Editorial

Adjuvant immunotherapy in resected early non-small cell lung cancer—battle lost, hopefully not the war!

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Lung cancer is major cancer killer in both sexes (1). In spite of improvements in diagnostic and therapeutic efforts in recent decades, still only a vast minority of patients with non-small cell lung cancer (NSCLC) undergo surgery. In these patients, additional chemotherapy (CHT) is considered a standard of care worldwide (2). Unfortunately, in spite of the lowest possible T and/or N burden of the disease, many people experience relapse, leading to a 5-year survival rates which range from more than 70% for stage IA to less than 25% in stage IIIA NSCLC (3). It is, therefore, not surprising that many efforts have been attempted to improve these figures. Building on recent success of drug therapy in advanced disease, usually labeled as targeted agents, some studies investigated adjuvant use of drugs such as erlotinib or gefitinib, but failed to demonstrate superiority over existing standards of care (4,5). Besides studies which showed the failure of tyrosine kinase inhibitors (TKIs), there were studies investigating the use of the DNA repair marker ERCC1 in adjuvant setting of NSCLC. While initial results were optimistic (6), more recent results were disappointing, leading to suggestion to abandon this research pathway (7-10).

One of the avenues explored in recent years include the use of immunotherapy. Several novel immunotherapeutic strategies have been evaluated in lung cancer such as immune checkpoint inhibition or vaccine therapy. While the former one targets the physiologic mechanisms of immune tolerance co-opted by some tumors, the latter one enables enhanced exposure to tumor antigen. Within the latter group, antigen-specific immunotherapy utilizes vaccines to induce specific antitumor immunity *de novo* against relevant tumor-associated antigens that have been incorporated into the vaccine formulation (11), while tumor vaccines (also known as whole vaccines) represent autologous or allogeneic immunologically active agents which influence the patient's immune system to allow recognition of the tumor as foreign and create *de novo* immunity towards the tumor cells (11,12). In the domain of antigen-specific immunotherapy, melanoma-associated antigen-A3 (MAGE-A3), membrane-associated glycoprotein (MUC-1), recombinant human epidermal growth factor (Cimavax EGF) and Bec2 combined with Bacillus Calmette-Guerin (BCG) have attracted significant research attention, while those in the tumor cell vaccines domain included Belagenpumatucel-L and Tergenpumatucel-L as the most frequently evaluated ones.

More specifically, one of the focuses was upon antigen-specific immunotherapies, designed to enhance T-cell responses against specifically expressed tumor antigens. Initial investigations pointed towards a human gene that encodes MAGE-A3 protein, expression of which ranges 25–50% in non-squamous and squamous cell NSCLC, respectively (13). In a tumor mouse model, the MAGE-A3+AS15 (an immunostimulant) immunotherapy efficiently induced an antigen-specific, functional and long-lasting immune response able to recognize and eliminate MAGE-A3-expressing tumor cells up to several months after the last immunization in mice (14). These results reconfirmed previous clinical data showing that AS15 is preferred immunostimulant (15). In additional, non-clinical safety study, potential local and systemic toxic effects induced by MAGE-A3 recombinant protein combined with AS15 immunostimulant were evaluated in rabbits and cynomolgus monkeys. Single or repeated intramuscular injections were well tolerated (16). In a

clinical setting of NSCLC, safety and immunogenicity of MAGE-A3 with or without adjuvant CHT was tested in patients with resected stage IB to III MAGE-A3-positive NSCLC (17). It was shown to be well tolerated and that it induced MAGE-A3 antigen-specific immune responses. Similarly, a randomized pilot trial confirmed the safety and immunologic effects of a MAGE-A3 protein plus AS15 immunostimulant administered into muscle or into dermal/subcutaneous sites (18). Recently (19), a double-blind, randomized, placebo-controlled phase II study was performed assessing clinical activity, immunologic response, and safety following immunization with recombinant MAGE-A3 protein combined with an immunostimulant (13 doses over 27 months) in completely resected MAGE-A3-positive stage IB to II NSCLC. The primary end point was disease-free interval (DFI). Patients were randomly assigned to either MAGE-A3 immunotherapeutic (n=122) or placebo (n=60). After a median postresection period of 44 months, recurrence was observed in 35% of patients in the MAGE-A3 arm and 43% in the placebo arm. No statistically significant improvement in DFI [hazard ratio (HR), 0.75; 95% CI, 0.46–1.23; two-sided P=0.254], disease-free survival (DFS) (HR, 0.76; 95% CI, 0.48–1.21; P=0.248), or overall survival (HR, 0.81; 95% CI, 0.47–1.40; P=0.454) was observed. Corresponding analysis after a median of 70 months of follow-up revealed a similar trend for DFI and DFS. All patients receiving the active treatment showed a humoral immune response to the MAGE-A3 antigen, although no correlation was observed with outcome. No significant toxicity was observed.

In the just-appearing issue of *Lancet Oncology*, data of the MAGRIT trial in adjuvant setting of adult patients with resected stage IB-IIIA, MAGE-A3-positive NSCLC who did or did not receive adjuvant CHT were fully published (20). This multinational, multi-institutional, double-blind, placebo-controlled trial randomly assigned patients (2:1) to receive 13 intramuscular injections of recMAGE-A3 with AS15 immunostimulant (MAGE-A3 immunotherapeutic) or placebo during 27 months. The primary endpoint was broken up into three co-primary objectives: DFS in the overall population, the no-chemotherapy population, and patients with a potentially predictive gene signature. The final analyses included the total treated population (all patients who had received at least one treatment dose). During the 5-year period, of 13,849 patients screened for MAGE-A3 expression 12,820 had a valid sample and of these, 4,210 had a MAGE-A3-positive tumour. After meeting all eligibility criteria, 2,312 of these were randomly assigned to treatment: 1,515 received MAGE-A3 and 757 received placebo, while 40 were randomly assigned but never started treatment. Seven hundred and eighty-four patients in the MAGE-A3 group also received CHT, as did 392 in the placebo group. Median follow-up was 38.1 months in the MAGE-A3 group and 39.5 months in the placebo group. In the overall population, median DFS was 60.5 months for the MAGE-A3 immunotherapeutic group and 57.9 months for the placebo group (HR, 1.02; 95% CI, 0.89–1.18; P=0.74). Of the patients who did not receive CHT, median DFS was 58.0 months in those in the MAGE-A3 group and 56.9 months in the placebo group (HR, 0.97; 95% CI, 0.80–1.18; P=0.76). Due to the absence of treatment effect, a gene signature predictive of clinical benefit to MAGE-A3 immunotherapeutic could not be identified. Forest plots for DFS in subgroups defined by baseline and treatment variables did not disclose any difference between subgroups investigated. The frequency of grade ≥3 adverse events was equal (16%) between the two treatment groups. The most frequently reported grade ≥3 adverse events were infections and infestations (2% in the MAGE-A3 group and 3% in the placebo group, respectively), vascular disorders (2% *vs.* 3%), and neoplasm (benign, malignant, and unspecified (2% *vs.* 2%).

This trial, which will definitely be considered by many investigators as negative (by all endpoints considered), probably represents the very last clinical investigational effort with MAGE-3 immunotherapeutic. It comes after previous failures with vaccination in NSCLC. In one such attempt (21), L-BLP25 (tecemotide, MUC-1 mucoprotein directed liposomal vaccine) was tested to improve survival in patients with stage III unresectable NSCLC when given as maintenance therapy within the 4–12 weeks after radiochemotherapy before randomisation and received confirmation of stable disease or objective response. No difference in overall survival was seen in this study accompanied with similar toxicity profile (21). In another vaccination study (22), in advanced (stage III/IV) NSCLC, patients who did not progress after platinum-based CHT were randomised to receive maintenance whole tumor cell vaccine belagenpumatucel-L or placebo. Patients were eligible for randomisation between one and four months from the end of induction CHT. Here as well, no difference in either overall survival or progression-free survival was observed between the two treatment groups (22).

Before one combines the findings of the aforementioned studies and forwards vaccination studies to the history shelf, readers are invited to take another look to the three studies

mentioned here in an attempt to get possibly additional and slightly different insight, if not for the sake of speculation. What both locally advanced (21) and advanced (22) NSCLC vaccination studies indicated is that effectiveness of previous treatment (concurrent radiochemotherapy being superior to sequential chemoradiotherapy in locally advanced NSCLC and CHT with radiotherapy in advanced NSCLC) may create favorable setting for vaccination success. If so, why then in a subset of patients with the least tumor burden, i.e., resected early NSCLC this did not work? One of possible explanation, which may also work as hypothesis generation, lies on the fact that 17% of patients in MAGRIT study were of stage IIIA. In them, as forest plot shows, vaccination did not offer anything, while, contrary to that, it offered 11% reduction in progression in patients with stage IB, i.e., those patients having smallest tumors and with no previously existing hilar and/or mediastinal lymph node metastasis. This may, at least partially, be the explanation for the difference in results between initial phase II trial (19) and MAGRIT study (20) having similar study design. Would then, with more patients and only in patients with N0 (and, perhaps, N1?) disease vaccination be more meaningful? This hypothesis may call for more focused research setting since current standards of treatment in stage IB do not include adjuvant therapies at all. Would one also consider immunocompetence of the patients with less tumor burden be less impaired (and, hence, easier to stimulate with vaccination) than that would be the case in cases with bigger tumor burden, another of "food for thoughts" possibilities. Not to be forgotten, too, the distant metastasis-free survival (DMFS) was not one of the endpoints, inclusion of which may have given us better insight into how this cancer immunotherapeutic would act on this, not so frequent event in early stage NSCLC. To that extent, using also local/regional recurrence-free survival as an endpoint would make additional sense in discriminating where, potentially and quite speculatively though, this cancer immunotherapeutic may have preferentially acted. Additional finding which may support consideration of, if not performing further vaccination studies, then perhaps looking deeper into potential causes of their failure, may include success dependent of the time gap between the administration of CHT and vaccination; the shorter it was, the better it was. Again, shorter time likely enabled fewer existing tumor cells to escape vaccination administration and its, subsequent, immunological responses. Interestingly, there was no forest plot regarding the extent of surgery, possibly an important issue since 17% of patients underwent pneumonectomy, likely reflecting the therapeutic need to address bigger tumor burden at presentation. Interesting, too, was the finding of a forest plot of gender subgroups, which seems to contradict general findings in lung cancer with females faring better. Here, placebo worked better in females with a 23% relative increase in DFS, while MAGE-A3 cancer immunotherapeutic worked better in male gender with only a 5% relative benefit in DFS, with total therapeutic difference regarding gender approaching a statistical trend (P=0.15).

While this, additional and quite personal insight into the data of three mature trials, does not aim in changing interpretation of the study findings and, hence, overall picture, it merely brings a few challenging observations and potentially builds on our continuously growing knowledge generation in this field. And the field of immunotherapy of lung cancer is very alive and vital as the data from a number of studies using approaches different from vaccine-based become increasingly available. Inhibitors of Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) such as Ipilimumab have shown efficacy when given sequentially after initial CHT with paclitaxel and carboplatin in a phase II study in metastatic NSCLC (23). Ipilimumab is also being studied in NSCLC in combination with radiation (NCT02239900, NCT02221739) and with other immunotherapy agents (NCT02039674, NCT02174172). Programmed death (PD)-1 inhibitors such as nivolumab showed efficacy in previously-treated NSCLC (24). A number of other PD-1 inhibitors and PDL-1 inhibitors (blocking interaction at the ligand level) are under active investigations. Also, agents that augment co-stimulatory signals are being studied. Ongoing studies are focused on 4-1BB (CD-137), OX40 (CD134), and CD-27 agonists that augment T-cell response, often in combination with checkpoint inhibitors. Combination with CHT has also been attempted due to former having an opportunity increase antigen release from tumor cells, potentially increasing efficacy of immunotherapy. Combination with targeted therapy, however, seems to be more challenging due to unexpectedly high toxicity in other tumor types (25), indicating a specific, rather challenging synergism between the two treatment approaches many see as the significant burden of the learning curve. What we have also been able to learn is that we need more insight of hidden, yet underlying aspects of the immune process which may help in differentiating patients which benefit from various immunotherapies from those that fail. With that regard, biomarker development became an important task.

Prediction for response from checkpoint inhibition (through expression of PD-L1) and investigation of mutational burden (based on hypothesis that a high mutation burden correlates with creation of neoantigens, which may be targets for immune cells activated by checkpoint inhibition), are currently receiving substantial attention. We are, however, at very early stage of using such information (gathered initially with these tasks) to test in a randomized fashion in clinic of lung cancer.

And, that may be the biggest advantage of MAGRIT trial. It entered research arena in a setting not traditionally connected with new drug investigation. Indeed, whenever one drug was tested, it was generally within the domain of metastatic/advanced/recurrent/incurable cancers, including those of lung, too. MAGRIT seems to have broken such unwritten rules and after initial and optimistic/confirmatory results of this immunotherapy pathway started pouring, jumped to adjuvant setting of curable cancer, early stage of NSCLC. Investigators should be commended for such move. In spite of negative results and not so bright future with MAGE-A3 immunotherapeutic, their effort may lead to similar attempts in the future in the rapidly growing field of immunotherapy of (early stage) NSCLC.

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