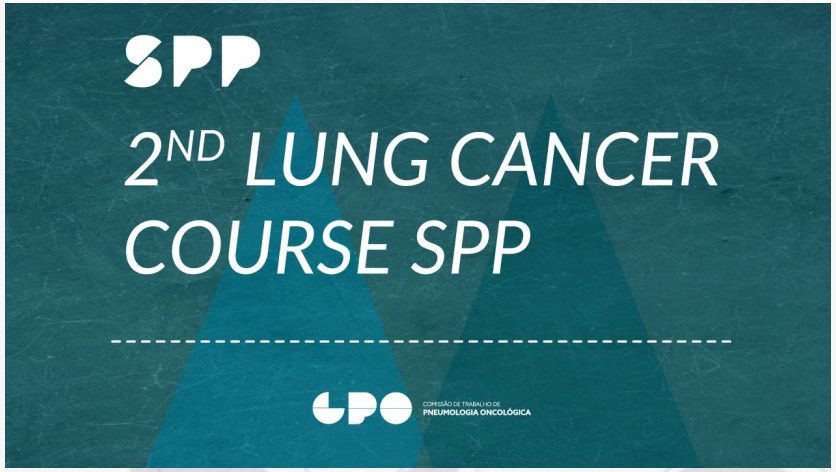
Locally advanced non surgical NSCL

a multidisciplinary approach



30th
JANUARY
2021

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FACULDADE DE MEDICINA DO PORTO
IBMC INSTITUTO DE BIOLOGIA MOLECULAR E CELULAR
INSTITUTE FOR MOLECULAR AND CELL BIOLOGY
I3S INSTITUTO DE INVESTIGAÇÃO E INOVAÇÃO EM SAÚDE
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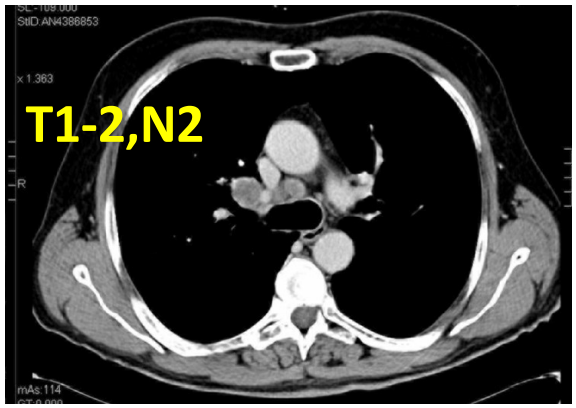
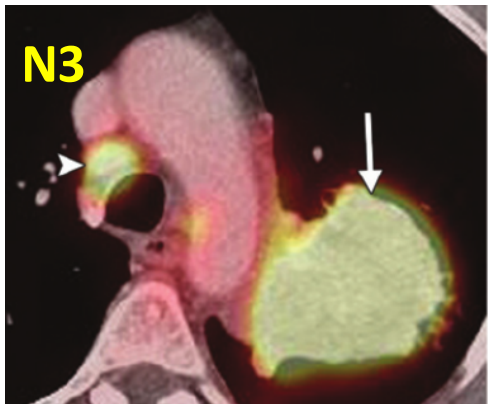
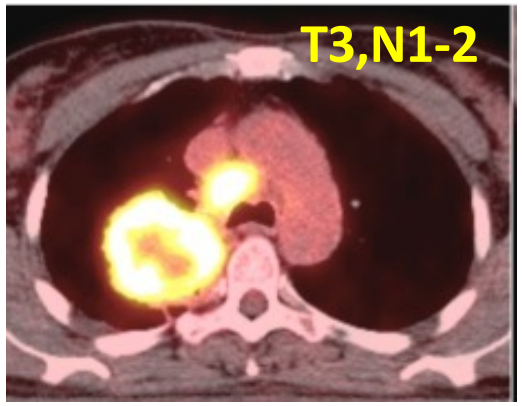
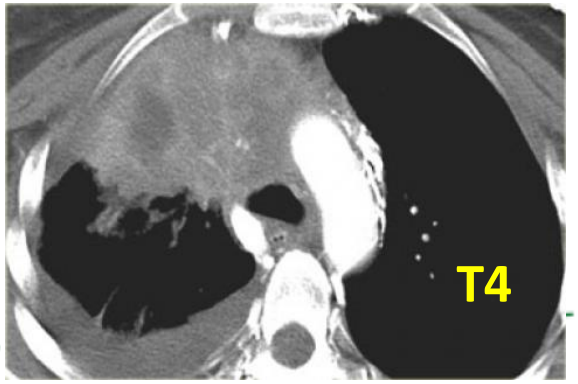
SPP SOCIEDADE PORTUGUESA DE PNEUMOLOGIA

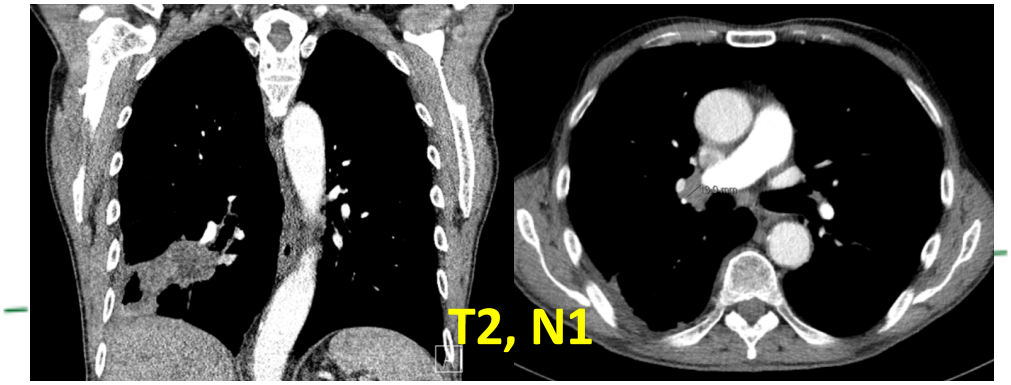
LA-NSCLC heterogeneity





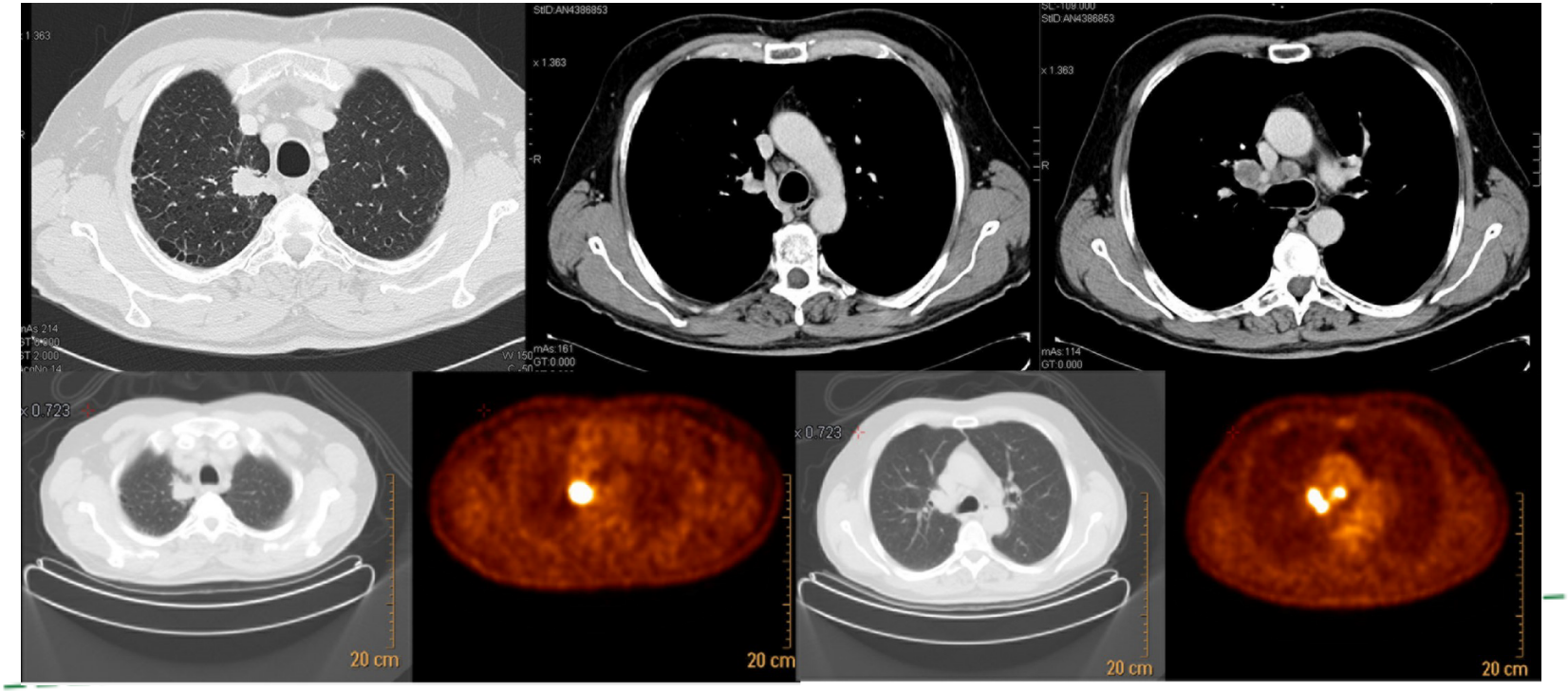






The management of LA-NSCLC differs among centers

LA-NSCLC clinical stage cT2N2, multiple stations, IIIA



Italian survey

- 32% radical cCRT
- 27% neoadjuvant CT
- 23% surgery after CT or cCRT

Bruni A, et al. PLoS ONE 2019;14(11): e0224027

How much can we improve survival of patients with LA-NSCLC?

HR 0.88

Radiotherapy alone vs
Chemoradiation[1]

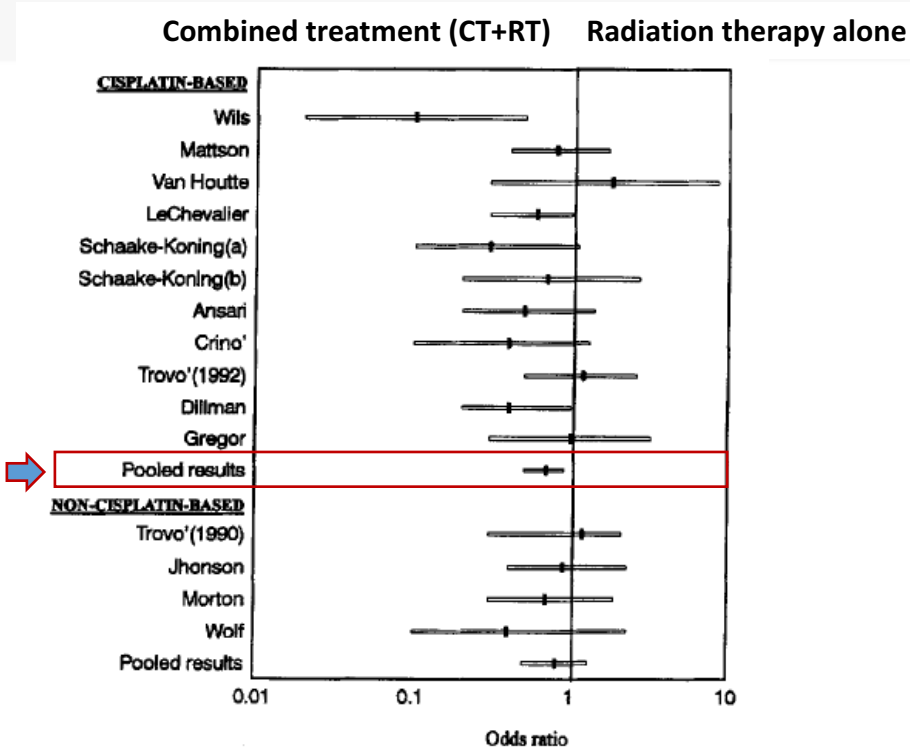
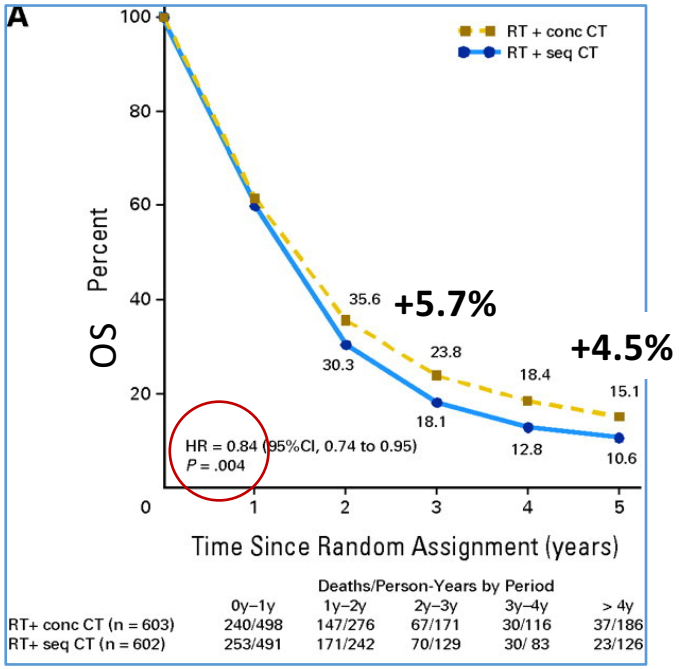


Figure 2. Odds ratio (OR) at 2 years (combined treatment: radiotherapy alone) — | — = Trial results and 95% confidence intervals. Solid vertical line represents OR of unity.

Marino et al. Randomized trials of radiotherapy alone versus combined chemotherapy and radiotherapy in stages IIIa and IIIb nonsmall cell lung cancer. A meta-analysis. Cancer 1995;76(4):593-601

[1] De Ruysscher & van Loon. Clin Oncol. 2016 Nov;28(11):708-711

Concomitant versus sequential radiotherapy and chemo.



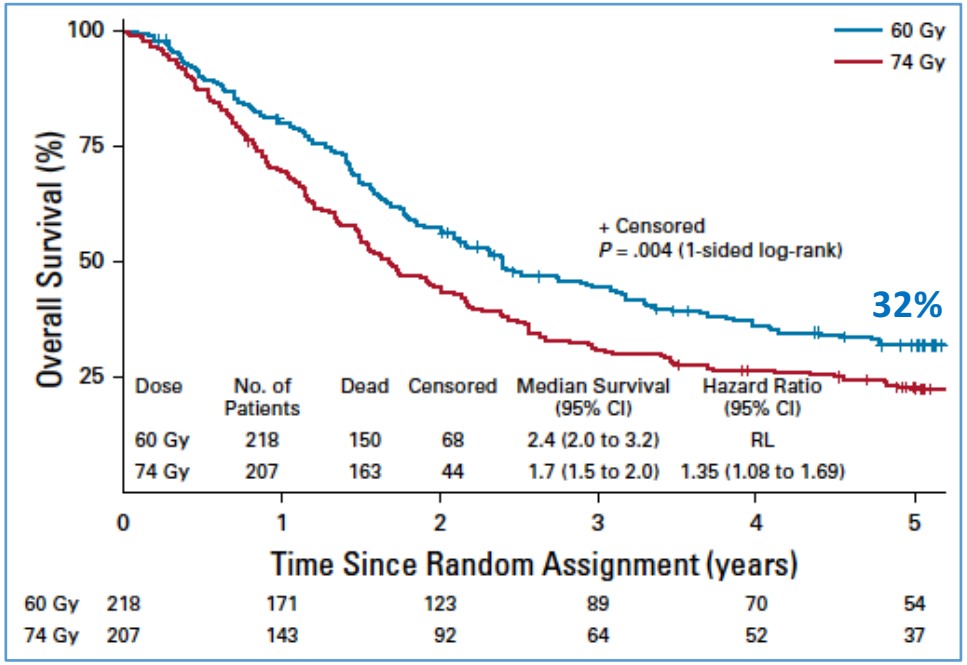
- Metanalysis of 6 trials (n=1205) showed **significant OS benefit** of concomitant chemoradiotherapy (HR 0.84)
- Concomitant radiochemotherapy **increase acute and late toxicities (esophagitis and pneumonitis)**
- Only 40% of LA-NSCLC patients are candidates for this approach

Aupérin et al. *Journal of Clinical Oncology* 2010;28(13):2181-2190 | Non-small Cell Lung Cancer Collaborative Group. BMJ 1995;311:899–909.

Chemoradiation is the standard of care

RTOG0617 trial

- **60-Gy radiation dose (2-Gy daily over 6 weeks)** with concurrent chemotherapy should remain the standard of care
- Cetuximab had no effect on OS, but increased toxicity (**grade ≥3 in 85.4%** vs 72.4%)
- The 2-year OS rates in the control arm are similar to the PACIFIC trial



Trial	2-year OS rate, % (95%CI)	2-year PFS rate, % (95%CI)
RTOG0617	**59.6%** (52.6-66%)	**30.7%** (24.6-37.1%)
PACIFIC	**66.3%** (61.7-70.4%)	**49.5%** (44.6-54.2%)

Bradley et al. J Clin Oncol 2019; https://doi.org/10.1200/JCO.19.01162

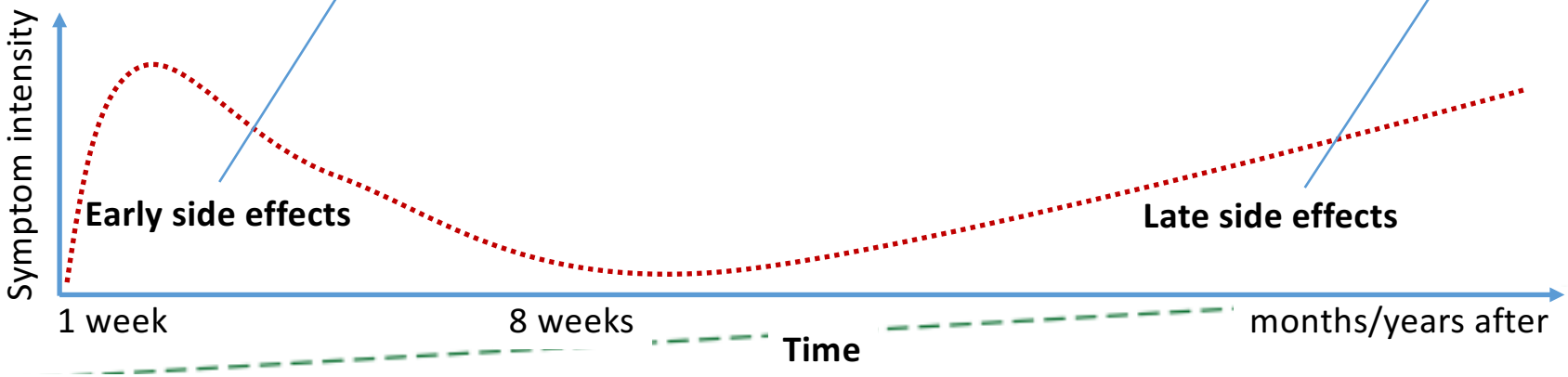
Safety issues regarding Thoracic Radiotherapy

Symptomatic pneumonitis occurs in 5-15%, with increased risk due to:

- Radio-sensitizing agents (eg, platinum-based therapies, **gemcitabine**, taxanes)
- Concurrent rather than sequential chemotherapy

Fatigue, nausea and vomiting, skin changes, sore mouth and throat, acute radiation pneumonitis, difficulty swallowing, local hair loss

Esophageal stricture, chronic radiation pneumonitis, pericarditis, spinal cord damage, rib fracture, pleural effusion, lung fibrosis, and radiation-induced heart disease



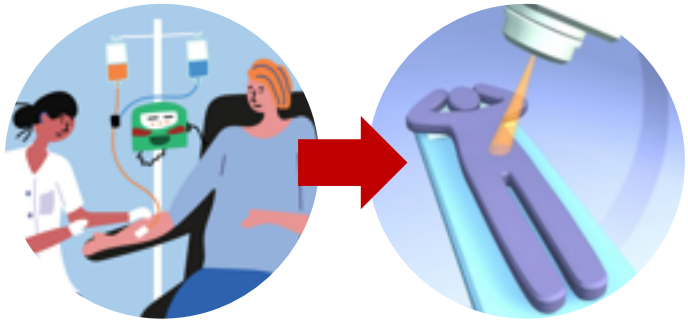
Lung cancer: Side effects of radiotherapy. https://www.cancerresearchuk.org/about-cancer/lung-cancer/treatment/radiotherapy/side-effects. Accessed May 27, 2020 | Ming X, et al. *Medicine*. 2016;96:41(e5051) | Aoki M, et al. *Radiat Oncol*. 2015;10:99 | Zhao J, et al. *Oncotarget*. 2017;8:97623–32 | Giridhar P, et al. *Asian Pac J Cancer Prev*. 2015;16:2613–17 | McDonald S, et al. *Int J Radiat Oncol Biol Phys*. 1995;31:1187-1203 | Merrill WM, et al. Radiation-induced lung injury. UpToDate. 2017. www.uptodate.com/contents/radiation-induced-lung-injury. Accessed June 21, 2017. 8. Caffo O. *Lung Cancer*. 2001;S81-S90.

Chemoradiotherapy in frail patients

Radiotherapy alone

- 5-year OS 5-20% (all cases)[1,2]
- ORR 45%, OS 17 months (>70y)[3]
- Grade 3-4 toxicity: Neutropenia 0%, infection 4%, pneumonitis 3%[3]

Sequential chemoradiation



- ORR 65%, OS 10 months, 5-year OS 9% (>70 y)[4]
- Grade 3-4 toxicity: hematological 22%, esophageal 7%, and pulmonary 4%[4]

Concurrent chemoradiation

- ORR 51.5%, OS 22 months (low dose daily carboplatin, >70y)[3]
- Grade 3-4 toxicity: Neutropenia 57.3%, infection 12.5%, pneumonitis 1%[3]

Overall conclusions:

- Age and comorbidities have impact in OS and may increase the rate of treatment-related adverse events
- OS benefit for different approaches is probably smaller than obtained in younger and fitter patients

[1] De Ruysscher & van Loon. Clin Oncol. 2016 Nov;28(11):708-711 | [2] Shuyan et al. Transl Lung Cancer Res. 2020; 9(5):2082–2096 | [3] Atagi et al (JCOG0301) Lancet Oncol 2012;13:671-678 | [4] Jeremic et al. Int J Radiat Oncol Biol Phys. 1999 May 1;44(2):343-8

How much can we improve survival of patients with LA-NSCLC?

HR **0.88** x **0.84** = **0.74**

Radiotherapy alone vs **Chemoradiation**[1]

Sequential vs **Concurrent Chemoradiation**[2]

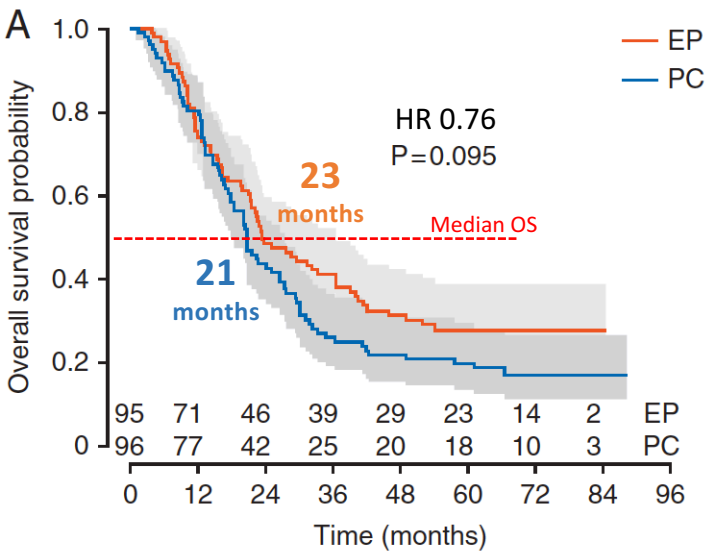
±7%

5-year OS gain

[1] De Ruysscher & van Loon. Clin Oncol. 2016 Nov;28(11):708-711 | [2] Aupérin et al. *Journal of Clinical Oncology* 2010;28(13):2181-2190

Which are the best concurrent chemo(radiation) regimens?

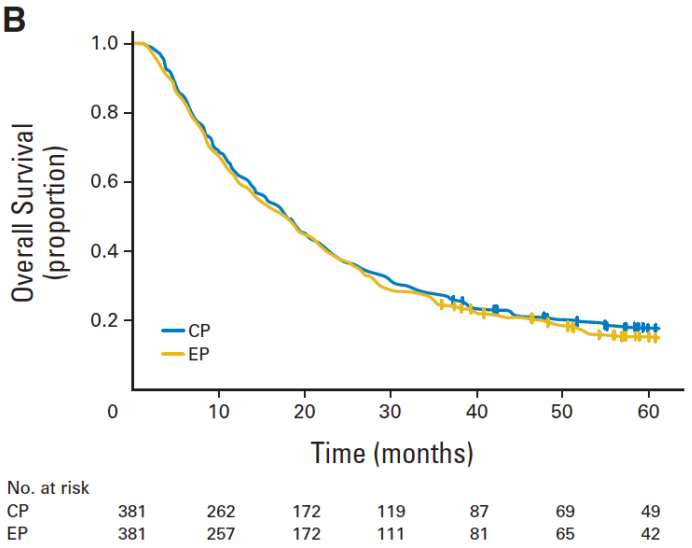
Cis+Etoposide slightly better than Carbo+Paclitaxel[1]



3-year OS rate **41% (EP)** vs **26% (PC)**; P=0.024

- Increased grade 2 radiation pneumonitis in the PC arm (33.3% versus 18.9%, P=0.036)
- Increased grade 3 esophagitis in the EP arm (20.0% versus 6.3%, P=0.009)

Cis+Etoposide and Carbo+Paclitaxel are equal[2]



EP was associated with increased morbidity:

- more hospitalizations (**2.4** vs 1.7), infectious complications (**47.3%** vs 39.4%), acute kidney disease/dehydration (**30.5%** vs 21.2%) and mucositis/esophagitis (**18.6%** vs 14.4%)

SPP

[1] Liang et al. Ann Oncol. 2017; 28(4):777-783 (RCT) | [2] Santana-Davila et al. J Clin Oncol. 2015; 33(6):567-74 (retrospective study)

Concurrent chemo(radiation) regimens

Nonsquamous NSCLC			
Regimen	**Outcome**	**Toxicity**	**Notes**
Carboplatin AUC 5 + Pemetrexed 500 mg/m^2 every 21 days for 4 cycles [1]	ORR 77% PFS 12.6 months OS 21.2 months	Grade ≥3 neutropenia 8% Grade ≥3 esophagitis 16% Grade ≥3 pneumonitis 12%	RT 70 Gy Included squamous hitology
Cisplatin 75 mg/m^2 + Pemetrexed 500 mg/m^2 every 21 days for 3 cycles + concurrent thoracic RT → Pemetrexed consolidation for 4 cycles **(PROCLAIM, 2)**	ORR 36% PFS 11.4 months OS 26.8 months	Grade ≥3 neutropenia 24% Grade ≥3 esophagitis 16% Grade ≥3 pneumonitis 2%	RT 60 to 66 Gy **Similar efficacy, with less hematological toxicity than Cis/Etop**
Nonsquamous or Squamous NSCLC			
Carboplatin AUC 2 + Paclitaxel 45–50 mg/m^2 weekly with concurrent thoracic RT ± additional 2 cycles every 21 days of Carboplatin AUC 6 + Paclitaxel 200 mg/m^2 [3]	ORR not reported PFS 11.8 months OS 28.7 months	Grade ≥3 neutropenia 24% Grade ≥3 esophagitis 7% Grade ≥3 pneumonitis 6% **Grade 1-2 neuropathy 30%**	Comparing groups received either 60 Gy or 74 Gy ± cetuximab
Cisplatin 50 mg/m^2 on days 1, 8, 29, and 36; Etoposide 50 mg/m^2 days 1–5 and 29–33	ORR not reported PFS not reported OS 15 months	Grade 4 neutropenia 32% Grade ≥3 Anemia 28% Grade ≥3 Esophagitis 20%	

[1] Govindan et al. J Clin Oncol 2011;29:3120-3125 | [2] Senan et al. (PROCLAIM trial) J Clin Oncol 2016;34:953-962 | [3] Bradley et al. Lancet Oncol 2015;16:187-199 | [4] Albain et al. (SWOG 9019). J Clin Oncol 2002;20:3454-3460

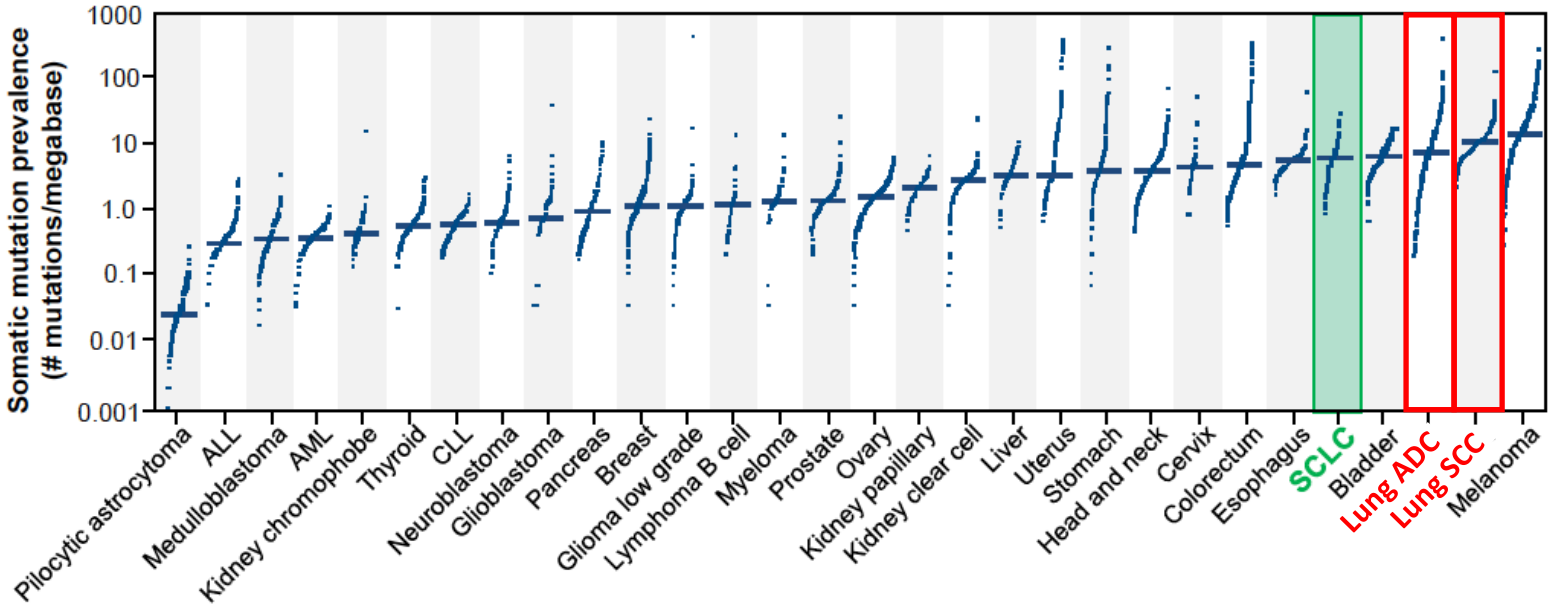
Consolidation or Maintenance Chemotherapy has failed

Trial (reference)	Design/treatment arm	Median OS, mo	HR (95% CI)	*P* value
CALGB 39801 [13]	cCRT vs.	12	N/R	0.3
	Induction Chemo→cCRT	14		
LUN 01–24 [14]	cCRT vs.	23.2	N/R	0.883
	cCRT→docetaxel	21.2		
SWOG S0023 [15]	cCRT→docetaxel→placebo vs.	35	0.63	0.013
	cCRT→docetaxel→gefitinib	23	(0.44–0.91)	
KCSG-LU05–04 [16]	cCRT vs.	20.6	0.91	0.44
	cCRT→docetaxel + cisplatin	21.8	(0.73–1.12)	
RTOG 0617 [17]	cCRT→Chemo vs.	24	1.07	0.29
	cCRT + cetuximab→Chemo + cetuximab	25	(0.84–1.35)	
START [18]	Sequential or cCRT→placebo	22.3	0.88	0.123
	Sequential or cCRT→tecemotide	25.6	(0.75–1.03)	
CALGB 30605 [19]	Chemo→RT + erlotinib	17	N/A	N/A

cCRT, concurrent chemo radiation; *Chemo*, chemotherapy; *N/A*, not applicable; *N/R*, not reported; *NSCLC*, non-small cell lung cancer; *RT*, radiation therapy

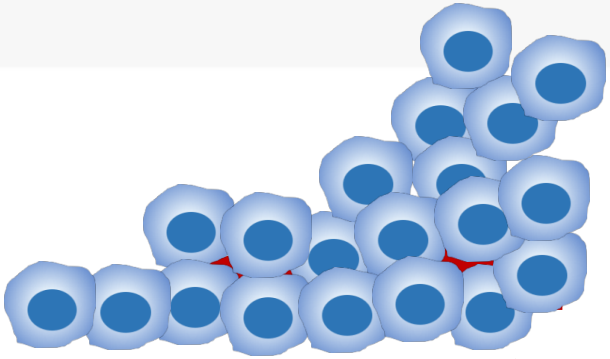
Puri et al. Current Oncology Reports (2020) 22:31

Clues for the success of immunotherapy in lung cancer

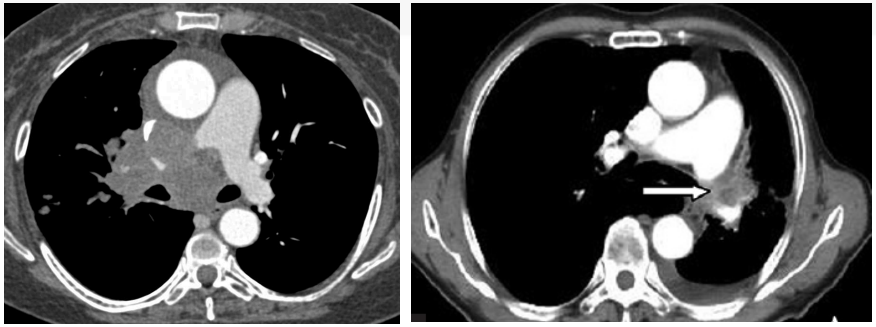


Alexandrov LB, et al. Nature 2013;500:415-421

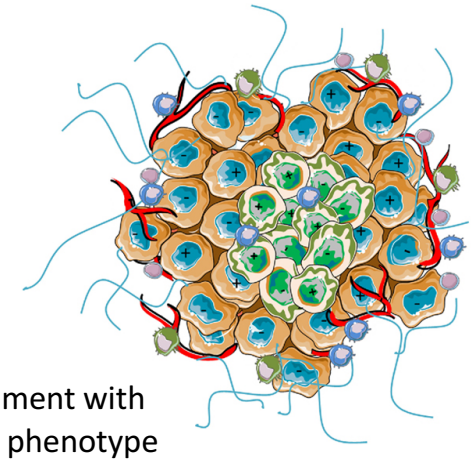
Hurdles for immunotherapy in lung cancer



Rapidly progressive

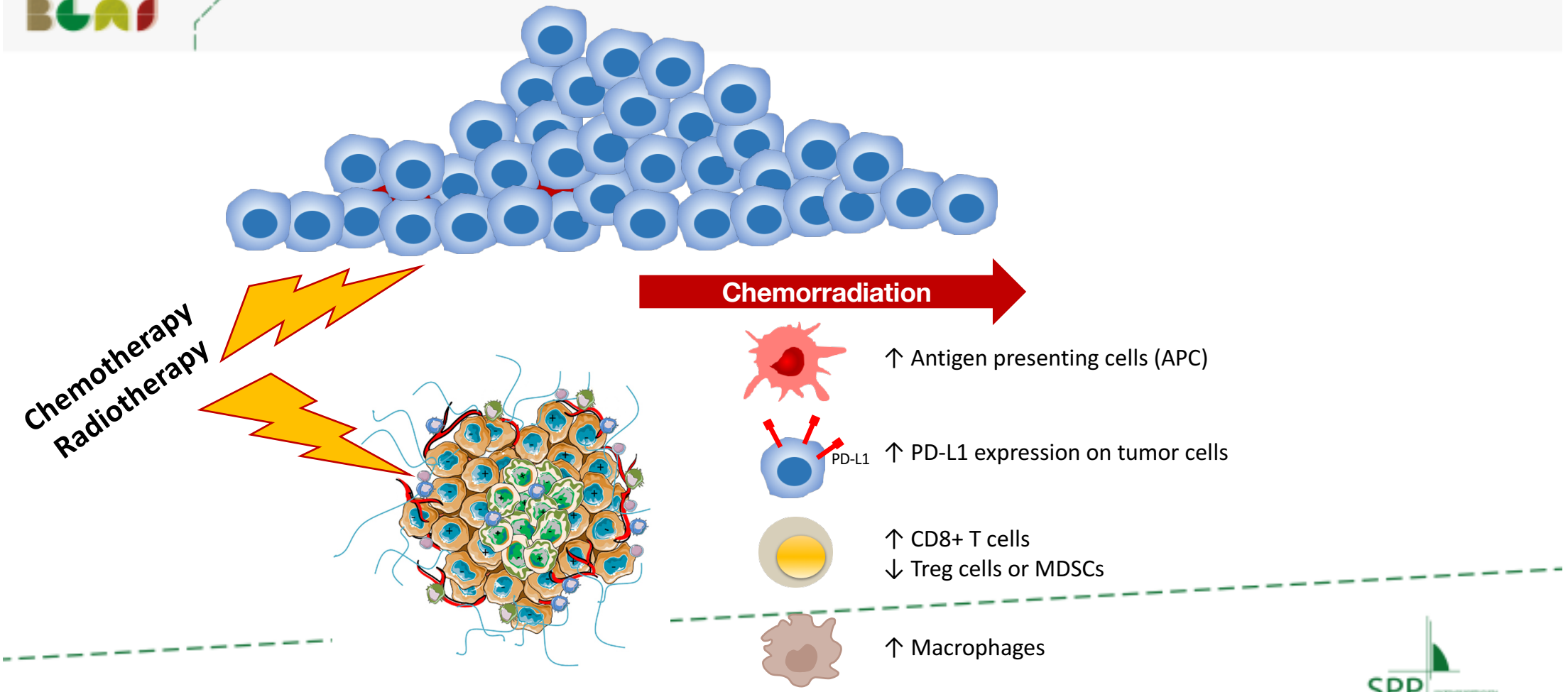


Debilitating conditions, frequently needing of high dose of corticosteroids (example, SVCS, atelectasis)



Tumor microenvironment with immunosuppressive phenotype

The complementary roles of chemorradiation and immunotherapy

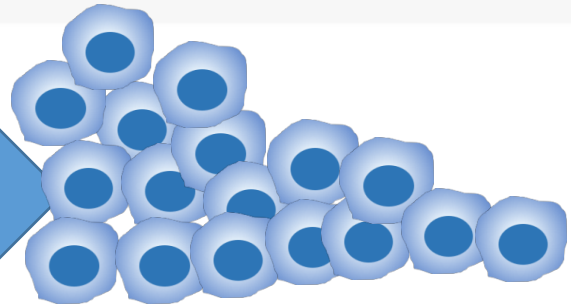


Lazzari et al. Ther Adv Med Oncol. 2018; 10: 1758835918762094

Synergistic drug administration

Induction therapy

- Risk of ineffective induction treatment will delay and thus be detrimental to the standard curative CCRT



Chemorradiation

Concurrent therapy

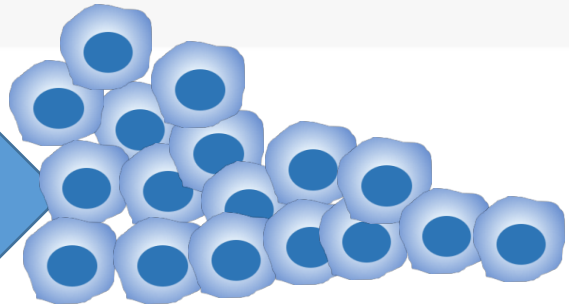
- Risk of increase pulmonary and cardio toxicities

Durvalumab (PACIFIC)

Consolidation therapy

- CRT up-regulates PD-L1 expression on tumor cells
- CRT reduces the tumor burden
- RT promotes infiltration of immune effector cells

Synergistic drug administration



Induction therapy

SPRINT (PD-L1 TPS≥50%)
Pembrolizumab 3 cycles → RT → Pembro consolidation

Chemorradiation

Concurrent therapy

PACIFIC-2
Durvalumab 1500 mg/4w + cCRT → Durva 1500 mg/4w consolidation

NICOLAS
Nivolumab 360 mg/3w + cCRT → Nivo 480 mg/4w consolidation

DETERRED
Atezolizumab + cCRT → CT + Atezo → Atezo 1200 mg/3w consolidation

KN-799
Pembrolizumab + CT → Pembro + cCRT → Pembro 200 mg/3w consolidation

Consolidation therapy

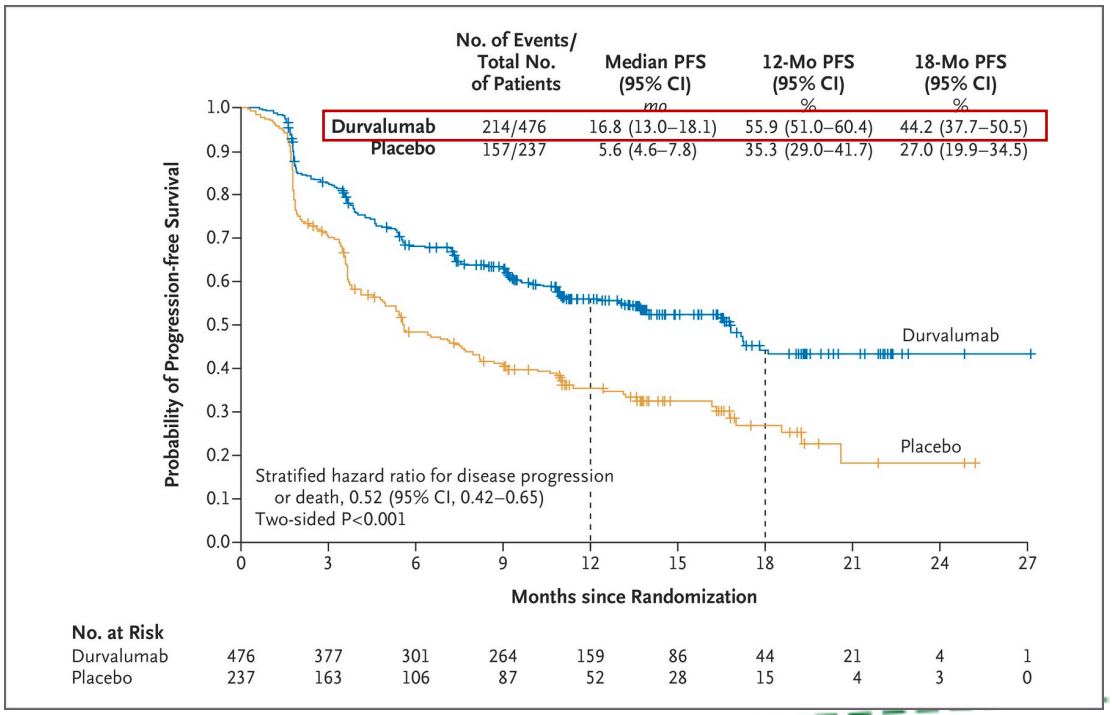
PACIFIC

PACIFIC-5/6
Durva 1500 mg/4w after sequen./conc. CRT

SkyScraper03
Atezolizumab + Tiragolumab (anti-TIGIT) vs Durva

LUN 14-179
Pembrolizumab 200 mg/3w after cCRT

PACIFIC trial: Durvalumab after Chemoradiotherapy in Stage III NSCLC



	Placebo	Durvalumab
PFS	5.6 months	16.8 (+11.2) months
	HR 0.52 (95% CI 0.42-0.65)	
OS	29.1 months	47.5 (+18.4) months
	HR 0.68 (95% CI 0.53-0.87)	
Grade 3-4 AE	26.1%	29.9%
Grade 3-4 Pneumonitis	2.6%	3.4%

Antonia et al. *N Engl J Med*. 2017;377(20):1919–1929 | Antonia et al. *N Engl J Med.* 2018;379:2342–2350 | Gray et al. *J Thorac Oncol* 2020;15:288–293 | Faivre-Finn et al. Annals of Oncology (2020) 31 (suppl_4): S1142-S1215. 10.1016/annonc/annonc325

How much can we improve survival of patients with LA-NSCLC?

HR 0.88 x 0.84 x 0.68 = 0.50

Radiotherapy alone vs **Chemoradiation**[1]

Sequential vs **Concurrent Chemoradiation**[2]

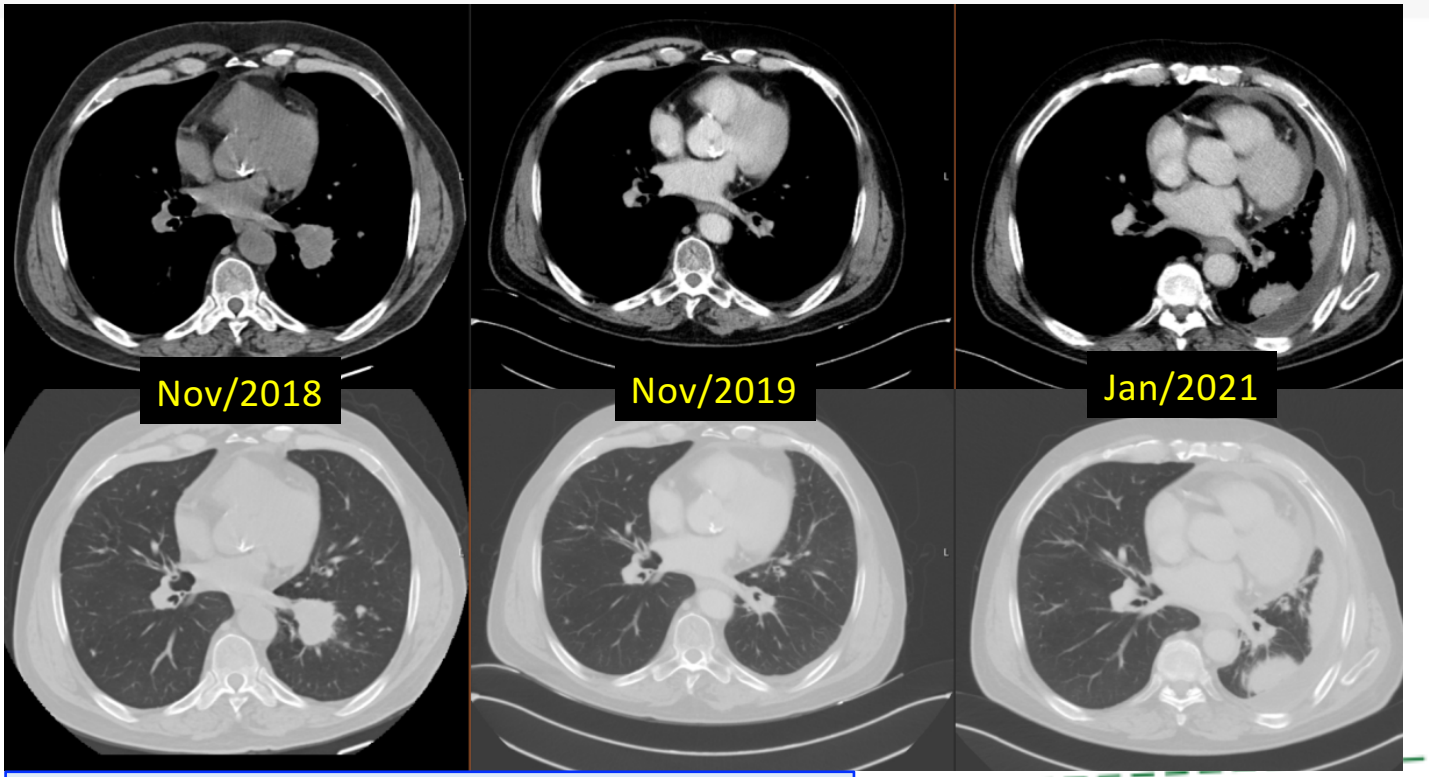
Concurrent Chemoradiation **with**/without **consolidation Immunotherapy**[3]

[1] De Ruysscher & van Loon. Clin Oncol. 2016 Nov;28(11):708-711 | [2] Aupérin et al. J*ournal of Clinical Oncology* 2010;28(13):2181-2190 | [3] Faivre-Finn et al. Annals of Oncology (2020) 31 (suppl_4): S1142-S1215. 10.1016/annonc/annonc325

Concurrent chemoradiation followed by durvalumab consolidation therapy

Male 67 years-old
COPD (FEV1 37.4%)
OSAS
Chronic respiratory failure with hypercapnia (NIV + O2)
HIV+

Squamous cell carcinoma, cT2bN1 (suspected N2 in EBUS-TBNA), PD-L1 ≥50%



Carboplatin + Vinorelbine (4 cycles) 26/02-25/06/2019

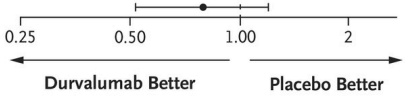
Radiation therapy (60 Gy, 2 Gy/daily) 07/08-17/09/2019

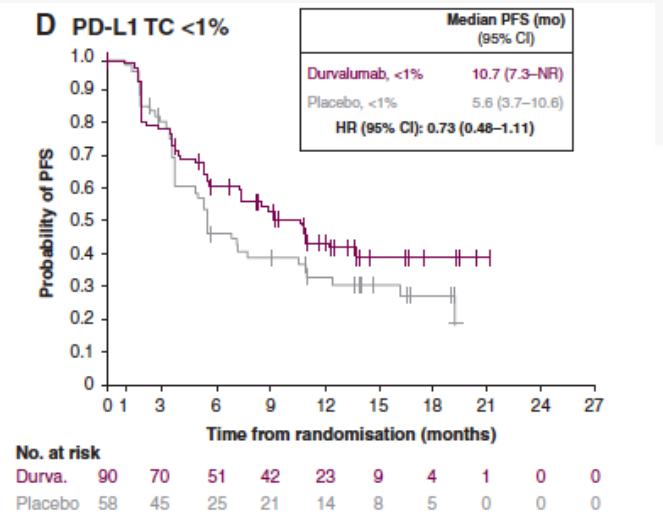
Durvalumab 10/12/2019-17/11/2020

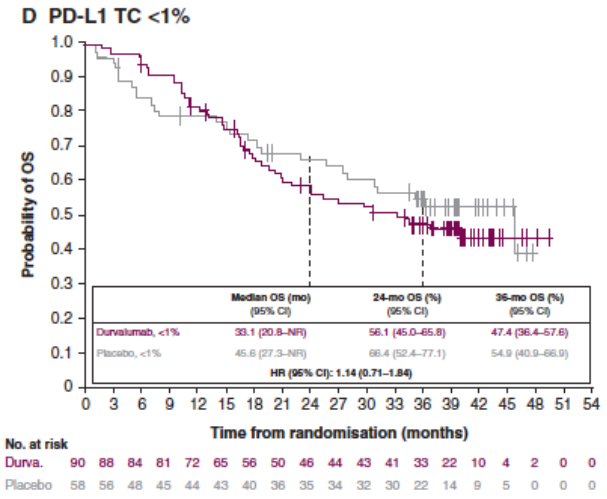
Postmus PE et al. Ann Oncol. 2017;28(supp 4):vi1-vi21. 3. eUpdate 04 May 2020 – Early and locally advanced non-small-cell lung cancer treatment recommendations. https://www.esmo.org/guidelines/lung-and-chest-tumours/early-stage-and-locally-advanced-non-metastatic-non-small-cell-lung-cancer/eupdate-early-and-locally-advanced-non-small-cell-lung-cancer-nsclc-treatment-recommendations. Accessed May 26, 2020

PACIFIC trial

Subgroup	Durvalumab	Placebo	Unstratified Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients		
All patients	476	237	0.55 (0.45–0.68)
Sex			
Male	334	166	0.56 (0.44–0.71)
Female	142	71	0.54 (0.37–0.79)
Age at randomization			
<65 yr	261	130	0.43 (0.32–0.57)
≥65 yr	215	107	0.74 (0.54–1.01)
Smoking status			
Smoker	433	216	0.59 (0.47–0.73)
Nonsmoker	43	21	0.29 (0.15–0.57)
NSCLC disease stage			
IIIA	252	125	0.53 (0.40–0.71)
IIIB	212	107	0.59 (0.44–0.80)
Tumor histologic type			
Squamous	224	102	0.68 (0.50–0.92)
Nonsquamous	252	135	0.45 (0.33–0.59)
Best response			
Complete response	9	7	—
Partial response	232	111	0.55 (0.41–0.75)
Stable disease	222	114	0.55 (0.41–0.74)
PD-L1 status			
≥25%	115	44	0.41 (0.26–0.65)
<25%	187	105	0.59 (0.43–0.82)
Unknown	174	88	0.59 (0.42–0.83)
EGFR mutation			
Positive	29	14	0.76 (0.35–1.64)
Negative	315	165	0.47 (0.36–0.60)
Unknown	132	58	0.79 (0.52–1.20)





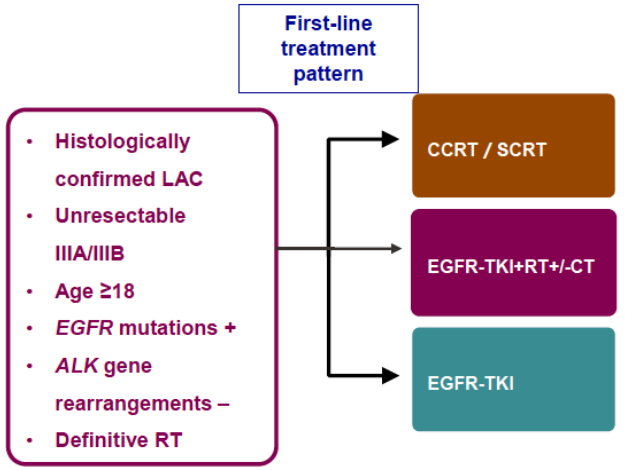


Antonia et al. *N Engl J Med*. 2017;377(20):1919–1929 | Paz-Ares et al. Ann Oncol. 2020 Jun;31(6):798-806

REFRACT: one retrospective clinical study investigating the treatment patterns in EGFR-mutant LA-NSCLC

Study design

NCT04304608



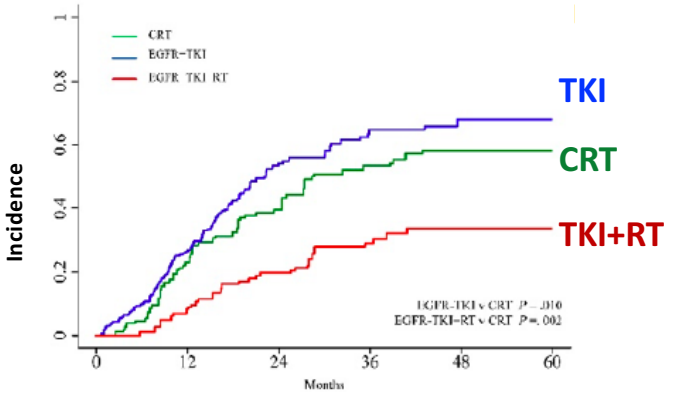
- Between Jan 2012 and Dec 2018
- 12 Chinese academic cancer institutions
- 440 patients in the efficacy analysis

- Group 1: concurrent or sequential chemoradiation.
- Group 2: combined RT and TKI with or without chemo
- Group 3: upfront TKIs alone until tumor progression

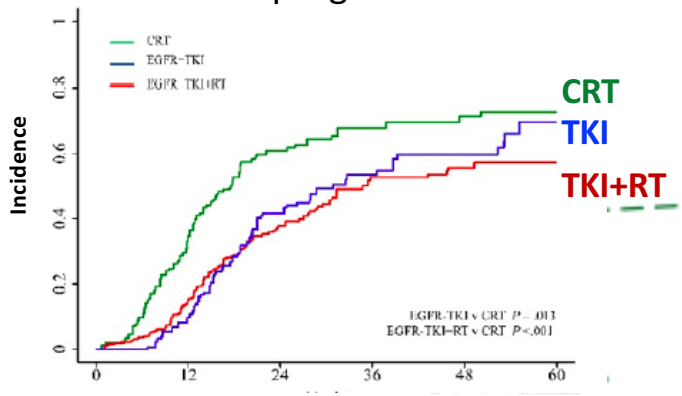
	Median OS (months)	95% CI
CRT	51.0	36.4–60.7
RT+TKI	67.4	50.1–NR
TKI	49.3	39.3–NR

	Median PFS (months)	95% CI
CRT	12.4	11.4–15.5
RT+TKI	26.2	19.8–36.4
TKI	16.2	14.1–19.5

Locoregional recurrence



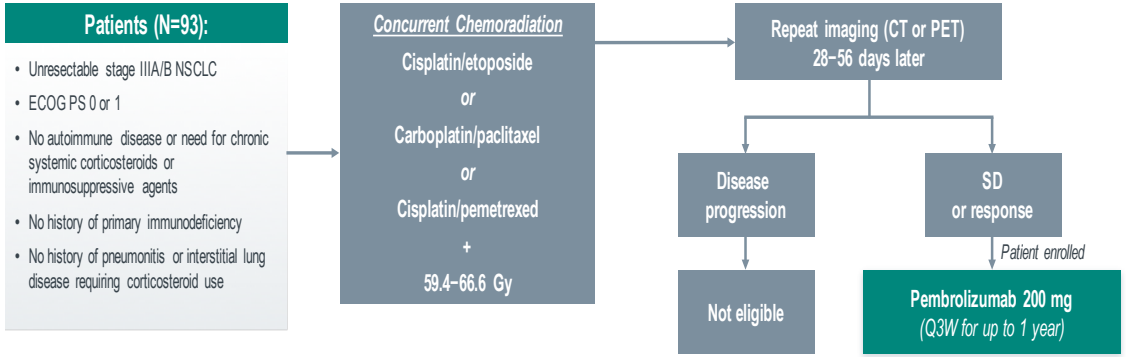
Distant progression



Nan Bi et al. Presented at WCLC Annual Meeting 2020; 29th January 2021; Virtual Meeting

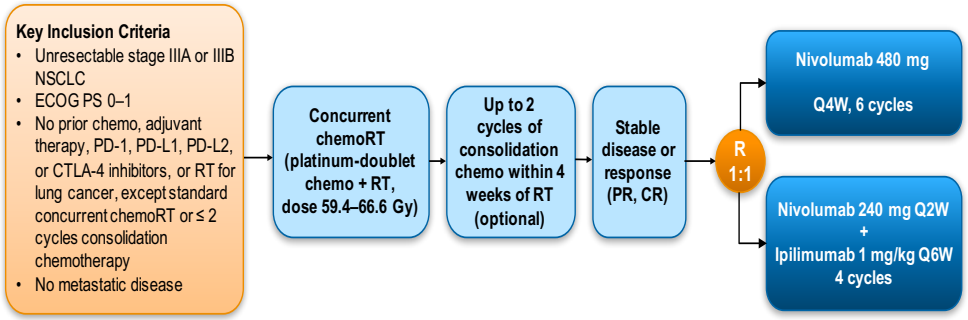
Pembrolizumab and Nivolumab as consolidation therapy in LA-NSCLC: results from phase 2 trials

LUN 14-179: Consolidation treatment with Pembrolizumab after cCRT



	Pembro consolidation	PACIFIC
Median PFS, months	19 m	17 m
12-mo PFS rate	61%	56%
Median OS, months	36 m	47.5 m
12-mo OS rate	81%	83%
Grade ≥3 pneumonitis	7%	3.4%

BTCRC-LUN16-081: Consolidation treatment with Nivo- or Nivo-/Ipilimumab after cCRT



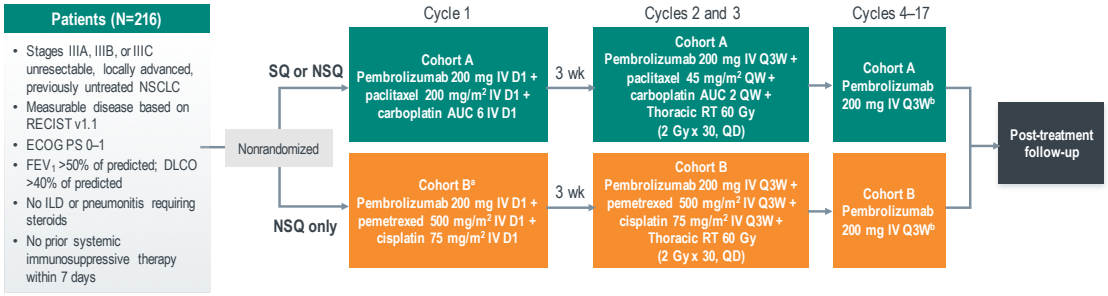
Interim analysis of first 50 patients

Grade 3-4 AE, n (%)	Nivolumab (n = 25)	Nivolumab plus ipilimumab (n = 25)
TRAE leading to discontinuation	2 **(8%)**	7 **(28%)**
Pneumonitis	1 **(4%)**	4 **(16%)**

Durm G et al. *Cancer.* 2020;10.1002/cncr.33083 [E-pub ahead of print] | Yan M et al. Presented at ASCO 2020. Abstract 9010. 2. Clinicaltrials.gov. NCT03285321. Accessed June 6, 2020

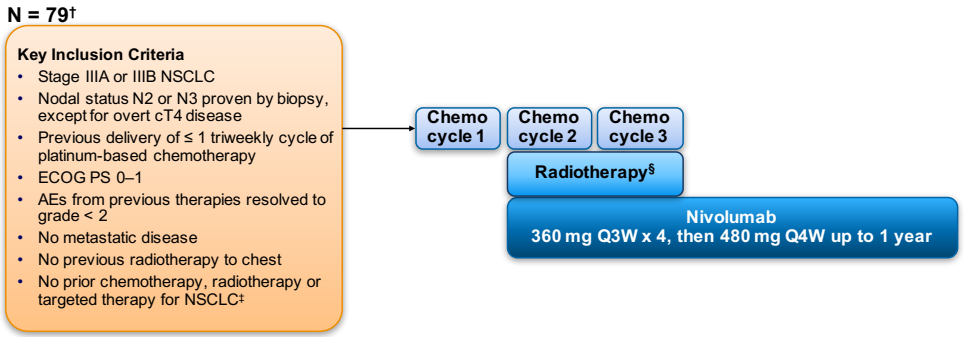
Pembrolizumab and Nivolumab as concurrently with chemoradiation therapy in LA-NSCLC: results from phase 2 trials

KN-799: Concurrent treatment with Pembrolizumab with CRT, followed by consolidation



Efficacy/Safety	Cohort A	Cohort B
ORR	69.6%	70.5%
Response duration ≥12 mo	82%	72%
12-mo PFS rate	67.7%	65.2%
12-mo OS rate	81.2%	88%
Grade ≥3 pneumonitis	8%	7.9%

NICOLAS: Nivolumab Plus Chemotherapy and Radiotherapy



Efficacy/Safety	
ORR, %	72%
PFS, months	12.7 m
OS, months	28 m
Grade ≥3 Pneumonitis, n (%)	8/77 (10.4%)
Grade ≥3 Esophagitis, n (%)	5/77 (6.5%)

Reck et al. Presented at WCLC Annual Meeting 2020; 29th January 2021; Virtual Meeting | Peters S et al. Poster presented at ESMO 2019. Abstract 2782

Treatment of LA-NSCLC during Covid-19 pandemic

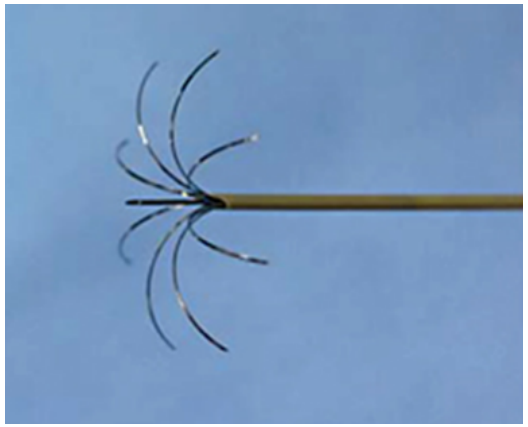
Topic	Recommendation
Chemoradiation	• Consider sequential chemoradiation (either systemic therapy or radiation first) • Consider durvalumab after concurrent or sequential chemoradiation • If using durvalumab after chemoradiation, consider 4-weekly dosing or delaying initiation of durvalumab (within 42 days)
Radiation techniques	• Use IMRT with a hypofractionated schedule (4 Gy*15 fractions; 3 Gy*20 fractions; 2.75 Gy*20 fractions) • Elective nodal coverage is not needed and may increase toxicity • In the absence of pathologic hilar or mediastinal staging, treat all hypermetabolic lymph nodes as if they are positive for the disease. If CT with contrast was used alone, consider treatment of all lymph nodes >1 cm in the short axis
Treating patients with COVID-19	• The focus of care should shift to supportive and anti-infectious methods so that the patient can resume optimal oncologic therapy as soon as possible • Hold treatment in patients who are symptomatic from the infection and whose malignancy would most likely not progress during the delay or interruption • Consider brief radiotherapy in patients who have tumor obstructions, hemoptysis, or are symptomatic from LA-NSCLC • In these patients, oncologic care can be possibly resumed when symptoms have resolved and the patient tests negative

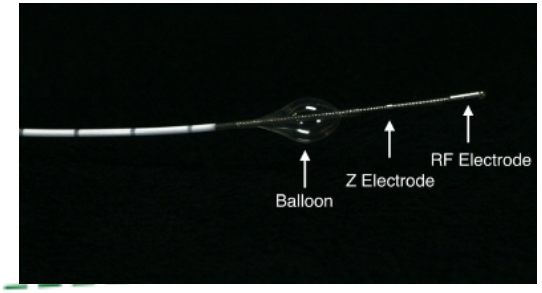
Kumar et al. J Thorac Oncol. 2020 Jul;15(7):1137-1146

SPP

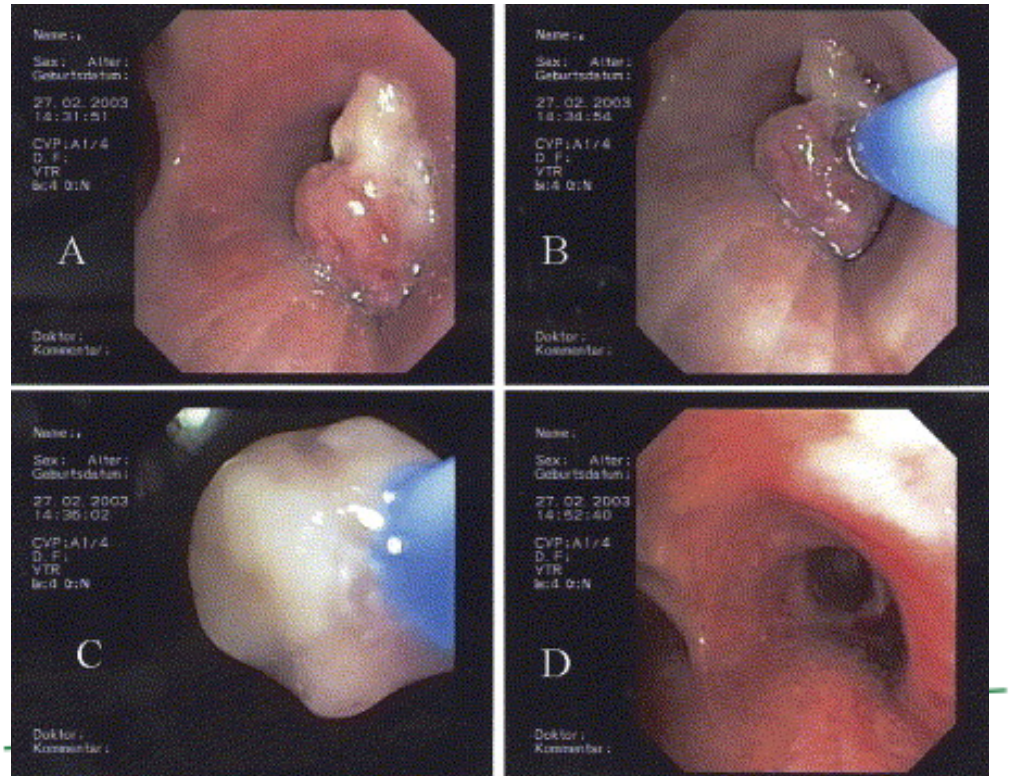
Bronchoscopic treatment of inoperable NSCLC

Radiofrequency ablation

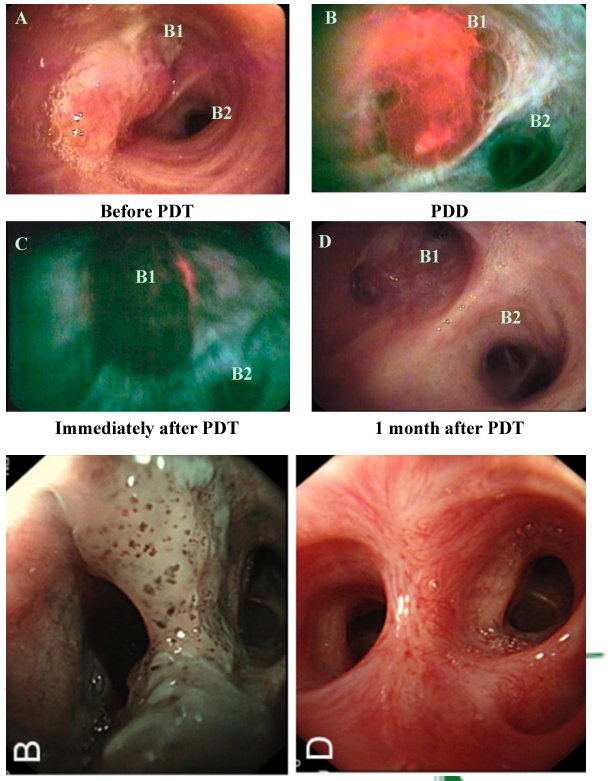




Cryotherapy



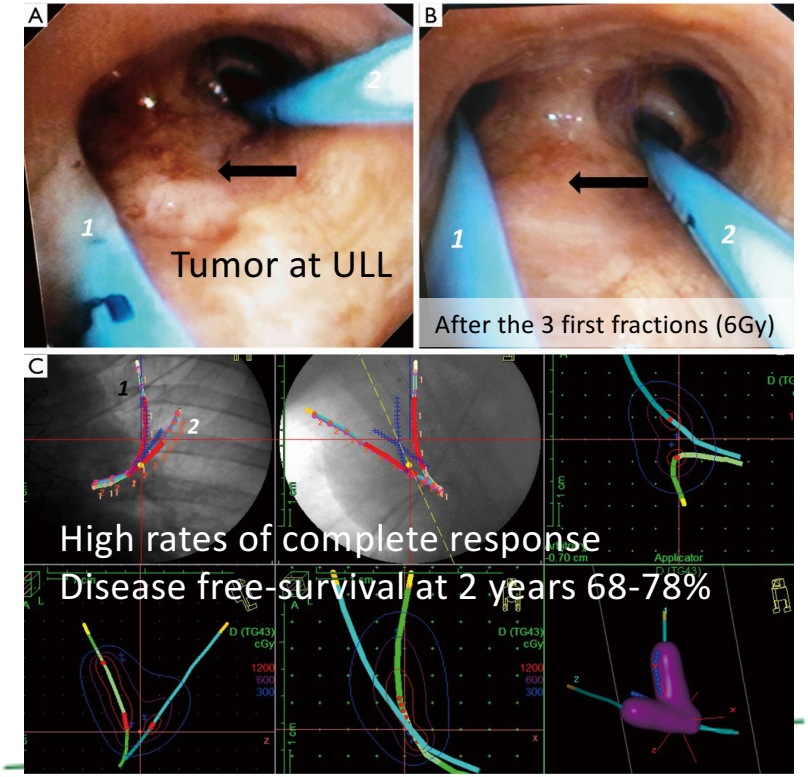
Photodynamic therapy



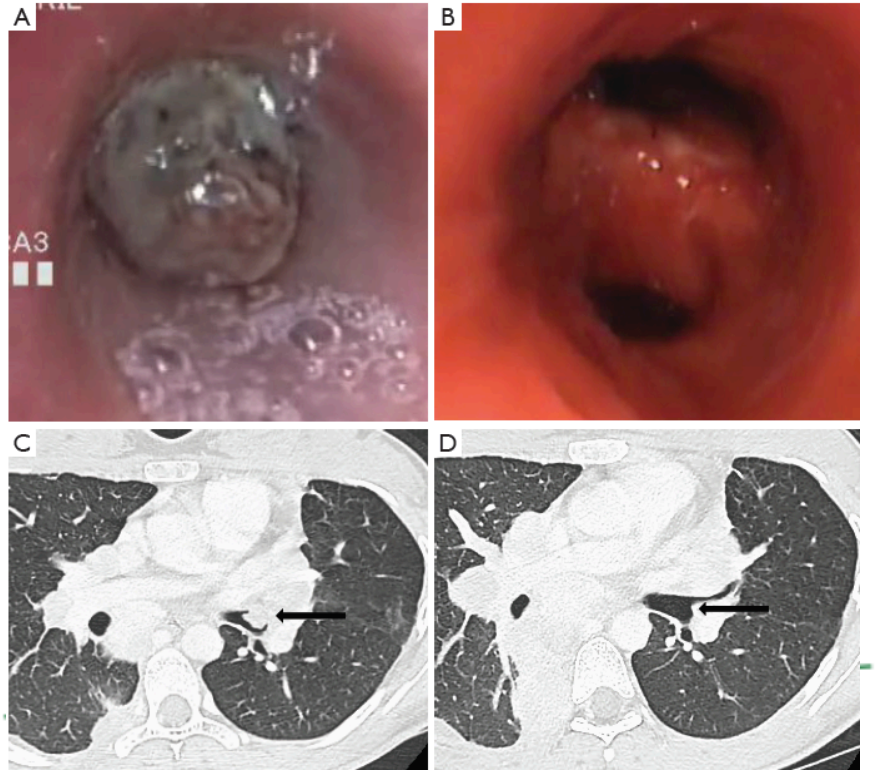
Kniese & Musani. European Respiratory Review 2020 29: 200035 | Steinfort & Herth. Respirology 2020;25(9):944-952 | Guibert et al. J Thorac Disease 2016;8(11) | Marchioni et al. (EVERMORE). Lung Cancer 2020;148:40-47

Bronchoscopic treatment of inoperable NSCLC

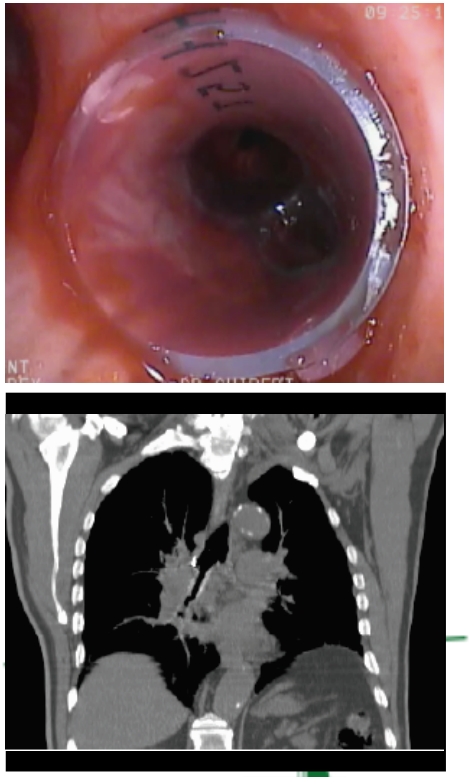
Brachytherapy



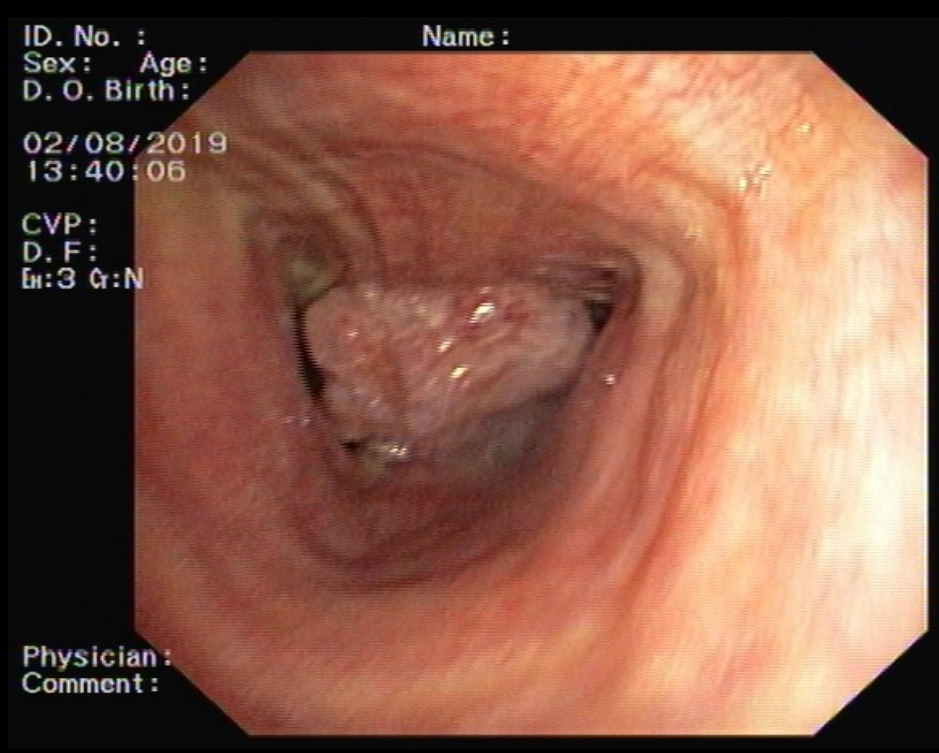
Laser/ electrocautery/ argon plasma coagulation + mechanical debulking



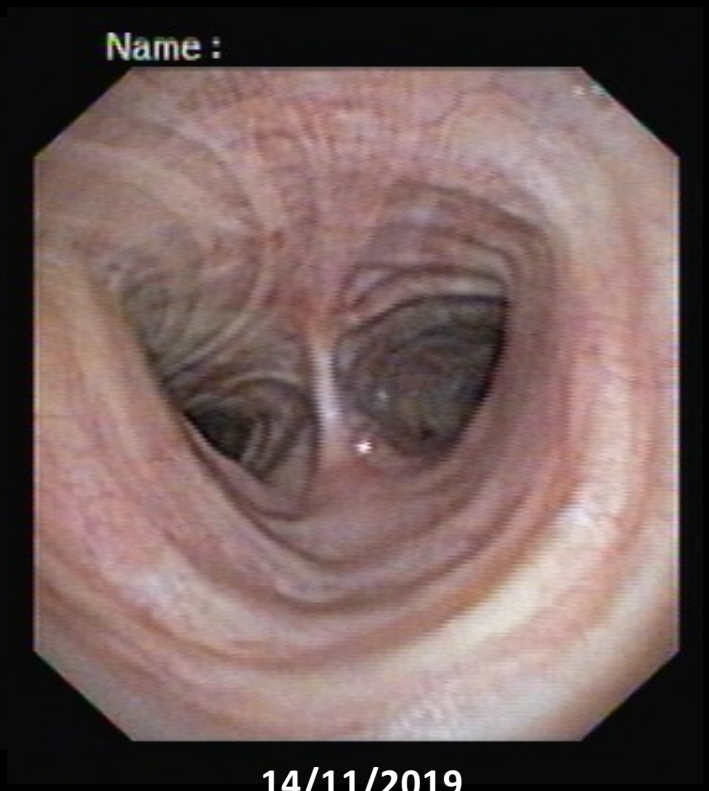
Airway senting



Kniese & Musani. European Respiratory Review 2020 29: 200035 | Steinfort & Herth. Respirology 2020;25(9):944-952 | Guibert et al. J Thorac Disease 2016;8(11) | Marchioni et al. (EVERMORE). Lung Cancer 2020;148:40-47



02/08/2019



14/11/2019

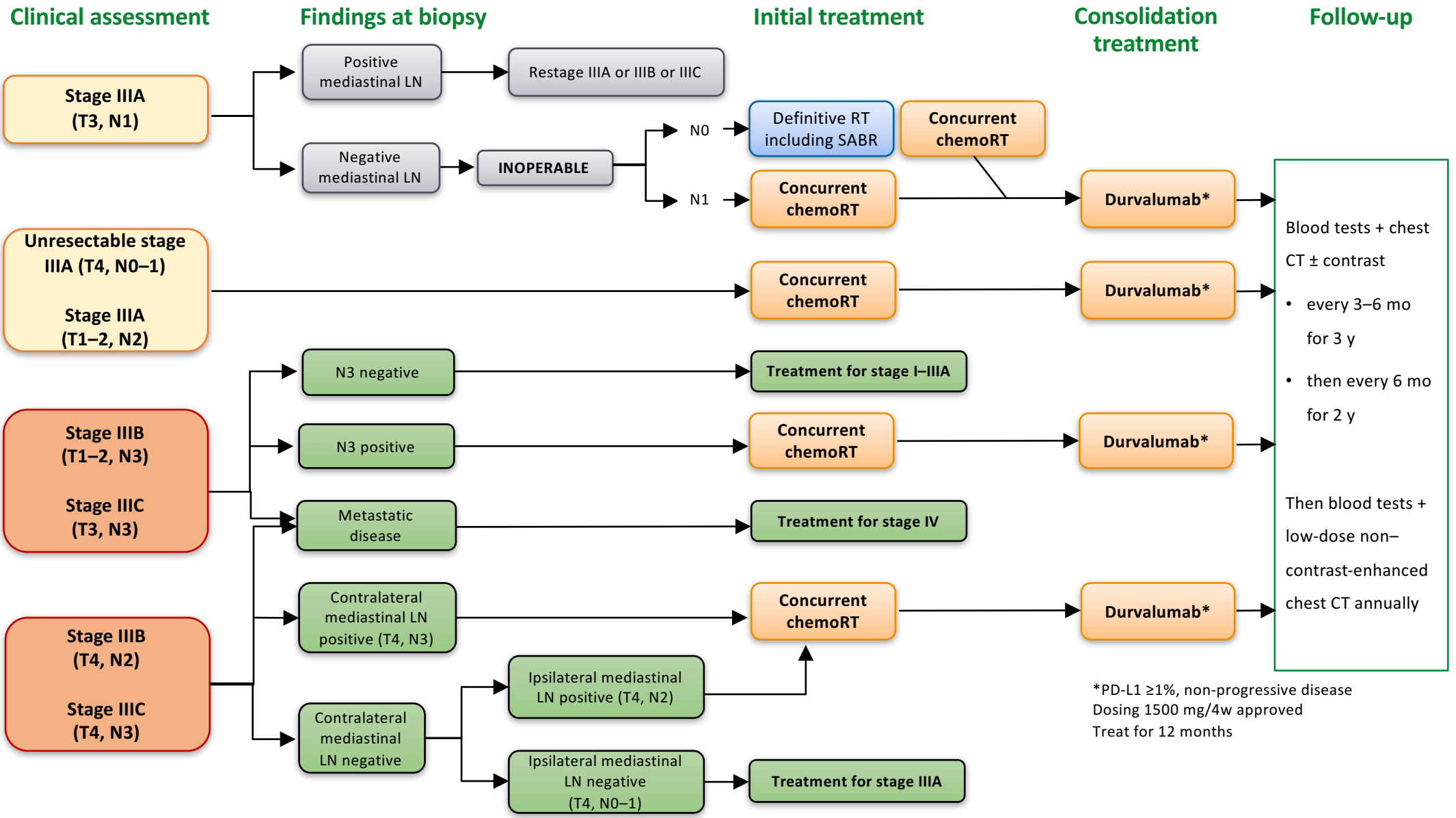
Conclusions and future perspectives

Key messages

- Concurrent chemoradiation followed by consolidation therapy with durvalumab is the standard of care therapy for unresectable disease
- 60-Gy radiation dose, with a protocol of 2-Gy daily over 6 weeks, is recommended
- Insufficient evidence (at least regarding efficacy) to prefer any particular chemotherapy regimen

Future perspectives

- A new trimodality therapy in unresectable tumors — concurrent chemo + immuno + radiation therapy, followed by consolidative immunotherapy
- Exploring the role of targeted-therapies
  - Preclinical studies have suggested that gefitinib may have a radiosensitizing effect, but lacks efficacy data
  - LAURA trial (Osimertinib maintenance after definitive chemoratiation in unresectable stage III EGFR+ NSCLC)


Clinical assessment
Findings at biopsy
Initial treatment
Consolidation treatment
Follow-up
Stage IIIA (T3, N1)
Positive mediastinal LN
Restage IIIA or IIIB or IIIC
Negative mediastinal LN
INOPERABLE
N0
N1
Definitive RT including SABR
Concurrent chemoRT
Concurrent chemoRT
Durvalumab*
Unresectable stage IIIA (T4, N0–1)
Stage IIIA (T1–2, N2)
Concurrent chemoRT
Durvalumab*
Stage IIIB (T1–2, N3)
Stage IIIC (T3, N3)
N3 negative
Treatment for stage I–IIIA
N3 positive
Concurrent chemoRT
Durvalumab*
Metastatic disease
Treatment for stage IV
Stage IIIB (T4, N2)
Stage IIIC (T4, N3)
Contralateral mediastinal LN positive (T4, N3)
Concurrent chemoRT
Durvalumab*
Contralateral mediastinal LN negative
Ipsilateral mediastinal LN positive (T4, N2)
Ipsilateral mediastinal LN negative (T4, N0–1)
Treatment for stage IIIA
Blood tests + chest CT ± contrast
• every 3–6 mo for 3 y
• then every 6 mo for 2 y
Then blood tests + low-dose non–contrast-enhanced chest CT annually
*PD-L1 ≥1%, non-progressive disease
Dosing 1500 mg/4w approved
Treat for 12 months