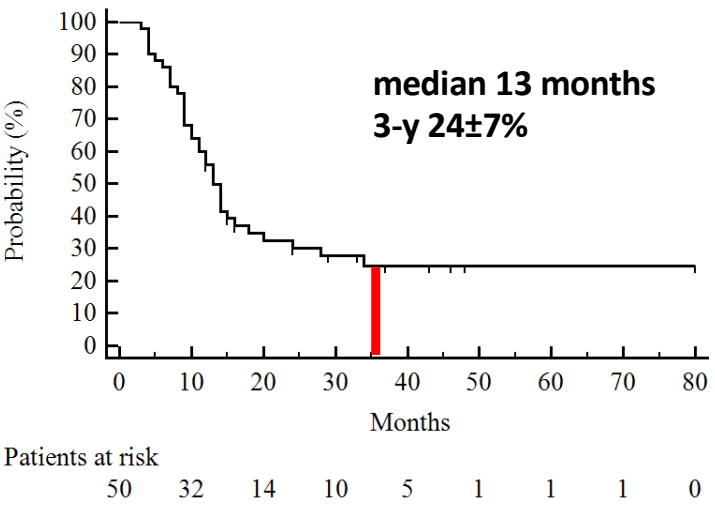


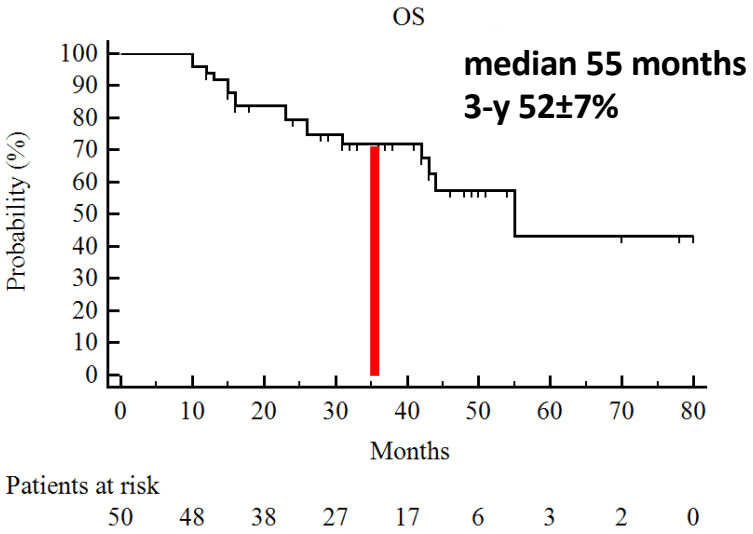


Outcomes

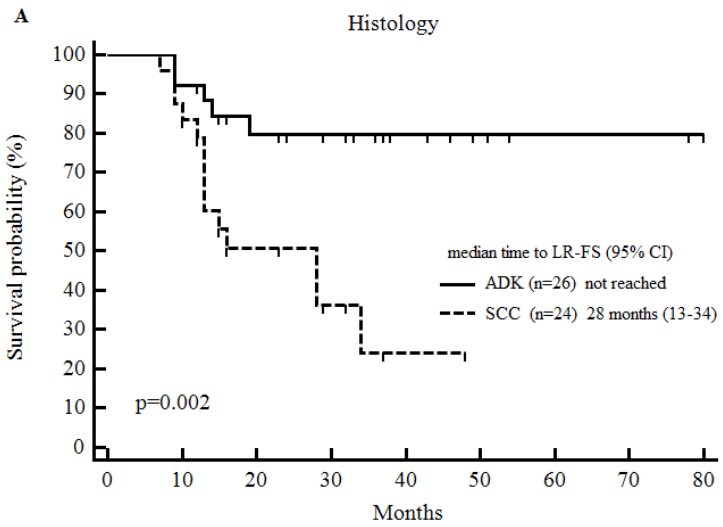

LR-FS
median not reached
3-y 56±8%
Probability (%)
Months
Patients at risk
50 43 25 18 9 4 2 2 0


d-PFS
median not reached
3-y 57±7%
Probability (%)
Months
Patients at risk
50 40 25 18 13 4 2 1 0


DFS
median 13 months
3-y 24±7%
Probability (%)
Months
Patients at risk
50 32 14 10 5 1 1 1 0

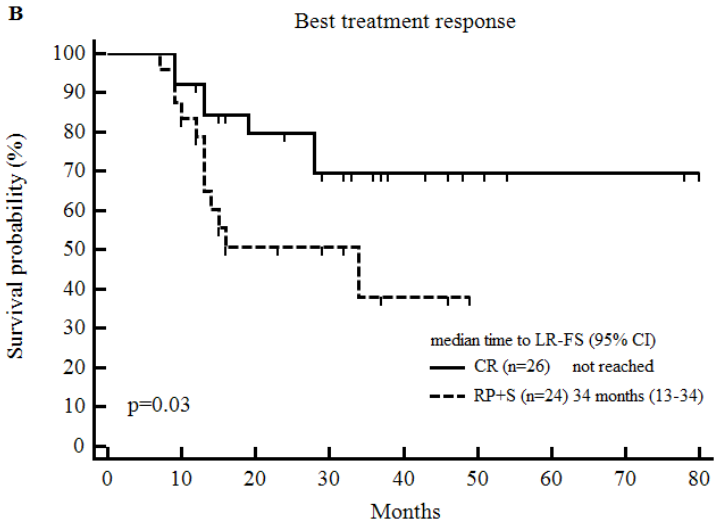

OS
median 55 months
3-y 52±7%
Probability (%)
Months
Patients at risk
50 48 38 27 17 6 3 2 0

Better LR-FS



Patients at risk

ADK	26	24	17	14	8	4	2	2	0
SCC	24	19	8	4	1	0	0	0	0



Patients at risk

CR	26	24	17	13	7	4	2	2	0
RP+S	24	19	8	5	2	0	0	0	0

adenocarcinoma and complete remission predictors of better local control

Multivariate analysis results of LR-FS, TNR-FS, distant progression, DFS and OS

Variables	LR-FS			TNR-FS			Distant progression			DFS			OS		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
N (single vs multiple)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
TNM stage **(IIB+ IIIA* vs IIIA^-IIIB)**	-	-	-	-	-	-	-	-	-	-	-	-	4.8	1.34-17	0.016
Histology (ADC vs SCC)	3.61	1.15-11.35	0.03	-	-	-	-	-	-	-	-	-	-	-	-
PTV (continuous)	-	-	-	-	-	-	-	-	-	-	-	-	1.004	1.001-1.010	0.008
Best treatment response (CR vs RP+S)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Multivariate analysis results of LR-FS, TNR-FS, distant progression, DFS and OS

Variables	LR-FS			TNR-FS			Distant progression			DFS			OS		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
N (single vs multiple)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
TNM stage **(IIB+ IIIA* vs IIIA^-IIIB)**	-	-	-	-	-	-	-	-	-	-	-	-	4.8	1.34-17	0.016
Histology (ADC vs SCC)	3.61	1.15-11.35	0.03	-	-	-	-	-	-	-	-	-	-	-	-
PTV (continuous)	-	-	-	-	-	-	-	-	-	-	-	-	1.004	1.001-1.010	0.008
Best treatment response (CR vs RP+S)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

SAbR for LA-NSCLC: comparison between trials

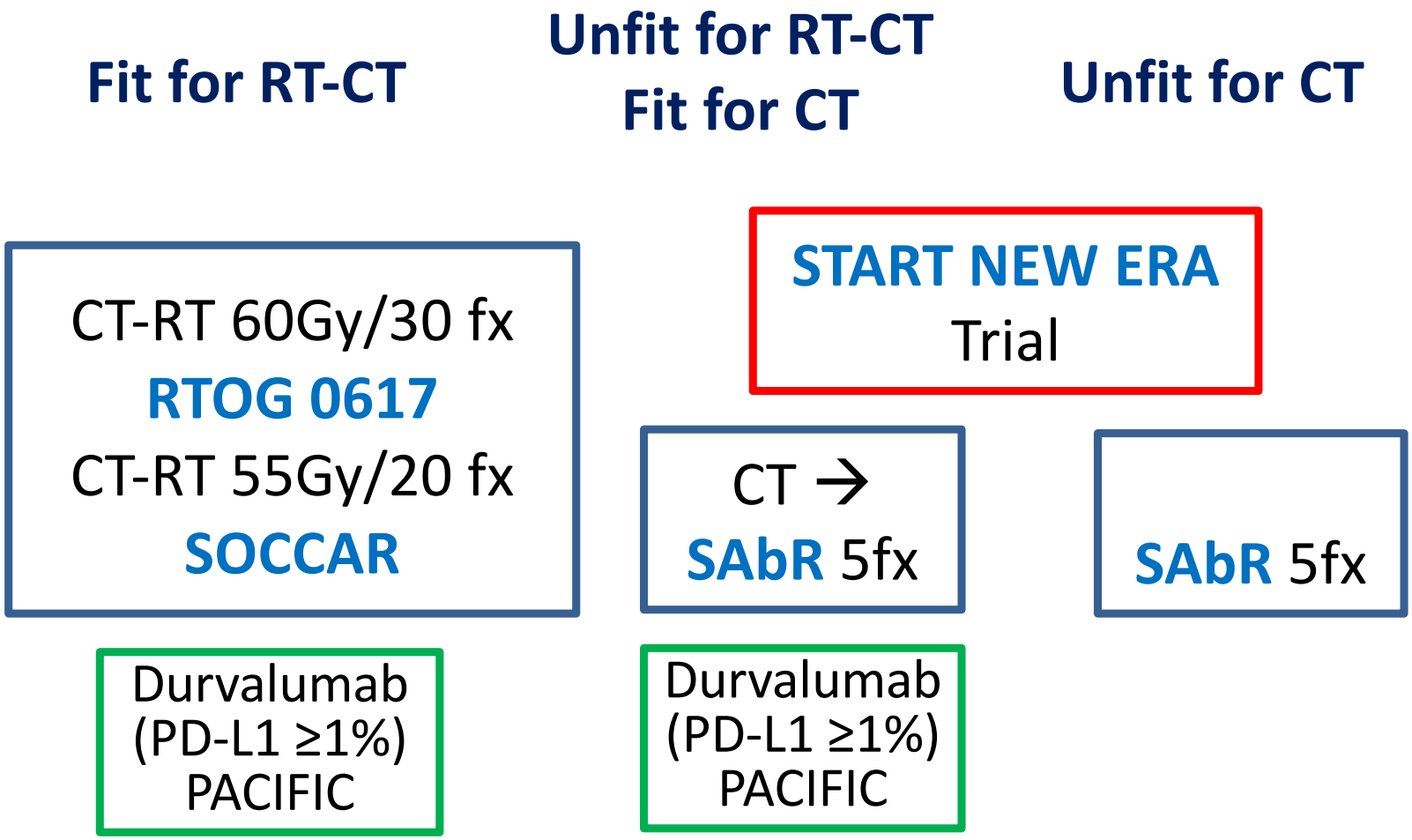
Trial	Study	RT	N. of pts	Median follow-up (months)	Neo-ad therapy	Total dose in 5 fractions (Gy)	Median BED_{10} (Gy)	Median PTV (cc)	**LC**	**OS**	**Toxicity ≥ G3**
Karam	R	SAbR	33	9	10(30%)	40	72	GTV 88.1	1-y 75%	1-y 48%	0%
Cong	R	SAbR Cyberknife	51	17	NS	35	59.5	NS	1-y 54% 3-y 40%	1-y 76.5% 3-y 20.6%	10% 4% G5
Parisi	Ph II	SAbR (HT)	17	NS	17(100%)	30 (T)* 25 (N)*	48 37.5	NS	77%	1-y 59% 3-y 29%	24% 4% G5
Kubicek	Ph II	SAbR Cyberknife	22	23.1	22(100%)	50 (T)^ 45 (N)	100 85.5	NS	1-y 100%	1-y 82% 2-y 53%	9% 4% G5
Our trial	**Ph II**	**SAbR VMAT**	**50**	**38**	**27(54%)**	**45 (T) 40 (N)**	**85.5 72**	**82**	**1-y 86±5% 3-y 56±8%**	**1-y 94±3% 3-y 72±7%**	**0%**

Safety

No patients developed **≥G3**

acute and **late** toxicities

our clinical practice in unresectable LA-NSCLC



Thanks for your attention!!!!

every component is important to complete this difficult and intriguing LA-NSCLC puzzle!!!!

P.Anselmo M.Casale S.Fabiani M.Italiani E.Maranzano F.Trippa