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REVIEW

Advanced non-small-cell lung cancer: how to manage non-oncogene disease

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Abstract

The therapeutic approach to patients affected by advanced non-small-cell lung cancer (NSCLC) is facing rapid and continuous evolution. In recent years, the emergence of new treatment strategies, such as immunotherapy and tyrosine kinase inhibitors, has revolutionized the treatment algorithm and the prognosis of patients with NSCLC. In the non-oncogene-addicted disease, immune-checkpoint inhibitors, either as single agents or combined with chemotherapy, outperformed standard chemotherapy in both untreated and previously treated patients. However, many patients still do not derive the expected benefit from current treatments. Despite representing the only biomarker currently used in clinical practice to guide treatment selection, PD-L1 expression has been proven an imperfect predictor of immunotherapy outcomes. The evaluation of clinical factors remains essential to detect patients that would benefit the most from a particular treatment approach, but the identification of additional biological and molecular predictive tools is a priority. Herein, we provide a comprehensive though concise review of the current treatment approaches to advanced NSCLC in patients without molecular driver alterations, with an additional focus on special populations, concomitant medications, and other considerations that might be useful for daily clinical practice.

Keywords: advanced non-small-cell lung cancer, chemotherapy, immunotherapy.

Citation

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Introduction

The transition from chemotherapy-based to personalized therapy transformed the face of advanced non-small-cell lung cancer (NSCLC) treatment, with a consistent increase in life expectancy and quality of life. The NSCLC identity card has been progressively enriched with genomic alterations that predict response to tyrosine kinase inhibitors. Almost 20% of lung adenocarcinomas are characterized by *EGFR* mutations, which are targets of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) (erlotinib, gefitinib, afatinib, dacomitinib, osimertinib).[1] A rearrangement of the *ALK* gene is found in 3–5% of lung adenocarcinomas, determining the sensitivity to anaplastic lymphoma kinase (ALK) TKIs of different generations (crizotinib, ceritinib, brigatinib, alectinib, lorlatinib).[1] In addition, *ROS1* and *RET* rearrangements, *MET* exon 14 skipping mutations, *BRAF V600E* mutation, and *HER2* alterations are rare but susceptible to specific TKIs.[1]

The PD-1–PD-L1 axis represents the co-stimulatory mechanism of T cell receptor downregulation[2] used as the primary mechanism of escape from the immune system by cancer cells. Several monoclonal antibodies, such as pembrolizumab, atezolizumab and nivolumab, have been developed to target this axis, allowing the adaptive immune system to hit efficaciously malignant cells.[2] Another class of antibodies, including ipilimumab and tremelimumab, have been designed to hit CTLA-4 involved primarily in a checkpoint in activated T cells and antigen-presenting cells.[3] Currently, in the context of non-oncogene-addicted disease, immune-checkpoint inhibitors (ICIs) constitute the upfront standard of care as single agents or in combination with platinum-based chemotherapy (CT).[1]

To date, intratumoural expression of PD-L1 is the only biomarker extensively validated within prospective clinical trials to identify patients who will more likely benefit from immunotherapy. In particular, PD-L1 positivity predicts

sensitivity to ICI single-agent strategy with the threshold of 50% as the demarcation point of maximum benefit in the first-line setting.[4] In parallel, combination strategies also demonstrated remarkable efficacy regardless of PD-L1 expression.[1,4] In this expanding scenario of upfront alternatives, medical oncologists must deal with the appropriate systemic therapy prescription.

The heterogeneity of clinical and biological characteristics between patients raises the demand for a tailored approach. The lack of direct prospective trials in specific settings, such as for high PD-L1 disease or for special populations, does not allow for standardizing the first-line treatment in a fixed algorithm fashion. Furthermore, the redefinition of the upfront approach created an urgent need for defining the subsequent lines of treatment consisting of CT or antiangiogenic agents with shreds of evidence mainly derived from the pre-immunotherapy era.

This practical review aims to address the proper interpretation of clinical cases within a real-world context focusing firstly on the diagnostic process, through the choice of upfront and subsequent therapies, and with a focus point on frail patients.

Biomarker for treatment selection

Despite the increasing identification of new molecular alterations and the development of targeted therapies, most patients with NSCLC are still affected by non-oncogene-addicted tumours. The introduction of immunotherapy, alone or in combination with other molecules, has dramatically changed prognosis in these patients. At the same time, identifying biomarkers of responsiveness is crucial to select which patient could benefit the most from monotherapy or combination therapy.

The assumption behind ICI efficacy is that non-synonymous mutations, resulting in mutated peptides, must arise in tumour cells to be presented to the immune system by major histocompatibility complex (MHC) proteins to activate recognition and elimination of aberrant cells. However, cancer cells are able to elude the immune system through evasion mechanisms, which represent the target of ICI agents.[1,4] With the PD-1–PD-L1 axis being one of the most studied pathways of immune evasion, the percentage of expression by immunohistochemistry of membranous PD-L1, evaluated on at least 100 neoplastic cells according to Tumor Proportion Score (TPS), is the first and currently only validated predictive biomarker for ICI response. Various immunohistochemistry assays, which consist of a specific anti-PD-1/PD-L1 antibody and its associated detection system, have been developed: Dako 22C3 (used in pembrolizumab and cemiplimab trials), Dako 28-8 (mostly used in trials testing nivolumab), Ventana SP142 (mostly used in trials testing atezolizumab), Ventana SP263 (mostly used in trials testing durvalumab) and Dako 73-10 (mostly used in trials testing avelumab). Many studies were performed to evaluate the concordance between these assays (excluding the avelumab one), showing that Dako 22C3, Dako 28-8 and Ventana SP263 produce comparable results whilst Ventana SP142 stains for fewer tumour cells.[5–8]

In selecting the correct treatment option, it is fundamental to report the positivity detected in relation to the available clinically relevant cut-offs (≥50% for first-line and ≥1% for second-line treatments). It is preferable to report a precise estimate of the percentage of PD-L1 expression according to TPS. In fact, despite the use of a specific cut-off, as a continuous variable, it has been noted that increasing levels of PD-L1 expression correspond to greater benefit from ICIs.[9,10]

However, PD-L1 TPS is not a perfect biomarker because remarkable responses to ICIs have also been observed in patients with PD-L1 negative/low tumours[11,12] and, on the other hand, higher levels of PD-L1 do not always reflect deeper efficacy of these agents. The reasons behind these observations are not entirely understood but some hypotheses may be proposed, including spatial and temporal variability of PD-L1 expression within the tumour, dependence from mechanisms of evasion other than PD-1–PD-L1 axis (for example, PD-L2, IDO1, LAG3, TIM3), constitutive PD-L1 expression rather than as a response to immune assault (e.g. NSCLC harbouring driver mutations), quality and quantity of tumour neoantigens and the capability to present them to immune system cells, the presence/absence of tumour immune infiltrates, and epigenetic mechanisms of regulation such as non-coding RNA or DNA methylation.[13–20]

Another alternative biomarker under assessment in clinical trials to predict ICI response is tumour mutational burden (TMB), defined as the number of non-synonymous missense mutations per megabase (Mb) in tumour genome evaluated through whole-exome/next-generation sequencing on tumour samples or blood samples (blood TMB). TMB is considered a surrogate for the presence of neoantigens, which could increase the probability of presentation, recognition and elimination of cancer cells by the host immune system. Issues about TMB as a biomarker in clinical practice may rely on non-univocal cut-off levels across trials (≥10 muts/Mb using the FoundationOne CDx assay in Checkmate-227;[21] ≥20 muts/Mb in Neptune trial[22]), tissue or circulating DNA availability, and technical artifacts during TMB analyses. Furthermore, as data regarding the correlation between TMB and blood TMB across clinical trials are inconsistent in terms of survival benefit,[21,23,24] these biomarkers are not approved and must not be used to select ICI responders.

Single-agent immunotherapy versus chemo-immunotherapy as upfront strategy: which one is better?

The Keynote 024 trial represents a milestone in the treatment of NSCLC, establishing the superiority of single-agent immunotherapy over platinum-based CT in patients with advanced NSCLC with PD-L1 expression ≥50%.[25,26] The median

overall survival (OS) was doubled by pembrolizumab, as it was 26.3 months with the PD-1 inhibitor versus 13.4 months with CT, with 5-year OS rates of 31.9% *versus* 16.3%, with a 43.7% of patients crossing over to pembrolizumab. Similarly, the Keynote 042 trial showed the superiority of pembrolizumab as single-agent therapy over platinum-based CT in advanced NSCLC with positive PD-L1 expression, setting the cut-off to ≥1%.[27] However, the subgroup analysis demonstrated that the advantage of pembrolizumab over CT was mainly evident in patients with PD-L1 expression ≥50% (HR 0.69, 95% CI 0.56–0.85), whilst the two treatment strategies led to similar survival outcomes when PD-L1 was 1–49% (HR 0.92, 95% CI 0.77–1.11). Therefore, pembrolizumab monotherapy became the treatment of choice for patients with high PD-L1 expression, but its approval was also extended to the population with any PD-L1 positivity by several regulatory agencies, including the FDA. More recently, the empty spots represented by the population of NSCLC with negative PD-L1 expression and, partially, by those with PD-L1 expression 1–49% were filled following the results of two pivotal trials: the Keynote 189 trial for patients with non-squamous histology, and the Keynote 407 trial for those with squamous histology.[28–31] These phase III trials enrolled patients diagnosed with stage IV NSCLC, randomized to receive histology-driven platinum-based CT plus pembrolizumab or placebo. Both showed a previously unobserved improvement of progression-free survival (PFS) and OS with the combination strategy, similar to that shown by trials testing single-agent pembrolizumab in the PD-L1-high population but regardless of PD-L1 expression. The addition of pembrolizumab to CT resulted in the prolongation of OS from 10.7 months to 22.0 months (HR 0.56, 95% CI 0.45–0.70) in non-squamous histology and from 11.6 months to 17.1 months (HR 0.71, 95% CI 0.58–0.88) in squamous histology.[28–31] Consistently, median PFS increased from 4.9 months with CT to 9.0 months with chemo-immunotherapy (HR 0.48, 95% CI 0.40–0.58) in the Keynote 189 trial and from 5.1 months with CT to 8.0 months with chemo-immunotherapy (HR 0.57, 95% CI 0.47–0.69) in the Keynote 407 trial. Besides the undoubted efficacy of immunotherapy, its improved tolerability represents a core strength point as it confers no additive toxicity in combination with CT, also allowing the treatment of patients who may not be fit enough to receive CT doublets. Further studies have confirmed the previous findings with other agents targeting the PD-1–PD-L1 axis. The Impower 110 and the EMPOWER-Lung 1, respectively, demonstrated the superiority of the PD-L1 inhibitor atezolizumab and of the PD-1 inhibitor cemiplimab as single agents over platinum-based CT amongst patients with NSCLC with high PD-L1 expression.[9,32] Similarly, IMpower 130 and IMpower 150 showed that combining CT with atezolizumab or atezolizumab plus bevacizumab, respectively, enhanced survival regardless of PD-L1 expression in non-squamous NSCLC.[33,34] Analogously, the combination of the anti-PD-1 sintilimab and CT prolonged median PFS (OS not reached) in Asian patients affected by locally advanced or advanced non-squamous NSCLC.[35]

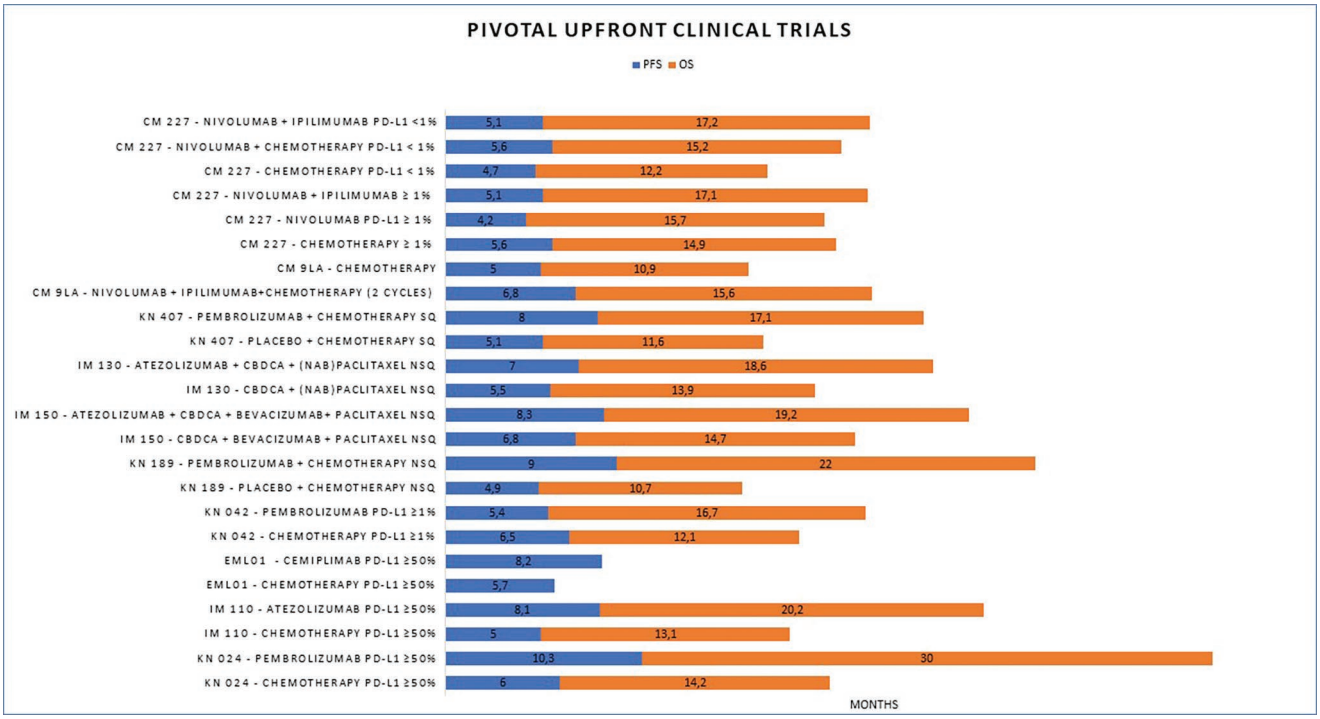
A notable mention is deserved by IMpower 131 and IMpower 132 trials, which evaluated the addition of atezolizumab to histology-driven platinum-based CT in squamous and non-squamous advanced NSCLC, respectively, regardless of PD-L1 expression.[36–38] Despite showing a PFS improvement, these trials did not meet the OS survival advantage with combination strategy as a co-primary endpoint.

Immune combinations between PD-1 and CTLA4 inhibitors also proved effective in advanced NSCLC, either with or without the addition of CT. The combination of nivolumab and ipilimumab was evaluated by the phase III CheckMate-227 trial, leading to prolonged PFS, OS and improved objective response rate (ORR) compared to CT in both squamous and non-squamous histology, regardless of PD-L1 expression.[39] The addition of short-course CT to the same immune combination also improved the outcomes of patients with PD-L1-unselected advanced NSCLC compared to standard CT and represents a further treatment option for patients with either squamous or non-squamous histology.[40] Figure 1 reports the survival outcomes of pivotal upfront clinical trials in advanced, non-oncogene-addicted NSCLC.

Interestingly, a recent meta-analysis of eight randomized clinical trials showed that the addition of a PD-1 inhibitor to histology-driven platinum-based CT was superior to that of a PD-L1 inhibitor in non-oncogene-addicted advanced NSCLC, either in terms of PFS (HR 0.82, 95% CI 0.71–0.95; p=0.007), OS (HR 0.77, 95% CI 0.65–0.91; p=0.002) or ORR (RR 1.33, 95% CI 1.08–1.56; p=0.0002).[16] Moreover, adding a PD-1 inhibitor to CT was also safer, in terms of grade ≥3 treatment-related adverse events, than adding a PD-L1 inhibitor to CT (RR 0.84, 95% CI 0.73–0.98; p=0.027).[41]

In light of these studies, the combination of histology-driven platinum-based CT and immunotherapy seems to represent the optimal treatment strategy for patients with low or absent PD-L1 expression. At the same time, indirect comparisons showed comparable survival with PD-(L)1 inhibitors alone or combined with CT in those with high (≥50%) PD-L1 expression. Nonetheless, by deeply analysing the Kaplan–Meier curves of PFS of these trials, a later separation between the curves of those evaluating single-agent ICIs *versus* CT compared to those testing ICIs plus CT *versus* CT alone can be easily detected.[42] Thus, a combination strategy may avoid the loss of approximately 20% of patients due to disease progression or death within the first 3–6 months of treatment, as observed with single-agent immunotherapy.[42] Moreover, in agreement with the lower early loss of patients progressing during the first months of treatment with the combination strategy, the ORR is also higher with the combination of ICI and CT (ORR 52–61%) compared to ICI monotherapy (ORR 37–44%).[42] A recent meta-analysis of 14 randomized clinical trials evaluated the best treatment option for non-oncogene-addicted advanced NSCLC with PD-L1 expression ≥50%.[43] The results evidenced that the addition of platinum-based CT to a PD-(L)1 inhibitor significantly improves both PFS

Figure 1. Overall survival and progression-free survival of pivotal upfront clinical trials in advanced, non-oncogene addicted, non-small-cell lung cancer.



CBDCA, carboplatin; CM, Checkmate; EML, Empower Lung; IM, Impower; KN, Keynote; NSQ, non-squamous; SQ, squamous.

(HR 0.59, 95% CI 0.43–0.79; p=0.0005) and ORR (RR 1.66, 95% CI 1.14–2.42; p=0.008) compared to PD-(L)1 inhibitors as single agents, though it has no statistically significant impact on OS (HR 0.99, 95% CI 0.77–1.27; p=0.95). On the other hand, expectedly, the addition of CT determined a higher risk of grade ≥3 treatment-related adverse events.[43] These studies indicate that selecting patients who should be treated with ICIs alone or combined with CT remains challenging and needs a thorough evaluation. Higher PD-L1 expression cut-offs may offer more reliability, as demonstrated by the improved outcomes obtained in patients with NSCLC with PD-L1 expression ≥90% reported in the retrospective analysis by Aguilar et al.[44] and by the analysis of the EMPOWER-Lung 1, which showed increasing ORR, PFS and OS according to higher PD-L1 levels.[9] Several gene mutations may also play a role. *STK11* and *KEAP1* mutations have been associated with poor responses to immunotherapy, possibly explained by a 'cold' tumour immune microenvironment.[45–47] However, more recent evidence shows that the detrimental role of these mutations might be limited to their co-occurrence with *KRAS* mutations, whilst their role in patients with wild-type *KRAS* remains controversial.[48] Moreover, these gene alterations have been associated with poor outcomes regardless of the treatment received, suggesting that they may retain a prognostic, but not predictive, significance.[49,50] Therefore, to date, the detection of *STK11* or *KEAP1* mutations should not guide the selection between single-agent ICIs and its combination with CT. Further clinical and biological factors, such as Eastern Cooperative Oncology Group (ECOG) performance status, tumour burden, the presence of symptomatic disease and metastatic sites (e.g. brain involvement), should be accounted for at the time of treatment selection, evidencing the inadequacy of PD-L1 expression as the only tool to guide treatment decision in non-oncogene-addicted advanced NSCLC.

Treatment strategy following first-line progression

Identifying the pattern of progression has an essential role in defining subsequent treatment strategies. When oligoprogression occurs, defined as a progression only in a small number of lesions (up to 3–5) out of the whole burden of disease, the use of local treatments, such as radiation therapy or surgery, has achieved an emerging role in prolonging the benefit of treatment in non-oncogene-addicted disease.[51–53] On the contrary, when disease occurs in more sites and no more benefit from current therapy is expected, the previously received systemic regimen guides the choice of second-line therapy.

In patients with advanced NSCLC progressing after first-line CT-only regimens, immunotherapy with nivolumab, atezolizumab

or pembrolizumab (the latter only in cases of PD-L1 ≥1%) should be considered compared with second-line CT. The role of nivolumab (anti-PD-1) *versus* docetaxel was evaluated in the CheckMate 017 and CheckMate057 trials in squamous and non-squamous histologies, respectively, regardless of PD-L1 expression.[54,55] Nivolumab arms were superior in terms of median OS (mOS; 9.2 *versus* 6.0 months; HR 0.59, 95% CI 0.44–0.71, $p<0.001$ and 12.2 *versus* 9.4 months, HR 0.73, 95% CI 0.59–0.89, $p=0.002$) with a low incidence of side-effects compared with docetaxel.[54,55] These data were also confirmed in a 5-year pooled analysis of these studies.[56] Even atezolizumab could be an option in this setting, as it has shown an improvement in mOS compared to docetaxel in POPLAR and OAK trials irrespective of PD-L1 expressions (12.6 *versus* 9.7 months; HR 0.73, 95% CI 0.53–0.99, $p=0.04$ and 13.8 *versus* 9.6 months; HR 0.73, 95% CI 0.62–0.87, $p=0.0003$).[57,58] Similarly, pembrolizumab (anti-PD-1), evaluated in the study KEYNOTE-010, has shown survival improvement in PD-L1-positive NSCLC compared to docetaxel (PD-L1 ≥50%: 16.9 *versus* 8.2 months, HR 0.53, 95% CI 0.42–0.66; $p<0.00001$; PD-L1 ≥1%: HR 0.69, 95% CI 0.60–0.80; $p<0.00001$).[12]

With the important caveat that, to our knowledge, no specific studies have been published regarding the second line after progression to chemo-immunotherapy or immunotherapy, in NSCLC with PD-L1 ≥50% in progression during pembrolizumab, platinum-doublet regimen with pemetrexed (adenocarcinoma only), paclitaxel, gemcitabine or vinorelbine are the first subsequent choice in platinum-fit patients.

Similarly, with the appearance of a new class of patients treated in first-line with chemo-immunotherapy combinations, at disease progression, available treatment options for these patients include single-agent CT. Amongst them, docetaxel has shown superior mOS compared to best supportive care, other chemotherapeutic agents such as ifosfamide or vinorelbine, and erlotinib.[59–61] Although pemetrexed was shown to be non-inferior to docetaxel in a randomized phase III trial, the frequent use of this drug in first-line or maintenance therapy of non-squamous histology limits its role in second-line treatment.[62]

Furthermore, to improve patient survival, the addition of nintedanib, an oral angio-kinase inhibitor drug (inhibiting VEGFR1-3, FGFR1-3, PDGFRα/β, RET, FLT3 and Src) to second-line CT with docetaxel was evaluated in the LUME-Lung study 1 though in patients progressing after first-line CT only. In the intention-to-treat population, the addition of nintedanib improved PFS (3.4 *versus* 2.7 months; HR 0.79, 95% CI 0.68–0.92; $p=0.0019$) regardless of histology. OS benefit was seen only in patients with adenocarcinoma who had progressed within 9 months from first-line therapy starting (10.9 *versus* 7.9 months; HR 0.75, 95% CI 0.60–0.92; $p=0.0073$) and for all patients with adenocarcinoma (12.6 *versus* 10.3 months; HR 0.83, 95% CI 0.70–0.99) but not in the total population (all histologies) (10.1 *versus* 9.1 months; HR 0.94, 95% CI 0.83–1.05). Regarding the nintedanib safety profile, the most common adverse events were diarrhoea, increased transaminases, nausea, and reduced appetite.[63] Based on these data, nintedanib could be an option in addition to docetaxel in fast progressor (<9 months) adenocarcinoma patients without active brain metastases, necrosis/cavitation or central neoplasms infiltrating mediastinal vessels, or recent history of haemoptysis or haemorrhagic events (Figure 2).

Of course, the benefits of all these treatments may be different from the expected as none of these trials were conducted in patients previously treated with ICIs. Furthermore, the role of docetaxel after progression to first-line carboplatin-paclitaxel-pembrolizumab in squamous NSCLC, regardless of the interval from discontinuation of previous taxanes, is still unknown and may limit treatment options at disease progression.

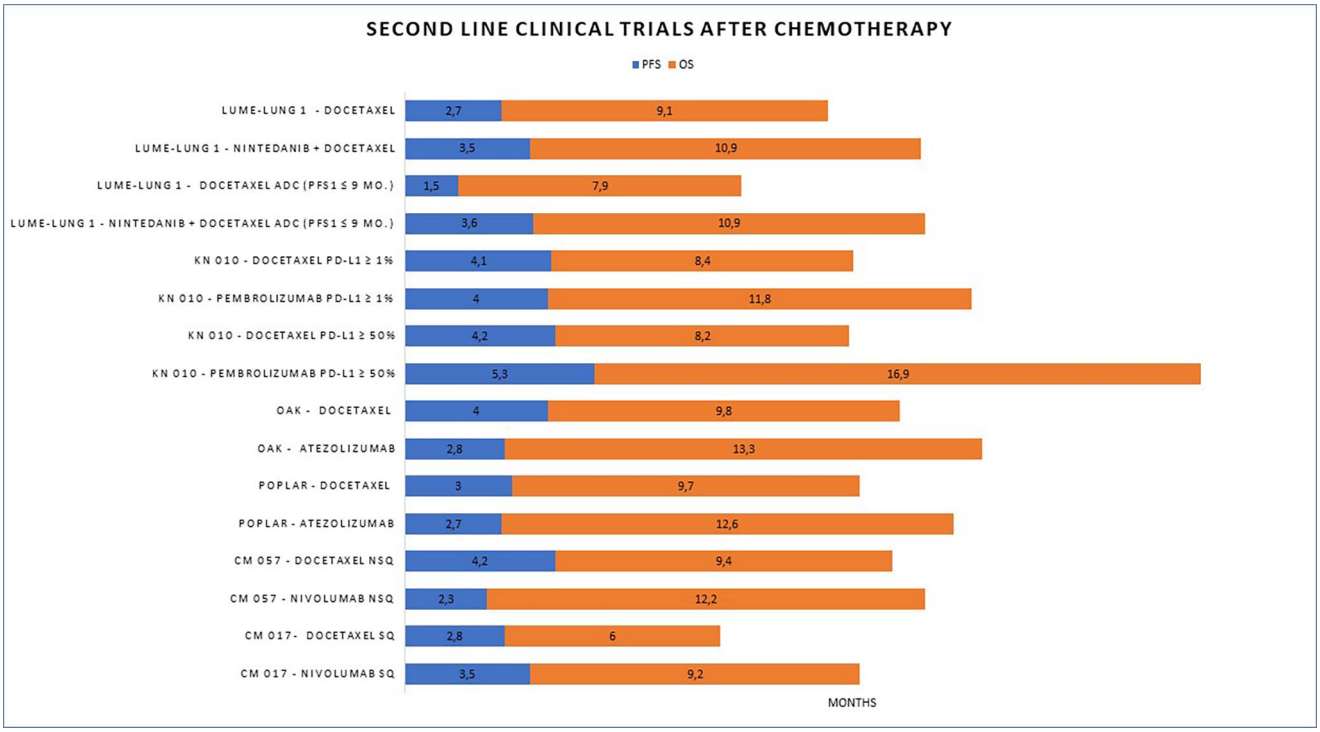
Finally, the opportunity to rechallenge ICIs after ≥6 months of treatment discontinuation is a question still being debated.[64,65] Current data highlight a benefit in terms of response rate with the rechallenge of pembrolizumab after completing the planned 2 years, both in first-line and second-line treatment,[12,26] whilst nivolumab reintroduction, after the end of 1 year in the subsequent line, fails to demonstrate a similar advantage.[66] Furthermore, no data are available about ICI treatment after progression during or after durvalumab maintenance therapy in stage III NSCLC. Likewise, when neoadjuvant and adjuvant ICI regimens will become part of clinical practice, concerns about treatment options at disease progression with ICI-based therapy will also arise. It could be hypothesized that, in patients experiencing a benefit from the ICI regimen and a subsequent progression after at least 3 months from the last ICI infusion, the rechallenge of the same treatment could be a feasible choice, as data showed a decline of the binding of ICI to PD-1/PD-L1 receptors following this period.[67] However, there is no consensus on this topic as some authors consider every type of progression, despite interval of discontinuation, as an acquired resistance to ICIs.[64,65]

Special populations (elderly, PS ≥2, concomitant medications)

Age

Elderly patients (>70 years) represent more than half of patients with NSCLC, with 10% of patients being over 80 years. Older age is associated with progressively deteriorated renal function, decreased hepatic function, and increased load of comorbidities and comedications, which may affect the pharmacokinetics and pharmacodynamics of immunotherapy strategies[68,69] globally. Notably, the immune system undergoes function decline with altered adaptive and innate surveillance, namely immunosenescence.[70,71] A pooled analysis of Keynote 010, Keynote 024 and Keynote 042 demonstrated improved overall survival and a sustainable toxicity profile for elderly patients (≥75 years) in comparison with standard CT.[72] In particular, a subgroup analysis of patients with PD-L1 ≥50% confirmed an increased OS. The Impower 110 study included only 23 patients aged >74 years.[32] Conversely, in the Empower

Figure 2. Overall survival and progression free survival of main clinical trials in advanced, non-oncogene-addicted, non-small-cell lung cancer progressing after first-line chemotherapy.



ADC, adenocarcinoma; CM, Checkmate; IM, Impower; KN, Keynote; MO, months; NSQ, non-squamous; SQ, squamous.

Lung 1 trial, patients older than 65 years were grouped with no further assessment for age group.[9] Recently, a multicentre retrospective study investigated the efficacy of single-agent immunotherapy amongst geriatric patients (aged ≥80 years) affected by multiple primary cancers, including 345 (37%) patients with NSCLC.[73] This study evidenced that the efficacy of immunotherapy is not compromised by older age, with a comparable incidence of immune-related adverse events.

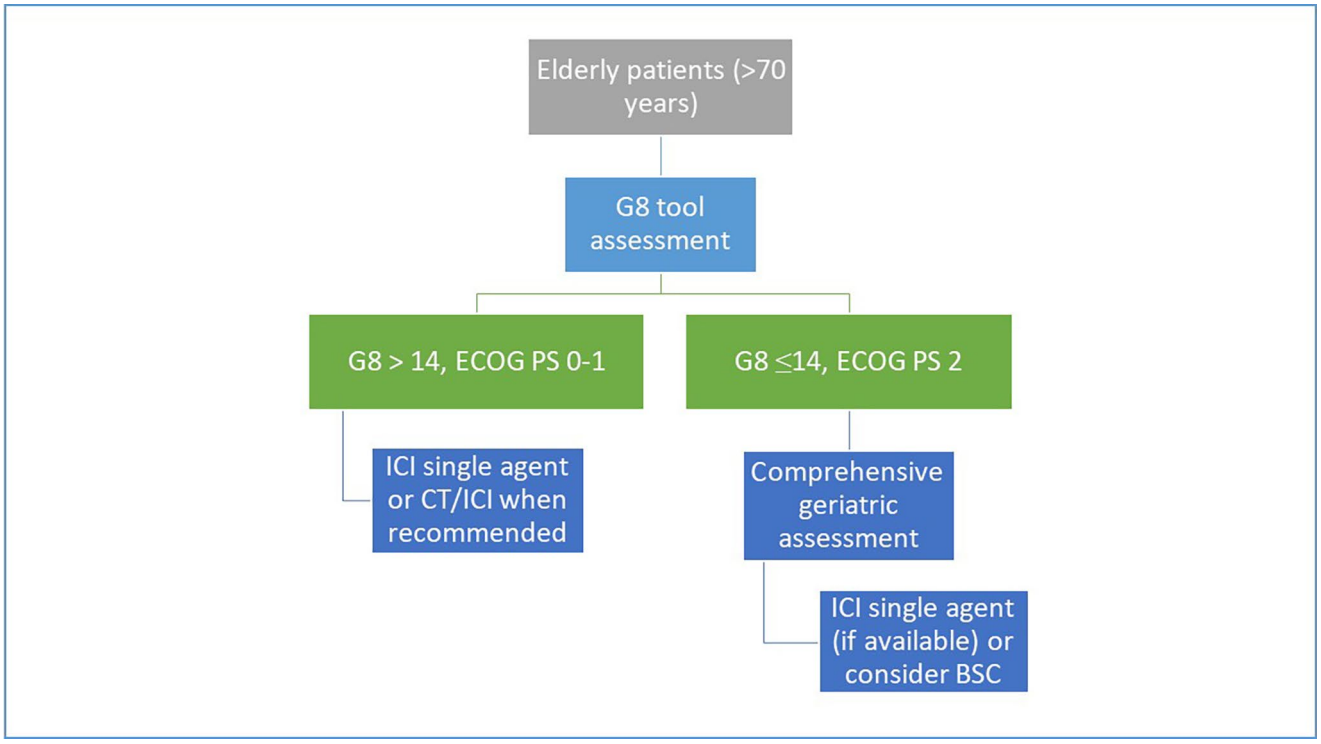
Combining immunotherapy agents with platinum-based doublets or other immunotherapeutic agents improved survival outcomes, even though the toxicity profiles may be challenging amongst frail patients. Pembrolizumab-based CT combination studies were designed to investigate efficacy outcomes amongst an age dichotomized subgroup (older or younger than 65 years), showing remarkable benefit regardless of age but impeding an appropriate analysis for the geriatric population. On the other hand, trials exploring atezolizumab-based combinations amongst non-squamous patients showed a lack of benefit in the elderly when stratified for age. Lastly, Checkmate-227 did not meet the primary endpoint (OS) for the comparison between the nivolumab-ipilimumab combination *versus* CT within the 65–74 and ≥75 years subgroup analysis, but no safety signals were reported for age groups.[39] As discussed earlier, single-agent immunotherapy seems safe and effective in older patients. Conversely, data on combination therapies are partially available and contrasting in this population. Concerning the use of immunotherapy for second or further lines of treatment, prospective trials do not allow to draw definitive conclusions.

A routine screening tool, such as the G8 questionnaire, is recommended to identify frail patients who need a preliminary comprehensive geriatric assessment.[74] Specifically, the G8 questionnaire provides complete items, including age, nutritional status, mobility impairment, mental status, number of ongoing medications and health self-assessment.[74] Patients scoring ≤14 should be referred for comprehensive geriatric assessment, namely a multidisciplinary evaluation under the coordination of a geriatrician to assess the domain of interventions. In conclusion, treatment should be tailored in this context, promoting single-agent immunotherapy rather than a combination strategy in frail patients (Figure 3).

ECOG PS2

A deteriorated performance status (PS) is associated with low tolerability to treatment and dismal prognosis.[75–77] Nevertheless, the conspicuous number of patients with advanced NSCLC with an ECOG PS of 2 (capable of self-care but unable to carry out light work) in clinical practice feeds the debate around the treatment choice in this setting. The PePS 2 trial was a phase II prospective trial assessing the

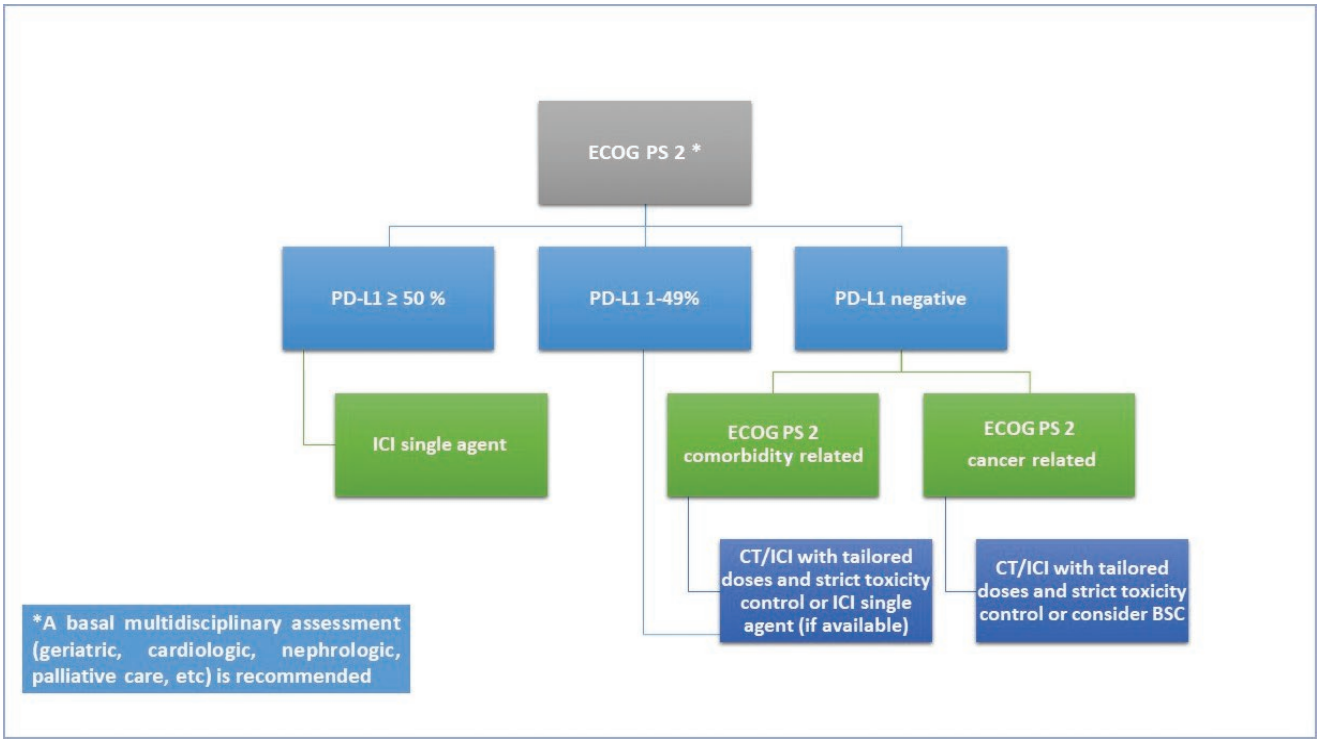
Figure 3. Proposed approach to elderly patients (>70 years old).



BSC, best supportive care; CT, chemotherapy; ECOG PS, Eastern Cooperative Group Performance Status; ICI, immune-checkpoint inhibitor.

efficacy of single-agent pembrolizumab amongst patients with ECOG PS 2, of whom 24 out of 60 received an upfront treatment.[78] Considering the first line-setting, mOS was 14.6 months amongst patients with high PD-L1 expression but 7.9 months globally. The safety profile was comparable with the pre-existing literature, with 28% of patients experiencing immune-related adverse events of any grade (15% grade ≥3). Two prospective studies explored the efficacy of nivolumab amongst pretreated patients with advanced NSCLC, also enrolling patients with ECOG PS 2.[79,80] Both studies confirmed acceptable toxicity even if evidencing a diminished OS in comparison to ECOG PS 0–1 subgroup. An analogous risk in terms of adverse events by single-agent immunotherapy ECOG PS 0–1 and 2 was recently confirmed by a meta-analysis.[81] Interestingly, a retrospective study analysed the efficacy of first-line pembrolizumab across a determinant-related analysis of ECOG PS 2 status.[82] Patients with cancer-related deteriorated PS had a significantly shorter mOS and PFS than those with comorbidity-related deteriorated PS. The CheckMate 817 trial was a phase IIIb, first line, multicohort study investigating the efficacy of an upfront nivolumab-ipilimumab combination amongst special populations, including 139 patients with ECOG PS2.[83] The safety profile was similar across the ECOG PS populations, even if numerically higher for patients with ECOG PS 0–1 than for those with ECOG PS 2 (18% *versus* 14%). On the other hand, the ECOG PS 2 group experienced a lower 1-year PFS (25% *versus* 36%). To date, CT-immunotherapy combination randomized controlled trials stated the ECOG PS 2 as an exclusion criterion, not allowing further assessment in this particular population. Recently, two extensive retrospective studies explored the efficacy of immunotherapy-based strategies amongst trial-ineligible patients (ECOG PS 2, elderly, brain metastasis) affected by multiple cancers. The first showed decreased survival outcomes for non-eligible patients with a confirmed negative prognostic role for the ECOG PS 2 subgroup treated by single-agent or combined immunotherapy.[84] Additionally, the second showed no difference in terms of survival between immunotherapy monotherapy, immunotherapy-based combinations and non-immunotherapy regimens.[85] The paucity of available data limits the possibility of a transversal indication in this special population, particularly for the combination strategies. The evidence regarding safety encourages single-agent immunotherapy rather than combinations for patients positive for PD-L1.[86] In addition, a selection based on the deteriorating causes of PS with a multidisciplinary assessment, tailoring of CT doses and schedules, as an intensive control of toxicity profile should be conducted when combination regimens are the only available treatments (Figure 4).

Figure 4. Proposed approach to patients with ECOG PS 2, according to their PD-L1 status.



BSC, best supportive care; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ICI, immune-checkpoint inhibitor.

Concomitant medications

Concomitant medications have been extensively investigated for the possible detrimental effect on immunotherapy. Notably, the administration of steroids (>10 mg of prednisone equivalents) is a typical exclusion criterion in immunotherapy trials. Patients with advanced NSCLC often require steroids to treat cancer-related symptoms or other conditions not strictly related to cancer (such as rheumatics and pneumatological issues) or receive them as concomitant medications of CT or radiotherapy. Several retrospective studies demonstrated the dismal prognosis of patients treated with immunotherapy and with a steroid prescription for any cause.[87–90] Nevertheless, recent findings elucidate a possible confounding role of the reason for administration. Specifically, patients administered steroids at baseline or during treatment did not experience a dismal prognosis if the steroids were prescribed for cancer-unrelated conditions.[91,92]

In addition, the temporary use of steroids planned for CT schedules, as for the management of immune-related adverse events, did not affect the prognosis.[93] On this basis, inappropriate tapering of steroid medications should be discouraged if clinically needed.

Preclinical studies evidenced a possible interplay between intestinal microbiota and immunotherapy impact, encouraging the investigation on antibiotics exposure.[94] Firstly, a retrospective experience on multiple cancers evidenced an impairment of survival outcomes, confirmed for the lung cancer cohort, linked to antibiotics administration.[95] A meta-analysis analysed survival outcomes of 2889 patients (59% affected by NSCLC) treated with immunotherapy, as single-agent or in combination, according to antibiotics exposure.[96] Patients receiving antibiotics, especially within the month before immunotherapy, had a detrimental effect on PFS and OS at the pooled analysis.[96] Recently, a multicentre retrospective investigation showed no impact on survival for patients treated with chemo-immunotherapy combinations.[97] Nevertheless, these data should be interpreted cautiously due to a deteriorated baseline clinical condition as a possible confounding factor.

Conclusion

Despite the discovery of new molecular targets, the majority of NSCLC remains non-oncogene addicted. The introduction of immunotherapy, both as monotherapy and in combination, has improved the survival of these patients. Future research for advanced non-oncogene-addicted NSCLC should focus on the following domains. Firstly, identifying patients more likely to experience primary resistance to upfront treatment will be

pivotal. Secondly, more profound knowledge of the tumour microenvironment and molecular resistance mechanisms will help resensitize patients progressing to an upfront treatment after initial disease control. In this field, the results of ongoing clinical trials exploring immunotherapy beyond the PD-1–PD-L1 axis will help fill this clinical need.[3] Recently, randomized clinical trials have demonstrated the efficacy of ICI monotherapy or in combination with CT in the non-metastatic setting. Managing patient relapse during or after the accomplishment of early immunotherapy remains an open issue, and novel clinical trials in this setting are warranted.

In conclusion, we expect to reach a comprehensive biological and clinical framework for patients with non-oncogene-addicted NSCLC and helpfully personalize the treatment of the non-oncogene-addicted disease from first to subsequent lines.

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