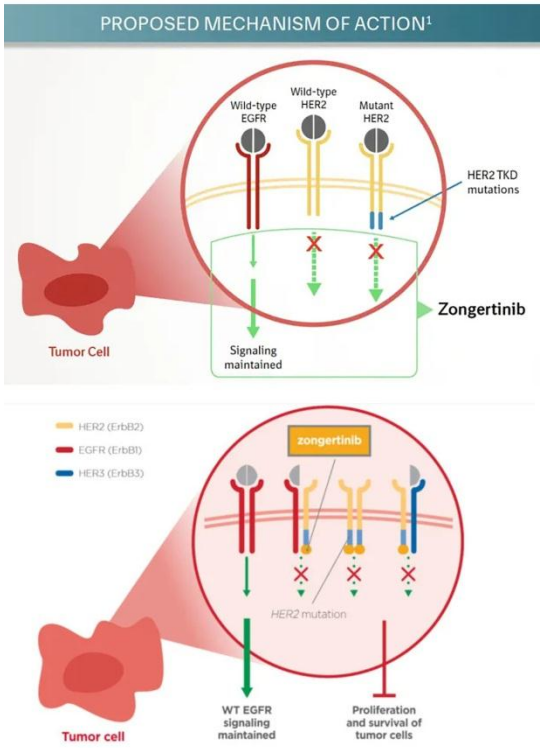
MD Anderson 2025 新进展: 有效治疗携带 *HER2* 基因突变的非小细胞肺癌

世界著名的美国 MD 安德森癌症中心在 2025 年的癌症研究中取得了多项突破性进展，尤其在肿瘤个体化精准治疗和靶向治疗领域展现了显著的创新能力。现将其中有效治疗携带 *HER2* 突变基因的非小细胞肺癌 (*HER2* mutant-NSCLC) 的最新成果及展望在此做一简单介绍。

与乳腺癌、胃癌、肠癌中常见的 HER2 蛋白过表达不同，非小细胞肺癌中编码 HER2 受体上的酪氨酸激酶结构域 (tyrosine kinase domain, TKD) 的 *HER2* 基因发生激活性突变 (第 20 外显子插入，*HER2* exon20) 才是驱动 NSCLC 细胞不可控生长的关键因素，因而造成以往静脉注射抗 HER2 蛋白抗体药物 (包括 ADC) 治疗 NSCLC 的疗效不佳。为此，德国勃林格殷格翰药企 (Boehringer Ingelheim) 成功开发出针对 *HER2* exon20 突变的第三代全新小分子靶向药物佐瑞替尼 (zongertinib, HERNEXEOS)，该口服小分子药物可与所有 HER2 受体中的野生型或突变型 TKD 蛋白相结合，不可逆地阻断其酪氨酸激酶活性，从而抑制 NSCLC 细胞生长。不同于可同时作用于 EGFR 和 HER2 的酪氨酸激酶抑制剂 (tyrosine kinase inhibitor, TKI)，佐瑞替尼作为具有识别功能的 TKI，选择性地只与 HER2 (包括 HER2-HER2、HER2-HER3、EGFR-HER2 二聚体) 中的 TKD 相结合并抑制其酪氨酸激酶活性，而不与野生型 EGFR 发生结合，从而减少了脱靶效应，并可避免因抑制 EGFR 导致的一系列毒副作用。



NSCLC 患者发生脑转移的比例很高，而许多靶向药因血脑屏障的阻碍难以入脑，导致脑部转移灶成为治疗难点。佐瑞替尼在设计之初特别考虑到了如何有效穿透血脑屏障，从而使得该药具有强大的脑渗透性，可在脑脊液中保持足够的药物浓度，为 NSCLC 脑转移患者带来了新的希望。

由 MD 安德森癌症中心 Dr. John Heymach 牵头，携欧美、澳大利亚及我国吴一龙教授团队参与的 Beamion LUNG-1 多中心临床试验显示，*HER2* exon20-NSCLC 患者使用佐瑞替尼后，客观缓解率 ORR 为 71.1%，中位缓解持续时间 DOR 为 14.1 个月，中位疾病无进展生存期 PFS 为 12.4 个月。28 例脑转移患者中，64% 达到确认的系统性客观缓解。该研究成果已在《新英格兰医学杂志》上得到发表 (Heymach et al. 2025 ***NEJM*** 392:2321)。该药并于 2025 年 8 月获得了美国 FDA 加速批准 (accelerated approval)，用于治疗远端转移且不可手术的 NSCLC。

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ORIGINAL ARTICLE

Zongertinib in Previously Treated *HER2*-Mutant Non–Small-Cell Lung Cancer

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ABSTRACT

BACKGROUND

Innovative oral targeted therapies are warranted for patients with human epidermal growth factor receptor 2 (*HER2*)–mutant non–small-cell lung cancer (NSCLC). Zongertinib is an oral, irreversible, HER2-selective tyrosine kinase inhibitor that has been shown to have efficacy in persons with advanced or metastatic solid tumors with HER2 alterations in a phase 1 study.

METHODS

We evaluated zongertinib in a multicohort, phase 1a–1b trial involving patients with advanced or metastatic *HER2*-mutant NSCLC. Here we report the primary analysis of zongertinib in previously treated patients: those with tumors harboring a mutation in the tyrosine kinase domain (cohort 1), those with tumors harboring a mutation in the tyrosine kinase domain previously treated with a HER2-directed antibody–drug conjugate (cohort 5), and those with tumors harboring a non–tyrosine kinase domain mutation (cohort 3). In cohort 1, patients were initially randomly assigned to receive zongertinib at a dose of 120 mg or 240 mg once daily. Patients in cohorts 5 and 3 initially received 240 mg daily. After an interim analysis of data from cohort 1, subsequently recruited patients across all cohorts received zongertinib at a dose of 120 mg. The primary end point was an objective response assessed by blinded independent central review (cohorts 1 and 5) or by investigator review (cohort 3). Secondary end points included the duration of response and progression-free survival.

RESULTS

In cohort 1, a total of 75 patients received zongertinib at a dose of 120 mg. At the data cutoff (November 29, 2024), 71% of these patients (95% confidence interval [CI], 60 to 80; P<0.001 against a ≤30% benchmark) had a confirmed objective response; the median duration of response was 14.1 months (95% CI, 6.9 to not evaluable), and the median progression-free survival was 12.4 months (95% CI, 8.2 to not evaluable). Grade 3 or higher drug-related adverse events occurred in 13 patients (17%). In cohort 5 (31 patients), 48% of the patients (95% CI, 32 to 65) had a confirmed objective response. Grade 3 or higher drug-related adverse events occurred in 1 patient (3%). In cohort 3 (20 patients), 30% of the patients (95% CI, 15 to 52) had a confirmed objective response. Grade 3 or higher drug-related adverse events occurred in 5 patients (25%). Across all three cohorts, no cases of drug-related interstitial lung disease occurred.

CONCLUSIONS

Zongertinib showed clinical benefit with mainly low-grade adverse events in patients with previously treated *HER2*-mutant NSCLC. (Funded by Boehringer Ingelheim; Beamion LUNG-1 ClinicalTrials.gov number, NCT04886804.)

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*The Beamion LUNG-1 investigators are listed in the Supplementary Appendix, available at NEJM.org.

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展望

针对新鲜肺癌组织标本的检测显示，1-2%的 NSCLC 患者具有 *HER2* exon20 基因突变。由于新鲜肿瘤组织标本一般只能采样一次，而肿瘤细胞的各种生物学性状 (包括各种基因突变) 始终处于动态变化中，因此新鲜组织标本检测极大地限制了监测患者后期可能动态出现的 *HER2* exon20 突变。肿瘤液体活检可对患者体内伴随肿瘤进展产生的各种肿瘤细胞进行全程无创性动态监测。北京大学肿瘤中心沈琳主任团队针对 115 例胃癌患者开展的为期 2 年、涵盖 600 例样本的临床实验发现，在 88%肿瘤组织活检呈现 HER2 蛋白表达阴性的患者中，应用赛特 SE-i•FISH 技术可在其中 76%的患者外周血中动态监测出 $HER2^+$ CTC (Li et al. 2018 ***Clin Cancer Res*** 24:5261)，证实肿瘤液体活检可有效弥补肿瘤组织活检不适于持续动态监测的不足。将肿瘤液体活检 SE-i•FISH 技术与精准靶向单细胞 DNA 测序 (precision/targeted scDNAseq) 相结合 (Wang et al. 2024 ***J Natl Cancer Ctr*** 4:335)，动态监测外周血或脑脊液 (Li et al. 2022 ***Cancer Sci*** 113:3535) CTC、CTEC 中的 *HER2* exon20 基因突变，对于临床指导用药、实时评估疗效、观察不同的预后等，将具有十分重要的临床意义，可能会使更多患者获益于该类治疗。