Immunotherapy in unresectable stage III non-small cell lung cancer

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REVIEW

Immunotherapy in unresectable stage III non-small-cell lung cancer: state of the art and novel therapeutic approaches

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The standard of care for patients with stage III non-small-cell lung cancer (NSCLC) is concurrent chemoradiotherapy (CCRT) followed by 1 year of adjuvant durvalumab. Despite the survival benefit granted by immunotherapy in this setting, only 1/3 of patients are alive and disease free at 5 years. Novel treatment strategies are under development to improve patient outcomes in this setting: different anti-programmed cell death protein 1/programmed death-ligand 1 [anti-PD-(L)1] antibodies after CCRT, consolidation immunotherapy after sequential chemoradiotherapy, induction immunotherapy before CCRT and immunotherapy concurrent with CCRT and/or sequential chemoradiotherapy. Cross-trial comparison is particularly challenging in this setting due to the different timing of immunotherapy delivery and different patients' inclusion and exclusion criteria. In this review, we present the results of clinical trials investigating immune therapy in unresectable stage III NSCLC and discuss in-depth their biological rationale, their pitfalls and potential benefits. Particular emphasis is placed on the potential mechanisms of synergism between chemotherapy, radiation therapy and different monoclonal antibodies, and how this affects the tumor immune microenvironment. The designs and questions tackled by ongoing clinical trials are also discussed. Last, we address open questions and unmet clinical needs, such as the necessity for predictive biomarkers (e.g. radiomics and circulating tumor DNA). Identifying distinct subsets of patients to tailor anticancer treatment is a priority, especially in a heterogeneous disease such as stage III NSCLC.

Key words: immunotherapy, locally advanced NSCLC, stage III NSCLC, biomarkers, circulating tumor DNA, radiomics

INTRODUCTION

Stage III non-small-cell lung cancer (NSCLC) accounts for approximately one-third of newly diagnosed NSCLC cases.[1] Stage III comprises a heterogeneous group of patients, for whom dedicated discussion within an experienced multidisciplinary team is mandatory. Even if the definition of unresectability (technical and oncological) may vary between centers, some patients with stage IIIA and very selected ones with stage IIIB-N2 can benefit from surgical multimodality treatment.[2] They were discussed in our previous review.[3] In light of the results of the CheckMate-816 study, chemo-immunotherapy, if approved by health authorities, is now the preferred neoadjuvant therapy in patients with resectable stage III-N2 NSCLC.[4] This approach should not be used to convert upfront unresectable stage III NSCLC to a resectable NSCLC, however, since surgical resectability should be determined at the time of initial diagnosis in a dedicated multidisciplinary tumor board.

The majority of patients with stage III, however, have 'unresectable stage III'. In case of good performance status (PS), their standard of care (SoC) is concurrent chemoradiotherapy (CCRT) completed by 1 year of adjuvant durvalumab.[2,5] In the PACIFIC trial, adjuvant durvalumab after CCRT improved median overall survival (OS) compared with placebo {47.5 versus 29.1 months [hazard ratio (HR) = 0.68]}. Only 1/3 of patients receiving adjuvant durvalumab, however, is alive and disease free at 5 years.[6,7] Retrospective series showed that only half of the patients with stage III NSCLC are treated with radical intent in daily practice, and of those receiving CRT, only 2/3 are treated with CCRT whereas 1/3 received sequential chemoradiotherapy (SCRT).[8-10] Furthermore, not all the patients treated with

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CCRT are eligible for adjuvant durvalumab due to residual toxicity, impaired PS, disease progression and, in the European Union, a programmed death-ligand 1 (PD-L1) level <1%.[8,11,12] For patients not cured with, or not eligible for adjuvant durvalumab, new treatments are urgently needed. Conversely, ~20% of patients are already cured after CCRT and do not need adjuvant durvalumab; identifying those patients would avoid unnecessary durvalumab-related toxicities and societal costs.[12,13] In this review, we present the results of clinical trials investigating immune therapy in unresectable stage III NSCLC, highlighting their pitfalls and potential benefits from a clinical and from a mechanistic point-of-view. The designs and questions tackled by ongoing clinical trials are also discussed. Last, we address open questions and unmet clinical needs, such as the necessity for predictive biomarkers.

CURRENT STATE OF THE ART—ADJUVANT DURVALUMAB

In the phase III PACIFIC trial, 709 patients were randomized (2 : 1) to receive either adjuvant durvalumab or placebo every 2 weeks for up to 12 months after the completion of CCRT [≥2 cycles of platinum-based chemotherapy and 54-66 Gray (Gy) radiotherapy]. The addition of durvalumab resulted in long-term benefit, with 5-year OS and progression-free survival (PFS) rates of 42.9% (versus 33.4% in the placebo arm), and 33.1% (versus 19.0%), respectively.[7] The survival benefit was irrespective of PD-L1 expression level (patients were stratified for PD-L1 expression <25% versus ≥25%). The addition of durvalumab did not seem to result in excessive toxicity; 30% of the patients experienced all-cause grade ≥3 adverse events (AEs) (versus 26% in the placebo arm).[5]

The results of the PACIFIC trial were confirmed in the international, retrospective PACIFIC-R study ($n = 1399$), enrolling patients who received at least one cycle of durvalumab as part of an AstraZeneca-initiated Expanded Access Program (EAP). In some countries, SCRT was also allowed. The median PFS—counted from the first dose of durvalumab—was 21.7 months [95% confidence interval (CI) 19.2-24.5 months] in the full population, 23.7 months (95% CI 20.1-25.8 months) in patients treated with CCRT (77%) and 19.4 months (95% CI 12.4-25.3 months) in patients treated with SCRT (14%). The survival curves of PACIFIC-R resemble the ones of PACIFIC suggesting a similar plateau and long-term benefit, even for patients treated with SCRT.[14] The EAP mandated, however, that patients fulfilled specific eligibility criteria, thus the results are probably comparable only to fit patients in daily clinical practice.

NEW STUDIES EVALUATING IMMUNOTHERAPY FOR UNRESECTABLE STAGE III NSCLC

Several studies are evaluating new strategies to improve survival: different anti-programmed cell death protein 1/programmed death-ligand 1 [PD-(L)1] antibodies after CCRT, consolidation immunotherapy after SCRT, induction immunotherapy before CCRT and immunotherapy concurrent with CCRT and/or SCRT. Cross-trial comparison is particularly challenging in this setting due to the different timing of immunotherapy delivery—before or after CCRT—and the consequent different starting point of PFS and OS assessment, and the difference in patient exclusion criteria. Moreover, within the same approach, windows of accrual were sometimes different (Figure 1). Trials with results available (Table 1) as well as ongoing trials (Table 2) are discussed below.

Consolidation immune therapy after concurrent or sequential CRT

Adjuvant single agent immunotherapy. The single-arm phase II LUN 14-179 trial ($n = 93$) evaluated 1 year of adjuvant pembrolizumab after CCRT in patients with unresectable NSCLC and met its primary endpoint: time to metastatic disease or death was 30.7 months [95% CI 18.7 months-not reached (NR)]. The median PFS was 18.7 months (95% CI 12.4-33.8 months) and the median OS was 35.8 months (95% CI 24.2 months-NR). The estimated 1-, 2-, and 3-year survival rates were 81.2%, 62.0% and 48.5%, respectively.[15] The first data about efficacy of consolidation immunotherapy after SCRT were presented in the phase III randomized, controlled trial (RCT) GEMSTONE-301 ($n = 381$). Patients who had not progressed after either CCRT or SCRT were randomized (2 : 1) to receive consolidation sugemalimab—a fully human anti-PD-L1 immunoglobulin G4 (IgG4)—or placebo, up to 24 months. At the preplanned interim analysis, carried out with a median follow-up of 14 months, median PFS was 9.0 months in the sugemalimab arm compared with 5.8 months in the placebo group (HR 0.64; 95% CI 0.48-0.85; $P = 0.0026$) and 1-year PFS was 45% (versus 25%). PFS benefit was observed in both the SCRT (median PFS 8.1 versus 4.1 months, HR 0.59) and CCRT groups (median PFS 10.5 versus 6.4 months, HR 0.66).[16] In the single-arm phase II open label PACIFIC-6 trial, 120 patients with Eastern Cooperative Oncology Group PS ≤ 2 received adjuvant durvalumab (up to 2 years versus 1 year in PACIFIC), if they did not have progressive disease (PD) after SCRT. The primary endpoint was safety, defined as the incidence of treatment-related AEs (TRAEs) grade ≥3. Overall, 18.8% of patients developed a grade ≥3 AE and 10% of the patients discontinued treatment due to pneumonitis (any grade). Median PFS and median OS were, respectively, 10.9 months (95% CI 7.3-15.6 months) and 25 months (95% CI 25 months-NR). One-year survival was 84.1% (95% CI 75.6% to 89.9%). The reason to use SCRT instead of CCRT (e.g. PS, radiation field, logistics, comorbidities) was not provided for these patients. It should be noted that only 2.6% of the patients enrolled in the study had a PS = 2.[17] Usually patients with PS 0/1 are fit enough to receive CCRT; reasons for receiving SCRT instead of CCRT should be elucidated, since patients receiving SCRT for logistic reasons and patients not fit enough for CCRT comprise two different populations, and it could be that they would derive a different benefit—and different AEs—from immunotherapy. Frailer patients are more prone to develop toxicities during CRT, and we can speculate that their

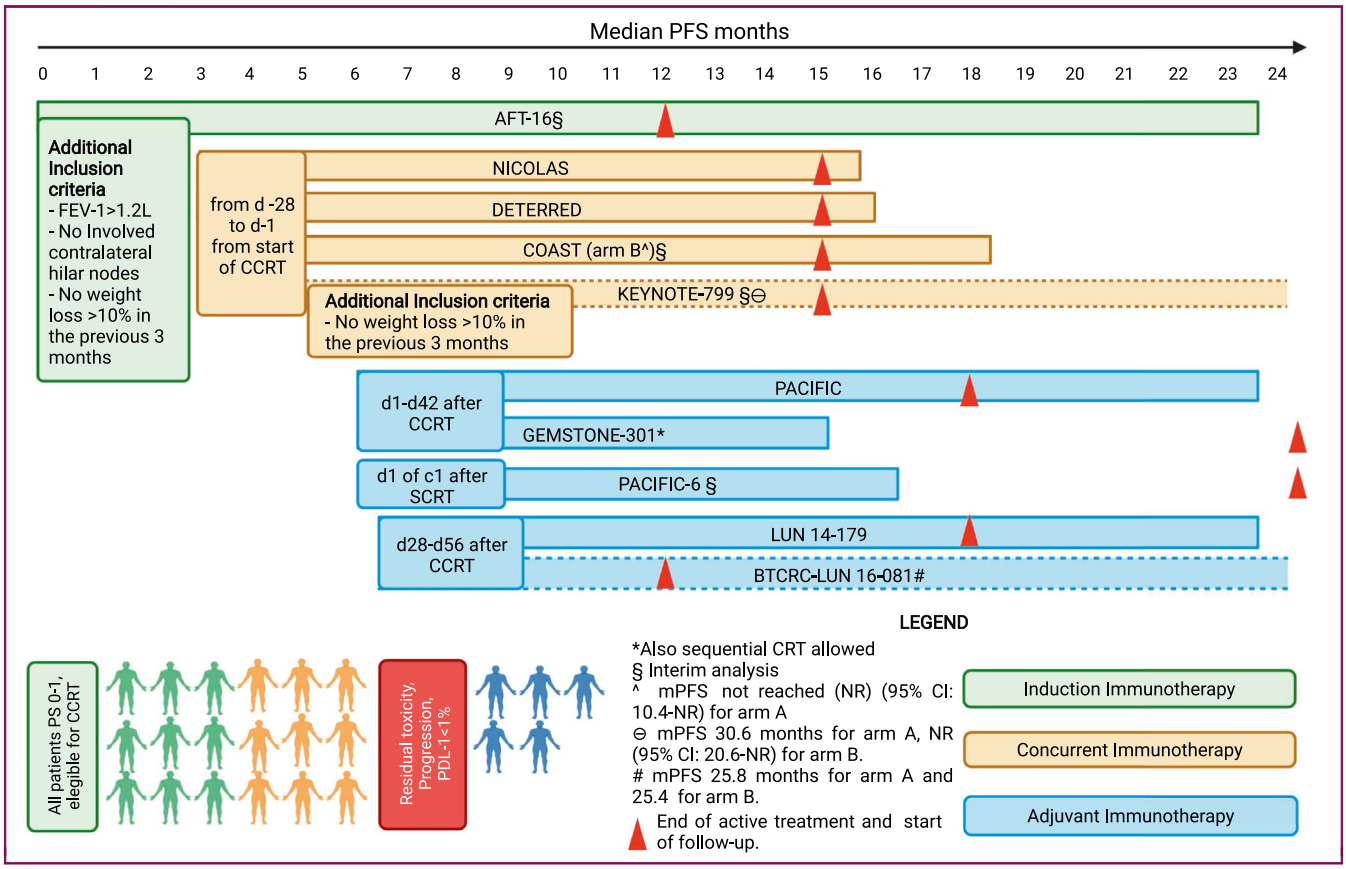

Figure 1. Median progression-free survival (mPFS) of different clinical trials investigating immunotherapy in stage III unresectable NSCLC. General inclusion criteria were the same for every trial (e.g. stage III NSCLC, PS ≤1). Meaningful additional inclusion criteria are reported in the figure. The figure is meant to highlight the difference in PFS calculation among different treatment strategies. It is not meant to suggest the superiority of one trial or treatment strategy over another.
c1, cycle 1; CCRT, concurrent chemoradiotherapy; CI, confidence interval; CRT, chemoradiotherapy; d, day; d1, day 1; FEV1, forced expiratory volume in the first second; NSCLC, non-small-cell lung cancer; PD-L1, programmed death-ligand 1; PS, performance status.
[a]Also sequential CRT allowed.
[b]Interim analysis.
[c]mPFS not reached (NR) (95% CI 10.4 months-NR) for arm A.
[d]mPFS 30.6 months for arm A, NR (95% CI 20.6 months-NR) for arm B.
[e]mPFS 25.8 months for arm A and 25.4 months for arm B.

immune system might be more severely impaired by CRT jeopardizing immunotherapy efficacy.[18] Based on the aforementioned trials and biological evidence, fit patients treated with SCRT might derive meaningful survival benefit from adjuvant immunotherapy, although data for patients with PS = 2 are largely lacking. Studies should be carried out in this patients' population, as well. A limitation of the design of the aforementioned trials—including the PACIFIC trial—is that they did not take into consideration the patients who progressed during CRT or who did not recover from CRT. This also precludes a comparison with survival data from trials evaluating immunotherapy concurrent with CRT.

Adjuvant combination immunotherapy. Combining monoclonal antibodies with complementary mechanisms of action represents another strategy to maximize immunotherapy potential benefit and to overcome resistance to anti-PD-(L)1 antibodies (Figure 2). Another potential major benefit of double checkpoint inhibition may be the chance of a long-lasting response, as seen in stage IV disease.[19-21]

Cytotoxic T-lymphocyte antigen 4 (CTLA-4) counteracts T-cell activation by inhibiting CD80/CD86 co-stimulation by antigen-presenting cells (APCs) in the tumor draining lymph nodes and within the tumor microenvironment (TME).[22-24] The role of CTLA-4 inhibitors in locally advanced NSCLC is particularly appealing since they theoretically might mitigate the immunosuppressive effects exerted by irradiation on the draining lymph nodes.[25] The open-label, randomized phase II BTCRC-LUN 16-081 (NCT03285321) study ($n = 105$) is investigating the combination of nivolumab plus ipilimumab—a human CTLA-4 inhibitor—compared with nivolumab alone after CCRT. In both arms, patients received 6 months of treatment. Primary endpoint is 18 months PFS, which was reached by 63.7% and 67.6% in the nivolumab and nivolumab plus ipilimumab arm, respectively. Median PFS was ~25 months in both arms. In the nivolumab/ipilimumab group, toxicity was higher: 52% versus 38% incidence of grade ≥3 AEs. PD-L1 analyses are pending.[26] Based on these data, there seems no additive value of an anti-CTLA-4 agent in this setting. The CheckMate-73L (NCT04026412) study will hopefully provide a final conclusion, as in this phase III RCT, 888 patients (1 : 1: 1) will be

Table 1. RCTs completed or with preliminary data available in unresectable stage III NSCLC

Study name (Registry number)	Study design	Experimental arm(s)	Treatment duration	Control arm	(Target) accrual	Primary End Point	Results
Consolidation immunotherapy after CCRT or SCRT							
PACIFIC (NCT02125461)	Randomized (2 : 1) phase III	Durvalumab 10 mg/kg i.v. Q2W (after CCRT)	1 Year	Placebo	709	PFS, OS	mPFS = 17.2 versus 5.6 months (HR = 0.51; 95% CI 0.41-0.63) mOS = 47.5 versus 29.1 months (HR = 0.68; 99% CI 0.47-0.9)
PACIFIC-R (NCT03798535)	Retrospective	Durvalumab 10 mg/kg i.v. Q2W (after CCRT/SCRT)	1 Year	Single arm	1399	PFS, OS	mPFS = 21.7 months (95% CI, 19.2-24.5 months)—interim analysis
LUN 14-179 (NCT02343952)	Phase II	Pembrolizumab 200 mg i.v. Q3W (after CCRT)	1 Year	Single arm	93	mTMDD	mTMDD = 30.7 months (95% CI 18.7 months-NR) mPFS = 18.7 months (95% CI 12.4-33.8 months)
GEMSTONE-301 (**NCT03728556**)	Randomized (2 : 1) phase III	Sugemalimab 1200 mg i.v. Q3W (after CCRT/SCRT)	2 Years	Placebo	381	mPFS	mPFS = 9 months versus 5.8 months (HR 0.64; 95% CI 0.48-0.85; P = 0.0026)—interim analysis
PACIFIC-6 (NCT03693300)	Phase II	Durvalumab (after SCRT)	1 Year	Placebo	120	% AEs grade ≥3	mPFS = 10.9 months (95% CI 7.3-15.6 months)
Concurrent immunotherapy with CCRT							
NICOLAS (NCT02434081)	Phase II	CCRT + nivolumab 360 mg Q3W → nivolumab 480 mg i.v. Q4W	1 Year	Single arm	79	Safety	1 year PFS = 53.5% (95% CI 39.9% to 60.1%)
DETERRED (NCT02525757)	Phase II	CCRT + atezolizumab → atezolizumab 1200 mg i.v. Q3W	1 Year	Single arm	52	% of AEs ≥3	AEs grade ≥3 = 80%; irAEs grade ≥3 = 20% mPFS = 13.2 months—interim analysis
KEYNOTE-799 (NCT03631784)	Phase II	CCRT + pembrolizumab → pembrolizumab 200 mg i.v. Q3W	1 Year	Single arm	216	ORR	ORR = 70.5% (95% CI ≈60% to 80%) 1 Year PFS ≈68% mPFS 30.6 months for cohort A (95% CI 16.6 months-NR) NR for cohort B (95% CI 20.6 months-NR)
Induction immunotherapy followed by CRT							
AFT-16 (NCT03102242)	Phase II	Atezolizumab 1200 mg i.v. Q3W × 4 cycles → CCRT → atezolizumab	1 Year	Single arm	64	DCR at 12 weeks	mPFS = 23.7 months (95% CI 13.2 months-NR)—interim analysis
Doublet checkpoint inhibition							
COAST (NCT03822351)	Randomized (1 : 1 : 1) phase II	CCRT → durvalumab 1500 mg i.v. + oleclumab 300 mg i.v. Q4W (arm A) CCRT → durvalumab 1500 mg i.v. Q4W + monalizumab 750 mg i.v. Q2W (arm B)	1 Year	CCRT → durvalumab 1 500 mg i.v. Q4W (arm C)	189	ORR	ORR = 30.0% (95% CI 18.8% to 43.2%) in arm A, 35.5% (95% CI 23.7% to 48.7%) in arm B, 17.9% (95% CI 9.6% to 29.2%) in arm C mPFS = NR (10.4 months-NR) (arm A), 15.1 months (95% CI 13.6 months-NR) arm B, 6.3 months (95% CI 3.7-11.2 months)—interim analysis
BTCRC-LUN 16-081 (NCT03285321)	Randomized (1 : 1) phase II	CCRT → nivolumab 3 mg/kg Q4W + ipilimumab 1 mg/kg Q6W	6 Months	CCRT → nivolumab 480 mg Q4W	108	18 months PFS	mPFS = 25.8 months (95% CI 16.5 months-NR) in the nivolumab arm and 25.4 months (95% CI 18.6 months-NR) in the nivolumab/ipilimumab arm

AEs, adverse events; CCRT, concurrent chemoradiotherapy; CI, confidence interval; DCR, disease control rate; HR, hazard ratio; irAEs, immune related adverse events; i.v., intravenous; mOS, median overall survival; mPFS, median progression free survival; mTMDD, median time to metastatic disease/death; NR, not reached; NSCLC, non-small-cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; RCTs, randomized, controlled trials; SCRT, sequential chemoradiotherapy.

Table 2. Ongoing phase II/III RCTs with immuno-(chemoRT) in unresectable stage III NSCLC

Registry number	Study design	Population	Experimental arm	Control arm	Target accrual	Primary endpoint
Consolidation immunotherapy after CRT (concurrent or sequential) if not PD						
NCT03379441	Phase II, randomized (1 : 1)	CCRT/SCRT	Pembrolizumab 200 mg Q3W i.v. up to 2 years	Follow-up	126	OS
NCT03728556	Phase III RCT (1 : 1)	CCRT/SCRT	CS1001 (anti PDL-L1) up to 2 years	Placebo	381	PFS
NCT04325763	Phase III RCT (1 : 1 : 1)	CCRT/SCRT	Arm A: TQB2450 (anti-PD-L1) + anlotinib Arm B: TQB2450 (anti-PD-L1)	Placebo	315	PFS
NCT03706690 (PACIFIC 5)	Phase III RCT (1 : 1)	CCRT/SCRT	Durvalumab 1500 mg i.v. Q4W until PD	Placebo	400	PFS
Concurrent immunotherapy with CCRT						
NCT03519971 (PACIFIC-2)	Phase III RCT (1 : 1)	All comers	CCRT + durvalumab → durvalumab up to 1 year	CCRT + placebo → placebo	327	PFS
NCT04092283	Phase III RCT (1 : 1)	All comers	CCRT + durvalumab → durvalumab up to 1 year	CCRT + placebo → durvalumab	660	OS
NCT04380636 (KEYLYNK-012)	Phase III RCT (1 : 1 : 1)	All comers	CCRT + pembrolizumab → pembrolizumab CCRT + pembrolizumab → pembrolizumab + olaparib (up to 1 year)	CCRT → durvalumab	870	PFS, OS
NCT04085250	Phase II, randomized (1 : 1)	All comers	CT + nivolumab (2 cycles) → CCRT + nivolumab (1 cycle) → nivolumab up to 1 year	CT + nivolumab (2 cycles) → CCRT + nivolumab (1 cycle) → FU	264	PFS
NCT03840902	Phase III RCT (1 : 1)	All comers	CCRT + M7824 (bintrafusp alpha) → M7824 up to 1 year	CCRT → durvalumab	350	PFS
NCT04765709 (BRIDGE trial)	Phase II	Pts not eligible for radical CCRT due to large tumors	CT + durvalumab → durvalumab + RT → durvalumab up to 2 years	None	65	PFS
Induction immunotherapy						
NCT04776447 (APOLO)	Phase II	All comers	Atezolizumab + CT (3 cycles q21) → CCRT (5 weeks) → atezolizumab up to 1 year	None	51	PFS
NCT04364048	Phase II	All comers	Durvalumab → CCRT → durvalumab to 1 year	None	54	PFS
NCT04230408 (PACIFIC BRAZIL)	Phase II	All comers	Durvalumab 1500 mg q21 days + CT (2 cycles) → CCRT + durvalumab → durvalumab up to 1 year	None	48	PFS
NCT05128630 (DEDALUS)	Phase II	All comers	CT + durvalumab → RT +durvalumab → durvalumab up to 1 year	None	45	Safety
Doublet checkpoint inhibition						
NCT04513925 (Skyscraper-03)	Phase III RCT (1 : 1)	Not progressive after CCRT	CCRT → atezolizumab 1680 mg i.v. + tiragolumab 840 mg i.v. Q4W up to 1 year	CCRT → durvalumab	800	PFS
NCT04026412 (Checkmate 73L)	Phase III RCT (1 : 1 : 1)	All comers	CCRT + nivolumab 360 mg Q3W → nivolumab 360 mg Q3W + ipilimumab CCRT + nivolumab 360 mg Q3W → nivolumab	CCRT → durvalumab	888	PFS, OS

Continued

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Table 2. Continued

Registry number	Study design	Population	Experimental arm	Control arm	Target accrual	Primary endpoint
NCT05221840 (Checkmate-9)	Phase III RCT (1 : 1 : 1)	Not progressive after CCRT	CCRT → durvalumab 1500 mg i.v. + oleclumab 300 mg i.v. Q4W (arm A) CCRT → durvalumab 1500 mg i.v. Q4W + monalizumab 750 mg i.v. Q2W (arm B)	CCRT → durvalumab	999	
NCT04905316 (CHORUS)	Phase II	All comers	CCRT + canakinumab → canakinumab + durvalumab	none	32	PFS
De-escalation strategies						
NCT03523702 (SPRINT)	Non-randomized phase II	PD-L1 ≥50%	Pembrolizumab 200 mg Q3W IV (3 cycles) → RT (60 Gy) → pembrolizumab up to 1 year	CCRT → durvalumab (patients with PD-L1 <50%)	63	PFS
NCT04249362	Phase II	PS 0-2	TRT → durvalumab up to 1 year	None	150	Safety
jRCTs031190070	Phase II	PS of 2 and/or >74 years	RT (60 Gy) + carboplatin daily → durvalumab	None	95	PFS
NCT04351256 (TRADE-hypo)	Randomized phase II (1 : 1)	PS 2 or PS 1 and CCI ≥1 and/or ≥70 years	RT (20 × 2.75 Gy) + durvalumab up to 1 year	RT (60 Gy/30) + durvalumab	88	Safety, ORR
NCT04003246	Phase II	All comers	TRT (60 Gy) + durvalumab → durvalumab up to 1 year	None	50	PFS
NCT03999710	Phase II	All comers	TRT (60 Gy) + durvalumab 1500 mg i.v. Q4W → durvalumab up to 1 year	None	53	PFS

CCI, Charlson comorbidity index; CCRT, concurrent chemoradiotherapy; CRT, chemoradiotherapy; CT, chemotherapy; FU, follow-up; Gy, Gray; i.v., intravenous; NSCLC, non-small-cell lung cancer; OS, overall survival; PD, progressive disease; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PS, performance status; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; Q6W, every 6 weeks; RCT, randomized, controlled trial; SC, subcutaneous; SCRT, sequential chemoradiotherapy; TRT, thoracic radiotherapy.

Studies in resectable stage III, studies enrolling patients with driver mutations and other studies NOT evaluating immunotherapy are not included in the present table.

If not otherwise specified, only patients with Eastern Cooperative Oncology Group PS 0-1 are eligible in the clinical trial.

Studies already presented in Table 1 are not included in this table.

If not otherwise specified, immunotherapy dosages are the following: durvalumab 1500 mg i.v. Q4W; pembrolizumab 200 mg i.v. Q3W; tiragolumab 840 mg i.v. Q4W; atezolizumab 1680 mg i.v. Q4W; CS1001 monoclonal antibody 1200 mg i.v. Q3W; TQB2450 1200 mg i.v. Q3W; M7824 (bintrafusp alpha) 1200 mg i.v. Q2W; ipilimumab 1 mg/kg Q6W; nivolumab 480 mg Q4W; canakinumab 200 mg s.c. Q3W → 200 mg i.v. Q4W.

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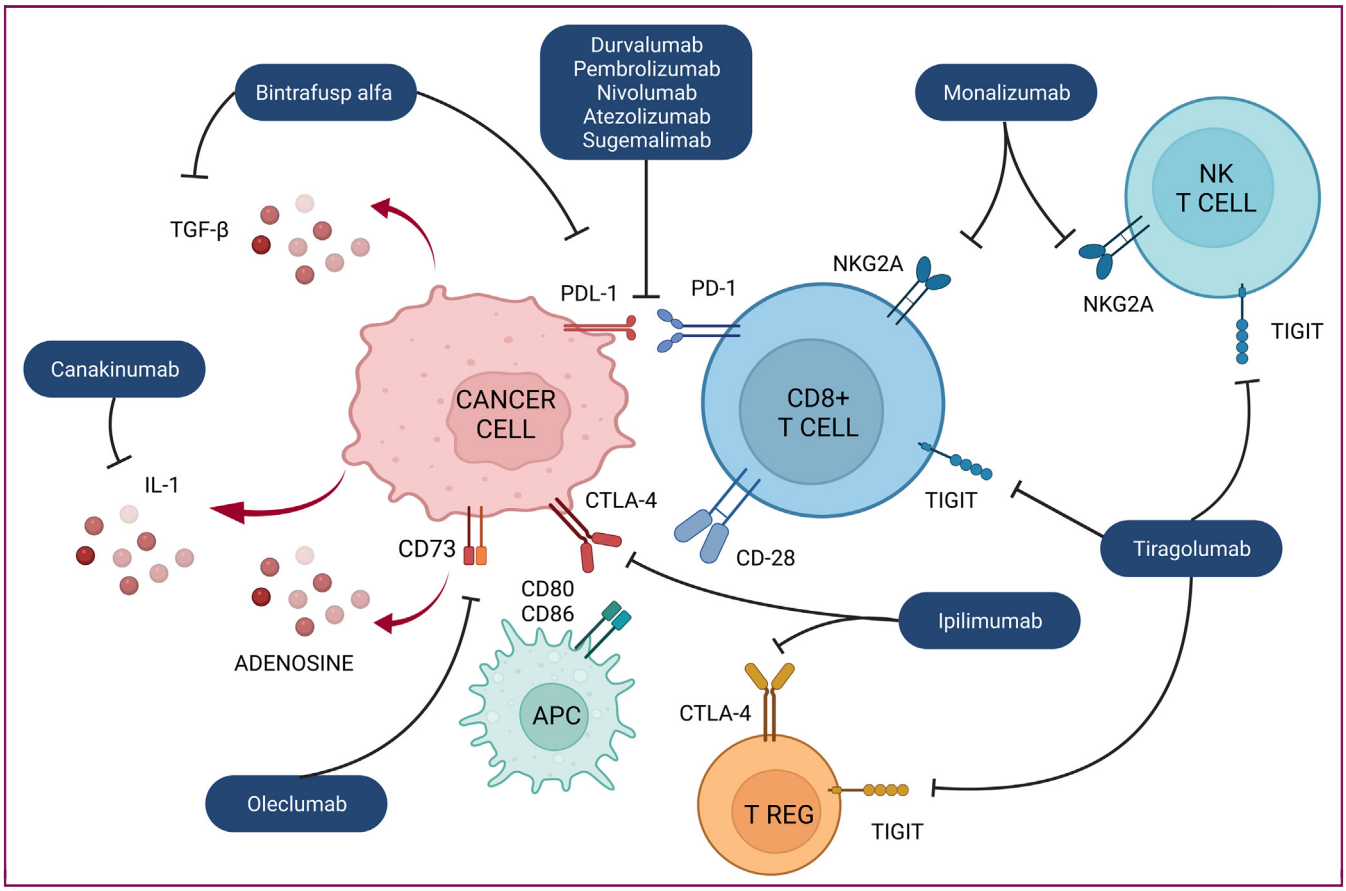

Figure 2. Ipilimumab is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor, which favors the CD80/CD86—CD28 binding and T-cell activation. Pembrolizumab, nivolumab, sugemalimab, durvalumab and atezolizumab are anti-PD-(L)1 antibodies, which block the interaction between PD-L1 and PD-1. Tiragolumab inhibits the T-cell immunoglobulin (Ig) and immunoreceptor tyrosine-based inhibition motif domain (TIGIT), which is expressed on T cells—CD8+, natural killer (NK) and T regulatory cells (Tregs). Monalizumab is an Ig targeting NKG2A receptors on NK and T cells. Oleclumab is an anti-CD73 monoclonal antibody, which promotes antitumor immunity by reducing adenosine levels. Canakinumab blocks IL-1β activity by blocking its interaction with the IL-1 receptor thus enhancing antitumor immune response. Bintrafusp alfa (M7824) is a bifunctional fusion protein targeting TGF-β and PD-L1.
APC, antigen-presenting cells; IL-1, interleukin 1; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TGF-β, transforming growth factor-β.

randomized to receive nivolumab plus CCRT followed by nivolumab plus ipilimumab (arm A), nivolumab plus CCRT followed by nivolumab (arm B) and CCRT followed by durvalumab (arm C). The primary endpoints are PFS and OS (arm A versus arm C).[27]

Extracellular adenosine (eADO) signaling in the TME strongly suppresses both innate and adaptive immune cells, favoring tumor escape. CD73, which converts extracellular adenosine monophosphate to eADO, is a key enzyme in adenosine production and thus an attractive therapeutic target.[28,29] Malignant cells, as well as immunosuppressive stromal and immune cells, express CD73, leading to higher eADO levels in the TME, which have been correlated with poor survival in NSCLC.[30] Oleclumab is an anti-CD73 monoclonal antibody, which promotes antitumor immunity by reducing adenosine levels. NKG2A is an inhibitory receptor expressed on natural killer (NK) and T cells. It is upregulated in response to chronic antigenic stimulation and it has been shown to be present on NK and T cells within the TME, suppressing their activity.[31,32] Its ligand, the nonclassical major histocompatibility complex (MHC) class I molecule HLA-E, is also overexpressed on tumor cells and it contributes to immune escape.[33] Moreover, NKG2A is often co-expressed with PD-1, providing rationale for combining anti-PD-(L)1 with NKG2A inhibition.[33] Monalizumab is an Ig targeting NKG2A receptors. The COAST study (NCT03822351) is a three-arm, randomized (1 : 1 : 1) phase II trial ($n = 189$) investigating the combination of durvalumab with oleclumab (arm A) and with monalizumab (arm B) compared with durvalumab alone (arm C), in patients without disease progression after CCRT. The primary endpoint is overall response rate (ORR) by investigator assessment. ORR was 17.9% (95% CI 9.6% to 29.2%) in the durvalumab arm compared with 30.0% (95% CI 18.8% to 43.2%) and 35.5% (95% CI 23.7% to 48.7%) in the durvalumab plus oleclumab and durvalumab plus monalizumab arms, respectively. The 12-month PFS rate was 62.6% (95% CI 48.1% to 74.2%) with durvalumab plus oleclumab and 72.7% (95% CI 58.8% to 82.6%) with durvalumab plus monalizumab and 33.9% (95% CI 21.2% to 47.1%) with durvalumab alone. The incidences of serious TRAEs, any cause grade $\geq$3 AEs and any grade pneumonitis were similar between treatment arms. In the COAST study, the durvalumab arm heavily underperformed compared with the PACIFIC trial. This might be due to different patient characteristics: 40% of patients in the durvalumab arm were

stage IIIA versus 53% in the PACIFIC and versus 45% and 51% in the experimental arms. Patients with PS = 0 in the durvalumab arm were 45% versus 50% in the PACIFIC and versus 55% in the durvalumab plus oleclumab arm.[34] The T-cell Ig and immunoreceptor tyrosine-based inhibition motif domain (TIGIT) is expressed on T cells—CD8+, NK and T regulatory cells (Tregs)—and it is a negative regulator of T-cell function. Cancer cells and cancer APCs express CD155 and CD112 which bind TIGIT, decreasing activity of T cells.[35] In stage IV NSCLC, atezolizumab plus the anti-TIGIT antibody tiragolumab has improved ORR and PFS compared with atezolizumab and placebo (phase II trial). Activity was particularly pronounced in the PD-L1 ≥50% subgroup (ORR 66% versus 24%).[36] Based on promising early phase trial data, several trials, including those in stage III NSCLC, are evaluating TIGIT inhibition. In the phase III RCT Skyscraper-03 (NCT04513925), 800 patients will be randomized (1 : 1) to atezolizumab plus tiragolumab or SoC durvalumab as consolidation therapy after CCRT.[37] After the first anti-TIGIT enthusiasm, optimism has now decreased, as in the first interim analysis of the phase III RCT Skyscraper-01 (enrolling patients with metastatic PD-L1 ≥50% NSCLC) the addition of tiragolumab to atezolizumab did not improve PFS (co-primary endpoint) although OS data are still immature.[38] Also, in patients with extended disease small-cell lung cancer (SCLC) the addition of tiragolumab to atezolizumab did not provide any PFS benefit.[39] The implications of these results for anti-TIGIT treatment in stage III NSCLC are still not clear, as patients with stage III NSCLC represent a different patient population: compared with stage IV NSCLC they have a lower disease burden and are pretreated with CCRT, and NSCLC biology is different compared with SCLC. A more effective immunotherapy treatment may also allow reduction of the dosages of CCRT and consequent toxicities. This scenario might be more likely in stage III disease since the disease burden is lower compared with stage IV NSCLC.[40] The development of new targets should be coupled with biomarkers research. Mechanistic studies should be the foundation for identifying the patients most likely to benefit from a specific treatment and the resistance mechanism.

Concurrent immunotherapy with CRT

A triplet upfront strategy offers the opportunity to receive immunotherapy to all patients eligible for CCRT. This is meaningful, since ∼5% of patients experience PD during CCRT and up to 30% of patients are reported—historical data and retrospective data—to present with PD at first radiological restaging after CCRT; a percentage that could be lowered by routine use of positron emission tomography-computed tomography (PET-CT) as baseline staging exam.[8,12,41] An upfront strategy would also exploit the potential synergism between chemotherapy and immunotherapy.[42,43] Certain classes of chemotherapeutic agents have been shown to induce immunogenic cell death and to promote antigen presentation, thus enhancing antitumor immune response.[44,45] Platinum derivates, which represent the backbone of CCRT treatment in NSCLC, up-regulate MHC class I expression on APCs.[46] They also deplete myeloid derived stem cells (MDSCs) and Tregs, while increasing T cells and dendritic cells within the TME.[47,48] Conversely, chemotherapy also induces myelosuppression and exerts immunosuppressive effects, such as up-regulating PD-L1 expression on tumor cells.[49] The effects of chemotherapy on the immune system might also be dose-dependent, adding another element of complexity.[50]

The single-arm phase II NICOLAS trial evaluated this concurrent approach for the first time: 79 patients received three cycles of platinum-based chemotherapy, concurrent radiotherapy and, from the second chemotherapy cycle, concurrent nivolumab, followed by consolidation nivolumab for 1 year. The primary endpoint was safety, defined as pneumonitis rate at 6 months after radiotherapy <33%. Overall, 11.7% of patients experienced pneumonitis grade ≥3.[51] The 1-year PFS was 53.7% (95% CI 42.0% to 64.0%); median PFS was 12.7 months (95% CI 10.1-22.8 months); median OS was 38.8 months (95% CI 26.8 months-NR), and 1-year and 2-year OS rates were 75.7% and 63.7%, respectively.[52] The single-arm phase II DETERRED trial ($n = 52$) had a similar design and evaluated atezolizumab—a fully humanized IgG1 monoclonal antibody targeting PD-L1—concurrent with CCRT, followed by consolidation atezolizumab for 1 year. Primary endpoint was safety defined as any grade ≥3, regimen-related—non-hematologic—toxicity. The endpoint was met; 20% of patients experienced grade ≥3 immune-related AEs (irAEs). Pneumonitis grade ≥3 was reported in only one patient (3%) although 'lung infection' grade ≥3 incidence was 13% (versus 1.3% in the NICOLAS trial), and it can be very challenging to differentiate immunotherapy- or radiotherapy-induced pneumonitis from infectious pneumonitis. The median PFS was 13.2 months, 1-year OS was 80% and 1-year PFS was 55%, in line with the NICOLAS findings.[53] The KEYNOTE-799 (NCT03631784) trial, a non-randomized phase II study ($n = 216$), evaluated the anti-PD-1 antibody pembrolizumab concurrently with CCRT followed by consolidation pembrolizumab for 1 year. Patients were divided into arm A (squamous and non-squamous histology) and arm B (non-squamous histology). Pembrolizumab, together with platinum doublet chemotherapy (histology based), was administered from the first cycle; concurrent radiotherapy was delivered from the second cycle. ORR—primary endpoint—was 70.5% (95% CI ≈ 60% to 80%) in both arms. Grade ≥3 TRAEs occurred in 64.3% (arm A) and 50.0% (arm B), with 8% and 6.9% grade ≥3 pneumonitis incidence, respectively. Median PFS was 30.6 months (95% CI 16.6 months-NR) in cohort A and NR (20.6 months-NR) in cohort B, with 2-year PFS rates of 55% and 61%, respectively. The 2-year OS was 64% and 71% in cohorts A and B, respectively.[54] This represents an interesting result as the percentage of patients with stage IIIA NSCLC was lower in the KEYNOTE-799 trial compared with the PACIFIC trial (37% versus 53%). By contrast, in the KEYNOTE-799 trial, additional inclusion criteria were demanded (Figure 1), potentially selecting fitter patients and smaller tumors. The percentage of patients with stage IIIA disease was similar (∼35%) also in the NICOLAS and the DETERRED trials. Hence, different

outcomes of these three trials with largely comparable design are probably due to the phase II design, small sample sizes and slightly different inclusion criteria. Overall, the efficacy of a triplet upfront regimen looks promising, but should be compared with the current SoC within a phase III RCT. Comparison of toxicity within a phase III RCT will also be important, as the incidence of pneumonitis and serious AEs might be increased. Two phase III RCTs are evaluating this strategy: the CheckMate-73L study, which is also evaluating double checkpoint inhibition (discussed in 'Adjuvant combination immunotherapy'), and the KEYLYNK-012 trial. In KEYLYNK-012 (NCT04380636) 870 patients will be randomized (1 : 1 : 1) to receive CCRT with pembrolizumab (arms A and B) followed by pembrolizumab (arm A) or pembrolizumab plus olaparib (arm B), or CCRT followed by adjuvant durvalumab (arm C). PFS and OS are the primary endpoints.[55] KEYLYNK-012 will also evaluate whether the inhibition of poly adenosine diphosphate-ribose polymerase (PARP) can enhance immunotherapy efficacy in this setting. PARPs are crucial to repair single-strand DNA breaks, inflicted by radiotherapy, preventing the generation of DNA double-strand (DS) DNA breaks during cell replication.[56] PARP inhibitor (PARPi) treatment leads to synthetic lethality of tumor cells harboring deficiencies in DS DNA repair pathways, which translates to outstanding outcomes in these tumors.[57] Moreover, in preclinical models, PARPis have been shown to activate the STING pathway, enhancing interferon- γ (IFN-γ) production, and CD4+/CD8+ lymphocytes activity.[58,59] In breast cancer-bearing mice the combination of olaparib and anti-PD-(L)1 inhibitors increased treatment efficacy compared with each agent alone.[60] This combination showed promising disease control rates in patients with germline *BRCA*-mutant ovarian cancer (phase II study, $n = 34$).[61]

Induction immunotherapy followed by CRT

The main perk of this approach is to engage with a healthy immune system, not impaired by chemotherapy and radiotherapy, as could be the case in an adjuvant approach.[18] Preclinically, a more robust activation of the immune system translated in more effective immune surveillance against micrometastatic disease.[62] An intact tumor itself might imply more neoantigens for priming the immune system.[63] Both chemotherapy and radiotherapy induce lymphopenia by directly killing circulating lymphocytes and stem cells.[64] Although radiotherapy at conventional dose has also been shown to increase neoantigens, this does not necessarily translate in effective T-cell infiltration, especially if the immune system has already been impaired.[65,66] Moreover, radiotherapy can promote or suppress the immune system depending on its dose to the tumor, timing and radiation dose to organs involved in mounting the immune response, such as draining lymph nodes. The interplay between radiotherapy and the immune system is shown in Figure 3.[67-72] In the phase II AFT-16 trial ($n = 64$), patients with stage III NSCLC received two cycles of atezolizumab, then they were restaged and, if not progressive, they received two more atezolizumab infusions followed by CCRT (without atezolizumab). Afterwards, patients received consolidation atezolizumab up to 1 year. If patients experienced PD at the first restaging, they immediately received CCRT. Primary endpoint was disease control rate at 12 weeks (the end of induction atezolizumab). Median PFS was 23.7 months (95% CI 13.2 months-NR), PFS at 1 year and at 18 months was 66% (95% CI 55% to 79%) and 57% (95% CI 45% to 71%), respectively. OS at 18 months was 84% (95% CI 75% to 94%). PFS at 12 months after the completion of CCRT was 78%, which is impressive compared with PACIFIC (12 months PFS = 55%). Although the AFT-16 population was highly selected (Figure 1) the study did not limit the eligibility only to responders to CCRT (as in the PACIFIC). Thirteen grade ≥3 all-cause AEs were reported.[73]

The immunotherapy induction approach may also yield some drawbacks. Platinum chemotherapy potentially works synergistically with immunotherapy and patients who progress during immunotherapy may not be able to receive curative CRT. A neoadjuvant chemo-immunotherapy approach followed by consolidation radiotherapy may be worth investigating.

De-escalation strategies

The toxicity of CCRT combined with the long-term survival reached with immunotherapy in stage IV NSCLC provides reasons to evaluate de-escalation treatment strategies in stage III NSCLC (e.g. replacing the chemotherapy with immunotherapy or lowering the dosages of chemotherapy and radiotherapy). This approach may reduce toxicities, especially in frailer patients, while still offering long-term survival and radical treatment. Although preclinical models showed that even lower radiotherapy dosages may still guarantee local control thanks to concurrent immunotherapy, this approach has not been evaluated yet in humans.[74] Furthermore, reducing or omitting chemotherapy may also jeopardize treatment efficacy.[42,75] Thus, this approach should be reserved, at least for now, to either patients unfit for CCRT and/or to patients most likely to benefit from immunotherapy (e.g. high PD-L1 levels). The phase II SPRINT study (NCT03523702) is evaluating a chemotherapy-free treatment schedule for patients with PD-L1 expression ≥50% ($n = 25$) who received three cycles of induction pembrolizumab followed by radiation and subsequently 12 additional cycles of pembrolizumab. At first interim analysis, 1-year PFS was 73% and 1-year OS was 91%. The study is also enrolling patients with PD-L1 <50% ($n = 38$) receiving SoC. Intriguingly, patients with partial response at the restaging PET-CT after three cycles of induction pembrolizumab ($n = 12$) had a 1-year PFS of 100% compared with 61% in patients with stable disease or PD highlighting the need for investigating early treatment adaptation in this setting.[76] The phase II, non-randomized, NEJ039A study (jRCTs031190070) is evaluating the efficacy of daily carboplatin plus concurrent radiotherapy followed by durvalumab in patients with a PS = 2 and/or who are older than 74 years.[77] In the open-label, randomized phase II TRADE-hypo trial (NCT04351256), patients unfit for

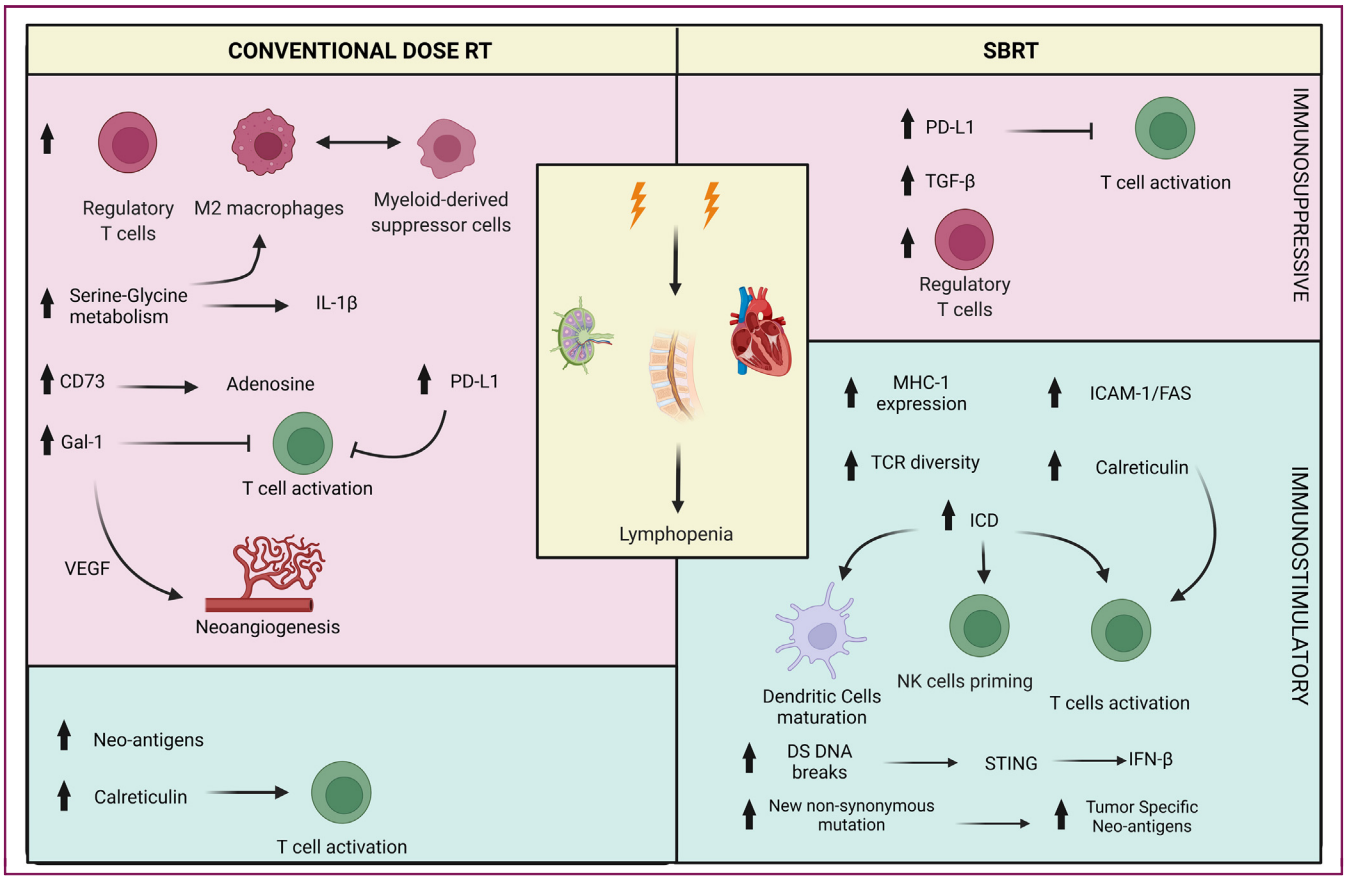

Figure 3. Both conventional dose radiotherapy (RT)—2-2.4 Gy per fraction—and stereotactic body radiation therapy (SBRT)—high dose of radiation per fraction (generally above 6-8 Gy, up to 20 Gy in a single fraction)—induce lymphopenia by directly killing circulating lymphocytes and stem cells.[64] RT increases the secretion of galectin-1 (Gal-1) from tumor cells, resulting in T-cell apoptosis.[67,68] Gal-1 together with vascular endothelial growth factor (VEGF) receptors promote neo-angiogenesis.[69] RT increases also: the serine/glycine metabolism in the tumor microenvironment (TME), resulting in higher levels of interleukin 1β (IL-1β) and M2 macrophages,[72] myeloid-derived suppressor cells in the TME[71] and CD73 expression.[115] Both RT and SBRT increase levels of T-regulatory cells and programmed death-ligand 1 (PD-L1), impairing T-cell activation.[116-118] SBRT increases the transforming growth factor-β (TGF-β) hampering T-cell function.[119] Both SBRT and RT result in neoantigen production and higher expression of calreticulin on the tumor cell surface, enhancing T-cell activation.[18,120] SBRT increases non-synonymous mutation inducing tumor-specific neoantigen development.[116] SBRT promotes the expression of major histocompatibility complex (MHC) class 1 and of immunogenic cell surface markers such as ICAM-1 and Fas, and increases the diversity of T-cell receptor repertoire in the TME.[121,122] SBRT induces immunogenic cell death (ICD), thus promoting the maturation of dendritic cells, T-cell activation and natural killer (NK) cell priming.[123] Cytoplasmic double strand (DS) DNA breaks induced by SBRT activates the stimulator of interferon genes (STING) pathway inducing interferon-β (IFN-β) production.[124]

chemotherapy will receive upfront durvalumab along with conventionally fractionated (30 fractions × 2 Gy) or hypofractionated (20 fractions × 2.75 Gy) thoracic radiotherapy.[78]

IMMUNOTHERAPY IN PATIENTS WITH STAGE III NSCLC HARBORING DRIVER MUTATIONS

Patients with stage IV NSCLC who harbor non-smoking-associated driver mutations, such as *EGFR* exon 19 and 21 mutations and *ALK* and *ROS-1* rearrangements, seldom benefit from immunotherapy.[79] The data regarding the use of immunotherapy in unresectable stage III NSCLC are derived mostly from subgroup analyses and retrospective series. In the PACIFIC trial, 43 patients (6% of the whole population) with *EGFR* mutations were enrolled, precluding firm conclusions, but results were not promising with a PFS HR of 0.84 (95 CI 0.40-1.75) and OS HR of 0.97 (95% CI 0.40-2.33).[5] A multicentre retrospective analysis ($n = 323$, driver mutation cohort $n = 17$) showed a median PFS—counted from the start of durvalumab—of 9 months in patients with *EGFR*-mutated NSCLC and ~8 months in patients with either *BRAF* V600E mutation or *ALK* alterations.[80,81] A multi-institutional retrospective analysis ($n = 37$) showed no statistically significant benefit in patients with *EGFR* mutation treated with durvalumab after CCRT compared with placebo. In addition, 40% of patients suspended durvalumab due to severe irAEs.[82] A retrospective analysis ($n = 20$) of stage III *ALK*-rearranged NSCLC showed no statistically significant benefit for adjuvant durvalumab either.[83] Receiving tyrosine kinase inhibitors during or after immune therapy is also associated with increased toxicity: up to 15% of patients receiving osimertinib after immunotherapy experience severe irAEs and 80% of them required hospitalization (retrospective data).[84,85] Thus, in patients with (common) *EGFR* mutations and *ALK* rearrangements, consolidation immune therapy is not recommended.[86] The randomized phase III *LAURA* trial is investigating the efficacy of adjuvant osimertinib after CCRT in patients with common *EGFR* sensitizing mutations and it will provide evidence on

the benefit of target therapy, instead of immunotherapy, in this setting.[87] Data about the efficacy of immunotherapy for NSCLC with uncommon *EGFR* mutations and other driver mutations (e.g. *MET, RET, HER-2*) in this setting are not existent and strongly needed, since we cannot be satisfied with extrapolating data from the stage IV setting.

PATIENT SELECTION AND PREDICTIVE BIOMARKERS

Ongoing and future trials should aim to differentiate distinct patient subgroups. Currently, the only biomarker guiding the treatment algorithm in stage III NSCLC is PD-L1 $\geq$1%, being highly controversial.[88] Identifying the patients who would benefit the most from a specific treatment or from a specific sequence of treatments is of utmost importance, in light of the different treatment strategies under development. Several studies have demonstrated the negative prognostic impact of the presence of minimal residual disease (MRD)—assessed through circulating tumor DNA (ctDNA)—after radical therapy.[89,90] Moding et al.[91] have shown that patients with stage III NSCLC with undetectable ctDNA after CCRT ($n = 13$) presented a 1-year PFS of 80%, without receiving consolidation immune therapy, and it was not different ($P = 0.23$) from the PFS of patients with undetectable ctDNA who received adjuvant immunotherapy ($n = 12$). Thus, ctDNA might help in identifying patients already cured by CCRT. The kinetics of ctDNA during consolidation immunotherapy predicted the outcome as well.[91] Drawbacks of ctDNA are costs, lack of sensitivity and the fact that not all patients have detectable pretreatment ctDNA.[92] Moreover, the use of different tests with varying sensitivities hinders the comparison of results between studies.[93] In an ongoing clinical trial (NCT04585490), patients MRD negative after CCRT will receive consolidation durvalumab whereas MRD-positive patients will receive durvalumab plus four additional cycles of platinum-based chemotherapy.[94] Considering the drawbacks of MRD, other selection approaches are being investigated. Tumor mutational burden (TMB) and IFN-γ signature were predictive of PFS in stage III melanoma and stage IV NSCLC treated with double checkpoint blockade.[95,96] Several immune cells and proteins are being evaluated for predicting immune-therapy efficacy, but neither a single feature nor more complex 'immunograms' have gathered enough evidence to be implemented in the clinical practice yet and immune profiling remains investigational.[97-99] Importantly, we do not know whether baseline tissue analyses can provide useful information, since CCRT may alter the TME. Performing translational research in locally advanced NSCLC is also challenging due to the paucity of tumor tissue available. Radiomics could overcome this problem: it is a quantitative imaging analysis process and it is a promising tool to identify the patients more likely to relapse, and to dynamically modulate treatment strategy.[100] In retrospective series of patients with stage III NSCLC, radiomics features at baseline were associated with treatment response ($n = 53$), tumor shrinkage ($n = 91$) and PFS ($n = 119$).[101-103] Radiomics on longitudinal imaging—such as CT scans carried out routinely during CCRT—could provide even more accurate prognostic and predictive information without additional costs.[104] Consensus about the best features to investigate, however, is still lacking and before implementing radiomics in the clinic, it should be evaluated prospectively and compared with the current prognostic and predictive gold standard within clinical trials.[100,105]

OPEN QUESTIONS AND FUTURE DIRECTIONS

The PACIFIC trial paved the way for immunotherapy in stage III NSCLC, and ongoing clinical trials promise to broaden the number of patients who will benefit from immunotherapy, and possibly will be cured. Results of phase III studies are needed, however, before changing the current clinical practice. The current duration of 12 months of consolidation immunotherapy after CCRT is also debatable and does not have a solid biological rationale. It will be interesting to compare the data of trials investigating 6, 12 and 24 months of consolidation treatment. Strategies to reduce (pulmonary) toxicity should also be further evaluated. For instance, avoiding upfront triplet therapy or using proton therapy for patients at high risk of toxicity might improve the benefit/risk ratio.[106] Immunological parameters (e.g. cell counts, cytokine levels, HLA type) and radiomics features might identify patients at higher risk.[107-109] If pneumonitis does occur in the context of radiotherapy/immunotherapy-treated NSCLC, management should be optimized. Currently, available clinical and radiological tools are insufficient to differentiate immune- from radiotherapy-induced pneumonitis, sometimes leading to unnecessary discontinuation of immunotherapy. Radiomics holds great promises to aid in making the correct diagnosis.[110,111] Importantly, although translational immunophenotyping studies unravel the underlying mechanisms of immunotherapy-induced pneumonitis, rational immunomodulatory treatment strategies that do not impact tumor surveillance should be pursued.[112-114] Finally, a severe limitation of current ongoing RCTs is that they are not biomarker driven and all unresectable NSCLCs are mixed together in clinical trials. 'Resectability' does not take into account any tumor biological characteristic and might be unrelated to the tumor aggressiveness. In the quest for improving survival outcomes, it is unlikely that a 'one fits all' model represents the solution. A deeper understanding of the tumor biology and behavior, along with biomarker implementation, might revolutionize the way we are treating patients. Identifying distinct subsets of patients to tailor anticancer treatment is a priority and the collaboration between different institutions and stakeholders, along with translational research, is the key for further improving the survival of patients with locally-advanced NSCLC.

MATERIALS AND METHODS

For the present review regarding the most recent development in unresectable stage III NSCLC, an updated literature search strategy was conducted using PubMed (http://www.ncbi.nlm.nih.gov/pubmed) for recent articles. For recent

abstracts we searched the American Society of Clinical Oncology (ASCO) Meeting Library (https://meetinglibrary.asco.org/), the International Association for the Study of Lung Cancer (IASLC) Past Meetings & Webinars collection (https://www.iaslc.org/meetings-webinars/past-meetings-webinars) and the European Society for Medical Oncology (ESMO) Past Meetings collection (https://www.esmo.org/meetings/pastmeetings). The PubMed/Medline database (1990-2022) was searched up until 1 March 2022 using the following search strategies: 'non-small cell lung cancer' and 'locally advanced'/'stage III'/'unresectable'; 'non-small cell lung cancer' and 'immunotherapy'/'checkpoint-inhibitors'. The same criteria were used to search the abstracts presented at the annual ASCO congress (2020-2022), at the Annual ESMO Congress (2020-2021), at the World Conference on Lung Cancer (WCLC; 2020-2022) and at the European Lung Cancer Congress (2020-2022). An additional bibliographic search of recent review articles and directed searches for updated reports of specific studies were also conducted. Full manuscripts and abstracts published or presented, evaluating the efficacy and safety of immunotherapy in stage III unresectable NSCLC, were eligible. The search criteria 'immunotherapy' and 'stage III lung cancer' were used in the clinicaltrials.gov database (https://www.clinicaltrials.gov/). The records were then screened one by one to present the ongoing phase II and III RCTs investigating immunotherapy in unresectable stage III NSCLC.

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