Second-line treatment of non-small cell lung cancer adenocarcinoma patients not harbouring an oncogene driver mutation anno 2017-2018: A consensus group meeting

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SUMMARY

The treatment landscape for patients with advanced non-small cell lung cancer, who do not harbour an oncogenic driver abnormality, has changed dramatically over the last years. Second-generation antiangiogenic agents, such as nintedanib and ramucirumab, and particularly PD-1/PD-L1 inhibitors, such as nivolumab, pembrolizumab and atezolizumab have shown to prolong survival in pretreated non-small cell lung cancer patients. Immune checkpoint inhibition in the treatment of advanced non-small cell lung cancer comes with the promise of durable responses in responding patients. Nevertheless, one must appreciate that the average response rate seen with these PD-1/PD-L1 targeting agents is only about 20%. While PD-L1 testing may be used as an enrichment biomarker, a substantial proportion of patients still do not benefit from these agents. They could benefit from alternative therapeutic options, including novel anti-angiogenic agents. In this paper, a treatment algorithm is proposed that aims to optimise the second-line treatment choice for patients with lung adenocarcinoma, based on the available clinical data.

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INTRODUCTION

The last decade has witnessed significant progress in therapeutic options for patients diagnosed with advanced non-small cell lung cancer (NSCLC). This is due in major part to the improved technological ability to interrogate the genome of cancer cells, which has enabled the development of targeted anticancer agents. The recognition that lung cancer is not a single disease entity dates back many decades to the histolog-

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ical sub-classification of malignant neoplasms of the lung into subcategories of small and non-small cell lung cancer. The NSCLC subset has undergone additional sub categorisations with distinct management algorithms for specific histologic subtypes (i.e. squamous cell carcinoma (SCC), adenocarcinoma, large cell carcinoma).[1]

The major advance in the treatment of NSCLC in the last decade grew from the recognition that specific genetic alterations define subsets of NSCLC.[2] This paved the way for the development of effective agents specifically counteracting the biological consequences of these genetic aberrations. While the previous standard of care in metastatic NSCLC was to uniformly treat patients with platinum-based chemotherapy for four to six cycles in first-line, the development of molecular tests allowed physicians to tailor treatment strategies based on the presence of specific driver mutations. As a result, patients with tumours having genetic alterations of e.g. epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*), ROS1 and MET exon 14 now benefit from targeted therapies in the first line and beyond.[2]

The upfront treatment for metastatic NSCLC patients without known driver mutations consists of platinum-based doublet chemotherapy. The positive data generated with the PD-1 immune checkpoint inhibitor pembrolizumab in patients with PD-L1 expression in at least 50% of tumour cells, recently changed this paradigm.[3] As a result, PD-L1 expression testing by immunohistochemistry (ICH) is currently performed in routine practice in the diagnosis of patients with advanced NSCLC.

Second-line treatment options for advanced NSCLC patients have substantially expanded in the past few years. The chemotherapy agents, pemetrexed and docetaxel and the EGFR tyrosine kinase inhibitor erlotinib were the only three approved therapies in this setting until 2014, achieving response rates (RRs) of approximately 8–10%, with a median progression-free survival (PFS) of approximately three to four months and a median overall survival (OS) of eight to ten months.[4] The standard second-line therapy is chemotherapy with either pemetrexed or docetaxel, while erlotinib is only considered a potential option in patients who cannot tolerate chemotherapy. In recent years, second-generation antiangiogenic agents, such as nintedanib and ramucirumab and particularly PD-1/PD-L1 inhibitors, such as nivolumab, pembrolizumab and atezolizumab, have improved the survival in pretreated NSCLC patients.[5-10] Immune checkpoint inhibition in the second-line treatment of advanced NSCLC comes with the promise of durable responses in responding patients. Nevertheless, one must appreciate that the response rates seen with these PD-1/PD-L1 targeting agents is only 20%. While PD-L1 testing may be used as an enrichment biomarker, a substantial proportion of patients still does not benefit from these agents. They could benefit more from alternative therapeutic options, including novel anti-angiogenic agents. The goal of this perspective paper is to define a treatment algorithm that optimises the clinical benefit for all lung adenocarcinoma patients.

SECOND-LINE TREATMENT OPTIONS FOR NSCLC ADENOCARCINOMA PATIENTS: WHAT DO WE KNOW TODAY?

PD-1 CHECKPOINT INHIBITION

Most patients with NSCLC will experience disease progression during or after first-line chemotherapy and there is a significant unmet need for new, effective second-line treatments. Until recently, docetaxel- and pemetrexed-based chemotherapy and erlotinib were the only registered treatment options for patients with previously treated NSCLC.[11,12] In recent years, however, the second-line treatment landscape for these patients has dramatically evolved with the introduction of several life-prolonging treatment options.

The most notable change in the treatment of NSCLC came with the introduction of immune-checkpoint inhibitors targeting the PD-1/PD-L1 axis. In the phase III Checkpoint 057 study (N=582), nivolumab significantly prolonged the OS compared to docetaxel in patients with non-squamous advanced NSCLC patients who progressed during or after platinum-based doublet chemotherapy (median OS: 12.2 *vs.* 9.4 months; HR[95%CI]: 0.73[0.59-0.89]; p=0.002).[7] Similar results were obtained with the PD-1 inhibitor pembrolizumab in the phase II/III Keynote 010 trial (N=1,034, 70% non-squamous). In this trial, the median OS was 10.4 months with pembrolizumab 2 mg/kg, 12.7 months with pembrolizumab 10 mg/kg, and 8.5 months with docetaxel. The OS was significantly longer for pembrolizumab 2 mg/kg versus docetaxel (HR[95%CI]: 0.71[0.58–0.88]; p=0.0008) and for pembrolizumab 10 mg/kg versus docetaxel (HR[95%CI]: 0.61, 0.49–0.75; p<0.0001).[9]

In both studies, the efficacy of the checkpoint inhibitor was linked to the PD-L1 status. In Checkmate 057, an exploratory analysis revealed that the magnitude of benefit was greater among the PD-L1 expressors compared to the non-expressors (although there were clinical benefits in both groups).[13] In Checkmate 057, no OS benefit could be demonstrated for nivolumab over docetaxel in patients expressing PD-L1 in less than 10% of tumour cells. On the contrary, in this subgroup of patients the median OS was even longer with docetaxel than with nivolumab (10.3 *vs.* 9.9 months; HR[95%CI]: 0.96[0.74-1.25]).[13] The survival benefit of pembrolizumab over docetaxel was also much more pronounced in patients with a PD-L1 tumour proportion score (TPS)

≥50% (HR[95%CI]: 0.53[0.40-0.70]), compared to patients with a TPS between 1% and 49% (HR[95%CI]: 0.76[0.60-0.96]). Based on these findings PD-L1 was established as an enrichment factor for benefit of PD-1 inhibition: the more PD-L1 the tumour expresses, the more likely that the patient will benefit from PD-1 immune checkpoint inhibition. In addition to this, *Rizvi et al.* demonstrated that a higher load of nonsynonymous mutations and neoantigens detected by whole-exome sequencing positively correlated with clinical response to an anti-PD-1 antibody (pembrolizumab) in NSCLC patients.[14] However, whole-exome sequencing is currently not used in daily practice.

Unfortunately, not all relapsed NSCLC patients benefit from anti PD-1 therapy. In fact, the objective response rate (ORR) with nivolumab in Checkmate 057 was 19%, which was significantly better than the 12% with docetaxel.[8] Nevertheless, some patients with stable disease also derive clinical benefit from immunotherapy.[8]

Similarly, in Keynote 010, the ORR with pembrolizumab was 18%. Looking more closely into these response results, it becomes clear that this response rate is mainly driven by the high response rate in patients with a higher PD-L1 TPS (TPS 1%-24%: 8.6%; TPS 25%-49%: 15.8%; TPS 50-74%: 22.6%; TPS ≥75% 33.7%).[15]

CLINICAL EVIDENCE FOR COMBINING TAXANES AND ANTI-ANGIOGENIC DRUGS

Antiangiogenic agents have been established as important and effective therapeutic targets in many cancers, including NSCLC. A meta-analysis reported by *Soria et al.* showed a consistent significant improvement of RR, PFS and OS for the combination of bevacizumab and platinum-based chemotherapy, compared with platinum-based chemotherapy alone in the first-line treatment of eligible patients with NSCLC.[16] Unfortunately, a recent study comparing paclitaxel-bevacizumab to docetaxel in the second- or third-line treatment of non-squamous NSCLC failed to show an OS benefit (despite a significant PFS improvement).[17] The VEGFR2 inhibitor ramucirumab was also evaluated in the second-line treatment of stage IV NSCLC. In the REVEL trial, the addition of ramucirumab to docetaxel led to a significantly longer OS in NSCLC patients who failed platinum-based chemotherapy (median 10.5 *vs.* 9.1 months; HR[95%]: 0.86[0.75-0.98]; p=0.032).[18] Despite the statistical significance of this difference in OS, the clinical relevance of one month improvement in OS is debatable and did not convince Belgian regulatory agencies to reimburse this drug in this setting.

More convincing data on anti-angiogenesis therapy in second-line NSCLC were generated with nintedanib, a potent oral angiokinase inhibitor that targets the pro-angiogenic pathways mediated by VEGFR1–3, fibroblast growth factor receptors (FGFR) 1–3, and platelet-derived growth factor receptors (PDGFR) α and β.[19] The combination of docetaxel and nintedanib has been investigated in 1,314 patients with pretreated advanced NSCLC in the LUME Lung 1 trial. Compared with docetaxel, a significant prolongation of PFS (primary endpoint) was reported when nintedanib was added to docetaxel (median PFS 3.4 *vs.* 2.7 months, HR[95%CI]: 0.79[0.68–0.92]; p=0.0019). Importantly, nintedanib-docetaxel was associated with a statistically significant and clinically relevant OS prolongation in patients with adenocarcinoma histology (median OS 12.6 *vs.* 10.3 months, HR[95%CI]: 0.83[0.7–0.99]; p=0.0359). Additional prespecified analyses revealed a particularly pronounced impact of the addition of nintedanib to docetaxel on OS in patients with fast-progressing disease (patients progressing within nine months after start of first line therapy: median OS 10.9 *vs.* 7.9 months; HR[95%-CI]: 0.75[0.60-0.92]; p=0.0073) and patients who were refractory to first-line chemotherapy (median OS 9.8 *vs.* 6.3 months; HR[95%CI]: 0.62[0.41-0.94]; p=0.0246).[5] Compared with docetaxel, the combination of nintedanib and docetaxel was associated with a higher incidence of gastrointestinal adverse events and transient elevation of liver enzymes, but this had no impact on the quality of life of patients.[5,20] Based on these findings, the European Society of Medical Oncology (ESMO) endorsed docetaxel-nintedanib as a second-line option in patients with lung adenocarcinoma, especially in those progressing within nine months from the start of first-line chemotherapy, and the Belgian regulatory agencies granted reimbursement for nintedanib in this setting.[21]

TREATMENT ALGORITHM FOR ADVANCED LUNG ADENOCARCINOMA WITHOUT ONCOGENIC DRIVER ABNORMALITIES

By combining the clinical data discussed above and taking into consideration the current reimbursement criteria in Belgium, the expert group distilled a treatment algorithm for patients with non-squamous advanced NSCLC who do not harbour known oncogenic driver abnormalities (*Figure 1*).

The key decision maker in the first line treatment of these patients is the level of PD-L1 expression. For patients with a PD-L1 TPS of 50% or more, pembrolizumab should be the new standard of care in the absence of symptomatic brain metastasis. In patients with a PD-L1 TPS of 0-49%, platinum based doublet chemotherapy remains the preferred upfront treatment.

As discussed earlier, the treatment landscape for advanced NSCLC beyond first-line changed dramatically over the last years. For patients who received pembrolizumab in first-line, chemotherapy is the preferred second line therapy.

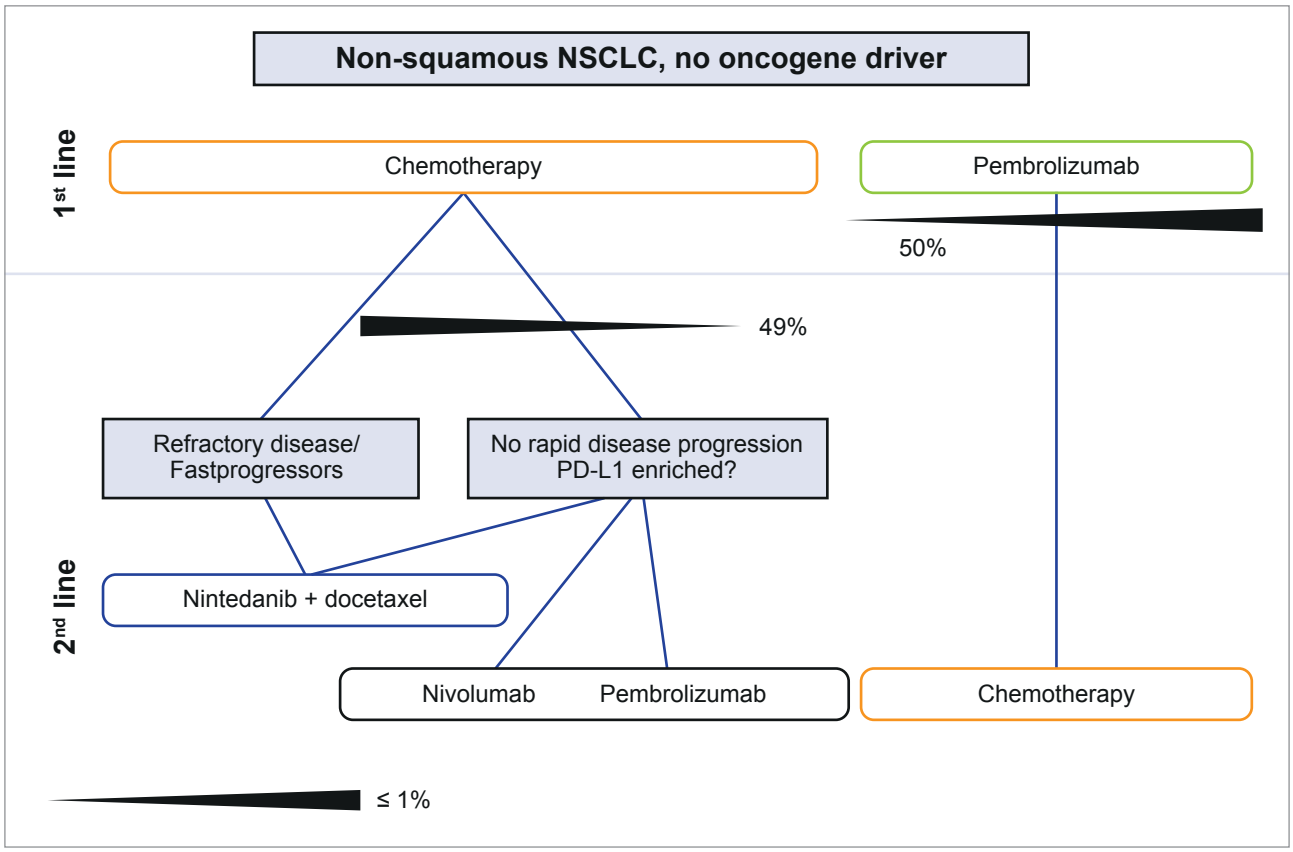

FIGURE 1. Treatment algorithm for patients with advanced non-squamous NSCLC without a targetable oncogene driver. When opting for a certain treatment option in NSCLC, it is essential to take into account some items (PD-L1, contra-indications for both immune checkpoint inhibition and anti-angiogenesis, performance status, co-morbidities and disease progression).

In third-line, these patients can be treated with the combination of nintedanib and docetaxel. For patients who received chemotherapy in first-line (i.e. patients with a PD-L1 TPS score below 50%), the situation is more complex. With the available data, important variables that can be put forward to determine the treatment choice in this setting are the PD-L1 expression status, the time to progression after first-line treatment and the eligibilities for anti-angiogenic or checkpoint inhibition treatment. Given the proven efficacy of nintedanib-docetaxel in patients who rapidly progress after platinum-based doublet chemotherapy or who proved to be refractory to this treatment regimen, nintedanib-docetaxel is a good treatment option in these cases. In patients who do not have rapid disease progression, the PD-L1 expression should be considered. For patients with PD-L1 expression below 50%, nivolumab and pembrolizumab are the preferred second-line treatment options. For patients with very low or negative PD-L1 expression, nintedanib-docetaxel also seems to be a good treatment option. PD-L1 is related to response, and thus acts as an enrichment biomarker. In this way, it can be helpful to make treatment choices when other valuable treatment options are in place. In the Checkmate 057 study, the HR for OS was not significantly different between nivolumab or docetaxel for patients with low (e.g. <10%) or negative PD-L1 expression.

Importantly, when opting for a certain treatment option in NSCLC, it is essential to consider the specific contra-indications for both immune checkpoint inhibition and anti-angiogenesis. In addition to this, the performance status of patients also remains a key factor. The proposed treatment algorithm mainly applies to patients with a performance status of 0-1.

PD-L1 TESTING IN NSCLC

As discussed above, several clinical studies have demonstrated that immune checkpoint inhibitors represent an important therapeutic option for NSCLC patients, both in the first- and second-line settings.[3,7-10] However, despite exciting overall treatment outcomes, a considerable number of patients fails to achieve long-term clinical benefit with these agents. As the cost of these molecules impacts significantly on health care systems, the identification of predictive biomarkers to select patients who are more likely to benefit is a challenging area of ongoing research. The attention in the search for a marker of immunotherapy benefit has focused mainly

on the expression of PD-L1 on tumour cells and/or immune infiltrates determined by IHC, since this protein seems to be critical in the PD-1/PDL-1 pathway. Unfortunately, the heterogeneity of tests, targets and scores has produced conflicting results in the literature.

It is important to appreciate that PD-L1 expression is substantially different from other biomarkers. PD-L1 can be constitutively expressed but most of the time is a functionally inducible receptor/ligand, potentially expressed by tumour cells, stromal cells and inflammatory cells at tumour sites. PD-L1 expression is continuously distributed with a different range of expression, which varies significantly over time and might be influenced by several factors, such as concurrent or prior treatments.[22,23] In contrast, classical predictive biomarkers such as EGFR activating mutations and ALK rearrangements are binary biomarkers: they are either present or absent. As such, these indicators define more clearly distinct tumour subgroups with different biology and clinical behaviour. The PD-L1 expression is very dynamic, according to a constantly evolving immune response. Therefore, questions regarding reliability, consistency, feasibility and selection of an expression threshold remain controversial. Despite these limitations, PD-L1 evaluation by IHC is now part of standard NSCLC testing.

The extent of PD-L1 expression could be scored using several tests, such as the TPS. The TPS is the percentage of viable tumour cells showing partial or complete linear membrane staining relative to all viable tumour cells present in the sample (positive and negative). Infiltrating immune cells, normal cells, necrotic cells and cellular debris must be excluded from the scoring. Importantly, a minimum of 100 viable tumour cells is needed to determine the PD-L1 expression.[24] In practice, the interpretation of PD-L1 IHC is not always straight forward (especially for cases with a low fraction of PD-L1 expressing cells). In this regard, *Scheel et al.* assessed the interobserver concordance of PD-L1 IHC. The data indicate that unidentified PD-L1 IHC scoring-criteria for tumour cells are feasible.[25] Also, Belgian experience (ring trials, training sessions) showed that pathologists should be trained before scoring PD-L1 IHC.

Different assays have been developed with different scoring criteria and different positivity thresholds: Dako 28-8 pharmDx (nivolumab), Dako 22C3 pharmDx (pembrolizumab), Ventana SP142 (atezolizumab), and Ventana SP263 (durvalumab).[28] The German harmonisation study also compared these four available trial assays for PD-L1 testing and showed that the assays 28-8 and 22C3 stained comparable tumour cell proportions, that the SP142 stained fewer tumour cells, but more immune cells, while the SP263 assay stained more tumour and immune cells. There is a general consensus that staining with SP142 should be avoided. This is of clinical importance, as the differences in tumour cell proportions would translate into different PD-L1 classifications. The concordance between different PD-L1 assays has been evaluated by different studies.[26,27] The results show that 28-8, 22C3 and SP263 clones show comparable performance when they are used with the appropriate test kits.

Another immediate challenge to PD-L1 testing in lung cancer patients is the access to adequate tumour tissue, given that NSCLC cancer samples are often limited in size. Obtaining enough tissue to perform PD-L1 testing together with the already established biomarker tests in NSCLC (EGFR, ALK and ROS testing) could be challenging.[28] Many questions related to PD-L1 testing remains unanswered. For example, it is not clear whether PD-L1 positivity on tumour cells has a different effect on outcome/response to treatment, compared to PD-L1 positivity on immune cells. Is there a need to perform a re-biopsy after a certain period, particularly when the patient was treated with chemotherapy/ radiation therapy? Should only the primary tumour be evaluated, or also metastases?[28] In 2016, Belgian guidelines were published for the optimal management of NSCLC samples (Pauwels *et al.*, BJMO). Introduction of immunotherapy has also changed biomarker testing algorithms for NSCLC patients. This is why an update with the goal of integrating PD-L1 testing into the previous guidelines will be submitted soon.

CONCLUSIONS

The treatment landscape for patients with advanced NSCLC, whose tumour does not harbour an oncogenic driver abnormality, changed dramatically over the last years. Immune checkpoint inhibitors caused an important paradigm shift in NSCLC and claimed their place in both the first- and second-line treatment of advanced NSCLC. However, a substantial proportion of patients does not benefit from immune checkpoint inhibition. For these patients, chemotherapy combined with anti-angiogenesis represents an effective, life-prolonging second-line treatment option. Based on the available clinical data, a contemporary treatment algorithm has been proposed for non-squamous patients with advanced NSCLC.

REFERENCES

1. Langer CJ, Besse B, Gualberto A, et al. The evolving role of histology in the management of advanced non-small-cell lung cancer. J Clin Oncol. 2010; 28(36):5311-20.

2. Berge EM, Doebele R. Targeted therapies in non-small cell lung cancer: emerging oncogene targets following the success of epidermal growth factor receptor. Semin Oncol. 2014;41(1):110-25.

3. Reck M, Rodriguez-Abreu D, Robinson A, et al. Pembrolizumab versus che-

motherapy for PD-L1 positive Non-small-cell lung cancer. N Engl J Med. 2016;375:1823-33.

4. Weiss JM, Stinchcombe TE. Second-line therapy for advanced NSCLC. Oncologist. 2013;18(8):947–53.

5. Reck M, Kaiser R, Mellemgaard A, et al. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. Lancet Oncol. 2014;15(2):143–55.

6. Garon E, Ciuleanu T-E, Arrieta O et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet. 2014;384(9944):665–73.

7. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med. 2015;373(17):1627–39.

8. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med. 2015;373(2):123–35.

9. Herbst RS, Baas P, Kim D-W, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016;387(10027):1540–50.

10. Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet. 2016;387(10030):1837–46.

11. Stinchcombe TE, Socinski MA. Considerations for second-line therapy of non-small cell lung cancer. Oncologist. 2008;13(Suppl 1):28–36.

12. Gridelli C, Ardizzoni A, Ciardiello F, et al. Second-line treatment of advanced non-small cell lung cancer. J Thorac Oncol. 2008;3(4):430–40.

13. Horn L et al., Phase 3, randomized trial (CheckMate 057) of nivolumab vs docetaxel in advanced non–squamous (non-SQ) non–small cell lung cancer (NSCLC): subgroup analyses and patient-reported outcomes (PROs). ESMO Asia 2015, abstract 417O.

14. Rizvi N, Hellmann M, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science. 2015;348:124–8.

15. Baas P, Garon E, Herbst R, et al. Relationship between level of PD-L1 expression and outcomes in the Keynote-010 study of pembrolizumab vs. docetaxel in previously treated PD-L1 positive NSCLC. J Clin Oncol. 2016;34(Suppl):abstr 9015.

16. Soria JC, Mauguen A, Reck M et al. Systematic review and meta-analysis of randomised, phase II/III trials adding bevacizumab to platinum-based chemotherapy as first-line treatment in patients with advanced non-small-cell lung cancer. Ann Oncol. 2013;24:20–30.

17. Cortot A, Audiger-Valette C, Molinier O, et al. Weekly paclitaxel plus bevacizumab versus docetaxel as second or third line treatment in advanced non-squamous non-small cell lung cancer (NSCLC): results from the phase III study IFCT-1103 ULTIMATE. J Clin Oncol. 2016;34(May 20 Suppl.):abstr 9005.

18. Garon E, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet. 2014;384:665–73.

19. Hilberg F, Roth GJ, Krssak M, et al. BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. Cancer Res. 2008;68:4774–82.

20. Novello S, Kaiser R, Mellemgaard A et al. Analysis of patient-reported outcomes from the LUME-Lung 1 trial: a randomised, double-blind, placebo-controlled, phase III study of second-line nintedanib in patients with advanced non-small cell lung cancer. Eur J Cancer. 2015;51:317–26.

21. Novello S, Barlesis F, Califano R, et al. Metastatic non-small cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;(Suppl 5):v1-v27.

22. Sheng J, Fang W, Yu J, et al. Expression of programmed death ligand-1 on tumour cells varies pre and post chemotherapy in non-small cell lung cancer. Sci Rep. 2016;6:20090.

23. Deng L, Liang H, Burnette B, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. J Clin Invest. 2014;124:687–95.

24. Dako Denmark A/S. PD-L1 IHC 22C3 pharmDx Interpretation Manual.

25. Scheel A, Bänfer G, Baretton G, et al. Interlaboratory concordance of PD-L1 IHC for NSCLC. J Clin Oncol. 2016;35(Suppl):abstr e20508.

26. Hirsch FR. et al. PD-L1 Immunohistochemistry Assays for Lung Cancer: Results from Phase 1 of the Blueprint PD-L1 IHC Assay Comparison Project. J Thorac Oncol. 2017;12(2):208-22.

27. Scheel AH, Dietel M, Heukamp LC, et al. Harmonized PD-L1 immunohistochemistry for pulmonary squamous-cell and adenocarcinomas. Mod Pathol. 2016;29(10):1165-72.

28. Sholl L, Aisner D, Allen T, et al. Programmed death ligand-1 immunohistochemistry - a new challenge for pathologists: a perspective from members of the pulmonary pathology society. Arch Pathol Lab Med. 2016;140(4):341-4.