Immunotherapy for locally advanced unresectable non-small cell lung cancer

T. Feys, MSc, MBA[1]

The progress that has been made in the last decades in the treatment of stage IV non-small cell lung cancer (NSCLC) has overall not been translated in the curative setting of stage I to III disease. In fact, the list of failed clinical trials aimed at improving the cure rates in this setting is long. The recent successes with immune checkpoint inhibition in stage IV NSCLC formed the basis to also study these agents in the curative setting. The first clinical trials to yield results in this setting evaluate immune checkpoint inhibition as consolidation treatment following chemoradiotherapy in locally advanced, unresectable NSCLC. The PACIFIC trial demonstrated that consolidation therapy with PD-L1 inhibitor durvalumab significantly prolongs both the progression-free (PFS) and overall survival (OS) compared to placebo in patients with disease control after chemoradiotherapy for stage III unresectable NSCLC. These findings have recently led to the EMA indication of durvalumab as a treatment of locally advanced, unresectable NSCLC patients whose tumors express PD-L1 on ≥1% of tumor cells and whose disease has not progressed following platinum-based chemoradiation therapy. In addition to this, recent phase II data show that consolidation pembrolizumab following concurrent chemoradiotherapy substantially prolongs the time to metastasis or death in patients with inoperable stage III NSCLC. Finally, the phase II ETOP NICOLAS trial demonstrated that the addition of nivolumab to concurrent chemoradiotherapy is safe and tolerable in stage III NSCLC with promising efficacy signals. Together all these data support the further exploration of immune checkpoint inhibition in the curative NSCLC setting. Several trials are currently ongoing, including studies on the potential of adjuvant immune checkpoint inhibition in stage II and IIIA disease and trials in the pre-operative setting.

INTRODUCTION

Approximately one third of patients with NSCLC present with unresectable stage III disease. The treatment of these patients remains one of the major challenges of respiratory oncology, despite gradual progress over the past decades. In the 1980s, patients with unresectable stage III NSCLC were treated with radiotherapy as a single modality, resulting in a median OS of about 10 months. However, a meta-analysis reported by *Aupérin et al.* (N= 1,764) demonstrated that adding cisplatin-based chemotherapy to radiotherapy improved the median OS. In fact, in this analysis, concomitant chemoradiotherapy (CRT) was associated with a 4% survival increase at 2 years compared to radiotherapy alone (median OS 12 vs. 14 months; 2-year OS 21.4 vs. 45.4%, 5-year OS 6% vs. 8.2%).[1] A second meta-analysis (N=1,205), also reported by *Aupérin et al.* later demonstrated the superiority of concurrent CRT over sequential CRT. In this analysis, concurrent CRT was associated with a median OS of 18 months, which was significantly longer than the 14 months seen with sequential CRT (HR[95%CI]: 0.84[0.74-0.95]; p= 0.004).[2] This translates into an increase in the 5-year OS rate of 4.5% (15.1% vs. 10.6%).[2] Based on these studies concurrent cisplatin based chemotherapy (cisplatin-etoposide, cisplatin-vinorelbine) delivered concurrently with radiotherapy has been adopted by ESMO as the recommended treatment for locally advanced, unresectable NSCLC.[3]

[1]Ariez International BV, Ghent, Belgium

Please send all correspondence to: T. Feys; Ariez international BV; Oude Houtlei 118, 9000 Gent; E-mail: t.feys@ariez.com; Tel: +32 (0)479 567890

Conflict of interest: The content of this article was not influenced by third parties.

Keywords: non-small cell lung cancer, NSCLC, curative, inoperable, stage III, immune checkpoint inhibition, durvalumab, nivolumab, pembrolizumab

TABLE 1. Ongoing clinical studies assessing checkpoint inhibitors following concurrent CRT in unresectable, locally advanced NSCLC.

	Primay endpoint	Phase	Sponsor	Name	Register
Durvalumab	**OS/ PFS**	**Ph3**	**Astra Zeneca**	**PACIFIC**	**NCT 02125461**
Nivolumab	**OS/ PFS**	**Ph3**	**RTOG + BMS**	**RTOG 3505**	**NCT 02768558**
Pembrolizumab	**OS/ PFS**	**Ph2**	**Hoosier Group**		**NCT 02343952**
Pembrolizumab	**Safety**	**Ph1**	**Rutgers + MSD**		**NCT 02621398**
Atezolizumab	**Safety / Timing**	**Ph2**	**MD Anderson**		**NCT 02525757**
Nivolumab*	**Safety**	**Ph2**	**ETOP + BM**	**NICOLAS**	**EudraCT 2014-005097-11**

** this trial also has a concurrent immunotherapy part*

Unfortunately, many clinical trials aimed at improving patient outcomes in this setting have failed. In the RTOG 017 study, an attempt to improve local therapy by increasing the RT dose from 60 Gy to 74 Gy did not lead to a better OS (in fact, it proved to be potentially harmful).[4] Also in this study, the addition of the targeted agent cetuximab to concurrent CRT did not improve the survival of patients with unresectable, locally-advanced NSCLC.[4] Researchers also tried to improve the treatment outcome by incorporating other chemotherapy regimens. In PROCLAIM, for example, cisplatin-pemetrexed concurrent with radiotherapy followed by consolidation pemetrexed was not superior to standard CTRT in patients with unresectable locally advanced non-squamous NSCLC (although it was more convenient to give).[5] The good news is that modern approaches emerging in the last years (i.e. modern staging, modern delivery of CRT) significantly raised the bar with CRT. Where the median OS with concurrent CRT in the previously mentioned meta-analysis from 2010 was 18 months (with a 2-year OS rate of 35.6%), the median OS in the control arms of PROCLAIM (cisplatin-etoposide, or cisplatin-pemetrexed) and RTOG 017 (60 Gy arm) ranged from 25 to 28.7 months (with a 2-year OS ranging from 52% to 57.6%).[4-5]

With respect to immunotherapy in locally-advanced, unresectable NSCLC, interesting data were generated with the MUC1 antigen-specific agent tecemotide.[6] The phase III START trial that investigated this agent, did not find a significant improvement in OS when tecemotide was given after CRT in the overall study population of patients with unresectable stage III NSCLC (median OS: 25.6 *vs.* 22.3 months; HR[95%CI]: 0.88[0.75-1.03], p= 0.123). However, in the subgroup of patients who initially received concurrent CRT (N= 806), the addition of tecemotide did lead to a significant 10-month improvement in median OS compared to placebo (median OS 30.8 *vs.* 20.6 months; HR[95%-CI]: 0.78[0.64-0.95]; p= 0.016).[6] Unfortunately, the development of tecemotide was stopped by the manufacturer and we will never know the full potential of this agent.

IMMUNE CHECKPOINT INHIBITION FOR LOCALLY ADVANCED, UNRESECTABLE NSCLC

As indicated earlier, the benefits achieved in stage IV disease in recent years were not translated into a benefit in patients with locally advanced, unresectable NSCLC. To change this situation, several immune checkpoint inhibitors are under evaluation as consolidation therapy following concurrent CRT (*Table 1*).

In the phase III PACIFIC trial, 713 patients with a WHO performance status 0/1 (any PD-L1 status) who received at least 2 cycles of platinum-based CTRT without progression were randomized (2:1) to receive durvalumab 10 mg/kg every two weeks (N=473) or placebo (N=236) for up to 12 months.[7,8] During ESMO 2017, results of a pre-planned interim analysis with 14.5 months of median follow-up demonstrated a median PFS of 16.8 months for patients in the durvalumab arm, which was significantly longer than the 5.6 months median PFS seen in the placebo arm (HR[95%-CI]: 0.52[0.42-0.65]; p< 0.0001). In addition, significantly more patients obtained an ORR with durvalumab than with placebo (28.4% *vs.* 16.0%; RR[95%CI]: 1.78[1.27-2.51]; p< 0.001) and the responses were also more durable with durvalumab consolidation therapy

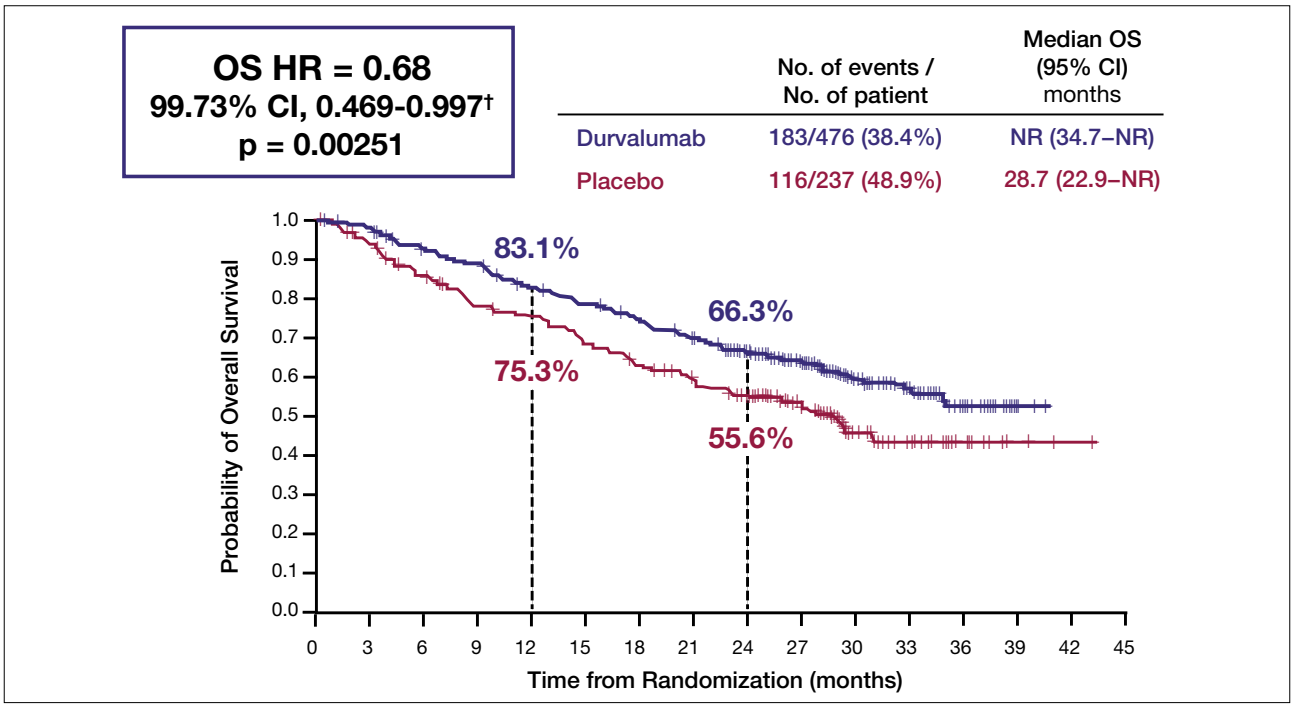

FIGURE 1. Overall survival in the phase III PACIFIC trial.[8]

(median DoR: not reached *vs.* 13.8 months; HR[95%-CI]: 0.43[0.22-0.84]). Durvalumab was also associated with a 48% decrease in the risk of the occurrence of distant metastases or death compared to placebo (median TTDM: 23.2 *vs.* 14.6 months; HR[95%CI]: 0.52[0.39-0.69]; p< 0.0001).[7] At the 2018 world congress on lung cancer (WCLC), PACIFIC also proved to be positive for its second co-primary endpoint of OS. In fact, the OS was significantly better in durvalumab treated patients than was the case for patients in the placebo arm (HR[99.73]: 0.68[0.469-0.997]; p= 0.00251) (*Figure 1*). At 2 years, this OS benefit translated into an absolute 10% increase in the survival rate (66.3% vs. 55.6%).[8,9] Updated results for PFS confirmed the previously reported data with a HR of 0.51 (95%CI: 0.41-0.63). At 18 months, 44% of patients was free of progression. This PFS and OS benefit with durvalumab was seen irrespective of sex, age, smoking status, disease stage, tumor histology, best response to previous treatment (complete response, partial response, or stable disease on CRT) and *EGFR* mutation status.[8,9]

At request of the EMA, an unplanned post-hoc analysis of PACIFIC was performed with a PD-L1 expression-level cut-off of 1%. Of note, PACIFIC was set up as an all-comer study and PD-L1 testing was not required. Consequently, the PD-L1 expression status was unknown for 37% of patients. In patients with a PD-L1 expression in at least 1% of cells, the PFS and OS were significantly improved with durvalumab compared to placebo. However, looking at the subgroup of patients with PD-L1 expression <1%, the PFS was still better with durvalumab (although no longer significant) compared to placebo, but this did not translate into an OS benefit in this patient population.[9] Based on these findings, the EMA granted an indication for durvalumab as monotherapy for the treatment of locally advanced, unresectable NSCLC in adults whose tumors express PD-L1 on ≥1% of tumor cells and whose disease has not progressed following platinum-based chemoradiation therapy.[10]

Overall there was a slight increase in toxicity in the durvalumab arm, but grade 3/4 toxicity was similar between groups (30.5% and 26.1%).[8,9] The treatment discontinuation rate due to adverse events (AEs) was 15.4% with durvalumab and 9.8% with placebo. At the start of the trial there had been much concern that the concurrence of radiation pneumonitis and immunotherapy-induced lung damage might result in unacceptable pulmonary toxicity. However, the safety profile turned out to be quite manageable. Any grade pneumonitis was reported in 33.9% of cases in the durvalumab arm and 24.8% of cases in the placebo arm. However, the incidence of grade 3 or 4 pneumonitis did not significantly differ between both treatment arms (3.6% vs. 3.0%).[8,9] Treatment had to be discontinued due to pneumonitis in 6.3% of patients on durvalumab and in 4.3% on placebo.[8,9]

In addition to PACIFIC, At least five other phase II and III trials with nivolumab, pembrolizumab and atezolizumab are ongoing in this setting (*Table 1*). Also during WCLC 2018, *Durm et al*. presented updated results of the phase II HCRN LUN 14-179 trial, assessing consolidation pembrolizumab following concurrent CRT in patients with unresectable stage III NSCLC. In this trial, 93 patients without progressive disease after CRT received pembrolizumab 200 mg IV q3wk for up to 1 year (starting 4-8 weeks off CRT). The primary endpoint was time to metastatic disease or death (TMDD). The median TMDD reported in this study was 22.4 months (95%CI: 17.9 - not reached [NR]), while the median OS was not yet reached. At 1 and 2 years, the estimates for OS were 81% and 61.9%, respectively. With respect to PFS, a median of 17 months (95%CI: 11.9-NR) was reported with 12, 18 and 24 month PFS rates of 60.2%, 50% and 44.6%, respectively. Overall, 23% of patients experienced pneumonitis, reaching grade 3/4 severity in 5%. There was 1 pneumonitis-related death. No other grade 3/4 toxicities exceeded 5% except dyspnea (5.4%).[11]

The phase II NICOLAS trial the European Thoracic Oncology Platform (ETOP) differs from PACIFIC and LUN 14-179 in a sense that it incorporates immunotherapy (nivolumab) from the start of radiotherapy (i.e. concurrently), with a flat dose of 360 mg every 3 weeks for the first four doses and then followed by a flat dose of 480 mg every 4 weeks up to 1 year from the start of immunotherapy.[12] The primary endpoint of this feasibility trial is grade 3 or higher pneumonitis observed any time during 6 months from the end of radiotherapy, while secondary endpoints include PFS and OS. A such, this trial brings the first data on concurrent use of radiotherapy and immunotherapy in stage III NSCLC.[12] At the time of the analysis presented at ASCO 2018, this single-arm phase II trial included 62 patients with locally advanced stage IIIA or IIIB NSCLC with nodal status N2 or N3, measurable disease and an ECOG performance status 0-1. The cisplatin-based chemotherapy regimen in this study consists of 3 cycles and radiotherapy was given concurrently during cycles 2 and 3 at a physical dose of 60 Gy or more. Nivolumab was initiated at cycle 2 at 360 mg every 3 weeks for 4 doses followed by 4-weekly doses of 480 mg for up to 1 year. The primary endpoint of this study is the pneumonitis-free rate of grade ≥3 during 6 months post radiotherapy, while the 1-year PFS rate was a key secondary endpoint.[12] The safety cohort included 58 patients, who received at least 1 dose of nivolumab (median number of nivolumab cycles was 8, range 1-17). In total, 89.7% of patients experienced an adverse event with a serious adverse event in 41.4%. The most frequently observed adverse events (AEs) were fatigue (41.4%), anemia (41.4%) and nausea (31%). Grade 3 pneumonitis was reported in 10.3% of the patients (all grade pneumonitis 22.4%). The authors concluded that overall the addition of nivolumab to concurrent CRT is safe and tolerable. However, it needs to be said that this 10% grade 3 pneumonitis rate is substantially higher than the 3% and 5% seen in the studies evaluating immune checkpoint inhibition as consolidation therapy after CTRT.[8,9-11,12]

CONCLUSIONS

Following the compelling successes with PD-(L)1 inhibitors in patients with stage IV NSCLC, these agents are now also under evaluation in earlier NSCLC disease stages. In patients with unresectable, locally advanced NSCLC, immune checkpoint inhibitors are currently being evaluated as consolidation therapy after concurrent CTRT. PACIFIC was the first of these studies to yield data and demonstrated a significant PFS and OS advantage with consolidation durvalumab compared to placebo in unresectable NSCLC.[8] In a similar setting, pembrolizumab yielded comparable results (of note in a non-randomized phase II trial).[9] Immune checkpoint inhibition concurrently with CTRT seems to be tolerable in a phase II trial, but efficacy data are not yet available. These data indicate the potential of immune checkpoint inhibition in earlier stage NSCLC.[10] Many clinical trials are still ongoing and their results are eagerly awaited. Especially in the neoadjuvant setting some exciting data have been observed and may further change clinical practice in the setting of non-metastatic NSCLC.

REFERENCES

1. Aupérin A, Le Péchoux C, Pignon JP, et al. concomitant radio-chemotherapy based on platin compounds in patients with LA-NSCLC: a meta-analysis of individual data from 1764 patients. Ann Oncol 2006;17:473-83.

2. Aupérin A, Le Péchoux C, Rolland E, et al. Meta-analysis of comcomitant versus sequential radiochemotherapy in LA-NSCLC. J Clin Oncol 2010;28:2181-90.

3. Vansteenkiste J, De Ruysscher D, Eberhardt W, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24(Suppl 6):vi89-98.

4. Bradley J, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus pacli-

taxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol 2015;16(2):187-99.

5. Senan S, Brade A, Wang L, et al. PROCLAIM: Randomized Phase III Trial of Pemetrexed-Cisplatin or Etoposide-Cisplatin Plus Thoracic Radiation Therapy Followed by Consolidation Chemotherapy in Locally Advanced Nonsquamous Non-Small-Cell Lung Cancer. J Clin Oncol 2016;34(9):953-62.

6. Butts C, Socinski M, Mitchell P, et al. Tecemotide (L-BLP25) versus placebo after chemoradiotherapy for stage III non-small-cell lung cancer (START): a randomised, double-blind, phase 3 trial. Lancet Oncol 2015;15(1):59-68.

7. Paz-Ares L, Villegas A, Daniel D, et al. PACIFIC: A double-blind, placebo-controlled phase III study of durvalumab after chemoradiation therapy (CRT) in patients with stage III, locally advanced, unresectable NSCLC. Presented at ESMO 2017; Abstract LBA1.

8. Antonia S, Villegas A, Daniel D, et al. Overall survival with durvalumab versus placebo after chemoradiotherapy in stage III NSCLC: updated results from PACIFIC. Presented at WCLC 2018; Abstract PL02.01.

9. Antonia S, Vileegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage II NSCLC. N Engl J Med 2018; Epub ahead of print.

10. https://www.ema.europa.eu/documents/smop-initial/chmp-summary-positive-opinion-imfinzi_en.pdf

11. Durm G, et al. Updated Results of a Phase II Trial of Concurrent Chemoradiation with Consolidation Pembrolizumab in Patients with Unresectable Stage III NSCLC. Presented at WCLC 2018; Abstract OA01-07.

12. Peters S, De Ruysscher P, Dafni U, et al. NICOLAS: safety evaluation of nivolumab added concurrently to radiotherapy in a standard first line chemo-RT regimen in unresectable locally advanced NSCLC – the ETOP NICOLAS phase II trial. Presented at ASCO 2018; Abstract 8510.