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Regimens combining radiation and immunotherapy for cancer: latest updates from 2024 ASCO Annual Meeting

Di Liu[1†], Leilei Wu[1†], Xiaoling Xu[1], Shuangyan Yang[1], Ming Liu[1], Min Hu[1], Shengxiang Ren[2*] and Yaping Xu[1*]

Abstract

Combination of immunotherapy with radiotherapy is under active investigation. The PACIFIC trial firmly established the treatment paradigm of consolidation immunotherapy following definitive chemoradiotherapy, inspiring a series of similar or exploratory combination regimens. This summary highlighted six reports updated in the 2024 ASCO Annual Meeting.

Consolidation immunotherapy following concurrent chemoradiotherapy

Consolidation immunotherapy following definitive concurrent chemoradiotherapy (cCRT) has been established as a standard treatment in unresectable locally advanced non-small cell lung cancer (LA-NSCLC) based on the PACIFIC trial [1]. This strategy was further validated in a real-world study with superior survival outcomes at ASCO 2024 [2]. Moreover, research has been conducted to investigate the efficacy of consolidation immunotherapy in limited-stage small-cell lung cancer (LS-SCLC). The phase III ADRIATIC study evaluated durvalumab as a consolidation treatment for LS-SCLC patients who had not experienced disease progression after cCRT (Table 1). Results from the study showed that durvalumab consolidation significantly prolonged overall survival [median OS (mOS): 55.9 vs. 33.4 months; HR 0.73; $p=0.0104$] and progression-free survival [median PFS (mPFS): 16.6 vs. 9.2 months; HR 0.76; $p=0.0161$] compared to placebo (Table 2). The incidence rates of grade 3/4 adverse events (AEs) were similar at 24%, with less than 3% experiencing grade 3/4 pneumonitis across both groups [3]. The ADRIATIC study would be a game-changer, and durvalumab would be a new standard of care for LS-SCLC after concurrent chemoradiotherapy.

While consolidation immunotherapy is the standard treatment for LA-NSCLC patients, its application in patients with a driver gene mutation is still largely unknown. A global retrospective study revealed consolidation with ALK tyrosine kinase inhibitors (ALK-TKI) significantly improved PFS in ALK-positive unresectable LA-NSCLC compared to durvalumab or observation after cCRT ([not reached [NR]] vs. 11.3 months vs. 7.4 months, $p<0.0001$) (Table 2) [4]. Meanwhile, the LAURA study in this year's ASCO meeting demonstrated that consolidation therapy with osimertinib following cCRT in EGFR-mutant locally advanced patients achieved a significantly prolonged median PFS of 39.1 months [5]. In contrast, in the PACIFIC trial, the median PFS of patients with EGFR mutations was 11.2 months. The ongoing

†Di Liu and Leilei Wu contributed equally to this work.

*Correspondence:
Shengxiang Ren
harry_ren@126.com
Yaping Xu
xuyaping1207@163.com
[1]Department of Radiation Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, PR China
[2]Department of Medical Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, PR China

Table 1 Combination studies with radiotherapy and immunotherapy in solid tumors

Cancer type	Stage	Study	Phase	Radiotherapy		Chemotherapy		Reference
				Scheme	Schedule	Scheme	Schedule	
SCLC*	Limited-stage	ADRIATIC	III	CFRT*	60-66 Gy/30fx*, qd* or 45 Gy/30fx, bid*	Concurrent	Etoposide + Platinum Q3W*, 3-4 Cycles	[3]
ALK + NSCLC	Unresectable locally-advanced	-	R*	CFRT	-	Concurrent	Platinum-based#	[4]
NPC*	Locoregionally advanced	BEACON	III	CFRT	PTVnx† 70 Gy/33fx, qd PTVnd† 70 Gy/33fx, qd PTV1† 60 Gy/33fx, qd PTV2† 54 Gy/33fx, qd	Induction-Concurrent	Induction: Gemcitabine + Cisplatin Q3W, 3 Cycles Concurrent: Cisplatin Q3W, 3 Cycles	[7]
NSCLC	Locally advanced	GASTO-1091	II	Hypo-RT*	Hypo-RT (40 Gy/10fx or 30 Gy/6fx) + Hypo-RT-boost (24-30 Gy/6fx), qd	Neoadjuvant-Concurrent	Neoadjuvant: Docetaxel + Cisplatin Q3W, 2 Cycles Concurrent: Docetaxel + Cisplatin QW*	[8]
STS*	III	SU2C-SARC032	II	CFRT	50 Gy/25fx, qd	-	-	[9]
SCLC	Extensive-stage	-	III	-	≥ 30 Gy/10fx, qd or 50 Gy/25fx, qd	Induction	Etoposide + Platinum Q3W, 4-6 Cycles	[11]

*Abbreviation: SCLC = Small-cell Lung Cancer; CFRT = Conventional Fractionated Radiotherapy; fx = fractions; qd = once a day; bid = Two times a day; Q3W = once every 3 weeks; R = Retrospective; NPC = Nasopharyngeal Carcinoma; Hypo-RT = Hypofractionated Radiotherapy; QW = once a week; STS = Soft Tissue Sarcoma

† PTVnx = planning target volumes for primary disease; PTVnd = planning target volumes involved lymph node; PTV1 = planning target volumes (high-risk); PTV2 = planning target volumes (low-risk)

At least 2 doses of concurrent platinum-based chemotherapy and definitive radiation given between 2015–2022

BO42777 trial aims to evaluate the safety and efficacy of multiple targeted therapies compared to durvalumab for patients with unresectable stage III NSCLC [6]. The anticipated results will provide valuable insights into the efficacy of consolidation targeted therapies.

Neoadjuvant immunotherapy plus chemotherapy followed by concurrent chemoradiotherapy and consolidation immunotherapy

Researchers have been exploring immunotherapy as a component of a neoadjuvant strategy to improve survival outcomes in locally advanced tumors. Dr. Mai et al. reported the interim findings from the phase III BEACON study, which compared the efficacy of induction tislelizumab versus placebo combined with chemotherapy (gemcitabine-cisplatin), followed by cCRT and adjuvant tislelizumab or placebo in patients with locoregionally advanced nasopharyngeal carcinoma. The tislelizumab arm demonstrated a significant increase in the complete response rate (CRR) compared to the placebo arm (30.5% vs. 16.7%; $p=0.0006$), meeting the primary endpoint (Table 2) [7]. It is expected that the significant tumor shrinkage effect would be converted into survival benefits.

The GASTO-1091 study enrolled unresectable LA-NSCLC patients who received neoadjuvant docetaxel, cisplatin, and nivolumab followed by hypofractionated cCRT (hypo-cCRT). The hypo-cCRT was administered with a dose of 40 Gy in 10 fractions (fx) or 30 Gy in 6fx, followed by a hypo-cCRT boost of 24-30 Gy in 6fx, resulting in a total dose of 60-64 Gy. Patients without progression or grade ≥ 2 pneumonitis after hypo-cCRT were subsequently randomized to receive nivolumab or undergo observation. The study's primary endpoint was met, with the nivolumab group demonstrating significantly extended PFS compared to the observation group (NR vs. 12.2 months, $p=0.002$) [8]. Notably, the control group in this study had a PFS of 12.2 months, which is substantially longer than the 5.6 months observed in the PACIFIC study's control group. Additionally, both groups exhibited high overall response rates (ORR) with a minor difference (98.8% vs. 97.7%). These findings support further investigation of this innovative modality.

Neoadjuvant immunotherapy plus radiotherapy followed by surgery and adjuvant immunotherapy

A phase II study (SU2C-SARC032) demonstrated a significant enhancement in disease-free survival (DFS) when utilizing neoadjuvant pembrolizumab and radiotherapy (50 Gy/25fx), followed by surgery and adjuvant pembrolizumab (EXP), compared to standard radiotherapy and surgery (SOC) in undifferentiated pleomorphic sarcoma (UPS) and liposarcoma (LPS) (HR 0.57, 90%CI: 0.35-0.91; $p=0.023$) (Table 2). The estimated 2-year DFS

Table 2 Outcomes of clinical trials with radiotherapy and immunotherapy in solid tumors

Treatment Patterns[#]	Patients (*N*[*])	CRR (%)	ORR[*] (%)	median OS (m[*])	median PFS (m)	Grade 3/4 AEs[*] (%)	Reference
cCRT→ColO vs. cCRT	264 vs. 266	-	-	55.9 vs. 33.4	16.6 vs. 9.2	24.4 vs. 24.2	[3]
cCRT→CoTKI vs. cCRT→ColO vs. cCRT	15 vs. 30 vs. 22	-	-	NR vs. NR vs. 70.6	NR vs. 11.3 vs. 7.4	27 vs. 7 vs. 6	[4]
NeIO + CT→cCRT→AdIO vs. CT→cCRT	223 vs. 227	30.5 vs. 16.7	93.3 vs. 90.7	-	-	2.3 vs. 1.3	[7]
NeIO + CT→hcCRT→AdIO vs. NeIO + CT→hcCRT	86 vs. 86	-	98.8 vs. 97.7	-	NR vs. 12.2	10.5 vs. 4.6	[8]
NeIO + RT→Surgery→AdIO vs. RT→Surgery	71 vs. 72	-	-	-	HR 0.57[†]	52 vs. 26	[9]
IO + CT→IO + RT→IOMaint	67	-	71.6	21.4	10.1	58.2	[11]

[#] The treatment patterns observed in the studies are described by the following abbreviations:

IO = Immunotherapy; ColO = Consolidation Immunotherapy; CoTKI = Consolidation TKI; NeIO = Neoadjuvant Immunotherapy; CT = Chemotherapy; AdIO = Adjuvant Immunotherapy; hcCRT = hypofractionated radiotherapy and concurrent chemotherapy; IOMaint = Immunotherapy maintenance. The arrow symbolized subsequent actions

[*] Abbreviation: N = Number; ORR = Objective Response Rate; m = months; AEs = adverse events

[†] The patients in this clinical trial underwent surgery, and therefore disease-free survival (DFS) was used as the evaluation factor. The hazard ratio (HR) of DFS for the two treatment arms was 0.57

rate was higher in the EXP arm (70% vs. 53%) [9]. The superior DFS found in this study would potentially revolutionize the treatment paradigm for these specific cancer types in the future.

However, in terms of the AEs, the incidence of grade ≥ 3 was significantly higher in the EXP arm compared to the SOC arm in this study (52% vs. 26%, $p = 0.002$) (Table 2). Meanwhile, the PACIFIC-2 study evaluated the efficacy and safety of durvalumab in combination with cCRT, followed by consolidation durvalumab, as compared to placebo in patients with LA-NSCLC. The study did not demonstrate a statistically significant improvement in PFS (mPFS: 13.8 vs. 9.4 months, HR 0.85; 95% CI: 0.65-1.12; $p = 0.247$) or OS (mOS: 36.4 vs. 29.5 months, HR 1.03; 95% CI: 0.78-1.39; $p = 0.823$). Moreover, a notably higher percentage of patients experienced adverse events leading to the discontinuation of durvalumab compared to those receiving placebo (25.6% vs. 12.0%) [10], underscoring the importance of vigilant monitoring for potential adverse effects when concurrent combining immunotherapy with radiotherapy.

Sequential radiotherapy after first-line immunotherapy plus chemotherapy for advanced cancer

Local radiotherapy has shown promise in managing metastatic malignancies. Chen et al. reported on the efficacy and safety of sequential thoracic radiotherapy following immunotherapy plus EP/EC (etoposide and cisplatin or carboplatin) as first-line treatment for extensive-stage small-cell lung cancer (ES-SCLC). Among patients who responded to treatment, radiotherapy was administrated at a dose of ≥ 30 Gy/10fx or 50 Gy/25fx. The median OS and PFS were 21.4 months (95%CI: 17.2-NR) and 10.1 months (95%CI: 6.9-15.5), respectively, after a median follow-up of 17.7 months. The one-year and two-year OS rates were found to be 74.1% and 39.7%, respectively, while grade ≥ 3 treatment-related AEs occurred in 58.2% of patients (Tables 1 and 2) [11]. Furthermore, a randomized phase III study on thoracic radiotherapy for ES-SCLC is ongoing, and its results are eagerly anticipated [12].

In conclusion, these results highlighted the importance of combining radiotherapy and immunotherapy in solid tumors. Consolidation immunotherapy following cCRT has demonstrated survival benefits in both LA-NSCLC and LS-SCLC. Meanwhile, neoadjuvant immunotherapy combined with chemotherapy/radiotherapy has shown significant tumor shrinkage effects and might convert to survival outcomes. Additionally, incorporating radiotherapy into first-line treatment for advanced tumors has yielded promising results. However, concurrent immunotherapy and radiotherapy are currently being tested for extremity sarcoma and might not be recommended

off-trial for chest tumors due to the negative results observed in the PACIFIC-2 trial. Further study is needed to elucidate the potential underlying mechanism for proper cooperation of radiotherapy and immunotherapy in the future.

Abbreviations

cCRT	Concurrent chemoradiotherapy
LA-NSCLC	Locally advanced non-small cell lung cancer
LS-SCLC	Limited-stage small-cell lung cancer
OS	Overall survival
PFS	Progression-free survival
AEs	Adverse events
TKI	Tyrosine kinase inhibitors
NR	Not reached
CRR	Complete response rate
hypo-cCRT	Hypofractionated concurrent radiotherapy and chemotherapy
fx	Fractions
ORR	Overall response rates
DFS	Disease-free survival
EXP	Neoadjuvant pembrolizumab and radiotherapy followed by surgery and adjuvant pembrolizumab
SOC	Standard radiation therapy and surgery
UPS	Undifferentiated pleomorphic sarcoma
LPS	Liposarcoma
ES-SCLC	Extensive-stage small-cell lung cancer

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This is not applicable for this summary.

Author contributions
Yaping Xu and Shengxiang Ren designed the study. Yaping Xu, Di Liu, and Leilei Wu drafted the manuscript. Di Liu and Leilei Wu prepared the tables. Di Liu, Leilei Wu, Xiaoling Xu, Shuangyan Yang, Ming Liu, and Min Hu participated in the drafting process. Yaping Xu and Shengxiang Ren revised the manuscript.

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Data availability
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Declarations

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This is not applicable for this summary.

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Competing interests
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