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Hans汉斯

免疫检查点抑制剂在肺癌治疗中的潜力与挑战

白红艳

齐鲁医院呼吸与危重症医学科，山东 济南

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摘　要

肺癌是全球最常见的癌症，其发病率逐渐上升，而且肺癌的5年存活率远低于其他癌症。虽然肺癌的治疗手段多种多样，但是肺癌早期检测困难，高异质性、强耐药性、易转移和复发给肺癌的治疗带来了许多挑战。免疫检查点抑制剂在肿瘤治疗中已得到广泛应用，已经成功应用在临床研究中。本研究对3种常见的免疫检查点，细胞毒性T细胞相关抗原4 (Cytotoxic T-Lymphocyte Antigen 4, CTLA-4)，程序性死亡受体1 (Programmed Death-1, PD-1)和程序性死亡受体配体1 (Programmed Death-Ligand 1, PD-L1)在肺癌上研究进行了综述，PD-L1可以作为肺癌治疗过程的潜在生物标志物。本研究通过系统综述这些免疫检查点在肺癌中的作用，帮助明确其在治疗中的有效性和潜力。这不仅为临床医生提供了更全面的治疗策略选择，也为未来的研究方向提供了科学依据。

关键词

肺癌，免疫检查点，抑制剂，抗体

Potential and Challenges of Immune Checkpoint Inhibitors in Lung Cancer Treatment

Hongyan Bai

Department of Pulmonary and Critical Care Medicine, Qilu Hospital, Jinan Shandong

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Abstract

Lung cancer is the most common cancer worldwide, its incidence is gradually increasing, and the 5-year survival rate of lung cancer is much lower than that of other cancers. Although there are

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various treatments for lung cancer, the difficulty of early detection of lung cancer, high heterogeneity, strong drug resistance, and the ease of metastasis and recurrence pose many challenges to the treatment of lung cancer. Immune checkpoint inhibitors have been widely used in tumour therapy and have been successfully applied in clinical studies. In this study, we investigated three common immune checkpoints, Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4), Programmed Death-1 (PD-1), and Programmed Death-Ligand 1 (PD-L1) studies on lung cancer were reviewed, and PD-L1 can be used as a potential biomarker for the therapeutic process of lung cancer. This study helps to clarify the effectiveness and potential of these immune checkpoints in therapy by systematically reviewing their role in lung cancer. This not only provides clinicians with a more comprehensive choice of treatment strategies, but also provides a scientific basis for future research directions.

Keywords

Lung Cancer, Immune Checkpoints, Inhibitors, Antibodies

1. 引言

肺癌是世界上最常见的癌症，肺癌的发病率逐渐呈上升状态[1]。肺癌患者根据其病理和临床特点可分为两大类，分别是小细胞肺癌(Small Cell Lung Cancer, SCLC)和(Non-Small-Cell Lung Cancer, NSCLC) [2]。肺癌 5 年存活率远低于其他癌症，尤其是 NSCLC 的IV期患者 5 年存活率不足 3% [3]。肺癌的发病机制受到多种因素的影响，如吸烟，饮酒，遗传，生活习惯和环境因素[4] [5]。吸烟是肺癌的最重要原因，80%的肺癌发生在吸烟者中[6]。

肺癌的治疗手段多种多样，如手术、放疗、化疗、靶向治疗和免疫治疗[7]-[9]。但是大部分肺癌患者发现通常在晚期，常规的治疗手段很难起作用。在早期阶段肺癌通常没有明显的症状，或者其症状与其他常见疾病相似[10]，如咳嗽、胸痛、呼吸困难等。这也导致很多患者往往在癌症已经发展到晚期时才被诊断出来。肺癌在影像学检查中的表现多种多样，常与其他肺部疾病相混淆，如肺炎、肺结核[11]。此外，一些肺癌亚型的影像学特征也可能不典型，增加了诊断的困难度。肺癌组织学异质性较高，肿瘤内部细胞类型、分化程度、生长模式等差异很大。这使得在组织学检查中往往需要对多个活检样本进行分析，增加了诊断的复杂性。而且肺癌较高的异质性，较强的耐药性，易转移和复发都给肺癌的治疗带来了极大的困难[12]。

免疫检查点抑制剂在肿瘤治疗中已经得到广泛应用，其中一些免疫检查点抑制剂已经被广泛应用于临床研究中[13]。T 细胞对抗原的免疫应答受复杂的抑制信号调控，这些信号被称为免疫检查点[14]。细胞毒性 T 细胞相关抗原 4 (Cytotoxic T-Lymphocyte Antigen 4, CTLA-4)和程序性死亡受体 1 (Programmed Death-1, PD-1)是 T 细胞表面的两种抑制性刺激分子，在免疫系统中发挥着关键作用，如调节 T 细胞活性和维持免疫平衡方面[15]。CTLA-4 和 PD-1 与相应的配体相互作用，T 细胞的活性就会受到抑制，从而减弱对肿瘤抗原的免疫应答，阻止 T 细胞攻击肿瘤。此外，肿瘤细胞和浸润淋巴细胞可以通过表达共刺激分子，如程序性死亡受体配体 1 (Programmed Death-Ligand 1, PD-L1)，来抑制初期的免疫反应。针对 CTLA-4 和 PD-L1/LD-1 的抑制剂可以阻断这种相互作用，引发免疫反应，达到抗肿瘤的作用[16]。目前，

研究最多的免疫检查点抑制剂包括抗 CTLA-4 抗体、抗 PD-1 抗体和抗 PD-L1 抗体，这些抗体在肺癌治疗的一些领域取得了成功。

2. CTLA-4 抑制剂

伊匹木单抗(Ipilimumab)是一种人源化 IgG1 抗 CTLA-4 单克隆抗体[17]。它可以通过阻断 CTLA-4 与 B7-1 和 B7-2 共刺激分子的结合，从而激活免疫系统，促进 T 细胞对肿瘤的攻击。Ipilimumab 的作用机制是通过增强 T 细胞对肿瘤抗原的免疫应答，从而抑制肿瘤生长和扩散，延长患者的生存期。

伊匹木单抗最初被用于治疗恶性黑色素瘤(皮肤癌)和一些其他类型的癌症，如晚期黑色素瘤、肾细胞癌、结直肠癌[18] [19]。近年来其在肺癌治疗作用引发了广泛关注。多项临床研究表明伊匹单抗单抗在 NSCLC 患者中显示出一定的临床活性[20] [21]。在一项随机对照研究中，伊匹单抗联合化疗用于晚期 NSCLC 患者显示出一定的生存益处[22]，特别是在鳞状细胞癌亚型中。然而在一些研究中，伊匹单抗的疗效并不理想，且常伴随着一定的不良反应。

3. PD-1 抑制剂

PD-1/PD-L1 抑制剂主要通过阻断 PD-1 受体与其配体之间的相互作用来解除 T 细胞的抑制状态，促进 T 细胞攻击肿瘤细胞。纳武利尤单抗(Nivolumab) [23]和派姆单抗(Pembrolizumab) [24]是两种代表性的 PD-1 抑制剂。

纳武利尤单抗是一种人源化 IgG4 单克隆抗体[24]，通过阻断 PD-1 及其配体(PD-L1/PD-L2)之间的相互作用，解除对 T 细胞的抑制，从而增强免疫系统对肿瘤细胞的攻击能力[23]。纳武利尤单抗通过阻断这一途径，恢复 T 细胞的活性，使其能够有效识别并杀伤肿瘤细胞。在临床前研究中，纳武利尤单抗显示出了显著的抗肿瘤活性。研究人员利用动物模型验证了其阻断 PD-1/PD-L1 通路的有效性，研究发现纳武利尤单抗可以显著抑制肿瘤生长，并延长模型动物的生存期[25]。多项临床试验已证实纳武利尤单抗在晚期或转移性 NSCLC 患者中的疗效。CheckMate-017 [26]和 CheckMate-057 [27]是两项关键的 III 期临床试验，分别针对鳞状和非鳞状 NSCLC 患者。结果显示纳武利尤单抗相比于多西他赛显著延长了患者的总生存期和无进展生存期。尤其在 PD-L1 表达阳性的患者中，疗效更为显著。纳武利尤单抗与其他药物联合治疗显示出更高的疗效。CheckMate-227 [28]研究发现纳武利尤单抗与伊匹单抗联合应用可显著延长高 TMB (肿瘤突变负荷)患者的总生存期。此外，纳武利尤单抗与化疗药物联合应用也在多项研究中展示了积极的疗效。多项研究表明，肿瘤细胞中 PD-L1 的表达水平与纳武利尤单抗的疗效具有一定相关性[29]，PD-L1 阳性患者的总体缓解率和总生存期均显著高于 PD-L1 阴性患者。

派姆单抗是一种 IgG4-κ 型人源化单克隆抗体，其机制与纳武利尤单抗相似，可选择性阻断 PD-1 功能。多项临床试验显示，派姆单抗在 NSCLC 治疗中具有显著疗效。KEYNOTE-001 [30]、KEYNOTE-010 [31]和 KEYNOTE-024 [32]是几项关键的临床试验，这些试验评估了派姆单抗在 PD-L1 高表达(TPS ≥ 50%)的晚期 NSCLC 患者中的疗效。KEYNOTE-024 [32]的结果尤为突出，研究发现派姆单抗相比于化疗显著延长了患者的总生存期和无进展生存期。派姆单抗作为一线治疗药物，在 PD-L1 高表达的晚期 NSCLC 患者中表现出优异的疗效。KEYNOTE-042 研究进一步证明了其作为一线单药治疗的有效性[33]，派姆单抗在 PD-L1 表达水平较低的患者中也显示出一定的疗效。派姆单抗与化疗的联合治疗也显示出显著效果。KEYNOTE-189 [34]和 KEYNOTE-407 [35]试验评估了派姆单抗联合铂类化疗在非鳞状和鳞状 NSCLC 患者中的疗效，结果显示联合治疗显著提高了总生存期和无进展生存期，并且这种疗效与 PD-L1 表达水平无关。

4. PD-L1 抑制剂

PD-L1 抑制剂是近年来癌症免疫治疗领域的重要突破之一[36]。PD-L1 抑制剂通过阻断 PD-1/PD-L1

通路来解除免疫抑制，从而增强机体的抗肿瘤免疫反应[37]。目前几种主要的 PD-L1 抑制剂已经获得批准并在临床中广泛应用，如阿替利珠单抗(Atezolizumab)、度伐利尤单抗(Durvalumab)和阿维鲁单抗(Avelumab)。

阿替利珠单抗(Atezolizumab)是一种人源化 IgG1 单克隆抗体，靶向程序性死亡配体-1 (PD-L1) [38]。其在肺癌治疗中的作用机制主要通过阻断 PD-1/PD-L1 通路来解除免疫抑制，增强机体的抗肿瘤免疫反应[39]。阿替利珠单抗通过与 PD-L1 结合，阻断 PD-L1 与 PD-1 以及 B7.1(CD80)的相互作用。这种阻断作用解除 T 细胞的抑制状态，使其能够恢复增殖、分泌细胞因子并直接杀伤肿瘤细胞的能力。通过解除 T 细胞的抑制状态，阿替利珠单抗能够增强 T 细胞介导的抗肿瘤免疫反应[40]。在非小细胞肺癌中，阿替利珠单抗的临床疗效得到广泛验证[41]。在 NSCLC 患者的试验中阿替利珠单抗与多西他赛相比显著延长了晚期 NSCLC 患者的总生存期[42]，特别是在 PD-L1 高表达的患者中效果更为明显。此外，IMpower150 研究显示阿替利珠单抗联合贝伐单抗和化疗相比单独化疗，在一线治疗 NSCLC 中也表现出显著的生存优势[43]。对于小细胞肺癌，IMpower133 研究表明阿替利珠单抗联合卡铂和依托泊苷作为一线治疗[44]。与单纯化疗，联合治疗显著延长了广泛期 SCLC 患者的总生存期和无进展生存期。

度伐利尤单抗(Durvalumab)是一种免疫检查点抑制剂，靶向程序性死亡配体 1 (PD-L1) [45]。它通过阻断 PD-L1 与其受体 PD-1 和 B7.1 的结合，恢复 T 细胞的抗肿瘤活性。在肺癌，特别是非小细胞肺癌(NSCLC)的治疗中，度伐利尤单抗的临床研究取得了显著成果[46]。PACIFIC 研究是一项 III 期临床试验，评估了度伐利尤单抗在接受了同步放化疗后的 III 期不可切除 NSCLC 患者中的疗效[47]。研究结果显示与安慰剂组相比，度伐利尤单抗显著延长了无进展生存期和总生存期。PD-L1 表达水平对度伐利尤单抗的疗效有一定预测作用，PD-L1 高表达患者从度伐利尤单抗中获益更多[48]。然而，即使在 PD-L1 低表达或阴性患者中，度伐利尤单抗也展示了一定的疗效。

5. 预测肺癌疗效的生物标志物

PD-1 和 PD-L1 抑制剂治疗晚期 NSCLC 的疗效约为 20% [49]，仍有约 80%的患者耐药，因此迫切需要寻找生物标志物来预测疗效。PD-L1 是目前研究最广泛的生物标志物，有研究发现 PD-L1 在多种肿瘤中表达，约 27%~50%的肺癌患者 PD-L1 阳性表达。这些研究表明 PD-L1 是一个潜在的理想预测因子[50]。

PD-L1 的表达水平是目前最常用的生物标志物之一，用于预测肺癌患者对免疫检查点抑制剂的疗效。PD-L1 的表达可以通过免疫组织化学方法检测，在临床试验和实际应用中，PD-L1 表达水平与治疗响应率之间的关联得到了广泛的研究和验证[51]。多项研究表明 PD-L1 高表达与免疫检查点抑制剂疗效之间存在正相关关系[52]。KEYNOTE-001 研究发现在 PD-L1 表达水平≥50%的患者中，派姆单抗的总体缓解率显著高于 PD-L1 低表达或阴性患者(45.2% vs. 16.5%) [53]。在 CheckMate-057 [27]试验中 PD-L1 表达水平与患者的总生存期显著相关。PD-L1 表达水平 ≥1%的患者中，纳武利尤单抗组的中位总生存期为 17.2 个月，而多西他赛组仅为 9.0 个月。

6. 总结

在本研究中我们重点讨论了三种主要的免疫检查点，CTLA-4、PD-1 和 PD-L1，及其在肺癌治疗中的应用与研究现状。CTLA-4 和 PD-1 均属于抑制性受体，是当前免疫靶向治疗的主要靶点。前者在参与初始抗原反应的 T 细胞(活化的 $CD8^+$ T 细胞)中表达，后者的基因在活化的 T 细胞、B 细胞、NK 细胞和不同类型的肿瘤浸润淋巴细胞中表达。免疫检查点抑制剂在肺癌治疗中的广泛应用，为临床医生治疗肺癌提供了新的治疗选择。

参考文献

[1] Minna, J.D., Roth, J.A. and Gazdar, A.F. (2002) Focus on Lung Cancer. *Cancer Cell*, **1**, 49-52. https://doi.org/10.1016/S1535-6108(02)00027-2

[2] Travis, W.D. (2020) Lung Cancer Pathology: Current Concepts. *Clinics in Chest Medicine*, **41**, 67-85. https://doi.org/10.1016/j.ccm.2019.11.001

[3] Thandra, K.C., Barsouk, A., Saginala, K., Aluru, J.S. and Barsouk, A. (2021) Epidemiology of Lung Cancer. *Contemporary Oncology*, **25**, 45-52. https://doi.org/10.5114/wo.2021.103829

[4] Zhao, Y., Liu, Y., Li, S., Peng, Z., Liu, X., Chen, J. and Zheng, X. (2021) Role of Lung and Gut Microbiota on Lung Cancer Pathogenesis. *Journal of Cancer Research and Clinical Oncology*, **147**, 2177-2186. https://doi.org/10.1007/s00432-021-03644-0

[5] Khan, S.A., Goliwas, K.F. and Deshane, J.S. (2021) Sphingolipids in Lung Pathology in the Coronavirus Disease Era: A Review of Sphingolipid Involvement in the Pathogenesis of Lung Damage. *Frontiers in Physiology*, **12**, Article 760638. https://doi.org/10.3389/fphys.2021.760638

[6] Chen, Y.-J., Roumeliotis, T.I., Chang, Y.-H., Chen, C.-T., Han, C.-L., *et al*. (2020) Proteogenomics of Non-Smoking Lung Cancer in East Asia Delineates Molecular Signatures of Pathogenesis and Progression. *Cell*, **182**, 226-244. https://doi.org/10.1016/j.cell.2020.06.012

[7] Vinod, S.K. and Hau, E. (2020) Radiotherapy Treatment for Lung Cancer: Current Status and Future Directions. *Respirology*, **25**, 61-71. https://doi.org/10.1111/resp.13870

[8] Carrasco-Esteban, E., Domínguez-Rullán, J.A., Barrionuevo-Castillo, P., Pelari-Mici, L., Leaman, O., Sastre-Gallego, S. and López-Campos, F. (2021) Current Role of Nanoparticles in the Treatment of Lung Cancer. *Journal of Clinical and Translational Research*, **7**, 140-155.

[9] Su, X.-L., Wang, J.-W., Che, H., Wang, C.-F., Jiang, H., Lei, X., Zhao, W., Kuang, H.-X. and Wang, Q.-H. (2020) Clinical Application and Mechanism of Traditional Chinese Medicine in Treatment of Lung Cancer. *Chinese Medical Journal*, **133**, 2987-2997. https://doi.org/10.1097/CM9.0000000000001141

[10] Guibert, N., Pradines, A., Favre, G. and Mazieres, J. (2020) Current and Future Applications of Liquid Biopsy in Nonsmall Cell Lung Cancer from Early to Advanced Stages. E*uropean Respiratory Review*, **29**, Article 190052. https://doi.org/10.1183/16000617.0052-2019

[11] Xiang, Y., Huang, C., He, Y. and Zhang, Q. (2021) Cancer or Tuberculosis: A Comprehensive Review of the Clinical and Imaging Features in Diagnosis of the Confusing Mass. *Frontiers in Oncology*, **11**, Article 644150. https://doi.org/10.3389/fonc.2021.644150

[12] Zhu, T., Bao, X., Chen, M., Lin, R., Zhuyan, J.N., Zhen, T., Xing, K., Zhou, W. and Zhu, S. (2020) Mechanisms and Future of Non-Small Cell Lung Cancer Metastasis. *Frontiers in Oncology*, **10**, Article 585284. https://doi.org/10.3389/fonc.2020.585284

[13] Shiravand, Y., Khodadadi, F., Kashani, S.M.A., Hosseini-Fard, S.R., Hosseini, S., Sadeghirad, H., Ladwa, R., O'Byrne, K. and Kulasinghe, A. (2022) Immune Checkpoint Inhibitors in Cancer Therapy. *Current Oncology*, **29**, 3044-3060. https://doi.org/10.3390/curroncol29050247

[14] Vafaei, S., Zekiy, A.O., Khanamir, R.A., Zaman, B.A., Ghayourvahdat, A., Azimizonuzi, H. and Zamani, M. (2022) Combination Therapy with Immune Checkpoint Inhibitors (ICIs); a New Frontier. *Cancer Cell International*, **22**, Article No. 2. https://doi.org/10.1186/s12935-021-02407-8

[15] Robert, C. (2020) A Decade of Immune-Checkpoint Inhibitors in Cancer Therapy. *Nature Communications*, **11**, Article No. 3801. https://doi.org/10.1038/s41467-020-17670-y

[16] Singh, S., Hassan, D., Aldawsari, H.M., Molugulu, N., Shukla, R. and Kesharwani, P. (2020) Immune Checkpoint Inhibitors: A Promising Anticancer Therapy. *Drug Discovery Today*, **25**, 223-229. https://doi.org/10.1016/j.drudis.2019.11.003

[17] Sondak, V.K., Smalley, K.S., Kudchadkar, R., Grippon, S. and Kirkpatrick, P. (2011) Ipilimumab. *Nature Reviews Drug Discovery*, **10**, 411-412. https://doi.org/10.1038/nrd3463

[18] Hodi, F.S., O'day, S.J., Mcdermott, D.F., Weber, R.W., Sosman, J.A., Haanen, J.B., Gonzalez, R., Robert, C., Schadendorf, D. and Hassel, J.C. (2010) Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. *New England Journal of Medicine*, **363**, 711-723. https://doi.org/10.1056/NEJMoa1003466

[19] Wolchok, J.D., Hodi, F.S., Weber, J.S., Allison, J.P., Urba, W.J., Robert, C., O'day, S.J., Hoos, A., Humphrey, R. and Berman, D.M. (2013) Development of Ipilimumab: A Novel Immunotherapeutic Approach for the Treatment of Advanced Melanoma. *Annals of the New York Academy of Sciences*, **1291**, 1-13. https://doi.org/10.1111/nyas.12180

[20] Paz-Ares, L.G., Ramalingam, S.S., Ciuleanu, T.-E., Lee, J.-S., Urban, L., Caro, R.B., Park, K., Sakai, H., Ohe, Y. and

Nishio, M. (2022) First-Line Nivolumab plus Ipilimumab in Advanced NSCLC: 4-Year Outcomes from the Randomized, Open-Label, Phase 3 CheckMate 227 Part 1 Trial. *Journal of Thoracic Oncology*, **17**, 289-308. https://doi.org/10.1016/j.jtho.2021.09.010

[21] Pinto, J.A., Raez, L.E., Oliveres, H. and Rolfo, C.C. (2019) Current Knowledge of Ipilimumab and Its Use in Treating Non-Small Cell Lung Cancer. *Expert Opinion on Biological Therapy*, **19**, 509-515. https://doi.org/10.1080/14712598.2019.1610380

[22] Hellmann, M.D., Paz-Ares, L., Caro, R.B., Zurawski, B., Kim, S.-W., Costa, E.C., Park, K., *et al*. (2019) Nivolumab plus Ipilimumab in Advanced Non-Small Cell Lung Cancer. *New England Journal of Medicine*, **381**, 2020-2031. https://doi.org/10.1056/NEJMoa1910231

[23] Gunturi, A. and Mcdermott, D.F. (2015) Nivolumab for the Treatment of Cancer. *Expert Opinion on Investigational Drugs*, **24**, 253-60. https://doi.org/10.1517/13543784.2015.991819

[24] Khoja, L., Butler, M.O., Kang, S.P., Ebbinghaus, S. and Joshua, A.M. (2015) Pembrolizumab. *Journal for Immunotherapy of Cancer*, **3**, 1-13. https://doi.org/10.1186/s40425-015-0078-9

[25] Wang, C., Thudium, K.B., Han, M., Wang, X.-T., Huang, H., Feingersh, D., Garcia, C., Wu, Y., Kuhne, M. and Srinivasan, M. (2014) *in Vitro* Characterization of the Anti-PD-1 Antibody Nivolumab, BMS-936558, and *in Vivo* Toxicology in Non-Human Primates. *Cancer Immunology Research*, **2**, 846-856. https://doi.org/10.1158/2326-6066.CIR-14-0040

[26] Borghaei, H., Gettinger, S., Vokes, E.E., Chow, L.Q., Burgio, M.A., de Castro Carpeno, J., Pluzanski, A., Arrieta, O., Frontera, O.A. and Chiari, R. (2021) Five-Year Outcomes from the Randomized, Phase III Trials Checkmate 017 and 057: Nivolumab versus Docetaxel in Previously Treated Non-Small-Cell Lung Cancer. *Journal of Clinical Oncology*, **39**, 723-733. https://doi.org/10.1200/JCO.20.01605

[27] Horn, L., Spigel, D.R., Vokes, E.E., Holgado, E., Ready, N., Steins, M., Poddubskaya, E., Borghaei, H., Felip, E. and Paz-Ares, L. (2017) Nivolumab versus Docetaxel in Previously Treated Patients with Advanced Non0-Small-Cell Lung Cancer: Two-Year Outcomes from Two Randomized, Open-Label, Phase III Trials (CheckMate 017 and CheckMate 057). *Journal of Clinical Oncology*, **35**, 3924-3933. https://doi.org/10.1200/JCO.2017.74.3062

[28] Brahmer, J.R., Lee, J.-S., Ciuleanu, T.-E., Bernabe, Caro, R., Nishio, M., Urban, L., Audigier-Valette, C., Lupinacci, L., Sangha, R. and Pluzanski, A. (2023) Five-Year Survival Outcomes with Nivolumab plus Ipilimumab versus Chemotherapy as First-Line Treatment for Metastatic Non-Small-Cell Lung Cancer in CheckMate 227. *Journal of Clinical Oncology*, **41**, 1200-1212. https://doi.org/10.1200/JCO.22.01503

[29] Li, J., Xuan, S., Dong, P., Xiang, Z., Gao, C., Li, M., Huang, L. and Wu, J. (2023) Immunotherapy of Hepatocellular Carcinoma: Recent Progress and New Strategy. *Frontiers in Immunology*, **14**, Article 1192506. https://doi.org/10.3389/fimmu.2023.1192506

[30] Leighl, N.B., Hellmann, M.D., Hui, R., Carcereny, E., Felip, E., Ahn, M.-J., Eder, J.P., Balmanoukian, A.S., Aggarwal, C. and Horn, L. (2019) Pembrolizumab in Patients with Advanced Non-Small-Cell Lung Cancer (KEYNOTE-001): 3-Year Results from an Open-Label, Phase 1 Study. *The Lancet Respiratory Medicine*, **7**, 347-357. https://doi.org/10.1016/S2213-2600(18)30500-9

[31] Herbst, R.S., Baas, P., Kim, D.-W., Felip, E., Pérez-Gracia, J.L., Han, J.-Y., Molina, J., Kim, J.-H., Arvis, C.D. and Ahn, M.-J. (2016) Pembrolizumab versus Docetaxel for Previously Treated, PD-L1-Positive, Advanced Non-Small-Cell Lung Cancer (KEYNOTE-010): A Randomised Controlled Trial. *The Lancet*, **387**, 1540-1550. https://doi.org/10.1016/S0140-6736(15)01281-7

[32] Reck, M., Rodriguez-Abreu, D., Robinson, A.G., Hui, R., *et al*. (2019) Updated Analysis of KEYNOTE-024: Pembrolizumab versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer with PD-L1 Tumor Proportion Score of 50% or Greater. *Journal of Clinical Oncology*, **37**, 537-546. https://doi.org/10.1200/JCO.18.00149

[33] Mok, T.S., Wu, Y.-L., Kudaba, I., Kowalski, D.M., Cho, B.C., Turna, H.Z., Castro, G., Srimuninnimit, V., Laktionov, K.K. and Bondarenko, I. (2019) Pembrolizumab versus Chemotherapy for Previously Untreated, PD-L1-Expressing, Locally Advanced or Metastatic Non-Small-Cell Lung Cancer (KEYNOTE-042): A Randomised, Open-Label, Controlled, Phase 3 Trial. *The Lancet*, **393**, 1819-1830. https://doi.org/10.1016/S0140-6736(18)32409-7

[34] Gadgeel, S., Rodriguez-Abreu, D., Speranza, G., Esteban, E., Felip, E., Dómine, M., Hui, R., Hochmair, M.J., Clingan, P. and Powell, S.F. (2020) Updated Analysis from KEYNOTE-189: Pembrolizumab or Placebo plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non-Small-Cell Lung Cancer. *Journal of Clinical Oncology*, **38**, 1505-1517. https://doi.org/10.1200/JCO.19.03136

[35] Paz-Ares, L., Vicente, D., Tafreshi, A., Robinson, A., Parra, H.S., Mazières, J., *et al*. (2020) A Randomized, Placebo-Controlled Trial of Pembrolizumab plus Chemotherapy in Patients with Metastatic Squamous NSCLC: Protocol-Specified Final Analysis of KEYNOTE-407. *Journal of Thoracic Oncology*, **15**, 1657-1669. https://doi.org/10.1016/j.jtho.2020.06.015

[36] Sunshine, J. and Taube, J.M. (2015) Pd-1/Pd-L1 Inhibitors. *Current Opinion in Pharmacology*, **23**, 32-38.

https://doi.org/10.1016/j.coph.2015.05.011

[37] Doroshow, D.B., Bhalla, S., Beasley, M.B., Sholl, L.M., Kerr, K.M., Gnjatic, S., Wistuba, I.I., Rimm, D.L., Tsao, M.S. and Hirsch, F.R. (2021) PD-L1 as a Biomarker of Response to Immune-Checkpoint Inhibitors. *Nature Reviews Clinical Oncology*, **18**, 345-362. https://doi.org/10.1038/s41571-021-00473-5

[38] Socinski, M.A., Jotte, R.M., Cappuzzo, F., Orlandi, F., Stroyakovskiy, D., Nogami, N., Rodr, Guez-Abreu, D., Moro-Sibilot, D., Thomas, C.A. and Barlesi, F. (2018) Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. *New England Journal of Medicine*, **378**, 2288-2301. https://doi.org/10.1056/NEJMoa1716948

[39] Horn, L., Mansfield, A.S., Szczęsna, A., Havel, L., Krzakowski, M., Hochmair, M.J., Huemer, F., Losonczy, G., Johnson, M.L. and Nishio, M. (2018) First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. *New England Journal of Medicine*, **379**, 2220-2229. https://doi.org/10.1056/NEJMoa1809064

[40] Finn, R.S., Qin, S., Ikeda, M., Galle, P.R., Ducreux, M., Kim, T.-Y., Kudo, M., Breder, V., Merle, P. and Kaseb, A.O. (2020) Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *New England Journal of Medicine*, **382**, 1894-1905. https://doi.org/10.1056/NEJMoa1915745

[41] Liu, W., Huo, G. and Chen, P. (2022) Efficacy of Atezolizumab for Advanced Non-Small Cell Lung Cancer Based on Clinical and Molecular Features: A Meta-Analysis. *Frontiers in Immunology*, **13**, Article 909027. https://doi.org/10.3389/fimmu.2022.909027

[42] Rittmeyer, A., Barlesi, F., Waterkamp, D., Park, K., Ciardiello, F., Von, Pawel, J., Gadgeel, S.M., Hida, T., Kowalski, D.M. and Dols, M.C. (2017) 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*, **389**, 255-265. https://doi.org/10.1016/S0140-6736(16)32517-X

[43] Reck, M., Mok, T.S., Nishio, M., Jotte, R.M., Cappuzzo, F., Orlandi, F., Stroyakovskiy, D., Nogami, N., Rodr, Guez-Abreu, D. and Moro-Sibilot, D. (2019) Atezolizumab plus Bevacizumab and Chemotherapy in Non-Small-Cell Lung Cancer (IMpower150): Key Subgroup Analyses of Patients with EGFR Mutations or Baseline Liver Metastases in a Randomised, Open-Label Phase 3 Trial. *The Lancet Respiratory Medicine*, **7**, 387-401. https://doi.org/10.1016/S2213-2600(19)30084-0

[44] Liu, S.V., Reck, M., Mansfield, A.S., Mok, T., Scherpereel, A., Reinmuth, N., Garassino, M.C., De Castro Carpeno, J., Califano, R. and Nishio, M. (2021) Updated Overall Survival and PD-L1 Subgroup Analysis of Patients with Extensive-Stage Small-Cell Lung Cancer Treated with Atezolizumab, Carboplatin, and Etoposide (IMpower133). *Journal of Clinical Oncology*, **39**, 619-630. https://doi.org/10.1200/JCO.20.01055

[45] Alvarez-Argote, J. and Dasanu, C.A. (2019) Durvalumab in Cancer Medicine: A Comprehensive Review. *Expert Opinion on Biological Therapy*, **19**, 927-935. https://doi.org/10.1080/14712598.2019.1635115

[46] Antonia, S.J., Villegas, A., Daniel, D., Vicente, D., Murakami, S., Hui, R., Yokoi, T., Chiappori, A., Lee, K.H., *et al.* (2017) Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. *New England Journal of Medicine*, **377**, 1919-1929. https://doi.org/10.1056/NEJMoa1709937

[47] Spigel, D.R., Faivre-Finn, C., Gray, J.E., Vicente, D., Planchard, D., Paz-Ares, L., Vansteenkiste, J.F., Garassino, M.C., Hui, R. and Quantin, X. (2022) Five-Year Survival Outcomes from the PACIFIC Trial: Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. *Journal of Clinical Oncology*, **40**, 1301-1311. https://doi.org/10.1200/JCO.21.01308

[48] Bang, A., Schoenfeld, J.D. and Sun, A.Y. (2019) PACIFIC: Shifting Tides in the Treatment of Locally Advanced Non-Small Cell Lung Cancer. *Translational Lung Cancer Research*, **8**, S139-S146. https://doi.org/10.21037/tlcr.2019.09.04

[49] Shen, X. and Zhao, B. (2018) Efficacy of PD-1 or PD-L1 Inhibitors and PD-L1 Expression Status in Cancer: Meta-Analysis. *British Medical Journal*, **362**, k3529. https://doi.org/10.1136/bmj.k3529

[50] Pillai, R.N., Behera, M., Owonikoko, T.K., Kamphorst, A.O., Pakkala, S., Belani, C.P., Khuri, F.R., Ahmed, R. and Ramalingam, S.S. (2018) Comparison of the Toxicity Profile of PD‐1 versus PD‐L1 Inhibitors in Non-Small Cell Lung Cancer: A Systematic Analysis of the Literature. *Cancer*, **124**, 271-277. https://doi.org/10.1002/cncr.31043

[51] Spagnuolo, A. and Gridelli, C. (2018) "Comparison of the Toxicity Profile of PD-1 versus PD-L1 Inhibitors in Non-Small Cell Lung Cancer": Is There a Substantial Difference or Not? *Journal of Thoracic Disease*, **10**, S4065. https://doi.org/10.21037/jtd.2018.09.83

[52] Sacher, A.G. and Gandhi, L. (2016) Biomarkers for the Clinical Use of PD-1/PD-L1 Inhibitors in Non-Small-Cell Lung Cancer: A Review. *JAMA Oncology*, **2**, 1217-1222. https://doi.org/10.1001/jamaoncol.2016.0639

[53] Hamid, O., Robert, C., Daud, A., Hodi, F., Hwu, W., Kefford, R., Wolchok, J., Hersey, P., Joseph, R. and Weber, J. (2019) Five-Year Survival Outcomes for Patients with Advanced Melanoma Treated with Pembrolizumab in KEYNOTE-001. *Annals of Oncology*, **30**, 582-588. https://doi.org/10.1093/annonc/mdz011