Editorial

Pembrolizumab and other immunotherapies in patients with extensive-stage small-cell lung cancer—are we entering a new era?

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Introduction

Small cell lung cancer (SCLC) is a very lethal and aggressive subtype of lung cancer, responsible for about 15% of all lung cancers (1). SCLC has a high somatic mutation burden and a strong association to tobacco use (2). In most countries, including Norway, a combination of cisplatin and etoposide has been employed as first line therapy for almost two decades (3-5). In cases of reduced kidney function, cisplatin has often been replaced by carboplatin. Four cycles have been the standard of care and prolonged therapy has not added any survival gain (6). Due to increased toxicity, the addition of granulocyte colony-stimulating factor (G-CSF) has not been recommended (7). Despite the fact that platinum containing regimens have shown high response rates (70–90%) (1,8-11), the prognosis of SCLC has been poor with a 2-year overall survival (OS) of only 5% (1,9,10).

Patients responding on a platinum based regimen (first line setting) and having a good performance status may be offered second line therapy (3,12). Whereas a platinum regimen may be re-implemented in late relapses (>3 months), a combination of adriamycin, vincristine and cyclophosphamide (ACO) has frequently been employed in early recurrence. Topotecan is another alternative and it is the present recommended second line therapy in United States, European Union, and Japan (13-15). Radiotherapy should always be kept in mind as an excellent supplement when palliation is needed.

Despite a response rate of up to 20% in second line therapy, the responses have been of short duration with very limited effect on OS. Consequently, there is an urgent need for new drugs/regimens providing better outcome. During the very last years, various new generation of immunotherapies have got significant attention and promising results have been achieved.

Pembrolizumab, an anti programmed death 1 (PD-1) immunotherapy, in SCLC

PD-1, an immune checkpoint receptor, is primarily expressed on activated T and B cells (1,16). Some tumors exploit the PD-1 pathway by constitutively expressing programmed death ligand 1 (PD-L1) or adaptively upregulating PD-L1 expression to evade immune attack and allowing growth. The PD-1 pathway is therefore a target for cancer immunotherapy. Pembrolizumab is a high-affinity humanized IgG highly selective monoclonal antibody against PD-1 that has shown important clinical activity in multiple tumor types (17). Especially, tumors with membranous PD-L1 expression on more than 50% of tumor cells have shown significant response to pembrolizumab therapy (18,19). Back in 2016, the KEYNOTE-010 study (1) was published and became in several countries a fundament for the implementation of this drug as standard therapy in advanced non-small cell lung cancer (NSCLC). SCLC is also a potential target for checkpoint immunotherapy as PD-L1, B7-H3 and B7-H4 are commonly present in this tumor. This suggests that

immunotherapy agents alone or in combinations may be effective in a subset of these patients (20). However, until recently, no studies exploring pembrolizumab in extensive SCLC have been reported (15).

Ott and colleagues (15) got their work on pembrolizumab in extensive SCLC published in the *Journal of Clinical Oncology* in late 2017. Patients with a PD-L1 expression in ≥1% of tumor cells were available for the study. A total of 163 patients were screened for enrolment and 145 patients had available biopsy samples available for PD-L1 analysis. Forty-six patients (31.7%) tested positive, but 15 out of them did not meet the inclusion criteria and seven were excluded of various reasons. remaining 24 patients for the final analysis. Median age was 60.5 years (41–80 years). The primary endpoints were safety and efficacy, and the objective response rate (ORR) was the primary efficacy endpoint. Pembrolizumab was well tolerated. Only 2 patients (8%) experienced treatment related grade 3–5 adverse events (AEs). Arthralgia, asthenia and rash were the most common adverse effects. The ORR was 33% and one complete remission (CR) (4.2%) was achieved during a median follow-up of 9.8 months (range, 0.5–24 months). The median duration of response was 19.4 months. These figures were impressive as patients had undergone standard therapy (cisplatin and etoposide had been employed as first line therapy in all cases) and most of them (21 of 24 patients) had received two or more regimens prior to inclusion.

Scientific and clinical relevance and beyond

The study of Ott *et al.* (15) is the first study of pembrolizumab in heavily pre-treated extensive stage SCLC. Looking at the primary endpoints, it revealed pembrolizumab a safe and tolerable drug with few serious AEs. This is in accordance with several other studies in various groups of patients (18,21). The finding is promising and should encourage researchers to run larger studies employing pembrolizumab in SCLC.

The ORR of 33% and a median duration of 19.4 months was remarkable. However, some selection criteria should be noticed when considering this finding. Patients selected for the study had a good performance status (ECOG 0 and 1). Furthermore, OS was not the primary endpoint of the study and only 24 patients were enrolled. The group consisted of patients with histologically confirmed SCLC or pulmonary neuroendocrine tumor. However, only one patient had the latter histology and consequently, the findings generally represents the SCLC histology.

Despite the results are impressive, they call for a larger study confirming the ORR, OS and the long lasting response. It is obvious that national health care services and insurers will not base their coverage of pembrolizumab therapy on a single study including only 24 patients. Looking at the median follow-up of 9.8 months, long-term survival data is still too immature to determine its overall impact on the prognosis of SCLC. Knowing the cost of pembrolizumab therapy and its possible budget impact (16), larger studies with efficacy (ORR and OS) as the primary endpoint will be requested. Furthermore, quality of life (QoL) instruments should be implemented, making it possible to clarify quality adjusted life years (QALYs) gained. Consequently, cost-effectiveness analysis should be implemented in future large-scale studies. If not included, transparency will be of utmost importance making details on survival gain available and a possibility for national health care services to indicate QALYs gained. Thus, making it possible to run health technology assessments (HTAs) to clarify whether pembrolizumab should be implemented into national guidelines/standards for the treatment of SCLC (16).

SCLC occurs almost exclusively among heavy smokers. Patients frequently asks their doctors what they can do to improve their own outcome. Various nutrition supplements and non-proven therapies are often on patients' mind in this setting. However, recently it was shown that continuing tobacco smoking during pembrolizumab therapy (KEYNOTE-001) did significantly influence on treatment outcome (communication Hellmann MD, WCLC 2015). When progression free survival (PFS) vary by as much as 50%, depending on smoking status during therapy, it is obvious that patients may add significant life expectancy, simply by quitting smoking. However, this has to be confirmed and published in international medical journals with a peer review system. Consequently, SCLC patients' smoking status should be monitored during immunotherapy in future large-scale studies. From a societal perspective, the spending of millions of dollars to improve and prolong lung cancer patients' lives calls for a cooperation from the patients (stop smoking) to optimize their treatment outcome.

The study by Ott and colleagues (15) documented a long lasting response (median, 19.4 months) and one CR was achieved. In such a setting, long lasting therapies will introduce significant treatment costs to health care insurers and public hospital trusts. Consequently, when to stop therapy when a CR has been achieved, will also be an important issue in future studies.

Other immunotherapies have been tested in SCLC. Both

other PD-1 monoclonal antibodies (in example nivolumab) and monoclonal antibodies that activate the immune system by targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) (in example ipilimumab) have been tested. The latter is a protein receptor that downregulates the immune system. One such major phase III trial included 1,132 and 954 patients received at least one dose of study therapy (NCT01450761) (22). In this study, ipilimumab (10 mg/kg every 3 weeks) versus placebo was tested in combination with standard first-line therapy in extensive stage SCLC. The median OS did not reveal any significant difference (11.0 and 10.9 months) between the two groups. The combined therapy increased toxicity, but did not prolong OS versus chemotherapy alone. The CheckMate 032 study (23) evaluated nivolumab monotherapy along with nivolumab in combination with ipilimumab in pre-treated patients suffering from extensive SCLC. They enrolled patients regardless of PD-L1 status. The ORR rates were 10% (nivolumab 3 mg/kg), 33% (nivolumab 1 mg/kg plus ipilimumab 1 mg/kg), 23% (nivolumab 1 mg/kg plus ipilimumab 3 mg/kg) and 19% (nivolumab 3 mg/kg plus ipilimumab 1 mg/kg), respectively. Combined therapy did also increase toxicity in this study. CheckMate 331 is an ongoing phase III study exploring nivolumab monotherapy for pre-treated advanced SCLC and CheckMate 451 is a phase III, randomized, double-blind study evaluating nivolumab monotherapy or in combination with ipilimumab versus placebo as maintenance therapy after platinum-based first-line chemotherapy in advanced SCLC (24). Primary endpoints include OS and PFS and the trial aims to recruit 810 patients.

The mentioned studies in SCLC indicate that pembrolizumab, nivolumab and ipilimumab are promising new immunotherapies in SCLC (25). In the near future, atezolizumab and durvalumab will probably be added to this list. Atezolizumab is a new checkpoint inhibitor that targets PD-L1. Compared to the mentioned PD-1 inhibitors, it interferes with the interaction between PD-L1 and the PD-1 as well as PD-L1 and B7-1, but does not interfere with the interaction between PD-L2 and PD-1 (2). This could have therapeutic implications when combination therapies are considered. Present data suggests that in SCLC combined PD-1 and CTLA-4 blockade (in example by combining nivolumab and ipilimumab) may produce a higher tumor response rate than PD-1 blockade alone. However, combined therapy is associated with an increased toxicity (22,23). Several large studies are ongoing and combination therapy has shown higher tumor response rates, but the significant ORR in the KEYNOTE-028 study (15), employing single drug pembrolizumab, is remarkable and should be considered carefully when future studies are planned and treatment guidelines are made.

Despite impressive effects of the new generation of immunotherapies, it should be kept in mind that the great majority of SCLC patients still do not respond to PD-1/PD-L1 inhibition. Consequently, a large and growing population have no benefit of these new therapies. In the study by Ott and colleagues (15), less than one-third (31.7%) tested positive for PD-L1 expression. This is half the frequency documented in the KEYNOTE-10 study in NSCLC (1). In NSCLC, the ORR has been shown varying with the cut off level of PD-L1 expressing cells (≥1%, ≥5% or ≥50%). This should also be explored in the SCLC setting. When national health services and public insurers are considering which group of patients should have these costly therapies covered, more details on response rates among various subgroups would be beneficial. Especially, when the cost per QALY is close or above frequently employed cut-off levels, such information may be crucial (16).

In summary, further evaluations are necessary to establish the role, order and optimal combination of immunotherapy in SCLC. Present studies are promising and we may be about to enter a new era for patients suffering from this highly malignant and deadly cancer. Checkpoint inhibitors, especially PD-1/PD-L1 inhibition therapy and CTLA-4 blockage, have shown notable activity in lung cancer and have been approved in the treatment of certain subgroups of patients with NSCLC. The introduction of these new drugs has revolutionized the treatment of NSCLC. Present data indicate that the time for immunotherapy in SCLC is about to come. Ott and co-workers' study (15) indicates single drug pembrolizumab therapy a possible useful therapeutic approach for SCLC. However, it should be kept in mind that the great majority of patients are still not candidates for this new therapy.

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