肝细胞癌免疫治疗临床研究进展

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摘 要： 原发性肝癌是中国癌症第2大死因，其中肝细胞癌占80%～90%，各种治疗方法疗效欠佳，总体生存期较短。以免疫检查点抑制剂为核心的免疫治疗在肝细胞癌临床研究中表现出较好疗效，并获得相关指南支持。对于晚期肝细胞癌，免疫检查点抑制剂可单药或双药联用，可联合血管内皮生长因子抑制剂或酪氨酸激酶抑制剂。对早期和中期肝癌，免疫检查点抑制剂可联合局部治疗。此外，免疫细胞治疗也逐渐进入临床试验阶段。就肝细胞癌免疫治疗临床研究的最新进展进行综述，以期为临床应用和深入研究提供参考。

关键词： 肝细胞癌；免疫治疗；免疫检查点抑制剂；免疫细胞治疗；临床研究

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Recent progress in immunotherapy of hepatocellular carcinoma

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Abstract: Primary liver cancer is the second leading cause of cancer death in China, of which hepatocellular carcinoma (HCC) accounts for 80%—90%. The therapeutic response of HCC is limited, with relatively disappointing overall survival. Immunotherapies, especially immune checkpoint inhibitors (ICI) have shown promising results in the systematic treatment of advanced or unresectable HCC with support by several guidelines. For advanced HCC, ICI can be used alone or in combination with another ICI, vascular endothelial growth factor inhibitors or tyrosine kinase inhibitors. For early- and middle-staged HCC, ICI could work with local-regional treatment. In addition, clinical trials evaluating the efficacy and safety of immune cell therapy are conducted. In this review, we summarized the latest progress of immunotherapy for HCC in order to provide some references for clinical application and further research.

Key words: hepatocellular carcinoma; immunotherapy; immune checkpoint inhibitor; immune cell therapy; clinical study

原发性肝癌为威胁国民健康的重大疾病之一，是中国癌症第2大死因，2020年全球有83万人死于肝癌，我国约占1/2[1-2]。原发性肝癌分为肝细胞癌（HCC）及肝内胆管癌，HCC占80%～90%[3]，其起病隐匿，许多患者确诊时错失手术机会，而晚期HCC全身治疗效果有限，预后较差[4-5]。以索拉非尼为代表的酪氨酸激酶抑制剂（TKI）可一定程度延长部分患者生存期，但全身治疗仍面临诸多挑战[6]。

随着程序性死亡受体1（PD-1）和细胞毒性T淋巴细胞相关蛋白4（CTLA4）抑制剂临床研究结果揭晓，免疫检查点抑制剂（ICI）为主的免疫治疗在多癌种中表现出令人鼓舞的疗效。作为人体关键的免疫器官，肝脏在维持机体免疫耐受中发挥重要作用[7]。早期HCC免疫治疗的临床效果欠佳，但随着研究不断深入和更新，新的ICI和联合用药给患者带来生存获益，为HCC的系统治疗带来新的可能。

本文综合近5年文献及2022年美国临床肿瘤

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学会（ASCO）年会研究报告[8]，就HCC免疫治疗最新进展及治疗策略进行综述，以期为临床研究与决策提供参考。

1 ICI单药治疗进展

HCC具有高度异质性，免疫微环境复杂，ICI单药通常效果不佳，多为中晚期HCC的2线治疗方案，以PD-1/PD-L1及CTLA-4为靶点[9-10]。美国食品药品监督管理局（FDA）和国家药品监督管理局（NMPA）批准的主要免疫治疗药物名称及适应症整理于表1。

目前，中国临床肿瘤学会（CSCO）免疫检查点抑制剂临床应用指南（2022版）[11]、原发性肝癌诊疗指南（2022年版）[12]及肝细胞癌免疫治疗中国专家共识（2021版）[13]推荐帕博利珠单抗、卡瑞利珠单抗和替雷利珠单抗为二线方案。

在所有ICI单药中，帕博利珠单抗对于晚期未进行过治疗的HCC患者II期临床获得了同类药物最高的18.3%的客观缓解率（ORR）[14-15]和17个月中位生存期（mOS）[16]（表2）。但该药之前作为二线用药的III期临床未达到预期的结局指标[36]（表3）。为便于比较，将I/II期及III期临床研究结果的ORR、mOS、治疗相关不良事件（TRAE）、严重不良事件（SAE）、风险比（HR）等数据分别整理于表2[14-35]、3[36-41]。

后续研究显示帕博利珠单抗对亚洲人群疗效更优（ORR为20.6%、mOS为13.8个月）[37,42]，据此被推荐为晚期HCC二线治疗（表4）。CSCO诊疗指南证据类别与推荐等级分I级推荐、II级推荐、III级推荐、1A类证据、2A类证据、2B类证据、2B类证据。I级推荐：适应症明确、可及性好、肿瘤治疗价值稳定，纳入医保的诊治措施；II级推荐：具有高级别证据，但可及性差或效价比不高；III级推荐：循证证据不足，但专家组认为可以接受。1A类证据：大型随机对照研究；2A类证据：小型随机对照研究、病例对照研究，专家一致共识；2B类证据：小型随机对照研究、病例对照研究，专家基本一致共识。原发性肝癌诊疗指南证据类别与推荐等级：A为绝大多数目标用户均应采纳该推荐意见；B为多数目标用户会采纳该推荐意见，执行过程中应注意考虑医患共同决策[11]。

卡瑞利珠单抗在II期临床中对进展后继续用药的患者疗效尚佳（mOS为16.9个月）[17-18]，尽管反应性皮肤毛细血管内皮增生发生率较高（66.8%），但这可能与良好预后相关[43]。替雷利珠单抗与卡瑞利珠单抗疗效相近[19]，不良事件的发生率更低[20]（表2），现正开展挑战一线适应症的临床研究[44]。纳武利尤单抗II期临床结果尚可[21,45]，包括在亚裔人群中[46]，但III期临床失败，导致其HCC适应症被撤回[38]（表2、3）。对不同的药物在CSCO免疫检查点抑制剂临床应用指南（2022版）[11]、原发性肝癌诊疗指南（2022年版）[12]、肝细胞癌免疫治疗中国专家共识（2021版）[13]中的证据等级对比见表4。

表1 获批上市及临床试验中的主要ICIs

Table 1 ICIs approved or in clinical trails

	ICIs	商品名	授权方	靶点	适应症
已上市	纳武利尤单抗(Nivolumab)	Opdyta	FDA	PD-1	联合伊匹木单抗用于曾接受索拉非尼治疗的患者
	帕博利珠单抗(Pembrolizumab)	Keytruda	FDA	PD-1	用于曾接受索拉非尼治疗的患者
	卡瑞利珠单抗(Camrelizumab)	艾瑞卡	NMPA	PD-1	既往接受过索拉非尼治疗和(或)含奥沙利铂系统化疗的晚期肝细胞癌患者的治疗
	阿替利珠单抗(Atezolizumab)	Tecentriq	FDA	PD-L1	联合贝伐珠单抗用于无法手术切除的HCC的一线治疗
	信迪利单抗(Sintilimab)	达伯舒	NMPA	PD-1	联合贝伐珠单抗,用于既往未接受过系统治疗的不可切除或转移性肝细胞癌的一线治疗
	替雷利珠单抗(Tislelizumab)	百泽安	NMPA	PD-1	至少经过一种全身治疗的肝细胞癌(HCC)的治疗
	伊匹木单抗(Ipilimumab)	Yervoy	FDA	CTLA-4	联合纳武利尤单抗用于索拉非尼后二线治疗
临床试验中	度伐利尤单抗(Durvalumab)	Imfinzi		PD-1	联合曲美木单抗用于晚期HCC一线治疗
	曲美木单抗(Tremelimumab)			CTLA-4	单药或联合度伐利尤单抗用于晚期HCC
	特瑞普利单抗(Toripalimab)	拓益		PD-1	用于肝癌根治术后的辅助治疗
	IBI310			CTLA-4	联合信迪利单抗用于晚期HCC一线治疗
	Relatlimab			LAG-3	联合纳武利尤单抗用于HCC二线治疗
	Ociperlimab			TIGIT	联合替雷利珠单抗用于HCC二线治疗

表2 HCC免疫治疗I/II期临床研究的结果比较

Table 2 Comparison of results of phase I/II clinical trails in HCC immunotherapy

治疗方案	试验名称	注册号	研究阶段	ORR/%	mOS/个月	3级以上TRAE/%	SAE/%
ICI单药							
帕博利珠单抗（*n*=104）[14-16]	KEYNOTE-224	NCT02702414	II期	18.30	17.0	25.00	15.00
卡瑞利珠单抗（*n*=217）[17-18]		NCT02989922	II期	14.70	14.2	22.00	11.00
替雷利珠单抗（*n*=249）[19-20]	RATIONALE 208	NCT03419897	II期	13.60	13.5	13.60	6.40
纳武利尤单抗（*n*=145）[21]	Checkmate 040	NCT01658878	I/II期	14.00	15.6	19.00	4.00
曲美木单抗（*n*=21）[22]		NCT02519348	II期	17.60	8.2	不详	不详
ICI双药							
纳武利尤单抗+伊匹木单抗（*n*=50）[23]	Checkmate 040	NCT01658878	I/II期	32.00	22.8	53.00	不详
度伐利尤单抗+曲美木单抗（*n*=75）[24]		NCT02519348	II期	24.00	18.7	28.00	17.60
信迪利单抗+IBI310（*n*=29）[25]		NCT04401813	I期	17.20	未达到	34.50	不详
ICI+VEGF抑制剂							
阿替利珠单抗+贝伐珠单抗（*n*=104）[26-27]		NCT02715531	I期	36.00	17.1	39.00	24.00
信迪利单抗+IBI305（*n*=50）[28]		NCT04072679	I期	33.30	未达到	12.00	不详
ICI+TKI							
帕博利珠单抗+仑伐替尼[29]	KEYNOTE-524	NCT03006926	I期	36.00	22.0	67.00	36.00
卡瑞利珠单抗+阿帕替尼（*n*=16）[30]		NCT02942329	I期	50.00	未达到	不详	不详
卡瑞利珠单抗+阿帕替尼（*n*=70，1线）[31-32]	RESCUE	NCT03463876	II期	34.30	20.1	77.40	不详
卡瑞利珠单抗+阿帕替尼（*n*=120，2线）[31-32]				23.80	21.8		
ICI+局部治疗							
纳武利尤单抗+TACE（*n*=49）[33]	IMMUTACE	NCT03572582	II期	71.40	28.3	34.70	
纳武利尤单抗+Y90（*n*=36）[34]	CA 209-678	NCT03033446	II期	30.60	未达到	6.00	14.00
帕博利珠单抗+Y90（*n*=26）[35]		NCT03099564	I期	27.00	22	不详	不详

表3 HCC免疫治疗III期临床研究的结果比较

Table 3 Comparison of results of phase III clinical trails in HCC immunotherapy

	试验组	对照组	mOS/个月	HR（95%CI）	*P*	SAE/%
帕博利珠单抗[36]	KEYNOTE 240	安慰剂	13.9 *vs* 10.6	0.781（0.611，0.998）	0.023 8	不详
帕博利珠单抗[37]	KEYNOTE 394	安慰剂	14.6 *vs* 13.0	0.79（0.63，0.99）	0.018	不详
纳武利尤单抗[38]	Checkmate 459	索拉非尼	16.4 *vs* 14.7	0.85（0.72，1.02）	0.075	12 *vs* 11
度伐利尤单抗+曲美木单抗[39]	HIMALAYA	索拉非尼	16.4 *vs* 13.8	0.78（0.65，0.92）	0.003 5	17.5 *vs* 9.4
阿替利珠单抗+贝伐珠单抗[40]	IMbrave150	索拉非尼	19.2 *vs* 13.4	0.66（0.52，0.85）	0.000 9	38 *vs* 30
信迪利单抗+IBI305[41]	ORIENT-32	索拉非尼	NR *vs* 10.4	0.57（0.43，0.75）	<0.000 1	32 *vs* 19

2 ICIs联合治疗进展

2.1 ICIs双药联合方案

目前主要的双药组合为PD-1联合CTLA-4抑制剂，也有研究聚焦于LAG-3、TIGIT等。纳武利尤单抗联合伊匹木单抗（O＋Y组合）是目前唯一获批的ICI双药联合，II期研究取得较好结果（ORR为32%、OS为22.8个月）[21]，尤其对于甲胎蛋白（AFP）＜400 ng·mL^{-1}的患者，mOS可达46.1个月[23]。度伐利尤单抗联合曲美木单抗[22]（T＋D组合），具有比O＋Y组合更好的耐受性[24]，III期临床证实，T＋D组合能够改善患者生存期（表3）[39]，提高生活质量[47]，且安全性良好[48]。国产双免组合信迪利单抗联合IBI310已进入III期临床[25]，其他值得期待的临床研究均总结于表5，可关注后续结果。

2.2 联合血管内皮生长因子抑制剂

抗血管生成是肝癌治疗的重要靶点[49-50]。阿替利珠单抗联合贝伐珠单抗（T＋A组合）在I期临床取得36%的ORR[26-27]，且III期临床疗效明显优于索拉

表 4 不同药物方案在指南中的对比

Table 4 Comparison of different drug regimens in guidelines

治疗方案	CSCO免疫检查点抑制剂临床应用指南(2022版)	原发性肝癌诊疗指南(2022年版)	肝细胞癌免疫治疗中国专家共识(2021版)
ICI单药			
帕博利珠单抗	二线策略(I级推荐,2A类证据)	未提及	中晚期HCC 二线治疗
卡瑞利珠单抗		二线治疗(证据等级3,推荐B)	
替雷利珠单抗			
纳武利尤单抗	未提及	未提及	中晚期HCC一线治疗(抗血管生成存在禁忌时)中晚期HCC二线治疗
ICI双药			
纳武利尤单抗+伊匹木单抗(O+Y组合)	二线策略(III级推荐,2A类证据)	二线治疗(证据等级3,推荐B)	中晚期HCC 二线治疗
度伐利尤单抗+曲美木单抗(T+D组合)	一线策略(I级推荐,1A类证据)	其他一线治疗	未提及
ICI联合VEGF抑制剂			
阿替利珠单抗+贝伐珠单抗(T+A组合)	一线策略(I级推荐,1A类证据)	一线治疗(证据等级1,推荐A)	中晚期HCC 一线治疗
信迪利单抗+IBI305(“双达”组合)			中晚期HCC 一线治疗
ICI联合TKI			
卡瑞利珠单抗+阿帕替尼(“双艾”组合)	一线策略(II级推荐,2A类证据)	其他一线治疗	中晚期HCC 一线及二线治疗
帕博利珠单抗+仑伐替尼(“可乐”组合)	一线策略(III级推荐,2B类证据)	其他一线治疗	中晚期HCC 一线治疗

表 5 其他进行中的ICIs治疗肝癌的研究

Table 5 Other ongoing clinical trails on treatment of HCC with ICIs

	合并用药	适应症	研究名	注册号	研究阶段
阿替利珠单抗	贝伐珠单抗	术后辅助治疗	IMbrave050	NCT04102098	II期
	贝伐珠单抗	新辅助治疗		NCT05137899	II期
	贝伐珠单抗	联合TACE	TALENTACE	NCT04712643	III期
	贝伐珠单抗	联合Y90放射栓塞		NCT05377034	II期
	索拉非尼/仑伐替尼	A+T组合治疗后的晚期HCC		NCT04770896	III期
度伐利尤单抗	曲美木单抗	联合TACE或Y90放射栓塞		NCT04522544	II期
卡瑞利珠单抗	阿帕替尼	晚期HCC 一线治疗	SHR-1210-III-310	NCT03764293	III期
纳武利尤单抗	伊匹木单抗	新辅助治疗	PRIME-HCC	NCT03682276	I期
	伊匹木单抗	联合TACE	Checkmate 74W	NCT04340193	III期
	单药	术后或射频消融术后的辅助治疗	Checkmate 9DX	NCT03383458	III期
帕博利珠单抗	单药	术后或射频消融术后的辅助治疗	KEYNOTE-937	NCT03867084	III期
	阿帕替尼	术后辅助治疗		CTR20202509	不详
	仑伐替尼	晚期HCC 一线治疗	LEAP 002	NCT03713593	III期
	仑伐替尼	A+T组合治疗后的晚期HCC		NCT05101629	II期
	仑伐替尼	新辅助治疗		NCT05185739	II期
	仑伐替尼	联合TACE	LEAP-012	NCT04246177	III期
	瑞戈非尼	免疫治疗无效或进展的晚期HCC		NCT04696055	II期
特瑞普利单抗	单药	术后辅助治疗	JUPITER 04	NCT03859128	II/III期
	贝伐珠单抗	晚期HCC		NCT04723004	III期
替雷利珠单抗	仑伐替尼	晚期HCC 一线治疗		CTR20200972	II期
信迪利单抗	IBI310	晚期HCC 一线治疗		NCT04720716	III期

非尼[40]，长期随访的mOS达到19.2个月，中国亚组疗效更佳（mOS为24.0个月）[51]。信迪利单抗（达伯舒）联合贝伐珠单抗类似物IBI305（达攸同）又称“双达”组合，I期结果与T＋A组合相近，但耐受更好[28]，II/III期临床试验结果同样优于索拉非尼[41]。目前，T＋A组合和双达组合已被推荐为中晚期HCC的一线治疗。此外，国产PD-1单抗特瑞普利单抗联合贝伐珠单抗的III期临床试验也已启动值得关注。

2.3 联合酪氨酸激酶抑制剂

仑伐替尼是一款多靶点TKI，临床前研究显示，仑伐替尼能够降低肿瘤PD-L1水平，提高抗PD-1疗效[52-53]。在I期临床中，帕博利珠单抗（可瑞达）联合仑伐替尼（乐卫玛）的“可乐”组合表现出较好疗效（ORR为36%、mOS为22个月，见表2）[29]。目前，评价“可乐”组合作为一线治疗的III期临床正在开展[54-55]，有望进一步扩大适应症。卡瑞利珠单抗（艾瑞卡）联合阿帕替尼（艾坦）的“双艾”组合在I期临床中获得了50%的ORR[30]；II期临床显示其作为一、二线治疗均有较好疗效[31-32]（表2）。目前，该组合的III期临床已达研究终点，结果尚未披露。此外，纳武利尤单抗联合仑伐替尼[56]及其他不同组合的多项研究正在进行中。

2.4 联合局部治疗

除中晚期HCC的系统性治疗外，免疫治疗也逐渐应用于HCC早中期。对可手术的患者可作为辅助或新辅助治疗，以减少复发。NIVOLVE研究证实，纳武利尤单抗作为术后或射频消融术后的辅助治疗可使1年无复发生存率提高至78.6%，且耐受性较好[57-58]。目前，纳武利尤单抗[59]、帕博利珠单抗[60]、特瑞普利单抗等单药方案作为辅助或新辅助治疗的研究均已进入III期临床（表5）。此外，T＋A组合[61]、O＋Y组合[62]在辅助或新辅助治疗中的探索也已开展。

对中期HCC，以TACE为主的介入治疗通常是第一选择[63-64]，而免疫治疗同样能起到协同增效的作用。纳武利尤单抗联合TACE在II期临床中取得较好疗效（ORR为71.4%、mOS为7.2个月）[33]；而O＋Y组合[65]、T＋A组合[66]和“可乐”组合[67]联合TACE的研究均进入III期临床。除传统的TACE术式外，钇-90（Y90）放射栓塞也是中期HCC的可选治疗[68]。纳武利尤单抗、帕博利珠单抗与Y90联合治疗的可行性均已在II期临床试验中得到验证[34-35]。

3 免疫细胞治疗进展

免疫细胞治疗，又称过继性免疫细胞治疗，是免疫治疗的重要领域之一，主要包括嵌合抗原受体T细胞（CAR-T）、T细胞受体（TCR）、工程T细胞（TCR-T）、肿瘤浸润淋巴细胞（TILs）等。但其应用在实体瘤治疗中尚处早期[69]。其中CAR-T和TCR-T前景较好[70-71]。

3.1 CAR-T治疗

CAR-T的原理是通过细胞工程在T细胞表面表达可识别肿瘤抗原并激活T细胞的嵌合抗原受体，使T细胞发挥识别并杀伤肿瘤细胞的作用。目前，多项基础研究已证实CAR-T对肝癌的作用[72-73]。相关的临床研究已在晚期、经治的HCC患者中开展，mOS为9～12个月[74-75]。然而，肝癌的异质性使得能作为CAR-T靶标的肿瘤抗原较少。其次，肿瘤内部的抑制性免疫微环境可能阻碍CAR-T功能[76]，肝脏的免疫耐受性则使情况尤为复杂，通过基因编辑敲除CAR-T中的PD1或CTLA-4[77-78]有望突破这一瓶颈，然而CAR-T的安全和耐受性仍是其应用于临床最需解决的问题。

3.2 TCR-T

不同于CAR-T细胞，TCR-T识别的是MHC的抗原肽，这使得TCR-T在乙型肝炎病毒（HBV）感染相关的HCC中更有优势[79]。由于HBV的基因片段在慢性感染期间整合进入肝细胞的染色体中[80]，因此工程化的TCR能够靶向HCC细胞中的HBV抗原已得到基础研究的证实[81-82]。临床研究显示TCR-T能够缩小人HCC的肺转移灶[83]。另1项研究显示，HCC肝移植患者的免疫抑制治疗不影响TCR-T的活性[84]，这意味着TCR-T有可能在HCC治疗中发挥更大作用。

3.3 TILs治疗

TILs是肿瘤中浸润的多种淋巴细胞的统称，其中部分细胞亚群具有抗肿瘤活性，但在体内受调节性T细胞（Treg）等抑制[85]。TILs治疗通常是从肿瘤样本中分离TILs，在体外进行激活和扩增，最后回输体内进行治疗。临床前研究显示寡克隆TILs具有较高的抗肿瘤活性，且与Treg比例呈负相关[86]；1项I期临床研究提示，活化和扩增的自体TILs在HCC患者中可能取得不错的治疗效果[87]。总体上来说，TILs治疗在HCC中研究较少，这可能与肝癌较低的免疫原性和抑制性免疫微环境相关。

3.4 其他免疫细胞治疗

除T细胞外，自然杀伤细胞（NK）和树突状细

胞（DC）也是免疫细胞治疗的研究热点[88]。与T细胞类似，NK细胞同样可以通过CAR激活，有个案报告了CAR-NK对HCC的疗效，患者在接受了17个疗程的治疗后，生存期达到了4年以上[89]。与CAR-T比较，CAR-NK的优势在于安全性较好，特别是细胞因子释放综合征发生率较低，但现有研究还不够深入。

DC细胞治疗的特殊性在于其主要是通过向DC细胞加载肿瘤抗原，刺激抗原呈递而间接发挥抗肿瘤作用，因此又被称为“DC肿瘤疫苗”[90]。现有的几项临床研究证实DC肿瘤疫苗的疗效和安全性，晚期HCC患者中的mOS为7～13个月[91-93]。目前，DC细胞治疗的短板在于DC细胞的自然丰度低、离体增殖能力差。此外，如何选择最佳的肿瘤抗原、高效地激活T细胞，也是后续要解决的问题[94]。

4 结语

随着免疫治疗在肝细胞癌中逐步开展，HCC系统治疗迎来了重大变革。免疫治疗策略由单药过渡到多药联合，以“T＋A”为代表的联合方案，和以“可乐组合”为代表的靶向免疫方案，均表现出较好的生存获益，为晚期HCC患者带来希望。在多学科联合的趋势下，特别是内科与外科联合治疗的策略下，免疫治疗的发展空间将更为广阔。从晚期HCC的2、3线治疗，到中期HCC联合血管介入治疗，再到早期HCC进行术后辅助治疗或术前新辅助治疗，免疫治疗将有更广阔的应用前景。在药物研发方面，开发不同的免疫检查点，或通过不同组合多靶点治疗，都是未来的研究方向。

HCC的免疫治疗也仍有诸多问题亟待解决。由于肝癌在病因学上的复杂性，是否合并肝炎病毒感染、是否合并代谢性肝病等，都会造成HCC免疫微环境的改变，从而影响免疫治疗的效果[95-96]。因此，针对患者的分层分析及精准用药是将来HCC免疫治疗研究的重点和难点。在基础研究中，对不同类型肝癌免疫细胞亚群和微环境的深入认识，进行相关生物标志物的研发，将为临床优势人群的确立提供帮助。在新药研发中，减少同质化和重复研发，充分利用祖国医学资源宝库，基础与临床研究相结合，才能让国内科研工作者领跑在免疫治疗的赛道上。

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