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• 特约来稿 •

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晚期非小细胞肺癌免疫治疗：研究进展和展望

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Immunotherapy for Advanced Non-small Cell Lung Cancer: Research Progress and Perspectives

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Abstract: Immunotherapy has changed the treatment landscape of advanced non-small cell lung cancer (NSCLC), showing great potential in the treatment of untreated and relapsed or refractory (R/R) patients. However, numerous issues that need further exploration remain with the wide application of immunotherapy. They include the exploration of biomarkers for efficacy prediction, the optimization of immunotherapy modalities, immune-related adverse effects, and the management of special populations. This review summarizes the progress of the research on immunotherapy for advanced NSCLC and discusses its challenges and future directions.

Key words: Non-small cell lung cancer; Immunotherapy; Immune checkpoint inhibitors

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摘　要：免疫治疗已经改变了晚期非小细胞肺癌（NSCLC）的治疗格局，在一线及后线治疗中均显现出巨大潜能。同时，随着免疫治疗的广泛应用，仍有许多问题需要进一步探讨，如疗效预测生物标志物的探索、免疫治疗模式的优化、免疫相关不良反应和特殊人群的管理等。本综述梳理了晚期NSCLC免疫治疗的研究进展，并探讨了面临的挑战和未来发展方向。

关键词：非小细胞肺癌；免疫治疗；免疫检查点抑制剂

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0　引言

2022年全球癌症统计报告显示[1]，肺癌是全球发病率第二、死亡率第一的恶性肿瘤。在中国，肺癌的发病率和死亡率也均居第一[2]。其中非小细胞肺癌（non-small cell lung cancer, NSCLC）是最主要的组织学类型，约占85%，多数患者在就诊时已处于中晚期，五年生存率低，如何改善晚期NSCLC患者的长期生存已成为当今研究热点[3]。肺癌的精准治疗进展迅速，免疫检查点抑制剂（immune checkpoint inhibitors, ICIs）已成为肺癌领域的研究热点，很大程度地改善了部分肺癌患者的预后。对于驱动基因阴性的NSCLC患者，ICI单药或联合治疗目前已成为晚期NSCLC一线标准治疗方案[4]。但随着免疫治疗的不断发展，仍有许多问题需要进一步探讨，如疗效预测生物标志物的探索、免疫治疗模式的优化、免疫相关不良反应和特殊人群的管理。在此，我们将总结晚期NSCLC免疫治疗的研究进展，探讨晚期NSCLC免疫疗法面临的挑战和未来发展方向。

1　免疫检查点抑制剂的作用机制

ICIs研究较为深入的靶点主要包括程序性死亡受体1（programmed cell death 1, PD-1）、程序性死亡受体配体1（programmed cell death ligand 1, PD-L1）以及细胞毒性T淋巴细胞相关抗原4（cytotoxic T lymphocyte-associated antigen 4, CTLA-4）等。PD-1/PD-L1抑制剂通过阻断肿瘤表面的PD-L1和免疫细胞表面的PD-1识别和结合，从而恢复T细胞活化的正向调控信号通路，激活T细胞活性，增强机体肿瘤免疫，最终发挥抗肿瘤作用[5]。CTLA-4（CD152）与CD28同源，均表达于活化T细胞表面，CD28与其配体B7（B7-1和B7-2）结合后可以产生刺激性信号。CTLA-4是一种负性调节分子，可以与CD28竞争性结合抗原提呈细胞表面的B7分子，从而抑制T细胞的增殖和活化。CTLA-4抑制剂能有效阻断CTLA-4与B7分子的结合，恢复共刺激信号通路CD28-B7的活性，减弱对T细胞活化的抑制作用，增加肿瘤特异性T细胞的浸润[6]。除此之外，ICIs的新靶点还包括淋巴细胞活化基因3（LAG-3）[7]、T细胞免疫球蛋白和ITIM结构域蛋白（TIGIT）[8]等。综上，各类ICIs通过阻断肿瘤细胞与免疫细胞之间的抑制性信号通路，解除对T细胞活化的抑制作用，重新激活和增强机体免疫系统对肿瘤的免疫应答，为肿瘤治疗提供新的治疗策略。

2　晚期NSCLC一线免疫治疗现状

免疫治疗改变了晚期NSCLC患者一线治疗的格局。我们汇总了目前被美国食品药品管理局（Food and Drug Administration, FDA）和（或）中国国家药品监督管理局（National Medical Products Administration, NMPA）批准用于晚期NSCLC一线治疗的免疫治疗方案，见表1。

2.1　免疫单药治疗

目前，帕博利珠单抗、阿替利珠单抗和西米普利单抗单药治疗被FDA推荐用于PD-L1高表达且驱动基因阴性的晚期NSCLC患者的一线治疗[4]。

KETNOTE-024研究被FDA授予了突破性疗法称号，改变了驱动基因阴性的晚期NSCLC既往以化疗为主的治疗格局[9-10]。研究结果显示，在PD-L1肿瘤细胞阳性比例（tumor proportion score, TPS）≥50%的人群中，相较于化疗，帕博利珠单抗可显著提高客观缓解率（objective response rate, ORR）（44.8% *vs*. 27.8%），并延长无进展生存期（progress-free survival, PFS）（10.3 *vs*. 6.0个月，*HR*=0.50）。5年最终数据显示，帕博利珠单抗的总生存期（overall survival，OS）也显著提高（26.3 *vs*. 13.4个月，*HR*=0.62）。随后KEYNOTE-042研究将入组标准扩大至PD-L1 TPS≥1%，结果提示与化疗相比，帕博利珠单抗显著降低死亡风险，但亚组分析提示主要获益人群为PD-L1 TPS≥50%的患者[11-12]。IMpower110研究[13-14]和EMPOWER-Lung 1[15-16]研究进一步拓展了晚期NSCLC患者的治疗方案。在PD-L1高表达患者中，免疫单药阿替利珠单抗和西米普利单抗相较于标准化疗方案均可带来显著生存获益（IMpower110，mOS：20.2 *vs*. 14.7个月，*HR*=0.76；EMPOWER-Lung 1，mOS：26.1 *vs*. 13.3个月，*HR*=0.57）。

对于PD-L1高表达人群，免疫单药治疗即可带

表 1 晚期非小细胞肺癌一线ICIs单药治疗的临床试验汇总

Table 1 Summary of clinical trials of first-line ICIs monotherapy for advanced NSCLC

Study	Patient	Arm	Primary endpoint	ORR (%)	PFS (months)	OS (months)	Updated ORR (%)	Updated PFS (months)	Updated OS (months)
KEYNOTE-024	PD-L1 TPS≥50% advanced NSCLC	Pembrolizumab *vs.* Chemotherapy	PFS	44.8 *vs.* 27.8	10.3 *vs.*6.0; *HR*=0.50	NR *vs.* NR; *HR*=0.60	46.1 *vs.* 31.1	7.7 *vs.* 5.5; *HR*=0.50	26.3 *vs.* 13.4; *HR*=0.62
KEYNOTE-042	PD-L1 TPS≥1% advanced NSCLC	Pembrolizumab *vs.* Chemotherapy	OS	27.0 *vs.* 27.0	5.4 *vs.* 6.5; *HR*=1.07	16.7 *vs.* 12.1; *HR*=0.81	27.3 *vs.* 26.7	5.6 *vs.* 6.8; *HR*=1.03	16.4 *vs.* 12.1; *HR*=0.79
IMpower110	PD-L1 TC≥50%/ IC≥10% advanced NSCLC	Atezolizumab *vs.* Chemotherapy	OS	38.3 *vs.* 28.6	8.1 *vs.* 5.0; *HR*=0.63	20.2 *vs.*13.1; *HR*=0.59	40.2 *vs.*28.6	8.2 *vs.* 5.0; *HR*=0.59	20.2 *vs.* 14.7; *HR*=0.76
EMPOWER-Lung 1	PD-L1 TPS≥50% advanced NSCLC	Cemiplimab *vs.* Chemotherapy	OS, PFS	39 *vs.* 20	8.2 *vs.* 5.7; *HR*=0.54	NR *vs.* 14.2; *HR*=0.57	46.5 *vs.* 21.0	8.1 *vs.* 5.3; *HR*=0.51	26.1 *vs.* 13.3; *HR*=0.57

Notes: ICI: immune checkpoint inhibitor; NSCLC: non-small cell lung cancer; TPS: tumor proportion score; TC: tumor cell; IC: immune cell; ORR: objective response rate; DOR: duration of response; PFS: progression-free survival; OS: overall survival; *HR*: hazard ratio; NR: not reached.

来显著的临床获益，改变了晚期NSCLC患者的治疗格局。但免疫单药在PD-L1低表达或不表达人群中的临床获益并不显著。免疫联合治疗对进一步扩大受益人群、优化肺癌免疫疗法的疗效具有重要意义。

2.2 免疫联合治疗

为了提高免疫治疗获益人群的覆盖率，解除PD-L1表达对治疗的限制，免疫联合治疗方案不断创新。

免疫联合化疗已经成为指南推荐的晚期驱动基因阴性NSCLC的一线标准治疗方案，且不需要考虑PD-L1表达水平，见表2。KEYNOTE-189研究[17-18]证实在晚期非鳞状NSCLC中，与标准化疗相比，帕博利珠单抗联合化疗可以显著改善PFS（9.0 *vs.* 4.9个月，*HR*=0.50）和OS（22.0 *vs.* 10.6个月，*HR*=0.60）。随后的KEYNOTE-407研究[19-20]将帕博利珠单抗联合化疗的受益人群拓宽到晚期鳞状NSCLC患者。帕博利珠单抗联合化疗被推荐作为非鳞状和鳞状NSCLC首选的一线治疗方案。EMPOWER-Lung 3研究[21-22]显示，在晚期NSCLC患者中，西米普利单抗联合化疗相较于化疗能带来OS获益（21.1 *vs.* 12.9个月，*HR*=0.65），被FDA批准用于晚期NSCLC的一线治疗。同时，基于IMpower130研究[23]的OS获益（18.6 *vs.* 13.9个月，*HR*=0.79），FDA批准阿替利珠单抗联合化疗用于晚期非鳞状NSCLC的一线治疗。此外，中国自主研发的PD-1/PD-L1抑制剂在ICIs联合化疗一线治疗晚期NSCLC的临床研究中也取得了显著成功。基于CameL[24-25]和CameL-sq[26-27]、ORIENT-11[28-29]和ORIENT-12[30]研究、RATIONALE-304[31-32]和RATIONALE-307研究[33-34]以及GEMSTONE-302研究[35]的优秀数据，NMPA分别批准卡瑞利珠单抗、信迪利单抗、替雷利珠单抗、舒格利单抗联合化疗用于晚期非鳞状/鳞状NSCLC的一线治疗。在非鳞状NSCLC方面，基于CHOICE-01研究[36-37]，NMPA批准特瑞普利单抗联合化疗用于晚期一线治疗；在鳞状NSCLC方面，基于AK105-302研究[38]和ASTRUM-004研究[39]，NMPA批准派安普利单抗和斯鲁利单抗联合化疗用于晚期一线治疗。

免疫联合抗血管生成治疗在晚期 NSCLC 一线治疗中也显示出良好的应用前景，见表3。IMpower150研究[40-41]结果显示，在晚期非鳞状NSCLC患者中，相较于贝伐珠单抗+卡铂+紫杉醇治疗（BCP），阿替利珠单抗+贝伐珠单抗+卡铂+紫杉醇治疗（ABCP）的PFS（8.4 *vs.* 6.8个月，*HR*=0.57）和OS（19.5 *vs.* 14.7个月，*HR*=0.80）显著获益。ABCP四药联合方案被FDA批准用于转移性非鳞状NSCLC的一线治疗。

与此同时，双免疫联合治疗（PD-1/PD-L1抑制剂联合CTLA-4抑制剂）一线治疗晚期NSCLC的相关研究也报道了阳性结果，见表3。CheckMate-227研究[42-43]是第一个报道双免疫联合治疗阳性结果的Ⅲ临床研究，无论PD-L1表达如何，纳武利尤单抗联合伊匹木单抗较标准化疗的OS均显著获益，达到主要研究终点。然而生存曲线在治疗初期出现交叉的情况，意味着有部分患者无法获益。CheckMate-9LA研究[44-45]在纳武利尤单抗联合伊匹木单抗的基础上进一步联合2周期化疗，较单独化疗可以显著改善OS（15.8 *vs.*11.0个月，*HR*=0.74）。POSEIDON研究[46-47]则探索了度伐利尤单抗联合曲美木单抗及化疗作为晚期NSCLC一线治疗的可行性，研究结果显示该联合方案可以带来PFS和OS获益（mPFS：6.2 *vs.* 4.8个月，*HR*=0.72；mOS：14.0 *vs.* 11.6个月，*HR*=0.76）。基于临床研究优秀的生

表 2　晚期非小细胞肺癌一线ICIs联合化疗的临床试验汇总

Table 2　Summary of clinical trials of first-line ICIs combined with chemotherapy for advanced NSCLC

Study	Patient	Arm	Primary endpoint	ORR (%)	PFS (months)	OS (months)	Updated ORR(%)	Updated PFS (months)	Updated OS (months)
KEYNOTE-189	Advanced non-squamous NSCLC	Pembrolizumab + chemotherapy *vs.* Chemotherapy	OS,PFS	47.6 *vs.* 18.9	8.8 *vs.* 4.9; *HR*=0.52	NR *vs.* 11.3; *HR*=0.49	48.3 *vs.* 19.9	9.0 *vs.* 4.9; *HR*=0.50	22.0 *vs.* 10.6; *HR*=0.60
KEYNOTE-407	Advanced squamous NSCLC	Pembrolizumab + chemotherapy *vs.* Chemotherapy	OS,PFS	57.9 *vs.* 38.4	6.4 vs 4.8; *HR*=0.56	15.9 *vs.* 11.3; *HR*=0.64	62.2 *vs.* 38.8	8.0 *vs.* 5.1; *HR*=0.62	17.2 *vs.* 11.6; *HR*=0.71
EMPOWER-Lung 3	Advanced NSCLC	Cemiplima + chemotherapy *vs.* Chemotherapy	OS	43.3 *vs.* 22.7	8.2 *vs.* 5.0; *HR*=0.56	21.9 *vs.* 13.0; *HR*=0.71	43.6 *vs.* 22.1	8.2 *vs.* 5.5; *HR*=0.55	21.1 *vs.* 12.9; *HR*=0.65
IMpower130	Advanced non-squamous NSCLC	Atezolizumab + chemotherapy *vs.* Chemotherapy	OS	49.2 *vs.* 31.9	7.0 *vs.* 5.5; *HR*=0.64	18.6 *vs.* 13.9; *HR*=0.79			
CameL	Advanced non-squamous NSCLC	Camrelizumab + chemotherapy *vs.* Chemotherapy	PFS	60.5 *vs.* 38.6	11.3 *vs.* 8.3; *HR*=0.60	NR *vs.* 20.9; *HR*=0.73	55.1 *vs.* 32.9	11.0 *vs.* 6.5; *HR*=0.55	27.1 *vs.* 19.8; *HR*=0.72
CameL-sq	Advanced squamous NSCLC	Camrelizumab + chemotherapy *vs.* Chemotherapy	PFS	64.8 *vs.* 36.7	8.5 *vs.* 4.9; *HR*=0.37	NR *vs.* 14.5; *HR*=0.55			27.4 *vs.* 15.5; *HR*=0.57
ORIENT-11	Advanced non-squamous NSCLC	Sintilimab + chemotherapy *vs.* Chemotherapy	PFS	51.9 *vs.* 29.8	8.9 *vs.* 5.0; *HR*=0.48	NR *vs.* NR; *HR*=0.61			24.2 *vs.* 16.8; *HR*=0.65
ORIENT-12	Advanced squamous NSCLC	Sintilimab + chemotherapy *vs.* Chemotherapy	OS	44.7 *vs.* 35.4	5.5 *vs.* 4.9; *HR*=0.54	NR *vs.* NR; *HR*=0.57			
RATIONALE 304	Advanced non-squamous NSCLC	Tislelizumab + chemotherapy *vs.* Chemotherapy	PFS	57.4 *vs.* 36.9	9.7 *vs.* 7.6; *HR*=0.65	NR *vs.* NR	51.6 *vs.* 27.9	9.8 *vs.* 7.6; *HR*=0.61	
RATIONALE 307	Advanced squamous NSCLC	Tislelizumab+ chemotherapy *vs.* Chemotherapy	PFS	72.5 *vs.* 49.6	7.6 *vs.* 5.5; *HR*=0.52	NR *vs.* NR	74.2 *vs.* 47.9	7.7 *vs.* 5.5; *HR*=0.45	
GEMSTONE-302	Advanced NSCLC	Sugemalimab+ chemotherapy *vs.* Chemotherapy	PFS	63.4 *vs.* 40.3	9.0 *vs.* 4.9; *HR*=0.48	22.8 *vs.* 17.7; *HR*=0.67			
CHOICE-01	Advanced NSCLC	Toripalimab + chemotherapy *vs.* Chemotherapy	PFS	65.7 *vs.* 46.2	8.4 *vs.* 5.6; *HR*=0.49	NR *vs.* 17.1; *HR*=0.69			23.8 *vs.* 17.0; *HR*=0.73
AK105-302	Advanced squamous NSCLC	Penpulimab + chemotherapy *vs.* Chemotherapy	PFS	71.4 *vs.* 44.0	7.6 *vs.* 4.2; *HR*=0.44	NR *vs.* 19.8; *HR*=0.55			
ASTRUM-004	Advanced squamous NSCLC	Serplulimab + chemotherapy *vs.* Chemotherapy	PFS	60.1 *vs.* 40.2	8.3 *vs.* 5.6; *HR*=0.50	22.7 *vs.*18.2; *HR*=0.73			

存数据，以上三种治疗方案均被FDA批准用于晚期NSCLC的一线治疗。

3　晚期NSCLC后线免疫治疗现状

对于既往未接受过ICI治疗的晚期NSCLC患者，PD-1/PD-L1抑制剂也已经成为后线治疗新标准，见表4。KEYNOTE 010[48-49]、CheckMate 017/057[50-52]和OAK[53]等大型Ⅲ期临床研究奠定了免疫单药治疗在晚期NSCLC患者二线治疗中的地位，与标准二线治疗多西他赛相比，帕博利珠单抗、那武利尤单抗和阿替利珠单抗均能带来更好的OS生存获益。因此，FDA批准帕博利珠单抗用于PD-

表 3 晚期非小细胞肺癌一线ICIs联合抗血管生成治疗或双ICIs联合治疗的临床试验汇总

Table 3 Summary of clinical trials of first-line ICIs combined with antiangiogenic therapy or dual-ICIs combination therapy for advanced NSCLC

Study	Patient	Arm	Primary endpoint	ORR (%)	PFS (months)	OS (months)	Updated ORR (%)	Updated PFS (months)	Updated OS (months)
ICIs combined with antiangiogenic therapy									
IMpower150	Advanced non-squamous NSCLC	Atezolizumab+ bevacizumab+ chemotherapy *vs.* Bevacizumab+ chemotherapy	OS, PFS	63.5 *vs.* 48.0	8.3 *vs.* 6.8; *HR*=0.62	19.2 *vs.* 14.7; *HR*=0.78		8.4 *vs.* 6.8; *HR*=0.57	19.5 *vs.* 14.7; *HR*=0.80
Dual-ICIs combination therapy									
CheckMate 227	Advanced NSCLC	Nivolumab+ ipilimumab *vs.* Chemotherapy	OS	33.1 *vs.* 27.8	5.1 *vs.* 5.5; *HR*=0.79	17.1 *vs.* 13.9; *HR*=0.73			
CheckMate 9LA	Advanced NSCLC	Nivolumab+ ipilimumab+ chemotherapy *vs.* Chemotherapy	OS	38.2 *vs.* 24.9	6.7 *vs.* 5.0; *HR*=0.68	15.6 *vs.* 10.9; *HR*=0.66	38 *vs.* 25		15.8 *vs.* 11.0; *HR*=0.74
POSEIDON	Advanced NSCLC	Tremelimumab+ durvalumab+ chemotherapy *vs.* Chemotherapy	PFS	38.8 *vs.* 24.4	6.2 *vs.* 4.8; *HR*=0.72	14.0 *vs.* 11.7; *HR*=0.77			14.0 *vs.* 11.6; *HR*=0.76

表 4 晚期非小细胞肺癌二线ICIs治疗的临床试验汇总

Table 4 Summary of clinical trials of second-line ICIs for advanced NSCLC

Study	Patient	Arm	Primary endpoint	ORR (%)	PFS (months)	OS (months)	Updated ORR (%)	Updated PFS (months)	Updated OS (months)
KEYNOTE 010	PD-L1 TPS≥1% previously treated advanced NSCLC	Pembrolizumab *vs.* Chemotherapy	OS, PFS	18 *vs.* 9	4.0 *vs.* 4.0; *HR*=0.79	12.7 *vs.* 8.5; *HR*=0.61	21.2 *vs.* 9.6	4.0 *vs.* 4.1; *HR*=0.84	11.8 *vs.* 8.4; *HR*=0.70
CheckMate 017	Previously treated advanced squamous NSCLC	Nivolumab *vs.* Chemotherapy	OS	20 *vs.* 9	3.5 *vs.* 2.8; *HR*=0.62	9.2 *vs.* 6.0; *HR*=0.59	20.0 *vs.* 8.8	3.5 *vs.* 2.6; *HR*=0.61	9.2 *vs.* 6.0; *HR*=0.62
CheckMate 057	Previously treated advanced non-squamous NSCLC	Nivolumab *vs.* Chemotherapy	OS	19 *vs.* 12	2.3 *vs.* 4.7; *HR*=0.92	12.2 *vs.* 9.4; *HR*=0.73	19.5 *vs.* 12.4	2.3 *vs.* 4.4; *HR*=0.90	12.2 *vs.* 9.5; *HR*=0.70
OAK	Previously treated advanced NSCLC	Atezolizumab *vs.* Chemotherapy	OS	14 *vs.* 13	2.8 *vs.* 4.0; *HR*=0.95	15.7 *vs.* 10.3; *HR*=0.74			
CheckMate-078	Previously treated advanced NSCLC	Nivolumab *vs.* Chemotherapy	OS	16.6 *vs.* 4.2	2.8 *vs.* 2.8; *HR*=0.77	12.0 *vs.* 9.6; *HR*=0.68	18 *vs.* 4	2.8 *vs.* 2.8; *HR*=0.78	11.9 *vs.* 9.5; *HR*=0.75
RATIONALE-303	Previously treated advanced NSCLC	Tislelizumab *vs.* Chemotherapy	OS	22.6 *vs.* 7.1	4.2 *vs.* 2.6; *HR*=0.63	16.9 *vs.*11.9; *HR*=0.66			

L1表达阳性晚期NSCLC患者的二线治疗；也批准那武利尤单抗和阿替利珠单抗用于晚期NSCLC患者的二线治疗。在中国肺癌人群中，CheckMate-078研究[54-55]首先报道了二线免疫治疗的研究成果，纳武利尤单抗较多西他赛显著延长了OS（11.9 *vs.* 9.5个月，*HR*=0.75）。RATIONALE-303研究[56]也证实了我国国产替雷利珠单抗对比标准化疗在晚期NSCLC二线治疗中的有效性（OS：16.9 *vs.* 11.9个月，*HR*=0.66）。因此，NMPA分别批准纳武利尤单抗和替雷利珠单抗用于晚期NSCLC患者的二

线治疗。

4　晚期NSCLC免疫治疗的挑战

4.1　免疫生物标志物的探索

近十年来，ICIs从最初的二线/后线治疗到现在的一线治疗，不断地在肺癌治疗领域取得突破性进展，但只有部分患者能长期获益，寻找能够指导免疫治疗的生物标志物是亟待解决的问题。目前研究比较深入的有PD-L1表达和肿瘤突变负荷（tumor mutation burden, TMB）。

NCCN指南推荐，所有晚期NSCLC患者在接受一线治疗之前（如果临床可行）应进行PD-L1表达的免疫组织化学检测，以评估是否可选择ICI方案[4]。多项前瞻性临床试验证明了PD-L1表达与免疫治疗疗效的相关性。基于Keynote 024和Keynote 010研究，帕博利珠单抗被批准用于PD-L1≥50%的NSCLC患者的一线治疗和PD-L1≥1% NSCLC患者的二线治疗。IMpower110和EMPOWER-Lung 1研究也获得了相似的结果。值得注意的是，一部分PD-L1表达阴性的患者也能从免疫治疗中获益[50,53]。随着免疫联合治疗策略的出现，PD-L1的预测价值有所降低。多项临床研究的亚组分析显示，无论PD-L1表达状态如何，晚期NSCLC患者均能从一线免疫联合治疗中获益。PD-L1作为生物标志物的不完美之处可归因于多种因素：PD-L1表达具有异质性，在肿瘤内部存在差异，在同一肿瘤样本的切片中也可能不一致，甚至会随着治疗而发生变化；其次，不同的检测方法和结果判读存在差异，需要标准化。尽管PD-L1并非完美的生物标志物，但目前PD-L1表达是评估患者是否适合接受PD-1/PD-L1抑制剂的最佳可用生物标志物，仍具有重要的指导意义。

TMB是指特定基因组区域内每兆碱基中发生的体细胞非同义突变的个数，反映了新抗原负荷，是癌症免疫原性的替代物。TMB作为NSCLC免疫相关生物标志物的证据主要来自于对临床试验的亚组分析。在CheckMate 227研究中[42]，无论PD-L1表达如何，在高TMB（每兆碱基≥10个突变）的NSCLC患者中，一线纳武利尤单抗联合伊匹木单抗的PFS明显优于化疗。但是长期随访数据显示，TMB水平与OS无关。此外，将TMB与PD-L1表达水平相结合也不能预测总生存期。目前，仍然缺乏支持使用TMB作为免疫生物标志物的充足临床数据，许多研究结果相互矛盾，TMB测量也难以量化和标准化。因此，这种诊断预测方法暂未获得批准，NCCN指南也不建议测量TMB水平以进行免疫治疗决策。

近年来，在NSCLC免疫疗效预测生物标志物的探索中，基于液体活检的新兴血基生物标志物备受关注，包括循环游离肿瘤DNA（ctDNA）、循环非编码RNA（microRNA）和外周血免疫细胞亚群等。同时，肿瘤免疫微环境、表观遗传特征和肠道微生物也是热点方向[57]。

4.2　免疫治疗模式的优化

免疫治疗已经改变了晚期NSCLC的治疗格局，单药和联合用药策略都显示出良好的抗肿瘤活性和可控的不良反应。目前还没有充分的循证医学证据来确定最佳的免疫治疗策略，也缺乏免疫联合不同化疗剂量（标准*vs.*减量）之间的头对头比较研究，免疫单药和免疫联合疗法的择优选择及药物使用剂量的优化还有待未来大型Ⅲ期随机对照临床研究的证实。同时，明确免疫治疗耐药机制和探索免疫治疗耐药后的治疗方案也是亟待解决的临床问题。

鉴于化疗严重的不良反应，在晚期NSCLC中也开启了仅运用免疫联合抗血管生成药物治疗、“去化疗”的模式探索。多项Ⅰ/Ⅱ期临床研究结果显示，阿替利珠单抗联合贝伐珠单抗[58]、帕博利珠单抗联合雷莫芦单抗[59]、信迪利单抗联合安罗替尼[60-61]、卡瑞利珠单抗联合阿帕替尼[62]等方案在晚期NSCLC一线治疗中展现出良好的抗肿瘤活性。但帕博利珠单抗联合仑伐替尼在晚期NSCLC一线/二线治疗中的研究均以失败告终，LEAP-006[63]和LEAP-008研究[64]均未达到PFS和OS双主要研究终点。免疫联合抗血管生成治疗方案还有待进一步大型Ⅲ期随机对照临床研究的证实。

此外，一系列新兴肿瘤免疫疗法正在研发中，将成为未来免疫治疗药物研究的重要方向。包括TIGIT、LAG-3、T淋巴细胞免疫球蛋白黏蛋白-3（TIM-3）、V域免疫球蛋白T细胞活化抑制因子（VISTA）等新型免疫检查点抑制剂，双/三特异性抗体、嵌合抗原受体T细胞（CAR-T）疗法、肿瘤疫苗等[65-66]。

4.3　免疫相关不良反应的管理

虽然免疫治疗相较于化疗的不良反应轻微，但它可能导致的免疫相关不良事件（immune-related adverse events, irAEs）不容忽视。irAEs可累及全身多器官，最常见的有皮肤毒性、内分泌毒性、胃肠毒性、免疫相关性肺炎等，临床症状往往缺乏特异性，早期识别困难。虽然3级以上irAEs的发生率较低，但一旦发生进展快，可能导致患者死亡。类固

醇激素是治疗irAEs的一线药物，治疗irAEs的短期小剂量用药不会影响ICIs的疗效，但长期或大剂量的使用可能导致不良预后，早期识别、分级管理和恰当处理irAEs至关重要[67]。同时，探索能预测irAEs的生物标志物也是未来发展方向。

4.4 特殊人群的免疫治疗

在精准治疗时代，老年人群、驱动基因阳性人群等特殊人群的免疫治疗选择也是有待明确的问题。多项大型Ⅲ期临床研究的亚组分析显示，不论一线还是二线免疫治疗，≥65岁老年人群的免疫治疗获益与整体人群基本一致[68]。但对于≥75岁的老年患者，免疫治疗的选择还缺乏足够的数据支持。2023 ASCO年会上NEJ057研究结果显示[69]，对于75岁以上PD-L1表达阳性且驱动基因阴性的晚期NSCLC老年患者，推荐优先使用免疫单药。而对于≥80岁老年群体，一项回顾性研究[70]结果显示该群体免疫治疗的PFS和OS均未获益，提示80岁以上患者在化疗和免疫治疗的选择上需更加慎重对待。其次，针对EGFR-TKIs耐药后特殊人群的免疫治疗，CheckMate-722[71]和KEYNOTE-789[72]研究结果显示，免疫联合化疗方案的PFS和OS均无获益。IMpower150[40]和ORIENT-31研究[73]结果则显示，EGFR-TKIs耐药的NSCLC患者可以从免疫联合化疗和抗血管生成治疗四药联合方案中获益。

5 总结与展望

免疫治疗已经改变了晚期NSCLC治疗的格局，但也面临很多挑战。应进一步开发新型免疫治疗，探索更优的免疫治疗组合方案，优化药物使用剂量、给药时间及特殊人群管理。同时，也应继续寻找最佳的预测ICI疗效和irAEs的生物标志物，通过构建综合预测和动态监测模型，以期实现个体化的精准免疫治疗。而阐明免疫耐药机制并探索克服策略也是未来研究的方向。未来，精准免疫治疗将造福更多的晚期NSCLC患者。

利益冲突声明：

所有作者均声明不存在利益冲突。

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