Approximately one third of all non-small cell lung cancer (NSCLC) patients present with unresectable locally advanced stage III disease. The treatment of these patients remains one of the major challenges of contemporary oncology. During the past three decades, gradual progress has been made in the curative-intent treatment. In the 80-ies, these patients were treated with radiotherapy as a single modality, resulting in a median overall survival (OS) of about 10 months. In a landmark trial in early 90ies, it became clear that adding cisplatin-based chemotherapy to radiotherapy improved median OS from approximately 10 to 14 months (1). Subsequent studies established that concurrent delivery of both modalities further improved median OS by an additional 4 to 18 months, compared with sequential delivery, which corresponded to an absolute 4.5% gain in 5-year OS to 15.1% (2). Based on these results, the concurrent delivery of 60 Gy of chest radiation and two cycles of cisplatin-based doublet chemotherapy is our current standard of care for fit patients with unresectable stage III NSCLC (3).

Strategies to increase survival further have mainly focused on three aspects: (I) improvements in systemic therapy; (II) improvements in radiation therapy; or (III) consolidation of the initial response by maintenance therapy (4).

Regarding the first point, cisplatin-etoposide remained the doublet of choice for many of us, because of the vast experience with it, and as only this regimen can be delivered in full dose concurrently with radiotherapy. More modern doublets with e.g., vinorelbine, paclitaxel, docetaxel, or gemcitabine need a clear dose reduction in concurrent schedules, so the gain of more modern chemotherapy may be offset by the lower dose. There were high hopes that pemetrexed doublets, which have been shown to be one of the most effective regimens in advanced non-squamous NSCLC and which can be safely delivered in full dose concurrent with radiotherapy (5), would be a step forward. This question was addressed in the PROCLAIM trial (ClinicalTrials.gov identifier NCT00686959), the phase III trial comparing cisplatin-etoposide with cisplatin-pemetrexed in this setting. However, hope was in vain. The safety monitoring committee had to stop the inclusion prematurely, because the goal of achieving the primary end point (significantly improved OS with cisplatin-pemetrexed) was deemed impossible. The addition of targeted agents to chemoradiotherapy is also very attractive. However, almost none of the agents that were successful in advanced NSCLC, such as gefitinib, erlotinib, bevacizumab, have made it to phase III trials yet. The best hopes were for the EGFR antibody cetuximab, which was studied in the phase III intergroup trial RTOG 0617 (ClinicalTrials.gov identifier NCT00533949). Hope was in vain, addition of cetuximab to contemporary chemoradiotherapy did not deliver significant benefit in OS (6).

Concerning the radiation therapy, the conviction was that delivery of higher doses in a setting with good quality control would improve OS without worrisome impact on toxicity. This aspect was studied as well in the phase 3 RTOG 0617 trial, comparing standard (60 Gy) and high-dose (74 Gy) radiotherapy. Hope was in vain, and quite unexpectedly, in the setting of chemoradiation for stage III NSCLC, higher dose (74 Gy) proved to be inferior, both in terms of OS and locoregional control (7).
Thirdly, as systemic maintenance therapy was shown to improve OS in advanced NSCLC, several attempts to similarly consolidate the results of the concurrent treatment phase in stage III NSCLC by a maintenance strategy were made. Consolidation with for instance docetaxel or gefitinib has been assessed. Hope was in vain, these strategies did not improve OS rates and tended to result in increased toxicity (8,9). Overall, these data clearly indicate the urgent need for novel therapeutic options in the challenging setting of stage III NSCLC.

New insights in the interaction between tumors and the immune system of the host have led to the development of promising immunotherapies for NSCLC treatment. The term cancer immunotherapy covers any interaction with the immune system to treat cancer, and two quite different approaches can be distinguished (10). The first approach is non-antigen-specific modulation of the immune system, for instance by inhibition of immune checkpoints on T-cells, one of the most promising developments in advanced NSCLC (11). The second approach is antigen-specific immunotherapy or therapeutic cancer vaccination. Tumor vaccines prime the immune system to produce antibodies and effector T-cells specifically directed against tumor-associated antigens.

In a recent issue of *Lancet Oncology*, the results of the phase III, placebo-controlled, randomized *START* trial with the tumor vaccine Tecemotide in the setting after chemoradiotherapy for stage III NSCLC were reported [Stimulating Targeted Antigenic Response To NSCLC, (12)]. Tecemotide is one of the modern vaccines with a relevant antigenic target and a strong immuno-adjuvant and delivery system. The antigenic target is a tandem repeat of 25 amino acids of the core of the MUC1 protein providing antigenic epitopes for T cells (hence its previous name BLP-25). The adjuvant is based on monophosphoryl lipid A, supporting the T-cell response by inducing pro-inflammatory cytokines (via toll-like receptor stimulation). Both components are presented in a liposomal formulation to further enhance the antigen uptake by antigen-presenting cells, thereby stimulating the resulting immune reaction (13). In a previous phase II randomized trial, a signal of prolonged OS in a subgroup analysis of stage IIIIB NSCLC patients treated with Tecemotide versus patients with best supportive care alone had been noted (median OS of 30.6 versus 13.3 months, respectively; HR 0.55, 95% CI: 0.30-1.00), together with excellent tolerability (14). In *START*, patients who had stable or responsive disease after chemoradiotherapy were randomly assigned in a double-blinded fashion (2:1 ratio) to receive Tecemotide vaccine (N=829) or placebo (N=410) weekly for 8 weeks, followed by once every 6 weeks until progression. The primary endpoint was OS, the authors hypothesized to observe a median OS of 20 months in the placebo arm versus an improved median OS of 26 months in the Tecemotide arm. The *START* investigators did not find a significant difference in median OS between patients that received Tecemotide and those that received placebo (25.6 versus 22.3 months, adjusted HR 0.88, 95% CI: 0.75-1.03; P=0.123). Interestingly, they did identify a favorable effect of the vaccine in the predefined large (N=806) subgroup of patients initially treated with concurrent chemoradiotherapy, with a remarkable 10.2 months improvement in median OS (30.8 versus 20.8 months in the placebo group, adjusted HR 0.78, 95% CI: 0.64-0.95; P=0.016). In contrast, patients that had previously been treated with sequential chemoradiotherapy obtained no clinical benefit from Tecemotide. Moreover, Tecemotide was very well tolerated, most reported reactions were grade 1 or 2 local or flu-like reactions. Importantly, there was no increase in severe immune-related adverse events and no increase in (symptoms of) radiation pneumonitis.

Overall, the study hypothesis of the *START* trial was well designed. The median OS estimates in the study hypothesis (20 and 26 months) were somewhat higher in comparison with observations made in contemporary trials in the setting of stage III NSCLC, but the *START* trial only included patients showing at least stable disease after completion of chemoradiotherapy, which supports the higher OS estimates in the *START* study design.

The *START* trial, however, leaves some important questions unanswered. Above all, the reason why Tecemotide was associated with improved OS in patients initially treated with concurrent and not with sequential chemoradiotherapy. As also hypothesized by the authors, differences in the patient’s performance status and tumor characteristics between both subgroups may have influenced the study result. Treatment with concurrent chemoradiotherapy requires a good performance status and usually smaller tumor sizes. Since both of these factors often coincide with better function of the immune system, differences in these variables may indeed have led to the OS benefit with Tecemotide in the concurrently treated subgroup. Variation in the time window between the delivery of radiation and vaccine therapy may also have influenced the effect of Tecemotide across both subgroups. In colon cancer cells, it has e.g., been shown that MUC1 expression is upregulated in the first days after radiotherapy.
and that its expression is higher in a pro-inflammatory microenvironment (15).

When looking at the median survival of patients that were randomized to the placebo arm, there are also some remarkable findings. Firstly, the median OS in the sequential chemoradiotherapy plus placebo arm was higher than in the concurrent chemoradiotherapy plus placebo arm (25 versus 21 months, respectively). This finding is surprising since, as stated before, concurrent delivery of chemo- and radiotherapy has been established as superior to sequential delivery in terms of disease control, which also implies that disease progression is more frequent after sequential chemoradiotherapy. As the START trial only included patients with at least stable disease after initial therapy, the patients in the sequential arm of the START trial likely form a unique subgroup that bares tumors with another (better) biology compared with tumors in the general sequentially treated stage III NSCLC population. Secondly, there is also no clear explanation for the observed difference in OS between the concurrent chemoradiotherapy plus placebo arm of the START study and placebo groups in other contemporary studies in stage III NSCLC [e.g., 28.7 months in the RTOG 0617 trial (7) versus 21 months in the START concurrent chemoradiotherapy plus placebo arm]. However, this may relate to differences in the staging work-up, e.g., the lesser use of PET-CT in the START study (16), leading to more frequent inclusion of patients with subclinical distant metastases. Moreover, some patients in START received what is now considered suboptimal radiotherapy, as the protocol mandated a dose of at least 50 Gy.

As with many oncological treatments, the separation of patients that do benefit from therapy from those who do not by the use of predictive factors is of paramount importance. In that respect, START did not perform very well, mainly due to difficulty of obtaining good tissue samples in stage III NSCLC in general, and certainly after chemoradiotherapy. Plasma samples were available, and in an exploratory analysis antinuclear antibody and soluble MUC1 protein emerged as of potential interest (17).

In summary, the START trial did not meet its overall primary endpoint, but the difference in median OS of about 10 months in the preplanned subanalysis of more than 800 patients with concurrent chemoradiotherapy is remarkable, certainly in the challenging setting of stage III NSCLC, where almost no progress in systemic therapy has been made over the last decade. To confirm the benefit of Tecemotide in patients treated with concurrent chemoradiotherapy, studies now restrict recruitment to this specific patient subgroup. The ongoing phase III INSPIRE trial assesses Tecemotide in Asian stage III NSCLC patients after concurrent chemoradiotherapy [ClinicalTrials.gov identifier NCT01015443 (18)]. Moreover, Tecemotide as maintenance therapy after initial concurrent chemoradiotherapy in stage III NSCLC will be studied in a global confirmatory trial (START 2, ClinicalTrials.gov identifier NCT02049151), which has just started recruitment. The latter trial will be more homogeneous than the previous START trial, as all patients will have concurrent therapy, and as radiotherapy is more standardized according to contemporary guidelines.

Of course, in parallel with confirmatory clinical trials, more fundamental studies assessing the importance of MUC1 in NSCLC, the mechanism of action of Tecemotide, and the interaction between chemoradiotherapy and immunotherapy also need to be performed. Analysis of tissue, preferably before chemoradiotherapy, before the start of Tecemotide and at the time of progression, will be important in this respect. Smaller exploratory trials in dedicated centers may be of additional benefit for this purpose.

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