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Treatment of advanced non-small-cell lung cancer: The 2019 AIOM (Italian Association of Medical Oncology) clinical practice guidelines

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ABSTRACT

The Italian Association of Medical Oncology (AIOM) has developed clinical practice guidelines for the treatment of patients with advanced non-small cell lung cancer (NSCLC). In the current paper a panel of AIOM experts in the field of thoracic malignancies discussed the available scientific evidences, with the final aim of providing a summary of clinical recommendations, which may guide physicians in their current practice.

1. Introduction

Lung cancer was the most important epidemic of the 20th century and it is likely to remain a major public health problem also in the current one, with about one out of four cancer-related deaths ascribed to this tumor, currently representing the first cause of cancer death worldwide.

In the last few decades several steps forwards have been made in prevention, diagnosis, and treatment of lung cancer, however, diagnosis is mainly obtained at advanced, not curable stages, with more than half of patients presenting metastatic disease, and 5-year survival rate ranging from 4.5 % to 5.5 % (The Numbers of Cancer in Italy, 2019).

The identification of oncogenic drivers and the development of targeted therapies led to a radical shift from pathological to molecular classification of lung adenocarcinoma, establishing a new paradigm of "personalized therapy". The recent understanding of the biological mechanisms driving cancer immune evasion has allowed the development of a new class of immunomodulatory agents, known as immune-checkpoint inhibitors (ICIs), which are able to reactivate host immune-response, offering the potential for long-term survival in a significant proportion of patients. The introduction of innovative therapies into clinical practice revolutionized the treatment algorithm of advanced non-small cell lung cancer (NSCLC). The Italian Association of Medical Oncology (AIOM), in collaboration with a national panel of experts in the field of thoracic malignancies, has developed clinical practice guidelines, with the final aim of providing evidence-based recommendations, which may guide physicians in the clinical management of advanced NSCLC patients.

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2. Molecular pathology

2.1. Pathological diagnosis

Pathological diagnosis is recommended prior to any treatment and should be made according to the 2015 World Health Organization (WHO) classification (Travis et al., 2011; Rossi et al., 2013).

NSCLC account for 80 %–95 % of lung cancers in Italy, including 50 % of adenocarcinoma, and 21 % of squamous cell carcinoma. Immunohistochemistry (IHC) including thyroid transcription factor-1 (TTF-1) for adenocarcinoma, and p40 for squamous cell carcinoma, are generally required to increase the specificity of diagnosis in the small sample setting and reduce the NSCLC-NOS (not otherwise specified) rate below 10 % (Yatabe et al., 2019; Lozano et al., 2018; Waila et al., 2017; Pelosi et al., 2015; Inamura, 2018; Pelosi et al., 2017; Gurda et al., 2015).

IHC analysis should be preferably performed on tissue samples obtained by surgery or tumor (forceps or core needle) biopsy. However, cell-block is considered a valid alternative option to be used when core biopsies are not available (Sagi, 2016; Thunnissen et al., 2012; Dong et al., 2017; van der Heijden et al., 2014a; Linderman et al., 2018). In metastatic patients, the majority of diagnoses come from small biopsy and/or cytological samples, which often include limited tumor material for analysis, thus requiring adequate handling and processing. The results of a recent multicentre observational study conducted at 13 different Italian institutions, including a total 1325 patients with newly diagnosed metastatic NSCLC, showed as about 82 % of samples were cytological or small biopsies (Vavalà et al., 2018). The last pathological classification of 2015 (Travis et al., 2011) highlighted the concept that personalized medicine for patients with advanced NSCLC is determined by both histology and genetics, and that tissue/cells management of small biopsy/cytology samples is critical for pathologic and molecular diagnosis in order to prevent the loss of tissue in less important analysis. Cell-block (CB) should be prepared from effusions (i.e., pleural) or fine-needle aspirations (from T, N or M sites) to permit more adequate IHC stains (i.e., TTF-1, p40, PD-L1) and should be considered as a micro-biopsy when enrolling patients for clinical trials requiring centralized biomarker determinations (van der Heijden et al., 2014b).

2.2. Molecular diagnosis

Predictive biomarker testing currently approved and recommended in Italy include: epidermal growth factor receptor (EGFR) gene mutations, anaplastic lymphoma kinase (ALK) and ROS proto-oncogene 1 (ROS1) rearrangements, and programmed-death ligand 1 (PD-L1) tumor IHC expression. Although there are not validated national platforms for molecular screening of NSCLC patients, recent prospective observational studies, involving several oncology and pathology units, revealed high adherence to molecular testing and matched targeted treatments across the different Italian regions (Bruni et al., 2018; Reale et al., 2018).

EGFR activating mutations have been identified in about 10–15 % of Caucasian (Sharma et al., 2007; Rosell et al., 2009) NSCLC patients. Exon19 deletion (*Del19*) and point mutation in exon21 (*L858R*) account for 90 % of overall *EGFR* activating mutations, but there are several others "uncommon" mutations in exons 18 (*G719C, G719S, G719A, V689 M, N700D, E709 K/Q, S720P*), 20 (*V765A, S768I, V769 L, T783A, T790M*, and insertions), 21 (*N826S, A839 T, K846R, L861Q, G863D*) resulting in a constitutively activated EGFR signaling, thus predicting variable clinical response to EGFR tyrosine kinase inhibitors (TKIs) (Sharma et al., 2007; Chang et al., 2019 Aug). Based on published data, *EGFR* mutations are more frequent in female, Asian, never-smoker patients with adenocarcinoma subtype (Sharma et al., 2007; Rosell et al., 2009). In a prospective multicenter observational Italian study, including 1787 patients, *EGFR* testing was carried out in 76 % of cases, showing a positive result in 23.6 % of tested samples, more frequently detected in young and never smokers (Gobbini et al., 2017). In the same NSCLC population the percentage of ALK and ROS1 positive cases were 8.9 % and 3.4 %, respectively (Gobbini et al., 2017). The higher percentage of both *EGFR* mutated and ALK/ROS1 rearranged samples reported in this study, compared to other published case series, was likely ascribed to a population enrichment in predictive clinical and histological features (Gobbini et al., 2017).

ALK rearrangements, have been detected as a potent oncogene drivers in about 2–7 % of NSCLC patients (Shaw et al., 2009), variably depending on histology, smoking status, age, gender and tumor stage across different cases series, resulting in a constitutive activation of the intracellular domain of ALK receptor (Chiarle et al., 2008), thus predicting clinical response to ALK-TKIs. Similarly, *ROS1* rearrangements occur in about 1–2 % of NSCLC patients and were associated with a great response to specific targeted inhibitors (Shaw et al., 2014a). Both *ALK* and *ROS1* rearrangements were more frequently detected in never-smokers and younger people with adenocarcinoma, while no significant association with gender or ethnicity have been found (Shaw et al., 2009, Shaw et al., 2014a).

EGFR (exons 18–21) mutational testing on tissue specimens is currently recommended in newly diagnosed, advanced, non-squamous NSCLC, and in squamous cell carcinoma patients who were never and former light smokers (< 15 packs-years). A plethora of different procedures are currently used in Italy: Real Time PCR (RT-PCR) represents the most widespread technique, followed by Pyrosequencing, Matrix Assisted Laser Desorption Ionization Time-of-Flight (MALDI – TOF) and Sanger Sequencing (Vavalà et al., 2018; Normanno et al., 2013; Barni et al., 2015). Many molecular pathology laboratories are equipped with a next generation sequencing (NGS) platform, but the implementations in clinical setting are still limited to a small number of large volume centers. A different rate of inadequate samples for *EGFR* testing are reported across different geographic regions (Vavalà et al., 2018; Normanno et al., 2013).

Considering the high diagnostic accuracy of circulating tumor (ct) DNA analysis (Luo et al., 2014; Qiu et al., 2015), *EGFR* mutation testing on liquid biopsy may be used as alternative approach to standard tissue genotyping at the time of disease diagnosis in patients who cannot undergo biopsy or received uninformative results from tissue molecular analysis.

Several studies demonstrated high concordance between IHC and Fluorescence in situ hybridization (FISH) analysis for the detection of *ALK* rearrangements (Yi et al., 2011; Selinger et al., 2013; Park et al., 2012; Conklin et al., 2013; Marchetti et al., 2013), in the same patient population tested for *EGFR* (Linderman et al., 2018). The main challenging issue is related to the availability of three different detecting approaches: fluorescence in situ hibridization (FISH), immunohistochemistry (IHC) (by using a CE – IVD kit by Ventana or a D5F3 antibody clone by Cell Signaling) and, more recently, NGS (Barni et al., 2015). Differently from *ALK*, *ROS1* testing by IHC (by using a CE – IVD kit by Ventana/Roche SP384 or a D5F3 antibody clone by Cell Signaling) showed a significant rate of inadequate results (high percentage of false positive cases), then requiring a confirmatory test (i.e, FISH analysis or extractive molecular techniques) (Pisapia et al., 2017; Huang et al., 2019).

In Italy, the IHC with D5F3 clone, is the most diffused approach used for the detection of ALK rearrangements, as compared to both FISH and NGS based procedures. Conversely, ROS1 fusions were mostly assessed by FISH, due to the high percentage of false positive cases obtained by the IHC approach. Following the approval of alectinib as first-line treatment for ALK positive NSCLC patients, a significant increase in the number of institution implementing an NGS based approach, for the simultaneous evaluation of ALK and ROS1 fusions, has been observed in Italy (Gobbini et al., 2017; Marchetti et al., 2013).

The assessment of PD-L1 tumor proportion score (TPS, i.e. the percentage of PD-L1 positive cells) by IHC analysis is currently recommended in patients with newly diagnosed advanced NSCLC,

regardless of histological subtypes or smoking habits, in order to select those patients (PD-L1 TPS ≥ 50 %, evaluated on at least 100 tumor cells) who are candidate to first-line immunotherapy (Reck et al., 2016). Different antibody clones were implemented in different laboratories to assess PD-L1, mainly used as Laboratory Developed Test (LDT). These differences, along with the complexity related to both scoring reproducibility and IHC positivity cut-offs used in clinical setting, led to significant discrepancies in terms of percentage of positive and negative samples in a recent Italian real-life PD-L1 evaluation study, in comparison with the results observed in prospective clinical trials (Vigliar et al., 2019). PD-L1 IHC procedures have been only validated on FFPE samples, thus a CB should be prepared to analyze PD-L1 expression on cytological samples (Vigliar et al., 2019). The AIOM and the Italian Association of Pathology (SIAPEC) have recently published specific recommendation regarding PD-L1 testing in lung cancer, including clinical indications, methodological approaches, report modalities and results interpretations, in order to support oncologists and pathologists in their everyday practice (Barbareschi et al., 2019).

Another important issue concerning the implementation of relevant biomarkers analysis for NSCLC patients in clinical setting is related to the differences in the Regional reimbursement systems. Indeed, some Italian regions still lack specific reimbursement codes and request procedures for *EGFR*, *ALK*, *ROS1* and PD-L1. For the centralized laboratories, receiving tumor samples from different institutions, the lack of standardization in both test request and reimbursement procedures represent an urgent problem from the administrative point of view.

The recent development of next generation sequencing (NGS) accomplishes massive parallel gene mutation analysis with low amount of tissue and costs, favoring the identification of several potentially targetable molecular alterations, including *BRAF*, *KRAS* (*G12C* on exon 2), *HER2*, *MET* exon 14 skipping mutations, *RET* and *NTRK* 1–3 rearrangements (Drilon et al., 2016; Drilon and Kummar, 2018; Paik et al., 2015; Fakih et al., 2019; Planchard et al., 2017a), which may allow access to targeted treatments in the context of clinical trials or compassionate use programs. Molecular testing beyond *EGFR*, *ALK*, *ROS1*, and IHC for PD-L1, are not currently reimbursed by the Italian Health System, thus should not be performed outside of clinical trials context.

3. Treatment of advanced NSCLC

The decision of first-line therapy should be discussed within an experienced multidisciplinary team, taking into account tumor-related features, including histology (squamous versus non-squamous), the presence of oncogenic drivers (*EGFR* mutations, *ALK* or *ROS1* rearrangements), PD-L1 TPS, along with patients' characteristics, like age, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), comorbidities and treatment preferences.

Treatment algorithms of patients with oncogene-addicted and non-oncogene addicted, advanced NSCLC, are detailed below and shown in Figs. 1 and 2, respectively.

3.1. Oncogene-addicted NSCLC

3.1.1. EGFR-mutated disease

Specific TKIs are recommended as standard first-line treatment for patients affected by advanced NSCLC harboring "classic" *EGFR* mutations (*Del19* and *L858R*).

Different first- (gefitinib, erlotinib) and second- (afatinib) generation EGFR-TKIs have demonstrated to significantly improve progression-free survival (PFS) (median PFS ranging from 8.4–13.1 months) compared to platinum-based chemotherapy (from 4.6 to 6.9 moths), together with a more favorable toxicity profile (Mok et al., 2009; Han et al., 2012; Mitsudomi et al., 2010; Maemondo et al., 2010; Zhou et al., 2011; Rosell et al., 2012; Sequist et al., 2013; Wu et al., 2014). In these studies, the lack of overall survival (OS) benefit was likely due to high crossover rate for patients who were included in the chemotherapy arm, along with a critical study design, underpowered to detect OS differences.

Direct comparisons between these inhibitors have been performed within clinical trials. Although limited by the exclusion of patients with brain metastases and by the relevant toxicity emerged in dacomitinib arm, the phase 3 ARCHER 1050 demonstrated a statistically significant PFS (median 14.7 *versus* 9.2 months, HR 0.59, 95 % CI 0.47-0.74; $p < 0.0001$) and, for the first time, OS benefit (median 34.1 *versus* 26.8 months, HR 0.76, 95 % CI 0.58-0.99; $p = 0.0438$) in favor of dacomitinib (a second-generation TKI) compared to gefitinib (Wu et al., 2017; Mok et al., 2018). The direct comparison between osimertinib (a third-generation, irreversible TKI targeting both *EGFR* mutations and *EGFR T790M* resistance mutation) and first-generation TKIs was recently performed in FLAURA trial, enrolling treatment-naive patients affected by "classic" *EGFR*-mutated advanced NSCLC. Osimertinib significantly prolonged PFS (the primary endpoint, median 18.9 *versus* 10.2 months, HR 0.46, CI 95 % 0.37-0.57; $p < 0.001$) and OS (median 38.6 *versus* 31.8 months, HR 0.79, CI 95 % 0.64-0.99; $p = 0.0462$). In the control arm, at disease progression 47 % of the patients crossed-over to osimertinib (after T790M resistance mutation detecting), retracing a reliable representation of T790M mutation detection and targeting. Moreover, osimertinib was characterized by higher intracranial objective response rate (ORR) (65.6 % *versus* 43.3 %, OR 2.5, 95 % CI 1.2–5.2; $p = 0.011$) and longer time to brain disease progression when compared to first-generation TKI (median not reached *versus* 13.9 months, HR 0.48, 95 % CI 0.26-0.86; $p = 0.014$) (Soria et al., 2018; Planchard et al., 2019; Ramalingam et al., 2019). These results, accompanied by an improvement in terms of toxicity, suggest osimertinib as the favorite first-line treatment option for *EGFR*-mutated NSCLC patients harboring "classic" mutations. At the time of these guidelines writing, in Italy osimertinib was approved although not yet reimbursed for first-line treatment of *EGFR*-mutated NSCLC, while dacomitinib was not available.

With regard to "uncommon" *EGFR* alterations, mutations or duplications occurring in exon 18–21 may be suitable for treatment with gefitinib, erlotinib or afatinib, whereas exon 20 insertions or *de novo T790M* mutation are considered not responsive to first- and second-generation TKIs (Yang et al., 2015; Wu and Yu CJ, 2011; Yu HA1 and Hellmann, 2014; Kuiper et al., 2016; Klughammer et al., 2016; Chang et al., 2019). Nevertheless, considering its pharmacological profile and proved activity in pretreated patients, osimertinib may be considered for the treatment of baseline *T790M*-mutant NSCLC, while not enough data are available for its application in exon 20 insertion mutations (Fang et al., 2019).

For those patients who still continue to be treated with upfront first- or second-generation *EGFR* TKIs, disease progression usually occurs after 9–13 months of therapy, with approximately 60 % of cases developing *EGFR* exon 20 *T790M* resistance mutation. When T790M mutation is detected, treatment with osimertinib should be administered as second-line therapy, given its superiority compared to platinum/pemetrexed-based chemotherapy in the phase 3 AURA 3 study, in terms of investigator-assessed PFS (median 10.1 *versus* 4.4 months, HR 0.30, 95 % CI 0.23-0.41, $p < 0.001$), ORR, intracranial activity and efficacy, safety profile and patient-reported outcomes (Mok et al., 2017; Wu et al., 2018a). Considering these results, all *EGFR*-mutated patients progressing under first- or second-generation TKI should be tested for *T790M* resistance mutation, whose presence should be first sought in circulating tumor DNA (ctDNA, i.e. through a blood sample) and afterwards, if negative on ctDNA, within a metastatic site accessible for re-biopsy (Passiglia et al., 2018; Oxnard et al., 2016). When T790M is absent both in ctDNA and tumor tissue, histology-driven chemotherapy regimens should be proposed. However the recent advent of osimertinib in first-line setting will inevitably reduce the number of requests regarding both ctDNA and tissue T790M molecular testing in clinical practice. Additional resistance mechanisms to *EGFR* TKI include, among

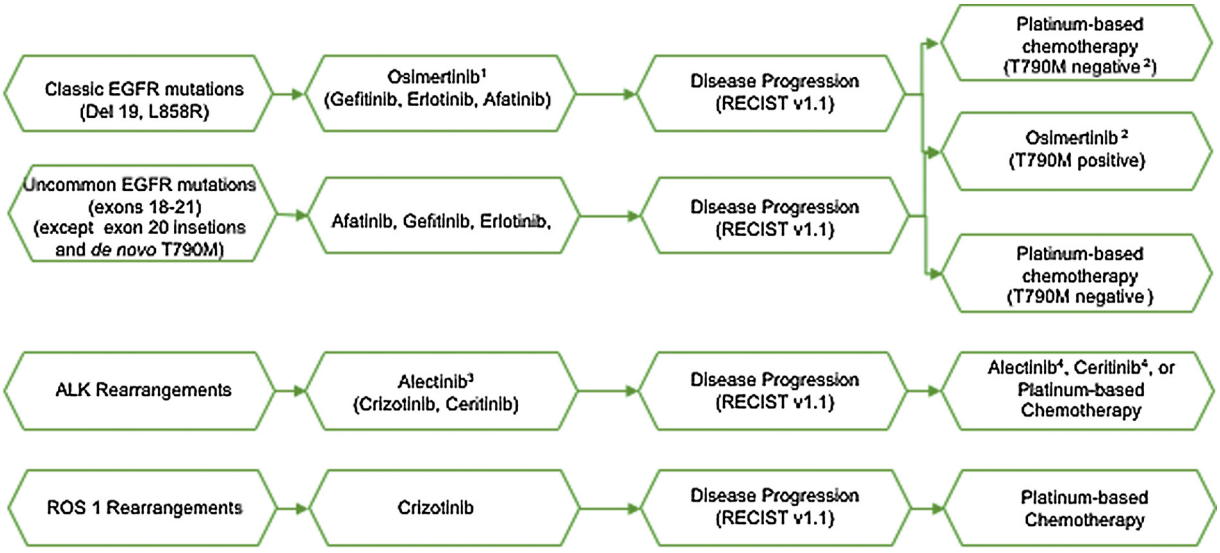

Fig. 1. Treatment algorithm of oncogene-addicted advanced NSCLC.

the others, *MET* and *HER2* amplifications, additional *EGFR* mutations (i.e. C797S for osimertinib) and phenotype transformation into small cell lung cancer (SCLC) (Sequist et al., 2011; Le et al., 2018). Treatment should be adapted according to the resistance mechanism detected (i.e. chemotherapy for SCLC), aware that some treatment options (i.e. combination of EGFR and MET inhibitors) are available only within clinical trials.

Treatment of oligoprogressive disease and beyond-progression strategies are applicable in *EGFR*-mutated NSCLC both after first/second- and third-generation TKIs, aiming to maintain the administration of these active and well-tolerated therapies for the longest timeframe (Park and Yu CJ, 2016; Lim et al., 2018; Xu et al., 2019; Jiang et al., 2019; Ni et al., 2019; Mu et al., 2019; Cortellini et al., 2019).

Although limited by the small number of oncogene-addicted patients included in the subgroup analysis of Impower 150 trial, the combination of carboplatin-paclitaxel-atezolizumab-bevacizumab may have some efficacy in these patients (Reck et al., 2019a). The quadruple combination, still not approved in Italy, is approved by EMA for the treatment of *EGFR*-mutated patients progressing to available *EGFR* inhibitors.

3.1.2. *ALK-rearranged disease*

Given the biological role of ALK as a targetable driver and the availability of several generations of ALK-inhibitors in clinical practice, their correct management is crucial to obtain the longest survival outcomes coupled with the best quality of life in advanced ALK-positive NSCLC patients.

The first-generation ALK-TKI crizotinib has been the standard of care in the first-line treatment of *ALK*-rearranged patients, achieving an ORR of 74 % (45 % in the comparator chemotherapy arm; $p < 0.001$) and a median PFS of 10.9 months (7.0 months with chemotherapy, HR 0.45, 95 % CI 0.35-0.60; $p < 0.001$) in the PROFILE 1014 phase 3 trial (Solomon et al., 2014, 2018a). Similar results in terms of ORR and PFS have been observed in the PROFILE 1029, an East-Asian phase 3 trial

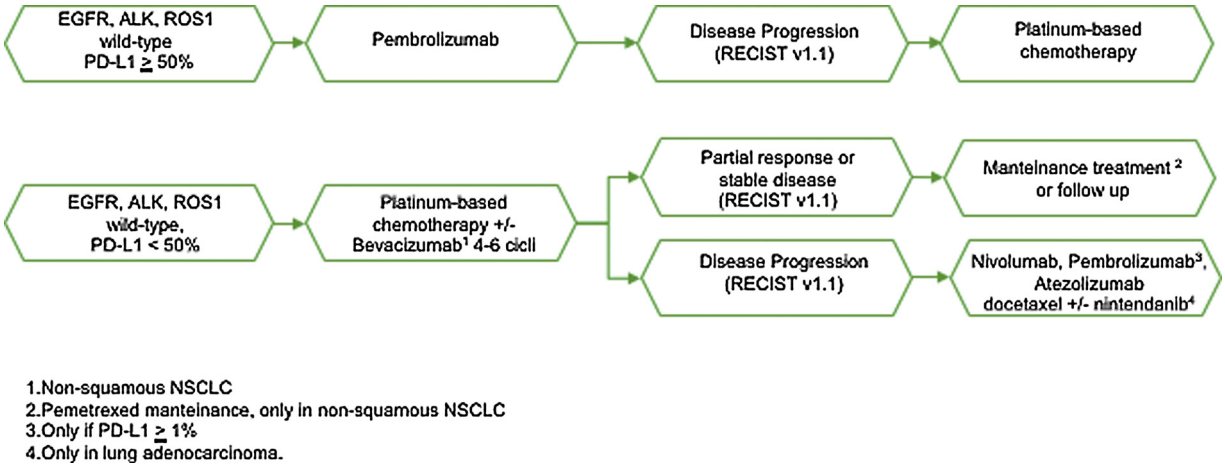

Fig. 2. Treatment algorithm of non oncogene-addicted advanced NSCLC.

Table 1
Clinical Recommendations for the Treatment of oncogene-addicted advanced NSCLC.

Global quality of evidence GRADE	Clinical recommendation	Strength of recommendation
Low	For patients with metastatic NSCLC harboring *"classic"* (exon 19 deletions, L858R) *EGFR* mutations, first-line therapy with osimertinib should be considered as treatment of choice, compared to first-generation EGFR inhibitors (gefitinib, erlotinib).	Strong for
Very low	For patients with metastatic NSCLC harboring *"classic"* (exon 19 deletions, L858R) *EGFR* mutations, first-line therapy with an EGFR inhibitor (gefitinib, erlotinib, afatinib) should be considered as treatment of choice, compared to chemotherapy.	Strong for
Very low	For patients with metastatic NSCLC harboring *EGFR* mutations, who experienced radiological progression to first/second generation EGFR inhibitors (gefitinib, erlotinib or afatinib), and had *T790M* mutation (detected through liquid or tumor biopsy), osimertinib should be considered as treatment of choice (compared to chemotherapy).	Strong for
Moderate	For patients with metastatic NSCLC harboring *ALK* rearrangements, first-line therapy with alectinib should be considered as treatment of choice compared to crizotinib.	Strong for
Moderate	For patients with metastatic NSCLC harboring *ALK* rearrangements, first-line therapy with crizotinib or ceritinib should be considered as treatment of choice, compared to chemotherapy.	Strong for
Low	For patients with metastatic NSCLC harboring *ALK* rearrangements, who experienced radiological progression to crizotinib, second-line therapy with ceritinib or alectinib should be considered as treatment of choice, compared to chemotherapy.	Strong for
Very low	For patients with metastatic NSCLC harboring *ROS1* rearrangements, first-line therapy with crizotinib should be considered as treatment of choice.	Strong for

with an overlapping design (Wu et al., 2018b). At the last update of PROFILE 1014, with a median follow-up of approximately 46 months, median OS was not reached and 47.5 months in the crizotinib and chemotherapy arms respectively, with 85 % of patients who had crossed-over to ALK inhibitors at progression to chemotherapy (HR 0.760, 95 % CI 0.54–1.05; p = 0.0978) (Solomon et al., 2014). After cross-over adjustment, first-line crizotinib was associated with a longer OS compared to chemotherapy (HR 0.346, 95 % CI bootstrap 0.08-0.71), thus sustaining the recommendation for the administration of the inhibitor in the upfront setting (Table 1).

As seen for *EGFR*-driven diseases, in the last years, second-generation ALK inhibitors, ceritinib (Soria et al., 2017), alectinib (Hida et al., 2017; Peters et al., 2017; Zhou et al., 2019), and brigatinib (Camidge et al., 2018), usually administered after crizotinib progression in a sequential treatment strategy, have been evaluated as first-line treatment options in phase 3 randomized trials enrolling ALK-positive patients (Recondo et al., 2018).

In the ASCEND-4 study, ceritinib (at the dose of 750 mg daily, fasted) was compared to first-line platinum/pemetrexed-based chemotherapy (Soria et al., 2017). The experimental arm was associated with a higher ORR (72.5 % *versus* 26.7 %) and a longer PFS (median 16.6 *versus* 8.1 months, HR 0.55, 95 % CI 0.42-0.73; p < 0.00001). With an immature data follow-up and frequent crossing-over to ALK inhibitors in the chemotherapy arm, there was a non-significant difference in OS (HR 0.73, 95 % IC 0.50–1.08, p = 0.056). Quality of life outcomes were better in the ceritinib arm, still considering that the dose utilized in ASCEND-4 is associated with a higher rate of adverse events compared with the current recommended dose of 450 mg daily with food, guaranteeing drug activity with a more favorable toxicity profile (Cho et al., 2019). Similar to crizotinib, ceritinib is currently recommended as a potential upfront therapy in this setting of patients (Table 1).

Given its design (with crizotinib as the comparator, including the systematic baseline and longitudinal evaluation of brain disease, indeed representing a stratification factor) and its long follow-up now available, ALEX trial is taken as a model (Hida et al., 2017). In alectinib and crizotinib arms respectively, median PFS was 34.8 *versus* 10.9 months (HR 0.43, 95 % CI 0.32-0.58), and ORR was 85.7 % *versus* 71.4 % (p = 0.009) (Camidge et al., 2019). Alectinib was moreover characterized by a higher intracranial ORR and by a longer time to brain disease progression when compared to crizotinib (HR 0.18, 95 % CI 0.09-0.36 in patients with baseline brain metastases; HR 0.14, 95 % CI 0.06-0.33 in patients without baseline brain metastases) (Gadgeel et al., 2018). Still waiting for mature OS estimations, these results, accompanied by a remarkable improvement of the toxicity profile, support panel recommendation of alectinib as treatment of choice for the first-line treatment of ALK-positive NSCLC patients (Table 1).

For those patients who still receive crizotinib in first-line, the administration of alectinib or ceritinib is recommended at the time of disease progression (Table 1), given the positivity of phase 3 trials conducted in this setting. In the ASCEND-5 study, ALK-positive patients who had progressed to one or two chemotherapy lines and to crizotinib were randomized to receive either ceritinib (750 mg daily, fasted) or chemotherapy (Shaw et al., 2017b). Ceritinib was superior in terms of PFS (median 5.4 *versus* 1.6 months, HR 0.49, 95 % CI 0.36-0.67; p < 0.0001), ORR (39.1 % *versus* 6.9 %), and intracranial ORR (35 % *versus* 5 %). The ALUR study compared alectinib with chemotherapy in *ALK*-rearranged patients who had previously received a line of chemotherapy and crizotinib (Novello et al., 2018). Again, alectinib performed better than chemotherapy in terms of PFS (median 9.6 *versus* 1.4 months, HR 0.15, 95 % CI 0.08–0.29; p < 0.001), ORR (37.5 % *versus* 2.9 %), and intracranial ORR in patients with brain metastases (36 % *versus* 0 %; p < 0.001).

Brigatinib, evaluated in the post-crizotinib setting in non-randomized phase 2 studies (Gettinger et al., 2016; Kim et al., 2017), is not approved yet in Italy.

The third-generation inhibitor lorlatinib has been proven to be active even at progression to two previous lines of ALK inhibitors (ORR 39 %, median PFS 6.9 months, intracranial ORR 55 %, median duration of intracranial disease response 14.5 months) (Shaw et al., 2017a; Solomon et al., 2018b), and it is currently available only in the context of clinical trials, expanded access or compassionate use programs.

With particular attention to brain metastases, treatment of oligo-progressive disease and beyond-progression strategies are applicable in *ALK*-rearranged disease as well as in *EGFR*-mutated one, aiming to maintain the administration of these active and well tolerated therapies for the longest timeframe (Ou et al., 2014; Gan et al., 2014; Zhao et al., 2019).

As seen for *EGFR*-mutated NSCLC, the combination of carboplatin-paclitaxel-atezolizumab-bevacizumab (Reck et al., 2019a), approved by EMA for the treatment of ALK-positive patients progressing to available ALK inhibitors, is not available yet for clinical use in Italy.

At the moment of these guidelines drafting (October 2019), crizotinib, alectinib and ceritinib are approved and reimbursed for the upfront treatment of ALK-positive NSCLC patients, while alectinib and ceritinib at progression or intolerance to crizotinib. Lorlatinib and Brigatinib are currently available in the context of an expanded access program, as well as the combination of carboplatin-paclitaxel-

Table 2
Clinical Recommendations for the Treatment of non oncogene-addicted advanced NSCLC.

Global quality of evidence GRADE	Clinical recommendation	Strength of recommendation
Moderate	For patients with EGFR/ALK wild-type, advanced NSCLC and PD-L1 TPS ≥ 50 %, first-line therapy with Pembrolizumab should be considered as treatment of choice	Strong for
Low	For patients with advanced, non-squamous NSCLC who completed 4–6 cycles of first-line chemotherapy with platinum-pemetrexed and experienced partial response or stable disease, maintenance therapy with single agent pemetrexed until disease progression or unacceptable toxicities could be considered as a treatment option.	Conditional for
Moderate	For patients with advanced NSCLC who experienced disease progression after first-line chemotherapy, immunotherapy with nivolumab, or atezolizumab, or pembrolizumab (PD-L1 TPS ≥ 1 %), should be considered as a treatment of choice	Strong for
Very low	For patients with advanced lung adenocarcinoma who experienced disease progression after first-line chemotherapy, the combination of nintedanib plus docetaxel could be considered as a treatment option.	Conditional for

atezolizumab-bevacizumab. The clinical assessment of resistance mechanisms to ALK-TKIs by liquid and/or tumor re-biopsy, is not currently recommended as standard practice, thus is limited to the research setting.

3.1.3. ROS1-rearranged disease

With some exceptions, ALK- and ROS1-driven diseases are targeted by the same inhibitors, whose administration generates unprecedented results in the peculiar population of *ROS1*-rearranged NSCLC. The relative rarity of *ROS1* rearrangements precludes the randomization of ROS1-positive patients in trials comparing ROS1 inhibitors with chemotherapy and the evidence sustaining its administration in the front-line setting are driven from single-arm studies.

Crizotinib is the only inhibitor approved for the treatment of ROS1-positive disease, currently recommended as treatment of choice in first-line setting (Table 1). Crizotinib has been evaluated in several phase 2 trials, mainly in chemotherapy-pretreated patients (Bergethon et al., 2012; Michels et al., 2019; Wu et al., 2018c; Landi et al., 2019). The results obtained in *ROS1*-rearranged NSCLC patients included in the phase 1 PROFILE 1001 study have been recently updated (Shaw et al., 2014b; Shaw et al., 2019). ORR, median PFS e median OS were respectively 72 %, 19.3 and 51.4 months. The adoption of beyond progression strategies and the local treatment of oligoprogressive disease (Liu et al., 2018) likely contributed to these long survival outcomes, as well as the peculiar activity of pemetrexed-based regimens (Mazières et al., 2015) along with the availability of several novel-generation ALK/ROS1 inhibitors under clinical evaluation. Among these latter, lorlatinib and repotrectinib have showed the most promising results. In ROS1-positive, crizotinib-pretreated patients, in the context of a phase 2 trial, lorlatinib demonstrated an ORR of 26 %, stable disease (almost invariably with disease shrinkage) 47 %, median PFS 8.5 months, while more than 50 % of patients with measurable brain metastases achieved intracranial disease response (Ou et al., 2018). Lorlatinib is not approved yet in Italy, nevertheless ROS1-positive patients progressing to crizotinib should be given the opportunity to receive the drug in the context of clinical trials, expanded access or compassionate use programs.

Albeit data on repotrectinib are preliminary, its successful targeting of the most frequent and recalcitrant *G2032R ROS1* resistance mutation, coupled with a potent activity against brain metastases, make it a suitable candidate (again within clinical trials, expanded access or compassionate use programs) in the sequential treatment strategy of ROS1-positive patients (Cho and Drilon, 2019).

3.1.4. Other oncogenic drivers

Of note, the combination of dabrafenib and trametinib, has recently received EMA approval for the first-line treatment of patients with advanced NSCLC harboring *BRAF V600E* mutation (Planchard et al., 2017b). However, this combination, as well as all the mentioned targeted therapies beyond EFGR, ALK and ROS1 inhibitors (Section 2.1), are not currently approved in Italy. Therefore, may be only considered in the context of clinical trials and compassionate use programs, or recurring to the special financial found for new innovative oncological drugs and/or to other founds (i.e. law 326/2003) promoted by the Italian Pharmacology Agency (AIFA).

3.2. Non oncogene-addicted NSCLC

3.2.1. First-line treatment: immunotherapy

The advent of immunotherapy produced a paradigm shift of first-line treatment for about 30 % of patients with *EGFR/ALK* wild-type, advanced NSCLC, whose tumors overexpress PD-L1 (TPS ≥ 50 %) (Reck et al., 2016). The results of the phase 3 KEYNOTE-024 randomized trial (Reck et al., 2016) first showed that the anti-PD1 pembrolizumab significantly improved ORR (44.8 % *versus* 27.8 %), PFS (median 10.3 *versus* 6.0 months, HR 0.50, 95 % CI 0.37-0.68; $p < 0.001$), OS (median 26.3 *versus* 14.2 months, HR 0.65, 95 % CI 0.50 to 0.86; $p = 0.001$), tolerability (grade 3–5 adverse events: 31.2 % *versus* 53.3 %), and quality of life, as compared to platinum-based chemotherapy, becoming the new standard of care in this subgroup of patients (Reck et al., 2016) (Table 2). A recent update of this trial was presented at the 2019 World Conference on Lung Cancer (WCLC) meeting, showing as about 43 % of patients treated with immunotherapy were alive at three years, compared with 25 % in the chemotherapy group (Reck et al., 2019b).

Recently, the phase 3 KEYNOTE-042 and IMPower-110 trials (Mok et al., 2019; Spigel et al., 2019) demonstrated the superiority of pembrolizumab (HR 0.69, 95 % CI 0.56-0.85; $p = 0.0003$) and atezolizumab (HR 0.59, 95 % CI 0.39- 0.89; $p = 0.0106$), respectively, over first-line platinum-based chemotherapy, in high PD-L1 expressors, confirming single-agent immunotherapy as an effective treatment option in this setting of patients.

Adding immunotherapy to platinum-chemotherapy is emerging also as an effective and tolerable upfront strategy, in non-oncogene addicted NSCLC. Four randomized phase 3 trials, including KEYNOTE-189, IMPower-150, IMPower-132, and IMPower-130 (Gandhi et al., 2018; Gadgeel et al., 2019; Socinski et al., 2018; Barlesi et al., 2018; West et al., 2019), have recently demonstrated that immune-chemotherapy combinations significantly increased ORR, PFS and OS, compared to chemotherapy alone (HR 0.56, 95 % CI 0.45-0.70; HR 0.78, 95 % CI 0.64-0.96; HR 0.81, 95 % CI 0.64–1.03; HR 0.79, 95 % CI 0.64-0.98, respectively), irrespectively of tumor PD-L1 expression levels, in patients with non-squamous metastatic disease. Conversely, the randomized phase 3 trials KEYNOTE-407 and IMPower-131 (Paz-Ares et al., 2018; Jotte et al., 2018), combining immunotherapy with first-line platinum-based chemotherapy in squamous NSCLC showed conflicting results in unselected populations. The addition of pembrolizumab to platinum/ (nab-)paclitaxel significantly increase OS (HR 0.61, 95 % CI 0.38-0.98), with benefit maintained across different PD-L1 selected subgroups (Paz-Ares et al., 2018), whereas no OS improvement has been reported for the combination of atezolizumab with the same chemotherapeutic regimen (HR 0.87, 95 % CI 0.67–1.13) (Jotte et al.,

2018), except for patients with high tumor PD-L1 expression (HR 0.48, 95 % CI 0.29, 0.81) (Cappuzzo et al., 2019).

Another promising approach, currently under investigation, include the potential combination of different immunotherapeutic agents, such as PD-1/PD-L1 and CTLA-4 inhibitors. The CheckMate-227 trial (Hellmann et al., 2018) first demonstrated that nivolumab plus ipilimumab significantly increased the primary end-point of PFS (HR 0.58, 97.5 % CI: 0.41–0.8; p < 0.001) compared to platinum chemotherapy, in non-oncogene addicted, advanced NSCLC patients with high tumor mutation burden (TMB ≥ 10 mutations per megabase, mut/Mb). This benefit was observed irrespectively of PD-L1 expression levels, while no PFS difference were reported in patients with TMB < 10 mut/Mb (HR 1.07, 95 % CI 0.84–1.35). Subsequent OS analysis confirmed a significant benefit in favor of nivolumab plus ipilimumab in both TMB-high (HR 0.68, 95 % CI: 0.51–0.91) and TMB-low (HR 0.75, 95 % CI: 0.59-0.94) subgroups, thus questioning the predictive role of this biomarker for the clinical selection of patients. Recently, the coprimary endpoint of the study (OS in PD-L1 ≥ 1 %) has been also met, with nivolumab plus ipilimumab combination associated to a significant improvement in OS compared to platinum chemotherapy, both in PD-L1 ≥ 1 % (HR 0.79, 95 % CI 0.65-0.96) and in PD-L1 < 1 % (HR 0.62, 95 % CI 0.49-0.79) populations (Hellmann et al., 2019).

Overall, the results of these studies suggested that immunotherapy combinations might become a new standard of care for non-oncogene addicted NSCLC patients. At the time of these guidelines writing (October 2019) pembrolizumab represents the only immunotherapeutic agents approved and recommended in Italy as standard first-line treatment of non-oncogene addicted, metastatic NSCLC patients, with PD-L1 TPS ≥ 50 % (Table 2).

3.2.2. First-line treatment: chemotherapy

For all other patients with *EGFR/ALK/ROS1* wild-type, PD-L1 expression < 50 %, advanced NSCLC, without major comorbidities, platinum-based combinations according to the tumor histological subtype should be recommended as upfront treatment. Particularly up to six cycles of platinum-combinations with a third generation cytotoxic agent, including gemcitabine, vinorelbine, or taxanes, are recommended in patients with both squamous and non-squamous subtypes (Schiller et al., 2002; Grossi et al., 2009), while platinum-pemetrexed is the preferred regimen in non-squamous histology (Scagliotti et al., 2008) (Table 2). Based on the results of PARAMOUNT trial (Paz-Ares et al., 2012), maintenance treatment with single agent pemetrexed until disease progression or unacceptable toxicities, is currently recommended as potential option for patients with non-squamous advanced NSCLC, who experienced partial response or stable disease after four cycles of platinum-pemetrexed (Table 2). There have been multiple meta-analysis comparing cisplatin and carboplatin regimens to date, without significant differences in survival (de Castria et al., 2013; Ardizzoni et al., 2007). However, the meta-analysis by Ardizzoni et al. (2007) showed that, when combined with third-generation agents, cisplatin was associated to a significant increase in response rate as well as more favorable OS, emerging as preferred option in this setting. Another meta-analysis suggested that four *versus* six cycles of platinum-based first-line chemotherapy led to similar OS in advanced NSCLC patients (Rossi et al., 2014), thus performing four cycles of chemotherapy could be considered as a rationale choice in real-world practice. Randomized trials and meta-analysis (Sandler et al., 2006; Reck et al., 2009, 2010; Lima et al., 2011; Soria et al., 2013) showed that the addition of bevacizumab to paclitaxel/carboplatin regimens improved ORR, PFS, and OS as compared to chemotherapy alone, in patients with non-squamous subtype and PS 0–1, thus the triplet may be considered as an alternative treatment option in selected patients (Table 2).

3.2.3. Subsequent lines of treatment

Recently, four phase 3 randomized trials consistently demonstrated that PD-1/PD-L1 inhibitors (nivolumab, pembrolizumab, atezolizumab) are more effective and better tolerated than second-line single agent docetaxel (Brahmer et al., 2015; Borghaei et al., 2015; Herbst et al., 2016; Rittmeyer et al., 2017), and are currently recommended as treatment of choice for NSCLC patients who experienced disease progression after platinum-combinations, regardless of tumor histological subtype and PD-L1 status, except for pembrolizumab, which received regulatory approval only in case of PD-L1-positivity (TPS ≥ 1 %) (Table 2). The introduction of immunotherapeutic agents in clinical practice was associated with unprecedent 5-year OS rate, ranging from 14.5%–15.5 %, in pre-treated unselected population (Gettinger et al., 2019). Antiangiogenic agents, such as the multi-kinase inhibitor nintedanib and the anti-vascular endothelial growth factor receptor 2 (VEGFR-2) monoclonal antibody ramucirumab have been investigated in combination with single agent second-line chemotherapy in two randomized phase 3 trials, LUMELung1 and REVEL respectively (Reck et al., 2014; Garon et al., 2014). The addition of nintedanib to docetaxel resulted in a significant improvement in OS in pre-treated NSCLC patients with adenocarcinoma subtype (median 12.6 *versus* 10.3 months, HR 0.83, 95 % CI 0.70-0.99), especially when patients had experienced disease progression within nine months from the beginning of first-line therapy (median 10.9 *versus* 7.9 months, HR 0.75, 95 % CI 0.60-0.92; $p = 0.0073$), even if at cost of increased severe gastrointestinal toxicities (Reck et al., 2014). Recently, a multicenter Italian phase 2 study revealed the combination of nintedanib with weekly docetaxel is equally effective (HR 0.88, 95 % CI 0.48–1.61; $p = 0.3131$) and better tolerated than standard three-weekly schedule, emerging as a valid alternative regimen for clinical use (Capelletto et al., 2019). To date the combination of nintedanib and docetaxel is recommended as potential second-line treatment option for patients with metastatic adenocarcinoma (Table 2), with weekly regimen currently under evaluation by regulatory authorities. Even if the REVEL trial showed a significant OS improvement from the addition of ramucirumab to docetaxel in the same setting of patients (Garon et al., 2014), however this combination is currently not approved in Italy for clinical use.

In absence of direct comparisons among these new approved agents as well as of validated predictive biomarkers, the decision about second-line therapy should take into account several factors, including tumor histology, best response and toxicities to prior treatment, patients' comorbidities and preference in order to select the most effective and tolerable treatment for each patient.

3.2.4. Elderly and performance status 2

Single agent chemotherapy with third-generation agents has been considered the standard of care in both elderly and ECOG PS 2 NSCLC populations for a long time. Several randomized studied included in a recent meta-analysis (Santos et al., 2015) showed that carboplatin-based combinations were associated to a significant increase in OS (HR 0.67; 95 % CI 0.59–0.78) as compared to single agent regimens in patients over 70 years of age, whereas cisplatin-based not (HR 0.91; 95 % CI 0.77–1.08). Conversely, a pooled analysis of MILES-3 and MILES-4 trials (Gridelli et al., 2018) demonstrated only a not significant trend toward a survival benefit with the addition of cisplatin to single agent chemotherapy (median OS 9.6 *versus* 7.5 months, HR 0.86, 95 % CI 0.70–1.04; $p = 0.14$), along with a significant increase of severe both hematological and non-hematological toxicities, in advanced NSCLC patients older than 70 years, with an ECOG PS of 0-1. Similarly, different randomized studies and meta-analysis showed that platinum-doublets significantly increase RR and OS in advanced NSCLC patients with ECOG PS 2, even if at cost of increased hematological toxicities (Bronte et al., 2015). Overall, these data suggest that both elderly and PS 2 patients are very heterogeneous populations, thus a careful selection of good candidate to platinum-chemotherapy (preferably carboplatin), based on clinical parameters and comprehensive geriatric assessment (CGA) is currently recommended in order to minimize the risk of excessive toxicity in frail populations.

Although no studies fully dedicated to elderly NSCLC patients have been conducted yet, evidences coming from subgroup analysis of randomized trials or retrospective/real world series, overall suggested that immunotherapy efficacy and tolerability are similar to that observed in the overall population, whereas data regarding PS 2 patients are currently lacking, with final results of ongoing clinical trials still pending (Marus et al., 2018; Nosaki et al., 2019; Passaro et al., 2019).

4. Methodology

The AIOM Clinical Practice Guidelines were developed in accordance to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) method.

4.1. Literature search

The literature search was conducted using Medline (PubMed), Embase-databases and Cochrane-Library, up to September 2019. The clinical question was formulated according to the P.I.C.O (P: Population; I: Intervention; C: Comparison; O: Outcome) process, and P.I.C.O keywords were used as literature search terms. The literature search was limited to human studies in English language, and relevant studies were selected by expert members of the AIOM Lung Cancer Working Group. Relevant abstracts from the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), International Society for the study of Lung Cancer and other international or national meetings were also included as scientific support to published evidences. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram was used to describe literature search and trials selection processes for each clinical question.

4.2. Quality of evidence

The following features were evaluated by the expert members of the Working Group in order to define the quality of available, selected studies: risk of bias, precision, directness, consistency, and publication bias.

The global quality of evidence was defined as follow:

- High (high grade of confidence in the study results): high probability that the estimated effect is similar to the true effect.
- Moderate (moderate grade of confidence in the study results): moderate probability that the estimated effect is similar to the true effect, but limited possibility that it is substantially different.
- Low (low grade of confidence in the study results): limited probability that the estimated effect is similar to the true effect, with high possibility that it is substantially different
- Very low (very low grade of confidence in the study results): very limited probability that the estimated effect is similar to the true effect, with very high possibility that it is substantially different.

4.3. Strength of recommendation

The strength of clinical recommendations is graduated on four levels according to their clinical relevance, considering the benefit/risk outcomes ratio, the quality of evidence and other additional variables (equity, acceptability, feasibility, and patients' preference):

- Strong for: The intervention should be considered as the treatment of choice (benefits are higher than risks)
- Conditional for: The intervention may be considered as treatment of choice (not sure that benefits are higher than risks)
- Conditional against: The intervention should not be considered as treatment of choice, except for selected cases after discussion with the patient (not sure that benefits are higher than risks)
- Strong against: The intervention must be never considered as a treatment option (risks are higher than benefits)

4.4. Clinical recommendation

Clinical recommendations were assessed reflecting the clinical relevance of a medical intervention, being formulated according to the P.I.C.O (P: Population; I: Intervention; C: Comparison; O: Outcome) process. All clinical recommendations include both strengths levels and global quality of evidence grading, according to the GRADE method.

Declaration of Competing Interest

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COI: consultant and/or speaker's fee for Eli Lilly, MSD, Roche, BMS, Takeda, Pfizer, Abbvie, Celgene, Astra Zeneca and Boehringer Ingelheim.

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