Advances in Clinical Medicine 临床医学进展, 2026, 16(1), 2072-2079
Published Online January 2026 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2026.161262

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EGFR-TKIs治疗EGFR突变耐药NSCLC的治疗策略

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收稿日期：2025年12月15日；录用日期：2026年1月8日；发布日期：2026年1月22日

摘　要

非小细胞肺癌(non-small cell lung cancer, NSCLC)是全球范围内发病率和死亡率最高的恶性肿瘤之一，其中表皮生长因子受体(epidermal growth factor receptor, EGFR)突变是NSCLC最重要的分子标志物之一。EGFR酪氨酸激酶抑制剂(EGFR-TKIs)已成为EGFR突变晚期NSCLC患者的标准治疗方案，并极大地改善了患者的生存预后。然而，尽管一线EGFR-TKIs治疗可取得较好的初始疗效，但几乎所有患者最终都会发生耐药并导致疾病进展。耐药机制包括EGFR基因二次突变(如T790M、C797S)、旁路通路激活(如MET扩增、HER2扩增)、组织学转化(如小细胞肺癌转化)及上皮－间质转化(epithelial-mesenchymal transition, EMT)等。此外，部分患者在初始EGFR-TKIs治疗时即表现出原发耐药。近年来，针对EGFR-TKIs耐药的研究取得了显著进展，包括联合治疗策略、靶向新突变药物以及免疫治疗等新兴疗法的探索。本文综述EGFR-TKIs治疗EGFR突变NSCLC进展的耐药机制、治疗策略及未来发展方向，以期为临床实践提供参考。

关键词

非小细胞肺癌，EGFR-TKIs，耐药机制，个体化治疗，联合治疗

Therapeutic Strategies for Overcoming Resistance to EGFR-TKIs Therapy in EGFR-Mutant NSCLC

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文章引用: 苗霖, 刘峥. EGFR-TKIs 治疗 EGFR 突变耐药 NSCLC 的治疗策略[J]. 临床医学进展, 2026, 16(1): 2072-2079.
DOI: 10.12677/acm.2026.161262

Received: December 15, 2025; accepted: January 8, 2026; published: January 22, 2026

Abstract

Non-small cell lung cancer (NSCLC) is one of the most prevalent and lethal malignancies worldwide, with epidermal growth factor receptor (EGFR) mutations being a key molecular biomarker. EGFR tyrosine kinase inhibitors (EGFR-TKIs) have become the standard treatment for patients with advanced EGFR-mutant NSCLC, significantly improving survival outcomes. However, despite the initial efficacy of first-line EGFR-TKIs therapy, nearly all patients eventually develop resistance, leading to disease progression. Resistance mechanisms include secondary EGFR mutations (e.g., T790M, C797S), activation of bypass pathways (e.g., MET amplification, HER2 amplification), histological transformation (e.g., small cell lung cancer transformation), and epithelial-mesenchymal transition (EMT). Additionally, some patients exhibit primary resistance to EGFR-TKIs at treatment initiation. In recent years, significant advances have been made in overcoming EGFR-TKIs resistance, including combination therapy strategies, targeted agents against emerging mutations, and novel immunotherapeutic approaches. This review summarizes the resistance mechanisms, therapeutic strategies, and future directions of EGFR-TKIs treatment in EGFR-mutant NSCLC, aiming to provide insights for clinical practice.

Keywords

Non-Small Cell Lung Cancer, EGFR-TKIs, Resistance Mechanisms, Personalized Therapy, Combination Therapy

1. EGFR-TKIs 获得性耐药机制

EGFR 酪氨酸激酶抑制剂(EGFR-TKIs)是 EGFR 突变阳性非小细胞肺癌(NSCLC)患者的主要治疗手段。然而，尽管 EGFR-TKIs 可有效延长患者生存期，绝大多数患者在治疗一段时间后仍会出现获得性耐药，导致疾病进展。三代 EGFR-TKIs (如奥希替尼)虽能克服 T790M 突变导致的耐药，但仍无法避免 C797S 突变、旁路通路激活、肿瘤微环境(TME)重塑、肿瘤异质性及组织学转化等多种耐药机制的影响[1]。深入理解 EGFR-TKIs 的耐药机制，对于优化后续治疗策略、延长患者生存期具有重要意义。

1.1. 二次突变介导的耐药

在 EGFR-TKIs 治疗过程中，肿瘤细胞可能通过获得性突变逃避药物抑制。T790M 突变是第一、二代 EGFR-TKIs (如吉非替尼、厄洛替尼、阿法替尼)耐药的主要机制之一，该突变增强 ATP 结合位点对 ATP 的亲和力，从而削弱药物抑制 EGFR 活性的能力[2] [3]。研究表明，约 45%~65%的患者在接受第一、二代 EGFR-TKIs 治疗后会发展出 T790M 突变[4]-[6]。

奥希替尼等第三代 EGFR-TKIs 可有效抑制 T790M 介导的耐药机制，但目前，C797S 突变已成为其主要耐药机制，显著限制了治疗效果和临床获益[7] [8]。C797S 突变发生在 EGFR 关键的 ATP 结合位点，使 TKIs 失去对 EGFR 的抑制作用。该突变可分为顺式(C797S 和 T790M 位于同一等位基因)和反式(C797S 和 T790M 位于不同等位基因)两种类型，其中顺式 C797S 对所有 EGFR-TKIs 均耐药，而反式 C797S 仍

可能对第一、二代 TKIs 保持敏感，提示联合使用第一代 TKIs 可能成为一种潜在策略[7] [8]。

1.2. 旁路通路的激活

在 EGFR 信号通路受抑制的情况下，肿瘤细胞可通过旁路通路维持信号传导，从而获得耐药性。MET 基因扩增是 EGFR-TKIs 耐药的重要机制之一，研究显示，MET 扩增在奥希替尼耐药患者中的发生率约为 5%~30% [9]。该扩增可激活 PI3K/AKT 和 MAPK/ERK 信号通路，使肿瘤细胞不依赖 EGFR 信号仍可存活，MET 抑制剂(如 capmatinib、tepotinib)联合 EGFR-TKIs 可部分克服该耐药机制[10] [11]。此外，HER2 (ERBB2)基因扩增也可促进 EGFR-TKIs 耐药，其机制涉及 PI3K/AKT 和 MAPK 信号通路的持续激活[12] [13]。针对 HER2 扩增的患者，HER2 靶向治疗(如 trastuzumab deruxtecan)在部分 EGFR-TKIs 耐药患者中展现出一定疗效。此外，FGFR 和 IGF1R 信号的异常激活亦被证实可促进 EGFR-TKIs 耐药，针对这些旁路通路的靶向治疗正在积极探索中[14]-[17]。

1.3. 肿瘤微环境介导的耐药

肿瘤微环境(TME)由肿瘤细胞、免疫细胞、成纤维细胞及基质成分构成，其动态变化在 EGFR-TKIs 耐药中发挥重要作用[2]。肿瘤相关巨噬细胞(TAMs)通过分泌炎症因子(如 IL-6、IL-10、TGF-β)促进肿瘤细胞存活，并通过极化为 M2 型巨噬细胞增强免疫抑制作用[18]。此外，M2 型 TAMs 可上调 PD-L1 表达，削弱免疫治疗和 EGFR-TKIs 的抗肿瘤作用[19]。

癌相关成纤维细胞(CAFs)通过分泌肝细胞生长因子(HGF)激活 MET 信号通路，促进耐药[20]。同时，CAF 释放的 TGF-β 可诱导肿瘤细胞发生上皮–间质转化(EMT)，进一步增强肿瘤侵袭和耐药能力[21]。此外，EGFR-TKIs 耐药后，PD-L1 表达上调、调节性 T 细胞(Tregs)浸润增多，进一步削弱机体的抗肿瘤免疫应答，因此 EGFR-TKIs 联合 PD-1/PD-L1 抑制剂成为研究热点[22] [23]。

1.4. 组织学转化

部分 EGFR 突变阳性的肺腺癌在耐药后可能转化为小细胞肺癌(SCLC)或鳞状细胞癌(SqCC)，这一现象被称为组织学转化[24]-[26]。研究发现，TP53 和 RB1 的失活是肺腺癌向 SCLC 转化的主要驱动因素，SCLC 具有高度增殖特征，并对 EGFR-TKIs 失去依赖性[27]。

此外，少数患者的耐药肿瘤可转化为鳞状细胞癌，该类型对 EGFR-TKIs 无效。因此，动态监测患者的组织学变化，并及时调整治疗策略，是提高 EGFR-TKIs 耐药患者生存率的重要手段[27]。

2. EGFR-TKIs 耐药后的治疗策略

2.1. 双特异性抗体为 EGFR-TKIs 耐药人群提供新的治疗选择

2.1.1. EGFR 与 c-MET 双抗联合化疗

埃万妥单抗(Amivantamab)是一种双特异性抗体，可同时靶向 EGFR 与 c-MET 在 EGFR-TKI 耐药的 NSCLC 患者中展现出潜在的治疗价值。基于 CHRYSALIS [28]和 CHRYSALIS 2 [29]研究，MARIPOSA-2 作为一项全球 III 期随机对照临床试验，进一步评估了该药物联合方案在 EGFR 突变、奥希替尼耐药 NSCLC 患者中的疗效和安全性。该研究设立了三个治疗组：埃万妥单抗 + 拉泽替尼 + 培美曲塞 + 卡铂(LACP 组)、埃万妥单抗 + 培美曲塞 + 卡铂(ACP 组)及单纯化疗组(CP 组)，以探讨拉泽替尼在联合方案中的作用。研究结果显示，ACP 组、LACP 组及 CP 组的中位无进展生存期(PFS)分别为 6.3、8.3 和 4.2 个月。与单纯化疗相比，ACP (HR = 0.48，95% CI 为 0.36~0.64；$P < 0.001$)和 LACP (HR = 0.44，95% CI 为 0.35~0.56；$P < 0.001$)均显著延长了患者的 PFS [30]，提示埃万妥单抗联合治疗可有效改善奥希替尼耐

药 EGFR 突变 NSCLC 患者的预后。基于这一研究结果，2023 年 11 月，研究团队已向美国 FDA 递交新适应证申请，拟批准埃万妥单抗联合化疗用于奥希替尼耐药的 EGFR 突变 NSCLC 患者。这一研究进展有望为 TKI 耐药患者提供新的治疗选择，进一步完善 EGFR-TKI 耐药 NSCLC 的管理策略。

2.1.2. PD-1 与 VEGF 双抗联合化疗

在 EGFR-TKI 耐药的 NSCLC 患者中，免疫治疗联合抗血管生成药物及化疗的四药方案已成为研究热点。其中，依沃西单抗(AK112)作为一种抗 PD-1/VEGF 双特异性抗体，在I、II期研究中展现出良好的抗肿瘤活性[31]。

HARMONi-A 研究的期中分析显示，依沃西单抗联合化疗较标准化疗可显著延长中位无进展生存期(7.06 个月 vs. 4.8 个月，HR = 0.46，P < 0.001)，并提高客观缓解率(50.6% vs. 35.4%)。此外，该联合方案在总生存期(OS)方面亦呈现延长趋势(17.1 个月 vs. 14.5 个月) [32]。基于该研究数据，2024 年 5 月，中国国家药品监督管理局(NMPA)批准其联合化疗用于 EGFR-TKI 耐药的非鳞状 NSCLC 患者。此外，针对三代 EGFR-TKI 耐药的 EGFR 突变 NSCLC 患者，HARMONi 国际多中心III期研究仍在进行，以进一步评估其临床价值。

这一研究进展为 EGFR-TKI 耐药患者提供了新的治疗策略，强调了免疫联合治疗在该人群中的潜在应用价值，同时也为未来的精准治疗探索提供了重要依据。

2.2. ADC 有望为 EGFR-TKIs 耐药人群提供全新的治疗策略

ADC 兼具靶向和细胞毒药物的双重抗肿瘤作用，多款 ADC 在 EGFR-TKIs 耐药人群显示了显著的初步疗效，例如靶向人滋养层细胞表面抗原 2 (trophoblast cell surface antigen 2, TROP2)、人表皮生长因子受体 3 (human epidermal growth factor receptor 3, HER3)、EGFR 以及 c-MET 的 ADC 均显示了极具前景的应用价值[33]。

2.2.1. TROP2 ADC

TROP2 是一种细胞表面糖蛋白，在 NSCLC 腺癌和鳞癌中的高表达率分别为 64%和 75%，并与不良预后密切相关[34]-[37]。针对 TROP2 的 ADC 成为 EGFR-TKIs 耐药后治疗的新兴策略。Dato-DXd 是一款 TROP2 靶向 ADC，由可切割四肽接头连接拓扑异构酶 I 抑制剂 DXd，药物抗体比(DAR)为 4 [38]。TROPION-Lung05 研究(NCT04484142)在 EGFR 突变 NSCLC 患者中显示客观缓解率(ORR)为 43.6%，提示其在 TKI 耐药后的潜在应用价值[39]。此外，另一款 TROP2 靶向 ADC-SKB264，在 EGFR-TKIs 耐药 NSCLC 患者中的 ORR 达 60%，中位无进展生存期(PFS)为 11.1 个月[40]，进一步验证了 TROP2 靶向治疗在此类患者中的临床潜力。这些研究结果表明，TROP2 靶向 ADC 可作为 EGFR-TKIs 耐药后的一种有效治疗选择，为 NSCLC 患者提供新的治疗策略，值得进一步探索和验证。

2.2.2. HER3 ADC

HER3 在约 83%的 NSCLC 患者中表达，并与耐药及不良预后相关。EGFR 突变患者在靶向治疗后 HER3 表达上调，可能通过 EGFR-HER3 异源二聚化促进 TKI 耐药[41]-[43]，使 HER3 靶向 ADC 成为潜在治疗选择。Patritumab deruxtecan (HER3-DXd)是首款 HER3 靶向 ADC，其I期研究(NCT03260491)在 EGFR-TKIs 及化疗耐药 NSCLC 患者中显示 ORR 41.0%，PFS 6.4 个月，OS 16.2 个月[44] [45]。II期研究(NCT04619004)结果相似，III期研究(NCT05338970)正在进行[46]。新型 HER3 ADC SHR-A2009 的I期研究显示，该药在 EGFR-TKIs 耐药患者中的 ORR 达 30.0%，DCR 76.7%，DOR 7.0 个月，安全性良好，III期研究已启动[47]。这些研究均初步显示了 HER3 ADC 良好的疗效及安全性，有望成为 EGFR-TKI 耐药 NSCLC 的新策略，但是临床研究开展少，样本量小，依据不足缺乏推广性，期待 HER3 靶向抗体偶联药

物的更多大样本研究。

2.2.3. HER3 与 EGFR ADC

BL-B01D1 是一种靶向 EGFR 和 HER3 的双特异性 ADC，通过可裂解接头连接新型拓扑异构酶 I 抑制剂。I期研究显示，在 139 例晚期或转移性实体瘤患者中，该药的 ORR 为 45.3%，其中 EGFR 突变患者(n = 40) ORR 达 67.5%，中位缓解持续时间(DOR) 8.5 个月，PFS 为 5.6 个月，展现出良好疗效[48]。目前，针对 EGFR-TKIs 耐药患者，BL-B01D1 与含铂化疗的III期临床研究正在进行，以进一步验证其疗效与安全性。该药物有望成为 EGFR-TKIs 耐药 NSCLC 的新型治疗选择。

2.2.4. 靶向 c-MET 的 ADC

Telisotuzumab vedotin (Teliso-V)是一种靶向 c-MET 的 ADC，已获 FDA 突破性疗法认定，用于铂类治疗失败且 c-MET 过表达的晚期 EGFR 野生型非鳞状 NSCLC 患者[49]。Ib 期研究显示，Teliso-V 联合厄洛替尼在 EGFR-TKIs 耐药且 c-MET 阳性 NSCLC 患者中的客观缓解率(ORR)为 32.1%，其中 c-MET 高表达患者的 ORR 达 52.6% [50]。另一项研究表明，Teliso-V 联合奥希替尼在 EGFR 突变且奥希替尼耐药且 c-MET 过表达患者中的 ORR 为 58% [51]。目前，III期研究(NCT06093503)正在评估 Teliso-V 联合奥希替尼相较于标准化疗在三代 EGFR-TKIs 耐药且 c-MET 过表达 NSCLC 中的疗效和安全性。该药物有望成为此类患者的重要治疗选择。

3. 小结

双特异性抗体、针对不同靶点的 ADC 药物以及相应的联合治疗方案为治疗 EGFR 突变耐药 NSCLC 的治疗策略提供了新的方向，但尚有诸多问题值得探索。首先，有些数据尚不成熟，还需要大样本前瞻性 III 期临床研究进行横向及纵向探索验证；其次，新靶向药物该如何寻找预测疗效的相关生物标志物，又该如何优化获益人群；再者，针对联合治疗方案来说，药物的最佳选择，剂量、时间、顺序以及毒性管理；最后，应积极探索联合治疗的相关协同机制及潜在耐药机制与对策。总之，抗血管生成药物、EGFR-TKIs、免疫检查点抑制剂、双特异性抗体、新型抗体偶联药物等治疗与化疗的联合应用，在 EGFR 突变耐药的晚期 NSCLC 的治疗中展现出广阔前景。未来研究将着重于利用多组学技术优化生物标志物体系，探索更高效的联合治疗模式，并建立个体化、动态调整的治疗策略。同时，结合人工智能预测模型提升治疗方案的敏感性与疗效，也将是领域内的重要发展趋势。

参考文献

[1] Peng, L., Deng, S., Li, J., Zhang, Y. and Zhang, L. (2025) Single-Cell RNA Sequencing in Unraveling Acquired Resistance to EGFR-TKIs in Non-Small Cell Lung Cancer: New Perspectives. *International Journal of Molecular Sciences*, **26**, Article 1483. https://doi.org/10.3390/ijms26041483

[2] Citri, A. and Yarden, Y. (2006) EGF-ERBB Signalling: Towards the Systems Level. *Nature Reviews Molecular Cell Biology*, **7**, 505-516. https://doi.org/10.1038/nrm1962

[3] Nguyen, K.H., Kobayashi, S. and Costa, D.B. (2009) Acquired Resistance to Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Non-Small-Cell Lung Cancers Dependent on the Epidermal Growth Factor Receptor Pathway. *Clinical Lung Cancer*, **10**, 281-289. https://doi.org/10.3816/clc.2009.n.039

[4] Katayama, Y., Yamada, T., Tokuda, S., Okura, N., Nishioka, N., Morimoto, K., *et al.* (2022) Heterogeneity among Tumors with Acquired Resistance to EGFR Tyrosine Kinase Inhibitors Harboring *EGFR*-T790M Mutation in Non-Small Cell Lung Cancer Cells. *Cancer Medicine*, **11**, 944-955. https://doi.org/10.1002/cam4.4504

[5] Wagener-Ryczek, S., Heydt, C., Süptitz, J., Michels, S., Falk, M., Alidousty, C., *et al.* (2020) Mutational Spectrum of Acquired Resistance to Reversible versus Irreversible EGFR Tyrosine Kinase Inhibitors. *BMC Cancer*, **20**, Article No. 408. https://doi.org/10.1186/s12885-020-06920-3

[6] Gazdar, A.F. (2009) Activating and Resistance Mutations of EGFR in Non-Small-Cell Lung Cancer: Role in Clinical

Response to EGFR Tyrosine Kinase Inhibitors. *Oncogene*, **28**, S24-S31. https://doi.org/10.1038/onc.2009.198

[7] Thress, K.S., Paweletz, C.P., Felip, E., Cho, B.C., Stetson, D., Dougherty, B., *et al.* (2015) Acquired EGFR C797S Mutation Mediates Resistance to AZD9291 in Non-Small Cell Lung Cancer Harboring EGFR T790m. *Nature Medicine*, **21**, 560-562. https://doi.org/10.1038/nm.3854

[8] Yang, Z., Yang, N., Ou, Q., Xiang, Y., Jiang, T., Wu, X., *et al.* (2018) Investigating Novel Resistance Mechanisms to Third-Generation EGFR Tyrosine Kinase Inhibitor Osimertinib in Non-Small Cell Lung Cancer Patients. *Clinical Cancer Research*, **24**, 3097-3107. https://doi.org/10.1158/1078-0432.ccr-17-2310

[9] Niederst, M.J. and Engelman, J.A. (2013) Bypass Mechanisms of Resistance to Receptor Tyrosine Kinase Inhibition in Lung Cancer. *Science Signaling*, **6**, re6. https://doi.org/10.1126/scisignal.2004652

[10] Wu, Y., Zhang, L., Kim, D., Liu, X., Lee, D.H., Yang, J.C., *et al.* (2018) Phase Ib/II Study of Capmatinib (INC280) Plus Gefitinib after Failure of Epidermal Growth Factor Receptor (EGFR) Inhibitor Therapy in Patients with *EGFR*-Mutated, MET Factor-Dysregulated Non-Small-Cell Lung Cancer. *Journal of Clinical Oncology*, **36**, 3101-3109. https://doi.org/10.1200/jco.2018.77.7326

[11] Ou, S.I., Kwak, E.L., Siwak-Tapp, C., Dy, J., Bergethon, K., Clark, J.W., *et al.* (2011) Activity of Crizotinib (PF02341066), a Dual Mesenchymal-Epithelial Transition (MET) and Anaplastic Lymphoma Kinase (ALK) Inhibitor, in a Non-Small Cell Lung Cancer Patient with De Novo MET Amplification. *Journal of Thoracic Oncology*, **6**, 942-946. https://doi.org/10.1097/jto.0b013e31821528d3

[12] Chmielecki, J., Mok, T., Wu, Y., Han, J., Ahn, M., Ramalingam, S.S., *et al.* (2023) Analysis of Acquired Resistance Mechanisms to Osimertinib in Patients with EGFR-Mutated Advanced Non-Small Cell Lung Cancer from the AURA3 Trial. *Nature Communications*, **14**, Article No. 1071. https://doi.org/10.1038/s41467-023-35962-x

[13] Le, X., Puri, S., Negrao, M.V., Nilsson, M.B., Robichaux, J., Boyle, T., *et al.* (2018) Landscape of EGFR-Dependent and -Independent Resistance Mechanisms to Osimertinib and Continuation Therapy Beyond Progression in *EGFR*-Mutant NSCLC. *Clinical Cancer Research*, **24**, 6195-6203. https://doi.org/10.1158/1078-0432.ccr-18-1542

[14] Kim, T.M., Song, A., Kim, D., Kim, S., Ahn, Y., Keam, B., *et al.* (2015) Mechanisms of Acquired Resistance to AZD9291: A Mutation-Selective, Irreversible EGFR Inhibitor. *Journal of Thoracic Oncology*, **10**, 1736-1744. https://doi.org/10.1097/jto.0000000000000688

[15] Ou, S.I., Horn, L., Cruz, M., Vafai, D., Lovly, C.M., Spradlin, A., *et al.* (2017) Emergence of FGFR3-TACC3 Fusions as a Potential By-Pass Resistance Mechanism to EGFR Tyrosine Kinase Inhibitors in EGFR Mutated NSCLC Patients. *Lung Cancer*, **111**, 61-64. https://doi.org/10.1016/j.lungcan.2017.07.006

[16] Hayakawa, D., Takahashi, F., Mitsuishi, Y., Tajima, K., Hidayat, M., Winardi, W., *et al.* (2019) Activation of Insulin-like Growth Factor-1 Receptor Confers Acquired Resistance to Osimertinib in Non-Small Cell Lung Cancer with *EGFR* T790M Mutation. *Thoracic Cancer*, **11**, 140-149. https://doi.org/10.1111/1759-7714.13255

[17] Manabe, T., Yasuda, H., Terai, H., Kagiwada, H., Hamamoto, J., Ebisudani, T., *et al.* (2020) IGF2 Autocrine-Mediated IGF1R Activation Is a Clinically Relevant Mechanism of Osimertinib Resistance in Lung Cancer. *Molecular Cancer Research*, **18**, 549-559. https://doi.org/10.1158/1541-7786.mcr-19-0956

[18] Yuan, S., Dong, Y., Peng, L., Yang, M., Niu, L., Liu, Z., *et al.* (2019) Tumor-associated Macrophages Affect the Biological Behavior of Lung Adenocarcinoma A549 Cells through the PI3K/AKT Signaling Pathway. *Oncology Letters*, **18**, 1840-1846. https://doi.org/10.3892/ol.2019.10483

[19] Wang, S., Wang, J., Chen, Z., *et al.* (2024) Targeting M2-Like Tumor-Associated Macrophages Is a Potential Therapeutic Approach to Overcome Antitumor Drug Resistance. *npj Precision Oncology*, **8**, Article No. 31.

[20] Wang, W., Li, Q., Yamada, T., Matsumoto, K., Matsumoto, I., Oda, M., *et al.* (2009) Crosstalk to Stromal Fibroblasts Induces Resistance of Lung Cancer to Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors. *Clinical Cancer Research*, **15**, 6630-6638. https://doi.org/10.1158/1078-0432.ccr-09-1001

[21] Mink, S.R., Vashistha, S., Zhang, W., Hodge, A., Agus, D.B. and Jain, A. (2010) Cancer-associated Fibroblasts Derived from EGFR-TKI-Resistant Tumors Reverse EGFR Pathway Inhibition by EGFR-TKIs. *Molecular Cancer Research*, **8**, 809-820. https://doi.org/10.1158/1541-7786.mcr-09-0460

[22] Lin, Z., Wang, Q., Jiang, T., Wang, W. and Zhao, J.J. (2023) Targeting Tumor-Associated Macrophages with STING Agonism Improves the Antitumor Efficacy of Osimertinib in a Mouse Model of EGFR-Mutant Lung Cancer. *Frontiers in Immunology*, **14**, Article 1077203. https://doi.org/10.3389/fimmu.2023.1077203

[23] Wang, S., Su, D., Chen, H., Lai, J., Tang, C., Li, Y., *et al.* (2024) PD-L2 Drives Resistance to EGFR-TKIs: Dynamic Changes of the Tumor Immune Environment and Targeted Therapy. *Cell Death & Differentiation*, **31**, 1140-1156. https://doi.org/10.1038/s41418-024-01317-2

[24] Sequist, L.V., Waltman, B.A., Dias-Santagata, D., Digumarthy, S., Turke, A.B., Fidias, P., *et al.* (2011) Genotypic and Histological Evolution of Lung Cancers Acquiring Resistance to EGFR Inhibitors. *Science Translational Medicine*, **3**, 75ra-26. https://doi.org/10.1126/scitranslmed.3002003

[25] Marcoux, N., Gettinger, S.N., O'Kane, G., *et al.* (2019) EGFR-Mutant Adenocarcinomas That Transform to Small-Cell Lung Cancer and Other Neuroendocrine Carcinomas: Clinical Outcomes. *Clinical Oncology*, **37**, 278-285.

[26] Ham, J.S., Kim, S., Kim, H.K., Byeon, S., Sun, J., Lee, S., *et al.* (2016) Two Cases of Small Cell Lung Cancer Transformation from EGFR Mutant Adenocarcinoma during AZD9291 Treatment. *Journal of Thoracic Oncology*, **11**, e1-e4. https://doi.org/10.1016/j.jtho.2015.09.013

[27] Lee, J., Lee, J., Kim, S., Kim, S., Youk, J., Park, S., *et al.* (2017) Clonal History and Genetic Predictors of Transformation into Small-Cell Carcinomas from Lung Adenocarcinomas. *Journal of Clinical Oncology*, **35**, 3065-3074. https://doi.org/10.1200/jco.2016.71.9096

[28] Cho, B.C., Kim, D., Spira, A.I., Gomez, J.E., Haura, E.B., Kim, S., *et al.* (2023) Amivantamab Plus Lazertinib in Osimertinib-Relapsed EGFR-Mutant Advanced Non-Small Cell Lung Cancer: A Phase 1 Trial. *Nature Medicine*, **29**, 2577-2585. https://doi.org/10.1038/s41591-023-02554-7

[29] Shu, C.A., Goto, K., Ohe, Y., Besse, B., Park, K., Wang, Y., *et al.* (2021) 1193MO Amivantamab Plus Lazertinib in Post-Osimertinib, Post-Platinum Chemotherapy EGFR-Mutant Non-Small Cell Lung Cancer (NSCLC): Preliminary Results from Chrysalis-2. *Annals of Oncology*, **32**, S952-S953. https://doi.org/10.1016/j.annonc.2021.08.1798

[30] Passaro, A., Wang, J., Wang, Y., Lee, S., Melosky, B., Shih, J.-., *et al.* (2024) Amivantamab Plus Chemotherapy with and without Lazertinib in EGFR-Mutant Advanced NSCLC after Disease Progression on Osimertinib: Primary Results from the Phase III MARIPOSA-2 Study. *Annals of Oncology*, **35**, 77-90. https://doi.org/10.1016/j.annonc.2023.10.117

[31] Frentzas, S., Austria Mislang, A.R., Lemech, C., Nagrial, A., Underhill, C., Wang, W., *et al.* (2024) Phase 1a Dose Escalation Study of Ivonescimab (AK112/SMT112), an Anti-PD-1/VEGF-A Bispecific Antibody, in Patients with Advanced Solid Tumors. *Journal for ImmunoTherapy of Cancer*, **12**, e008037. https://doi.org/10.1136/jitc-2023-008037

[32] Fang, W., Zhao, Y., Luo, Y., Yang, R., Huang, Y., He, Z., *et al.* (2024) Ivonescimab Plus Chemotherapy in Non-Small Cell Lung Cancer with *EGFR* Variant: A Randomized Clinical Trial. *JAMA*, **332**, 561-570. https://doi.org/10.1001/jama.2024.10613

[33] Flynn, P., Suryaprakash, S., Grossman, D., Panier, V. and Wu, J. (2024) The Antibody-Drug Conjugate Landscape. *Nature Reviews Drug Discovery*, **23**, 577-578. https://doi.org/10.1038/d41573-024-00064-w

[34] Goldenberg, D.M., Stein, R. and Sharkey, R.M. (2018) The Emergence of Trophoblast Cell-Surface Antigen 2 (TROP-2) as a Novel Cancer Target. *Oncotarget*, **9**, 28989-29006. https://doi.org/10.18632/oncotarget.25615

[35] Li, Z., Jiang, X. and Zhang, W. (2016) TROP2 Overexpression Promotes Proliferation and Invasion of Lung Adenocarcinoma Cells. *Biochemical and Biophysical Research Communications*, **470**, 197-204. https://doi.org/10.1016/j.bbrc.2016.01.032

[36] Liao, S., Wang, B., Zeng, R., Bao, H., Chen, X., Dixit, R., *et al.* (2021) Recent Advances in Trophoblast Cell-Surface Antigen 2 Targeted Therapy for Solid Tumors. *Drug Development Research*, **82**, 1096-1110. https://doi.org/10.1002/ddr.21870

[37] Inamura, K., Yokouchi, Y., Kobayashi, M., Ninomiya, H., Sakakibara, R., Subat, S., *et al.* (2017) Association of Tumor TROP2 Expression with Prognosis Varies among Lung Cancer Subtypes. *Oncotarget*, **8**, 28725-28735. https://doi.org/10.18632/oncotarget.15647

[38] Okajima, D., Yasuda, S., Maejima, T., Karibe, T., Sakurai, K., Aida, T., *et al.* (2021) Datopotamab Deruxtecan, a Novel Trop2-Directed Antibody-Drug Conjugate, Demonstrates Potent Antitumor Activity by Efficient Drug Delivery to Tumor Cells. *Molecular Cancer Therapeutics*, **20**, 2329-2340. https://doi.org/10.1158/1535-7163.mct-21-0206

[39] Paz-Ares, L., Ahn, M., Lisberg, A.E., Kitazono, S., Cho, B.C., Blumenschein, G., *et al.* (2023) 1314MO TROPION-Lung05: Datopotamab Deruxtecan (Dato-DXd) in Previously Treated Non-Small Cell Lung Cancer (NSCLC) with Actionable Genomic Alterations (AGAs). *Annals of Oncology*, **34**, S755-S756. https://doi.org/10.1016/j.annonc.2023.09.2348

[40] Fang, W., Cheng, Y., Chen, Z., Wang, W., Yin, Y., Li, Y., *et al.* (2023) SKB264 (TROP2-ADC) for the Treatment of Patients with Advanced NSCLC: Efficacy and Safety Data from a Phase 2 Study. *Journal of Clinical Oncology*, **41**, 9114-9114. https://doi.org/10.1200/jco.2023.41.16_suppl.9114

[41] Yonesaka, K., Tanizaki, J., Maenishi, O., Haratani, K., Kawakami, H., Tanaka, K., *et al.* (2021) HER3 Augmentation via Blockade of EGFR/AKT Signaling Enhances Anticancer Activity of Her3-Targeting Patritumab Deruxtecan in EGFR-Mutated Non-Small Cell Lung Cancer. *Clinical Cancer Research*, **28**, 390-403. https://doi.org/10.1158/1078-0432.ccr-21-3359

[42] Scharpenseel, H., Hanssen, A., Loges, S., Mohme, M., Bernreuther, C., Peine, S., *et al.* (2019) EGFR and HER3 Expression in Circulating Tumor Cells and Tumor Tissue from Non-Small Cell Lung Cancer Patients. *Scientific Reports*, **9**, Article No. 7406. https://doi.org/10.1038/s41598-019-43678-6

[43] Chen, Q., Jia, G., Zhang, X. and Ma, W. (2024) Targeting HER3 to Overcome EGFR TKI Resistance in NSCLC. *Frontiers in Immunology*, **14**, Article 1332057. https://doi.org/10.3389/fimmu.2023.1332057

[44] Jänne, P.A., Baik, C., Su, W., Johnson, M.L., Hayashi, H., Nishio, M., *et al.* (2021) Efficacy and Safety of Patritumab Deruxtecan (HER3-DXd) in EGFR Inhibitor-Resistant, *EGFR*-Mutated Non-Small Cell Lung Cancer. *Cancer Discovery*, **12**, 74-89. https://doi.org/10.1158/2159-8290.cd-21-0715

[45] Yu, H.A., Baik, C., Kim, D.-., Johnson, M.L., Hayashi, H., Nishio, M., *et al.* (2024) Translational Insights and Overall Survival in the U31402-A-U102 Study of Patritumab Deruxtecan (HER3-DXd) in EGFR-Mutated NSCLC. *Annals of Oncology*, **35**, 437-447. https://doi.org/10.1016/j.annonc.2024.02.003

[46] Yu, H.A., Goto, Y., Hayashi, H., Felip, E., Chih-Hsin Yang, J., Reck, M., *et al.* (2023) HERTHENA-Lung01, a Phase II Trial of Patritumab Deruxtecan (HER3-DXd) in Epidermal Growth Factor Receptor-Mutated Non-Small-Cell Lung Cancer after Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy and Platinum-Based Chemotherapy. *Journal of Clinical Oncology*, **41**, 5363-5375. https://doi.org/10.1200/jco.23.01476

[47] Zhou, Q., Wu, Y., Li, J., Liu, A., Cui, J., Kuboki, Y., *et al.* (2023) 658MO Phase I Study of SHR-A2009, a HER3-Targeted ADC, in Advanced Solid Tumors. *Annals of Oncology*, **34**, S463. https://doi.org/10.1016/j.annonc.2023.09.1844

[48] Ma, Y., Huang, Y., Zhao, Y., Zhao, S., Xue, J., Yang, Y., *et al.* (2024) BL-B01D1, a First-In-Class EGFR-HER3 Bispecific Antibody-Drug Conjugate, in Patients with Locally Advanced or Metastatic Solid Tumours: A First-In-Human, Open-Label, Multicentre, Phase 1 Study. *The Lancet Oncology*, **25**, 901-911. https://doi.org/10.1016/s1470-2045(24)00159-1

[49] Strickler, J.H., LoRusso, P., Salgia, R., Kang, Y., Yen, C.J., Lin, C., *et al.* (2020) Phase I Dose-Escalation and -Expansion Study of Telisotuzumab (ABT-700), an Anti-c-Met Antibody, in Patients with Advanced Solid Tumors. *Molecular Cancer Therapeutics*, **19**, 1210-1217. https://doi.org/10.1158/1535-7163.mct-19-0529

[50] Camidge, D.R., Barlesi, F., Goldman, J.W., Morgensztern, D., Heist, R., Vokes, E., *et al.* (2023) Phase Ib Study of Telisotuzumab Vedotin in Combination with Erlotinib in Patients with C-Met Protein-Expressing Non-Small-Cell Lung Cancer. *Journal of Clinical Oncology*, **41**, 1105-1115. https://doi.org/10.1200/jco.22.00739

[51] Goldman, J.W., Horinouchi, H., Cho, B.C., Tomasini, P., Dunbar, M., Hoffman, D., *et al.* (2022) Phase 1/1b Study of Telisotuzumab Vedotin (Teliso-V) + Osimertinib (Osi), after Failure on Prior Osi, in Patients with Advanced, C-Met Over-expressing, *EGFR*-Mutated Non-Small Cell Lung Cancer (NSCLC). *Journal of Clinical Oncology*, **40**, 9013. https://doi.org/10.1200/jco.2022.40.16_suppl.9013