

免疫检查点抑制剂联合抗血管生成药物治疗晚期非小细胞肺癌的研究进展

曾爱菊^{1,2}, 马代远^{1,2}

Research Progress of Immune Checkpoint Inhibitors Combined with Anti-Angiogenic Drugs in Treatment of Advanced Non-Small Cell Lung Cancer

ZENG Aiju^{1,2}, MA Daiyuan^{1,2}

1. Department of Oncology, Affiliated Hospital of North Sichuan Medical College, Nanchong 637000, China; 2. School of Clinical Medicine, North Sichuan Medical University, Nanchong 637000, China

Corresponding Author: MA Daiyuan, E-mail: mdylx@163.com

Abstract: The use of immune checkpoint inhibitors (ICIs) improves the prognosis of patients with advanced non-small cell lung cancer (NSCLC). However, some patients still fail to benefit from them. In recent years, studies have demonstrated that the combination of antiangiogenic agents with ICIs can enhance the antitumor effect, and guidelines at home and abroad have suggested that the combination of ICIs with antiangiogenic regimens can be used in patients with advanced NSCLC. Therefore, the mechanism of action and the latest clinical studies on the combination of ICIs and anti-angiogenic drugs in the treatment of advanced NSCLC were reviewed in this article to provide reference for treating advanced NSCLC.

Key words: Non-small cell lung cancer; Immune checkpoint inhibitors; Anti-angiogenic drugs

Competing interests: The authors declare that they have no competing interests.

摘 要: 免疫检查点抑制剂 (ICIs) 的应用改善了晚期非小细胞肺癌 (NSCLC) 患者的预后。然而, 仍有部分患者未能从中获益。近年来, 研究证明抗血管生成药与ICIs联合可增强抗肿瘤效应, 国内外指南中也建议晚期NSCLC患者可采用ICIs联合抗血管治疗方案。因此, 本文就ICIs与抗血管生成药物联合治疗晚期NSCLC的作用机制和最新临床研究进行综述, 以期对晚期NSCLC的治疗提供参考。

关键词: 非小细胞肺癌; 免疫检查点抑制剂; 抗血管生成药物

中图分类号: R734.2

开放科学(资源服务)标识码(OSID):



0 引言

肺癌是临床常见的恶性肿瘤之一, 且发病率和死亡率呈上升趋势, 是全球恶性肿瘤相关性死亡的主要原因^[1]。非小细胞肺癌 (Non-small lung cancer, NSCLC) 占肺癌总数的80%~85%^[2]。由于早期肺癌症状通常较为隐匿, 因此, 约55%的NSCLC患者在初诊时已处于晚期^[3]。针对晚期NSCLC患者, 传统治疗以系统性化疗为主, 然而5年生存率很低。近年来, 靶向药物和免疫检查点抑制剂 (Immune checkpoint inhibitors, ICIs) 的应用延长了患者的生存时间, 但Ⅳ期NSCLC患者的5年生存率仅4.7%^[3],

且临床耐药在治疗过程中也是不可避免的问题^[4-5]。急需更加有效的治疗策略来延长患者的生存时间。已有研究表明抗血管生成药物与ICIs联合可增强抗肿瘤效应^[6-7]。因此, 本文旨在总结晚期NSCLC的ICIs联合抗血管生成药物治疗的作用机制和最新临床研究进展, 以期对临床治疗提供参考。

1 ICIs与抗血管生成药物联合治疗的作用机制

异常的脉管系统是肿瘤的标志特征, 其与肿瘤免疫逃逸相关。这些异常与促血管生成因子, 主要是血管内皮生长因子 (VEGF) 表达的增加相关, 同时促血管生成因子参与免疫细胞的功能调节^[8]。研究发现肿瘤组织在缺氧过程中会上调VEGF, 通过激活内皮细胞表达的VEGF受体-2 (VEGFR-2) 来协调血管形成^[9]。而VEGF会抑制胸腺造血干细胞向CD4⁺和CD8⁺ T细胞的分化, 并且通过下调血管内皮细胞黏附分子及血管细胞黏附分子的表达来

收稿日期: 2024-12-18; 修回日期: 2025-03-10

作者单位: 1. 637000 南充, 川北医学院附属医院肿瘤科; 2. 637000 南充, 川北医学院临床医学院

通信作者: 马代远, 男, 博士, 教授, 主任医师, 主要从事肿瘤的综合治疗, E-mail: mdylx@163.com, ORCID: 0000-0002-0757-9487

作者简介: 曾爱菊, 女, 硕士在读, 住院医师, 主要从事胸部肿瘤的综合治疗, ORCID: 0009-0008-4403-5252

阻止免疫细胞浸润；同时又可直接调节抑制性免疫细胞包括调节性T细胞（Treg）、髓源性抑制细胞（MDSC）的分化和增殖，抑制树突状细胞（DC）成熟和抗原提呈，阻碍T细胞活化^[8,10-11]。此外，VEGF能促使肿瘤相关巨噬细胞（TAM）从促炎M1样类型转化为促肿瘤M2样类型^[12]，将免疫支持性肿瘤微环境重新编程为免疫抑制性微环境，从而实现肿瘤生长与转移。临床前研究和临床证据表明，抗血管生成治疗可暂时性地使肿瘤脉管系统恢复正常^[13-14]。通过增加周细胞覆盖率、改善肿瘤灌注和降低血管通透性，产生结构和功能与正常组织血管相似的肿瘤血管，从而改善肿瘤乏氧^[15-16]。血管正常化又可以减少VEGF分泌，促进CD4+ T细胞和CD8+ T细胞浸润^[17]，减少Treg和MDSC的募集^[18]，增加免疫应答能力。Zhao等的研究表明，低剂量阿帕替尼用于肺癌小鼠模型上可以减轻缺氧，增加CD8+ T细胞的浸润，且联合抗程序性死亡配体1（PD-L1）时可明显延缓肿瘤的生长，减少转移的数量^[19]。另外，血管正常化能改善缺氧导致的乳酸增多所形成的酸性环境及免疫抑制状态^[20]，减少缺氧刺激产生的粒细胞-巨噬细胞（GM-CSF）、IL-10等免疫抑制细胞因子，恢复T细胞的功能^[21]。

ICIs主要通过恢复T细胞的功能，使免疫细胞可以有效地辨认和攻击肿瘤细胞来发挥作用^[22]。既往有研究表明，阻断程序性死亡受体1（PD-1）或

细胞毒性T淋巴相关蛋白4（CTLA-4）能降低肿瘤血管密度、增加周细胞覆盖率、增强血管灌注并减少组织缺氧，同时也能观察到IFN- γ 降低了内皮VEGF-A的表达，说明ICIs治疗本身可以诱导肿瘤血管正常化^[16,23]。

综上所述，抗血管生成药和ICIs的联合使用具有协同抗肿瘤效应。肿瘤血管的正常化可以促进效应T细胞的聚集、增强免疫治疗疗效，而免疫细胞的激活又能反过来促进肿瘤血管的正常化，理论上形成正反馈。

2 ICIs联合抗血管生成药物治疗NSCLC的临床研究

近年来，免疫检查点抑制剂联合抗血管生成药治疗晚期肺癌的临床试验取得了一定成果。这些评估联合治疗疗效及安全性的试验为临床实际应用提供可靠数据。目前公布的数据显示，不论一线或是后线治疗，晚期NSCLC均能从中获益。一些重要的临床试验结果见表1。

2.1 驱动基因阴性患者的ICIs联合抗血管生成药物治疗

2.1.1 大分子单抗类药物联合ICIs IMpower150研究^[29]是首个评估阿替利珠单抗联合贝伐珠单抗联合化疗（ABCP）对比贝伐珠单抗联合化疗（BCP）一线治疗非鳞NSCLC疗效的Ⅲ期临床试验。结果

表 1 ICIs联合抗血管生成药治疗晚期NSCLC的临床研究
Table 1 Clinical study of ICIs combined with anti-angiogenic drugs for advanced NSCLC

Study	Patient	Research program	Sample size	Primary endpoint	Result
IMpower150 (Phase 3) ^[24]	Stage IV non-squamous NSCLC	ABCP: Atezolizumab + bevacizumab + platinum-based doublet chemotherapy ACP: Atezolizumab + platinum-based doublet chemotherapy BCP: Bevacizumab + platinum-based doublet chemotherapy	1 202	PFS OS	ABCP vs. BCP mPFS: 8.3 vs. 6.8 m (ITT-WT) mPFS: 11.3 vs. 6.8 m (Teff-High WT) mOS: 19.2 vs. 14.7 m (Teff-High WT)
ENPOWER (Phase 2) ^[25]	Stage IV EGFR/ALK-negative non-squamous NSCLC	Queue 1: rh-Endostatin + PD-1 + platinum-based doublet chemotherapy Queue 2: rh-Endostatin + platinum-based doublet chemotherapy	50	ORR PFS	Queue 1 vs. Queue 2 ORR: 57.7% vs. 34.2% mPFS: 16.7 vs. 16.4 m
LEAP007 (Phase 3) ^[26]	Stage IV EGFR/ALK-negative NSCLC	Trial group: Lenvatinib + Pembrolizumab Control group: Placebo + pembrolizumab	623	PFS OS	Trial vs. Control group mPFS: 6.6 vs. 4.2 m mOS: 16.4 vs. 14.1 m (P=0.797 44)
IMpower151 (Phase 3) ^[27]	Stage IV non-squamous NSCLC	ABCP: Atezolizumab + bevacizumab + platinum-based doublet chemotherapy BCP: Placebo + bevacizumab + platinum-based doublet chemotherapy	305	PFS	ABCP vs. BCP mPFS: 9.5 vs. 7.1 m (P=0.183 8)
ORIENT-31 (Phase 3) ^[28]	Stage III/IV EGFR mutant non-squamous NSCLC	Sintilimab + bevacizumab bio-drugs + chemotherapy bevacizumab bio-drugs+ chemotherapy	1 011	PFS	Four medicines vs. Chemotherapy group mPFS: 7.2 vs. 4.3 m mOS: 21.1 vs. 19.2 m

显示在野生型患者中, ABCP组中位无进展生存期(mPFS)和中位总生存期(mOS)均显著延长(mPFS: 8.3个月 vs. 6.8个月, $P<0.001$) (mOS: 19.2个月 vs. 14.7个月, $P=0.02$); 且两组治疗相关不良事件(Treatment-related adverse reaction, TRAE)发生率大致相等。Lee等^[30]研究阿替利珠单抗联合贝伐珠单抗对免疫单药治疗后疾病进展的NSCLC患者(无EGFR/ALK突变)的疗效, 结果表明mPFS为5.6个月, mOS为14个月。以上两个研究均显示联合治疗方案对晚期驱动基因阴性NSCLC具有良好的疗效。@Be研究^[31]进一步发现PD-L1 TPS $\geq$ 50%的患者更能从中获益。而TELMA研究^[32]中高肿瘤突变负荷(TMB)的NSCLC患者(TBM $\geq$ 10 mut/Mb或 $\geq$ 16 mut/mB) mPFS达13个月。然而, 目前关于联合方案治疗NSCLC患者预测疗效的研究较少, 值得进一步的研究, 以便更好地筛选出能从联合治疗中获益的人群。

2.1.2 小分子多靶点酪氨酸酶抑制剂联合ICIs 在Chu等^[33]研究中, 安罗替尼联合信迪利单抗一线治疗驱动基因阴性晚期NSCLC患者mPFS高达15个月, 3级以上TRAE发生率为54.5%。而TISAL-FE-01研究^[34]则是让患者先接受2周期化疗, 随后接受替雷利珠单抗联合安罗替尼维持治疗。纳入的20例患者客观缓解率(ORR)和疾病控制率(DCR)分别为75%和100%, 与Chu等报道结果基本一致(分别为72.5%和100%), 1年PFS率(36.1%)在数值上低于Chu等研究报道的数据(71.4%), 可能与TISAL-FE-01研究纳入更多IV期患者有关(90% vs. 59.1%)。值得注意的是, 该研究未纳入鳞状NSCLC, 而Chu等研究中鳞状NSCLC占比54.9%。安全性方面, 未发现 $\geq$ 3级TRAE。另外, 一项回顾性比较队列研究显示当安罗替尼联合ICIs作为二线甚至后线治疗时, 驱动基因阴性患者PFS、OS更能获益^[35]。

有关仑法替尼联合ICIs的III期临床研究(包括LEAP-006研究^[36]、LEAP-007研究^[26]、LEAP-008研究^[37])均已揭露研究结果。LEAP-007研究评估一线仑法替尼或安慰剂联合帕博利珠单抗治疗转移性驱动基因阴性NSCLC的疗效, 主要研究终点为PFS和OS, 联合治疗组PFS从单免疫4.2个月提高到6.9个月, 然而联合治疗组OS为14.1个月, 单免疫组16.4个月($P=0.79744$), 且TRAE发生率明显增加。而LEAP-006研究、LEAP-008研究均未达到主要研究终点PFS和OS。此外, 关于阿替利珠单抗联合卡博替尼联合化疗治疗免疫检查点抑制剂和化疗后转移性NSCLC III期 CONTACT-01研究亦没有达

到其OS主要研究终点^[38]。分析其原因可能是肿瘤血管修饰过度导致肿瘤内环境缺氧, 进一步导致免疫抑制。未来ICIs联合抗血管生成药物治疗策略仍需要进一步探索和优化。

2.1.3 重组人血管内皮抑制素联合ICIs 一项回顾性研究显示, 一线接受至少2周期卡瑞利珠单抗联合重组人血管内皮抑制素联合化疗治疗的mPFS为8.9个月; 将患者分为接受 <4 周期治疗及 ≥ 4 周期治疗两组进行亚组分析, 结果显示接受 ≥ 4 周期治疗的mPFS为12.4个月^[39]。表明接受4周期以上治疗的患者能从中获得更大的临床益处, 然而该研究样本量较小(27例), 临床证据相对不足, 需要前瞻性临床研究予以验证。后续ENPOWER研究^[25]进行了探索, 这是一项多中心、II期前瞻性队列研究, 旨在评价重组人血管内皮抑制素联合化疗联合或不联合PD-1抗体一线治疗EGFR/ALK阴性晚期NSCLC的有效性及安全性。结果显示联合免疫组无论是ORR(57.7%)还是mPFS(16.7个月)均优于未联合免疫组(分别为34.2%和16.4个月)。Yuan等^[40]的II期临床研究中, 29例患者一线接受恩沃利单抗联合重组人内皮抑素治疗, 总体ORR和DCR分别为72.4%和93.1%(ENPOWER研究分别为57.7%和88.5%)。从初步数据来看, 与ENPOWER研究相比, 患者似乎更能从去化疗方案中获益, 然而缺乏头对头对比研究, 期待后续临床研究验证。

2.2 EGFR阳性患者的ICIs联合抗血管治疗

2.2.1 大分子单抗类药物联合ICIs IMpower150研究^[24]是首个EGFR突变人群的探索性分析, 结果表明EGFR突变NSCLC患者或经EGFR酪氨酸激酶抑制剂(Tyrosine kinase inhibitors, TKI)治疗后的NSCLC患者能从ABCP方案中获益(mOS分别为29.4个月和27.8个月), 且毒性可控, 这表明该方案可能是一种新的治疗方向。后续在中国进行了III期IMpower151研究^[27], 主要探讨患者基因组组成和临床用药的差异。次要终点包括EGFR/ALK阳性人群中的PFS。结果显示EGFR/ALK各亚组PFS相似。IMpower151研究并没有显示出较好的临床获益。初步分析这一结果可能与IMpower151与IMpower150使用化疗药物不同(培美曲塞 vs. 紫杉醇)以及EGFR阳性患者比例较高(53% vs. 10%)相关。同样, II期NEJ043研究^[41]纳入60例经EGFR-TKI治疗后的EGFR突变患者, 目的是评估ABCP方案的疗效, 尽管研究并未达到主要终点PFS, 但在EGFR突变的NSCLC患者中ABCP方案显示出具有一定临床意义的疗效(ORR为56%、mOS为23.1个月), 为

未来EGFR突变患者治疗方案的选择提供新方向。

ATLAS研究^[42]则是一项在韩国开展的Ⅲ期临床试验,旨在进一步评估IMpower150研究中ABCP方案的疗效和安全性,该研究招募了228例患者,其中95.5%的患者携带EGFR突变基因。结果显示,ABCP组对比单纯化疗组, mPFS明显改善(8.48个月 vs. 5.62个月, $P=0.004$), mOS无显著差异,这可能与两组患者不同的后续治疗相关,提示未来应进一步探索与OS相关的因素。ATLAS研究初步验证了IMpower150研究亚组分析中的初步结果,这表明TKI治疗后疾病进展的EGFR/ALK突变患者可以从ABCP方案中获益。APPLE研究^[43]则是将患者随机分配至APPB组(阿替利珠单抗、卡铂联合培美曲塞和贝伐珠单抗)与APP组(阿替利珠单抗、卡铂联合培美曲塞),尽管该研究的结果并未显示出APPB方案治疗非鳞状NSCLC优于APP方案,然而在亚组探索性分析中,对于驱动基因阳性患者,APPB组的PFS改善明显(9.7个月 vs. 5.8个月),提示在驱动基因阳性和阴性患者中VEGF可能在肿瘤微环境中发挥不同的功能,抑制VEGF可能改变驱动基因阳性患者的肿瘤微环境,从而增加其对PD-1/PD-L1的敏感性,但与贝伐珠单抗相关的毒性也明显增加,应注意联合用药时药物不良反应的累加。

随后,中国开展的ORIENT-31研究进一步验证了ICIs联合抗血管生成药物的疗效。将EGFR-TKI治疗后进展患者随机分配至信迪利单抗联合贝伐珠单抗生物类药联合化疗组或单纯化疗组。在第二次中期分析结果中,四药联合组在PFS上继续获益(7.2个月),安全性结果与第一次中期分析一致,≥3级TRAE的发生率为56%^[28]。基于此研究,信迪利单抗联合贝伐珠单抗、培美曲塞和顺铂被国家药品监督管理局批准用于治疗经EGFR-TKI治疗失败的EGFR突变晚期非鳞状NSCLC患者。

2.2.2 小分子多靶点酪氨酸酶抑制剂联合ICIs
ALTER-L038研究^[44]是对贝莫苏拜单抗联合安罗替尼治疗既往EGFR突变晚期NSCLC治疗失败的Ⅰ/Ⅱ期研究。纳入的55例患者mPFS高达9个月, mOS更是高达28.9个月,且不良反应可控。与以往任何联合治疗EGFR突变NSCLC患者临床研究相比,疗效更佳,不良反应发生率更低,我们分析可能与ALTER-L038研究是去化疗治疗方案有关,减少了化学相关毒性,这可能为不可耐受化学毒性患者提供新选择。未来需要更大规模的随机对照试验进一步验证其疗效及安全性。

2.2.3 新型双特异性抗体 由于ICIs与抗血管生成药联合治疗晚期NSCLC取得了一定疗效。近年来,研究者们深入研究与开发,引入了新型靶向PD-1/PD-L1和血管内皮生长因子的双特异性抗体,如Ivonescimab和PM8002/BNT327。在2024年ASCO会议上,报道了Ivonescimab联合化疗治疗接受EGFR-TKI治疗期间疾病进展的NSCLC患者的研究结果^[45]。研究招募的322例患者均接受了4周期Ivonescimab或安慰剂联合培美曲塞和卡铂治疗,随后接受Ivonescimab加培美曲塞或安慰剂加培美曲塞维持治疗,主要研究终点为PFS。截至2023年3月10日,安慰剂组与Ivonescimab组ORR分别为35.4%和50.6%。与安慰剂组相比,Ivonescimab组的患者显示出更好的预后(mPFS为7.1个月 vs. 4.8个月, mOS数据尚不成熟)。吴一龙教授就PM8002/BNT327联合化疗治疗EGFR-TKI治疗进展的EGFR突变NSCLC患者的单臂Ⅱ期研究初步数据在2024年ESMO大会作了口头汇报^[46]。纳入的64例患者总体ORR为54.7%、DCR为95.3%。同时亚组分析发现疗效与肿瘤PD-L1表达水平呈正相关。晚期NSCLC的联合治疗方案在不断发展,从双药治疗到一药双靶,尽管仍在试验阶段,但初步展示了良好的疗效,期待后续更多数据披露。近年来免疫检查点抑制剂联合抗血管生成药物治疗NSCLC的部分前瞻性研究,见表2。

3 总结与展望

临床前研究表明,免疫检查点抑制剂和抗血管生成药物联合治疗可诱导肿瘤血管正常化,减少免疫抑制细胞,将冷肿瘤转变为热肿瘤,协同增效。多个临床研究公布数据,并且大部分研究表现了较好的抗肿瘤活性。当前肿瘤治疗领域应用的联合治疗模式主要包括以下三种:(1)免疫治疗与抗血管生成治疗的联合应用;(2)免疫治疗、抗血管生成治疗与化疗的三联方案;(3)基于双特异性抗体的靶向治疗。前两者均有大型Ⅲ期临床试验验证,且部分治疗方案已获批用于相关适应证。有关双特性抗体的临床试验仍在进一步验证当中,尚未达到研究终点。

综上,ICIs联合抗血管生成药物治疗能延长晚期NSCLC患者生存时间,为晚NSCLC患者带来希望,同时也带来一些问题和挑战。联合化疗药物势必会增加毒性,“去化疗”治疗模式是否会带来更大的获益尚无研究论证,未来需要头对头研究验证。此外,对于不同的免疫检查点抑制剂如PD-1、PD-

表 2 免疫检查点抑制剂联合抗血管生成药物治疗NSCLC的部分前瞻性研究
Table 2 Some prospective studies of immune checkpoint inhibitors combined with antiangiogenic agents in treatment of NSCLC

Study	Study staging	Patient	Research program	Primary endpoint
NCT05184712 (HARMONi-A) ^[45]	Phase 3	Stage III B/IV NSCLC with disease progression after treatment with EGFR-TKI	Experimental group: Ivonescimab + platinum-based doublet chemotherapy Control group: Placebo + platinum-based doublet chemotherapy	PFS
NCT05756972 ^[46]	Monobrachial stage II	Stage III B/IV NSCLC with disease progression after treatment with EGFR-TKI	PM8002 Combined pemetrexed and carboplatin	ORR and PFS
NCT03377023 ^①	Phase I / II	Stage IV NSCLC	Nivolumab + ipilimumab + nintedanib	Maximum tolerated dose and ORR
NCT02681549 ^[47]	Phase 2	Brain metastatic melanoma or NSCLC	Pembrolizumab + bevacizumab	BMS response rates using modified RECIST criteria
NCT05972460 ^②	Phase I a	Advanced solid tumor	IMM2510 dose escalation via intravesical administration every two weeks until 52 weeks	AE

Notes: ①: registered on Clinical Trail website, currently closed to recruitment, no study results yet published; ②: registered on Clinical Trail website, currently recruiting patients.

L1联合不同的抗血管生成药如大分子类单抗、小分子TKI、重组人血管内皮抑制素到底哪个效果更佳，目前也尚无定论，需要未来进一步探索。而明确用药的最佳顺序及剂量、探索生物标志物以及免疫联合抗血管治疗不良反应累加所致的安全性问题、新型药物的开发等问题均需要更多基础研究及更加全面的前瞻性临床试验进一步探索。随着分子生物学及免疫学的发展，未来将更加深入地探索肿瘤微环境的变化，以便更好地指导临床个体化用药。

利益冲突声明：
所有作者均声明不存在利益冲突。

参考文献：

[1] Sung H, Ferlay J, Siegel RL, *et al.* Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries[J]. *CA Cancer J Clin*, 2021, 71(3): 209-249.

[2] Chen P, Liu Y, Wen Y, *et al.* Non-small cell lung cancer in China[J]. *Cancer Commun(Lond)*, 2022, 42(10): 937-970.

[3] 李岚, 许斌, 武杰, 等. 原发灶手术对IV期非小细胞肺癌患者生存的影响[J]. *中华肿瘤杂志*, 2021, 43(3): 335-344. [Li L, Xu B, Wu J, *et al.* Survival benefit of primary site surgery acquired by stage IV non-small cell lung cancer: a retrospective study based on seer database[J]. *Zhonghua Zhong Liu Za Zhi*, 2021, 43(3): 335-344.]

[4] Meador CB, Hata AN. Acquired resistance to targeted therapies in NSCLC: Updates and evolving insights[J]. *Pharmacol Ther*, 2020, 210: 107522.

[5] Lefler DS, Manobianco SA, Bashir B. Immunotherapy resistance in solid tumors: mechanisms and potential solutions[J]. *Cancer Biol Ther*, 2024, 25(1): 2315655.

[6] Li A, Fang J. Anti-angiogenic therapy enhances cancer immunotherapy: Mechanism and clinical application[J]. *Interdiscip Med*, 2024, 2(1): e20230025.

[7] Aguiar RBD, Moraes JZD. Exploring the Immunological Mechanisms Underlying the Anti-vascular Endothelial Growth Factor Activity in Tumors[J]. *Front Immunol*, 2019, 10: 1023.

[8] Ren S, Xiong X, You H, *et al.* The Combination of Immune Checkpoint Blockade and Angiogenesis Inhibitors in the Treatment of Advanced Non-Small Cell Lung Cancer[J]. *Front Immunol*, 2021, 12: 689132.

[9] Lugano R, Ramachandran M, Dimberg A. Tumor angiogenesis: causes, consequences, challenges and opportunities[J]. *Cell Mol Life Sci*, 2020, 77(9): 1745-1770.

[10] He D, Wang L, Xu J, *et al.* Research advances in mechanism of antiangiogenic therapy combined with immune checkpoint inhibitors for treatment of non-small cell lung cancer[J]. *Front Immunol*, 2023, 14: 1265865.

[11] Fukumura D, Kloepper J, Amoozgar Z, *et al.* Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges[J]. *Nat Rev Clin Oncol*, 2018, 15(5): 325-340.

[12] Zhang W, Wang M, Ji C, *et al.* Macrophage polarization in the tumor microenvironment: Emerging roles and therapeutic potentials[J]. *Biomed Pharmacother*, 2024, 177: 116930.

[13] Dings RPM, Vang KB, Castermans K, *et al.* Enhancement of T-cell-Mediated Antitumor Response: Angiostatic Adjuvant to Immunotherapy against Cancer[J]. *Clin Cancer Res*, 2011, 17(10): 3134-3145.

[14] Heist RS, Duda DG, Sahani DV, *et al.* Improved tumor vascularization after anti-VEGF therapy with carboplatin and nab-paclitaxel associates with survival in lung cancer[J]. *Proc Natl Acad Sci U S A*, 2015, 112(5): 1547-1552.

[15] Lee WS, Yang H, Chon HJ, *et al.* Combination of anti-angiogenic therapy and immune checkpoint blockade normalizes vascular-immune crosstalk to potentiate cancer immunity[J]. *Exp Mol Med*, 2020, 52(9): 1475-1485.

[16] Tian L, Goldstein A, Wang H, *et al.* Mutual regulation of tumour vessel normalization and immunostimulatory reprogramming[J]. *Nature*, 2017, 544(7649): 250-254.

[17] Huang Y, Yuan J, Righi E, *et al.* Vascular normalizing doses of antiangiogenic treatment reprogram the immunosuppressive tumor microenvironment and enhance immunotherapy[J]. *Proc Natl Acad Sci U S A*, 2012, 109(43): 17561-17566.

[18] Du Four S, Maenhout SK, Niclou SP, *et al.* Combined VEGFR and CTLA-4 blockade increases the antigen-presenting function of intratumoral DCs and reduces the suppressive capacity of intratumoral MDSCs[J]. *Am J Cancer Res*, 2016, 6(11): 2514-2531.

[19] Zhao S, Ren S, Jiang T, *et al.* Low-Dose Apatinib Optimizes

- Tumor Microenvironment and Potentiates Antitumor Effect of PD-1/PD-L1 Blockade in Lung Cancer[J]. *Cancer Immunol Res*, 2019, 7(4): 630-643.
- [20] Jing X, Yang F, Shao C, *et al.* Role of hypoxia in cancer therapy by regulating the tumor microenvironment[J]. *Mol Cancer*, 2019, 18(1): 157.
- [21] Qian B, Pollard JW. Macrophage Diversity Enhances Tumor Progression and Metastasis[J]. *Cell*, 2010, 141(1): 39-51.
- [22] Zhang Y, Zhang Z. The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications[J]. *Cell Mol Immunol*, 2020, 17(8): 807-821.
- [23] Zheng X, Fang Z, Liu X, *et al.* Increased vessel perfusion predicts the efficacy of immune checkpoint blockade[J]. *J Clin Invest*, 2018, 128(5): 2104-2115.
- [24] Nogami N, Barlesi F, Socinski MA, *et al.* IMPower150 Final Exploratory Analyses for Atezolizumab Plus Bevacizumab and Chemotherapy in Key NSCLC Patient Subgroups With EGFR Mutations or Metastases in the Liver or Brain[J]. *J Thorac Oncol*, 2022, 17(2): 309-323.
- [25] Wang D, Feng Y, Wang H, *et al.* EP11.02-09 Rh-endostatin Combined With PD-1 inhibitors as First-line Treatment for EGFR/ALK-Negative, Non-squamous NSCLC[J]. *J Thorac Oncol*, 2023, 18(11_Suppl): S618.
- [26] Yang JC, Han B, De La Mora Jiménez E, *et al.* Pembrolizumab With or Without Lenvatinib for First-Line Metastatic NSCLC With Programmed Cell Death-Ligand 1 Tumor Proportion Score of at least 1% (LEAP-007): A Randomized, Double-Blind, Phase 3 Trial[J]. *J Thorac Oncol*, 2024, 19(6): 941-953.
- [27] Zhou C, Dong X, Chen G, *et al.* OA09.06 IMPower151: Phase III Study of Atezolizumab + Bevacizumab + Chemotherapy in 1L Metastatic Nonsquamous NSCLC[J]. *J Thorac Oncol*, 2023, 18(11_Suppl): S64-S65.
- [28] Lu S, Wu L, Jian H, *et al.* Sintilimab plus chemotherapy for patients with EGFR-mutated non-squamous non-small-cell lung cancer with disease progression after EGFR tyrosine-kinase inhibitor therapy (ORIENT-31): second interim analysis from a double-blind, randomised, placebo-controlled, phase 3 trial[J]. *Lancet Respir Med*, 2023, 11(7): 624-636.
- [29] Socinski MA, Jotte RM, Cappuzzo F, *et al.* Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC[J]. *N Engl J Med*, 2018, 378(24): 2288-2301.
- [30] Lee J, Koh J, Kim HK, *et al.* Bevacizumab Plus Atezolizumab After Progression on Atezolizumab Monotherapy in Pretreated Patients With NSCLC: An Open-Label, Two-Stage, Phase 2 Trial[J]. *J Thorac Oncol*, 2022, 17(7): 900-908.
- [31] Seto T, Nosaki K, Shimokawa M, *et al.* Phase II study of atezolizumab with bevacizumab for non-squamous non-small cell lung cancer with high PD-L1 expression (@Be Study)[J]. *J Immunother Cancer*, 2022, 10(2): e004025.
- [32] Provencio M, Ortega AL, Coves-Sarto J, *et al.* Atezolizumab Plus Bevacizumab as First-line Treatment for Patients With Metastatic Nonsquamous Non-Small Cell Lung Cancer With High Tumor Mutation Burden: A Nonrandomized Controlled Trial[J]. *JAMA Oncol*, 2023, 9(3): 344-353.
- [33] Chu T, Zhong R, Zhong H, *et al.* Phase 1b Study of Sintilimab Plus Anlotinib as First-line Therapy in Patients With Advanced NSCLC[J]. *J Thorac Oncol*, 2021, 16(4): 643-652.
- [34] Tang JW, Qian X, Luo J, *et al.* 80P Efficacy and safety of tislelizumab combined with anlotinib and 2-cycles chemotherapy as first-line treatment for advanced NSCLC (TISAL-FE-01)[J]. *IOTCH*, 2023, 20(Suppl): 100552.
- [35] Yu L, Xu J, Qiao R, *et al.* Comparative efficacy and safety of multitarget angiogenesis inhibitor combined with immune checkpoint inhibitor and nivolumab monotherapy as second-line or beyond for advanced lung adenocarcinoma in driver-negative patients: a retrospective comparative cohort study[J]. *Transl Lung Cancer Res*, 2023, 12(5): 1108-1121.
- [36] Herbst RS, Cho BC, Zhou C, *et al.* 64O Lenvatinib plus pembrolizumab, pemetrexed, and a platinum (len + pembro + chemo) as first-line therapy for metastatic non squamous non-small cell lung cancer (NSCLC): Phase III LEAP-006 study[J]. *IOTCH*, 2023, 20(Suppl): 100536.
- [37] Leighl N, Paz-Ares L, Abreu DR, *et al.* 65O Phase III LEAP-008 study of lenvatinib plus pembrolizumab versus docetaxel for metastatic non-small cell lung cancer (NSCLC) that progressed on a PD-(L)1 inhibitor and platinum-containing chemotherapy[J]. *IOTCH*, 2023, 20(Suppl): 100537.
- [38] Neal J, Pavlakis N, Kim SW, *et al.* CONTACT-01: A Randomized Phase III Trial of Atezolizumab + Cabozantinib Versus Docetaxel for Metastatic Non-Small Cell Lung Cancer After a Checkpoint Inhibitor and Chemotherapy[J]. *J Clin Oncol*, 2024, 42(20): 2393-2403.
- [39] Wu L, Pu X, Chen B, *et al.* P40.14 Efficacy and Safety of Endostar Combined With Camrelizumab and Chemotherapy in Treatment of Advanced NSCLC: A Multi-Center Retrospective Study[J]. *J Thorac Oncol*, 2021, 16(10_Suppl): S1075-S1076.
- [40] Yuan S, Miao C. 70P Phase II clinical study of envafolelimab combined with recombinant human endostatin and chemotherapy as a first-line treatment for driver gene-negative advanced non-small cell lung cancer[J]. *ESMO Open*, 2024, 9: 102649.
- [41] Watanabe S, Furuya N, Nakamura A, *et al.* A phase II study of atezolizumab with bevacizumab, carboplatin, and paclitaxel for patients with EGFR-mutated NSCLC after TKI treatment failure (NEJ043 study)[J]. *Eur J Cancer*, 2024, 197: 113469.
- [42] Park S, Kim TM, Han JY, *et al.* Phase III, Randomized Study of Atezolizumab Plus Bevacizumab and Chemotherapy in Patients With EGFR- or ALK-Rearranged or Translocated Non-Small-Cell Lung Cancer (ATTLAS, KCSG-LU19-04)[J]. *J Clin Oncol*, 2024, 42(11): 1241-1251.
- [43] Shiraishi Y, Kishimoto J, Sugawara S, *et al.* Atezolizumab and Platinum Plus Pemetrexed With or Without Bevacizumab for Metastatic Nonsquamous Non-Small Cell Lung Cancer: A Phase 3 Randomized Clinical Trial[J]. *JAMA Oncol*, 2024, 10(3): 315-324.
- [44] Shi M, Chen P, Cui B, *et al.* Benmelstobart plus anlotinib in patients with EGFR-positive advanced NSCLC after failure of EGFR TKIs therapy: a phase I/II study [J]. *Signal Transduct Target Ther*, 2024, 9(1): 283.
- [45] Harmoni-A Study Investigators, Fang W, Zhao Y, *et al.* Ivonescimab Plus Chemotherapy in Non-Small Cell Lung Cancer With EGFR Variant: A Randomized Clinical Trial[J]. *JAMA*, 2024, 332(7): 561-570.
- [46] Wu Y L, Wang Z, Cheng Y, *et al.* 1255MO A phase II safety and efficacy study of PM8002/BNT327 in combination with chemotherapy in patients with EGFR-mutated non-small cell lung cancer (NSCLC)[J]. *Ann Oncol*, 2024, 35(Suppl_2): S804.
- [47] Weiss SA, Djureinovic D, Wei W, *et al.* Phase II Trial of Pembrolizumab in Combination With Bevacizumab for Untreated Melanoma Brain Metastases[J]. *J Clin Oncol*, 2025, JCO-24-02219. Online ahead of print.

[编辑: 刘红武; 校对: 邱颖慧]

作者贡献:

曾爱菊: 文献查阅, 文章撰写

马代远: 文章修改