Editorial

NSCLC – immunogenic after all?

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Hauke Winter and colleagues (1) review the active immunotherapies in non-small cell lung cancer (NSCLC) which they rightly call the deadliest cancer in the world. Defying the efforts of researchers in the field, not a single pivotal trial has achieved a median overall survival (OS) of only one year in advanced NSCLC. Theoretically, cancer immunotherapies could result in long-term survival and hopefully, even cure of cancer patients. Yet, despite the desperate need for life-prolonging therapies in NSCLC, Winter and colleagues count only four randomized phase III trials with active immunotherapies in NSCLC, to which two randomized trials (2,3) with oral talactoferrin (TLF), an activator of dendritic cells leading to antigen-specific T-cell immunity (4,5) in advanced NSCLC could be added. So where does the disparity between therapeutic need and pivotal trials to address this need stem from?

Cancer immunotherapies differ from other therapeutic moieties in that the objective response is inappropriate to determine clinical activity early in development. The phase II trial with TG4010 (6), a vaccine based on modified vaccinia virus Ankara expressing MUC1 and IL-2, highlights the point: TG4010 administered concomitantly with chemotherapy (arm 1) was superior to TG4010 followed by TG4010 plus chemotherapy (arm 2) in terms of objective response. Arm 2 was stopped early according to the minimax design employed, but actually achieved better median overall survival (14.9 vs 12.7 months) and one-year survival (60% vs 53%). As the recent experience with ipilimumab demonstrates, initial progression might be followed by long-term disease stabilization and (complete) regression, possibly resulting in unusually long survival (7). Attributing such effects unambiguously to the cancer immunotherapy under investigation, however, mandates randomized phase II trials with a survival endpoint. Both, the peptide adjuvanted vaccine L-BLP25 (8) and the MAGE-A3 (9) vaccine were thus able to demonstrate clinical activity, i.e. substantial survival advantages, but with 171 and 182 patients, respectively, and years of follow-up, both trials required large financial and temporal investments to do so. The barriers to entry of immunotherapies into further clinical development after phase I are therefore high and put cancer immunotherapy at a competitive disadvantages in the priorization processes within pharma companies.

Selection of the right clinical setting is another challenge. The effect on overall survival of L-BLP25 was only detectable in the patients with NSCLC stage IIIB locoregional disease after chemoradiation, but not in stage IV or IIIB with malignant pleural effusion after chemotherapy alone as first-line therapy. Lower tumor burden after first-line chemoradiation given with curative

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intent, could be one explanation, but it is also conceivable that combined chemoradiation resulted in activation of the immune system, so that subsequent vaccinations might have only augmented a preexisting immune response. Earlier disease stages, such as operable NSCLC stage IB-III wherein MAGE-A3 vaccine is developed, also allow to administer more vaccinations. The phase III trial with SRL172 (10) (killed Mycobacterium vaccae) underlined the importance of frequent vaccinations, since a treatment difference compared to the control arm was only noted in patients with less rapidly progressive disease receiving more vaccinations. A later analysis confirmed this conclusion and additionally demonstrated, that improved survival was only detectable in patients with adenocarcinoma, but not squamous cell carcinoma (11).

A hallmark of the trials summarized in Winter´s review is also that the survival curves in the successful trials do not separate right from the start, but take between 4 and 12 months to diverge. This has also been observed in the Sipeuleucel-T trials (12) that lead to approval for the treatment of prostate carcinoma. Different interpretations are possible: are 4 - 12 months needed to mount sufficient strength of the immune response to deal with the tumor or is late separation a reflection of inability to elicit an immune response in some patients or are there patients whose tumors are resistant to immune attacks? Depending on which of these aspects is dominant, very different consequences for the development of immunotherapies in NSCLC would entail.

In the TGN4010 trial an immune response could be induced in only part of the patients which had a better survival. A positive immune response also indicated better clinical responsiveness in the phase II study with belagenpumatucel-L (13), a vaccine consiting of four different allogeneic NSCLC cell lines incorporating anti-sense modifications that reduce expression of the immunosuppressive TGFβ (transforming growth factor β). At the two highest doses administered, a 15% objective response rate was accompagnied by impressive 1- and 2-year survival rates of 68 and 52% even in patients with advanced disease (stage IIIB, IV) and attributed to the immunosuppressive effects of TGFβ. Alternatively, suppression of TGFβ activity probably shifted the nature of the immune response: TGFβ and IL-6 [involved in therapy resistant NSCLC (14)] push the immune system towards a Th17 response (15) and counteracting TGFβ might have potentially resulted in a more desirable Th1 activation. Interestingly, talactoferrin, which supports Th1 immune responses, also impacted very favourably on survival in patients with advanced NSCLC (16,17) which stresses the importance to better understand the interplay between cancers and the immune system (18,19).

Another common trait in the L-BLP25 phIIb, the SRL172 phase III trial as well as the TLF trials, was the largely improved quality of life recorded with all three different immunotherapies. Improved quality of life is an additional and highly relevant sign of clinical activity or benefit of these immunotherapies that is also relevant for drug approval. Quality of life is also a cornerstone of health technology assessments which will become increasingly important in the future given the financial strains weighing on all healthcare systems.

In all, Winter and colleagues appear right to be optimistic and claim activity of immunotherapies in NSCLC, particularly when factoring in newer, more sophisticated vaccines. However, activity is not equal to successful clinical development and approval, in other words widespread availability of cancer immunotherapies to patients. Schedule, i.e. number and frequency of vaccinations are of major importance, as is the intercalation with existing or novel therapies and selection of the right clinical setting in which to develop the therapy. In the absence of reliable and easy to use biomarkers, that allow to preselect patients or to determine the pharmacodynamic and clinical effects without having to resort to laborious, technically and logistically demanding immunoassays or lengthy controlled trials to make decisions on the clinical development path, this is still a daunting task. In our opinion, making clinical development of cancer immunotherapies successful on a broad scale will therefore require a change of culture that allows to integrate all tools of modern medicine even when the assets are in different hands. We should face up to this challenge, ultimately for the benefit of the patients in desperate need of more effective and not just more expensive therapies.

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