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ADVANCED NON-SMALL-CELL LUNG CANCER. THE SIGNIFICANCE OF PERSONALIZED THERAPY

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Abstract. For several entities of advanced non-small-cell lung cancer (NSCLC), tyrosine kinase and immune checkpoint inhibitors are the basis for the so-called personalized or precision therapy and have become the standard of care in the first- and second-line setting.

In previously untreated NSCLC patients with activating EGFR-mutation, ALK or ROS1 translocation status, tyrosine kinase inhibitors (TKIs) replace the chemotherapy and are the new standard of care.

In previously untreated patients with a high level of programmed cell death ligand 1 (PD-L1), pembrolizumab leads to significantly longer PFS, longer OS, and fewer adverse events than platinum-based chemotherapy regardless the histologic subtype.

In previously treated patients with squamous carcinoma, nivolumab is the new standard of care, independent of PD-L1 expression.

In the future, combination therapies have to be proved, whether they are more effective than monotherapy.

Key words: NSCLC, personalized therapy, combination therapies, stratified treatment, monotherapy, efficiency of therapy, molecular markers.

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Personalization is one of the most important subjects and challenges of actual medicine generally and of cancer medicine, particularly. The prediction of diseases as well as a targeted therapy are not new, but recent developments and findings in molecular biology have changed the research as well as healthcare fundamentally. Due to more thorough knowledge about biological features, completely new perspectives are nowadays opened – for clinicians, for investigators, and, eventually, for the patients.

Solid tumours are initiated by specific genomic alterations, each with unique features, driver mutations, but also with starting points for a targeted, personalized therapy. Lung cancer, until recently classified only into two substantial types, the small-cell and the non-small-cell lung cancer, is now divided into at least two dozen generally different entities, which can and should be treated differentially.

Even in patients with advanced stages of the non-small-cell lung cancer (NSCLC) with multiple metastases, longer progression-free (PFS) and overall survival (OS) rates as well as a reduction of adverse events can be obtained by the treatment with new drugs following molecular genetic diagnostics. Under the actual development, molecular genetic diagnostics is an attempt for a causal therapy. The treatment of patients with advanced NSCLC, however, still remains a palliative one.

Lung cancer patients have a poor prognosis. According to the most recent publication on "Cancer in Germany 2016", edited by the Robert-Koch Institute and the Society of Epidemiological Cancer Registers in Germany in November 2016, lung cancer is the most frequent cancer-induced cause of death in males, the third frequent in females [1].

From the about 53,500 patients, diseased in Germany in 2013, about 34,500 are males; about 44,800 died, 29,700 males and 15,100 females. The relative 5-year-survival rate, thus, is only 16 % for males, 21 % for females. In males as well as in females, the proportion of adenocarcinomas appears to be increasing, when the subtypes are differentiated.

NSCLC is the most prevalent type of lung cancer and accounts for around 85 % of the patients. About 60% are diagnosed in stage IV [2]. Beyond other factors, like general condition, comorbidity, and patient preferences, the selection of the drugs to be administered is determined by the histological classification of the tumour, immunophenotyping, molecular pathologic alterations, and the degree of PD-L1 expression of the tumour cells. For the palliative treatment of NSCLC, a platinum-based chemotherapy was the former standard in first-line treatment, mostly in combination with one of the following drugs: Pemetrexed, Vinorelbine, Paclitaxel, Nab-Paclitaxel, Docetaxel, Gemcitabine, Etoposide.

Even by these highly effective, empirically selected cytotoxic chemotherapy regimens, the life expectancy of most NSCLC patients is unsatisfying. In recent years, two classes of drugs were developed, the TKIs effective in distinct mutations by interrupting the signal ways of the cancer cells, and the immune checkpoint inhibitors, which are able to summon the endogenous immune system in the fight against the cancer.

Although driver mutations are known in the majority of patients with NSCLC, only a small proportion of patients have mutations, which can be treated with tailored TKIs. Of the NSCLC, about 10-15 % are EGFR positive, about

2.5 % show the ALK-translocation and 1-2 % ROS1-rearrangement. In Asian populations, however, up to 55 % of the NSCLC are EGFR-positive. Patients with these genetic aberrations show a better prognosis than patients without when treated with targeted drugs. The median prognosis can be improved from 8-10 months to up to >30 months. The efficacy of the treatment can be predicted by molecular pathologic tests. For this personalized therapy, the most relevant biomarkers should be screened for each patient with non-squamous NSCLC and non-smokers with squamous carcinoma prior to the start of first-line treatment (table 1).

Table 1

Predictive molecular markers for a stratified NSCLC treatment

EGFR-Mutation
EGFR: epidermal growth factor receptor
EML4-ALK-Translocation
EML4: echinoderm microtubule-associated protein-like 4
ALK: anaplastic lymphoma kinase
ROS1-Rearrangement
ROS1: c-ros oncogene 1 receptor tyrosine kinase
KIF5B-RET Fusion
KIF5B: kinesin family member 5B gene

The knowledge of the therapeutic options enables an optimal patient management. In Germany, the treatment to be applied, is individually discussed in a local Tumour Board either in an academic center or in the community for every patient according to the actual guidelines and the patients' personal data.

Sex appears to be an independent prognostic factor, whereas smoking status, age, and histology appear to have no influence.

EGFR-Mutations

In patients with activating EGFR-mutations (membrane-standing receptor protein kinase), the TKIserlotinib,gefitinib or afatinib show remission rates of 50-75 %, PFS of 9-13 months, and a median OS of 30-36 months (in comparison to 10 months under chemotherapy) [3]. Afatinib is a second-generation TKI, which irreversibly inhibits signalling of EGFR, HER2 and HER4, whereas the first-generation TKIserlotinib and gefitinib reversibly inhibit EGFR. Under afatinib, patients with del19 show a significantly better OS and 27 % less progress in comparison to gefitinib.Even after two years, 18% are progression free (in the gefitinibarm only 8 %) [4].Dacomitinib, a further powerful second-generation EGFR-inhibitor, is still an investigational agent, not approved by any regulatory agency at this time. Dacomitinib seems to be a more effective new option in the treatment of EGFR-positive NSCLC, but at a cost of greater toxicity [5].

Specific resistance mutations may occur, especially the T790M-mutation. If this mutation is proved by biopsy, a treatment with the third-generation inhibitorosimertinib is recommended: the remission rate of TKI-pretreatedpatients amounts to 65-70 %, the PFS to 9-11 months [6]. Due to its potential for blood-brain barrier penetration, osimertinib is also highly effective in relapsed patients with CNS metastases developing in up to 40 % of patients, with a response rate of 70 % [7].

In patients with this mutation and progressive disease after prior TKI, rociletinib appears also to be effective with ORR of 60 % and median PFS of 8-10.3 months [8].

ALK- or ROS1 Translocations

NSCLC patients with activating ALK-translocation or ROS1-rearrangement show remission rates of 60-80 %, a PFS of 9-11 months (18 months in ROS1+) and OS of 30-36 months when treated with the TKI crizotinib. Together with an improvement of the quality of life and less side effects, however, these results are significantly better than chemotherapy with platinum and pemetrexed. Various treatment-related adverse events may occur. Thus, crizotinib has hitherto been regarded as the treatment of choice in first-line therapy [9]. In the second-line treatment of ALK-positive patients, ceritinib and alectinib show response rates of 44-65 %, PFS of 6-15 months, and intracranial activity against CNS metastases [10]. In a recently reported trial comparing alectinib with crizotinib in first-line treatment of ALK-positive NSCLC, alectinib showed highly significant longer PFS (25.7 months) and delay of CNS progression. Alectinib, thus, appears to be the new standard of care, although OS and the handling of relapses still is open [11]. A pemetrexed-containing chemotherapy is recommended in patients after failure of an ALK-inhibitor or ROS1-positive patients after failure of crizotinib.

Immunotherapy by Immune Checkpoint Inhibitors

The immune checkpoint inhibitors are a new class of substances utilizing the natural ability of the patient's own immune system for the fight against cancer.

The principle of the checkpoint inhibitors is [12, 13, 14, 15]: Inhibitory molecules are blocked by monoclonal antibodies. The body's own immune system is able to block the overreaction of activated T cells. This occurs by activation of the programmed cell death (PD-1) receptor. This natural blockade inhibits an effective reaction of the immune system against malignant cells. Nivolumab and pembrolizumab are monoclonal anti-PD-1 antibodies directed against PD-1. They bind to the PD-1 receptor, found on T cells, block the interaction with the PD-1 ligands PD-L1 and PD-L2, reactivate the activity of the T cells, and intensify the body's own immune reaction. They show anti-tumour activity in melanoma [16, 17, 18, 19, 20], NSCLC [22, 23, 24, 25], renal cell [27, 28, 29], head and neck [30], and bladder cancers [31, 32, 33, 34], as well as in Hodgkin lymphoma [35, 36], among others. In tumours with high mutational load, expressing programmed death ligand 1 (PD-L1), nivolumab and pembrolizumab show increased activity [24, 25, 37]. Beyond the CTLA-4

antibody ipilimumab and the PD-1 inhibitors nivolumab and pembrolizumab, three PD-L1 inhibitors have been approved (table 2).

Table 2

Immune Checkpoint Inhibitors

Ipilimumab
Humanized monoclonal antibody of type IgG1κ
Binding on CTLA-4
Blockade of the checkpoint receptor CTLA-4
Nivolumab
Human monoclonal antibody of type IgG4κ
Binding on the PD-1-receptor on T-cells, thereby inhibition of the interaction with the ligands PD-L1 and PD-L2 on cancer cells
Blockade of the checkpoint receptor PD-1
Pembrolizumab
Human monoclonal antibody of type IgG4κ
Interaction with the PD-1-receptor on T-cells, thereby inhibition of the binding of the ligands
Blockade of the checkpoint receptor PD-1
Atezolizumab
Humanized monoclonal antibody of IgG1 isotype against the protein programmed cell death-ligand1 (PD-L1)
Avelumab
Fully human monoclonal antibody targeting the protein programmed death-ligand 1 (PD-L1)
Durvalumab
Selected human monoclonal antibody against PD-L1

The most common treatment-related side effects of immune checkpoint inhibitors are diarrhoea, fatigue, and pyrexia. In up to 30 % of the patients, immune-related toxicity is observed including pneumonitis, colitis, hepatitis, hypophysitis, thyroiditis, and severe skin reactions [22, 23, 26, 38]. Most immune-mediated events were of grade 1 or 2, but up to 10 % of grade 3 or 4 [23]. Even lethal events due to toxicity were reported [22].

Non-squamous Carcinomas without Activating EGFR-, ALK- or ROS1-Aberrations

The immune checkpoint inhibitors have changed the therapeutic action in at least a fraction of patients. About 25-30 % of the patients show a high level of programmed cell death ligand 1 (PD-L1) expression defined as membraneous PD-L1 expression on at least 50 % of tumour cells [23]. In previously untreated patients without activating EGFR, ALK- or ROS1-aberrations,pembrolizumableads to significantly longer PFS (+6 months), longer OS and fewer adverse events than platinum-containing chemotherapy [23]. For those patients, for whom pembrolizumab is not as effective as cytotoxic chemotherapy, combinations with chemotherapy or other immunotherapies might be needed [22]. Whether previously untreated patients with a tumour proportion score between 1 and 50 % will also have benefit of pembrolizumab over chemotherapy, is examined in ongoing phase 3 studies.

Platinum-based chemotherapy is still the standard of care for all other patients. The selection of the drugs is mainly determined by their toxicity profile and by the patients' preferences. The combination with the angiogenesis inhibitor bevacizumab, a recombinant humanized monoclonal antibody inhibiting vascular growth factor A (VEGF-A), proceeds with an enhancement of the remission rate and a prolongation of PFS [39, 40, 41].

After progress, the combination of docetaxel with the TKI and angiokinase inhibitor nintedanib or with the monoclonal antibodyramucirumab improves OS.

In comparison with docetaxel monotherapy, nivolumab and pembrolizumab lead to an improvement of survival and a higher remission rate in immune checkpoint inhibitor-naïve patients with a PD-L1 expression of ≥1 % [22, 24].

Squamous Carcinomas without Activating EGFR-, ALK- or ROS1-Aberrations

For untreated patients with squamous carcinoma and without activating EGFR-, ALK- or ROS1-aberrations,aplatinum-based chemotherapy is indicated. Patients with a tumour proportion score of at least 50 % may benefit from pembrolizumab [23]. Bevacizumab and pemetrexed are not approved and not indicated in squamous carcinoma.

In previously treated recurrent patients with squamous carcinoma, nivolumab is the standard of care. In contrast to non-squamous carcinomas, PD-L1 expression in tumour tissue is not a predictive marker. Nivolumab leads to a significantly better PFS, OS, remission rate and tolerability than docetaxel monotherapy [25]. In PD-L1 expression tumours, pembrolizumab is also effective [22].

Atecolizumab, the humanized monoclonal antibody of IgG1 isotype against the protein programmed cell deathligand 1 (PD-L1), is approved only in USA by the Food and Drug Administration for previously treated NSCLC, regardless of their PD-L1 status and histology. In a phase III trial, a prolongation of OS of 4.2 months was shown for previously treated squamous or non-squamous NSCLC patients versus docetaxel regardless of PD-L1 expression [26].

The drugs approved in Germany for the first-line treatment of advanced NSCLC are summarized in an algorithm published in onkopedia-guidelines, edited by the German Society of Haematology and Medical Oncology on April 11, 2017 [42]. Most recently, an update of the 2015 ASCO guideline on systemic therapy for patients with advanced NSCLC has been published [43].

Combination Therapies

Due to the huge growth in knowledge at present, it does not take much of an imagination to realize that seemingly innumerable biomarker therapy combinations lay ahead in the near future. At the ASCO Annual Meeting 2017,

for example, more than 250 contributions involving checkpoint inhibitors, were presented, more than 1,000 studies are underway [44]. Combination trials and optimal sequencing are a challenge for optimizing the use of TKIs and checkpoint inhibitors. In a Japanese trial, for instance, the combination of the TKI erlotinib with the monoclonal VEGF-antibody bevacizumab extends median PFS 6 months (16.0 months versus 9.7 months) with comparable quality of life in EGFR-mutation-positive patients with advanced non-squamous NSCLC [45]. It has now to be proved, whether rational combinations of TKIs or immune checkpoint inhibitors with cytotoxic therapies or with angiogenesis inhibitors are superior to monotherapies with regard to the antitumor immune response, but also to the side effects and the tolerability.

In order not to financially overtax the health system, the financial viability of these medically necessary, cost-intensive drugs appears only to be possible by cooperation and concerted actions. Networking of all involved groups, healthcare providers and payers, is, for instance, proposed by the German Cancer Society in the complex recently published position paper «Knowledge Generating Oncological Care» [46].

References

1. Barnes B. Bericht zum Krebsgeschehen in Deutschland. Berlin: Robert Koch-Institute; 2016. 269 p.

2. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA. Cancer statistics review, 1975-2014. SEER National Cancer Institute, Bethesda.

3. Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, Geater SL, Orlov S, Tsai CM, Boyer M, Su WC, Bennouna J, Kato T, Gorbunova V, Lee KH, Shah R, Massey D, Zazulina V, Shahidi M, Schuler M. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *Journal of Clinical Oncology.* 2013;31(27):3327-34. DOI: 10.1200/JCO.2012.44.2806.

4. Park K, Tan EH, O'Byrne K, Zhang L, Boyer M, Mok T, Hirsh V, Yang JC, Lee KH, Lu S, Shi Y, Kim SW, Laskin J, Kim DW, Arvis CD, Kölbeck K, Laurie SA, Tsai CM, Shahidi M, Kim M, Massey D, Zazulina V, Paz-Ares L. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. *The Lancet Oncology*. 2016;17(5):577-89. DOI: 10.1016/S1470-2045(16)30033-X.

5. Mok T, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S. Dacomitinib versus gefitinib for the first-line treatment of advanced EGRF mutation positive non-small cell lung cancer (ARCHER 1050): A randomized, open-label phase III trial. *Journal of Clinical Oncology* 2017;35. DOI: 10.1200/JCO.2017.35.15_suppl.LBA9007.

6. Yang J, Ramalingam SS, Jänne PA, Cantarini M, Mitsudomi T. LBA2_PR: Osimertinib (AZD9291) in pre-treated pts with T790M-positove advanced NSCLC: updated phase 1 (P1) and pooled phase 2 (P2) results. *Journal of Thoracic Oncology.* 2016;11(4):152-3. DOI: 10.1016/S1556-0864(16)30325-2.

7. Mok T, Ahn MJ, Han JY, Kang JH, Katakami N, Kim HR. CNS response to osimertinib in patients with T790M-positive advanced NSCLC: Data from a randomized phase III trial (AURA3). *Journal of Clinical Oncology* 2017;(35). DOI: 10.1200/JCO.2017.35.15_suppl.9005.

8. Sequist LV, Goldman JW, Wakelee HA, Camidge DR, Yu HA, Varga A. Efficacy of rociletinib (CO-1686) in plasma-genotyped T790M-positive non-small cell lung cancer patients. *Journal of Clinical Oncology*. 2015;(33). DOI: 10.1200/jco.2015.33.15_suppl.8001.

9. Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, Felip E, Cappuzzo F, Paolini J, Usari T, Iyer S, Reisman A, Wilner KD, Tursi J, Blackhall. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *The New England Journal of Medicine*. 2014; 371(23):2167-77. DOI: 10.1056/NEJMoa1408440.

10. Ou SHI, Ahn JS, Petris LD, Govindan R, Yang JCH, Hughes BGM. Efficacy and safety of the ALK inhibitor alectinib in ALK+ non-small-cell lung cancer patients who have failed prior crizotinib: an open-label, single-arm, global phase 2 study. *Journal of Clinical Oncology*. 2015;(33). DOI: 10.1200/jco.2015.33.15_suppl.8008.

11. Shaw AT, Peters S, Mok T, Gadgeel SM, Ahn JS, Ou SHI. Alectinib versus crizotinib in treatment-naïve advanced ALK-positive non-small cell lung cancer (NSCLC): Primary results of the global phase III ALEX study. *Journal of Clinical Oncology.* 2017;(35). DOI: 10.1200/JCO.2017.35.18_suppl.LBA9008.

12. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nature Reviews Cancer.* 2012;12(4):252-64. DOI: 10.1038/nrc3239.

13. Blank C, Brown I, Peterson AC, Spiotto M, Iwai Y, Honjo T, Gajewski TF. PD-L1/B7H-1 inhibits the effector phase of tumor rejection by T cell receptor (TCR) transgenic CD8+ T cells. *Cancer Research.* 2004;64(3):1140-5.

14. Okazaki T, Honjo T. PD-1 and PD-1 ligands: from discovery to clinical application. *International Immunology.* 2007;19(7):813-24.

15. Quezada SA, Peggs KS. Exploiting CTLA-4, PD-1 amd PD-L1 to reactivate the host immune response against cancer. *British Journal of Cancer.* 2013;108(8):1560-5. DOI: 10.1038/bjc.2013.117.

16. Postow MA, Chesney J, Pavlick AC, Robert C, Grossmann K, McDermott D, Linette GP, Meyer N, Giguere JK, Agarwala SS, Shaheen M, Ernstoff MS, Minor D, Salama AK, Taylor M, Ott PA, Rollin LM, Horak C, Gagnier P, Wolchok JD, Hodi FS. Nivolumab and

ipilimumab versus ipilimumab in untreated melanoma. *The New England Journal of Medicine*. 2015; 372(21):2006-17. DOI: 10.1056/NEJMoa1414428.

17. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, Daud A, Carlino MS, McNeil C, Lotem M, Larkin J, Lorigan P, Neyns B, Blank CU, Hamid O, Mateus C, Shapira-Frommer R, Kosh M, Zhou H, Ibrahim N, Ebbinghaus S, Ribas A. Pembrolizumab versus ipilimumab in advanced melanoma. *The New England Journal of Medicine*. 2015;372(26):2521-32. DOI: 10.1056/NEJMoa1503093.

18. Robert C, Ribas A, Hamid O, Daud A, Wolchok JD, Joshua AM, Hwu WJ, Weber JS, Gangadhar TC, Joseph RW, Dronca RS, Patnaik A, Zarour HM, Kefford R, Hersey P, Li X, Diede SJ, Ebbinghaus S, Hodi FS. Three-year survival for patients with advanced melanoma treated wotjpembrolizumab in KEYNOTE-001. *Journal of Clinical Oncology*. 2016;(34). DOI: 10.1200/JCO.2016.34.15_suppl.9503.

19. Larkin J, Hodi FS, Wolchok JD. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *The New England Journal of Medicine*. 2015;373(13):1270-1. DOI: 10.1056/NEJMc1509660.

20. Schachter J, Ribas A, Long GV, Arance A, Grob JJ, Mortier L, Daud A, Carlino MS, McNeil C, Lotem M, Larkin J, Lorigan P, Neyns B, Blank C, Petrella TM, Hamid O, Zhou H, Ebbinghaus S, Ibrahim N, Robert C. Pembrolizumab versus ipilimumab for advanced melanoma: Final overall survival analysis of KEYNOTE-006. *Journal of Clinical Oncology*. 34 (2016) suppl; abstr 9504.

21. Ribas A, Puzanov I, Dummer R, Schadendorf D, Hamid O, Robert C, Hodi FS, Schachter J, Pavlick AC, Lewis KD, Cranmer LD, Blank CU, O'Day SJ, Ascierto PA, Salama AK, Margolin KA, Loquai C, Eigentler TK, Gangadhar TC, Carlino MS, Agarwala SS, Moschos SJ, Sosman JA, Goldinger SM, Shapira-Frommer R, Gonzalez R, Kirkwood JM, Wolchok JD, Eggermont A, Li XN, Zhou W, Zernhelt AM, Lis J, Ebbinghaus S, Kang SP, Daud A. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomized, controlled, phase 2 trial. *The Lancet Oncology*. 2015;16(8):908-18. DOI: 10.1016/S1470-2045(15)00083-2.

22. Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han JY, Molina J, Kim JH, Arvis CD, Ahn MJ, Majem M, Fidler MJ, de Castro GJr, Garrido M, Lubiniecki GM, Shentu Y, Im E, Dolled-Filhart M, Garon EB.Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *The Lancet*. 2016;387(10027):1540-50. DOI: 10.1016/S0140-6736(15)01281-7.

23. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M, Rao S, Hotta K, Leiby MA, Lubiniecki GM, Shentu Y, Rangwala R, Brahmer JR. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *The New England Journal of Medicine*. 2016;375(19):1823-1833. DOI: 10.1056/NEJMoa1606774.

24. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Felip E, Holgado E, Barlesi F, Kohlhäufl M, Arrieta O, Burgio MA, Fayette J, Lena H, Poddubskaya E, Gerber DE, Gettinger SN, Rudin CM, Rizvi N, Crinò L, Blumenschein GR Jr, Antonia SJ, Dorange C, Harbison CT, Graf Finckenstein F, Brahmer JR. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *The New England Journal of Medicine*. 2015;373(17):1627-39. DOI: 10.1056/NEJMoa1507643.

25. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E, Waterhouse D, Ready N, Gainor J, Arén Frontera O, Havel L, Steins M, Garassino MC, Aerts JG, Domine M, Paz-Ares L, Reck M, Baudelet C, Harbison CT, Lestini B, Spigel DR. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung. *The New England Journal of Medicine*. 2015;373(2):123-35. DOI: 10.1056/NEJMoa1504627.

26. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, Gadgeel SM, Hida T, Kowalski DM, Dols MC, Cortinovis DL, Leach J, Polikoff J, Barrios C, Kabbinavar F, Frontera OA, De Marinis F, Turna H, Lee JS, Ballinger M, Kowanetz M, He P, Chen DS, Sandler A, Gandara DR. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *The Lancet*. 2017;389(10066):255-265. DOI: 10.1016/S0140-6736(16)32517-X.

27. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, Tykodi SS, Sosman JA, Procopio G, Plimack ER, Castellano D, Choueiri TK, Gurney H, Donskov F, Bono P, Wagstaff J, Gauler TC, Ueda T, Tomita Y, Schutz FA, Kollmannsberger C, Larkin J, Ravaud A, Simon JS, Xu LA, Waxman IM, Sharma P; CheckMate 025 Investigators. Nivolumab versus everolimus in advanced renal-cell carcinoma. *The New England Journal of Medicine*. 2015; 373(19):1803-13. DOI: 10.1056/NEJMoa1510665.

28. McDermott DF, Drake CG, Sznol M, Choueiri TK, Powderly JD, Smith DC, Brahmer JR, Carvajal RD, Hammers HJ, Puzanov I, Hodi FS, Kluger HM, Topalian SL, Pardoll DM, Wigginton JM, Kollia GD, Gupta A, McDonald D, Sankar V, Sosman JA, Atkins MB. Survival, durable response, and long-term safety in patients with previously treated advanced renal cell carcinoma receiving nivolumab. *Journal of Clinical Oncology*. 2015;33(18):2013-20. DOI: 10.1200/JCO.2014.58.1041.

29. McDermott DF, Motzer RJ, Atkins MB, Plimack ER, Sznol M, George S. Long-term overall survival with nivolumab in previously treated patients with advanced

renal cell carcinoma from phase I and II studies. *Journal of Clinical Oncology*. 2016;34. DOI: 10.1200/JCO.2016.34.15_suppl.4507.

30. Ferris RL, Blumenschein GJr, Fayette J, Guigay J, Colevas AD, Licitra L, Harrington K, Kasper S, Vokes EE, Even C, Worden F, Saba NF, Iglesias Docampo LC, Haddad R, Rordorf T, Kiyota N, Tahara M, Monga M, Lynch M, Geese WJ, Kopit J, Shaw JW, Gillison ML. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *The New England Journal of Medicine*. 2016;375(19):1856-67.

31. Balar AV, Galsky MD, Rosenberg JE, Powles T, Petrylak DP, Bellmunt J, Loriot Y, Necchi A, Hoffman-Censits J, Perez-Gracia JL, Dawson NA, van der Heijden MS, Dreicer R, Srinivas S, Retz MM, Joseph RW, Drakaki A, Vaishampayan UN, Sridhar SS, Quinn DI, Durán I, Shaffer DR, Eigl BJ, Grivas PD, Yu EY, Li S, Kadel EE 3rd, Boyd Z, Bourgon R, Hegde PS, Mariathasan S, Thåström A, Abidoye OO, Fine GD, Bajorin DF. Atezolizumab as first-line therapy in cisplatin-ineligible locally advanced/metastatic urothelial carcinoma: primary analysis of IMvigor210 cohort 1. *Journal of Clinical Oncology.* 2017;389(10064):67-76. DOI: 10.1016/S0140-6736(16)32455-2.

32. Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, Necchi A, Dawson N, O'Donnell PH, Balmanoukian A, Loriot Y, Srinivas S, Retz MM, Grivas P, Joseph RW, Galsky MD, Fleming MT, Petrylak DP, Perez-Gracia JL, Burris HA, Castellano D, Canil C, Bellmunt J, Bajorin D, Nickles D, Bourgon R, Frampton GM, Cui N, Mariathasan S, Abidoye O, Fine GD, Dreicer R. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *The Lancet*. 2016;387(10031):1909-20. DOI: 10.1016/S0140-6736(16)00561-4.

33. Galsky MD, Retz M, Siefker-Radtke AO, Baron A, Necchi A, Bedke J, Plimack ER, Vaena D, Grimm MO, Bracarda S, Arranz Arija J, Pal SK, Ohyama C, Saci A, Lambert A, Krishnan S, Azrilevich A, Sharma P. Efficacy and safety of nivolumab monotherapy in patients with metastatic urothelial cancer who have received prior treatment. Results from the phase II CheckMate 275 study. *Annals of Oncology.* 2016;(27). DOI:org/10.1093/annonc/mdw435.24.

34. Balar A, Bellmunt J, O'Donnell PH, Castellano D, Grivas P, Vuky J, Powles T, Plimack ER, Hahn NM, Wit R. Pembrolizumab as first-line therapy for advanced/unresectable or metastatic urothelial cancer: Preliminary results from the phase 2 KEYNOTE-052 study. *Annals of Oncology*. 2016;(27). DOI:org/10.1093/annonc/mdw435.25

35. Younes A, Santoro A, Shipp M, Zinzani PL, Timmerman JM, Ansell S, Armand P, Fanale M, Ratanatharathorn V, Kuruvilla J, Cohen JB, Collins G, Savage KJ, Trneny M, Kato K, Farsaci B, Parker SM, Rodig S, Roemer MG, Ligon AH, Engert A. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximabvedotin: a multicenter, multicohort, single-arm phase 2 trial. *The Lancet Oncology*. 2016;17(9):1283-94. DOI: 10.1016/S1470-2045(16)30167-X.

36. Timmerman JM, Engert A, Younes A, Santoro A, Armand P, Fanale MA, Collins GP, Ratanatharathorn V, Kuruvilla J, Cohen JB, Savage KJ, Trneny M, Paul De Boer J, Shipp MA, Rodig SJ, Kato K, Sumbul A, Ansell S. CheckMate 205 update with minimum 12-month follow-up: a phase 2 study of nivolumab in patients with relapsed/refractory classical Hodgkin lymphoma. ASH 2016, presentation 1110

37. Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, Lee W, Yuan J, Wong P, Ho TS, Miller ML, Rekhtman N, Moreira AL, Ibrahim F, Bruggeman C, Gasmi B, Zappasodi R, Maeda Y, Sander C, Garon EB, Merghoub T, Wolchok JD, Schumacher TN, Chan TA. Cancer immunology: Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science.* 2015;348(6230):124-8. DOI: 10.1126/science.aaa1348.

38. Postow MA. Managing immune checkpoint-blocking antibody side effects. *American Society of Clinical Oncology educational book.* 2015:76-83. DOI: 10.14694/EdBook_AM.2015.35.76.

39. Di Costanzo F, Mazzoni F, Micol Mela M, Antonuzzo L, Checcacci D, Saggese M, Di Costanzo F. Bevacizumab in non-small cell lung cancer. *Drugs*. 2008;68(6):737-46.

40. Reck M, von Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, Leighl N, Mezger J, Archer V, Moore N, Manegold C. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small cell lung cancer. AVAiL. *Journal of Clinical Oncology*. 2009;27(8):1227-34. DOI: 10.1200/JCO.2007.14.5466.

41. Vokes EE , Salgia R, Karrison TG. Evidence-based role of bevacizumab in non-small cell lung cancer. *Annals of Oncology*. 2013;24:6–9. DOI:10.1093/annonc/mds608.

42. Griesinger F, Eberhardt W. DGHO-Leitlinie Lungenkarzinom, nicht-kleinzellig (NSCLC) [Internet]. URL:https://www.onkopedia.com/de/onkopedia/guidelines/lungenkarzinom-nicht-kleinzellig-nsclc/@@view/html/index.html (retrieved on 12 May 2017).

43. Hanna N, Johnson D, Temin S, Baker S Jr, Brahmer J, Ellis PM, Giaccone G, Hesketh PJ, Jaiyesimi I, Leighl NB, Riely GJ, Schiller JH, Schneider BJ, Smith TJ, Tashbar J, Biermann WA, Masters G. Systemic therapy for stage IV non-small-cell lung cancer: American Society of ClinicalOncology Clinical Practice Guideline Update.

Journal of Clinical Oncology. 2017 Aug 14:JCO2017746065. DOI: 10.1200/JCO.2017.74.6065.

44. Allison JP. History of immunotherapy in solid tumors. Educations session, 2017 ASCO Annual Meeting, Chicago [Internet]. URL: https://am.asco.org/history-immunotherapy-solid-tumors.

45. Seto T, Kato T, Nishio M, Goto K, Atagi S, Hosomi Y, Yamamoto N, Hida T, Maemondo M, Nakagawa K, Nagase S, Okamoto I, Yamanaka T, Tajima K, Harada R, Fukuoka M, Yamamoto N. Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGRF mutation (JO25567): an open-label randomised, multicentre, phase 2 study. *The Lancet Oncology*. 2014;15(11):1236-44. DOI: 10.1016/S1470-2045(14)70381-X.

46. Bruns J, Dittmar S, Elmer A, Michaei D. Positionspapier zur «Wissen generierenden onkologischen Versorgung». *Forum*. 2017;32(2):114-117. DOI:10.1007/s12312-017-0244-8.

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БЕЛОК-ЛИГАНДНЫЕ ВЗАИМОДЕЙСТВИЯ: ВЛИЯНИЕ МИНОРНЫХ КОМПОНЕНТОВ МЕТАБОЛИЗМА

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Резюме. Научный обзор посвящен вопросу изучения влияния минорных компонентов на белок-лигандные взаимодействия. Практически в любом биологическом процессе, происходящем в клетке, участвуют белки, показывая неисчерпаемое разнообразие функций: регуляторная, каталитическая, транспортная, защитная и многие другие. Полифункциональность белков обусловлена их возможностью изменять конформацию молекулы при взаимодействии с лигандами. Белки могут взаимодействовать практически со всеми типами молекул – от небольших органических соединений: металлов, сахаров, жирных кислот, фосфолипидов клеточных мембран до высокомолекулярных белков и нуклеиновых кислот. В статье изложены актуальные аспекты взаимодействия в системе белок-белкового, белок-лигандного, фермент-субстратного взаимодействия, приведены примеры влияния малых молекул на белковые структуры клетки.

Ключевые слова: белок-белковые взаимодействия, белок-лигандные взаимодействия, белок-ферментные взаимодействия, минорные компоненты метаболизма, малые молекулы, лиганды, метаболом.

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PROTEIN-LIGAND INTERACTIONS: THE INFLUENCE OF MINOR COMPONENTS OF METABOLISM

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Abstract. The scientific review is devoted to the study of the influence of minor components to protein-ligand interactions. Practically in any biological process occurring in the cell, proteins are involved, showing an inexhaustible variety of functions: regulatory, catalytic, transport, protective and many others. Polyfunctionality of proteins is due to their ability to change the conformation of the molecule when interacting with ligands. Proteins can interact with almost all types of molecules - from small organic compounds: metals, sugars, fatty acids, phospholipids of cell membranes to high molecular proteins and nucleic acids. The article contains the topical aspects of interaction in the system of protein-protein, protein-ligand, enzyme-substrate interaction, examples of the effect of small molecules on the protein structure of the cell are given.

Key words: protein-protein interactions, protein-ligand interactions, protein-enzyme interactions, minor metabolism components, small molecules, ligands, metabolite.

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Метаболические пути, в которых осуществляются взаимопревращения основных метаболитов, чрезвычайно похожи у всех живых организмов и носят название центральных [1]. Многообразие метаболических путей нашло отражение в метаболических картах, в которых собрана информация об образующихся в