Disease progression in non-small cell lung cancer on immune-checkpoint inhibition, what are the options?

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Abstract: Most patients with advanced non-small cell lung cancer (NSCLC) and without driver mutations get or will get in the near future pembrolizumab (high expressers of PD-L1) or a combination of PD-1-/PD-L1- with chemotherapy or perhaps a combination of PD-1- and CTLA4-inhibition. In stage III after chemoradiotherapy consolidation with durvalumab is in use. If there is a response to first-line therapy, most patients will still get a recurrence or progress. The question is what kind of therapy we can offer to these patients. With the introduction of PD-1- and PD-L1-inhibition in the recurrent disease situation we got a good treatment option with solid evidence from randomized trials. As these immune-checkpoint-inhibitors are moving in first-line we have to find alternatives for recurrent or refractory tumours. Until now almost no relevant data exist what the best options are. Extrapolating from the knowledge we have from earlier situations we can suggest the following scenarios, but they have to be confirmed by prospective clinical trials: (I) if in first-line pembrolizumab alone was given, probably a classical chemotherapy doublet should be given. In the case of mono/oligo-progression local therapies can be added. Alternatively the addition of a further immune modulating drug can be examined in clinical trials; (II) if in first-line a combination of immune-checkpoint-inhibition and chemotherapy was applied, probably classical second-line chemotherapy is reasonable. If in first-line pemetrexed was not given, it could be applied in non-squamous NSCLC for second-line. Else usually docetaxel will be chosen. The question of rapid recurrence/progression leads to the option of adding antiangiogenetic drugs in early progression/recurrence. Of course a further immune modulating drug can be tested in prospective clinical trials and in mono/oligo-progression local treatment can be discussed; (III) if in first-line a combination of PD-1- and CTLA4-inhibition was used, classical doublet chemotherapy is probably the preferred option. Alternatively prospective clinical trials can examine further immune modulating agents. In case of mono/oligo-progression local treatments can be evaluated. For the situation of 2nd recurrence at the moment only individualized treatment decisions can be offered. Overall there is unfortunately no good evidence until now how to proceed after disease progression after treatment with immune-checkpoint-inhibitors. Prospective clinical trials in order to select good sequence options for the treatment of advance NSCLC without driver mutations are urgently needed.

Keywords: Non-small cell lung cancer (NSCLC); immune oncology; immune check-point inhibition; recurrence

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Introduction

Immune-checkpoint inhibitors are moving into first-line therapy of advanced non-small cell lung cancer (NSCLC) for tumours without driver-mutation. For high expressers of PD-L1, i.e., a tumour proportional score (TPS) of 50% or higher pembrolizumab monotherapy demonstrated in comparison to doublet chemotherapy an advantage regarding toxicity, progression-free survival and overall survival (1,2). For all-comers regarding PD-L1-expression the combination of pembrolizumab with pemetrexed and cis-/carboplatin was superior in comparison to the chemotherapy alone group in non-squamous NSCLC (3). Atezolizumab plus Paclitaxel, Carboplatin and Bevacizumab was also superior in comparison to the three-drug regimen (4). In squamous cell cancer atezolizumab plus carboplatin plus nab-paclitaxel improves progression-free and overall survival (5). This is also true for pembrolizumab plus paclitaxel or nab-paclitaxel and carboplatin (6). In NSCLC with high mutational burden the combination of PD-1- and CTLA4-inhibition showed a benefit over chemotherapy irrespective the PD-L1 expression (7). Furthermore a consolidation therapy with durvalumab after simultaneous chemoradiotherapy had relevant advantage in survival (8,9). We have good evidence that PD-1-/PD-L1 inhibition works after first-line chemotherapy (10-13), but there are very few and almost no prospective data how we should proceed with refractory or progressive tumours having first-line therapy with immune-checkpoint inhibition. We present therefore in the following strategies according to the various first-line settings how we can treat after first-line immune check-point inhibition. These strategies have of course to be checked and confirmed with prospective data in registries and clinical trials.

Disease progression after stopping immune check-point inhibition due to toxicity or after an extended period of treatment

If there is disease progression after stopping immune check-point inhibition due to toxicity re-establishing immune check-point inhibition seems to be an option (14). After long-term application of immune check-point inhibition and durable response re-induction at progression seems to be possible (15). This topic will be elaborated in a separate manuscript in this issue of PMC.

Disease progression during PD-1 inhibition as monotherapy

In case of disease progression during PD-1 inhibition as monotherapy a classical chemotherapy doublet can be given (3) and is probably adequate. In the case of only one or few sites of progression local therapies, especially radiotherapy can be added (16,17). Radiation therapy leads to an immunological reaction, which can end in tumour destruction distant to the irradiated area (abscopal effect) (18). In a systematic review of 46 cases between 1969 and 2014 there was a wide variety in the cases and the abscopal effect was described after up to 12 months (19). The abscopal effect was also described after radiotherapy and ipilimumab (20). In a phase II trial pembrolizumab after locally ablative therapy in the oligometastatic setting demonstrated a reasonable progression-free and overall survival (21). The combination with other immune therapies is also an option for clinical trials (22,23). One principle of acquired resistance is the exhaustion of T-cells, which could be overcome by adding an alternative stimulation. One example is the addition of nivolumab after the CTLA4-antibody ipilimumab (24). Also targeting TGF-ß in addition to PD-1 may be an option (25).

Disease progression during or after immune check-point inhibition and chemotherapy (plus bevacizumab)

After the combination of immune check-point inhibition and doublet chemotherapy (plus bevacizumab) probably standard second-line mono-chemotherapy with docetaxel or pemetrexed (in non-squamous NSCLC, if not given already in first-line) is a reasonable choice. Chemotherapy may also be immunogenic and enable further immune check-point inhibition (26). In the second-line setting after doublet chemotherapy the addition of ramucirumab or nintedanib (in non-squamous NSCLC) is of benefit. This seems to be true especially for tumours who relapse or progress early (27-29). Probably this is also true after immune check-point inhibition, even in the third-line setting after chemotherapy and nivolumab (30,31). As described already above also in the setting of mono- or oligo-progression with immune check-point inhibition and chemotherapy (plus bevacizumab) locally ablative therapies can be useful. If available also further immune therapy approaches can
be tested in clinical trials (32). Examples are pegilodecakin (IL-10) (33), entinostat (HDAC inhibitor) (34), toll-like receptor 9 agonists, e.g., lefitolimod (35), Adenosine-antagonists (36,37) and adoptive cell transfer using tumour infiltrating lymphocytes (38).

**Disease progression during or after a combination of PD-1- and CTLA4-inhibition**

If in first-line a combination of PD-1- and CTLA4-inhibition was used, classical doublet chemotherapy is probably the preferred option. Alternatively prospective clinical trials can examine further immune modulating agents. In case of mono- or oligo-progression local treatments can be evaluated—as already described above.

**Necessary research**

We have good evidence for the second-line setting in NSCLC without driver mutation after a doublet chemotherapy in first-line. As immunotherapy is moving in first-line we have no adequate evidence, how we should handle primary progression or recurrence. The situation can be improved when in all first-line clinical trial the monitoring of second- and third-line therapy is mandatory and includes the treatment regimens, their efficacy and the second and third progression-free survival. Also prospective registries of the patients which get immunotherapy in first-line would be of help. Of course it would be nevertheless necessary to use trial designs where the best approach over the several lines of therapy is tested.

**Conclusions**

As immunotherapy in NSCLC without driver mutation is moving into first-line we need strategies to treat progression and recurrence. At the moment only recommendations at the level of expert opinions can be given. Our recommendations are outlined in *Figure 1*. Depending on the regimen in first-line mostly chemotherapy will be applied: as doublet chemotherapy, if only immune check-point inhibition was used, as classical second-line mono chemotherapy after the combination of immune check-point inhibition and doublet chemotherapy (plus bevacizumab) and chemoradiotherapy with immune check-point inhibition. If the progress/recurrence is early the addition of an antiangiogenetic agent (nintedanib, ramucirumab) is probably useful. If there is mono- or oligo-progression only locally ablative therapies may be adequate and foster the efficacy of immune check-point inhibition. Mostly in clinical trials further immune therapy combinations can be applied. Overall we urgently need prospective data to these concepts.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

5. Socinski MA, Koynov KD, Berard H, et al. LBA651MPower131: Progression-free survival (PFS) and overall survival (OS) analysis of a randomised phase III study of atezolizumab + carboplatin + paclitaxel or nab-paclitaxel vs carboplatin + nab-paclitaxel in 1L advanced squamous NSCLC. Ann Oncol 2018;29.


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