Associazione Italiana Radioterapia e Oncologia clinica

Società Italiana di Radiobiologia

Quale ruolo della RT nel setting ED-SCLC alla luce delle recenti introduzioni in terapia sistemica

Azienda Ospedaliero Universitaria Careggi

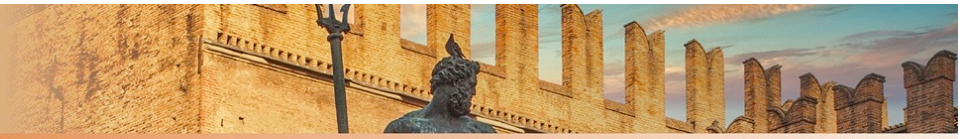
Vieri Scotti

26 novembre 2022

FONDAZIONE RADIOTERAPIA ONCOLOGICA

Associazione Italiana Radioterapia e Oncologia clinica

Società Italiana di Radiobiologia

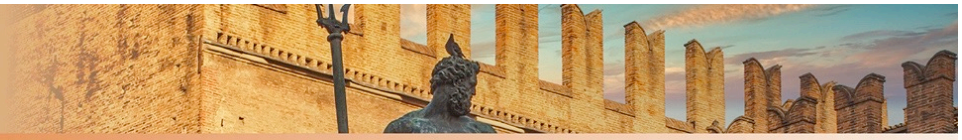


DICHIARAZIONE

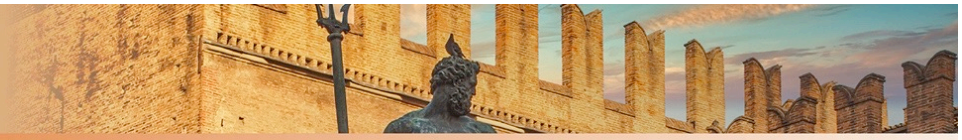
Relatore: Vieri Scotti

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 **(ASTRA ZENECA-ROCHE-BOHERINGER INGHELEIM)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(AZ-ROCHE-BMS-MSD-NOVARTIS-TAKEDA-JANSEN-DAHICHI SANCHIO-LILLY-AMGEN)**
- 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)**

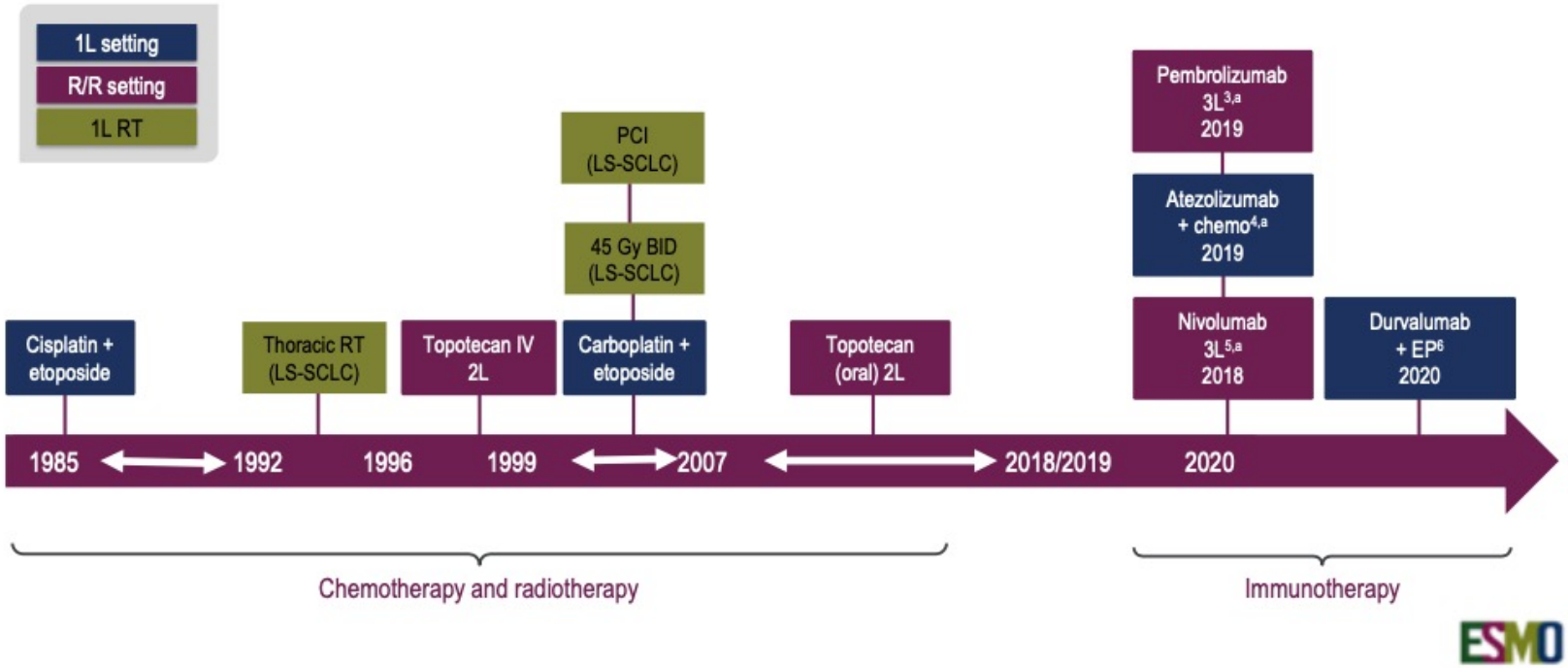


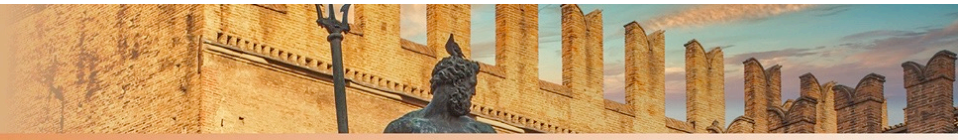
- WHAT IS NEW?
- WHAT IS CHANGING FOR THORACIC RT IN ED-SCLC?
- WHAT IS CHANGING FOR PCI IN ED-SCLC?



- WHAT IS NEW?
- WHAT IS CHANGING FOR THORACIC RT IN ED-SCLC?
- WHAT IS CHANGING FOR PCI IN ED-SCLC?

.....Introduction.... SCLC is blowing a new wind?





	IMPOWER 133	CASPIAN	KEYNOTE 604
Exp	**Atezolizumab**	**Durvalumab**	**Pembrolizumab**
Platinum agent	Carboplatin	Cisplatin Carboplatin	Cisplatin Carboplatin
N of cycles	4	6	4
CNS mets	yes, treated	yes	yes, treated
ORR	60.2%	68%	70.6%
PFS	5.2m	5.1m	4.8m
OS	12.3m	12.9m	10.8m
G≥3 AEs	58.1%	62.3%	76.7%

3 RCT IT-CT vs CT

2 positive in OS

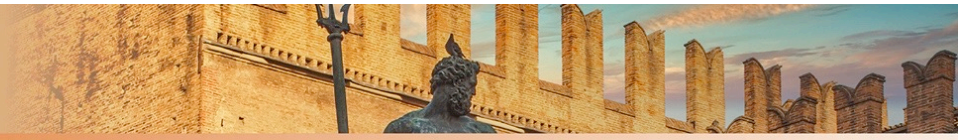
PCI permitted

Toracic RT non considered

Horn L et al, N Eng J Medicine 2018

Rudin CM et al, JCO 2020

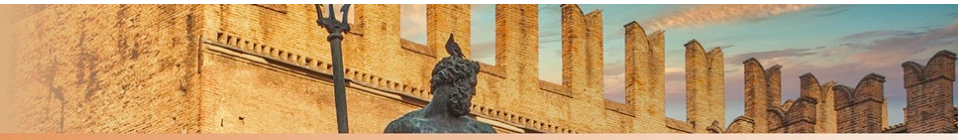
Goldman J et al, Lancet Oncology 2021



In summary...

	IMPOWER 133	CASPIAN	KEYNOTE 604	CAPSTONE-1	ASTRUM 005	SKYSCRAPER
Exp	**Atezolizumab**	**Durvalumab**	**Pembrolizumab**	**Adebrelimab**	**Serplulimab**	**Atezolizumab + Tiragolumab**
Platinum agent	Carboplatin	Cisplatin Carboplatin	Cisplatin Carboplatin	Carboplatin	Carboplatin	Carboplatin
N of cycles	4	6	4	6	4	4
CNS mets	yes, treated	yes	yes, treated	yes	yes	yes
ORR	60.2%	68%	70.6%	70.4%	80.2%	70.8%
PFS	5.2m	5.1m	4.8m	5.8m	5.7m	5.4m
OS	12.3m	12.9m	10.8m	15.3m	15.4m	13.6m
G≥3 AEs	58.1%	62.3%	76.7%	84.8%	82.5%	52.7%

Courtesy of J.Menis



- WHAT IS NEW?
- WHAT IS CHANGING FOR THORACIC RT IN ED-SCLC?
- WHAT IS CHANGING FOR PCI IN ED-SCLC?

Prospective and retrospective studies of TRT for ES-SCLC in the chemotherapy era and immunotherapy era.

Study	Groups	TRT (Concurrent or Sequential with CHT)	OS	PFS and local control	Toxicity
Chemotherapy Era					
Jeremic et al., 1999 [16] Randomized Phase 3, N = 109	1, TRT + CHT 2, CHT	Concurrent 54Gy/36f (1.5Gy bid)	Median OS: 17 m vs 11 m, 5-year OS: 9.1% vs 3.7% ($P = 0.041$).	Median LRFS: 30 m vs 22 m, 5-year LRFS: 20% vs 8.1% ($P = 0.062$).	Acute G3-5 AEs were lower with TRT.
Slotman et al., 2015 [17] Randomized Phase 3, N = 495	1, TRT 2, Non-TRT	Sequential 30Gy/10f	Median OS: 8 m vs 8 m, 1-year OS: 33% vs 28% ($P = 0.066$), 2-year OS: 13% vs 3% ($P = 0.004$).	Median PFS: 4 m vs 3 m, 6-month PFS: 24% vs 7% ($P = 0.001$).	G3-5 AEs: 10.5% vs 7.3%
Gore et al., 2017 [18] Randomized Phase 2, N = 86	1, PCI + cRT to thorax and extracranial mets 2, PCI	Sequential 45Gy/15f	Median OS: 13.8 m vs 15.8 m, 1-year OS: 50.8% vs 60.1% ($P = 0.21$).	Median PFS: 4.9 m vs 2.9 m ($P = 0.01$) 3-month progression: 14.5% vs 53.3%, 1-year progression: 75.0% vs 79.6% ($P = 0.01$).	G3-5 AEs: 36.4% vs 23.8%
Yee et al., 2012 [23] Non-randomized Phase 2, N = 32	TRT	Sequential 40Gy/15f	Median OS: 8.3 m.	Median PFS: 4.2 m; Symptomatic chest recurrences: 5/32	G2 esophagitis: 56.3%
Zhu et al., 2011 [24] Retrospective, N = 119	1, CHT + TRT 2, CHT	Concurrent/Sequential 40–60Gy, 1.8–2.0Gy/f	Median OS: 17 m vs 9.3 m, 2-year OS: 35% vs 17%, 5-year OS: 7.1% vs 5.1% ($P = 0.014$).	Median PFS: 10 m vs 6.2 m, 2-year PFS: 12.6% vs 7.2%, 5-year PFS: 6.3% vs 5.4% ($P = 0.0005$)	G3-5 leucopenia was higher with TRT.
Li et al., 2017 [25] Retrospective, N = 306	1, CHT + TRT 2, CHT	Sequential 30–48Gy/10-16f, 50–60Gy/25-30f	2-year OS: 21.4% vs 10.3% ($P < 0.001$).	2-year PFS: 7.7% vs 4.6% ($P < 0.001$); 2-year LC: 34.5% vs 6.3%	G2-3 pneumonitis and G2 esophagitis were higher with TRT.

- 1999-2017
- 3 RCTs
- 2 metanalisys

- Different RT approaches
- Different RT doses
- PCI as per clinical practice

Yaru Tian et al, Cancer Letters 2022

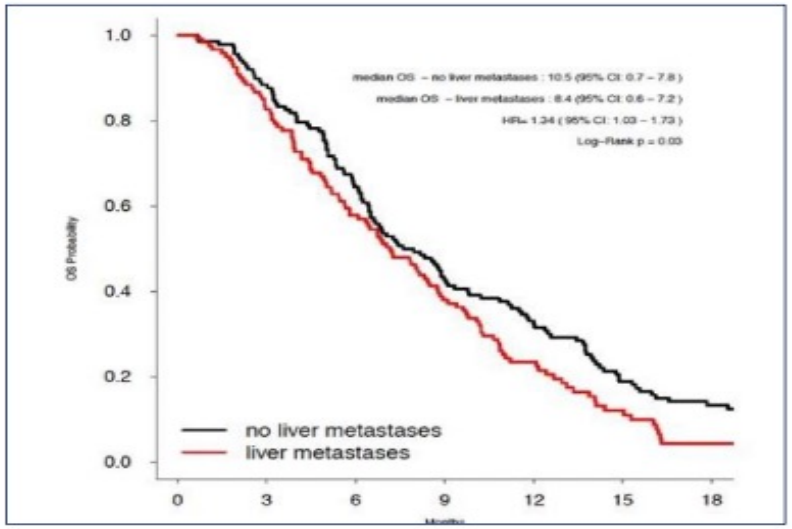
Which patients with ES-SCLC are most likely to benefit from more aggressive radiotherapy: A secondary analysis of the Phase III CREST trial

Ben J Slotman [1], Corinne Faivre-Finn [2], Harm van Tinteren [3], Astrid Keijser [4], John Praag [5],

2017

Top 9 of 42 initial recruiting Centers
260 pts Vs 235 Crest

		selected patients (n=260)	non-selected patients (n=235)	significance
Age	median (years)	63	63	NS
Sex	Male	136 (52.3%)	135 (57.4%)	NS
	Female	124 (47.7%)	100 (42.6%)	
WHO performance score	0	62 (23.8%)	105 (44.7%)	p<0.0001
	1	179 (68.8%)	118 (50.2%)	
	2	71 (27.3%)	12 (5.1%)	
Response	CR	10 (3.8%)	16 (6.8%)	
	PR	179 (68.8%)	170 (72.3%)	NS
	'Good response'	71 (27.3%)	49 (20.9%)	



No Liver MTS
No Bone MTS
<3 MTS lesions

Better OS

Indipendently from RT

Courtesy of A. Bruni

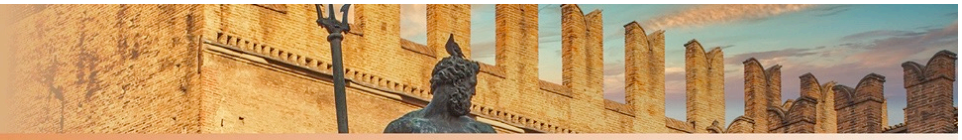
Slotman B et al, Lung Cancer 2017

Prospective and retrospective studies of TRT for ES-SCLC in the chemotherapy era and immunotherapy era.

Study	Groups	TRT (Concurrent or Sequential with CHT)	OS	PFS and local control	Toxicity
Chemotherapy Era					
Jeremic et al., 1999 [16] Randomized Phase 3, N = 109	1, TRT + CHT 2, CHT	Concurrent 54Gy/36f (1.5Gy bid)	Median OS: 17 m vs 11 m, 5-year OS: 9.1% vs 3.7% ($P = 0.041$).	Median LRFS: 30 m vs 22 m, 5-year LRFS: 20% vs 8.1% ($P = 0.062$).	Acute G3-5 AEs were lower with TRT.
Slotman et al., 2015 [17] Randomized Phase 3, N = 495	1, TRT 2, Non-TRT	Sequential 30Gy/10f	Median OS: 8 m vs 8 m, 1-year OS: 33% vs 28% ($P = 0.066$), 2-year OS: 13% vs 3% ($P = 0.004$).	Median PFS: 4 m vs 3 m, 6-month PFS: 24% vs 7% ($P = 0.001$).	G3-5 AEs: 10.5% vs 7.3%
Gore et al., 2017 [18] Randomized Phase 2, N = 86	1, PCI + cRT to thorax and extracranial mets 2, PCI	Sequential 45Gy/15f	Median OS: 13.8 m vs 15.8 m, 1-year OS: 50.8% vs 60.1% ($P = 0.21$).	Median PFS: 4.9 m vs 2.9 m ($P = 0.01$) 3-month progression: 14.5% vs 53.3%, 1-year progression: 75.0% vs 79.6% ($P = 0.01$).	G3-5 AEs: 36.4% vs 23.8%

- Thoracic RT reduces LR in thorax despite of DOSE, TIMING and fractionation
- OS is positive in 2 out of 3 series

Yaru Tian et al, Cancer Letters 2022



Clinical Practice Guideline

Radiation Therapy for Small Cell Lung Cancer: An ASTRO Clinical Practice Guideline

Radiation Therapy for Small-Cell Lung Cancer: ASCO Guideline Endorsement of an ASTRO Guideline

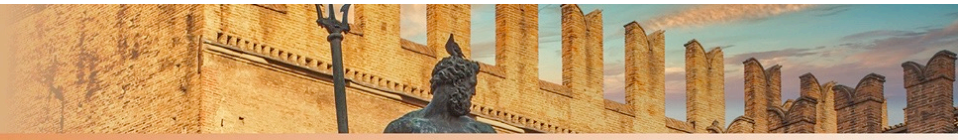
Megan E. Daly, MD[1]; Nofisat Ismaila, MD[2]; Roy H. Decker, MD, PhD[3]; Kristin Higgins, MD[4]; Dawn Owen, MD, PhD[5]; Ashish Saxena, MD, PhD[6]; Gregg E. Franklin, MD, PhD[7]; Dusty Donaldson, MA[8]; and Bryan J. Schneider, MD[9]

Table 6 Recommendations for thoracic consolidation for ES-SCLC

KQ4 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with ES-SCLC with a response to chemotherapy alone but residual tumor in the thorax, thoracic RT is recommended.	Strong	High 11,105-107
2. For patients with ES-SCLC with a response to chemotherapy alone, thoracic RT to a dose of 3000 cGy in 10 fractions is conditionally recommended. Implementation Remark: In patients expected to have a prolonged survival, higher doses may be appropriate.	Conditional	Moderate 11,106,107
3. For patients with ES-SCLC who will receive thoracic RT, the treatment should be given after completion of chemotherapy alone.	Strong	High 11,106,107
4. For patients with ES-SCLC with a response to chemotherapy and immunotherapy and residual disease in the thorax, thoracic RT to 3000 cGy in 10 fractions within 6-8 weeks is conditionally recommended.	Conditional	Expert Opinion

Abbreviations: cGy = centigray; ES = extensive-stage; KQ = key question; RT = radiation therapy; SCLC = small cell lung cancer.

Simone CB et al, PRO 2020
Dali ME et al, JCO 2021



versial discussion about who might profit from thoracic radiotherapy is ongoing. Based on German guidelines (Onkopedia and consultation version of new S3-guideline), thoracic radiation can be offered to patients with residual disease following systemic treatment on an individual basis. This is in line with the ESMO guidelines, which mention consolidation radiotherapy to the residual tumor and lymph nodes as a treatment option (grade C, level II recommendation) for patients with a performance score of 0-2 who achieve a response after chemotherapy, while the ASTRO guidelines strongly recommend thoracic radiotherapy for patients with a response to chemotherapy alone but residual tumor in the thorax. At the same time, all guidelines stress that there is a lack of data considering the implementation of consolidation thoracic radiotherapy to immunochemotherapy in ED-SCLC. The advent of immunotherapies

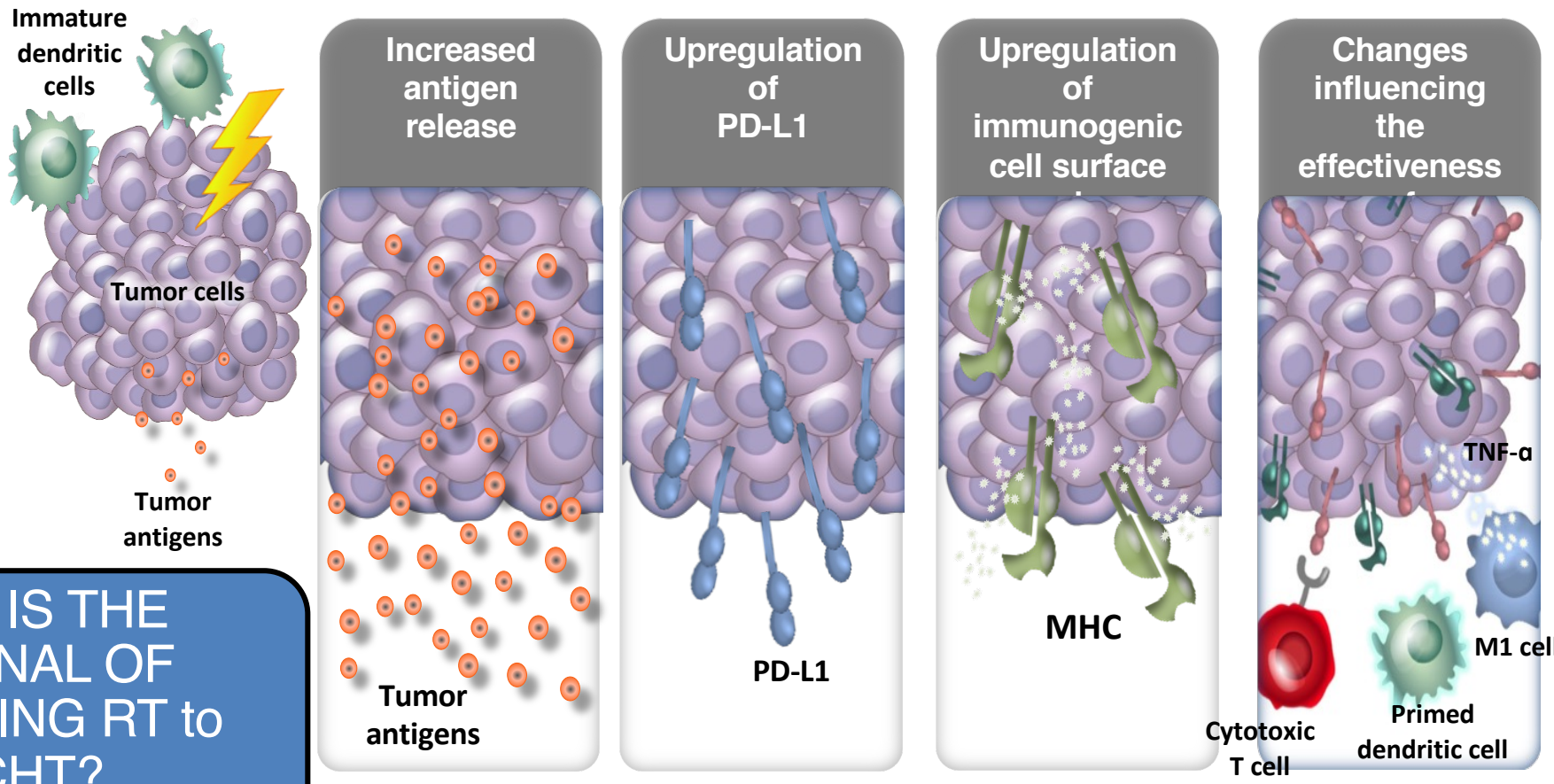
WHAT IS THE RATIONAL OF COMBINING RT to IT/CHT?

WHAT DO WE EXPECT BY ADDING RT TO MANTEINANCE IT?

WHICH EVIDENCES DO WE NEED TO TRANSLATE IT INTO CLINICAL PRACTICE?

Bozorgmehr F et al, BMC Cancer 2022

WHAT IS THE RATIONAL OF COMBINING RT to IT/CHT?

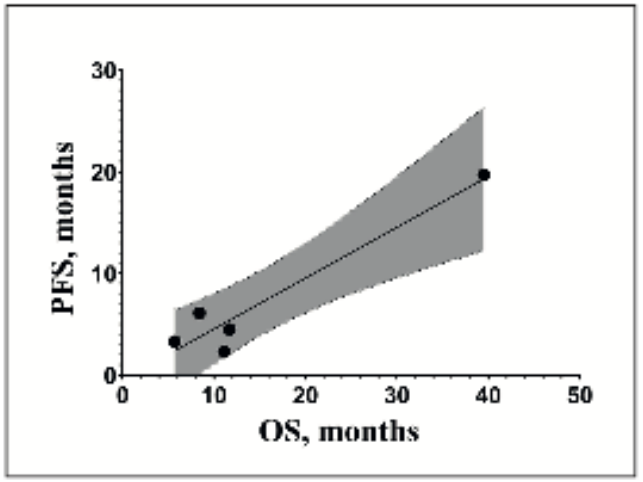


The incidences of adverse events in small-cell lung cancer patients after radiotherapy and immunotherapy treatment: a systematic review and meta-analysis

WHAT DO WE EXPECT BY ADDING RT TO MANTEINANCE IT?

- 9 REFERENCES ON LD-ED and relapsed SCLC
- 2RCT, 3 prospective CTs, 4 retrospective series

  - Any ≥ grade 3 AEs 59.8%
  - 14.9 % < grade 3 pneumonitis
  - 8.7% ≥ grade 3 pneumonitis
  - 4.9 % lung infections
  - 5.1% fatal adverse events
  - 12-16% diarrea

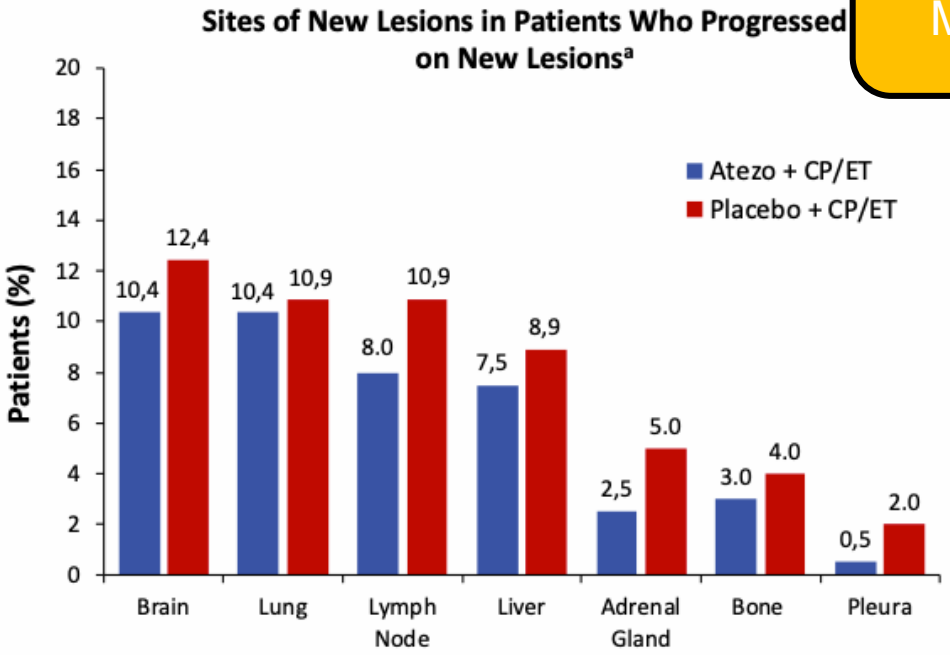


Wang et al, ERMPS 2022

PD Patterns (ITT Population)

WHAT DO WE EXPECT BY ADDING RT TO MANTEINANCE IT?

n (%)	Atezo + CP/ET (n = 201)	Placebo + CP/ET (n = 202)
PD	160 (79.6)	173 (85.6)
PD on target lesion	103 (51.2)	114 (56.4)
PD on non-target lesion	32 (15.9)	47 (23.3)
PD on new lesion	86 (42.8)	99 (49.0)



[a] Sites of new lesions in ≥ 2% of patients in either treatment arm are shown.

#ASTRO20

Higgins et al. IMpower133 Progression Patterns. 8

ASTRO 2022

Chemo-immunotherapy with or without consolidative radiotherapy in ES-SCLC: an initial report of clinical outcome and safety.

ID #5239

A. Bruni1*, F. Bertolini2, E. D'Angelo1, F. Barbieri2, J. Imbrescia1, L. Trudu3 , A. Cappelli4, F. Lohr4, M. Dominici3, G. Guaitoli5.

1Radiotherapy Unit, University Hospital "Policlinico" of Modena, Modena, Italy, 2 Department of Oncology and Hematology- Medical Oncology Unit, University Hospital of Modena, Modena, Italy, 3 Department of Oncology and Hematology - Medical Oncology Unit, University of Modena and Reggio Emilia - University Hospital "Policlinico" of Modena, Modena, Italy, 4Department of Oncology and Hematology - Radiotherapy Unit, University of Modena and Reggio Emilia – University Hospital"Policlinico" of Modena, Modena, Italy, 5Department of Oncology and Hematology- Medical Oncology Unit, Ph. D. Program Clinical and Experimental Medicine (CEM), Department of biomedical Metabolic and Neural Sciences, University of Modena and Reggio Emilia - "Policlinico" Hospital of Modena, Modena, Italy

Background

Extensive stage small cell lung cancer (ES-SCLC) is still characterized by a poor prognosis. The recent introduction of concomitant immunotherapy (IT) allowed to obtain better results in terms of clinical outcomes without increasing toxicity, while the role of thoracic radiotherapy (TRT) is still largely unknown in this setting.

The aim of our study was to evaluate clinical outcome and safety of chemo-immunotherapy (CT-IT) with or without consolidative TRT in ES-SCLC patients.

Materials and methods

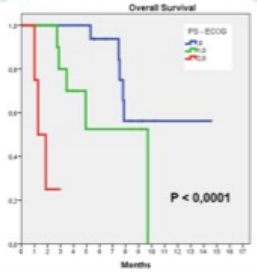
Thirty-one pts consecutively treated from February 2020 to October 2021 were retrospectively reviewed. Median age was 66 yrs. Twenty-one were male, 10 were female. All pts treated had ES-SCLC. Overall survival (OS) and progression free survival (PFS) were analyzed using the Kaplan Meier method.

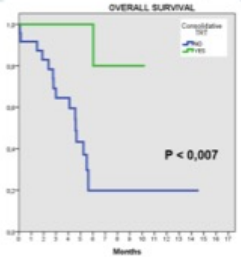
Univariate analysis was performed to investigate patient, tumor or treatment related prognostic factors influencing clinical outcomes. Toxicity was recorded based on CTCAE 4.0 scale

Results

At a median FUP of 6 months, 31 pts were treated using 1st line platinum-based CT-IT and 22 with maintenance Atezolizumab. Consolidative TRT was delivered to 7 pts, while 2 underwent PCI. Median and 1-year OS was 7.7 months and 33.3%. Median and 1-yr PFS was 5.4 months and 37,1%. At univariate analysis TRT, PS ECOG=0 and no brain metastases were positive statistically significant prognostic factors for PFS and OS.

Tox >G2 was reported in 11 pts: neutropenia was the most common one(G4 in 2 pts). No significant differences in terms of symptomatic side effects was found between who did or did not undergo TRT.





Conclusions

CT-IT is an effective therapeutic option for ES-SCLC. PFS was comparable to registration RCTs. Safety is satisfactory, also adding consolidative TRT. Controlled conditions, longer FUP and larger cohorts are now needed to further assess the impact of TRT on LC and OS.

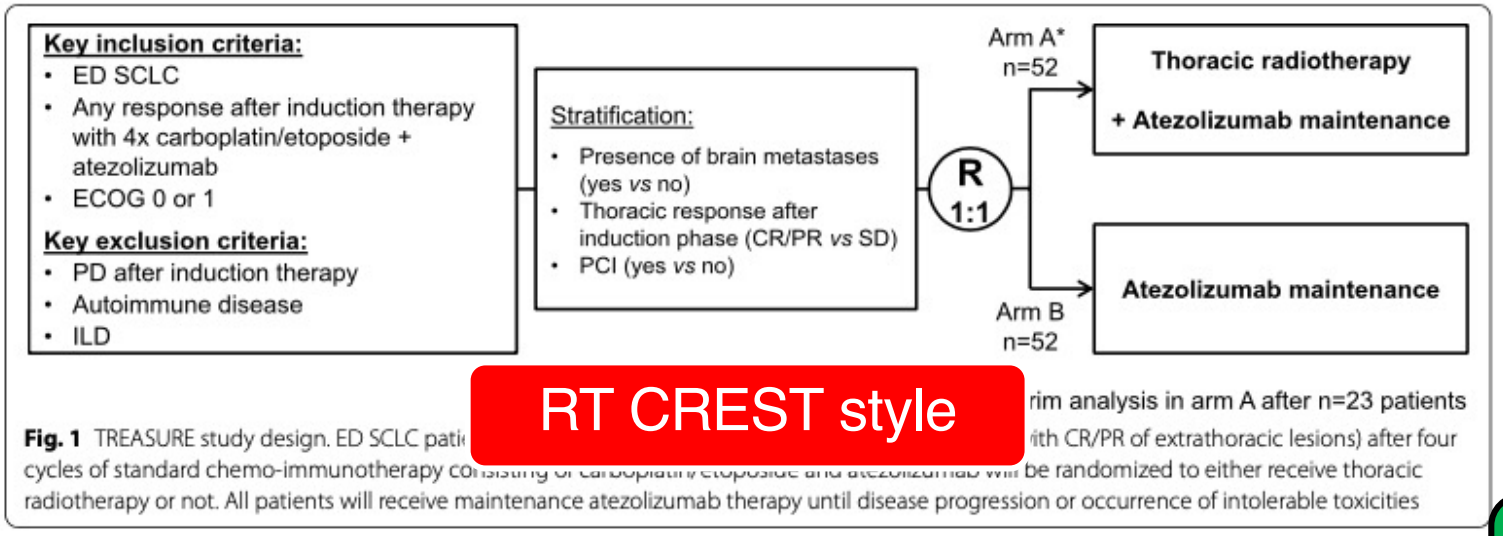
WHICH EVIDENCES DO WE NEED TO TRANSLATE IT INTO CLINICAL PRACTICE?

Courtesy of A. Bruni

STUDY PROTOCOL Open Access

Protocol of the TREASURE study: Thoracic RadiothErapy with Atezolizumab in Small cell lUng canceR Extensive disease – a randomized, open-label, multicenter phase II trial

Conducted in Germany and Austria
Results expected in 2024



RT CREST style

Fig. 1 TREASURE study design. ED SCLC pati… rim analysis in arm A after n=23 patients …ith CR/PR of extrathoracic lesions) after four cycles of standard chemo-immunotherapy co…sisting of carboplatin/etoposide and atezolizumab will be randomized to either receive thoracic radiotherapy or not. All patients will receive maintenance atezolizumab therapy until disease progression or occurrence of intolerable toxicities

Bozorgmehr F et al, BMC Cancer 2022

ENDPOINTS
1. EFFICACY OF RT plus atezo manteinance
2. SAFETY and TOLERABILITY

WHICH EVIDENCES DO WE NEED TO TRANSLATE IT INTO CLINICAL PRACTICE?

ES-SCLC management

CT+IT prolongs survival compared with CT alone in ES SCLC, but survival benefit is modest.

Two phase III trials ongoing to investigate whether there is a synergistic/additive effect of **concurrent tRT in ES SCLC pts receiving platinum-based CT + ICI.**

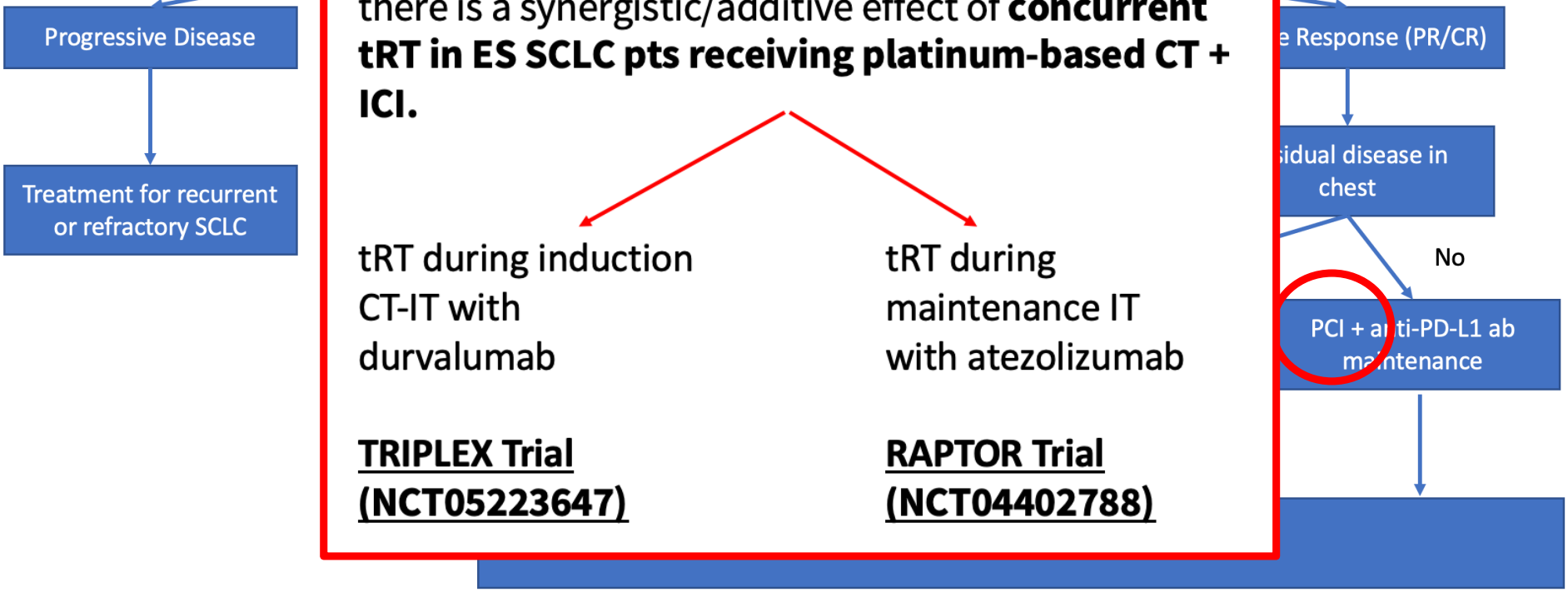
tRT during induction CT-IT with durvalumab

TRIPLEX Trial (NCT05223647)

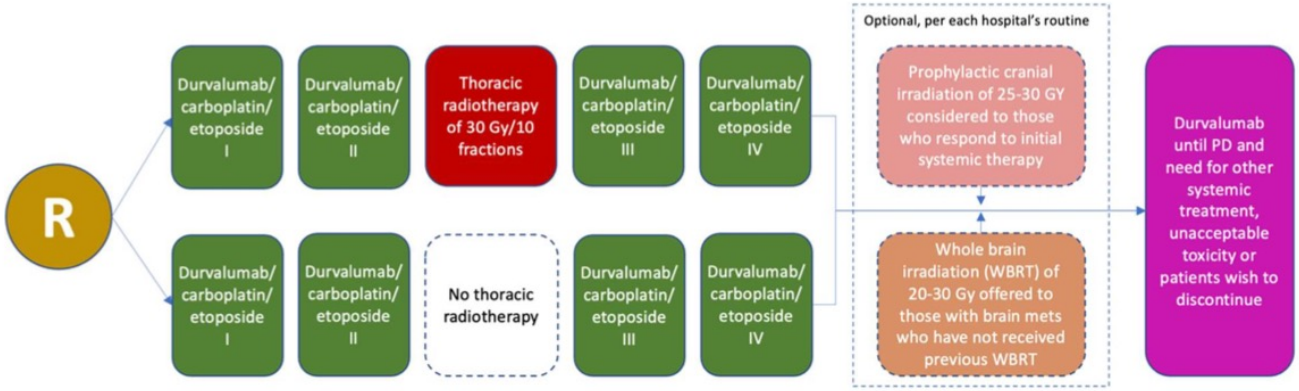
tRT during maintenance IT with atezolizumab

RAPTOR Trial (NCT04402788)

WHICH EVIDENCES DO WE NEED TO TRANSLATE IT INTO CLINICAL PRACTICE?



TRIPLEX – trial design



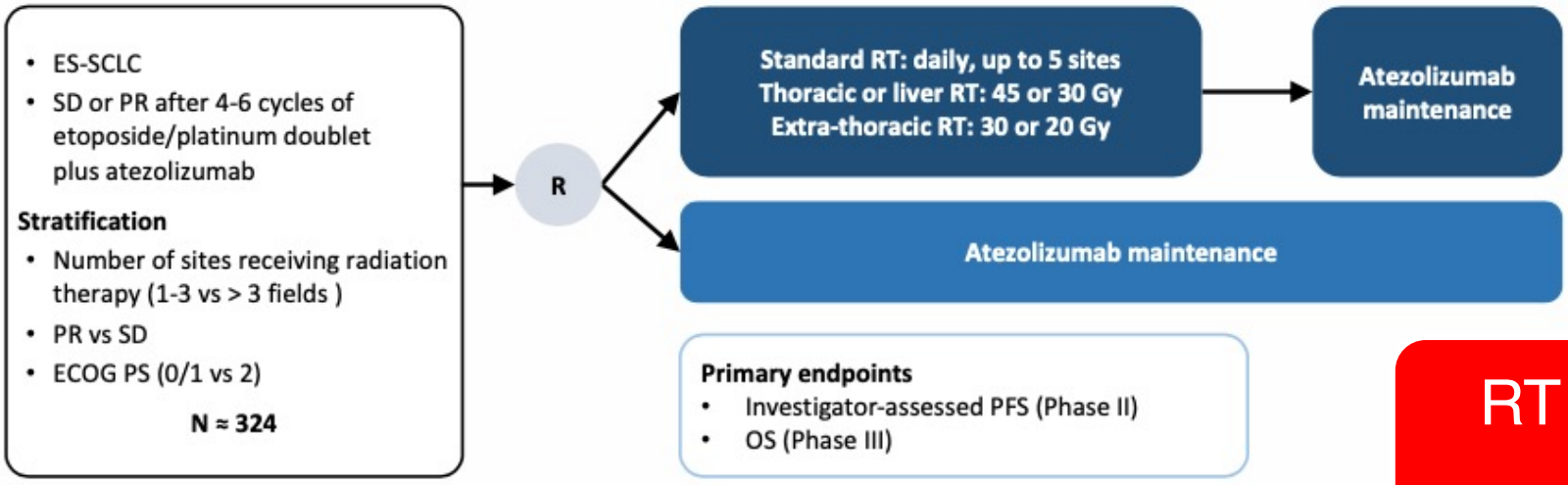
Experimental Arm: 30Gy/10fx tRT given between 2nd and 3rd course of CT-IT.
Primary Obj: 1y OS

RT CREST style

WHICH EVIDENCES DO WE NEED TO TRANSLATE IT INTO CLINICAL PRACTICE?

- Randomized Phase II/III trial of consolidation radiation + immunotherapy in patients with ES-SCLC
- Data from this exploratory analysis of IMpower133 support enrollment in the RAPTOR trial

WHICH EVIDENCES DO WE NEED TO TRANSLATE IT INTO CLINICAL PRACTICE?



RT RTOG 0937 style

PR, partial response; RT, radiotherapy; SD, stable disease. ClinicalTrials.gov Identifier: NCT04402788.

#ASTRO20

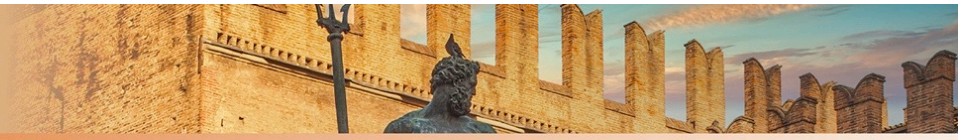
ASTRO 2022

Higgins et al. IMpower133 Progression Patterns. 10

WHICH EVIDENCES DO WE NEED TO TRANSLATE IT INTO CLINICAL PRACTICE?

WE WANT YOU!

Trial	Phase	Setting	Treatment arms	Primary Endpoint(s)	
NCT03262454	II	Recurrent/refractory SCLC	Atezolizumab + SHRT	OS	
NCT03923270	I	ES-SCLC	Thoracic RT + durvalumab Thoracic RT + durvalumab + tremelimumab (75 mg) Thoracic RT + durvalumab + olaparib Thoraci RT + durvalumab + tremelimumab (300 mg)	Safety (Phase 1); PFS (Phase IB)	
NCT05544149	II	ES-SCLC	First line ICI → tRT	Local recurrence free survi Adverse events.	
NCT05092412	II	ES-SCLC	Low-dose radiotherapy + durvalumab + etoposide-cisplatin/carboplatin	PFS	OS; ORR; 6-month PFS rate; 12-month PFS rate
NCT05552846	II	ES-SCLC with no evidence of PD after 4 cycle of platinum-based chemotherapy in combination with an anti-PD-1/L1	tRT + IT maintenance	1-year PFS	1-year OS; toxicities; 5-year OS
NCT04462276 (TREASURE)	II	ES-SCLC with a response after induction therapy with carboplatin/etoposide + atezolizumab	tRT + atezolizumab atezolizumab	Overall survival (OS)	PFS; ORR; Intrathoracic tumor control; AEs; Cancer related quality of life (Functional Assessment of Cancer Therapy for patients with Lung cancer (FACT-L))
NCT04472949	II	ES-SCLC with CR; PR or SD after induction therapy with carboplatin/etoposide + durvalumab	tRT + durvalumab	PFR	PFS; PFS outside the brain; PFS after induction chemotherapy (PFS-IND); OS; ORR; DoR; AE.



- WHAT IS NEW?
- WHAT IS CHANGING FOR THORACIC RT IN ED-SCLC?
- WHAT IS CHANGING FOR PCI IN ED-SCLC?

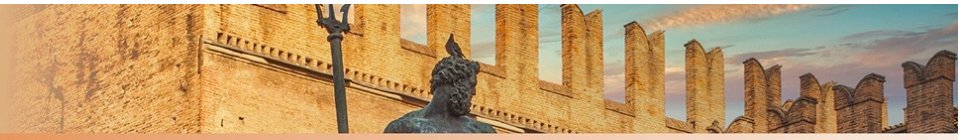
Study	Enrollment	Groups	BRT dose	Key results	Toxicity
Slotman et al., 2007 [19] Randomized phase 3, N = 286	ES-SCLC	1, PCI 2, Non-PCI	20Gy/5f or 8f, 24Gy/12f, 25Gy/10f, 30Gy/10f or 12f	Median OS:6.7 m vs 5.4 m (HR 0.68, $P = 0.003$), 1-year OS: 27.1% vs 13.3%; Median DFS: 14.7w vs 12w (HR 0.76, $P = 0.02$). 1-year cumulative risk of BM: 14.6% vs 40.4% (HR 0.27, $P < 0.001$);	AEs were increased with PCI, but the global health status was not affected.
Takahashi et al., 2017 [20] Randomized phase 3, N = 224	ES-SCLC; No BM by MRI examination.	1, PCI 2, Periodic MRI examination	25Gy/10f	Median OS: 11.6 m vs 13.7 m (HR 1.27, $P = 0.094$); Median PFS: 2.3 m vs 2.4 m (HR 0.98, $P = 0.75$); 1-year cumulative incidence of BM: 32.9% vs 59.0% ($P < 0.001$)	G3-4 anorexia: 6% vs 2%, G3-4 malaise: 3% vs <1%.
Bernhardt D et al., 2017 [59] Retrospective, N = 136	ES-SCLC	PCI	30Gy/15f	Median OS: 12 m Median neurologic PFS: 19 m	No severe AEs were observed.
Schild SE et al., 2012 [60] Pooled analysis, N = 739	ES-SCLC LS-SCLC	1, PCI 2, Non-PCI	30Gy/15f, 25Gy/10f	ES-SCLC + LS-SCLC: Median OS: 14 m vs 9 m, 5-year OS rate: 11% vs 3% (HR 0.61, $P < 0.0001$); ES-SCLC: Median OS: 10 m vs 8 m (HR 0.77, $P = 0.0282$); LS-SCLC: Median OS: 17 m vs 14 m (HR 0.68, $P = 0.0045$).	G3-5 AEs: 64% vs 50% ($P = 0.0004$).
Bang A et al., 2018 [61] Retrospective, N = 155	ES-SCLC; No BM	1, PCI 2, Non-PCI	25Gy/10f, 20Gy/5f.	Median OS: 13.5 m vs 8.5 m (HR 0.41, $P < 0.0001$); Median time to BM: 23.8 m vs 10.2 m (HR 0.36, $P < 0.0001$).	–
Chung JH et al., 2020 [67] Retrospective, N = 190	ES-SCLC; No BM	1, PCI 2, Observation	25Gy/10f, 20Gy/5f	1-year BMFS (high-risk): 94.7% vs 62.1% ($P = 0.001$) 1-year BMFS (low-risk): 100.0% vs 87.7% ($P = 0.943$)	–
FIRE-SCLC,2020 [69] multicenter cohort study, N = 710, N = 219	ES-SCLC; with BM	1, SRS 2, WBRT	–	Median OS: 8.5 m vs 5.2 m ($P < 0.001$) Median TTCP: 8.1 m vs NR ($P < 0.001$)	–

- 2007-2017
- 2 RCTs
- DIFFERENT OUTCOMES

EORTC TRIAL
WBRT reduces BM
better PFS
better OS
MRI non mandatory before WBRT

JAPANESE TRIAL
WBRT reducesBM
but does not influence OS
over MRI surveillance

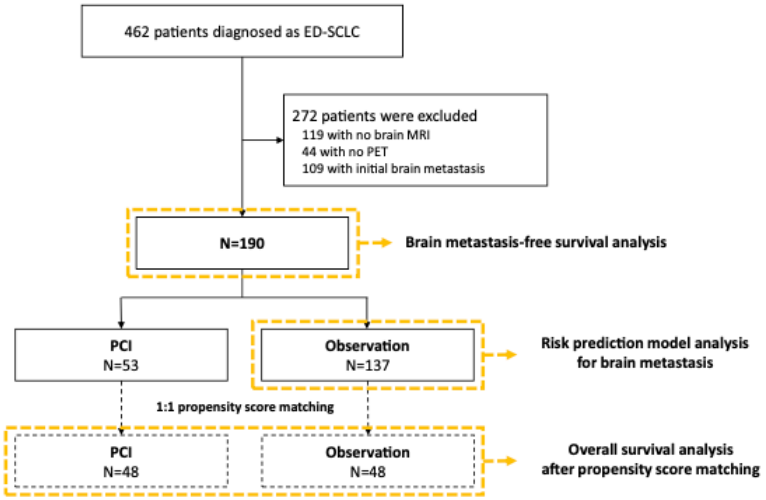
Yaru Tian et al, Cancer Letters 2022



Study	Enrollment	Groups	BRT dose	Key results	Toxicity
Chemotherapy Era					
Slotman et al., 2007 [19] Randomized phase 3, N = 286	ES-SCLC	1, PCI 2, Non-PCI	20Gy/5f or 8f, 24Gy/12f, 25Gy/10f, 30Gy/10f or 12f	Median OS:6.7 m vs 5.4 m (HR 0.68, $P = 0.003$), 1-year OS: 27.1% vs 13.3%; Median DFS: 14.7w vs 12w (HR 0.76, $P = 0.02$). 1-year cumulative risk of BM: 14.6% vs 40.4% (HR 0.27, $P < 0.001$);	AEs were increased with PCI, but the global health status was not affected.
Takahashi et al., 2017 [20] Randomized phase 3, N = 224	ES-SCLC; No BM by MRI examination.	1, PCI 2, Periodic MRI examination	25Gy/10f	Median OS: 11.6 m vs 13.7 m (HR 1.27, $P = 0.094$); Median PFS: 2.3 m vs 2.4 m (HR 0.98, $P = 0.75$); 1-year cumulative incidence of BM: 32.9% vs 59.0% ($P < 0.001$).	G3-4 anorexia: 6% vs 2%, G3-4 malaise: 3% vs <1%.
Bernhardt D et al., 2017 [59] Retrospective, N = 136	ES-SCLC	PCI	30Gy/15f	Median OS: 12 m Median neurologic PFS: 19 m	No severe AEs were observed.
Schild SE et al., 2012 [60] Pooled analysis, N = 739	ES-SCLC LS-SCLC	1, PCI 2, Non-PCI	30Gy/15f, 25Gy/10f	ES-SCLC + LS-SCLC: Median OS: 14 m vs 9 m, 5-year OS rate: 11% vs 3% (HR 0.61, $P < 0.0001$); ES-SCLC: Median OS: 10 m vs 8 m (HR 0.77, $P = 0.0282$); LS-SCLC: Median OS: 17 m vs 14 m (HR 0.68, $P = 0.0045$).	G3-5 AEs: 64% vs 50% ($P = 0.0004$).
Bang A et al., 2018 [61] Retrospective, N = 155	ES-SCLC; No BM	1, PCI 2, Non-PCI	25Gy/10f, 20Gy/5f.	Median OS: 13.5 m vs 8.5 m (HR 0.41, $P < 0.0001$); Median time to BM: 23.8 m vs 10.2 m (HR 0.36, $P < 0.0001$).	–
Chung JH et al., 2020 [67] Retrospective, N = 190	ES-SCLC; No BM	1, PCI 2, Observation	25Gy/10f, 20Gy/5f	1-year BMFS (high-risk): 94.7% vs 62.1% ($P = 0.001$) 1-year BMFS (low-risk): 100.0% vs 87.7% ($P = 0.943$)	–
FIRE-SCLC,2020 [69] multicenter cohort study, N = 710, N = 219	ES-SCLC; with BM	1, SRS 2, WBRT	–	Median OS: 8.5 m vs 5.2 m ($P < 0.001$) Median TTCP: 8.1 m vs NR ($P < 0.001$)	–

RETROSPECTIVE TRIALS and METANALYS: WBRT prolongs OS, reduce and/or delays BM

Yaru Tian et al, Cancer Letters 2022



Clinical Variable	β	HR	p value
Presence of extrathoracic metastases[1]	2.160	8.674	0.004
PET uptake in BM or spleen[2]	1.442	4.229	< 0.001
High neutrophil-to-lymphocyte ratio[3]	0.983	2.674	0.018

Prognostic Index = 2.160*(1)+1.442*(2)+0.983*(3)

PI ≥ 3.0 | PI < 3.0

High risk (n=42) | **Low risk (n=95)**

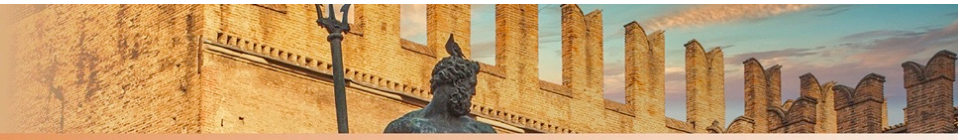
PROGNOSTIC INDEX was CALCULATED on OBSERVATION group and APPLIED to whole study population

PCI REDUCES BMFS IN HIGH RISK but not in low risk patients

PI was then APPLIED to the PS matched coort

PCI does not influence OS neither in low nor in high risk patients

Chung et al., Radiat Oncol 2020



S1827 SWOG clinical trial number

MRI Brain Surveillance Alone Versus MRI Surveillance and Prophylactic Cranial Irradiati (PCI): A Randomized Phase III Trial in Small-Ce Lung Cancer (MAVERICK)

Open Phase

17%

Accrual

Abbreviated Title	MRI Brain Surveillance Alone Versus MRI Surveillanc Prophylactic Cranial Irradiation (PCI): A Randomizec Phase III Trial in Small-Cell Lung Cancer (MAVERICK)
Status Notes	This study is open to accrual effective January 10, 2(2:00 p.m. Pacific.
Activated	01/10/2020
Participants	ALL NATIONAL CLINICAL TRIALS NETWORK MEMBEI

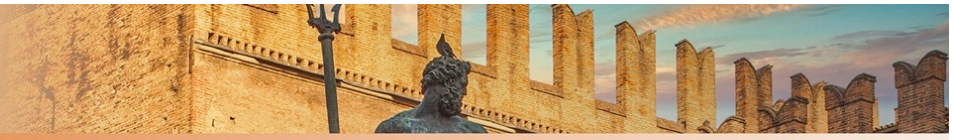
…waiting the results o

Table 5 Recommendations for prophylactic cranial RT

KQ3 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with SCLC who respond to initial therapy, restaging with brain MRI to guide decision-making regarding PCI is recommended.	Strong	Low 73,74
2. For patients with stage I SCLC, PCI is conditionally not recommended. Implementation Remark: In lieu of PCI, surveillance using brain MRI with contrast can serve as an alternative.	Conditional	Low 75-78
3. For patients with stage II-III LS-SCLC who are less than 70 years of age with good performance status (ECOG 0-2) and respond to thoracic chemoradiation, PCI is recommended.	Strong	High 8,75,79-87
4. For patients with LS-SCLC who have limited performance status, older age, and/or significant comorbidities, shared decision-making on PCI (considering patient- and disease-specific characteristics) is recommended.	Strong	Low 80,85,88-92
5. For patients with LS-SCLC receiving PCI, 2500 cGy in 10 fractions is recommended.	Strong	Moderate 82,83,91-93
6. For patients with ES-SCLC who respond to chemotherapy, consultation with a radiation oncologist to enhance shared decision-making on PCI versus MRI surveillance (considering patient- and disease-specific characteristics) is recommended.	Strong	Moderate 10,13,81,94-96
7. For patients with ES-SCLC who elect PCI, 2500 cGy in 10 fractions or 2000 cGy in 5 fractions is recommended.	Strong	Moderate 10,13,92,93,97,98

Abbreviations: cGy = centigray; ECOG = Eastern Cooperative Oncology Group; ES = extensive-stage; KQ = key question; LS = limited-stage; MRI = magnetic resonance imaging; PCI = prophylactic cranial irradiation; RT = radiation therapy; SCLC = small cell lung cancer.

Simone CB et al, PRO 2020
Dali ME et al, JCO 2021



TAKE HOME MESSAGES:

- CHT/IT for at least 4 cycles and IT manteinance is the new standard of treatment in ED SCLC
- Thoracic consolidation RT can play a role in obtaining more from manteinance IT
- PCI could be evaluated in selected patients with ED-SCLC but MRI follow up can be a valid alternative in older patients, with neurocognitive impairment and without response to CHT/IT

Acnowledgments:
Dott.ssa Maria Grazia Carnevale

Scuola Specializzazione
Radioterapia Oncologica
Università degli Studi di Firenze

vieri.scotti@unifi.it