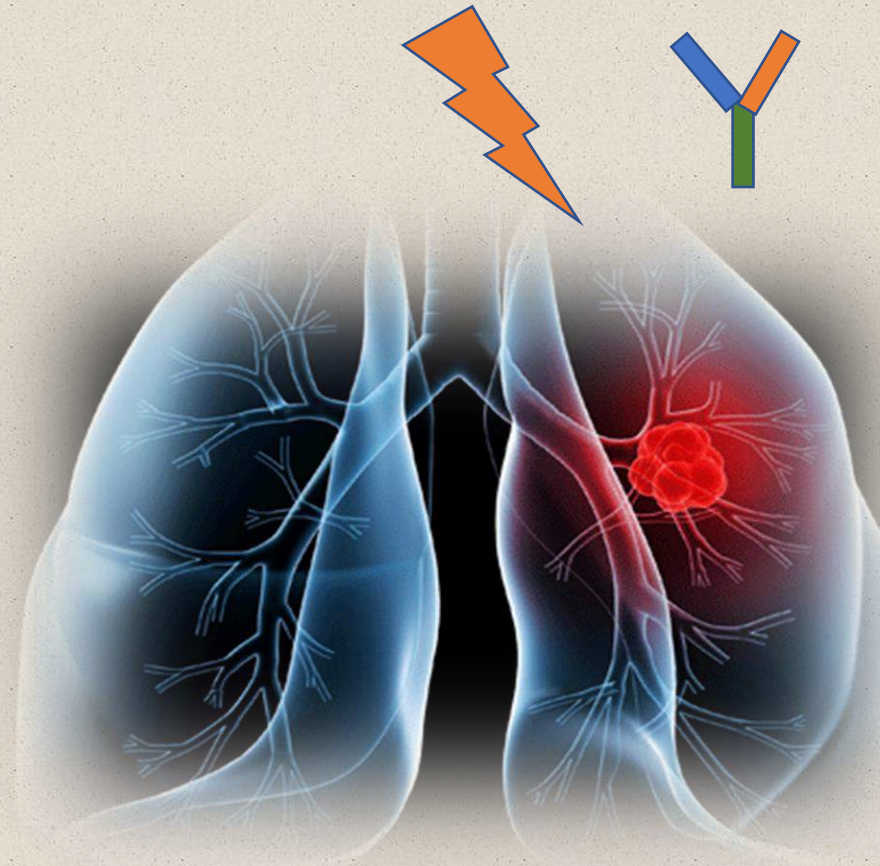
Combining Radiotherapy with Immunotherapy in thoracic malignancies



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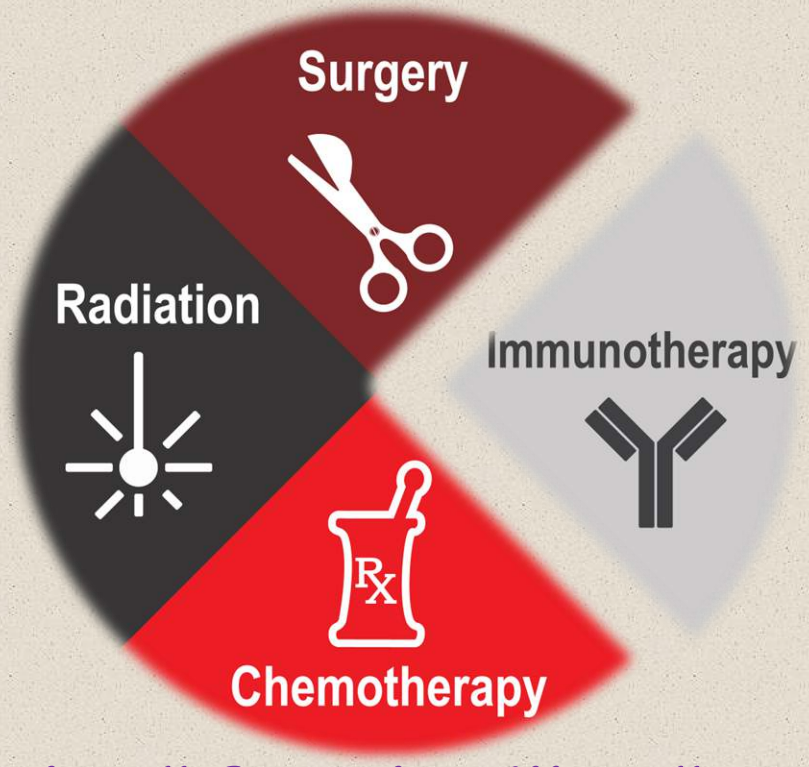
Head of Department
Radiation Oncology
Mahavir Cancer Sansthan, Patna

Need to combine..???

- Thoracic malignancies-predominantly of
  - Non-small cell lung cancer
  - Small cell lung cancer
  - Malignant pleural mesothelioma
  - Advanced oesophageal cancers
  - Advanced stage thymoma, and thymic carcinoma

Distant metastases & poor prognosis

Need to combine..???



Treatment modalities-

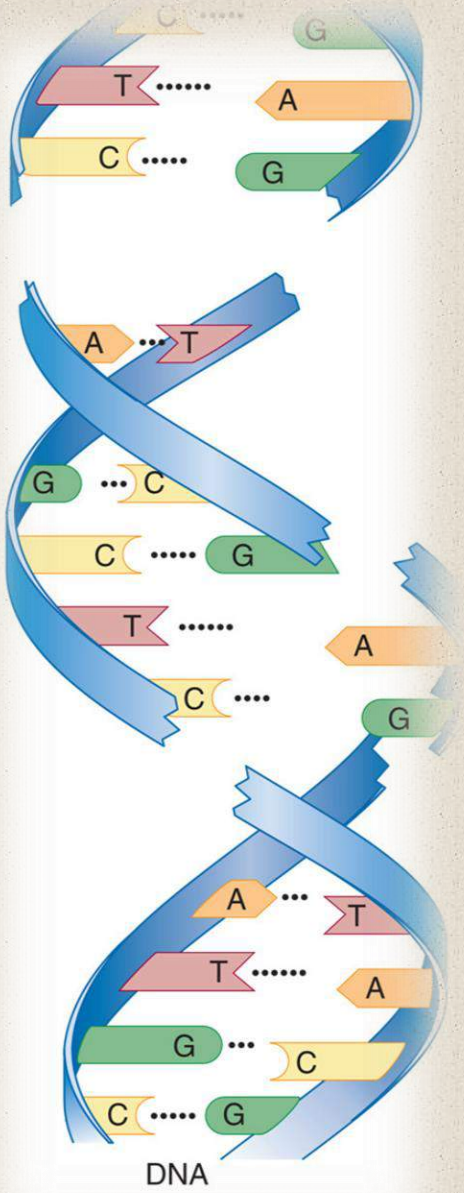
- **Radiotherapy**
- **Chemotherapy**
- **Surgery**
- ***Immunotherapy -now considered to be the " fourth pillar " of cancer care***

Introduction

- Radiation therapy is one of local ablative therapies uses high energy radiation for cancer treatment .

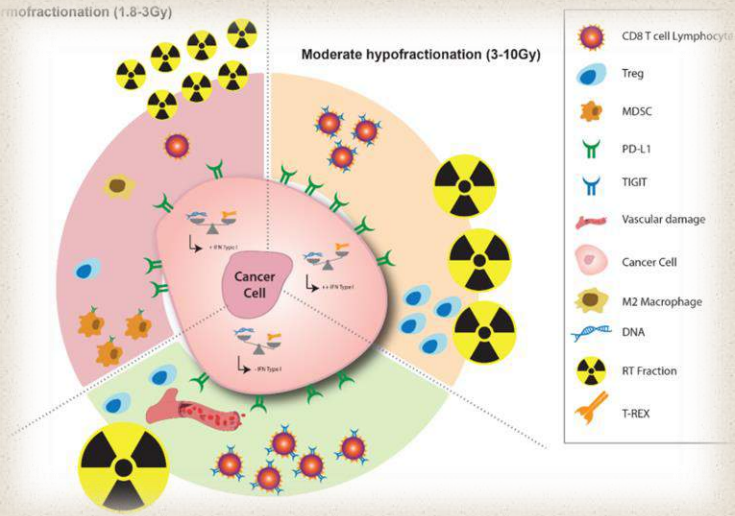
- It induces double-strand DNA damage in cancer cells, single strand breaks, misrepair, and chromosome aberrations.
- All of these events are direct actions of RT . The cells are killed mainly by mitotic catastrophe, but also by apoptosis, necrosis, autophagy, or replicative senescence.

- As we focus on investigations of new technologies such as FLASH RT, proton RT, and carbon ion RT which aim to improve the therapeutic ratio, increasing evidence on immunomodulatory effects of RT casts new light on its systemic antitumor response.

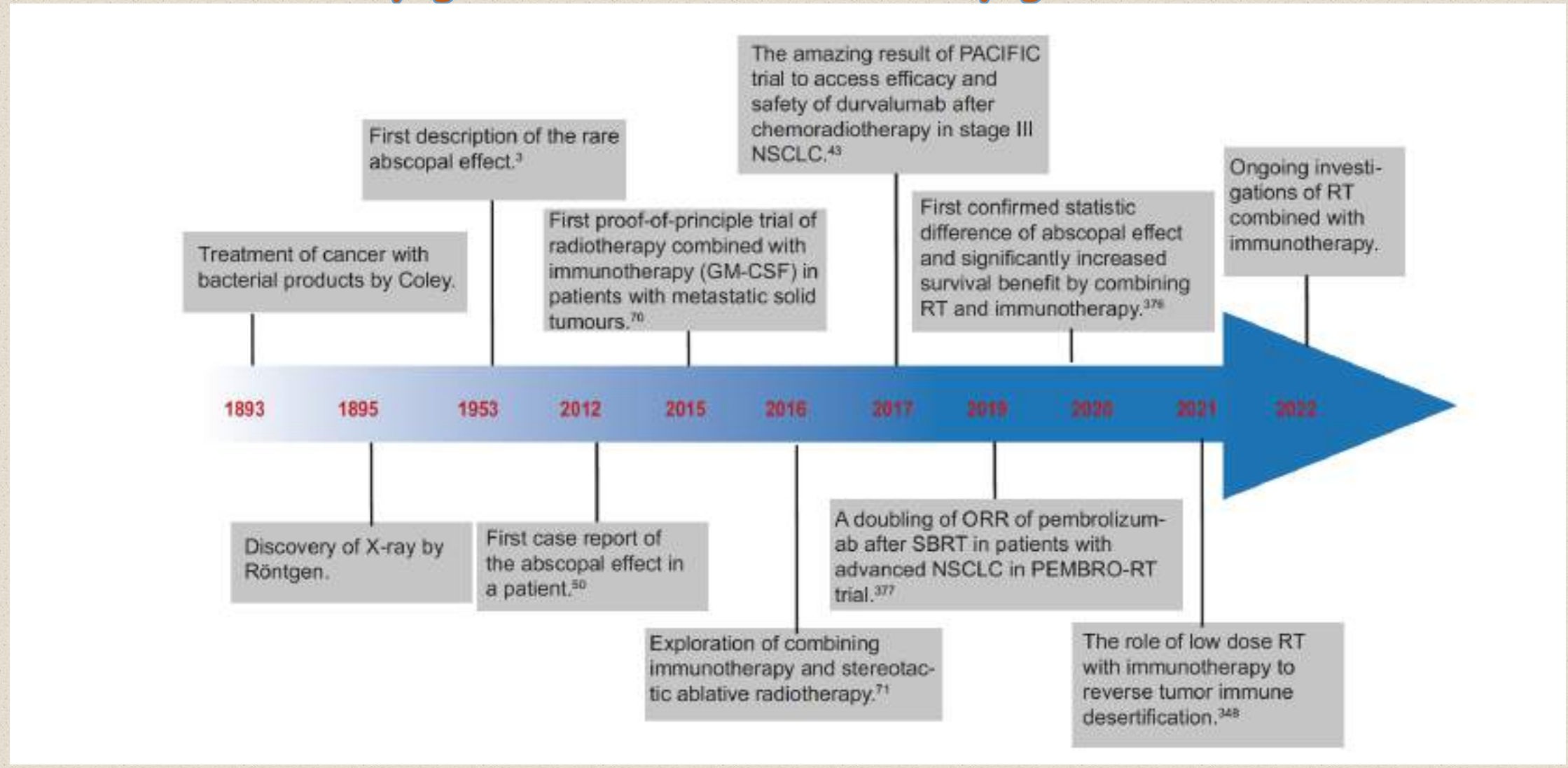


- Recent studies have found RT may be similar to an “accelerant” by means of inducing in situ vaccination by killing tumor cells and triggering a systemic immune response.

- The most representative example is the abscopal effect: radiation on one site may cause regression of tumor at remote and distant nonirradiated sites. The potential systemic antitumor capacity provides a sound basis for combining radiotherapy and Immunotherapy.

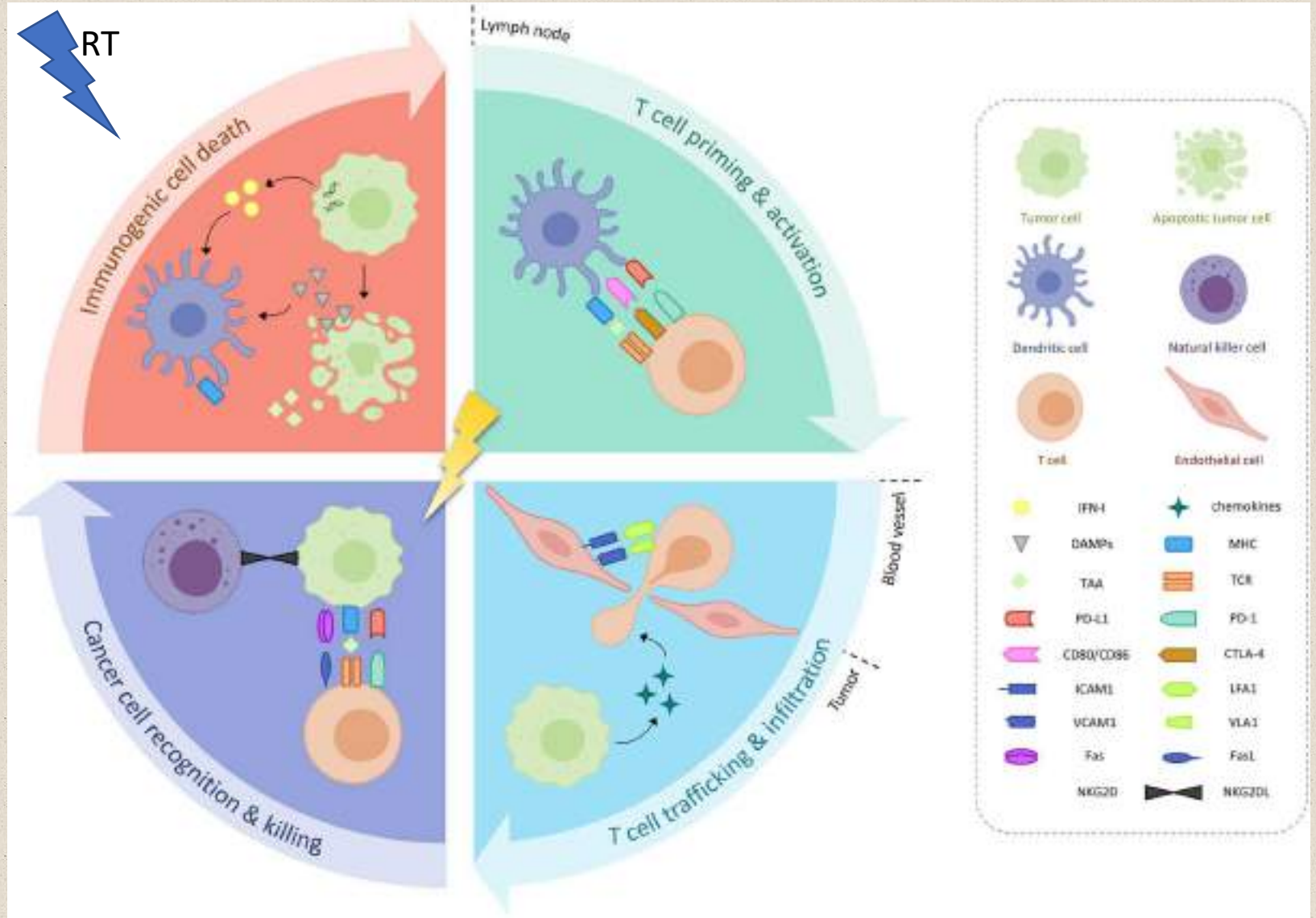


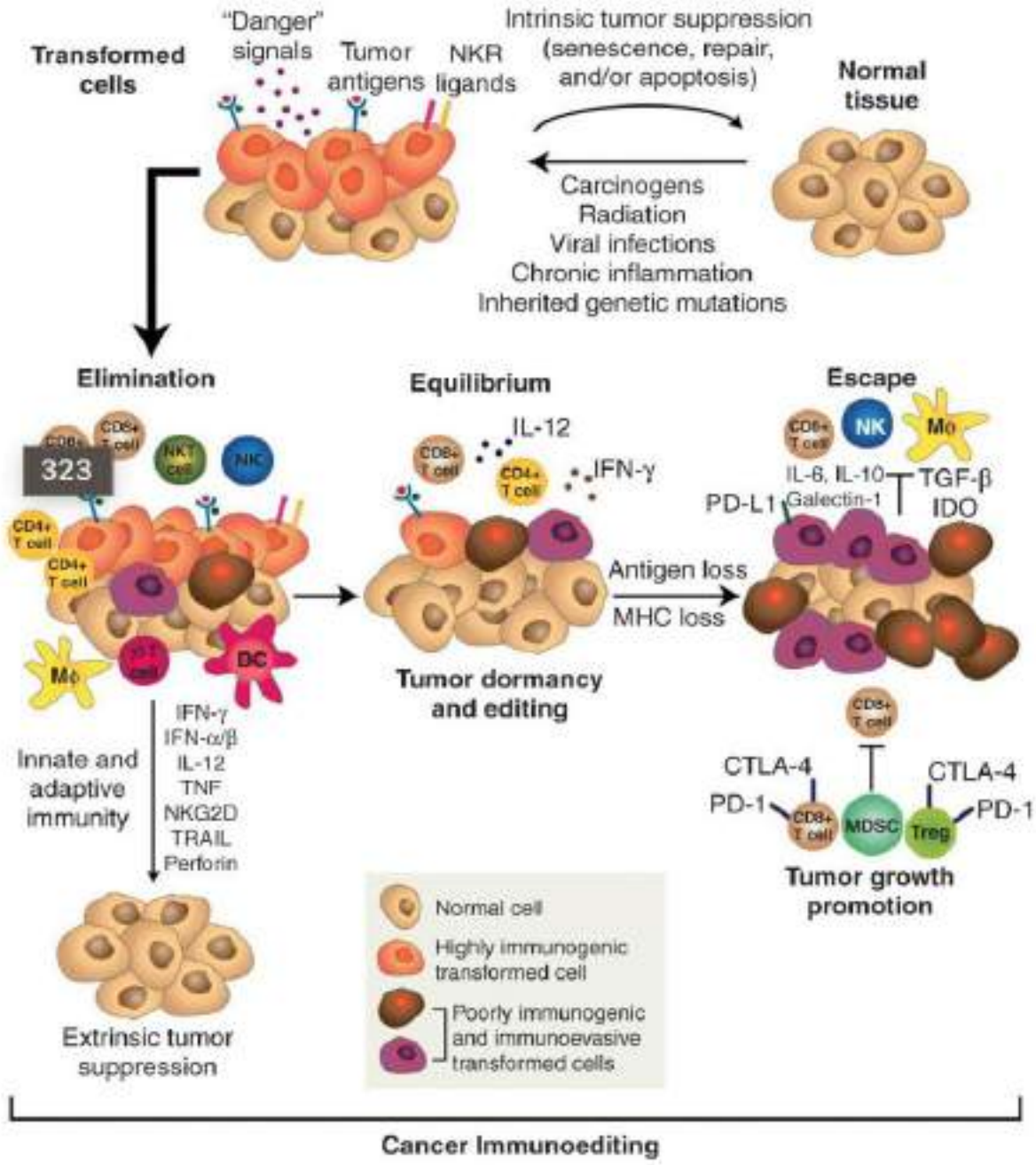
Historical Timeline- Radiotherapy/Immunotherapy



Immunologic effects of Radiotherapy

- In-situ vaccination



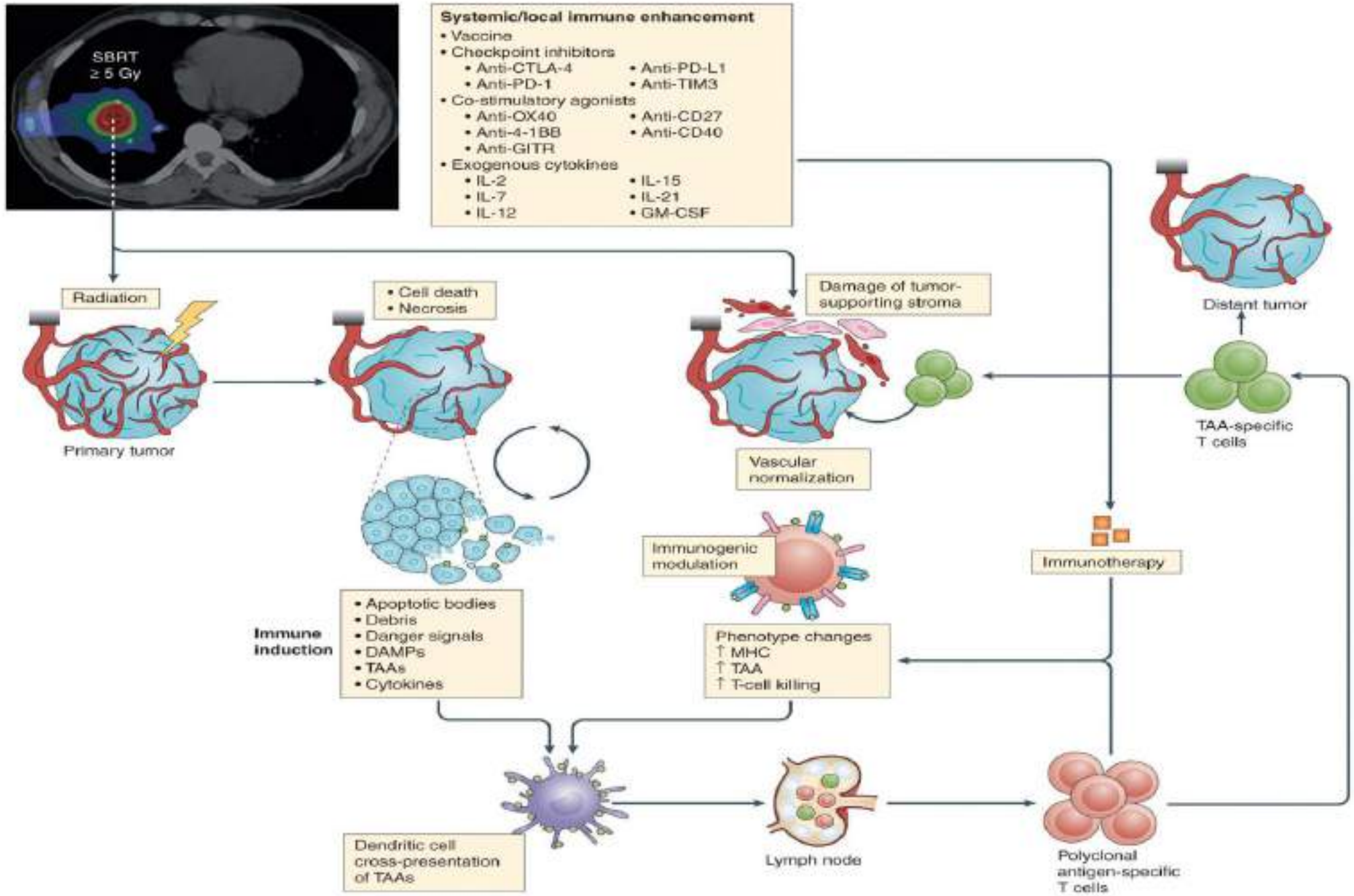


3 E's of immune surveillance include ***Elimination, Equilibrium, and Escape.***

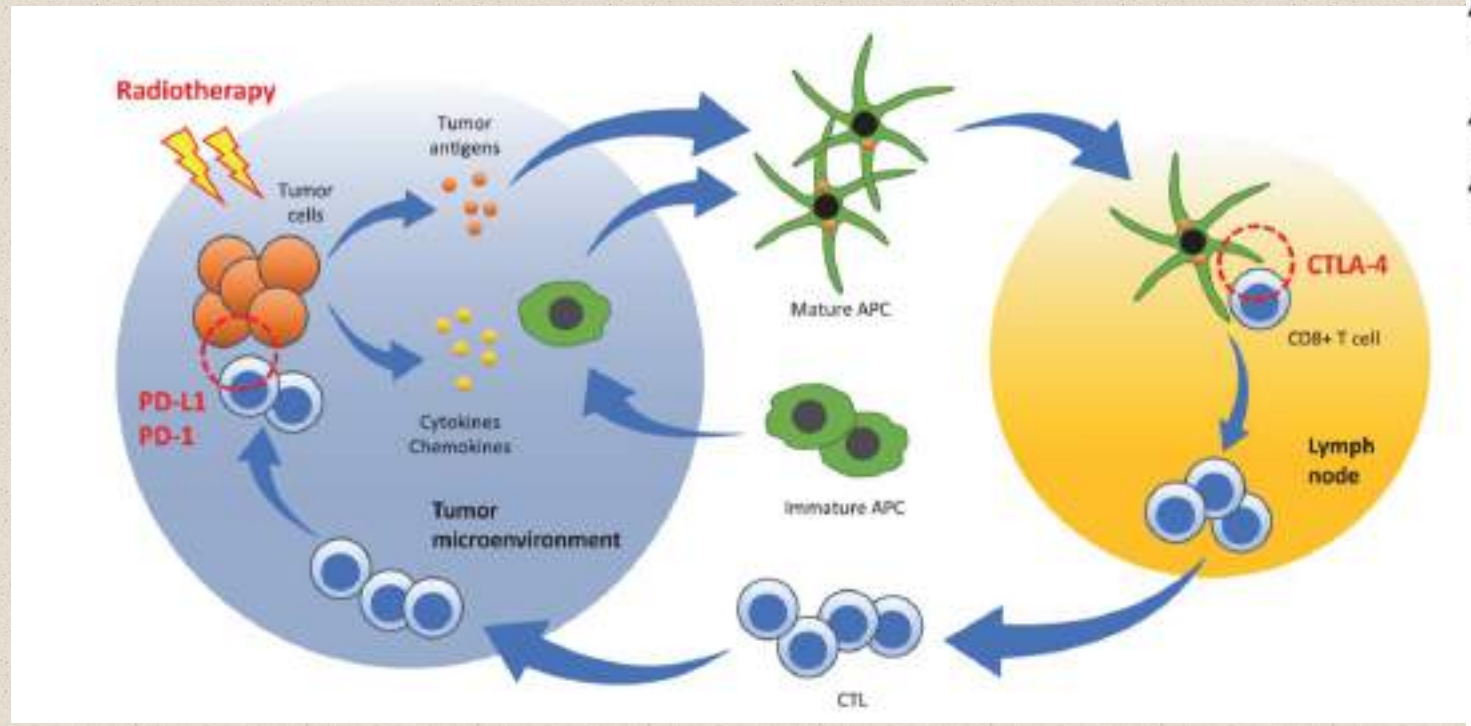
The immune system can control tumor growth with various immune mediators.

However, tumor suppressor cells and immunosuppressive cytokines can permit tumor escape.

Anti-PD-1,Anti-CTLA-4+ Radiation


SBRT
≥ 5 Gy
Systemic/local immune enhancement
• Vaccine
• Checkpoint inhibitors
• Anti-CTLA-4
• Anti-PD-1
• Anti-PD-L1
• Anti-TIM3
• Co-stimulatory agonists
• Anti-OX40
• Anti-4-1BB
• Anti-GITR
• Anti-CD27
• Anti-CD40
• Exogenous cytokines
• IL-2
• IL-7
• IL-12
• IL-15
• IL-21
• GM-CSF
Radiation
Primary tumor
• Cell death
• Necrosis
Damage of tumor-supporting stroma
Vascular normalization
Distant tumor
TAA-specific T cells
Immunogenic modulation
Immunotherapy
Immune induction
• Apoptotic bodies
• Debris
• Danger signals
• DAMPs
• TAAs
• Cytokines
Phenotype changes
↑ MHC
↑ TAA
↑ T-cell killing
Dendritic cell cross-presentation of TAAs
Lymph node
Polyclonal antigen-specific T cells

RT and Immune check point inhibitors



RT

Anti-PD-1
Anti-PD-L1

- IFN-γ and type I IFN production (latter dependent on cancer cell-intrinsic cGAS-STING activation)
- MHC tumor antigen complexes and tumor antigen cross-presentation
- TCR clonality and diversity
- PD-1/PD-L1 expression on immune and tumor cells

- CD8+ TILs
- Tregs

- CD8+/Treg ratio
- CD8+ TILs with a CD44+ effector memory phenotype
- Immunosuppressive MDSCs
- Reinvigoration of CD8+ TILs with an exhausted phenotype
- TCR diversity in irradiated and out-of-field sites
- Abscopal effects and systemic immunity

ENHANCED ANTITUMOR ACTIVITY

- **Radiotherapy has the potential to convert immunologically ‘cold’ tumors into ‘hot’ tumors by a combination of distinct mechanisms including:**

(a)increasing tumor immunogenicity via the upregulation of antigenic expression, antigen processing, major histocompatibility molecules, and costimulatory signals;

(b) overcoming an immunosuppressive tumor microenvironment by shifting the cytokine balance in favour of immunostimulation (e.g. by increasing the production of immunostimulatory cytokines);

(c) recruiting antigen-presenting and immune effector cells to the tumor microenvironment

Ongoing Clinical trials

Table 1 Ongoing clinical trials investigating combining radiation therapy and immunotherapy for thoracic cancers

National clinical trial ID number	Phase	Participating institution(s)	Histology	Stage	Immunotherapy agent	Immunotherapy mechanism of action	Radiation
NCT03110978	II randomized	MD Anderson Cancer Center	NSCLC	I	Nivolumab	PD-1	SBRT
NCT02599454	I	UC Davis and David Grant United States Air Force Medical Center	NSCLC	I	Atezolizumab	PD-L1	SBRT
NCT03050554	I/II	UC San Diego	NSCLC	I	Avelumab	PD-L1	SBRT
NCT03148327	II randomized	UCLA	NSCLC	I	Durvalumab	PD-L1	SBRT
NCT03446911	II randomized	VU Medical Center	NSCLC	I	Pembrolizumab	PD-1	SBRT
NCT03383302	II	Multi Center led by Royal Marsden	NSCLC	I–II	Nivolumab	PD-1	SBRT
NCT02621398	I	Multicenter led by Rutgers Cancer Institute of New Jersey	NSCLC	II–IIIB	Pembrolizumab concurrently with carboplatin and paclitaxel	PD-1	Conventionally fractionated IMRT or 3D-CRT
NCT02434061	II	European Thoracic Oncology Platform	NSCLC	IIIA–IIIB	Nivolumab concurrently with	PD-1	Conventionally fractionated RT
NCT03245177	I	University of Manchester	NSCLC	III	Pembrolizumab	PD-1	Conventionally fractionated RT
NCT03237377	II	Johns Hopkins University	NSCLC	IIIA	Durvalumab/tremelimumab	PD-L1/CTLA-4	Conventionally fractionated RT
NCT03035890	n/a	West Virginia University	NSCLC	IV	Nivolumab/pembrolizumab/ atezolizumab	PD-1/PD-1/PD-L1	Hypofractionated RT
NCT03509584	I	Assistance Publique Hôpitaux De Marseille	NSCLC	IV	Nivolumab/ipilimumab	PD-1/CTLA-4	Hypofractionated RT
NCT02463994	I	Multicenter let by University of Michigan	NSCLC	IV	Atezolizumab	PD-L1	Hypofractionated RT
NCT03176173	II	Stanford University	NSCLC	IV	Nivolumab/pembrolizumab/ atezolizumab	PD-1/PD-1/PD-L1	Hypofractionated RT
NCT03313804	II	University of Kentucky	NSCLC	IV	Nivolumab/pembrolizumab/ atezolizumab	PD-1/PD-1/PD-L1	SBRT or conventional palliative RT
NCT02839265	II	Montefiore Medical Center	NSCLC	IV	CDX-301	FLT3 ligand	SBRT
NCT03168464	I/II	Weill Medical College of Cornell University	NSCLC	IV	Nivolumab/ipilimumab	PD-1/CTLA-4	Hypofractionated RT

Table 1 (continued)

jtd.amegroups.com J Thorac Dis 2018;10(Suppl 21):S2492-S2507

Table 1 (continued)

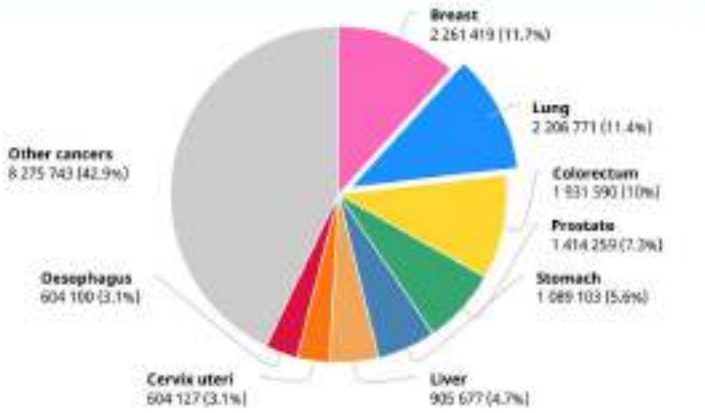
National clinical trial ID number	Phase	Participating institution(s)	Histology	Stage	Immunotherapy agent	Immunotherapy mechanism of action	Radiation
NCT03275597	Ib	University of Wisconsin	NSCLC	IV	Durvalumab/tremelimumab	PD-L1/CTLA-4	SBRT
NCT03223155	I	University of Chicago	NSCLC	IV	Nivolumab/ipilimumab	PD-1/CTLA-4	SBRT
NCT03224871	Pilot	UC Davis	NSCLC	IV	IL-2/nivolumab/pembrolizumab	IL-2/PD-1/PD-1	Hypofractionated RT
NCT03391869	III randomized	MD Anderson Cancer Center	NSCLC	IV	Nivolumab/ipilimumab	PD-1/CTLA-4	Hypofractionated RT or SBRT
NCT02221739	II	New York University	NSCLC	IV	Ipilimumab	CTLA-4	Hypofractionated RT
NCT02402920	I	MD Anderson Cancer Center	SCLC	Limited and extensive stage	Pembrolizumab with carboplatin and etoposide	PD-1	Hyperfractionated or Hypofractionated RT
NCT02701400	II randomized	Emory University	SCLC	Recurrent	Durvalumab and Tremelimumab	PD-L1 and CTLA-4	Hypofractionated RT and SBRT
NCT03399552	I/II	Memorial Sloan Kettering Cancer Center	Malignant pleural mesothelioma	Recurrent	Avelumab	PD-L1	SBRT
NCT03377400	II	Samsung Medical Center	Esophageal squamous cell carcinoma	Inoperable T2–3N0M0 or T1–3N1–3M0	Durvalumab/tremelimumab with 5-Flurouracil and cisplatin	PD-L1/CTLA-4	Conventionally fractionated RT
NCT03437200	II randomized	European Organisation for Research and Treatment of Cancer	Esophageal cancer	Inoperable T1N1–3M0 or T2–3N0–3M0	Nivolumab/ipilimumab with FOLFOX	PD-1/CTLA-4	Conventionally fractionated RT
NCT02642809	I	Washington University in St Louis	Esophageal cancer	IV	Pembrolizumab	PD-1	Intracavitary brachytherapy
NCT02735239	I/II	Ludwig Institute for Cancer Research	Esophageal cancer	II–IV	Durvalumab/tremelimumab with capecitabine and paclitaxel	PD-L1/CTLA-4	Conventionally fractionated RT

SBRT, stereotactic body radiation therapy; IL-2, interleukin-2; PD-1, programmed cell death protein 1; PD-L1, programmed death1ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; FOLFOX, 5-flurouracil, leucovorin, oxaliplatin; RT, radiation therapy; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

Lung Cancer

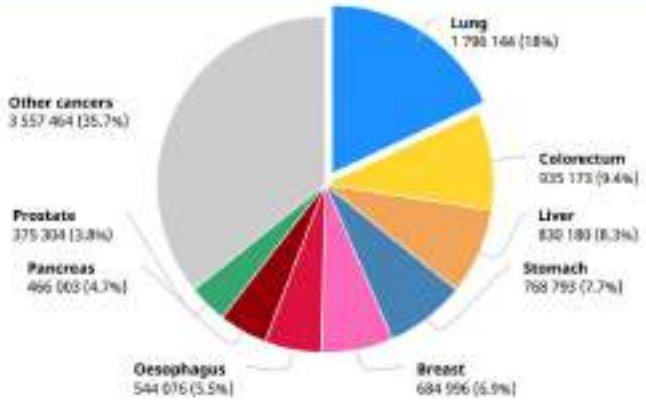
Lung
Source: Globocan 2020

Number of new cases in 2020, both sexes, all ages



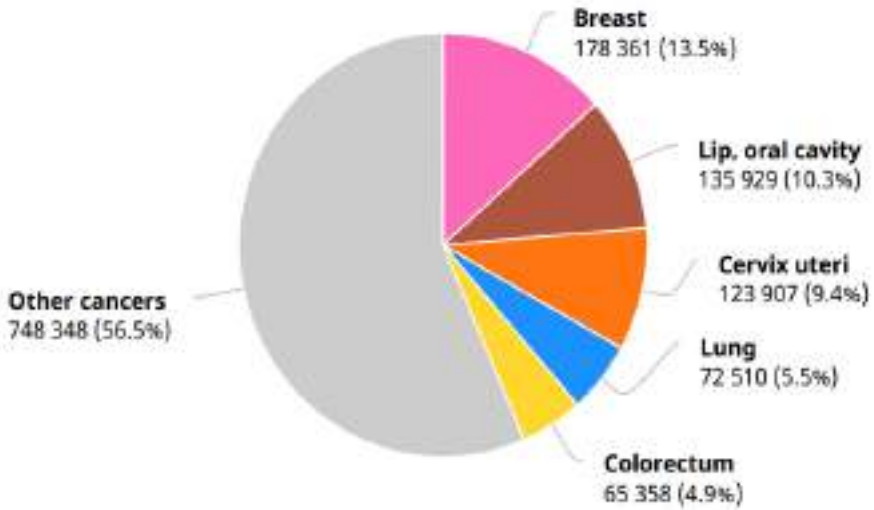
Total: 19 292 789 cases

Number of deaths in 2020, both sexes, all ages



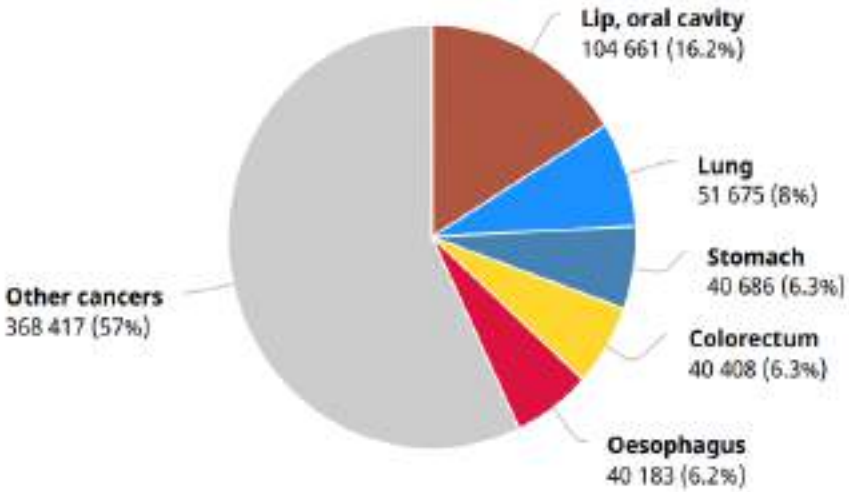
Total: 9 958 133 deaths

Number of new cases in 2020, both sexes, all ages



Total: 1 324 413

Number of new cases in 2020, males, all ages



Total: 646 030

Estimated Incidence, Mortality and Prevalence in 2020

	Incidence	Deaths	5 year prevalence
 World	2206771	1796144	2604791
 India	72510	66279	80817

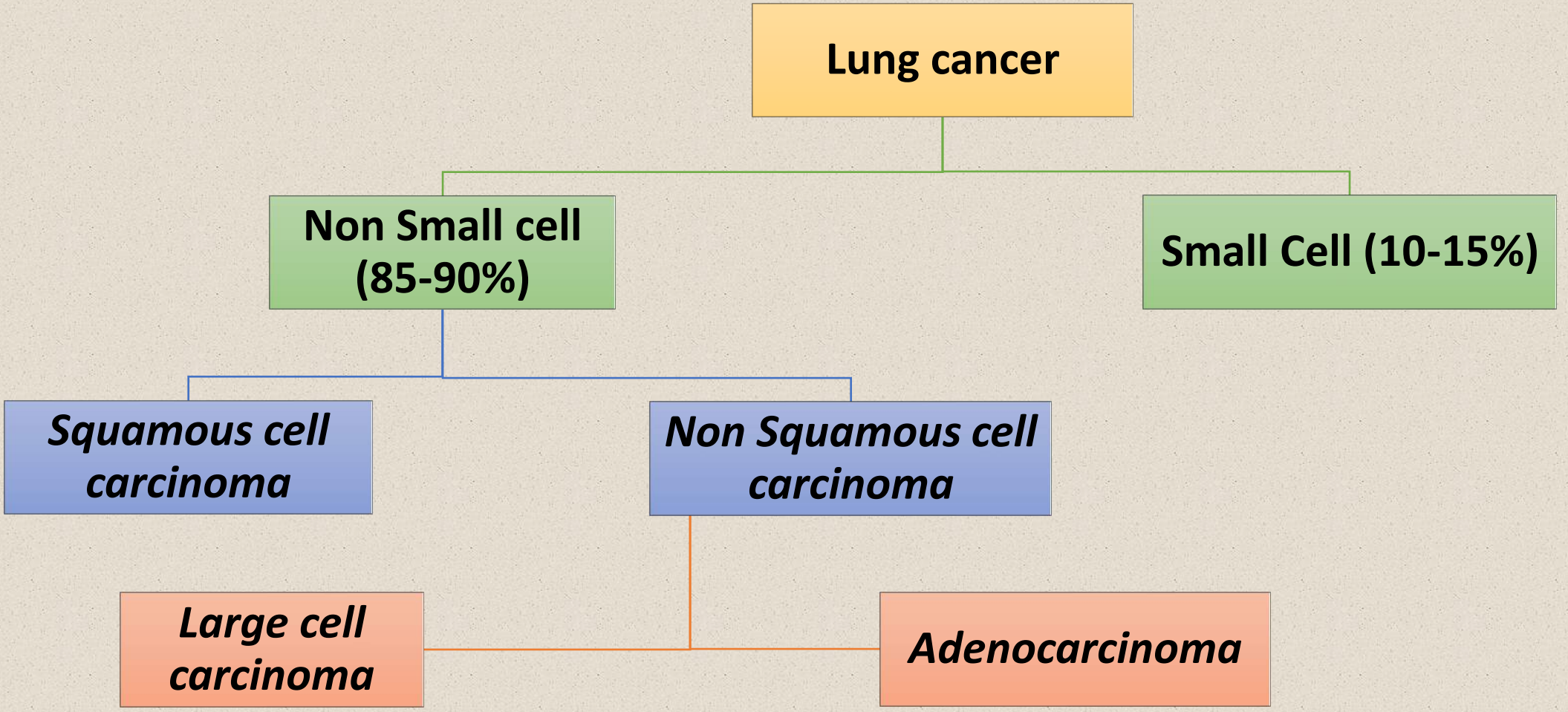
No. 1 cancer across the world in terms of death.

4th most common cancer in India in terms of incidence.

3rd most common cancer causing death in India.

Globocan 2020

Lung Cancer Types



Non-Small cell Lung Carcinoma

- **Although a significant proportion of patients can be cured with surgery, with or without adjuvant or neoadjuvant chemotherapy and radiation, a significant proportion of patients will fail, particularly distantly.**

- **More than half of patients with NSCLC present with distant metastases at the time of diagnosis**
- **5-year overall survival (OS) less than 5% .**

- **For patients with stage IV NSCLC RT has historically been used only for palliative purposes**
- **NSCLC patients with a low burden of metastatic disease to a limited number of distant sites (oligometastatic), RT can improve PFS and potentially OS – [SABR-COMET].**

- Platinum-based doublet chemotherapy- first line,taxane-based regimens as second-line regimens
- There are multiple forms of immunotherapy available including T-cell transfer, cytokine therapy, and oncolytic viruses.
- **Checkpoint inhibitors** have shown tremendous activity in NSCLC and are currently under intense study given promising data on response.
- Immunotherapy and radiation therapy (RT) both show significant immune editing activity in NSCLC that may allow the innate and adaptive immune system to help control systemic disease by both radio sensitization and a sustained systemic immune response.
- Multiple clinical trials are underway exploring the role of adjuvant or neoadjuvant immunotherapy in operable NSCLC.

- **A substantial amount of progress is to be made in terms of optimizing radiation dose and fractionation, immunotherapy type and dose, and integrating both to best realize the benefits of immunotherapy and radiation in operable lung cancer.**

Radiation plus immunotherapy for metastatic NSCLC

Positive First-line Advanced NSCLC Immunotherapy Trials: An Ever-Growing List

Trial	Comparison	Selection	ORR, %	PFS HR	OS HR
KEYNOTE-024[1-3]	Pembro vs plt-doublet CT	PD-L1 ≥50%	46.1 vs 31.1	0.50	0.62
IMpower110[4,5]	Atezo vs plt-doublet CT	PD-L1 ≥50% (TC) or 10% (IC)	38.3 vs 28.6	0.63	0.59
EMPOWER-Lung 1[6]	Cemiplimab vs plt-doublet CT	PD-L1 ≥50%	39.2 vs 20.4	0.54	0.57
KEYNOTE-042[7,8]	Pembro vs plt-doublet CT	PD-L1 ≥1%	27.3 vs 26.7	1.05	0.80
KEYNOTE-189[9,10]	Pembro or placebo + carbo/pem	PD-L1 unselected; nonsquamous	48.3 vs 19.9	0.49	0.56
IMpower130[11]	Atezo + carbo/nab-pac vs CT alone	PD-L1 unselected; nonsquamous	49.2 vs 31.9	0.64	0.79
IMpower150[12,13]	Atezo + carbo/pac + bev vs CT + bev	PD-L1 unselected; nonsquamous	63.5 vs 48.0	0.62	0.80
KEYNOTE-407[14-16]	Pembro or placebo + carbo/pac or nab-pac	PD-L1 unselected; squamous	62.6 vs 38.8	0.59	0.71
EMPOWER-Lung 3[17]	Cemiplimab or placebo + plt-doublet CT	PD-L1 unselected	43.3 vs 22.7	0.56	0.71
CheckMate 227[18-20]	Nivo + ipi vs plt-doublet CT	TMB high (≥10 mut/Mb)	45.3 vs 26.9	0.58	NR
		PD-L1 ≥1%	36.4 vs 30.0	0.81	0.76
		PD-L1 <1%	27.3 vs 23.1	0.74	0.64
CheckMate 9LA[21,22]	Nivo + ipi + plt-doublet CT vs plt-doublet CT	PD-L1 unselected	38.0 vs 25.4	0.67	0.72

1. Reck. NEJM. 2016;375:1823. 2. Reck. JCO. 2019;37:537. 3. Reck. JCO. 2021;39:2339. 4. Herbst. NEJM. 2020;383:1328. 5. Herbst. WCLC 2020. Abstr FP13.02.
6. Sezer. Lancet. 2021;397:592. 7. Mok. Lancet. 2019;393:1819. 8. Cho. WCLC 2020. Abstr FP13.04. 9. Gandhi. NEJM. 2018;378:2078. 10. Rodríguez-Abreu. Ann Oncol. 2021;32:881. 11. West. Lancet Oncol. 2019;20:924. 12. Socinski. NEJM. 2018;378:2288. 13. Socinski. J Thorac Oncol. 2021;16:1909. 14. Paz-Ares. NEJM. 2018;379:2040.
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19. Hellmann. NEJM. 2019;381:2020. 20. Paz-Ares. J Thorac Oncol. 2022;17:289. 21. Paz-Ares. Lancet Oncol. 2021;22:198. 22. Reck. ESMO Open 2021;6:100273.

Overall Survival With First-line ICI Monotherapy for NSCLC With High PD-L1 Expression

KEYNOTE-024: OS With Pembrolizumab in NSCLC With PD-L1 Expression ≥50%*[1]

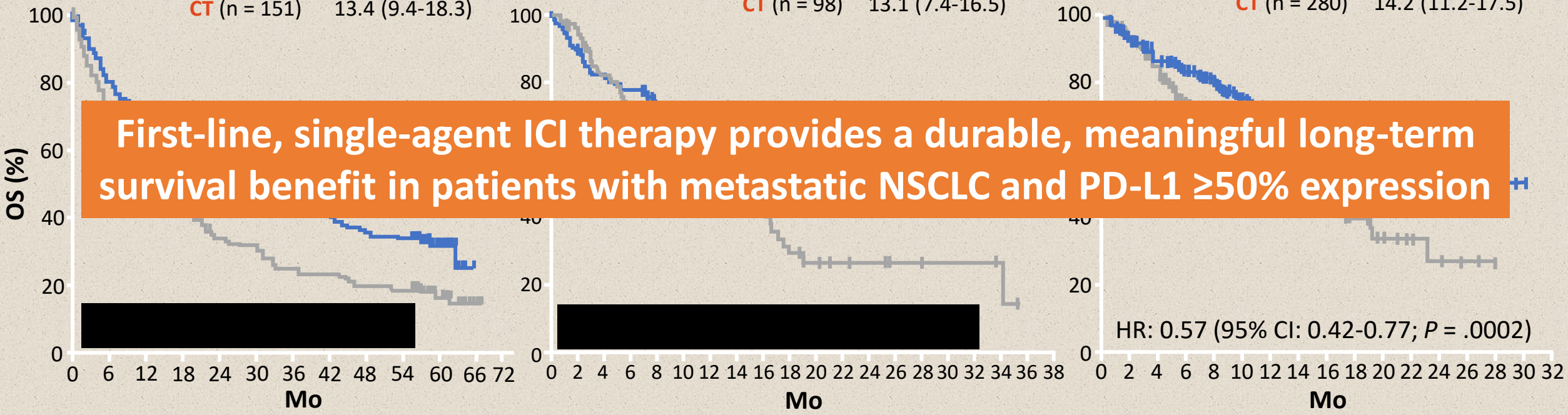
	Median OS, Mo (95% CI)
Pembro (n = 154)	26.3 (18.3-40.4)
CT (n = 151)	13.4 (9.4-18.3)

IMpower110: OS With Atezolizumab in NSCLC With High PD-L1 Expression[2]

	Median OS, Mo (95% CI)
Atezo (n = 107)	20.2 (16.5-NE)
CT (n = 98)	13.1 (7.4-16.5)

EMPOWER-Lung 1: OS With Cemiplimab in NSCLC With High PD-L1 Expression[3]

	Median OS, Mo (95% CI)
Cemiplimab (n = 283)	NR (17.9-NE)
CT (n = 280)	14.2 (11.2-17.5)



First-line, single-agent ICI therapy provides a durable, meaningful long-term survival benefit in patients with metastatic NSCLC and PD-L1 ≥50% expression

1. Reck. JCO. 2021;39:2339. 2. Herbst. NEJM. 2020;383:1328. 3. Sezer. Lancet. 2021;397:592. 4. Mok. Lancet. 2019;393:1819. 5. Cho. WCLC 2020. Abstr FP13.04.

*Single-agent pembrolizumab approved for PD-L1 ≥1% but not broadly recommended by experts.[4,5]

CheckMate 017 trial

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Nivolumab versus Do
small Cell Lung Canc

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Abstract

Background—Options for patients with non-squamous non-small cell lung cancer (NSCLC) whose disease progresses after first-line chemotherapy are limited. This randomized, open-label, international phase 3 study evaluated efficacy and safety of nivolumab versus docetaxel in this patient population after failure of platinum doublet chemotherapy.

Methods—Patients were randomized to nivolumab 3 mg per kilogram every 2 weeks or docetaxel 75 mg per square meter every 3 weeks. The primary endpoint was overall survival.

Results—Nivolumab improved overall survival versus docetaxel. Median overall survival was 12.2 months (95% CI, 9.7 to 15.0) for nivolumab (n=292) and 9.4 months (95% CI, 8.1 to 10.7) for docetaxel (n=290) (hazard ratio, 0.73; 96% CI, 0.59 to 0.89; P=0.002). One-year overall survival rates were 51% (95% CI, 45 to 56) for nivolumab and 39% (95% CI, 33 to 45) for docetaxel. Updated efficacy results with additional follow up are available for overall survival only: 18-month overall survival rates were 39% (95% CI, 34 to 45) for nivolumab and 23% (95% CI, 19 to 28) for docetaxel. Response rates were 19% for nivolumab and 12% for docetaxel (P=0.02). Although progression-free survival did not favor nivolumab (2.3 months for nivolumab versus 4.2 months for docetaxel), 1-year progression-free survival was higher for nivolumab (19%) than docetaxel (8%). Nivolumab further improved efficacy across all endpoints at predefined ≥1%, ≥5%, and ≥10% programmed death-1 ligand 1 (PD-L1) tumor membrane expression levels. Grade 3–5 treatment-related adverse events were reported in 10% of nivolumab and 54% of docetaxel-treated patients.

Conclusions—Compared to docetaxel, nivolumab demonstrated superior overall survival, with PD-L1 expression conferring enhanced efficacy in patients with advanced non-squamous NSCLC after failure of platinum-based chemotherapy. The safety profile of nivolumab was favorable versus docetaxel.

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Pembrolizumab versus docetaxel for previously treated, PD-L1-positive advanced controlled

Prof Roy S Herbst

José L Pérez-Grac

Published: Decem

Pembrolizu
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Abstract

Introduction: In the KEYNOTE-010 study, pembrolizumab improved overall survival (OS) versus docetaxel in patients with previously treated, advanced NSCLC with programmed death-ligand 1 (PD-L1) tumor proportion score (TPS) ≥50% and ≥1%. We report 5-year efficacy and safety follow-up for the KEYNOTE-010 study.

Methods: Patients were randomized to pembrolizumab 2 mg/kg or 10 mg/kg once every 3 weeks or docetaxel 75 mg/m^2 once every 3 weeks for up to 35 cycles (2 y). Patients who completed pembrolizumab treatment and subsequently had recurrence could receive second-course pembrolizumab for up to 17 cycles (1 y). Pembrolizumab doses were pooled in this analysis.

Results: A total of 1034 patients were randomized (pembrolizumab, n = 691; docetaxel, n = 343). Median study follow-up was 67.4 months (range: 60.0–77.9). The hazard ratio (95% confidence interval) for OS was 0.55 (0.44–0.69) for patients with PD-L1 TPS ≥50% and 0.70 (0.61–0.80) with PD-L1 TPS ≥1%. The 5-year OS rates for pembrolizumab versus docetaxel were 25.0% versus 8.2% in patients with PD-L1 TPS ≥50% and 15.6% versus 6.5% with PD-L1 TPS ≥1%. Among 79 patients who completed 35 cycles/2 years of pembrolizumab, the OS rate 3 years after completion (~5 y from randomization) was 83.0%. A total of 21 patients received second-course pembrolizumab; 11 (52.4%) had an objective response after starting the second course and 15 (71.4%) were alive at data cutoff. Exploratory biomarker analysis revealed that higher tissue tumor mutational burden (≥175 mutations per exome) was associated with improved outcomes with pembrolizumab.

Conclusions: Pembrolizumab continued to provide long-term benefit than docetaxel in patients with previously treated advanced NSCLC with PD-L1 TPS ≥50% and ≥1%. Our findings confirm pembrolizumab as a standard-of-care treatment in the second-line or later setting.

et [10],
[5],

ARTICLES | VOLUME 387, ISSUE 10030, P1837-1846, APRIL 30, 2016

Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial

Dr Louis Fehrenbacher, MD • Alexander Spira, MD • Marcus Ballinger, PhD • Marcin Kowanetz, PhD • Prof Johan Vansteenkiste, MD • Prof Julien Mazieres, MD • et al. Show all authors • Show footnotes

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Atezolizumab Versus Docetaxel in Pretreated Patients With NSCLC: Final Results From the Randomized Phase 2 POPLAR and Phase 3 OAK Clinical Trials

Julien Mazieres, MD, PhD • Achim Rittmeyer, MD • Shirish Gadgeel, MD • ... Christina Matheny, PhD • Marcus Ballinger, PhD • Keunchil Park, MD • Show all authors

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Long-term follow-up suggests a consistent survival benefit with atezolizumab versus docetaxel in patients with previously treated NSCLC regardless of PD-L1 expression, histology, or subsequent immunotherapy. Atezolizumab had no new safety signals, and the safety profile was similar to that in previous studies.

- Based on the results of these ground-breaking clinical trials, the FDA approved nivolumab, pembrolizumab, and atezolizumab for second-line treatment of metastatic NSCLC.

MOLECULAR AND BIOMARKER-DIRECTED THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]

PD-L1 ≥50% First-line Therapy

ADENOCARCINOMA, LARGE CELL, NSCLC NOS

Preferred
- Pembrolizumab (category 1)[46,47]
- (Carboplatin or cisplatin) + pemetrexed + pembrolizumab (category 1)[48,49]
- Atezolizumab (category 1)[50]
- Cemiplimab-rwlc (category 1)[51]

Other Recommended
- Carboplatin + paclitaxel + bevacizumab[c,d] + atezolizumab (category 1)[52]
- Carboplatin + albumin-bound paclitaxel + atezolizumab[53]
- Nivolumab + ipilimumab + pemetrexed + (carboplatin or cisplatin) (category 1)[54]
- Cemiplimab-rwlc + paclitaxel + (carboplatin or cisplatin) (category 1)[55]
- Cemiplimab-rwlc + pemetrexed + (carboplatin or cisplatin) (category 1)[55]
- Tremelimumab-actl + durvalumab + carboplatin + albumin-bound paclitaxel (category 2B)[56]
- Tremelimumab-actl + durvalumab + (carboplatin or cisplatin) + pemetrexed (category 2B)[56]

Useful in Certain Circumstances
- Nivolumab + ipilimumab (category 1)[57]

SQUAMOUS CELL CARCINOMA

Preferred
- Pembrolizumab (category 1)[46,47]
- Carboplatin + (paclitaxel or albumin-bound paclitaxel) + pembrolizumab (category 1)[58]
- Atezolizumab (category 1)[50]
- Cemiplimab-rwlc (category 1)[51]

Other Recommended
- Nivolumab + ipilimumab + paclitaxel + carboplatin (category 1)[53]
- Cemiplimab-rwlc + paclitaxel + (carboplatin or cisplatin) (category 1)[55]
- Tremelimumab-actl + durvalumab + carboplatin + albumin-bound paclitaxel (category 2B)[56]
- Tremelimumab-actl + durvalumab + (carboplatin or cisplatin) + gemcitabine (category 2B)[56]

Useful in Certain Circumstances
- Nivolumab + ipilimumab (category 1)[57]

PD-L1 ≥1-49% First-line Therapy
Continuation Maintenance

[a] Monitoring During Initial Therapy: Response assessment after 2 cycles, then every 2–4 cycles with CT of known or high-risk sites of disease with or without contrast or when clinically indicated. Timing of CT scans within Guidelines parameters is a clinical decision.
[b] Monitoring During Subsequent Therapy or Maintenance Therapy: Response assessment with CT of known or high-risk sites of disease with or without contrast every 6–12 weeks. Timing of CT scans within Guidelines parameters is a clinical decision.
[c] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[d] Criteria for treatment with bevacizumab: nonsquamous NSCLC, and no recent history of hemoptysis.

References

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

MOLECULAR AND BIOMARKER-DIRECTED THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]

PD-L1 ≥1%–49% First-line Therapy

ADENOCARCINOMA, LARGE CELL, NSCLC NOS

Preferred
- (Carboplatin or cisplatin) + pemetrexed + pembrolizumab (category 1)[48,49]

Other Recommended
- Carboplatin + paclitaxel + bevacizumab[c,d] + atezolizumab (category 1)[52]
- Carboplatin + albumin-bound paclitaxel + atezolizumab[53]
- Nivolumab + ipilimumab + pemetrexed + (carboplatin or cisplatin) (category 1)[54]
- Nivolumab + ipilimumab (category 1)[57]
- Cemiplimab-rwlc + paclitaxel + (carboplatin or cisplatin) (category 1)[55]
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- Tremelimumab-actl + durvalumab + carboplatin + albumin-bound paclitaxel (category 1)[56]
- Tremelimumab-actl + durvalumab + (carboplatin or cisplatin) + pemetrexed (category 1)[56]

Useful in Certain Circumstances
- Pembrolizumab (category 2B)[e,46,47]

SQUAMOUS CELL CARCINOMA

Preferred
- Carboplatin + (paclitaxel or albumin-bound paclitaxel) + pembrolizumab (category 1)[58]

Other Recommended
- Nivolumab + ipilimuab + paclitaxel + carboplatin (category 1)[53]
- Nivolumab + ipilimumab (category 1)[57]
- Cemiplimab-rwlc + paclitaxel + (carboplatin or cisplatin) (category 1)[55]
- Tremelimumab-actl + durvalumab + carboplatin + albumin-bound paclitaxel[56]
- Tremelimumab-actl + durvalumab + (carboplatin or cisplatin) + gemcitabine[56]

Useful in Certain Circumstances
- Pembrolizumab (category 2B)[e,46,47]

PD-L1 ≥50% First-line Therapy

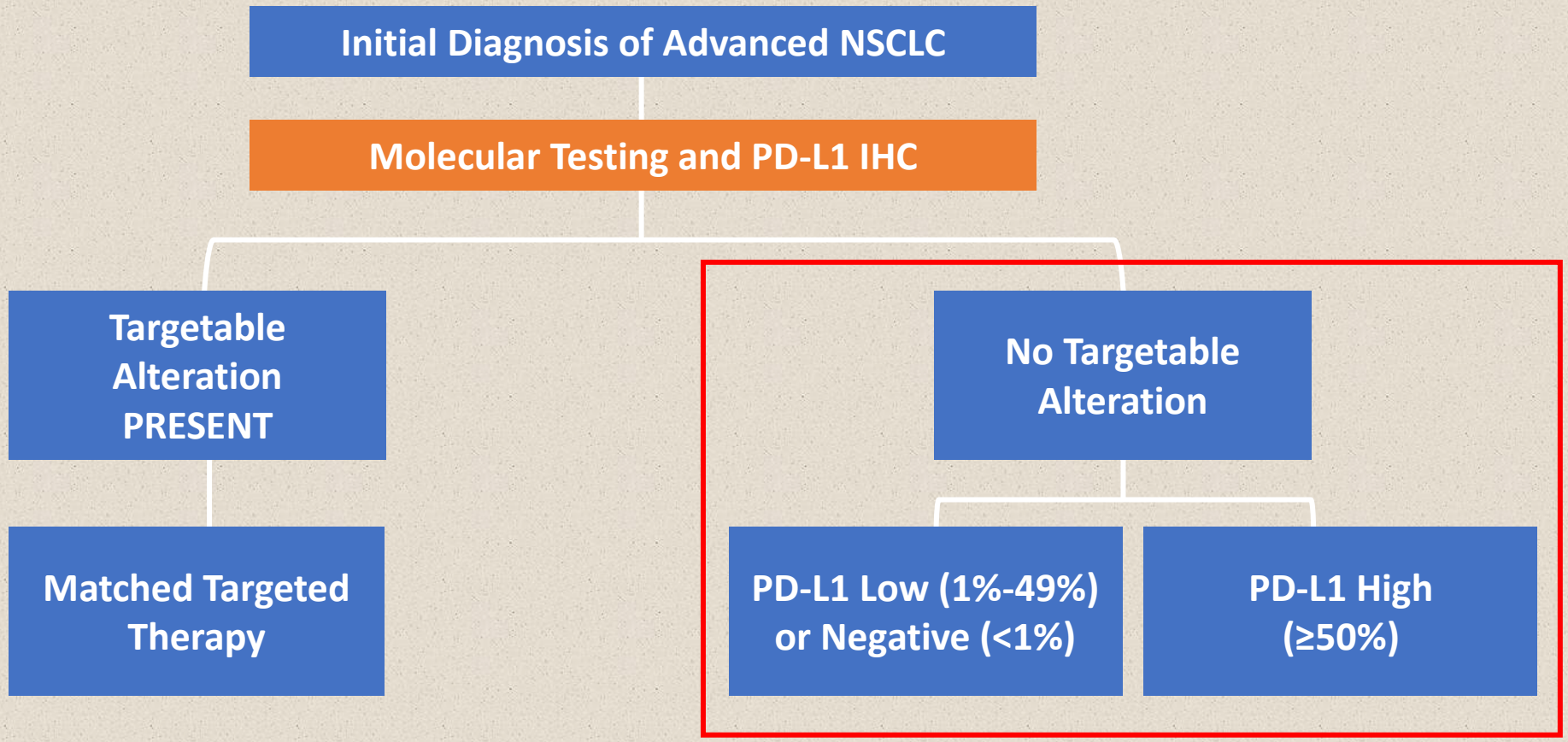
Continuation Maintenance

[a] Monitoring During Initial Therapy: Response assessment after 2 cycles, then every 2–4 cycles with CT of known or high-risk sites of disease with or without contrast or when clinically indicated. Timing of CT scans within Guidelines parameters is a clinical decision.
[b] Monitoring During Subsequent Therapy or Maintenance Therapy: Response assessment with CT of known or high-risk sites of disease with or without contrast every 6–12 weeks. Timing of CT scans within Guidelines parameters is a clinical decision.
[c] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[d] Criteria for treatment with bevacizumab: nonsquamous NSCLC, and no recent history of hemoptysis.
[e] Pembrolizumab monotherapy can be considered in PD-L1 1%–49%, when there are contraindications to combination chemotherapy.

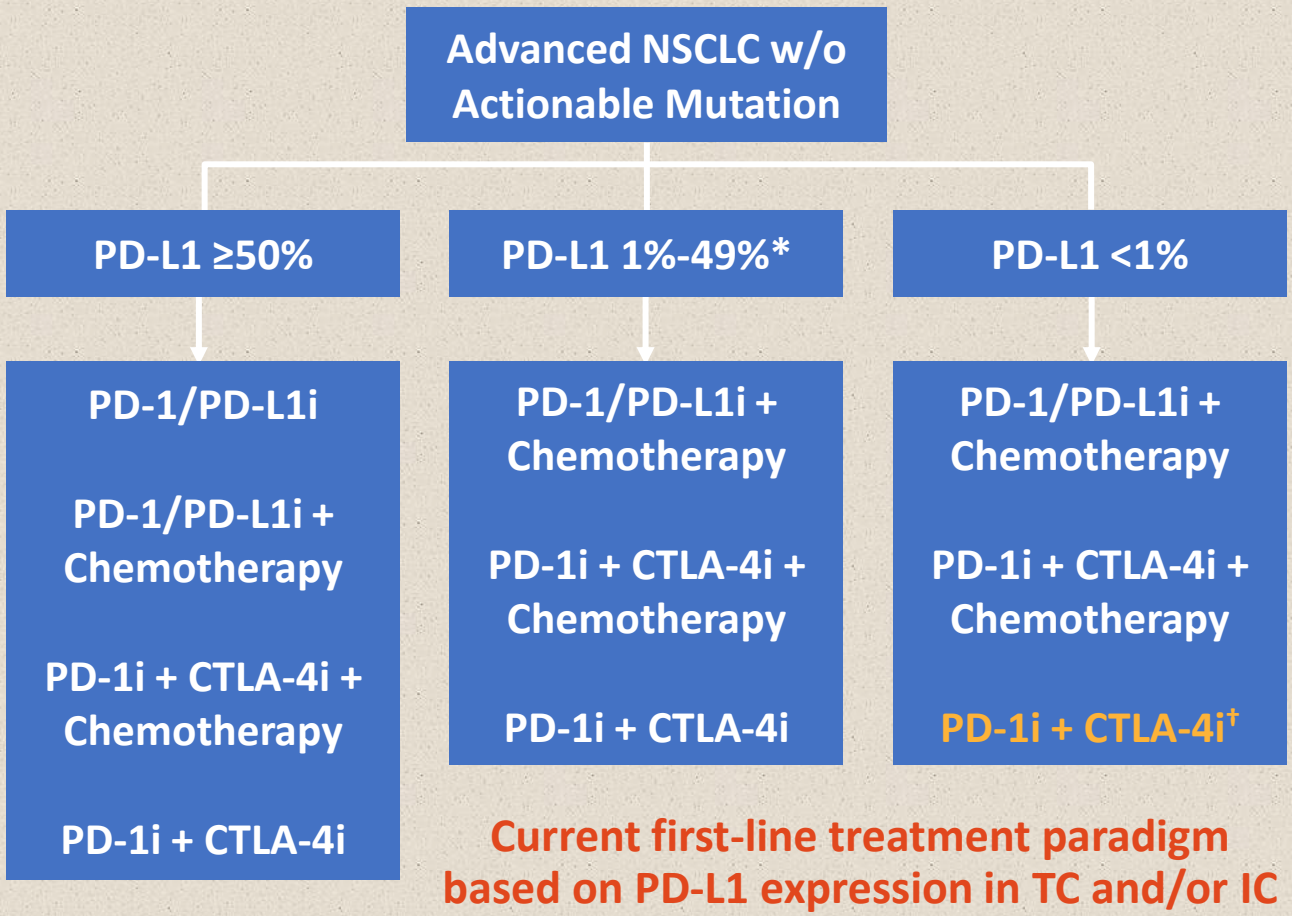
References

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Molecular and PD-L1 Testing Should Be Done at Initial Diagnosis of Advanced NSCLC to Guide firstline Tx Decisions



2022 Paradigm for Immunotherapy in Advanced NSCLC Without an Actionable Mutation



Current first-line treatment paradigm based on PD-L1 expression in TC and/or IC

- ICI monotherapy: pembrolizumab,* atezolizumab, cemiplimab
- ICI + chemotherapy
  - Pembrolizumab/carboplatin or cisplatin/pemetrexed (Nsq)
  - Atezolizumab/carboplatin/paclitaxel/ bevacizumab (Nsq)
  - Atezolizumab/carboplatin/nab-paclitaxel (Nsq)
  - Pembrolizumab/carboplatin/taxane (Sq)
  - Nivolumab/ipilimumab + 2 cycles of CT (Sq/Nsq)
- ICI combination: nivolumab/ipilimumab

*Single-agent pembrolizumab also approved for ≥1% PD-L1 but not broadly recommended by experts; guideline-recommended for PD-L1 1-49% if poor PS or contraindications to combining w/CT. †Not an FDA approved indication, but guideline recommended.

NCCN. Clinical practice guidelines in oncology: NSCLC. v.3.2022. nccn.org.

TABLE 2 | Clinical studies evaluating immunotherapy-radiotherapy combinations in metastatic non-small cell lung cancer (M-NSCLC), with primary endpoint results published or presented during the last decade (2009–2019).

References	Phase	NSCLC setting (accrual)	Immunotherapy	Radiotherapy	Design	Primary outcome
NON-SPECIFIC IMMUNOTHERAPY						
van den Heuvel et al. (84)	IB	Stage IV, CR/PR/SD after 1st line CT (N=13)	NHS-IL2	20 Gy/5 fx, single pulmonary nodule	RT > NHS-IL2	≥G3 treatment-related toxicity in 3 pts
Golden et al. (85)	NS	Stage IV, ≥3 sites of measurable disease, SD/PD on CT (*N* = 16)[a]	GM-CSF	35 Gy/10 fx, 2 lesions consecutively	CT + RT lesion 1 + GM-CSF > CT + RT lesion 2 + GM-CSF	Abscopal response in 4/18 pts
Ohri et al. (86)	II	Stage IV, ≥2 measurable disease sites (*N* = 9)	CDX-301	30–64 Gy/1–5 fx, single intrathoracic site of disease	SBRT + CDX-301	5/9 pts with PFS at 4 m
ANTIGEN-SPECIFIC IMMUNOTHERAPY						
Papachristofilou et al. (87)	IB	Stage IV, PR/SD after 1st line CT or TKI, ≥2 sites of disease (*N* =	CV9202	20 Gy/4 fx, single lesion	• RT + CT + CV9202 • RT + CV9202	≥G3 treatment-related AE in 4/26 pts
IMMUNE CHECKPOINT BLOCKADE						
Formenti et al. (88)	I/II	Stage IV, ≥2 measurable metastatic sites (*N* = 39)	Ipi	• 30 Gy/5 fx • 27 Gy/3 fx Single lesion	RT + Ipi	CR, PR and SD in 2, 5 and 5/21 evaluable pts resp.
Tang et al. (89)	I	Stage IV, ≥2 sites of disease (*N* = 21)	Pembro	• 50 Gy/4 fx, single liver or lung lesion • 45 Gy/15 fx, SIB allowed up to 60 Gy larger field	RT + pembro	G2 and G3 treatment-related AE in 8 and 3/21 pts resp.
Kumar et al. (90) (PEAR)	I	Stage IV, requiring palliative thoracic RT (*N* = 14)	Pembro	• 20 Gy/5 fx • 36 Gy/12 fx	RT + pembro	No DLT
Decker et al. (91)	I/II	Stage IV, ≥2 measurable disease sites (*N* = 9)	Pembro	30 Gy/3–5 fx, single site of disease	Pembro until irPD > SBRT + pembro	No ≥G2 treatment-related AE during and post-SBRT
Moreno et al. (92)	I	Stage IV, PD after ≥1st line treatment, requiring palliative RT (*N* = 53)	Cemi	27 Gy/3 fx	• RT + cemi • Cemi	G5 treatment-related pneumonitis (n = 1). ORR 18.2 vs. 40.0%; DCR 72.7 vs. 80/0%
Alsaeddine et al. (93)	I	Stage IV, ≤10 cc untreated brain metastases (*N* = 7)[a]	Nivo	15–20 Gy/1 fx, brain metastasis	SRS + nivo	Treatment-related AE in 3/5 evaluable pts
Miyamoto et al. (94)	NS	Stage IV, ≥1 lesion amenable to SBRT outside brain/bone (*N* = 6)	Nivo	25.5–48 Gy/3–4 fx, single lesion	SBRT > nivo	G3 pneumonitis in 1/6 pts
Theelen et al. (95) (PEMBRO-RT)	II	Stage IV, ≥2 separate lesions, after ≥1st line treatment (*N* = 76)	Pembro	24 Gy/3 fx, single tumor site	• SBRT > pembro • Pembro	ORR at 12 w 36 vs. 18% (*p* = 0.07)
Luke et al. (96)	I	Stage IV, ≥2 metastases, after ≥1st line treatment (*N* = 7)[a]	Pembro	30–50 Gy/3–5 fx, 2–4 metastases, partial for metastases >65 mL	SBRT > pembro	≥G3 treatment-related toxicity in 6/73 pts
Bauml et al. (97)	II	Stage IV, ≤4 metastases (*N* = 45)	Pembro	Stereotactic or standard fraction, dose NS	LAT > pembro	PFS after LAT 19.1 m vs. historical 6.6 m (*p* = 0.005)

AE, adverse event(s); atezo, atezolizumab; cc, cubic centimeter; cemi, cemiplimab; CR, complete response; CT, chemotherapy; DCR, disease control rate; fx, fraction(s); G, grade; GM-CSF, granulocyte-macrophage colony-stimulating factor; Gy, Gray; m, month(s); mL, milliliter; ipi, ipilimumab; ir, according to immune-related response evaluation criteria in solid tumors; LAT, local ablative treatment (i.e. surgery, chemotherapy, radiotherapy, radiofrequency ablation or a combination of the above); nivo, nivolumab; NR, not reached; NS, not specified; ORR, objective response rate; pembro, pembrolizumab; PD, progressive disease; PR, partial response; pts, patients; resp., respectively; RT, radiotherapy; SAE, serious adverse event(s); SD, stable disease; surg, surgery; TE, tracheoesophageal; TKI, tyrosine kinase inhibitor; TMDD, time to metastatic disease or death; +, concurrently with; >, followed by.

[a]*For the purpose of this review, only data relevant to the combination of radiotherapy and immunotherapy for M-NSCLC are represented in this table.*

JAMA Oncology | Original Investigation

Effect of Pembrolizumab After Stereotactic Body Radiotherapy vs Pembrolizumab Alone on Tumor Response in Patients With Advanced Non–Small Cell Lung Cancer
Results of the PEMBRO-RT Phase 2 Randomized Clinical Trial

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IMPORTANCE Many patients with advanced non-small cell lung cancer (NSCLC) receiving immunotherapy show primary resistance. High-dose radiotherapy can lead to increased tumor antigen release, improved antigen presentation, and T-cell infiltration. This radiotherapy may enhance the effects of checkpoint inhibition.

OBJECTIVE To assess whether stereotactic body radiotherapy on a single tumor site preceding pembrolizumab treatment enhances tumor response in patients with metastatic NSCLC.

Invited Commentary page 1291

Supplemental content

Theelen et al. performed a RCT of pembrolizumab either without or after SBRT (3 x 8Gy) of a single NSCLC metastasis . While the study's primary endpoint criteria were not met, a significant improvement of DCR was observed in the experimental arm (64 vs. 40%; p = 0.04).
Moreover, subgroup analyses showed patients benefiting most from SBRT were those with PD-L1 negative tumors at baseline. This finding is particularly intriguing, since this is a population for which single-agent PD-(L)1 inhibition is known to be of limited benefit. Perhaps, pembrolizumab following SBRT may represent a less toxic alternative to chemoimmunotherapy when aiming to enhance response rates in M-NSCLC patients with a low PD-L1 tumor proportion score.

No increase in treatment-related toxic effects was observed in the experimental arm.

CONCLUSIONS AND RELEVANCE Stereotactic body radiotherapy prior to pembrolizumab was well tolerated. Although a doubling of ORR was observed, the results did not meet the study's prespecified end point criteria for meaningful clinical benefit. Positive results were largely influenced by the PD-L1–negative subgroup, which had significantly improved progression-free survival and overall survival. These results suggest that a larger trial is necessary to determine whether radiotherapy may activate noninflamed NSCLC toward a more inflamed tumor microenvironment.

Author Affiliations: Author affiliations are listed at the end of this article.
Corresponding Author: Willemijn

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Safety and Clinical Activity of Pembrolizumab and Multisite Stereotactic Body Radiotherapy in Patients With Advanced Solid Tumors

Jason J. Luke, Jeffrey M. Lemons, Theodore G. Karrison, Sean P. Pitroda, James M. Melotek, Yuanyuan Zha, Hania A. Al-Hallaq, Ainhoa Arina, Nikolai N. Khodarev, Linda Janisch, Paul Chang, Jyoti D. Patel, Gini F. Fleming, John Moroney, Manish R. Sharma, Julia R. White, Mark J. Ratain, Thomas F. Gajewski, Ralph R. Weichselbaum, and Steven J. Chmura

Author affiliations and support information (if applicable) appear at the end of this article.

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J.J.L. and J.M.L. contributed equally to this work.

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0732-183X/18/3616w-1611w/$20.00

A B S T R A C T

Purpose

Stereotactic body radiotherapy (SBRT) may stimulate innate and adaptive immunity to augment immunotherapy response. Multisite SBRT is an emerging paradigm for treating metastatic disease. Anti-PD-1–treatment outcomes may be improved with lower disease burden. In this context, we conducted a phase I study to evaluate the safety of pembrolizumab with multisite SBRT in patients with metastatic solid tumors.

Patients and Methods

Patients progressing on standard treatment received SBRT to two to four metastases. Not all metastases were targeted, and metastases > 65 mL were partially irradiated. SBRT dosing varied by site and ranged from 30 to 50 Gy in three to five fractions with predefined dose de-escalation if excess dose-limiting toxicities were observed. Pembrolizumab was initiated within 7 days after completion of SBRT. Pre- and post-SBRT biopsy specimens were analyzed in a subset of patients to quantify interferon-γ–induced gene expression.

Results

A total of 79 patients were enrolled; three patients did not receive any treatment and three patients only received SBRT. Patients included in the analysis were treated with SBRT and at least one cycle of pembrolizumab. Most (94.5%) of patients received SBRT to two metastases. Median follow-up for toxicity was 5.5 months (interquartile range, 3.3 to 8.1 months). Six patients experienced dose-limiting toxicities with no radiation dose reductions. In the 68 patients with imaging follow-up, the overall objective response rate was 13.2%. Median overall survival was 9.6 months (95% CI, 6.5 months to undetermined) and median progression-free survival was 3.1 months (95% CI, 2.9 to 3.4 months). Expression of interferon-γ–associated genes from post–SBRT tumor biopsy specimens significantly correlated with nonirradiated tumor response.

Conclusion

Multisite SBRT followed by pembrolizumab was well tolerated with acceptable toxicity. Additional studies exploring the clinical benefit and predictive biomarkers of combined multisite SBRT and PD-1–directed immunotherapy are warranted.

Luke et al. applied this logic in their phase I study, allowing multisite SBRT of 2–4 metastases up to 1 week before starting pembrolizumab in patients with advanced solid tumors

JAMA Oncology | Original Investigation

Pembrolizumab After Completion of Locally Ablative Therapy for Oligometastatic Non–Small Cell Lung Cancer
A Phase 2 Trial

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IMPORTANCE Patients with oligometastatic non–small cell lung cancer (NSCLC) may benefit from locally ablative therapy (LAT) such as surgery or stereotactic radiotherapy. Prior studies were conducted before the advent of immunotherapy, and a strong biological rationale for the use of immunotherapy exists in a minimal residual disease state.

OBJECTIVE To evaluate whether the addition of pembrolizumab after LAT improves outcomes for patients with oligometastatic NSCLC.

DESIGN, SETTING, AND PARTICIPANTS This single-arm phase 2 trial of pembrolizumab therapy was performed from February 1, 2015, through September 30, 2017, at an academic referral cancer center. The 51 eligible patients enrolled had oligometastatic NSCLC (≤4 metastatic sites) and had completed LAT to all known sites of disease. Data were analyzed from February 1, 2015, to August 23, 2018.

INTERVENTIONS Within 4 to 12 weeks of completing LAT, patients began intravenous pembrolizumab therapy, 200 mg every 21 days, for 8 cycles, with provision to continue to 16 cycles in the absence of progressive disease or untoward toxic effects.

MAIN OUTCOMES AND MEASURES The 2 primary efficacy end points were progression-free survival (PFS) from the start of LAT (PFS-L), which preceded enrollment in the trial, and PFS from the start of pembrolizumab therapy (PFS-P). The study was powered for comparison with historical data on the first efficacy end point. Secondary outcomes included overall survival, safety, and quality of life as measured by the Functional Assessment of Cancer Therapy–Lung instrument.

RESULTS Of 51 patients enrolled, 45 (24 men [53%]; median age, 64 years [range, 46-82 years]) received pembrolizumab. At the time of analysis, 24 patients had progressive disease or had died. Median PFS-L was 19.1 months (95% CI, 9.4-28.7 months), significantly greater than the historical median of 6.6 months ($P = .005$). Median PFS-P was 18.7 months (95% CI, 10.1-27.1 months). Eleven patients died. Overall mean (SE) survival rate at 12 months was 90.9% (4.3%); at 24 months, 77.5% (6.7%). Neither programmed death ligand 1 expression nor CD8 T-cell tumor infiltration was associated with PFS-L. Pembrolizumab after LAT yielded no new safety signals and no reduction in quality of life.

CONCLUSIONS AND RELEVANCE Pembrolizumab after LAT for oligometastatic NSCLC appears to improve PFS with no reduction in quality of life.

TRIAL REGISTRATION ClinicalTrials.gov identifier: NCT02316002

Invited Commentary

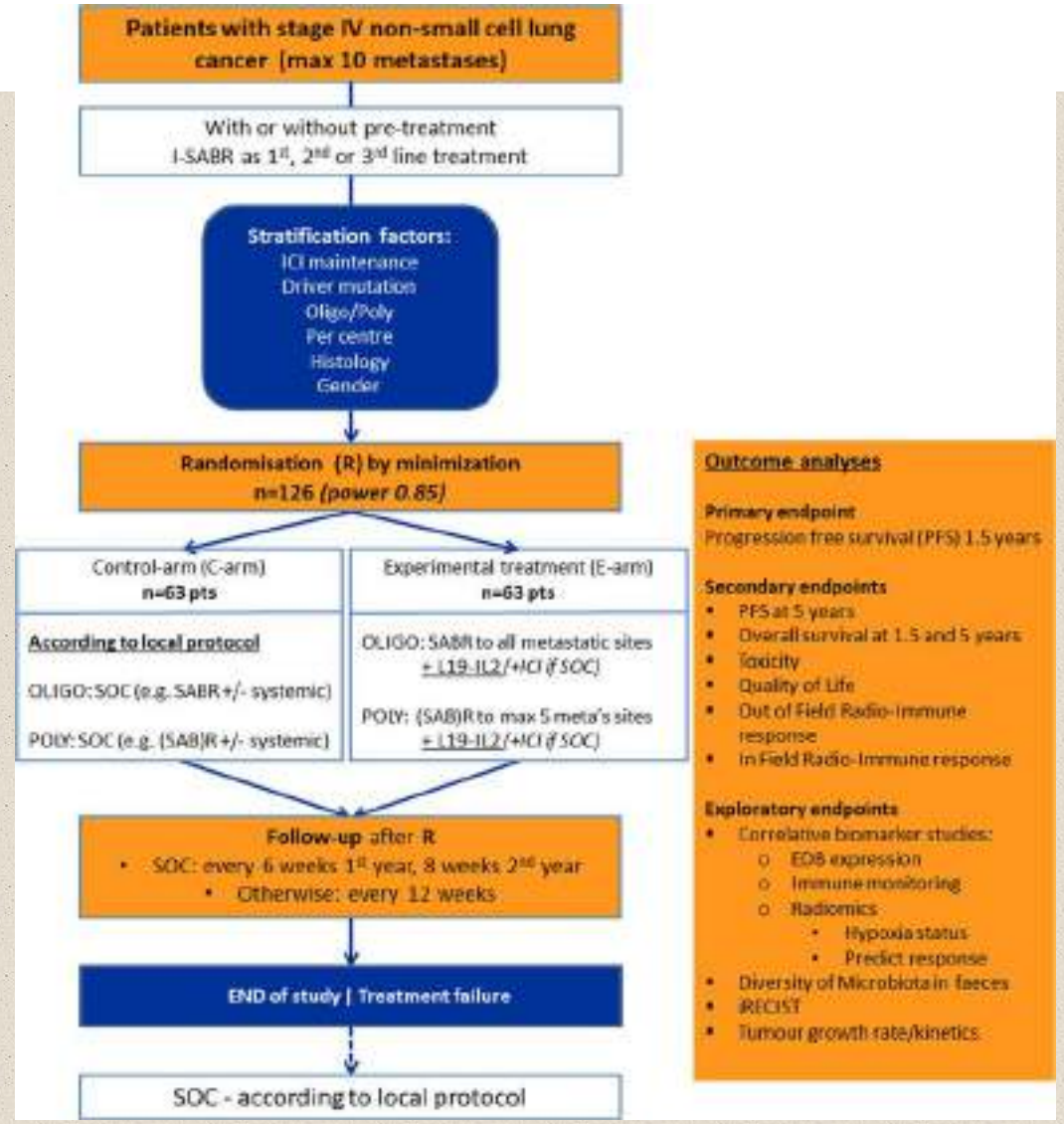
Supplemental content

Bauml et al. initiated a phase II trial offering adjuvant pembrolizumab to patients with a limited tumor burden (4 metastases) after eradication of all known sites of disease

Author Affiliations: Abramson Cancer Center, Perelman Center for Advanced Medicine, University of Pennsylvania, Philadelphia (Bauml, Mick, Ciunci, Aggarwal, Davis, Deshpande, Miller, Patel, Alley, Knepley, Mutale, Cohen, Langer); Division of Hematology/Oncology, Lankenau Medical Center, Wynnewood, Pennsylvania (Evans).

IMMUNOSABR2 - IMMUNOtherapy and Stereotactic ABlative Radiotherapy (IMMUNOSABR) a Phase II Study Jun 2020

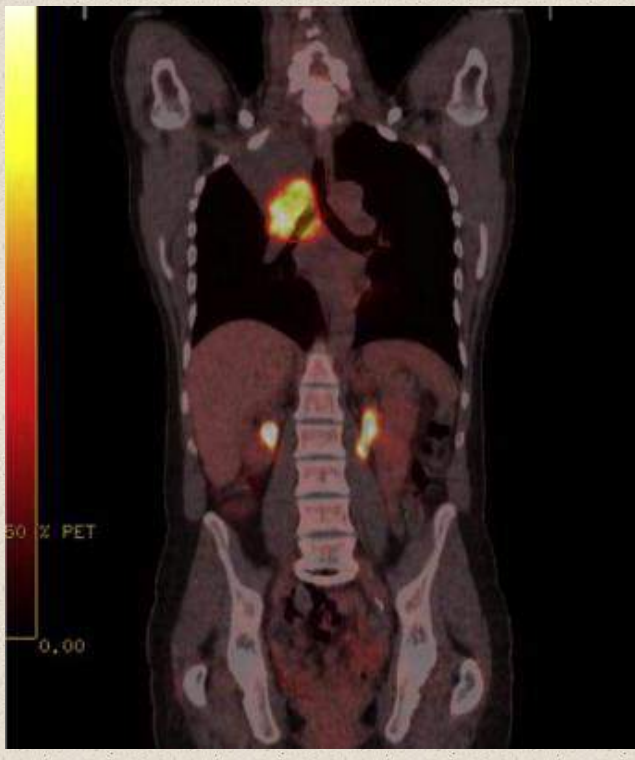
P2 • Maastricht University • N=126 • Recruiting



Radiation Plus Immunotherapy ---- Locally Advanced NSCLC

- RT- adjunct to surgery in operable patients, be it in the preoperative setting or after incomplete resection, but will most frequently be used as definitive treatment combined with chemotherapy (concurrently of sequentially) in stage IIIB or (unresectable) stage IIIA disease.

- When combined with platinum-based doublet chemotherapy, RT doses ranging between 60 and 66Gy in 2Gy daily fractions over 6–7 weeks are advocated



- 2-year overall and progression-free survival, typically <60 and 30% respectively, with median OS ranging between 2 and 2.5 years.
- Analyses of failure patterns after CRT reveal a substantial contribution of locoregional recurrence, but an even greater proportion of about 50% of patients experiencing distant progression
- Therefore, this setting may represent an exciting opportunity for the development of innovative strategies integrating immunotherapeutic agents into combined modality

TABLE 1 | Clinical studies evaluating immunotherapy-radiotherapy combinations in locally advanced non-small cell lung cancer (LA-NSCLC), with primary endpoint results published or presented during the last decade (2009–2019)[a].

References	Phase	NSCLC setting (accrual)	Immunotherapy	Radiotherapy	Design	Primary outcome
ANTIGEN-SPECIFIC IMMUNOTHERAPY						
Ohyanagi et al. (48)	I	Stage III, unresectable, CR/PR/SD after CRT ($N = 6$)	Tecemotide	≥50 Gy, sequentially or concurrently with CT	CRT > tecemotide[b]	≥1 AE in 83.3% of pts, all G1
Butts et al. (49)	IIB	Stage IIIB, CR/PR/SD after CRT ($N = 65$)[c]	Tecemotide	Dose NS, sequentially or concurrently with CT	• CRT > BSC + tecemotide[b] • CRT > BSC	Median OS 30.6 vs. 13.3 m (HR 0.548, 95% CI 0.301–0.999)[c]
Mitchell et al. (50) (START)	III	Stage III, unresectable, CR/PR/SD after CRT ($N = 1,239$)	Tecemotide	≥50 Gy, sequentially or concurrently with CT	• CRT > tecemotide[b] • CRT > placebo	Median OS 58.7 vs. 57.3 m (HR 0.89; $p = 0.111$)
Patel et al. (51)	II	Stage III, unresectable, non-squamous ($N = 33$)	Tecemotide	66 Gy/33 fx, concurrently with CT	CRT > CT > tecemotide + bevacizumab	≥G3 toxicity in 11 pts, G3 hypertension ($n = 6$)
Brunsvig et al. (52)	II	Stage III, inoperable ($N = 23$)	GV1001 + GM-CSF	60 Gy/30 fx, concurrently with CT	CRT > GV1001 + GM-CSF	No treatment-related SAE
Pujol et al. (53)	I/II	Stage III, unresectable, MAGE A3-positive ($N = 12$)[c]	MAGE-A3 immunotherapeutic	NS	CT > RT > MAGE-A3	Treatment-related AE in 7/12 pts; all <G3. Induced CD4+ and CD8+ T-cell response in 5/6 and 2/6 pts resp.[c]
IMMUNE CHECKPOINT BLOCKADE						
Antonia et al. (31) (PACIFIC)	III	Stage III, unresectable ($N = 713$)	Durva	54–66 Gy, concurrently with CT	• CRT > durva • CRT > placebo	Median OS NR vs. 28.7 m (HR 0.68; $p = 0.0025$); median PFS 17.2 vs. 5.6 m (HR 0.51)
Durm et al. (54)	II	Stage III, unresectable, CR/PR/SD after CRT (N=92)	Pembro	59–66.6 Gy, concurrently with CT	CRT > pembro	Median TMDD 22.4 m (95% CI 17.9-NR)
Lin et al. (55) (DETERRED)	II	Stage III, unresectable ($N = 40$)	Atezo	60–66 Gy/30–33 fx, concurrently with CT	• CRT > CT + atezo • CRT + atezo > CT + atezo	≥G3 atezo-related toxicity in 6 pts; G5 TE fistula ($n = 1$). G3 radiation pneumonitis ($n = 1$)
Peters et al. (56, 57) (NICOLAS)	I/II	Stage III, unresectable ($N = 79$)	Nivo	• 66 Gy/33 fx, concurrently with CT • 66 Gy/24 fx, sequentially after CT	CRT + nivo > nivo	No ≥G3 post-RT pneumonitis, 1-year PFS 50%

AE, adverse event(s); atezo, atezolizumab; BSC, best supportive care; CI, confidence interval; CR, complete response; CRT, chemo-radiotherapy; CT, chemotherapy; durva, durvalumab; fx, fraction(s); G, grade; GM-CSF, granulocyte-macrophage colony-stimulating factor; Gy, Gray; HR, hazard ratio; m, month(s); nivo, nivolumab; NR, not reached; NS, not specified; pembro, pembrolizumab; PD, progressive disease; PR, partial response; pts, patients; resp., respectively; RT, radiotherapy; SAE, serious adverse event(s); SD, stable disease; surg, surgery; TE, tracheoesophageal; TMDD, time to metastatic disease or death; +, concurrently with; >, followed by.

[a]Included studies published before 2009 are not represented, as the authors feel the quality of these reports may not correspond to the current standards of evidence and/or practice (e.g., due to the use of outdated RT techniques), thus may confound interpretation of the table contents.

[b]Administration of tecemotide was preceded by a single low dose of cyclophosphamide.

[c]For the purpose of this review, only data relevant to the combination of radiotherapy and immunotherapy for LA-NSCLC are represented in this table.

PACIFIC TRIAL

Progression-free survival was si
points also favoured durvaluma

Check for updates

original reports abstract

Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

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PURPOSE The phase III PACIFIC trial compared durvalumab with placebo in patients with unresectable, stage III non–small-cell lung cancer and no disease progression after concurrent chemoradiotherapy. Consolidation durvalumab was associated with significant improvements in the primary end points of overall survival (OS; stratified hazard ratio [HR], 0.68; 95% CI, 0.53 to 0.87; $P = .00251$) and progression-free survival (PFS [blinded independent central review; RECIST v1.1]; stratified HR, 0.52; 95% CI, 0.42 to 0.65; $P < .0001$), with manageable safety. We report updated, exploratory analyses of survival, approximately 5 years after the last patient was randomly assigned.

METHODS Patients with WHO performance status 0 or 1 (any tumor programmed cell death-ligand 1 status) were randomly assigned (2:1) to durvalumab (10 mg/kg intravenously; administered once every 2 weeks for 12 months) or placebo, stratified by age, sex, and smoking history. Time-to-event end point analyses were performed using stratified log-rank tests. Medians and landmark survival rates were estimated using the Kaplan-Meier method.

RESULTS Seven hundred and nine of 713 randomly assigned patients received durvalumab (473 of 476) or placebo (236 of 237). As of January 11, 2021 (median follow-up, 34.2 months [all patients]; 61.6 months [censored patients]), updated OS (stratified HR, 0.72; 95% CI, 0.59 to 0.89; median, 47.5 *v* 29.1 months) and PFS (stratified HR, 0.55; 95% CI, 0.45 to 0.68; median, 16.9 *v* 5.6 months) remained consistent with the primary analyses. Estimated 5-year rates (95% CI) for durvalumab and placebo were 42.9% (38.2 to 47.4) versus 33.4% (27.3 to 39.6) for OS and 33.1% (28.0 to 38.2) versus 19.0% (13.6 to 25.2) for PFS.

CONCLUSION These updated analyses demonstrate robust and sustained OS and durable PFS benefit with durvalumab after chemoradiotherapy. An estimated 42.9% of patients randomly assigned to durvalumab remain alive at 5 years and 33.1% of patients randomly assigned to durvalumab remain alive and free of disease progression, establishing a new benchmark for standard of care in this setting.

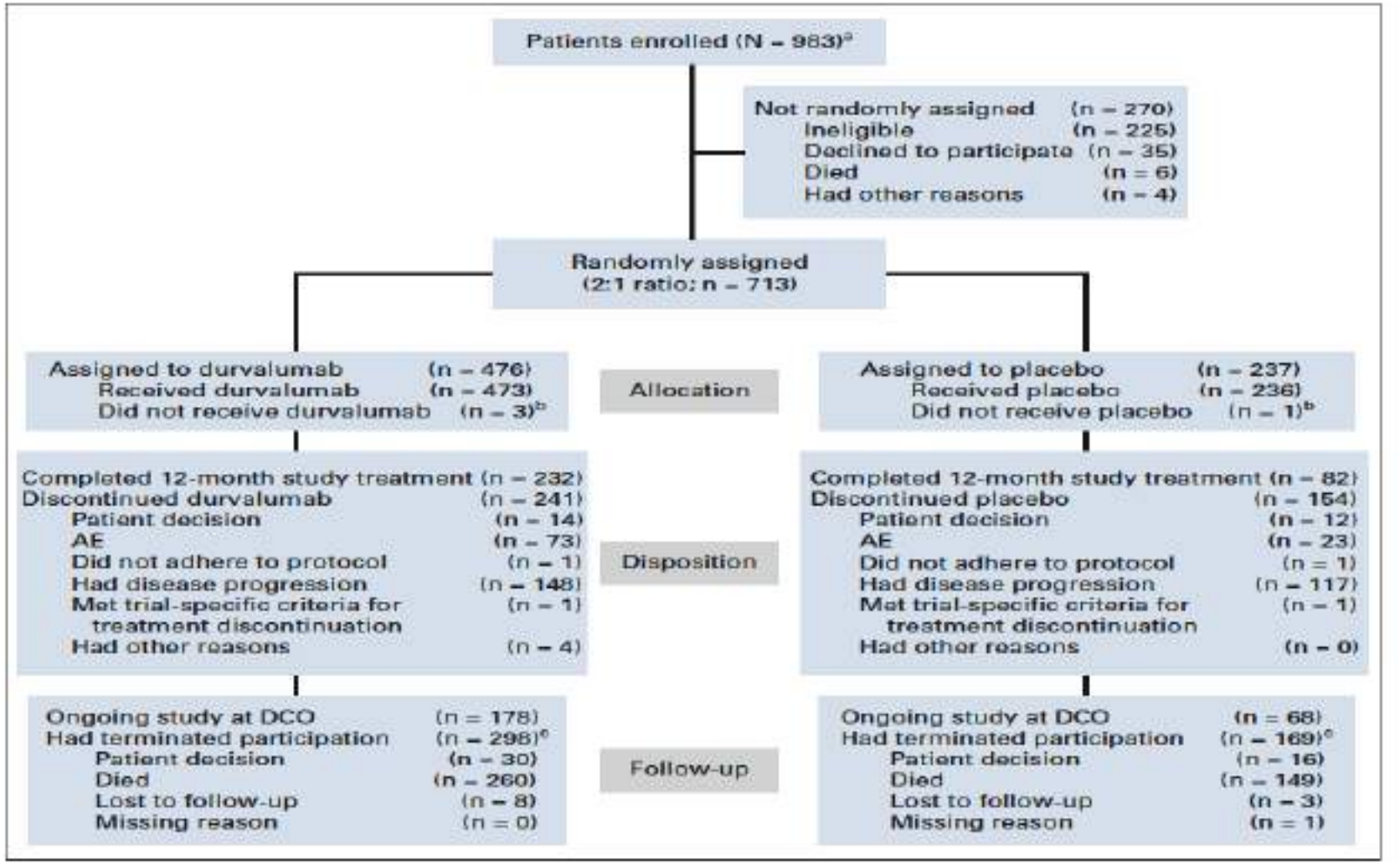

FIG 1. CONSORT diagram. Study data collected up to the DCO date of January 11, 2021. Patients who completed 12 months of study treatment are those for whom the electronic case report form showed that they had received the maximum number of cycles of study treatment. [a]Informed consent received. [b]Four patients did not receive their assigned study treatment because of neutropenia (n = 1), worsening chronic obstructive pulmonary disease (n = 1), and patient decision (n = 2). [c]Nine patients (durvalumab, n = 4; placebo, n = 5) who terminated the study because of patient decision have subsequently died; one additional patient (placebo arm) with missing termination reason has subsequently died. AE, adverse event; DCO, data cutoff.

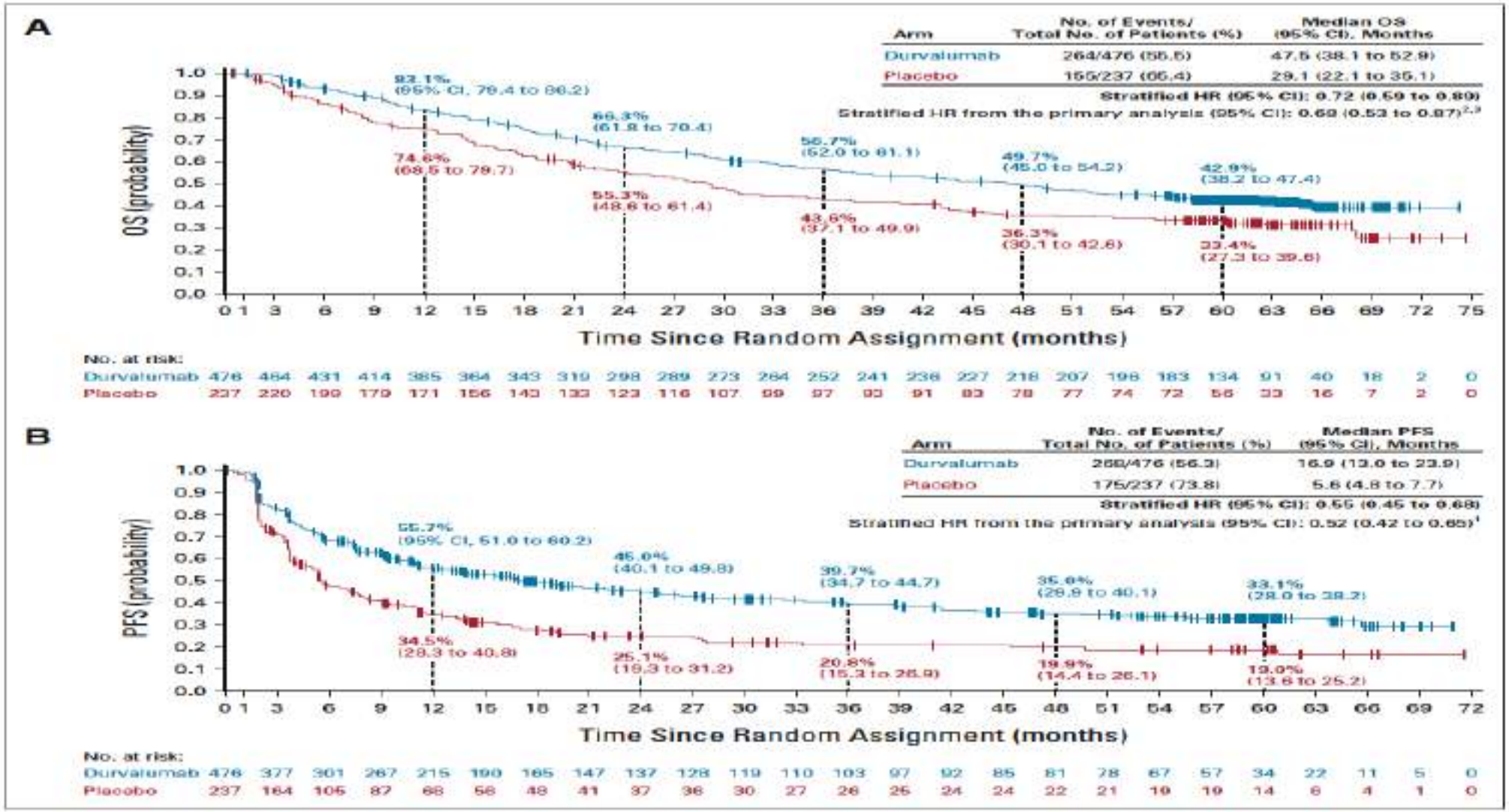

FIG 2. Updated (A) OS and (B) PFS (blinded independent central review) in the intent-to-treat population. The vertical dashed lines indicate yearly landmarks; the associated numerical values represent the OS and PFS rates at the landmark. OS was defined as time from random assignment until death from any cause. PFS was defined as time from random assignment to the date of the first documented event of tumor progression or death in the absence of disease progression. For PFS, patients who had not progressed or died at the time of the data cutoff were censored at the time of their last evaluable RECIST assessment; however, if the patient progressed or died after ≥ 2 missed visits, they were censored at the time of the latest evaluable RECIST assessment before the two missed visits. HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Group	No. of Events / No. of Patients (%) Durvalumab	Placebo	Unstratified HR (95% CI)
All patients	264/476 (55.5)	155/237 (65.4)	0.72 (0.59 to 0.87)
Sex			
Male	192/334 (57.5)	112/166 (67.5)	0.75 (0.59 to 0.96)
Female	72/142 (50.7)	43/71 (60.6)	0.64 (0.44 to 0.94)
Age at random assignment			
< 65 years	130/261 (49.8)	79/130 (60.8)	0.66 (0.50 to 0.87)
≥ 65 years	134/215 (62.3)	76/107 (71.0)	0.79 (0.60 to 1.05)
Smoking status			
Smoker	244/433 (56.4)	140/216 (64.8)	0.75 (0.61 to 0.93)
Nonsmoker	20/43 (46.5)	15/21 (71.4)	0.42 (0.21 to 0.82)
NSCLC disease stage			
IIIA	136/252 (54.0)	91/125 (72.8)	0.61 (0.47 to 0.80)
IIIB	121/212 (57.1)	61/107 (57.0)	0.86 (0.63 to 1.17)
Tumor histologic type			
Squamous	138/224 (61.6)	67/102 (65.7)	0.82 (0.61 to 1.09)
All other	126/252 (50.0)	88/135 (65.2)	0.62 (0.47 to 0.81)
Best response to prior treatment			
Complete response	6/9 (66.7)	3/7 (42.9)	Not calculated[a]
Partial response	116/237 (49.8)	68/112 (60.7)	0.71 (0.52 to 0.96)
Stable disease	135/223 (60.5)	81/115 (70.4)	0.70 (0.53 to 0.92)
Prior chemotherapy type			
Gemcitabine-based	5/9 (55.6)	2/5 (40.0)	Not calculated[a]
Non–gemcitabine-based	259/467 (55.5)	153/232 (65.9)	0.70 (0.58 to 0.86)
Cisplatin	134/266 (50.4)	81/129 (62.8)	0.65 (0.50 to 0.86)
Carboplatin	121/189 (60.8)	69/102 (67.6)	0.81 (0.60 to 1.09)
Cisplatin and carboplatin	6/8 (75.0)	4/5 (80.0)	Not calculated[a]
Last radiation to random assignment			
< 14 days	64/120 (53.3)	43/62 (69.4)	0.54 (0.37 to 0.80)
≥ 14 days	200/356 (56.2)	112/176 (64.0)	0.79 (0.63 to 1.00)
WHO PS			
0 — Normal	121/234 (51.7)	65/114 (57.0)	0.84 (0.62 to 1.14)
1 — Restricted[b]	143/242 (59.1)	90/123 (73.2)	0.62 (0.47 to 0.80)
Region			
Asia	54/109 (49.5)	37/68 (54.4)	0.79 (0.52 to 1.20)
Europe	126/217 (57.8)	64/102 (62.7)	0.84 (0.62 to 1.14)
North and South America	85/150 (56.7)	54/67 (80.6)	0.47 (0.34 to 0.67)
Race			
White	200/337 (59.3)	110/157 (70.1)	0.72 (0.57 to 0.91)
Black or African American	5/12 (41.7)	2/2 (100)	Not calculated[a]
Asian	58/120 (48.7)	39/72 (54.2)	0.73 (0.48 to 1.09)
Other[c]	3/6 (50.0)	4/6 (66.7)	Not calculated[a]
EGFR or *ALK* aberration status			
Positive[d]	17/29 (58.8)	8/14 (57.1)	0.85 (0.37 to 1.97)
Negative	166/317 (52.4)	109/165 (66.1)	0.66 (0.52 to 0.84)
Unknown	81/130 (62.3)	38/58 (65.5)	0.85 (0.57 to 1.24)
PD-L1 expression level			
≥ 25%	51/115 (44.3)	27/44 (61.4)	0.52 (0.32 to 0.82)
< 25%	111/187 (59.4)	64/105 (61.0)	0.90 (0.67 to 1.23)
Unknown	102/174 (58.6)	64/88 (72.7)	0.68 (0.50 to 0.93)
1%-24% (post hoc analysis)	52/97 (53.6)	29/47 (61.7)	0.73 (0.46 to 1.14)
≥ 1% (post hoc analysis)	103/212 (48.6)	56/91 (61.5)	0.61 (0.44 to 0.85)
< 1% (post hoc analysis)	59/90 (65.6)	35/58 (60.3)	1.15 (0.75 to 1.75)

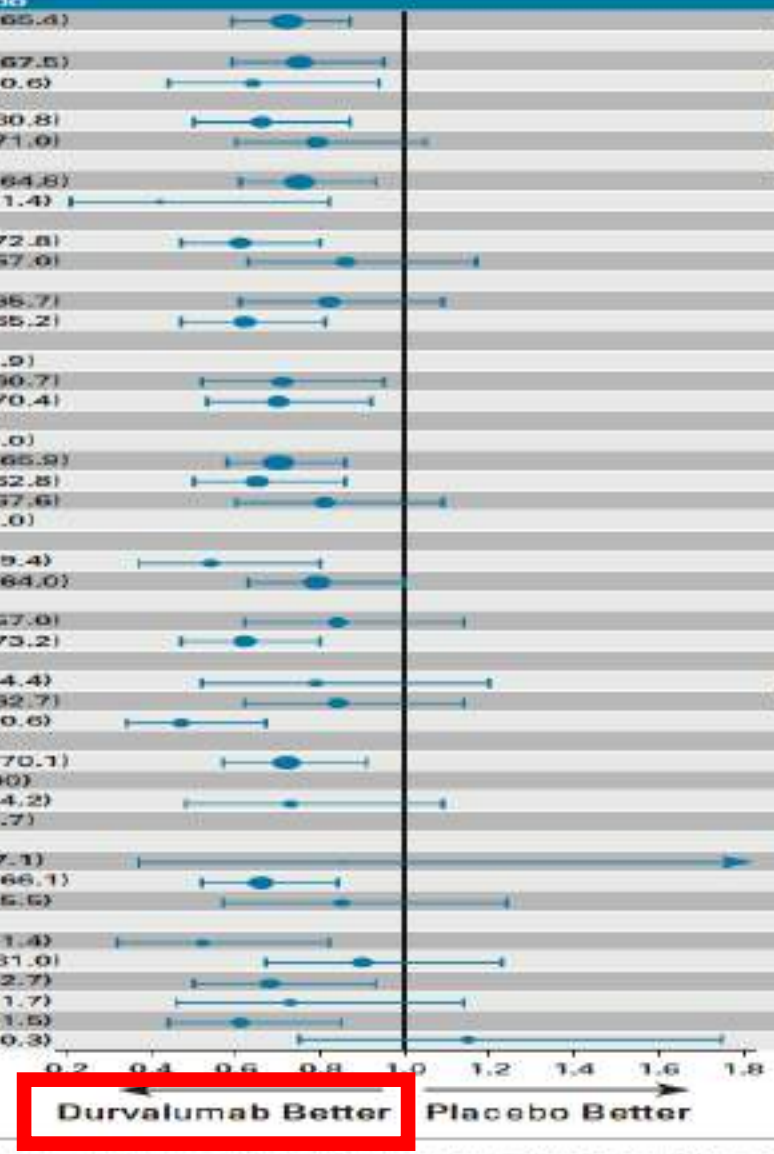

FIG 3. Updated OS by prespecified and exploratory, post hoc subgroups. [a]HRs and 95% CIs were not calculated if the subgroup had < 20 events. [b]Three patients with missing WHO PS were included in the PS 1 subgroup. [c]The other race category includes American Indian or Alaskan Native (n = 9), Native Hawaiian or Other Pacific Islander (n = 2), and Other (n = 1). [d]The subgroup includes 35 patients with tumors harboring *EGFR* mutations and, on the basis of local testing, eight patients with tumors harboring *ALK* alterations. ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non–small-cell lung cancer; OS, overall survival; PD-L1, programmed cell death-ligand 1; PS, performance status.

- Updated analyses demonstrate robust and sustained OS and durable PFS benefit with durvalumab after chemoradiotherapy.

- An estimated 42.9% of patients randomly assigned to durvalumab remain alive at 5 years and 33.1% of patients randomly assigned to durvalumab remain alive and free of disease progression, establishing a new benchmark for standard of care in this setting.

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NCCN Guidelines Version 2.2023
Non-Small Cell Lung Cancer

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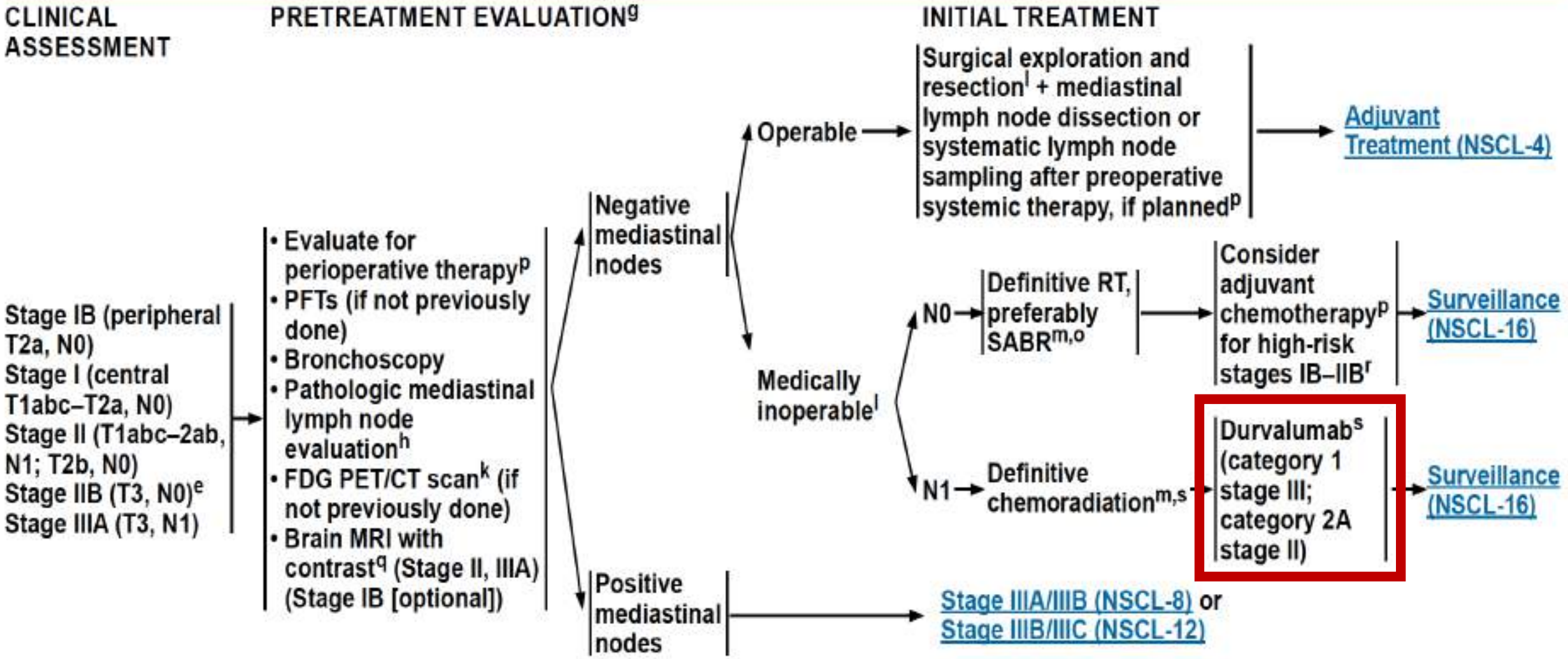

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Pembrolizumab Plus Concurrent Chemoradiation Therapy in Patients With Unresectable, Locally Advanced, Stage III Non–Small Cell Lung Cancer

The Phase 2 KEYNOTE-799 Nonrandomized Trial

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To evaluate treatment outcomes and safety of pembrolizumab plus cCRT in stage III NSCLC.

This phase 2, nonrandomized, 2-cohort study suggest promising antitumor activity of pembrolizumab plus cCRT and manageable safety in patients with previously untreated, locally advanced, stage III NSCLC

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Published: Octob

Abstract

Introduction: The phase II DETERRED trial assessed the safety and efficacy of consolidation and concurrent immunotherapy with chemoradiation in unresectable locally advanced non-small cell lung cancer. We present updated efficacy analysis of this trial.

Methods: The trial was conducted in 2 parts with patients in part 1 (n = 10) receiving chemoradiation with consolidation atezolizumab, while patients in part 2 (n = 30) received concurrent and consolidation atezolizumab. Progression-free survival (PFS), time to second progression (PFS2), and overall survival (OS) were assessed using Kaplan-Meier analysis. Subset analyses were performed by programmed cell death ligand-1 (PD-L1) status and targetable driver oncogene mutation status.

Results: At a median follow-up of 39.2 months, the median PFS for part 1 was 18.9 months and 15.1 months for part 2. Median OS for part 1 was 26.5 months and was not reached for part 2. For the

Highlights

Stage 3 non-small cell lung cancer is treated with durvalumab after chemoradiation.

DETERRED trial showed similar efficacy using a different immunotherapy agent.

Tumors with driver oncogene mutations may derive less benefit from this approach.

Tumors with low PD-L1 may derive less benefit from this approach.

Targeted therapy.

ORIGINAL ARTICLE

IASLC

Progression-Free and Overall Survival for Concurrent Nivolumab With Standard Concurrent Chemoradiotherapy in Locally Advanced Stage IIIA-B NSCLC: Results From the European Thoracic Oncology Platform NICOLAS Phase II Trial (European Thoracic Oncology Platform 6-14)

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The NICOLAS study is the first completed single-arm phase II trial in stage III NSCLC evaluating hierarchically first the safety and then the efficacy of adding nivolumab concurrently to standard definitive concurrent chemoradiotherapy. The safety end point was reported earlier; here, we present the efficacy results.

Conclusion: PFS and OS are arithmetically higher in studies involving the same population. However, on the basis of the formal hierarchical efficacy analysis, we could not reject that the 1-year PFS rate is at least 45%

Both radiation and immunotherapy can cause a similar presentation of pneumonitis, and to date, there are little prospective data on the potential synergistic toxicity of the combination. This combination is, therefore, being approached with caution

TABLE 3 | Currently ongoing trials (i.e. not yet recruiting, recruiting and enrolling by invitation) evaluating immunotherapy-radiotherapy combinations in non-small cell lung cancer[a].

Study identifier (acronym)	Phase	NSCLC setting (accrual)	Immunotherapy	Radiotherapy	Design	Outcome	Institution/group
NCT02599454	I	Stage I, inoperable (*N* = 33)	Atezo	50 Gy/4–5 fx	SBRT + atezo	MTD (DFS, ORR)	University of California, Davis
NCT03148327 (ISABR)	I/II	Stage I/IIA, inoperable (*N* = 105)	Durva	• 50 Gy/4 fx • 54 Gy/3 fx • 65 Gy/10 fx	• SBRT + durva • SBRT	Tox, PFS (OS, LC)	Jonsson Comprehansive Cancer Center
NCT03446547 (ASTEROID)	II	Stage I-IIA, not suitable for surg (*N* = 216)	Durva	3–4 fx, dose NS	• SBRT > durva • SBRT	PFS (OS, LC, QoL)	Vastra Gotaland Region
NCT03833154 (PACIFIC-4)	III	Stage I-II lymph node negative, planned for SBRT (*N* = 630)	Durva	NS	• SBRT > durva • SBRT > placebo	PFS (OS, QoL, tox, IM)	AstraZeneca
NCT03110978	II	Stage I-IIA or isolated lung parenchymal recurrent/persistent (*N* = 140)	Nivo	• 50 Gy/4 fx • 70 Gy/10 fx	• SABR + nivo • SABR	EFS (OS, tox)	M.D. Anderson Cancer Center
NCT03574220	I	Stage IA-IB, inoperable (*N* = 15)	Pembro	• 50 Gy/5 fx • 60 Gy/3 fx	SBRT > pembro	Tox (DMFS, DFS, OS, LC)	Case Comprehensive Cancer Center
NCT03383302 (STILE)	Ib/II	Stage I-IIA, not suitable for surg (*N* = 31)	Nivo	• 54 Gy/3 fx • 55 Gy/5 fx	SBRT > nivo	Tox (DFS, OS, QoL, IM)	Royal Marsden NHS Foundation Trust
NCT03546829	I	Early-stage, planned for SBRT (*N* = 40)	Vancomycin	NS	• SBRT > vancomycin • Vancomycin > SBRT	IM	Abramson Cancer Center of the University of Pennsylvania
NCT01720836	I/II	Stage IA-IIB (*N* = 30)	Hiltonol (MUC1 + poly-ICLC)	NS	SOC > Hiltonol	IM	University of Pittsburgh Medical Center
NCT03217071 (PembroX)	II	Stage I-IIIA (*N* = 40)	Pembro	12 Gy/1 fx, 50% of primary tumor	• Pembro > SBRT > surg • Pembro > surg	IM (OS, DFS, tox)	University of California, San Francisco
NCT03801902 (ARCHON-1)	I	Stage II-III, unresectable or inoperable (*N* = 24)	Durva	• 60 Gy/15 fx • 60 Gy/30 fx	• Accelerated RT + durva • Conventional RT + durva	Tox (feas, PFS, IM)	NRG Oncology
NCT02621398	I	Stage II inoperable or stage III (*N* = 30)	Pembro	3D-RT or IMRT, 30 fx, dose NS	CRT + pembro	MTD, DLT (ORR, LC, DMFS OS, PFS)	Rutgers Cancer Institute of New Jersey
NCT04013542	I	Stage II unresectable or stage III (*N* = 20)	• Nivo • Ipi	6–7 w, dose NS	RT + nivo + ipi > nivo	Tox (PFS, OS, LC, ORR, DOR)	M.D. Anderson Cancer Center
NCT03523702 (SPRINT)	II	Stage II unresectable or stage III (*N* = 63)	Pembro	4–7 w, dose NS	• PD-L1 <50%: CT + RT • PD-L1 ≥50%: Pembro + RT	PFS (DMFS, OS)	Albert Einstein College of Medicine
NCT04062708 (CHIO3)	II	Stage III, resectable (*N* = 55)	Durva	54 Gy, number of fx NS	CT + durva > surg > RT > durva	Nodal response (pathologic and radiologic ORR, EFS, OS, tox)	Alliance Foundation Trials, LLC
NCT03237377	II	Stage III, resectable (*N* = 32)	• Durva • Treme	45 Gy/25 fx	• RT + durva > surg • RT + durva + treme > surg	Tox, feas (pathologic and radiologic ORR, DOR, OS)	Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
NCT03871153	II	Stage III, resectable (N2) (*N* = 25)	Durva	45–61.2 Gy/25–34 fx	CT + durva > RT + durva > surg > durva	Pathologic CR (nodal response, tox, PFS)	Indiana University School of Medicine

(Continued)

TABLE 3 | Continued

Study identifier (acronym)	Phase	NSCLC setting (accrual)	Immunotherapy	Radiotherapy	Design	Outcome	Institution/group
NCT03631784 (KEYNOTE-799)	II	Stage III, unresectable, 1st line ($N = 216$)	Pembro	60 Gy/30 fx	CRT + pembro > pembro	Tox, ORR (PFS, OS)	Merck Sharp & Dohme Corp.
NCT03663166	I/II	Stage III, unresectable ($N = 50$)	• Nivo • Ipi	60 Gy/30 fx	CRT + ipi > nivo	Tox, PFS (DMFS, ORR)	H. Lee Moffitt Cancer Center and Research Institute
NCT03285321	II	Stage IIIA/B, unresectable or inoperable, CR/PR/SD with CRT (N=108)	• Nivo • Ipi	59.4–66.6 Gy, number of fx NS	• CRT > nivo • CRT > nivo + ipi	PFS (OS, DMFS, tox)	Big Ten Cancer Research Consortium
NCT03589547	II	Stage III, PR/SD with CRT ($N = 25$)	Durva	20 Gy/2–3 fx, primary tumor only	SBRT + durva	Tox, PFS (OS, LC, DMFS)	Brown University
NCT03102242	II	Stage IIIA/B, unresectable ($N = 63$)	Atezo	60 Gy/30 fx	Atezo > CRT	DCR	Alliance Foundation Trials
NCT03644823 (COM-IT-1)	II	Stage III-IV, palliative treated ($N = 30$)	Atezo	18 Gy/3 fx	RT + atezo	Tox (PFS)	Oslo University Hospital
NCT03774732 (NIRVANA- Lung)	III	Stage IIIB-IV ($N = 510$)	• Nivo • Pembro • Atezo	• SABR: NS • 3D-RT: 18 Gy/3 fx	• RT + ICB • ICB	OS (ORR, PFS, LC, QoL, tox)	UNICANCER
NCT02830295	II	Stage III-IV, ≥2 measurable disease sites ($N = 29$)	CDX-301	30–54 Gy/1–5 fx, single intrathoracic site of disease	SBRT + CDX-301	PFS (DLT)	Albert Einstein College of Medicine
NCT03965468 (CHESS)	II	Stage IV, oligometastatic (≤3 lesions) ($N = 47$)	Durva	• SBRT: up to 10 fx, dose NS • Definitive RT: 60–66 Gy, fx NS	SBRT + CT + durva > surg or definitive RT + durva	PFS (OS, ORR, DOR, QoL, tox)	European Thoracic Oncology Platform
NCT03275597	Ib	Stage IV, oligometastatic (≤6 lesions) ($N = 21$)	• Durva • Treme	30–60 Gy/5 fx, all sites of disease	SBRT > durva + treme	Tox (PFS, OS, IM)	University of Wisconsin, Madison
NCT03509584	I	Stage IV ($N = 24$)	• Nivo • Ipi	24 Gy/3 fx, single bone or extracranial metastasis	• RT + nivo • RT + nivo + ipi	Tox	Assistance Publique Hopitaux De Marseille
NCT03223155 (COSINR)	I	Stage IV ($N = 80$)	• Nivo • Ipi	3–5 fx, dose NS, 2–4 sites	SBRT > nivo + ipi	Tox (ORR, LC, IM)	University of Chicago
NCT03168464	I/II	Stage IV, ≥2 measurable metastatic sites ($N = 45$)	• Nivo • Ipi	30 Gy/5 fx, single lesion	RT + ipi > nivo + ipi	ORR (PFS, DOR, OS, IM)	Weill Medical College of Cornell University
NCT02444741	I/II	Stage IV, ≥2 disease sites ($N = 104$)	Pembro	• 4 fx: SBRT • 15 fx: IMRT, 3D-RT or PBRT	• Pembro + RT • Pembro > RT upon PD	Tox, ORR (PFS, OS)	M.D. Anderson Cancer Center
NCT03035890	NS	Stage IV, ≥3 disease sites ($N = 33$)	• Nivo • Pembro • Atezo	• 24–45 Gy/3 fx • 30–50 Gy/5 fx Single lesion	RT + ICB	ORR (PFS, OS, tox, QoL)	West Virginia University
NCT03825510	NS	Stage IV, ≥2 lesions amenable to SBRT ($N = 100$)	• Nivo • Pembro	3–5 fx, dose NS, ≤3 sites	SBRT > ICB	OS, tox (PFS, LC)	Crozer-Keystone Health System
NCT03867175	III	Stage IV, ≤8 disease sites ($N = 116$)	Pembro	3–10 fx, dose NS	• SBRT > Pembro • Pembro	PFS (OS, LC, tox)	Wake Forest University Health Sciences

(Continued)

TABLE 3 | Continued

Study identifier (acronym)	Phase	NSCLC setting (accrual)	Immunotherapy	Radiotherapy	Design	Outcome	Institution/group
NCT03391869 (LONESTAR)	III	Stage IV (*N* = 270)	• Nivo • Ipi	NS	Nivo + ipi > LCT > nivo + ipi	OS (PFS, tox, QoL)	M.D. Anderson Cancer Center
NCT03705403 (IMMUNOSABR2)	II	Stage IV (*N* – 130)	Darleukin (L19–IL2)	24 Gy/3 fx	• SOC + Darleukin • SOC	PFS (OS, QoL, IM)	Maastricht University
NCT03158883	I	Stage IV, ≥2 measurable disease sites, non-responsive or refractory to ICB (*N* = 25)	Ave	50 Gy/5 fx	SBRT + ave	ORR (OS, PFS, DCR, DOR)	University of California, Davis
NCT03224871	I	Stage IV, ≥2 disease sites, non-responsive or refractory to ICB (*N* – 30)	• Nivo • Pembro • Intralesional IL-2	24 Gy/3 fx, single lesion	RT + ICB > ICB + IL-2	DLT (DFS)	University of California, Davis
NCT03406468	II	Stage IV, refractory to ICB (*N* = 40)	• Nivo • Pembro • Atezo	• 24 Gy/3 fx • 30 Gy/10 fx • 20 Gy/5 fx • 20–24 Gy/1 fx Single lesion	RT + ICB	PFS (LC, tox)	Maastricht University
NCT03176173	II	Stage IV, ≥1 extracranial disease site, after ≥4 w ICB (*N* – 85)	• Nivo • Pembro • Atezo	≤10 fx, dose NS	• RT + ICB • ICB	PFS (tox, OS, IM)	Stanford University
NCT03044626 (FORCE)	II	Stage IV, non-squamous, 2nd or 3rd line (*N* = 130)	Nivo	20 Gy/5 fx, single metastatic site	• RT + nivo • Nivo	ORR (PFS, OS, tox, QoL)	AIO-Studien-gGmbH
NCT03489616 (CRAGMOLC)	NS	Stage IV, oligometastatic (2–5 metastases), PR/SD after first-line CT (*N* = 45)	rhGM-CSF	BED >45 Gy, >4 Gy per fx	• CT + RT + rhGM-CSF • CT	PFS (OS)	Shandong Cancer Hospital and Institute

3D-RT, 3-dimensional conformal radiotherapy; atezo, atezolizumab; ave, avelumab; BED, biologically effective dose; CR, complete response; CRT, chemo-radiotherapy; CT, chemotherapy; DCR, disease control rate; DFS, disease-free survival; DLT, dose-limiting toxicity; DMFS, distant metastasis-free survival; DOR, duration of response; durva, durvalumab; EFS, event-free survival; feas, feasibility; fx, fraction(s); Gy, Gray; ICB, immune checkpoint blockade; IL, interleukin; IM, immunomonitoring; IMRT, intensity-modulated radiotherapy; ipi, ipilimumab; MTD, maximum tolerated dose; nivo, nivolumab; LC, local control; LCT, local consolidation treatment; NS, not specified; NSCLC, non-small cell lung cancer; OS, overall survival; ORR, overall response rate; PBRT, proton beam radiotherapy; PD, progressive disease; pembro, pembrolizumab; PFS, progression-free survival; PR, partial response; QoL, quality of life; rhGM-CSF, human recombinant granulocyte-macrophage colony-stimulating factor; RT, radiotherapy; SABR, stereotactic ablative radiation therapy; SBRT, stereotactic body radiation therapy; SD, stable disease; SOC, standard of care; tox, toxicity; treme, tremelimumab; w, week(s); +, concurrently with; >, followed by.

[a]*Only studies focusing exclusively on a NSCLC patient population are represented in this table.*

Epub 2021 Sep 20.

Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial

Enriqueta Felip [1], Nasser Altorki [2], Caicun Zhou [3], Tibor Csőszi [4], Ihor Vynnychenko [5], Oleksandr Goloborodko [6], Alexander Luft [7], Andrey Akopov [8], Alex Martinez-Marti [9], Hirotsugu Kenmotsu [10], Yuh-Min Chen [11], Antonio Chella [12], Shunichi Sugawara [13], David Voong [14], Fan Wu [15], Jing Yi [14], Yu Deng [14], Mark McCleland [14], Elizabeth Bennett [14], Barbara Gitlitz [14], Heather Wakelee [16]; IMpower010 Investigators

Affiliations + expand

PMID: 34555333 DOI: 10.1016/S0140-6736(21)02098-5

Adjuvant therapy with atezolizumab versus best supportive care in 1005 patients with resected early-stage NSCLC and various PD-L1 levels.

- In patients with resected stage II to IIIA NSCLC and PD-L1 of 1% or more, disease-free survival was improved in those receiving adjuvant atezolizumab compared with best supportive care (HR, 0.66; 95% CI, 0.5–0.88; P = .0039).

- Treatment-related grade 3 and 4 adverse events were reported in 11% (53/495) of patients; 4 deaths occurred (1%, 4/495)

- The NCCN Panel recommends atezolizumab as an adjuvant therapy option for eligible patients with completely resected stage IIB to IIIA or high-risk stage IIA NSCLC and with PD-L1 of 1% or more who have previously received adjuvant chemotherapy based on clinical trial data and the FDA approval.

NCCN Guidelines Version 2.2023
Non-Small Cell Lung Cancer

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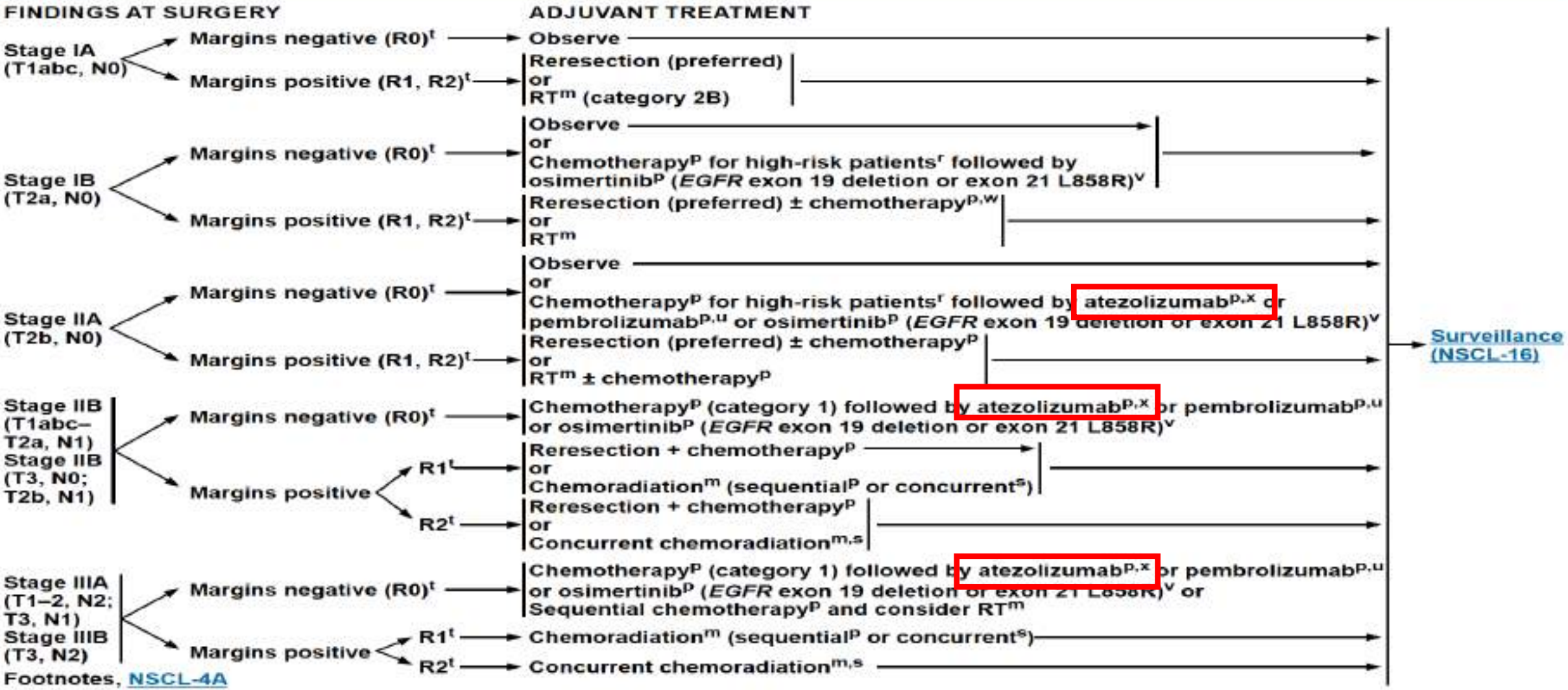

Footnotes, NSCL-4A

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

National Comprehensive Cancer Network®

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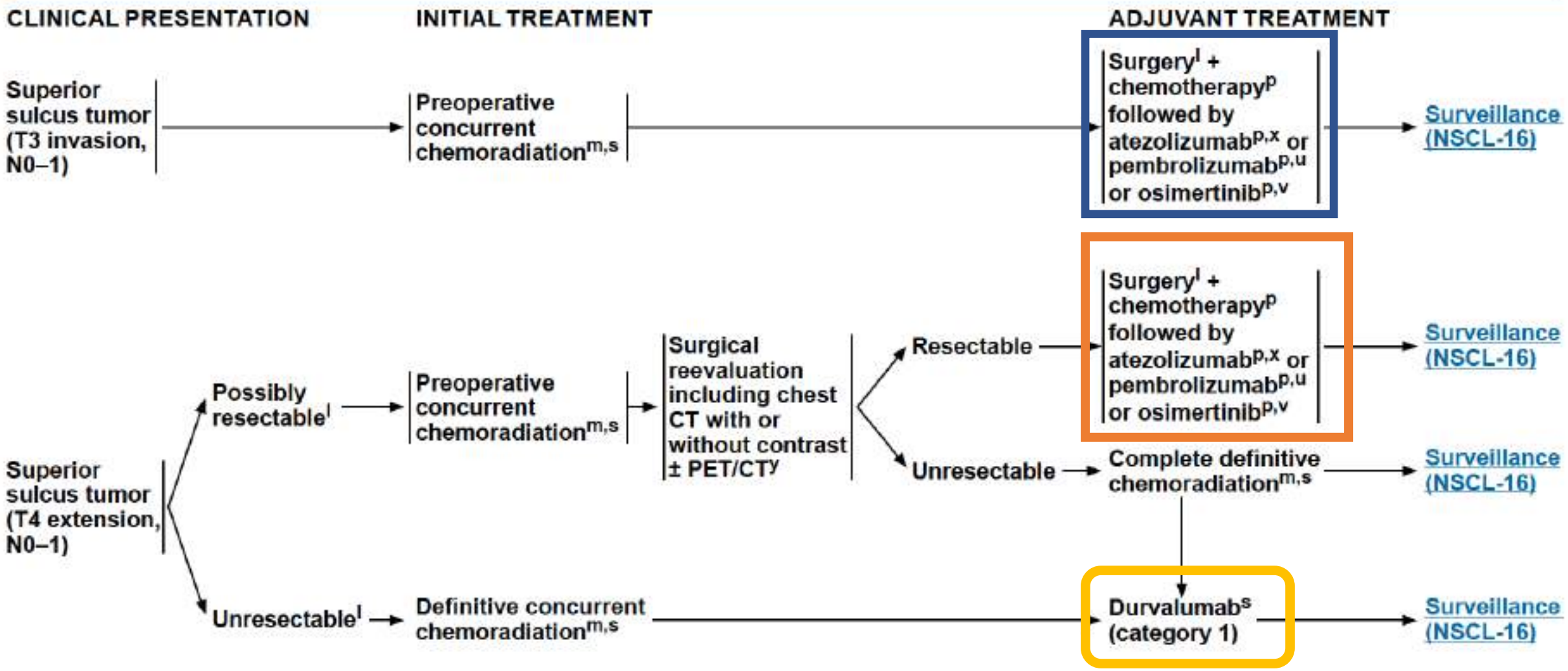

[l] Principles of Surgical Therapy (NSCL-B)

Early stage NSCLC

- Early-stage NSCLC (ES-NSCLC) represents about 15–20% of all new lung cancer diagnoses .
- According to the latest consensus guidelines, surgery remains the treatment of choice for operable ES-NSCLC patients.
- For those unfit for or unwilling to undergo surgical resection, SBRT is now the gold standard, with an excellent safety profile and local control rates of approximately 90% at 5 years.
- Trials are exploring whether the combination of SBRT with immunotherapy can be performed safely, as patients with early stage NSCLC have longer life expectancies and thus are at risk of developing long-term toxicities.

Table 1 Ongoing clinical trials investigating combining radiation therapy and immunotherapy for thoracic cancers

National clinical trial ID number	Phase	Participating institution(s)	Histology	Stage	Immunotherapy agent	Immunotherapy mechanism of action	Radiation
NCT03110978	II randomized	MD Anderson Cancer Center	NSCLC	I	Nivolumab	PD-1	SBRT
NCT02599454	I	UC Davis and David Grant United States Air Force Medical Center	NSCLC	I	Atezolizumab	PD-L1	SBRT
NCT03050554	I/II	UC San Diego	NSCLC	I	Avelumab	PD-L1	SBRT
NCT03148327	II randomized	UCLA	NSCLC	I	Durvalumab	PD-L1	SBRT
NCT03446911	II randomized	VU Medical Center	NSCLC	I	Pembrolizumab	PD-1	SBRT
NCT03383302	II	Multi Center led by Royal Marsden	NSCLC	I–II	Nivolumab	PD-1	SBRT
NCT02621398	I	Multicenter led by Rutgers Cancer Institute of New Jersey	NSCLC	II–IIIB	Pembrolizumab concurrently with carboplatin and paclitaxel	PD-1	Conventionally fractionated IMRT or 3D-CRT
NCT02434081	II	European Thoracic Oncology Platform	NSCLC	IIIA–IIIB	Nivolumab concurrently with	PD-1	Conventionally fractionated RT
NCT03245177	I	University of Manchester	NSCLC	III	Pembrolizumab	PD-1	Conventionally fractionated RT
NCT03237377	II	Johns Hopkins University	NSCLC	IIIA	Durvalumab/tremelimumab	PD-L1/CTLA-4	Conventionally fractionated RT
NCT03035890	n/a	West Virginia University	NSCLC	IV	Nivolumab/pembrolizumab/atezolizumab	PD-1/PD-1/PD-L1	Hypofractionated RT
NCT03509584	I	Assistance Publique Hôpitaux De Marseille	NSCLC	IV	Nivolumab/ipilimumab	PD-1/CTLA-4	Hypofractionated RT
NCT02463994	I	Multicenter let by University of Michigan	NSCLC	IV	Atezolizumab	PD-L1	Hypofractionated RT
NCT03176173	II	Stanford University	NSCLC	IV	Nivolumab/pembrolizumab/atezolizumab	PD-1/PD-1/PD-L1	Hypofractionated RT
NCT03313804	II	University of Kentucky	NSCLC	IV	Nivolumab/pembrolizumab/atezolizumab	PD-1/PD-1/PD-L1	SBRT or conventional palliative RT
NCT02839265	II	Montefiore Medical Center	NSCLC	IV	CDX-301	FLT3 ligand	SBRT
NCT03168464	I/II	Weill Medical College of Cornell University	NSCLC	IV	Nivolumab/ipilimumab	PD-1/CTLA-4	Hypofractionated RT

Table 1 (*continued*)

SBRT With Immunotherapy in Early Stage Non-small Cell Lung Cancer: Tolerability and Lung Effects (STILE)

Study Description

Go to

Brief Summary:

This is a single arm, multi-centre, phase II open label study of nivolumab with stereotactic body radiotherapy (SBRT) for early stage non-small cell lung cancer.

SBRT will be delivered in either 3 or 5 fractions. A flat dose of 240 mg nivolumab infusion will begin after the final fraction of SBRT, within 24 hours and typically on the same day. Nivolumab will subsequently be given every 2 weeks at a flat dose of 240 mg until 1 year of total treatment unless any study drug discontinuation criteria are met.

Assessment of toxicities will be performed at each clinic visit during treatment, at 30 days after the final nivolumab infusion and until 100 days after the final nivolumab infusion. Changes in spirometry values and PFTs will be assessed throughout the trial.

Relapse rates will be assessed with staging CT scans at 3, 6, 12, 18 and 24 months post SBRT.

An exploratory assessment will be made of the effect pre-treatment pulmonary function tests (PFTs) have on outcome measures.

Condition or disease	Intervention/treatment	Phase
Non-small Cell Lung Cancer Stage II	Radiation: Stereotactic body radiotherapy	Phase 1
Non-small Cell Lung Cancer Stage I	Drug: Nivolumab	Phase 2

Primary Outcome:
Assessment of lung toxicity (pneumonitis) from treatment with Nivolumab after SBRT for early stage NSCLC
Rate of grade ≥ 3 pneumonitis with nivolumab after stereotactic body radiotherapy (SBRT) within 6 months of the final fraction of SBRT. A rate that exceeds 20% will be deemed unacceptable and will lead to a rejection of the null hypothesis.

Challenges

- Combining immunotherapy and RT for early-stage NSCLC is still in its infancy.
- Selection of the patients that are most likely to benefit from combined modality treatment as well as optimal sequencing and duration of immunotherapy.
- The optimal radiation dose and fractionation for SBRT alone remain to be determined for peripheral and central tumors, much less when SBRT is combined with immunotherapy.
- Pseudo progression after immunotherapy also will likely make assessing response only more challenging based on current RECIST size-based criteria.
- Nonetheless, there is promising potential synergy between radiation and immunotherapy to reduce systemic failures and improve cure rates in early stage patients

Radiation plus Immunotherapy for SCLC

- Despite a plethora of clinical trials for patients with SCLC over the last two decades, little progress has been made and patient outcomes remain poor, with OS ranging between 10 and 30 months.
- Although very responsive to first-line chemotherapy, SCLC frequently relapses, and response to second-line agents is extremely poor
- Immunotherapy has thus been an exciting development for SCLC as it has the potential to overcome the limitations of chemotherapy by targeting SCLC in a novel way.

Small cell Lung Carcinoma

High tumor mutation burden

- correlated with response to checkpoint inhibitors due to re-awakening of pre-existing strong anti-tumor CD8+ cytotoxic T-cell responses
- immunomodulatory effect of SCLC tumor cells on host immune system
- higher propensity of paraneoplastic syndromes in SCLC ----- several cross-reacting antibodies recruited by the host immune response target both tumor as well as normal cells.

- SCLC tumor cells also exhibit a regulatory effect through induction of CD4+ Treg cells and decreased expression of HLA-class 1 antigen on host immunity.
- This balance between the effector and regulatory effects may distinguish extensive stage SCLC (ES-SCLC) from limited stage SCLC

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Pembrolizumab in Patients With Extensive-Stage Small-Cell Lung Cancer: Results From the Phase Ib KEYNOTE-028 Study

Patrick A. Ott, Elena Elez, Sandrine Hiret, Dong-Wan Kim, Anne Morosky, Sanatan Saraf, Bilal Piperdi, and Janice M. Mehnert

The safety of pembrolizumab was consistent with the known safety profile in other tumor types. Pembrolizumab demonstrated promising antitumor activity in patients with pre-treated, PD-L1–expressing SCLC.

Clinical Trial > Lancet Oncol. 2016 Jul;17(7):883-895. doi: 10.1016/S1470-2045(16)30098-5. Epub 2016 Jun 4.

Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial

Scott J Antonia [1], José A López-Martin [2], Johanna Bendell [3], Patrick A Ott [4], Matthew Taylor [5], Joseph Paul Eder [6], Dirk Jäger [7], M Catherine Pietanza [8], Dung T Le [9], Filippo de Braud [10], Michael A Morse [11], Paolo A Ascierto [12], Leora Horn [13], Asim Amin [14], Rathi N Pillai [15], Jeffry Evans [16], Ian Chau [17], Petri Bono [18], Akin Atmaca [19], Padmanee Sharma [20], Christopher T Harbison [21], Chen-Sheng Lin [21], Olaf Christensen [21], Emiliano Calvo [22]

Nivolumab monotherapy and nivolumab plus ipilimumab showed antitumour activity with durable responses and manageable safety profiles in previously treated patients with SCLC.
These data suggest a potential new treatment approach for a population of patients with limited treatment options and support the evaluation of nivolumab and nivolumab plus ipilimumab in phase 3 randomised controlled trials in SCLC.

Small Cell Lung Carcinoma Trial With Nivolumab and IpiliMUmab in LImited Disease (STIMULI)

ORIGINAL ARTICLE

IASLC

Check for updates

Phase I Trial of Pembrolizumab and Radiation Therapy after Induction Chemotherapy for Extensive-Stage Small Cell Lung Cancer

James W. Welsh, MD,[a,*] John V. Heymach, MD, PhD,[b] Dawei Chen, MD,[a,c] Vivek Verma, MD,[d] Taylor R. Cushman, BS,[a] Kenneth R. Hess, PhD,[e] Girish Shroff, MD,[f] Chad Tang, MD,[a] Ferdinandos Skoulidis, MD,[b] Melenda Jeter, MD,[a] Hari Menon, BS,[a] Quynh-Nhu Nguyen, MD,[a] Joe Y. Chang, MD, PhD,[a] Mehmet Altan, MD,[b] Vassiliki A. Papadimitrakopoulou, MD,[b] George R. Simon, MD,[b] Uma Raju, MD,[a] Lauren Byers, MD,[b] Bonnie Glisson, MD[b]

Journal for ImmunoTherapy of Cancer

Durvalumab and tremelimumab with or without stereotactic body radiation therapy in relapsed small cell lung cancer: a randomized phase II study

Suchita Pakkala,[1] Kristin Higgins,[2] Zhengjia Chen,[1] Gabriel Sica,[3] Conor Steuer,[1] Chao Zhang,[4] Guojing Zhang,[1] Shuhua Wang,[1] Mohammad S Hossain,[1] Bassel Nazha,[1] Tyler Beardslee,[1] Fadlo R Khuri,[1] Walter Curran,[2] Sagar Lonial,[1] Edmund K Waller,[1] Suresh Ramalingam,[1] Taofeek K Owonikoko [1]

To cite: Pakkala S, Higgins K, Chen Z, *et al*. Durvalumab and tremelimumab with or without stereotactic body radiation therapy in relapsed small cell lung cancer: a randomized phase II study. *Journal for ImmunoTherapy of Cancer* 2020;**8**:e001302. doi:10.1136/jitc-2020-001302

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jitc-2020-001302).

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ABSTRACT

Background Immune checkpoint blockade (ICB) targeting programmed cell death protein 1 and cytotoxic T lymphocyte-associated protein 4 has achieved modest clinical activity as salvage therapy in relapsed small cell lung cancer (SCLC). We conducted this signal-finding study to assess the efficacy of ICB with or without radiation in relapsed SCLC.

Methods Patients with relapsed SCLC and ≤2 previous lines of therapy were randomized to (1) arm A: durvalumab (D) 1500 mg/tremelimumab (T) 75 mg (intravenously every 4 weeks without stereotactic body radiation therapy (SBRT)) or (2) arm B: immune-sensitizing SBRT to one selected tumor site (9 Gy × 3 fractions) followed by D/T. Treatment continued until progression or a maximum of

and B (n=9 each): median age 70 years; 41.2% women. The median PFS and ORR were 2.1 months and 0% in arm A and 3.3 months and 28.6% in arm B. The median overall survival (OS) was 2.8 months in arm A and 5.7 months in arm B (p=0.3772). Pooled efficacy of D/T±SBRT in 15 Response evaluation criteria in solid tumors (RECIST) evaluable patients across both arms showed the best ORR in terms of partial response in 13.3%, stable disease in 26.6% and progressive disease in 60.0%; the overall median PFS and OS were 2.76 and 3.9 months. The most common adverse events were grade 1 fatigue (66%) and grade 1 elevated amylase (56%) in arm A, and grade 1 fatigue (58%) and pain (44%) in arm B. There was a significant increase in activated CD8(+)ICOS+ T cells (p=0.048) and a reduction in naïve T cells (p=0.0454) in peripheral blood following treatment, along with a significant amount of activated CD8+ICOS+ T cells in TILs from responders.

Conclusions The D/T combination with and without SBRT was safe but did not show sufficient efficacy signal in relapsed SCLC. Changes in peripheral blood lymphocyte and TILs were consistent with an immunologic response.

Trial registration number NCT02701400.

INTRODUCTION

Effective salvage therapy for small cell lung cancer (SCLC) remains a challenge and an area of great need yet unmet.[1] There is a strong rationale for testing immune checkpoint inhibitors in SCLC. It is already well established that the development of effective antitumor immunity manifesting as paraneoplastic syndrome in patients with SCLC is associated with prolonged and durable disease control in contrast to that in patients without paraneoplastic syndrome.[2] Simi-

clinical benefit of pharmacologic blockade of programmed cell death protein 1 (PD-1) or its ligand (PD-L1) in relapsed SCLC.[4–7] Moreover, the addition of ipilimumab, a cytotoxic T lymphocyte-associated protein 4 (CTLA-4) inhibitor, to nivolumab showed greater benefit over nivolumab alone in a subset of SCLC defined by high tumor mutation burden.[8] Nonetheless, only a third of patients derived any clinical benefit from this combination therapy strategy. In the absence of a reliable biomarker for patient enrichment, a complementary therapeutic intervention that can enhance antitumor efficacy of immune checkpoint blockade (ICB) without increasing toxicity will expand the benefit of immune checkpoint inhibitors to a larger proportion of patients.

Limited institutional experience and large randomized studies suggested a survival

The D/T combination with and without SBRT was safe but did not show sufficient efficacy signal in relapsed SCLC. Changes in peripheral blood lymphocyte and TILs were consistent with an immunologic response

- These studies will address the toxicity concerns of combining these agents with radiation, especially in the context of the relatively large target volumes seen in SCLC as well as providing valuable data on the appropriate dose, combination, and timing of the treatments.

Radiation plus Immunotherapy for Oesophageal cancer

- Trimodality therapy consisting of concurrent chemoradiation followed by surgical resection is the standard of care for locally advanced esophageal cancer patients who are surgical candidates.
- The 5-year OS with this approach ranges from 39–47% .
- In patients that are medically inoperable or have unresectable disease, definitive chemoradiation is recommended; however, survival rates are poor and persistence of locoregional disease occurs in nearly half of patients.
- More aggressive treatments such as radiation dose-escalation and the addition of targeted systemic agents against receptors commonly expressed in oesophageal cancer have failed to improve patient outcomes

- PD-L1 expression is present in 45% of oesophageal cancer tissues and is associated with more locally aggressive disease and decreased survival
- Monoclonal antibodies directed against PD-L1 receptors may act synergistically with RT in killing tumor cells.
- This is the subject of several ongoing phase I–II trials evaluating safety and efficacy of the combination of chemoradiation with ICIs in both the metastatic/inoperable (NCT03377400, NCT03437200, NCT02642809) and neoadjuvant settings .

Radiation plus Immunotherapy for Mesothelioma

- MPM is a rare disease with poor OS and limited effective treatment options
- Patients with MPM often have a large burden of disease and poor performance status, thus the discovery of effective immunotherapies has long been of interest.
- Anti PD-1/PD-L1 drugs, however, have shown promising results in a series of small studies. Phase-I/II studies incorporating pembrolizumab, nivolumab, and avelumab have shown 9.4–20% partial response rates with stabilization of disease in 50% of patients

- Combined PD-L1 inhibition is also being explored in two ongoing clinical trials (NCT03048474 and NCT02899299).
- A report from the University of Toronto found that the growth of tumors in a murine mesothelioma model was significantly reduced by hypofractionated radiation and combining radiation with a CTLA-4 inhibitor enhanced the effect in the irradiated and unirradiated tumors.
- Combining radiotherapy and immunotherapy for mesothelioma is a promising treatment strategy
- A single arm phase II study has recently been initiated by Memorial Sloan Kettering Cancer Centre and will evaluate response rates with Avelumab and SBRT in MPM

ORIGINAL ARTICLE

IASLC

A Phase 1 Safety Study of Avelumab Plus Stereotactic Body Radiation Therapy in Malignant Pleural Mesothelioma

Andreas Rimner, MD,[a,*] Prasad S. Adusumilli, MD,[b] Michael D. Offin, MD,[c] Stephen B. Solomon, MD,[d] Etay Ziv, MD,[d] Sara A. Hayes, MD,[d] Michelle S. Ginsberg, MD,[d] Jennifer L. Sauter, MD,[e] Daphna Y. Gelblum, MD,[a] Annemarie F. Shepherd, MD,[a] David M. Guttmann, MD,[a] Jordan E. Eichholz, MS,[c] Zhigang Zhang, PhD,[f] Erika Ritter, BS,[g] Phillip Wong, PhD,[g] Afsheen N. Iqbal, MD,[c] Robert M. Daly, MD,[c] Azadeh Namakydoust, MD,[c] Henry Li, BS,[a] Megan McCune, BS,[a] Emily H. Gelb, BS,[a] Neil K. Taunk, MD,[a] Donata von Reibnitz, MD,[a] Neelam Tyagi, PhD,[h] Ellen D. Yorke, PhD,[h] Valerie W. Rusch, MD,[b] Marjorie G. Zauderer, MD[c]

Combination avelumab plus SBRT seems tolerable on the basis of the prespecified toxicity end points of the first stage of this Simon two-stage design phase 1 study

Radiation plus Immunotherapy for Thymoma

- Thymomas represent 20% of all primary mediastinal tumors
- Due to its rarity, there is a dearth of understanding of the molecular biology of these tumors, and immunotherapy approaches are limited to small patient cohorts.
- There are two ongoing phase II trials evaluating the efficacy of ICIs in thymomas (NCT02721732 and NCT02607631); however, none currently are in combination with radiation.
- The efficacy of immunotherapy combined with radiation will likely be of greater interest as our understanding of thymoma tumor biology and its interaction with the immune system improves.

Conclusion

- The combination of immunotherapy and RT has the potential to revolutionize treatments for thoracic malignancies.
- Preclinical data have demonstrated impressive synergy between the two therapies that appears to extend beyond the irradiated target.
- For patients with advanced NSCLC, recent clinical trials incorporating ICIs have exhibited dramatic improvements in outcomes compared to conventional chemotherapies.
- We anxiously await results from ongoing and future preclinical research and clinical trials to better define the optimal approaches to combining these two pillars of cancer care
- Emerging evidence of nanotechnology-enabled therapeutics can potentiate both radiotherapy and immunotherapy.


THANK YOU