Second-line treatment options in Non-Small Cell Lung Cancer (NSCLC): report from an International Experts Panel Meeting of the Italian Association of Thoracic Oncology

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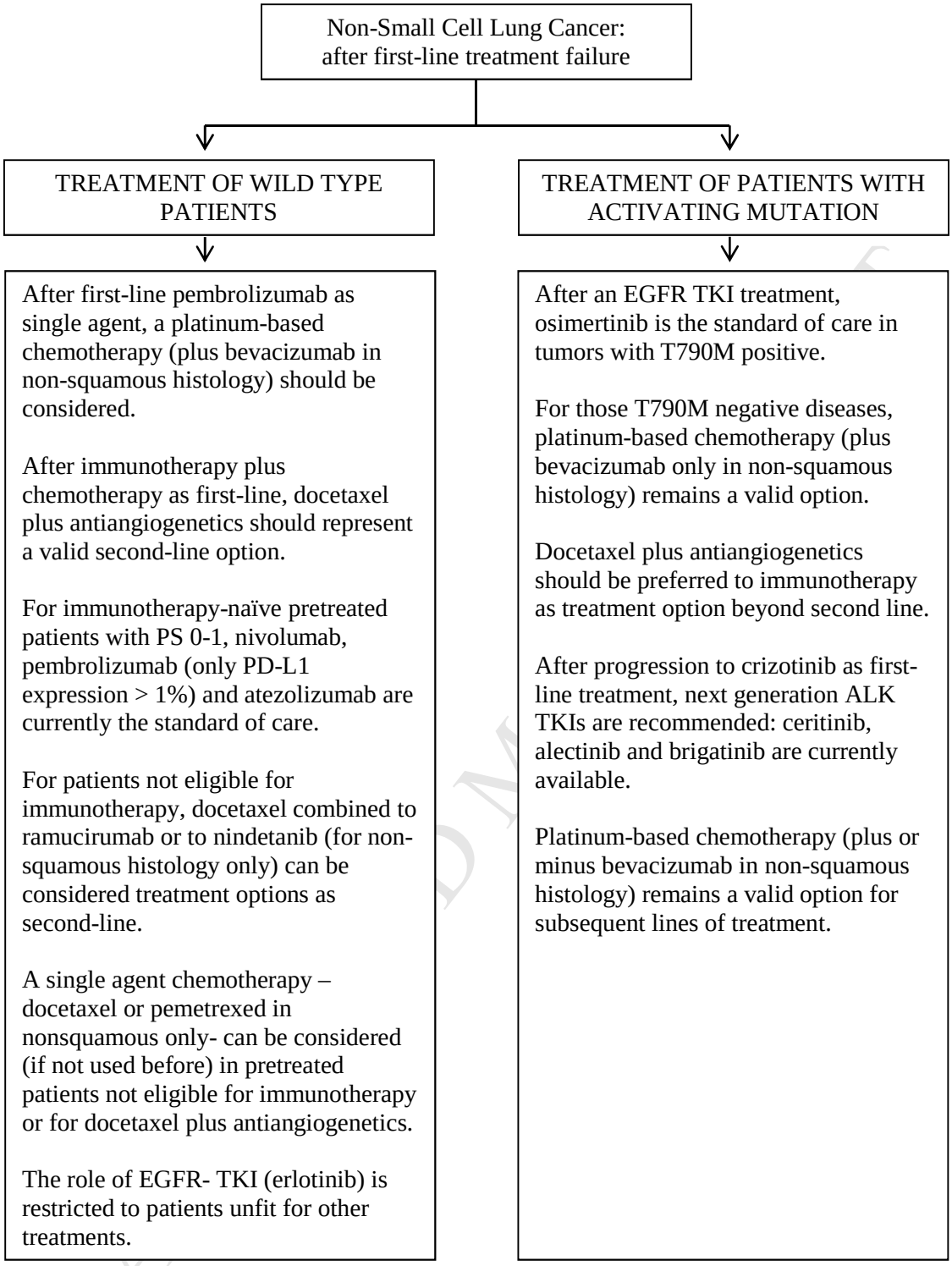

1. INTRODUCTION

Non-small cell lung cancer (NSCLC) represents 85% of all new lung cancer diagnosis and includes different histologic sub-types: adenocarcinoma, squamous cell and large cell carcinoma [1]. The majority of patients had advanced disease at diagnosis and palliative treatments are the standard-of-care. In presence of oncogene-addicted NSCLC, new agents are developed in last decades as first-line, using correspondent inhibitors of epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) and proto-oncogene tyrosine-kinase ROS (ROS1). Without any of those genetic alterations, the standard first line treatment is platinum-based chemotherapy consisting of an induction phase for 4-6 cycles, and of maintenance phase, either switch or continuation maintenance in non squamous histology. Recently the approval of the immune-agent pembrolizumab as first-line treatment for advanced NSCLC patients with PD-L1 tumor proportion score (TPS) ≥50% has expanded therapeutic options for wild type NSCLC patients. Unfortunately, disease progression occurs in all patients and active treatment is needed.

2. MATERIALS AND METHODS

The International Experts Panel Meeting on second-line treatment of NSCLC was held on 12 May 2017, in Sperlonga, Italy. Thirteen medical oncologists (four from Italy, three from the United States, three from France, two from Spain and one from The Netherlands) formed the scientific panel. Published data useful for panel discussion were identified by a PubMed search, performed with combinations of the following search terms: “non-small-cell lung cancer” and “second-line treatments”. Only articles written in English were considered. For the discussion, each panelist selected the references that were considered relevant to the assigned topic. Abstracts presented between 2000 and 2017 at the main international meetings also were searched. The search has been updated for this article with the proceedings of 2017 American Society of Clinical Oncology meeting. Relevant references from selected articles also were included, and other articles were selected from the personal collections of the panelists. The level of evidence and the strength of recommendation have been evaluated according to Center for Disease Control and Prevention grading system [2].

3. TREATMENT OF WILD-TYPE PATIENTS

3.1 Old and new chemo- and antiangiogenetics agents in second-line

Several options are approved as second-line setting or more: docetaxel alone and in combination to ramucirumab or nindetanib (the last one in adenocarcinoma only, but not approved in USA), pemetrexed as single agent for non-squamous histology only.

Firstly, docetaxel was approved as second-line option based on its superiority when compared to supportive care or control regimen (vinorelbine or ifosfamide), nearly 17 years ago [3, 4]. Since then, comparable efficacy outcomes and significantly lower side effects for pemetrexed over docetaxel were reported, with its approval by FDA in 2004 as second line for any histologies firstly, and later narrowed to non-squamous only [5]. However, the median survival remains poor and not longer than eight months, with only one third of patients alive at one year.

The increased responses achieved with the combination of chemo-agents as second line strategies did not correlate to significant improvement of survival outcomes, confirming single agent chemotherapy as the standard for the vast majority of pretreated patients [6]. New interesting combinations of a taxane drug to a vascular endothelial growth factor (VEGF) pathway inhibitor favored over docetaxel alone, with statistically significant but clinically only modest improvement in survival. In particular, the addition of the monoclonal antibody ramucirumab to docetaxel increased responses (objective response rate [ORR]: 22.9% vs. 13.6%) and prolonged progression-free survival (PFS, hazard ratio [HR] 0.76) and small overall survival benefit (OS, HR 0.86) [7]. To note, a small proportion of patients having received bevacizumab in the first line setting were also included. The small OS improvement, although statistically significant, was consistent across histologies, with benefit in both squamous and non-squamous NSCLC patients, given that the study was not stratified accord to histology (in contrast to the majority of bevacizumab studies enrolling squamous only) and not powered to demonstrate survival benefit for each histological subgroup. Interestingly, the effect of ramucirumab plus docetaxel was approximately the same across patients with refractory disease (progression as best response to first-line treatment) and intention to treat population (ITT) [8]. This REVEL trial led to U.S. Food and Drug Administration (FDA) approval of ramucirumab in combination with docetaxel regardless of histological subtype.

Similarly, weekly paclitaxel in combination with bevacizumab confirmed the superiority than docetaxel in pretreated non-squamous patients [9]. Approximately 30% of patients of trial had received bevacizumab as first-line and two previous lines of therapy. The ULTIMATE study met its primary endpoint with a significant improvement of PFS (median PFS: 5.4 vs. 3.9 months for combination and single agent arm, respectively; HR 0.62). The allowed crossover between two arms at progression probably explained the absence of OS benefit (HR 1.18), but demonstrated the benefit of the combination following progression on docetaxel [10]. However, this combination is not approved for use in clinical practice by regulatory agencies.

Nindetanib, a multitarget tyrosine-kinase inhibitor (TKI), in association to docetaxel as second-line improved PFS across histologies of patients enrolled in the LUME-lung 1 trial. The small but significant magnitude of PFS benefit (HR 0.79) was not associated to OS improvement in all population (HR 0.94), but only for adenocarcinoma subgroup, with 2.3 months as increase of median survival (HR 0.83) [11]. Once again, nindetanib remained active in patients with refractory disease, reporting an impressive improvement of median survival more than three months, despite small number of patients at subgroup analysis.

Comparing phase III trials, the magnitude of PFS and OS benefits for non-squamous NSCLC pretreated patients was similar across all three antiangiogenetic agents (ramucirumab, nindetanib and bevacizumab) when added to taxanes. The main issue with an anti-VEGFR therapy is the short duration of benefit, probably due to mechanisms of resistance, above all the activation and the upregulation of alternate pro-angiogenic pathways (such as HIF1α) with a potential shift to an aggressive phenotype of tumor cells.

Another promising prospective consists to use anti-angiogenic drugs targeting VEGF-A/VEGFR in combination with immune-agents, with aim to reduce the immunosuppressive effects of this axis inhibition (restoration of proportion and maturation of dendritic cells, decrease of myeloid-derived-suppressor cells number in tumors, inhibition of Treg accumulation and increase of CD4+ and CD8+ T cells in tumors). Preliminary data from phase Ia study of ramucirumab plus pembrolizumab suggested activity in pretreated patients with solid tumors regardless PD-L1 status [12]. In conclusion, antiangiogenic drugs targeting the VEGF pathway have achieved success in combination with chemotherapy exploiting the concept of "vascular normalization", including antibodies to VEGF-A (bevacizumab as first- and second line) or to VEGFR-2 (ramucirumab as second line) and only one VEGFR-TKI (nintetanib as second line). In the second line setting, there is a consistent improvement of PFS, but modest magnitude of OS benefit, probably due to a short duration of effect, with still no predictive biomarker. Interestingly, the activity maintained in refractory patients, suggesting their role for this subgroup of patients.

3.2 The role of tyrosine-kinase inhibitors in EGFR wild type

After the first approval in 2005 as one of the standards in second-line therapy, in the recent past EGFR-TKIs showed less PFS efficacy in comparison to docetaxel in EGFR wild type patients but saving an advantage in tolerability and quality of life. Analyzing the cost/benefit balance, in the last five years the costs of these drugs were evaluated too high in order to be considered a standard in this setting [13]. To date, erlotinib still represents a potential option in pretreated patients with unknown or wild type EGFR status (not in the USA where is no longer approved by FDA) and

preferably in patients not suitable for chemotherapy, but to date with a very limited use in clinical practice. [14-18]. An additional option could be represented by afatinib, mainly for PS 0-2 patients with locally advanced squamous-cell carcinoma progressing on or after platinum-based chemotherapy but the drug has not been approved by regulatory agencies [14, 19].

3.3 The role of immunotherapy: anti-PD1 and anti-PD-L1 agents

Chemotherapy is no longer standard second-line therapy in most patients with NSCLC. Several immune modulating drugs have been developed, differing about dosing, duration of infusion time and duration of treatment. Two class of drugs have been developed: anti-programmed cell death protein 1 (PD-1) and anti-PD-L1 agents.

- **Anti-PD1 agents: nivolumab and pembrolizumab**

Nivolumab, an immune checkpoint inhibitor that targets PD-1, is currently approved by the U.S. FDA and European Medicine Agency (EMA) as second-line therapy for both squamous and non-squamous advanced NSCLC.

In terms of efficacy, the initial data on Nivolumab came from phase Ib dose-ranging study (CA209-003), where nivolumab as monotherapy at three different doses (1, 3, and 10 mg/kg given intravenously every 2 weeks for < 96 weeks) was administered to 129 heavily pretreated NSCLC patients, mainly as second-/third-line setting. There was reported an ORR of 17%, without major differences between two histologies. To note, the responses were not delayed, occurring at first tumor evaluation (8 weeks) in the half of cases, similarly to chemotherapy responders. If they do happen, responses were long lasting, and the true “pseudo-progressions” were very rare events [20]. Median OS was 9.9 months and an impressive 5-year survival rate of 16% was recently reported, quadrupling the survival rate obtained with standard chemotherapy [21]. These long-term survival rates were consistent across histologies, and more frequently in those patients initially responders to the immune. Concerning the potential predictive role of PD-L1 status, the 5-year survival rates increased according to PD-L1 increasing levels (5-yr OS rate at PD-L1<1%, ≥1% and >50%: 20%, 23% and 43%, respectively), but the lack of adequate samples for PD-L1 assessment in about 50% of patients did not allow its clear validation [21].

Similar activity (ORR: 15%) was assessed in 117 squamous refractory NSCLC patients treated with Nivolumab at 3 mg/kg biweekly as third-line or more (Check-Mate 063). A poor median PFS of two months happened in this unselected population, and no difference of OS between varying degrees of PD-L1 expression in tumor specimen was reported in the exploratory analyses of this small trial [22]. In the squamous phase III Check-Mate 017 trial, nivolumab as second-line

monotherapy improved of three months the median survival (OS as primary endpoint) comparing to docetaxel arm (median OS: 9.2 vs. 6 months with nivolumab and docetaxel, respectively; HR 0.59) [23]. The updated survival data at two years confirmed the fork across the curves, with 25% of patients treated with nivolumab still alive [24]. Analyzing the data in terms of PD-L1 expression levels (predefined subgroups using 1%, 5%, and 10% as cutoff), there was not an impact on the survival outcomes. With similar study design, CheckMate-057 trial was conducted on 582 non-squamous NSCLC patients [25]. In this larger cohort (good PS of 0-1; as second-line after one platinum-based chemotherapy; as third-line allowed only for patients with oncogenic mutated NSCLC), the response rates again improved (ORR: 19% vs. 12% for nivolumab and docetaxel, respectively), consisting with squamous data (ORR: 20%). A relevant impact of PD-L1 status on responses was reported for nivolumab patients, with an ORR over 30% for PD-L1 positive patients, irrespective of cut-off used (1%, 5%, 10%), contrasting to 10% or lower reported in PD-L1 negative. Unlikely squamous population, an absence of PFS improvement was reported (HR 0.92), with more rapid progression observed in the initial nivolumab treatment, but with long term disease control (1yr PFS: 19% with nivolumab and 9% with docetaxel). Although the obvious impact of early progressions on survival curves, the primary endpoint of OS was met, reducing the risk of death of 27% (p=0.0015), with the cross occurring after 6-8 months. Updated survival data at 2-years confirmed the survival benefit (HR 0.75; 2-yr OS: 29% vs 16%) [24]. Higher PD-L1 expression correlated to better survival benefit with nivolumab in term of both PFS and OS, as well as the PD-L1 negativity correlates to shorter PFS (HR range 1.19-1.31) and lower ORR (about 10%) than docetaxel [26]. Although the study was not designed or powered to prospectively evaluate Tumor Proportion Scores, the survival benefit might be started from 10% or more of PD-L1 expression status.

An interesting analysis about clinical data suggested a higher risk of death on nivolumab than on docetaxel therapy in those patients with more aggressive disease (fewer than 3 months since last treatment, progressive disease as the best response to the prior treatment, and PS of 1) when combined with low or no tumor PD-L1 expression. However, cautions for clinical data interpretation is due, considering the limits of the analysis's nature (retrospective, post-hoc and unplanned) and considering that most of patients with worst prognostic factors are not doing well with anything, not only with immunotherapy [27]. Another group of patients not benefiting from nivolumab were those EGFR mutated and never smokers, probably due to lower genomic alterations of those tumor cells, thereby to the negativity of PD-L1 status. Not least, a better toxicity profile of nivolumab than docetaxel was reported (lower frequency of grade 3-4 AEs: 10% vs. 50%; AEs leading to treatment discontinuation: 5% vs. 15%).

Pembrolizumab is approved as treatment for previously treated advanced NSCLC pts with PD-L1 TPS ≥1%, unlike the first-line approval (PD-L1 TPS ≥50%). The anti PD-L1 pembrolizumab (registered dose: 2 mg/kg every 3-weekly) is a fully human monoclonal IgG4 kappa antibody with an impressive half-life of 14-27 days.

The phase Ib Keynote 001 is the first trial evaluating pembrolizumab in 550 advanced NSCLC patients (101 treatment naïve, and 449 pretreated). Recently, three-year survival outcomes of the trial confirmed the efficacy of pembrolizumab for both first-line and previously treated advanced NSCLC patients expressing PD-L1 (26% and 19% alive at 36 months for untreated and pretreated patients, respectively) [28].

The Keynote 010 trial tested two different doses of pembolizumab (at 2 mg/kg and at 10 mg/kg, every 3-weeks) comparing both to docetaxel in PD-L1 positive patients (PD-L1 expression level over than 1%): an improvement of OS was significantly reached in all population (HR 0.71 and 0.61 for 2 mg/kg and 10 mg/kg doses, respectively), as well as in strongly positive patients (PD-L1 more than 50%), with better results in those one (HR 0.54 and 0.50 for 2 mg/kg and 10 mg/kg doses, respectively) [29]. The proportional linkage of pembrolizumab efficacy and PD-L1 TPS was confirmed beyond first-line above all. The superiority of pembrolizumab remains confirmed from updated data after one more year of follow-up, doubling rates of patient survivors at two years and with an apparent plateauing of the OS curves [30].

Recently, exploratory post-hoc multivariate analyses showed that some laboratory (normal baseline lactate dehydrogenase), and tumor characteristics (non-squamous histology, PD-L1 TPS ≥50%, and wild-type EGFR mutation status) were associated with better OS among patients treated with pembrolizumab [31].

Concerning the small sample of 47 patients stopped pembrolizumab after preplanned two years as protocol details, the chance of having progression in the following 9-10 moths is about 4%. If the treatment should keep to continue or not, and if a delayed every four-weeks schedule could be used as maintenance after an induction phase are questions still open [32].

As new combination strategies beyond first-line therapy, preliminary phase I/II results of ECHO-202/KEYNOTE-037 (NCT02178722) were recently presented about epacadostat (an indoleamine 2,3-dioxygenase (IDO)-pathway inhibitor) plus pembrolizumab: the ORR and DCR were 35% (14/40; 14 PR) and 60% (24/40; 10 SD), respectively [32].

- **Anti-PDL1 agents: atezolizumab, durvalumab, and avelumab**

Two main differences are between PD-1 and PD-L1 agents: first, the type of targets firstly (anti-PD-L1 agents inhibit the PD-L1/PD-1 and PD-L1/B7.1 interactions) [33]; second, anti-PD-L1

agents leaves the PD-L2/PD-1 interaction intact, thereby potentially preserving peripheral immune homeostasis, but few preclinical data available to date.

The anti-PD-L1 atezolizumab is the last immune-agent approved as second-line in advanced NSCLC. From phase I trials, different pharmacokinetics profile of atezolizumab resulted from different ethnicity, with longer elimination half-life for Caucasian than Japanese population (21-23 days and 11-13 days, respectively) [33, 34].

The phase II Birch Trial included only patients whose tumors expressed PD-L1 using the SP142 immunohistochemistry (IHC) assay on ≥ 5% of tumor cell membranes (TC) or immune cell membranes (IC), classified as TC2/3 or IC2/3: the efficacy-evaluable patients received atezolizumab at three different lines of treatment (cohort 1 as first-line, cohort 2 as second-line, and cohort 3 as third-line or higher) at the standard dose of 1200 mg intravenously three-weekly. In terms of activity, the ORR reported as first-line treatment (22%) was similar to those reported in subsequent lines (ORR of 19% and 18% for cohort 2 and 3, respectively) with higher responses according to TC3 or IC3 (ORR: 31%, 26%, and 27% for each cohort subgroup, respectively). Responses occurred regardless of EGFR or KRAS mutation status. Median progressions occurred at 2.8 months for two pretreated cohorts, and over 4 months in the favorable subgroup of TC3 or IC3 patients. From an updated survival analysis (minimum of 20 month follow up), the median OS for untreated patients was 23.5 months (26.9 months for TC3 or IC3 patients), while the median OS in two pretreated cohorts was 15.5 and 13.2 months, respectively [35].

The approval by FDA of atezolizumab as second-line options was based on improved survival data from a large phase III randomized clinical trial (OAK), that compared atezolizumab to docetaxel. After the gain in survival of 2.9 months achieved in the randomized phase II POPLAR trial [36], the larger phase III OAK trial enrolled 1225 NSCLC pretreated patients, independently of PD-L1 expression status (centrally evaluated on TCs and ICs with the VENTANA SP142 IHC assay). The survival data about primary population, consisting in the first 850 patients enrolled, were analyzed for the ITT and for PD-L1 positive population (TC1/2/3 or IC1/2/3), both co-primary end-points [36]. For baseline characteristics of the primary population, EGFR mutated patients and those with brain metastases represented about 10%, while squamous patients or those received more than one line of chemotherapy represented one quarter of. After median follow up of 21 months, a significant survival improvement was reached in the ITT population, with a reduction of death risk of 27% (HR 0.73; p=0.0003) and an increase by 4 months in the median OS (13.8 months in the atezolizumab arm vs. 9.6 months in docetaxel arm), while PFS was numerically favorable in docetaxel arm. Concerning 55% of primary population with PD-L1 positive status, survival data were completely comparable (HR 0.74; p= 0.0102), translating in an increase of more than 5

months in the median survival of those patients (median OS: 15.7 months vs. 10.3 months). A significant 25% improvement in survival was reported among those patients with negative PD-L1-expression (TC0 or IC0), differing from nivolumab data, and suggesting benefit irrespective of PD-L1 expression level. The meaning of those PD-L1 negative results have to clarify, considering that the antibody used for IHC (SP142) performed somewhat differently from the three others in use, as established in the Blueprint study [38]. In addition, atezolizumab was more efficacy than docetaxel in all predefined subgroups, reducing the risk of death by 18% to 65%, regardless of how PD-L1 status was assessed (IHC vs. gene expression) and in patients differing with respect to tumor histology, age, smoking status, and presence of central nervous system (CNS) metastases. The lone exception was noted in patients with EGFR mutations, who did not derive any greater benefit than docetaxel (OS HR 1.24), as was seen in trials of other anti PD-1 agents. The same survival benefit derived for different histological subgroups across PD-L1 expression levels (HR 0.73 for squamous and no-squamous): the shape of curves clearly separated at same times, despite longer median OS for no-squamous than for squamous treated with either agent, similarly to other trials of nivolumab and pembrolizumab. In terms of activity, higher PD-L1 expression levels seems to correlate with greater ORR (31% for TC3 or IC3 vs 8% for TC0 and IC0), with no influence on duration of response [39].

The survival benefit of atezolizumab extended beyond radiographic progression is recently supported by phase IIII OAK trial, with a median OS post-progression of 12.7 months for atezolizumab arm compared to 9.7 months for docetaxel arm. This analysis coming from a large cohort (about 50% of atezolizumab arm prolonged the treatment beyond progression) highlighted the inadequacy of RECIST to capture the full clinical benefit of immunotherapy and supports the concept of immuno-treatment beyond disease progression, but further randomized clinical trials are needed to confirm it [40].

Predictive factors of atezolizumab efficacy are still under investigation. Data from POPLAR trial have suggested tumor mutation burden (TMB) as potential predictive factor of atezolizumab efficacy: higher TMB seems to be correlated to better PFS and OS outcomes for patients receiving atezolizumab, while no impact for patient receiving chemotherapy [41]. The INFγ gene signature and B7.1 expression superior to median seems to favor more atezolizumab than chemotherapy, suggesting new future prospective. About patients with EGFR activating mutations, no difference for immunotherapy compared to chemotherapy outcomes. In the OAK study, the rate of PD-L1 negativity status (TC0 or IC0) was greater for EGFR mutant subgroup, probably explaining the lower activity (ORR: 5%) and poorer survival outcomes (HR for OS: 1.24; HR for PFS:1.21). So,

the immunotherapy might be detrimental for EGFR mutant patients, even if the number of those is quite low.

Finally, atezolizumab has efficacy and a good safety profile in pre-treated patients (independently of PD-L1 expression), possibly also in naïve patients (trials ongoing).

Durvalumab, a selective, high-affinity, engineered human IgG1 monoclonal antibody, blocks PD-L1 binding to PD-1 and CD80. First data coming from phase I trial showed clinical activity of Durvalumab in the NSCLC expansion cohort, with higher ORR in PD-L1 high (≥25% of tumor cells) than PD-L1 low patients (ORR: 25% vs. 6%), irrespective of treatment line, histological subtype, and smoking status. Despite best survival outcomes in the first line setting, durvalumab showed its work also in pretreated patients, with more than half of those alive at one year (OS 1-yr rate of PD-L1 high: 56% and 51% for second- and third- line setting, respectively) [42].

Data from the phase II single-arm ATLANTIC trial were recently reported, demonstrating activity in heavily pretreated (≥3rd-line) advanced NSCLC patients. The study initially enrolled patients regardless the PD-L1 status, but was later restricted to patients whose tumor expressed PD-L1 at least 25% by IHC (Ventana SP263 assay). Similar to other agents in this setting, degree of activity of durvalumab seems related to PD-L1 expression, rising proportionally to its level of positivity: the ORR was 16.4% and 30.9% in patients with ≥ 25% and ≥ 90% of tumor cells positive for PD-L1, both cohorts having EGFR and ALK wild-type tumors. Consistent survival outcomes showed half of PD-L1 positive patients still alive at 1 year (1-yr OS rate: 47% for PD-L1≥25% and 50.8% for PD-L1 ≥90%). The main limitation for clinical interpretations is that these are uncontrolled data, so subject to patient selection. If these agents should be used in first- and second line setting, especially in tumors with high PD-L1, rather than in third- or more line monotherapy remain still unknown [43]. For the first time, in this trial durvalumab was prospectively evaluated in 111 EGFR mutated/ALK rearranged heavily pretreated patients (mean 4 prior regimens) [44]. As baseline characteristic, this cohort included 87% of EGFR mutated and 13% of ALK rearranged patients, mainly never smokers (58%). Higher PD-L1 expression (25% cutoff) appeared to be associated with higher ORR, with comparable activity data to those reported for EGFR/ALK wild type PD-L1 high cohort (ORR: 12.2% and 16.4%, respectively). Analyzing data by oncogenic alteration, durvalumab seemed to work better for EGFR mutated (ORR:14%; 1-yr OS:57%) than ALK rearranged patients (ORR: 0%; 1-ys OS: 35%), despite limited numbers of those last. Interestingly, quite encouraging survival results were in PD-L1 low/negative patients, with 40% of those alive at one year, but duration of follow up is still short [44].

In the lung-map design, squamous patients with no-match specific molecular alterations (EGFR, PI3K, CCCGA) might receive durvalumab or docetaxel at least as second-line treatment: the 16% of all population responded to atezolizumab and higher responders in PD-L1 ≥25% subgroup, according to other previous trial, while no differences from docetaxel arm were reported using durvalumab in PD-L1 low patients. Survival outcomes seemed to favoring atezolizumab than docetaxel (median OS: 11.6 vs. 7.7 months for atezolizumab and docetaxel, respectively), but higher number of patients, longer follow up and more data are needed [45].

After the promising data and impressive response rates (ORR: 78-92%) reported with the combination of nivolumab plus ipilimumab as first-line in higher PD-L1 (≥25%) NSCLC, another combination of durvalumab and tremelimumab seems promising for pretreated patients. In the dose-escalation phase I study, clinical activity did not appear dependent on PD-L1 status. In the combined cohorts of tremelimumab in doses of 1 mg/kg every 4 weeks and durvalumab in doses 10-20 mg/kg every 2 or 4 weeks, the ORR was 22% for PD-L1 ≥25%, quite low if compared to impressive data reported using nivolumab and ipilimumab as first-line. On the other hand, this combination cohorts revealed an impressive activity in PD-L1 low (<25%) and PD-L1 negative patients, with an ORR of 29% and of 40%, respectively, suggesting the potential clinical role of tremelimumab added to durvalumab for those patients [46].

Several phase III trials are investigating the safety and clinical activity of the durvalumab and tremelimumab combination in different lines of treatment and selected population. Durvalumab has been evaluated in a phase I study enrolling EGFR mutated patients: the osimertinib/durvalumab combination arm of the TATTON study was interrupted due to an increase in the incidence of interstitial lung disease-like events observed, while the combination with gefitinib as first-line is still ongoing (NCT02088112).

In the large phase I multicohort dose-escalation and dose-expansion JAVELIN trial, preliminary findings for 184 NSCLC pretreated patients unselected for PD-L1 expression and treated with avelumab, another anti-PD-L1 agents, reported objective responses in 22 patients only (12%), with median OS of 8 months. Focusing on PD-L1 status (1% as cut-off for tumor cell staining), longer PFS occurred in those patients with PD-L1-positive tumors (PFS at 48 weeks: 21% for PD-L1 positive vs 5% for PD-L1 negative), in contrast survival curves are approached at 1 year, with not clearly differences between two subgroups (1-yr OS: 39% vs 36% for PD-L1 positive and negative, respectively) [47].

To date, it is difficult to identify which of three agents approved in second-line setting (nivolumab, pembrolizumab and atezolizumab) has the greatest efficacy based on the results of the large phase III clinical trials within the limitations of comparing across studies with significant differences.

4. TREATMENT OF PATIENTS WITH ACTIVATING MUTATIONS

The current standard first-line therapy for oncogene addicted patients is EGFR- and ALK- TKI, respectively. However, the true question is how to best manage patients who progress on first-line treatment. The subsequent strategies include treatment beyond progression or changing of it. The choice between these two options should be guided by the type of progression: primary versus acquired, systemic versus oligoprogression, symptomatic versus asymptomatic, rapid versus slow progression, CNS metastases versus no CNS metastases. In presence of oligo-progressive disease, the use of local therapy, such as stereotaxic ablative radiotherapy, may be added to continuing first-line TKIs. On the other hand, a multisite progression might guide to consider re-biopsy (if possible) at the time of disease progression, in order to switch to next-generation TKI tailored to the selected mutation, if present.

4.1 Second-line for EGFR mutated positive patients

The mechanisms of therapeutic resistance to EGFR TKIs was classified as primary or acquired resistance [48, 49]. Primary resistance is defined as a “de novo” lack of treatment response and can be mediated by tumor intrinsic factors (such as coexistent genetic alterations in the drug target, coexistent mutations in other signaling genes and inactivation of pro-apoptotic pathways), and by patient-specific factors (such as plasma drug levels and drug–drug interactions). Conversely, acquired resistance refers to disease progression after an initial response to the targeted therapy. The “escape” mechanisms to evade continuous blockade of the target include target modification (target gene amplification such as MET amplification detected in 5-10% of tumors, “second site” mutation within the target gene mostly T790M detected in 60% of tumors, alternative splicing of the target gene), the emergence of bypass signaling tracks (activation of “compensatory loops” to circumvent the inhibited target), histologic transformation (epithelial-to-mesenchymal transition [EMT], phenotypic change from NSCLC to SCLC, about 5% of tumors), as well as other less well-characterized mechanisms such as increased growth factor production. Of these, the EGFR T790M mutation is the most common mechanism of drug resistance to first- or second-generations EGFR-TKIs in patients who have EGFR mutated lung cancer and, for this reason, it had been more investigated in clinical research. Examples of strategies to overcome acquired resistance include alternative doses or schedules of the targeted inhibitor, development of more potent “next-generation” inhibitors, dual blockade of the initial target with two or more target-specific agents, and combination drug strategies designed to suppress compensatory signaling loops [48, 49].

- **Osimertinib**

In the scenario of EGFR T790M mutations, osimertinib is an oral, potent, irreversible EGFR-TKI that is selective for both EGFR-TKI sensitizing and T790M resistance mutations. Osimertinib reported impressive results in patients with EGFR T790M mutation advanced NSCLC progressing to EGFR-TKI treatment across all dose levels (ranking from 20 to 240 mg once daily) in the phase I dose expansion cohort trial (AURA) [50]. The drug was associated with a response rate of 71% with limited skin (rash grouped terms 37% [no Grade 3 (G3)]) and gastrointestinal (diarrhoea 35% [2%]) adverse events (AE). The response rate achieved in phase I trial were confirmed in AURA study phase II extension component and in the updated analyses of a pre-planned pooled analysis of two phase II studies (AURA extension and AURA2), providing a high ORR of 62% and 66%, respectively. The median PFS and the proportion of patient progression-free at 1-year were 11 months and 47.5%, respectively, in the pooled analysis [51, 52].

A recent study investigated 143 patients with detectable EGFR mutations at baseline (median allelic fraction for Ex19del: 7.09%; L858R: 3.81%; T790M: 2.12%) enrolled in the AURA phase I study in order to assess whether changes in the levels of plasma EGFR mutations post-osimertinib treatment were associated with clinical outcome. Clearance of plasma EGFR mutations after 6 weeks of osimertinib therapy appears to be associated with improved ORR and median PFS in patients with T790M positive NSCLC. Evidence or lack of such a “plasma response” measured at 6 weeks could, potentially, be used to predict subsequent outcomes on therapy [53].

Results from the first predefined interim analysis of the ongoing ASTRIS study, the largest reported clinical study of osimertinib in T790M-positive NSCLC enrolling 1217 patients from 120 sites, demonstrated clinical activity similar to that observed in the osimertinib clinical trial program (ORR of 64%) with no new safety signals [54].

The AURA3 trial was the confirmatory phase III study comparing osimertinib (at a dose of 80 mg once daily) with the standard of care platinum-pemetrexed chemotherapy (maintenance pemetrexed allowed) in patients with metastatic EGFR T790M mutation-positive NSCLC who had progressive disease following first-line EGFR TKI therapy [55]. The population evaluated was quite similar to prior studies but CNS metastases was allowed only if were asymptomatic otherwise a typical population. A total of 419 patients were randomly in a 2:1 ratio assigned (279 patients to osimertinib and 140 patients to platinum-pemetrexed) and the baseline demographics and characteristics patient were well balanced across AURA3 treatment groups, in particular about one third of patients have asymptomatic CNS metastasis previously treated or too small to be treated (33% vs. 36%) and usual mutation consisting in EGFR T790M (99% each one), exon 19 deletion (68% vs. 62%), L858R mutation (30% vs. 32%), other (2% vs. 4%) in osimertinib and chemotherapy group, respectively. The median duration of PFS (primary end-point) was

significantly longer with osimertinib than with platinum-based therapy (10.1 vs. 4.4 months; HR 0.30; p<0.001). Osimertinib benefit was observed in all categories, including CNS metastases. The ORR was significantly better with osimertinib than with chemotherapy (70% vs. 31%; p = 0.015) in 46 evaluable for response patients included in CNS full analysis set, as well as the median duration of response (DoR: 8.9 vs. 5.7 months in chemotherapy arms) and median CNS PFS (11.7 vs 5.6 months; HR 0.32; p = 0.004) [55, 56].

FDA and EMA granted regular approval to osimertinib for the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC whose disease has progressed on or after EGFR TKI therapy.

In clinical practice, the use of plasma EGFR genotyping allow to draw a potential new paradigm. Plasma and tumor genotyping can have complementary roles for T790M testing, where plasma genotyping could be the initial step and a biopsy for tumor genotyping could be supplementary. If plasma genotype is positive for T790M, this may obviate the need for a biopsy—this predicts for excellent outcomes on osimertinib (ORR 63%; median PFS 9.7 months), similar to that observed when treating with osimertinib on the basis of tumor genotyping results (ORR 62%; median PFS 9.7 months).

Focusing on CNS disease, up to 40% of patients with EGFR mutation-positive NSCLC may develop CNS metastases over the course of their disease. Patients with CNS metastases treated with EGFR-TKI have shown a lower risk of progression in the CNS compared with chemotherapy. In this field, osimertinib showed a promising activity in CNS response rate and CNS disease control rate in patients with T790M positive NSCLC with baseline CNS metastases, following progression after an EGFR-TKI not only in the pooled analysis (AURA extension and AURA2) but also in AURA phase III trial [52, 55]. The BLOOM study is assessing the safety, tolerability and preliminary efficacy of osimertinib 160 mg once daily in two cohorts of patients: T790M unselected and T790M positive (by central test) [57]. Preliminary results showed a clear activity of osimertinib in leptomeningeal metastases demonstrated by efficacy assessment conducted on 32 patients (41 enrolled): 23/32 patients had a 12-wk brain image assessment with 10 radiological improvement and 13 stable disease. Furthermore, the geometric mean decrease in EGFR-mutant DNA copy was 57% in 22 patients with pre-dose and cycle 2 day 1 cerebrospinal fluid samples [57].

Based on the impressive clinical activity of osimertinib, the clinical research is evaluating its role as front-line treatment. Data from expansion cohorts in the phase I AURA study reported high ORR (overall ORR of 77%: 67% in the 80mg cohort and 87% in the 160mg cohort) with disease control rate (DCR) nearing 100% when osimertinib was administered as first-line [58]. The ongoing phase III double-blind, randomized FLAURA study (NCT02296125) is assessing the efficacy and safety

of osimertinib at the dose of 80 mg versus standard of care EGFR-TKI (gefitinib or erlotinib) in treatment-naïve patients with locally advanced or metastatic EGFR mutated NSCLC, with PFS as primary endpoint in both T790M positive or negative (PFS in patients with tumors harboring T790M is a key secondary objective).

The mechanisms of resistance to third-generation EGFR-TKIs can be summarized in EGFR-dependent and EGFR-independent, similarly to early-generation TKIs. The first group include the insurgence of secondary mutation such as C797S (in trans: could be sensitive to combined therapy with first and third generation TKI, cis: resistant), C797G, L798I, E790K, L692V, L781Q, T790M reduction, disappearance or loss and EGFR amplification. In the second one (EGFR-independent) are described HER2 amplification, MET amplification, PIK3CA mutations, PTEN loss, RAS-MAPK pathway activation (KRAS mut, BRAF mut, MAPK1/AKT3), FGF2-FGFR1 autocrine loop, EMT, NRAS mut/CNG, IGF1R activation, or phenotypic transformation (histological transformation to SCLC) [59, 60]. Among these, MET amplification (30%) and C797S (22%) were commonly observed: the first seems more common post-osimertinib than after first-line TKIs and patients seems to benefit from the combination EGFR plus MET TKIs [60]. As these new compounds become widely available for clinical use, patients will be treated with multiple lines of EGFR-targeted therapies with increasing frequency. A recent work *in vivo* model of acquired resistance to EGFR-inhibitors, tried to define the efficacy of sequential treatment with first-, second- and third-generation EGFR-inhibitors and to investigate the potential role of Hedgehog (Hh) pathway in the acquisition of cancer cell resistance. Of note, Hh is another pathway recently identified in the EMT setting and responsible for acquisition of resistance to first-generation EGFR-TKIs: its activation has been implicated in tumourigenesis, metastatisation and progression along with cancer stem-like cell maintenance and treatment resistance in several types of human cancer. The authors demonstrated that EGFR-mutant NSCLC can benefit from continuous treatment with EGFR-inhibitors, independently from mechanisms of resistance and showed an important role of Hh in mediating resistance to EGFR-inhibitors through the induction of mesenchymal properties [61].

Several ongoing trials are evaluating different approaches for managing patients with resistant tumors including osimertinib in combination with several molecules (ramucirumab, bevacizumab, necitumumab, savolitinib, durvalumab, INCB039110 [JAK inhibitor], selumetinib, INK128 [TORC1/2], navitoclax [Bcl2], AZD6094 [MET], EGF816 + INC280 [MET], EGF816 + nivolumab, agents targeting C797S) or targeting T790M-negative (MET inhibition, MEK inhibitor combinations, EMT: AXL inhibition, SMO gene amplification (Hh receptor) with MET activation,

FGFR 1, 2, 3 activation, ErBB2 activation mutations, IGF1R activation, BRAF (Val600Glu, Gly469Ala) mutation, PIK3CA mutation).

4.2 Second-line for ALK positive patients

The genetic alterations in ALK define a unique subtype of NSCLC that are highly responsive to genotype-directed TKIs, such as crizotinib. Unfortunately, despite this initial sensitivity, the long-term effectiveness of such therapies is limited by the development of resistance (median PFS with first-line crizotinib of 10-11 months) [62]. In general, mechanisms of acquired resistance to TKIs are divided into two classes, preserving or not the dominance of ALK signaling in the crizotinib resistant-state (ALK dependent or ALK independent). First, the target gene itself can be altered either by secondary mutation or by gene amplification of the primary oncogene, limiting the ability of the drug to inhibit the kinase. In the presence of the drug, the kinase remains active and drives aberrant signaling. Second, alternative signaling pathways, or so-called bypass tracks, can be activated in resistant cells, bypassing the need for signaling from the target. Understanding the mechanistic bases for acquired resistance is crucial to developing strategies to overcome (or delay) resistance in the clinic [63]. Furthermore, advanced ALK-positive NSCLC is characterized by a high lifetime risk of CNS metastases and a high frequency of brain metastases at diagnosis, with the CNS being the most common site of disease progression (in about 70% of the patients with CNS metastases at baseline). On the other side, about 20% of the patients without CNS metastases at baseline develops new intracranial lesions as manifestation of acquired resistance [64]. Clearly, there is the need of develop drugs that not only can work on mechanisms of acquired resistance to crizotinib but can also provide activity against CNS metastases.

For one third of patients in whom crizotinib resistance is mediated by ALK mutation or amplification, cancers are still addicted to ALK, and therefore, next-generation ALK inhibitors may be effective in re-inducing remissions. These next-generation ALK inhibitors are structurally distinct from and more potent than crizotinib. To date, two new ALK inhibitors are approved for patients with metastatic ALK positive NSCLC, such as ceritinib (LDK378) and alectinib (CH5424602), while brigatinib (AP26113) received granted accelerated approval by United States FDA.

- **Ceritinib**

Ceritinib (LDK378) is an oral TKI 20 times more potent than crizotinib against ALK in enzymatic assays. Ceritinib inhibits ROS1 and the insulin-like growth factor 1 (IGF-1) receptor, although the inhibition of the IGF-1 receptor is less potent than the inhibition of ALK. Unlike crizotinib, it does

not inhibit the kinase activity of MET [65]. Ceritinib crosses the blood–brain barrier *in vivo*, and shows clinical responses in patients with crizotinib-resistant disease.

ASCEND-1 was an open-label, phase I trial that recruited 255 patients with ALK-rearranged locally advanced or metastatic cancer that had progressed despite standard therapy (163 of 246 ALK-rearranged patients were pretreated with an ALK inhibitor, mainly crizotinib) to receive oral ceritinib at the recommended dose of 750 mg/day in the dose-escalation and expansion phases [66]. Ceritinib reported an ORR of 72% in ALK inhibitor-naive patients and 56% in ALK inhibitor-pretreated patients with a median DoR of 17 and 8.3 months, respectively. Median PFS was 18.4 months in ALK inhibitor-naive patients and 6.9 months in ALK inhibitor-pretreated patients. Ceritinib showed intracranial activity reporting partial response in 6 of 11 patients with brain metastases. Ceritinib treatment was related to serious AEs in 48% of cases: the most common grade 3–4 laboratory abnormalities were increased alanine aminotransferase (30%) and increased aspartate aminotransferase (10%), while the most common grade 3–4 non-laboratory adverse events were diarrhea, nausea (6% for each) and vomiting (4%) [66].

ASCEND-2 was a phase II trial including ALK positive NSCLC patients pre-treated with chemotherapy (≥ 1 platinum doublet) who progressed ≤30 days from last treatment with crizotinib. A total of 140 patients received oral ceritinib 750 mg daily: both the median DoR and the median PFS in all patients (DOR, 9.7 months; PFS, 5.7 months) were similar to those reported for ASCEND-1, regardless the presence or not of brain metastases [67].

ASCEND-5 was the first phase III study to assess whether the second-generation ALK inhibitor ceritinib was superior to chemotherapy in 231 patients progressed to crizotinib [68]. Patients were randomized 1:1 to receive therapy with ceritinib (N=115) or chemotherapy (N=116, pemetrexed or docetaxel; crossover to ceritinib was allowed). Median PFS (primary endpoint) was significantly improved with ceritinib compared to chemotherapy (5.4 vs. 1.6 months, HR 0.49, $p<0.001$). At subgroup analyses, all categories benefit from ceritinib regardless age, race, sex, the presence or not of brain metastases, PS, smoking history or previous response to crizotinib. Ceritinib increased ORR compared to chemotherapy (39.1% vs. 6.9%). There was no improvement in OS, probably because the patients who crossed over diluted the potential benefit (75 patients with progressive disease crossed over to ceritinib) [68].

Consistent with ASCEND-1, ceritinib resulted in a durable median PFS of 16.6 and 18.4 months by investigator and by Blinded Independent Review Committee in 124 ALKi-naïve patients with ALK positive NSCLC (of whom 54.8% had received ≥2 prior antineoplastic regimens) enrolled in the single-arm phase II ASCEND-3 study. Whole body response rates were robust, irrespective of the presence of baseline brain metastases [69].

Based on the induction of PD-L1 expression due to constitutive oncogenic signaling reported in NSCLC models harboring EML4–ALK rearrangements, an ongoing phase I dose-escalation study is exploring whether ceritinib (at 450 mg/day or 300 mg/day) in combination with nivolumab (3mg/kg intravenously be-weekly) might provide sustained clinical benefit to previously treated (ALK inhibitor or chemotherapy) or treatment-naive patients with ALK positive NSCLC [70]. The combination demonstrated to be active (confirmed /unconfirmed ORR in ALKi-pretreated: 63%, and 33%; in ALKi-naïve: 83% and 70%), however, the protocol will be amended to address observed toxicities: diarrhea (64%), ALT increase (56%), AST increase (44%) and vomiting (42%) were the most common any-grade AEs while, the most frequent grade ≥3 AEs were increases in ALT (22%), GGT (17%), amylase (11%), and lipase (11%), and maculopapular rash (11%). Incidence of rash (grouped term) was 61% [70].

U.S. FDA and EMA granted regular approval to ceritinib. As EGFR mutated patients in the field of CNS metastases, an ongoing phase II trial (ASCEND-7) is evaluating efficacy and safety of oral ceritinib treatment in ALK rearranged patients with brain and/or leptomeninges metastases (NCT02336451).

Concerning first-line setting, ceritinib showed a statistically significant and clinically meaningful improvement in PFS versus platinum-based chemotherapy in ALK positive patients included in the randomized phase III ASCEND-4 study. In the total of 376 patients randomly assigned to ceritinib (N=189) or chemotherapy (N=187), median PFS was 16.6 and 8.1 months, respectively (HR 0.55; $p<0.00001$) [71].

The long-term efficacy of ceritinib is limited by development of resistance, mainly due to secondary ALK mutations that could predict sensitivity to third-generation ALK inhibitors (like lorlatinib). By biopsies of 103 ALK-positive patients progressing on various ALK inhibitors, there was identified that each ALK inhibitor is associated with a distinct spectrum of ALK resistance mutations and that the frequency of one mutation, ALKG1202R, increases significantly after treatment with second-generation agents [72]. Ceritinib demonstrated activity against different ALK mutations including L1196M, G1269A, I1171 and S1206Y crizotinib-resistant mutations, however it was not active against G1202R mutation. Furthermore, novel V1180L gatekeeper mutation and a second novel I1171T mutation identified in patient progressed to alectinib conferred resistance also to crizotinib, but the sensitivity to ceritinib and other next-generation ALK-TKIs is preserved in cell line models [73]. These findings highlight the importance of repeat biopsies and genotyping following disease progression on targeted therapies, particularly second-generation ALK inhibitors, in order to guide proper sequencing of next generation ALK inhibitors.

– **Alectinib**

Alectinib is a potent ALK-TKI with activity against the effects of several ALK mutations that confer resistance to crizotinib (such as Thr1151_Leu1152insThr, Leu1196Met, Cys1156Tyr, Phe1174Leu, and Gly1269Ala). Unlike crizotinib, alectinib is a CNS penetrant; it is not a substrate of P-glycoprotein, a key efflux transporter located at the blood–brain barrier. In both preclinical and clinical investigations, alectinib was active in the CNS [74-76].

In a Japanese single-arm, open-label, phase I/II study (AF-001JP) conducted prior to the availability of crizotinib, alectinib 300 mg twice per day showed high activity in chemotherapy-pretreated, ALK TKIs-naive patients with ALK-positive NSCLC. At the primary analysis, the proportion of patients who achieved an objective response was 93.5% with 43 of 46 evaluable patients responding to treatment [77]. To assess PFS and OS, patients from the phase II part of AF-001JP were followed up for approximately 3 years. At the updated data cutoff (September 10, 2015), alectinib seemed to be an effective treatment when administered for an extended time frame, with a 3-year PFS rate of 62%, with 25 of 46 phase II patients were still receiving alectinib [78]. Fourteen patients had brain metastases at baseline: of these, 6 (43%) remained in the study without CNS and systemic progression. Overall, efficacy outcomes were similar in patients with or without CNS metastases at baseline, suggesting that alectinib would be suitable for ALK-positive disease, regardless of CNS involvement. Despite the long administration time, AEs reported were still only mild to moderate in severity, with no treatment-related grade 4 or 5 AEs. Increased blood bilirubin was the most common treatment-related AEs (all grades, 36.2%) [78]. Based on these results, a phase I/II study of alectinib was conducted in United States to establish the recommended phase II dose of the drug and examine its activity in 47 ALK-rearranged patients resistant or intolerant to crizotinib. Alectinib was well tolerated with promising antitumour activity reported in all population (ORR 54.5%) as well as in 21 patients with CNS metastases (ORR of 52%). On the basis of activity, tolerability, and pharmacokinetic data, alectinib 600 mg twice a day was chosen as the recommended dose for phase II [75]. These findings led to the approval of alectinib in Japan in July, 2014. Alectinib received accelerated approval by the U.S. FDA in 2015 and more recently in Europe by EMA following results from two pivotal single-arm phase II trials (the North American NP28761 and the global NP28673 studies) in patients with disease progression while on crizotinib [76, 79, 80]. The first trial, enrolling 87 patients, reported an ORR of 52.2% in the response evaluable population (N=67) by independent review committee (IRC) (CNS ORR of 75% in 16 patients with baseline measurable lesions) and a median DOR of 14.9 months (median follow-up: 17.0 months). Median PFS and OS were 8.0 and 22.7 months, respectively [79, 80]. The global phase II NP28673 reported similar rates: ORR by IRC of 50% and median DOR of 11.2 months in

138 patients, including those with CNS metastases (N=84 patients; CNS ORR of 57% in 35 patients with baseline measurable lesions) [76]. To further evaluate the efficacy of alectinib in the CNS, a pooled efficacy and safety analysis has been conducted on patients with CNS disease from previous phase II trials [81]. A total of 225 patients were enrolled, of whom 136 with baseline CNS disease were included in this pooled CNS analysis. Regarding prior treatments, radiotherapy was not done in about one third of the patients, while among patients who received prior CNS radiotherapy, the majority of these patients had completed it greater than 6 months before starting alectinib. This suggest that the activity observed with alectinib was unlikely related to prior radiation. Alectinib demonstrated good CNS efficacy, with IRC CNS ORRs of 64.0% and 42.6% for patients with measurable and/or non-measurable CNS disease at baseline, respectively. Thirty-seven complete responses (27%) was observed for patients with measurable and/or non-measurable CNS disease at baseline, demonstrating that alectinib can provide CNS benefit regardless of whether the disease is measurable according to RECIST. Of note, the activity was seen irrespective of radiation history: the response was a bit lower in patients pretreated with CNS radiotherapy compared to radiotherapy naïve (CNS ORR 35.8% vs. 58.5%, respectively) while a similar CNS DCR was reported (CNS DCR 86.3% vs. 82.9%, respectively). At the median follow-up of 12 months, in the overall population only 17% of the patients had CNS progressive disease, while only 8% of patients without baseline CNS metastases had CNS disease progression. Responses observed in the CNS were durable, with a CNS DOR of approximately 11 months, and were comparable to those observed for the overall systemic disease assessment [81].

Alectinib has the potential to be a new standard therapy for ALK-positive NSCLC also in first-line setting. Two randomized phase III trials compared alectinib (600 mg twice daily) to crizotinib in previously untreated ALK-positive patients, including those with asymptomatic CNS disease (J-ALEX, N=207 patients; ALEX, N=303 patients) [82, 83]. In both, alectinib showed superior efficacy and lower toxicity than crizotinib. The Japanese study met its primary endpoint of showing superiority of alectinib in independent review facility-assessed PFS: median PFS was 25.9 months compared to 10.2 months with crizotinib (PFS HR 0.38; $p<0.0001$). The superior efficacy of alectinib over crizotinib was consistent across most predefined patient subgroups, including that with brain metastases at baseline: for patients without brain metastasis at baseline (N = 164), alectinib prevented CNS metastasis onset compared to crizotinib (HR 0.19); for patients with brain metastasis at baseline (N = 43), alectinib also prevented CNS progression compared to crizotinib (HR 0.51). Grade 3 or 4 AEs occurred at a greater frequency with crizotinib than alectinib (56.7% vs. 32%, respectively) [82, 84].

Similarly, in the ALEX trial alectinib demonstrated statistically significant superiority versus crizotinib, reducing risk of progression/death by 53% (HR 0.47); median PFS for alectinib was not reached rather than 11.1 months of crizotinib arm. Regarding CNS metastases, the time to CNS progression was significantly longer with alectinib (cause-specific HR, 0.16; P<0.001) with an ORR of 83% versus 76% (p=0.09). Serious grade AEs were less frequent with alectinib (41% vs. 50% with crizotinib) [83, 85].

- **Other new ALK inhibitors**

The activity of brigatinib and lorlatinib in patients with advanced ALK-positive NSCLC highly pretreated with chemotherapy and crizotinib, has been evaluated in phase II trials [86-89]. Brigatinib achieved a promising intracranial and whole-body activity in an ongoing phase I/II trial in 137 ALK positive NSCLC patients pretreated or not with crizotinib. Based on this result, a phase II trial (ALTA) randomly assigned (1:1) 222 patients with crizotinib-resistant ALK-rearranged NSCLC (69% with brain metastases at baseline) to oral brigatinib 90 mg once daily or 180 mg once daily with a 7-day lead-in at 90 mg (180 mg once daily [with lead-in]. Brigatinib confirmed substantial whole-body and intracranial responses as well as robust PFS. The dose of 180 mg (with lead-in) showed consistently better efficacy than 90 mg (confirmed ORR of 54% versus 45%; median PFS 12.9 versus 9.2 months, respectively) [87]. Intracranial efficacy was assessed by an IRC evaluating baseline brain image in 217 patients (153 with baseline brain metastases and 44 with measurable lesions). An ORR of 42% and 67% has been reported in patients with measurable lesions at the dose of 90 mg and 180 mg, respectively. Among those with non-measurable lesions, response rates were 7% versus 18%. The median duration of intracranial response was not reached in either group. The median intracranial PFS was 15.6 versus 12.8 months [88]. As other ALK inhibitors, the toxicity was generally mild with few grade 3 AEs. Gastrointestinal symptoms (nausea in 33% vs 40%, diarrhea in 19% vs 38%), headache (28% vs 27%), and cough (18% vs 34%) were the most common AEs of any grade included. The most common grade ≥ 3 AEs were hypertension (6% vs 6%), increased creatine phosphokinase (CPK; 3% vs 9%), pneumonia (3% vs 5%), and increased lipase (4% vs 3%) [88].

Based on these results, the ALTA-1L phase III trial was designed to assess the efficacy and safety of brigatinib versus crizotinib in approximately 270 patients with advanced ALK positive NSCLC naive to TKI therapy (including ALK inhibitors) (NCT02737501).

On April 28, 2017, the U.S. FDA granted accelerated approval to brigatinib for the treatment of patients with metastatic ALK-positive NSCLC who have had disease progression on or are intolerant to crizotinib.

Lorlatinib is a potent next generation ALK/ROS1 TKI active against most known resistance mutations and with an excellent penetration in the brain. In the phase I part of a phase I/II study, lorlatinib showed robust clinical activity in ALK positive or ROS1 positive advanced NSCLC patients, most of whom had CNS metastases and were heavily pre-treated. The phase II part of the same study evaluated efficacy based on prior ALK-TKI treatment as well as safety across all patients treated at the recommended phase II dose (100 mg QD). Patients were enrolled into 6 expansion cohorts (EXP) based on prior treatment: EXP 1 included treatment naïve, EXP 2-5 included patients pretreated with crizotinib only or other ALK inhibitor therapy other than crizotinib or chemotherapy regimens other than one or more ALK inhibitors, EXP 6 included ROS1 patients. Lorlatinib showed compelling clinical activity, with substantial intracranial activity in 82 ALK positive patients enrolled in cohorts EXP 2-5, pretreated with one or more ALK-TKI, many of whom were heavily pre-treated: no clear trend in response rate was observed based on number of prior ALK-TKIs or ALK kinase domain mutation status. Most common AEs and grade 3-4 AEs were hypercholesterolemia (90%, 17%) and hypertriglyceridemia (72%, 17%) [88].

On April 27, lorlatinib was granted breakthrough therapy designation from FDA for the treatment of patients with ALK-positive metastatic NSCLC previously treated with one or more ALK inhibitors.

According to different kind of ALK resistance mutations, brigatinib has activity in G1202R, D1203N, and S1206Y/C more than crizotinib and alectinib; while the presence of ALK resistance mutations is highly predictive for sensitivity to lorlatinib [72].

5. EXPERT OPINION

5.1 Consensus for clinical practice

The International Experts Panel Meeting on second-line treatment of NSCLC has provided a summary of recommendations for clinical practice in Table 1.

Which role for immunotherapy (anti PD-1 and anti PD-L1) in second-line treatment in immunotherapy-naive NSCLC WT?

RECOMMENDATION

The standard of care for patients with PS 0-1 is nivolumab, pembrolizumab (only PD-L1 expression > 1%) and atezolizumab. Of note, for non-squamous histology, nivolumab is recommended with

caution in patients at risk of early death [combined PD-L1 low or negative, progressive disease at first line chemotherapy, PS 1]). Regarding re-challenge strategy, no data are available.

Level of evidence: I - Strenght of recommendation: A [I, A]

Level of evidence for PS 2: V - Strenght of recommendation for PS 2: C [V, C]

Any difference among check-point inhibitors?

RECOMMENDATION

Currently, no comparative trials among drugs are available. However, few differences emerged from pivotal trials are: restricted use of pembrolizumab in PD-L1 positive tumors, different administration schedules (bi-weekly for nivolumab and three-weekly for pembrolizumab and atezolizumab) and the duration of treatment (until progression for nivolumab and atezolizumab; maximum 2 years for pembrolizumab).

Any predictive biomarker for immunotherapy in second-line treatment with check-point inhibitors?

RECOMMENDATION

PD-L1 expression > 1% is a predictive/restrictive biomarker only for pembrolizumab, with no difference between archival and fresh sample tissue. However, a benefit correlation with level PD-L1 expression for nivolumab in non-squamous and for atezolizumab in both histology has been reported.

Level of evidence: II - Strenght of recommendation: B [II, B]

Which second-line treatment in patients with NSCLC WT receiving 1st-line immunotherapy?

RECOMMENDATION

For patients receiving single agent pembrolizumab, a platinum-based chemotherapy (plus bevacizumab in non-squamous histology) should be considered, reserving docetaxel plus antiangiogenetics in third-line setting. On the other hand, for patients receiving chemotherapy plus immunotherapy, docetaxel plus antiangiogenics should represent a valid second-line treatment.

Level of evidence: V - Strenght of recommendation: C [V, C]

Which role for combination of docetaxel and antiangiogenetics in second-line treatment of fit patients with NSCLC WT?

RECOMMENDATION

To date, no comparative trials among docetaxel plus antiangiogenetics and immunotherapy are available. In squamous histology, docetaxel plus ramucirumab can be considered as third-line (as second-line in patients not eligible for immunotherapy). In non-squamous histology, docetaxel plus ramucirumab or plus nindetanib can be considered as third-line (as second-line in patients not eligible for immunotherapy).

Level of evidence: V - Strenght of recommendation: C [V, C]

Which role for single agent chemotherapy (docetaxel or pemetrexed) in pretreated NSCLC WT?

RECOMMENDATION

It can be considered (if not used before) in pretreated patients not eligible for immunotherapy or for docetaxel plus antiangiogenetics (due to controindications to antiangiogenetics or not rembursed drug in some countries).

Level of evidence: V - Strenght of recommendation: C [V, C]

Which role for EGFR TKI's in pretreated NSCLC WT?

RECOMMENDATION

Their role is restricted to patients not eligible for other treatments.

Level of evidence: V - Strenght of recommendation: C [V, C]

Which second-line treatment of NSCLC EGFR positive?

RECOMMENDATION

Osimertinib is the standard of care in tumors with T790M positive. For those T790M negative, platinum-based chemotherapy (plus bevacizumab only in non-squamous histology) remains a valid option. As subsequent treatment, docetaxel plus antiangiogenetics should be preferred to immunotherapy.

Level of evidence for second-line: I - Strenght of recommendation: A [I, A]

Level of evidence for subsequent line: V - Strenght of recommendation: C [V, C]

Which second-line treatment of NSCLC ALK positive crizotinib treated?

RECOMMENDATION

Ceritinib or alectinib or brigatinib are available. As subsequent treatment, platinum-based chemotherapy (plus or minus bevacizumab in non-squamous histology) remains a valid option.

Level of evidence for second-line: I - Strenght of recommendation: A [I, A]

Level of evidence for subsequent line: V - Strenght of recommendation: C [V, C]

5.2 Consensus for clinical research

Finally, the International Experts Panel Meeting on second-line treatment of NSCLC has been concluded focusing on new goals for future clinical research (Table 2).

6. CONCLUSION

Until a few years ago, another treatment than single-agent chemotherapy (such as docetaxel) seemed to be utopia for patients progressed to first-line therapy. Currently, the introduction of an increasing number of drugs (such as targeted therapy and immunotherapy) has revolutionized the therapeutic strategy in clinical practice. In order to clarify the best sequencing of available treatments, the knowledge of the complete molecular profile is mandatory at baseline, but it seems to be crucial also at the time of disease progression. The phenotypic valuation of PD-L1 expression status has intrinsic limits, but to date it is the only tool to select patients for immunotherapy. The research of new predictive biomarkers for “tailored” immunotherapy is still ongoing, with new promising markers under valuation, such as INFgamma, TILs, mutational burden. The duration of immunotherapy treatment, the re-challenge with anti PD-1 or anti PD-L1 agents in immunotherapy pretreated patients, the combination strategies (such as combinations with other immune-agents or with single agent chemotherapy or with antiangiogenetics) and the role in special patient populations (brain metastases, PS 2, elderly) represent new goals for future clinical research. In oncogene-driven tumors, the better knowledge of mechanisms of acquired resistance to earlier TKIs is leading to novel active inhibitors now available/in development. Although, it has been described a long survival in these patients when treated with TKIs, at present, a cure for these patients is still not available and sequential therapies are needed, focusing on T790M positive patients progressed to osimertinib, on ALK positive patients progressed to first-line alectinib and on ROS-1 positive patients after first-line crizotinib.

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Table 1. Summary of recommendations for Clinical Practice

Second-line treatment of EGFR- and ALK-negative disease
• For patients receiving pembrolizumab as single agent, a platinum-based chemotherapy (plus bevacizumab in non-squamous histology) should be considered [V, C]. • For patients receiving immunotherapy plus chemotherapy as first-line, docetaxel plus antiangiogenetics should represent a valid second-line option [V, C]. • For immunotherapy-naïve pretreated patients with PS 0-1, nivolumab, pembrolizumab (only PD-L1 expression > 1%) and atezolizumab are currently the standard of care. Nivolumab is recommended with caution in non-squamous patients at risk of early death (combined PD-L1 low or negative, progressive disease at first line chemotherapy, PS 1) [I, A]. • For patients not eligible for immunotherapy, docetaxel combined to ramucirumab or to nindetanib (for non-squamous histology only) can be considered treatment options as second-line [V, C]. • A single agent chemotherapy – docetaxel or pemetrexed in nonsquamous only- can be considered (if not used before) in pretreated patients not eligible for immunotherapy or for docetaxel plus antiangiogenetics [V, C]. • The role of EGFR- TKI (erlotinib) is restricted to patients unfit for other treatments [V, C].
Second-line treatment of EGFR mutated disease
• After an EGFR TKI treatment, osimertinib is the standard of care in tumors with T790M positive [I, A]. • For those T790M negative diseases, platinum-based chemotherapy (plus bevacizumab only in non-squamous histology) remains a valid option [I, A]. • Docetaxel plus antiangiogenetics should be preferred to immunotherapy as treatment option beyond second line [V, C].
Second-line treatment of ALK rearranged disease
• After progression to crizotinib as first-line treatment, next generation ALK TKIs are recommended: ceritinib, alectinib and brigatinib are currently available [I, A]. • Platinum-based chemotherapy (plus or minus bevacizumab in non-squamous histology) remains a valid option for subsequent lines of treatment [V, C].

Table.2 New goals for future clinical research

Issue	**Priority**
Rechallenge with anti PD-1 or anti PD-L1 agents in immunotherapy pretreated patients	Medium
New predictive biomarkers	High
Immunotherapy combinations	High
Combination of single agent chemotherapy and check-point inhibitors	Medium
Combination of check-point inhibitors and antiangiogenetics	Medium
Immunotherapy in special patient populations (brain metastases, PS 2, elderly)	High
Duration of immunotherapy treatment	Medium
Treatment of patients with other driven genetic alterations (ROS-1, B-RAF, RET, RAS etc.)	Medium
New TKI for patients T790M positive progressing to osimertinib	High
New TKI for patients ALK positive progressing to 1-line alectinib	High
New TKI for patients ROS-1 positive progressing to 1-line crizotinib	High