doi:10.3971/j.issn.1000-8578.2023.23.0901

• 特约来稿 •

恶性淋巴瘤的分子诊断及个体化治疗研究进展

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Research Progress on Molecular Diagnosis and Individualized Treatment for Malignant Lymphoma

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Abstract: Lymphoma refers to a group of heterogeneous malignancies originating from the reticuloendothelial and lymphatic systems. The clinical manifestations, treatment strategies, and disease outcomes of different types of lymphoma considerably vary. Recent developments in high-throughput sequencing technologies have enhanced understanding of the pathogenesis and molecular stratification of lymphoma. In the era of new drugs, precise stratification and targeted drug selection can not only improve the prognosis of patients with lymphoma but also reduce the toxic side effects of traditional chemotherapy, ultimately achieving the accurate diagnosis and individualized treatment of tumors. This article reviews the research progress of molecular diagnosis and individualized treatment of different lymphoma subtypes and lymphoma-related research in important meetings such as ASCO, EHA, and ICML in 2023.

Key words: Malignant lymphoma; Molecular diagnosis; Personalized medicine; Research progress

Funding: Tianjin Key Medical Discipline (Specialty) Construction Project (No. TJYXZDXK-009A)

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

收稿日期：2023-08-23；**修回日期**：2023-09-18

基金项目：天津市医学重点学科（专科）建设项目（TJYXZDXK-009A）

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摘　要：淋巴瘤是起源于人体淋巴造血系统的一组异质性恶性肿瘤，不同类型淋巴瘤在临床表现、治疗策略和疾病转归方面存在较大差异。近年来，高通量测序等新技术的快速发展大大推动了淋巴瘤的分子诊断和发病机制等方面的研究进展。在新药时代，通过精准分层有的放矢地选择靶向药物，不但能够改善淋巴瘤患者的预后，而且可以减少传统化疗的不良反应，并最终实现肿瘤的个体化精准治疗，从而使更多患者受益。本文就近期不同淋巴瘤亚型的分子诊断及个体化治疗的研究进展以及2023年ASCO、EHA、ICML等重要会议中淋巴瘤相关的研究作一综述。

关键词：淋巴瘤；分子诊断；个体化治疗；研究进展
中图分类号：R733
开放科学(资源服务)标识码(OSID)：

0　引言

淋巴瘤是一组起源于B细胞、T细胞或自然杀伤（NK）细胞的异质性恶性肿瘤，分为霍奇金淋巴瘤（hodgkin lymphoma, HL）和非霍奇金淋巴瘤（non-Hodgkin lymphoma, NHL），其中弥漫大B细胞淋巴瘤（diffuse large B cell lymphoma, DLBCL）是最常见的淋巴瘤亚型。传统放化疗仅对部分淋巴瘤患者有效，且不良反应大，部分患者表现为短期内肿瘤进展或原发耐药，主要原因可能是淋巴瘤在临床、分子遗传学及肿瘤微环境等方面具有高度异质性。目前，基于其预后和分子机制的精准分层治疗被认为是突破这些高危难治患者治疗瓶颈的重要方向。

1　霍奇金淋巴瘤

霍奇金淋巴瘤分为经典型霍奇金淋巴瘤（classical Hodgkin lymphoma, cHL）和结节性淋巴细胞为主型霍奇金淋巴瘤。cHL占所有HL的95%，分为结节性硬化型、混合细胞型、淋巴细胞削减型和富于淋巴细胞型[1]，目前认为cHL肿瘤细胞（Hodgkin Reed-Sternberg, HRS）来源于生发中心B细胞，具有与CD30+滤泡外B细胞相似的基因表达，缺乏CD19和CD79α等标志物，多数病例有染色体9p24.1拷贝数变异和基因改变，以及通路异常，如JAK-STAT通路和NF-κB通路[2]。

目前，早期HL标准治疗模式仍以短疗程化疗联合放疗为主[3]。多项研究提示不管是维布妥昔单抗（BV）[4]、纳武利尤单抗（nivolumab）[5]还是帕博利珠单抗（pembrolizumab）[6]，联合AVD方案（阿霉素、长春碱和达卡巴嗪）治疗早期HL，尤其是对预后不良组患者，均显示出较高的缓解率和生存获益。短疗程ABVD方案（阿霉素、博莱霉素、长春碱和达卡巴嗪）化疗后行BV巩固治疗，可以减少化疗次数和放疗，减少不良反应[4-5,7]。但这些方案能否成为早期HL的一线新选择，尚需进一步探索。晚期HL的治疗策略为长疗程化疗。2022年美国临床肿瘤学会（ASCO）更新了ECHELON-1试验6年随访数据，再次证实BV+AVD较ABVD方案在晚期cHL患者中的优效性和安全性[8]。2023年ASCO公布的SWOG S1826研究[9]对比了nivolumab或BV与化疗联合（N-AVD *vs.* BV-AVD）治疗晚期cHL的临床疗效，结果显示，采用nivolumab与化疗联合方案的患者无进展生存期（progression-free survival, PFS）更低，患者耐受程度更好。在随后的2023年第十七届国际淋巴瘤大会（ICML）上，德国霍奇金淋巴瘤研究组（GHSG）更新了HD21Ⅲ期研究结果，2个周期化疗后按PET分层接受4或6周期BrECADD方案（维布妥昔单抗、依托泊苷、环磷酰胺、多柔比星、达卡巴嗪和地塞米松）治疗，3年PFS达到94.9%，非劣效于对照组eBEACOPP方案（博来霉素、依托泊苷、多柔比星、环磷酰胺、长春新碱、丙卡巴肼和泼尼松），且治疗相关毒性更低，进一步证实了该方案是目前晚期cHL成年患者有效的治疗方案之一。此外，nivolumab单药2周期后联合AVD方案一线治疗晚期cHL也显示出良好的疗效和安全性[10]。与之类似的还有今年在ICML亮相的替雷利珠单抗+AVD方案一线治疗高危ⅡB及晚期cHL的研究，该研究证实PD-1序贯AVD方案显示了良好的潜力，在部分晚期cHL患者中实现了去化疗[11]。对于老年体弱不适合标准化疗的患者，可以给予BV或PD-1单药治疗或序贯化疗，或BV联合PD-1（程序性死亡受体-1）治疗[12-13]。

大多数cHL可以通过化疗或化疗联合放疗达到治愈，但仍有10%早期和30%晚期患者一线治疗后出现复发或一线治疗失败后发生难治性疾病[14]，这部分患者预后较差，大剂量化疗（high dose chemotherapy, HDC）联合自体造血干细胞移植（autologous stem cell transplantation, ASCT）目前仍然是这部分患者的标准治疗选择。为了预防或延缓移植后病情进展，尤其是伴不良风险因素的患者，一些研究[15-16]提示在ASCT后患者接受BV或PD-1进行巩固治疗，可以改善PFS。ASCT后复发的患者预后很差，但随着BV和PD-1单抗的应用，其预后得到了一定程度的改善[17-18]。在BV治疗ASCT后失败HL患者的关键Ⅱ期研究中[17]，3/4的患者可获得临床缓解，其中完全缓解（CR）达1/3。Kuruvilla等[19]比较了pembrolizumab

对比BV治疗复发难治性cHL的疗效，与BV相比，pembrolizumab治疗组的PFS得到显著改善，从而支持PD-1单抗作为ASCT后复发或不适合ASCT患者的首选方案。而对于PD-1/PD-L1耐药之后如何选择，在今年欧洲血液学协会（EHA）大会上，来自信达生物的一项CD47/PD-L1双特异性抗体（IBI322）治疗PD-1或PD-L1耐药的cHL研究[20]显示，IBI322治疗组的ORR可达47.8%，显示出较好的治疗前景。

其他有前景的疗法包括嵌合抗原受体T细胞疗法（chimeric antigen receptor T-cell therapy, CAR-T）和新型抗体偶联药物（antibody-drug conjugates, ADC）等。此外，过度激活的JAK-STAT通路也是常见的靶点之一，ITF2357可以杀死JAK2突变的细胞（V617F）[21]，idelalisib和everolimus可以阻断JAK下游的PI3K/AKT通路[22]。目前针对这些通路异常激活所涉及的靶向治疗是该领域重要的研究方向。

2 弥漫性大B细胞淋巴瘤

弥漫性大B细胞淋巴瘤是恶性淋巴瘤最常见的类型，其在分子遗传学、免疫表型等方面具有高度异质性，患者的临床预后也截然不同[23]。R-CHOP方案（利妥昔单抗，环磷酰胺，多柔比星，长春新碱，泼尼松）仅能使50%~60%的患者治愈，其余约1/3患者因发生难治性疾病或复发导致预后较差[24]。如何尽早识别复发/难治或者高风险DLBCL患者，进行方案调整，实现个体化精准治疗，是近年来淋巴瘤领域研究的热点。

目前，基于新算法和新测序技术，制定的5分类或7分类[25-26]分子分型，对DLBCL进行更加精准分层，并提供了个体化靶向治疗的选择。我科既往研究[27-28]发现TP53WT&CD58MUT患者与TP53MUT&CD58WT患者相比预后更差，而TP53WT&CD58WT患者预后最好。此外，DLBCL中PIM1基因突变频率高，依据PIM1相关的基因标记可对DLBCL患者进行有效的危险分层。这些分子分层有助于我们筛选出复发/难治或高危人群，从而制定有针对性的个体化治疗方案，最终改善患者的预后。

对于低危（IPI<2分）年轻DLBCL患者，建议4~6周期R-CHOP或R-CHOP联合放疗治疗[29]。对于高危（IPI>2分）年轻DLBCL患者，2023年ICML公布Pola（维泊妥珠单抗）-R-CHP与R-CHOEP方案比较研究[30]，显示两者疗效相似，但Pola-R-CHP方案组安全性更好，从而再次验证了Pola-R-CHP方案的一线治疗地位[31]。另外，上海瑞金医院赵维莅教授团队根据不同的基因亚型在R-CHOP中加入不同靶向药物（R-CHOP-X），初步探索了基于分子分型实现个体化治疗的可行性。高级别B细胞淋巴瘤（HGBL）患者预后较差，既往研究[32-33]显示R-DA-EPOCH方案（依托泊苷、强的松、长春新碱、环磷酰胺和阿霉素）治疗效果更佳，但最近一些研究似乎在质疑这一观点。2023年EHA公布的Glofit（CD20/CD3双特异性抗体）联合R-CHOP或Pola-RCHP治疗年轻高危DLBCL患者或HGBL患者的1/2期研究[34]显示，对于高风险DLBCL患者，Glofit治疗可能获益，这些结果很值得期待。此外，BCL-2抑制剂venetoclax和CAR-T也是正在探索的方法之一[35-36]。对于老年患者，R-mini-CHOP方案与足剂量R-CHOP方案疗效相当且安全性可控[37]，联合来那度胺并未提高疗效[38]。今年ASCO公布了POLARIXⅢ期研究老年患者亚组分析，Pola-R-CHP方案降低了患者36%的疾病进展风险，且安全性好，是老年DLBCL患者的一线治疗选择。对于不适合使用蒽环类药物的患者，可考虑使用依托泊苷或吉西他滨替代阿霉素[39-40]。对于复发DLBCL患者，其中对挽救化疗敏感患者行ASCT有重要意义[41]。但是约有半数患者因难治或早期复发而无法进行移植。基于ZUMA-7、TRANSFORM研究结果[42-43]，Axi-cel和liso-cel目前都被FDA批准作为原发难治或早期复发DLBCL患者的二线治疗方法。此外，在今年ASCO上公布了我科牵头的一项泽布替尼联合来那度胺治疗复发/难治性弥漫性大B细胞淋巴瘤（R/R DLBCL）的初步安全性和有效性多中心临床Ⅰ期研究[44]，显示该疗法有效且安全。其他被批准用于治疗R/R DLBCL的新药包括tafasitamab（人源化抗CD19单克隆抗体）、Lonca（靶向CD19 ADC药物）、Selinexor（核输出蛋白XPO1抑制剂）、异基因CART、双特异性抗体等，这些新药多数在临床研究中[42,45-47]。

3 滤泡性淋巴瘤

滤泡性淋巴瘤（follicular lymphoma, FL）起源于滤泡中心B细胞，是最常见的惰性非霍奇金淋巴瘤，t（14;18）染色体的易位导致Bcl-2基因过表达的淋巴细胞在淋巴结增殖，呈密集“滤泡”生长方式[48]。FL是一组异质性疾病，大多数为1、2级，临床表现为惰性，预后较好；3级FL可进一步分为

3a、3b级。目前普遍认为，FL3a与FL1~2的临床进程及预后相似，而FL3b与DLBCL的病程类似，具有更强的侵袭性和更高的死亡率[49]。但近期有研究发现，FL3a与FL3b的预后并无明显差异[50-52]，进一步研究显示两者基因表达谱高度相似[51]，且明显不同于FL1~2和DLBCL，FL3b预后优于DLBCL[52]。

虽然免疫化疗使FL患者的预后得到明显改善，但仍有约20%接受免疫化疗的FL患者会出现24个月内的疾病进展（POD24），这部分患者的预后较差，五年总生存率（overall survival, OS）仅为34%~50%[53]。如何早期识别这类高危患者并构建预测模型是研究难题和热点。我科回顾性分析2002年3月—2020年8月我院新诊断的926例滤泡性淋巴瘤患者，发现Ⅲ~Ⅳ期、β2-MG升高和B症状的患者似乎更容易发生POD24。在预测发生POD24方面，FLIPI-2的特异性最好，FLIPI的敏感性最好[54]。同时还进行了一项荟萃分析[53]，结果显示sIL-2R 升高、TMTV>510 cm^3、β2-MG升高、LDH升高、维生素D缺乏、病理3a级、淋巴瘤相关巨噬细胞/高倍视野（LAM/HPF）≥15与POD24风险增加显著相关。该研究将有助于未来优化FL患者POD24危险分层模型。此外，我们团队还将T细胞亚群与临床特征结合起来，创建免疫-临床预后指数（ICPI）[55]，与FLIPI、FLIPI2和PRIMA-PI相比，ICPI具有较好的识别能力。

对于局限期FL，放疗（RT）通常是首选，推荐剂量为24 Gy[56]。一项研究显示放疗联合利妥昔单抗或化疗（CVP或R-CVP）可改善患者的PFS，但对OS没有提高[57]。对于肿瘤负荷高的患者，以利妥昔单抗或者奥妥珠单抗为基础的免疫化疗可以提高总体反应率、PFS和OS[58]。对于晚期FL患者，尚不可治愈，要把握好治疗指征。GALLIUM研究提示奥妥珠单抗联合化疗方案（G-化疗组）对比利妥昔单抗联合化疗方案（R-化疗组）治疗晚期FL，在改善PFS、OS等方面均更优[59-60]。因此也写入中国临床肿瘤学会（CSCO）淋巴瘤指南并确立为一线治疗新标准。BRIGHT研究发现BR方案（苯达莫司汀、利妥昔单抗）非劣于R-CHOP和R-CVP方案，支持BR方案作为FL的主要治疗方案[61]。来那度胺联合利妥昔单抗（R^2方案）在多项研究中显示较好疗效[62-64]，初治FL患者R^2方案是一种可行的无化疗替代方案。复发FL患者的治疗有许多选择，从利妥昔单抗单药治疗到联合化疗、放射免疫治疗、激酶抑制剂，细胞疗法及HSCT等，2023年EHA更新了Mosunetuzumab（CD20/CD3双特异性抗体）对接受过≥2种既往治疗的复发/难治性FL的研究[65]随访数据，CR率超过60%，具有不俗的疗效。另外，在今年ASCO公布的EPCORE NHL-2研究[66]，评价Epco（CD20/CD3双特异性抗体）+R^2方案治疗复发/难治性FL患者的疗效，结果显示：无论POD24风险状态如何，Epco+R^2方案都可获得较高缓解率，且安全性好，结果令人鼓舞。还有其他很多研究正在开展中。

目前FL治疗指南尚未将预后模型纳入指导一线治疗选择中，在新药时代，临床指标与分子生物指标等相结合的预后模型，可能是重要的研究方向之一；采用这些预后模型进行危险分层，进一步指导个体化精准治疗是未来的发展方向。

4　套细胞淋巴瘤

套细胞淋巴瘤（mantle cell lymphoma, MCL）是一种罕见且无法治愈的B细胞恶性肿瘤，以t（11;14）（q13;q32）染色体异常及细胞周期蛋白D1（cyclin D1）过表达为其独特的分子生物学特征[67]，兼具惰性及侵袭性淋巴瘤的临床特点，可以分成经典型MCL、白血病样非淋巴结性MCL、原位套细胞瘤变（ISMCN）。目前临床仍采用套细胞淋巴瘤国际预后指数（MCL International Prognostic Index, MIPI）及结合了Ki-67指数的MIPI-c评分系统。Ferrero等[68]将KMT2D突变和TP53缺失或突变引入MIPI-c评分系统，得到一个新的预后指数MIPI-g。我们团队也构建了IRPI模型[69]，可以更好地将MCL患者分层。此外，有研究表明微小残留病灶（MRD）阳性可以预测复发，同时可以指导治疗[70]。

治疗方面，对于一些无症状、老年、体质较差及惰性的患者可以考虑观察等待。观察等待需考虑的临床特征和生物学指标包括无临床症状、低肿瘤负荷、无淋巴结肿大、MIPI评分为低危、惰性、Ki-67低、无TP53突变等。对于少部分局限性肿块且未伴不良预后因素的早期MCL患者，推荐传统化疗短期诱导后再予以巩固放疗。对于伴有高肿瘤负荷或伴不良预后因素的早期患者，则应按照晚期MCL患者治疗方案进行治疗。晚期患者中，对于年轻初治的MCL患者，一线治疗强调大剂量阿糖胞苷的化疗方案+ASCT和利妥昔单抗维持治疗[71]；今年EHA公布了LYSA研究的长期随访结果[72]，结果说明维持治疗对无事件生存（event-free survival,

EFS）和PFS方面持续获益，但在OS方面无获益。停止维持治疗与复发率增加无关。对于老年初治MCL患者，主要使用低强度的免疫化疗以减少化疗毒性，然后维持治疗以延长缓解时间。

近年来，多项研究对如何在控制药物毒性的同时提高高危患者疗效方面进行探索。WINDOW-1研究中[73]，布鲁顿激酶抑制剂（BTKi）伊布替尼联合利妥昔单抗（IR）诱导治疗后序贯短疗程的R-Hyper-CVAD/MA（环磷酰胺+长春新碱+多柔比星+地塞米松与甲氨蝶呤+阿糖胞苷交替）巩固治疗方案高效低毒，但在亚组分析中显示该方案并不能改善高危患者的预后。WINDOW-2研究中[74]，研究者在IR基础上中加入BCL-2抑制剂维奈克拉，2023年ICML公布Ⅱ期研究结果[75]提示该策略高效低毒，能够克服部分高危患者的不良预后，对于低危MCL患者未来或许不需要化疗。TRIANGLE研究[76]结果显示，联合伊布替尼的强化诱导方案似乎可以省去ASCT，但仍需进一步随访证实。我们团队牵头的全国多中心的Ⅱ期POLARIS研究，探索了奥布替尼、来那度胺联合利妥昔单抗（OLR）的无化疗方案在MCL一线治疗中的应用，初步结果显示，各危险分层的亚组人群均获得较好的疗效，不良反应均可耐受。一项Ⅱ期研究[77]探索了IR方案治疗老年初治MCL患者疗效及安全性，结果显示该方案在老年MCL患者中安全有效。SHINE研究[78]试图在IR基础上联合苯达莫司汀（IBR）方案进一步增效，但不良反应较大，获益受限。因此仍有必要继续探索其他新型治疗方案，以进一步改善初治、老年MCL患者的预后。

对于复发/难治性MCL，BTKi及联合治疗方案已经成为治疗标准，但治疗失败或早期复发的风险大。一代BTKi耐药后的治疗选择包括CAR-T、新型BTK抑制剂、BCL-2抑制剂、CDK4/6抑制剂、ROR1抗体、抗体药物偶联物（ADC）等[79-82]。

5 外周T细胞淋巴瘤

外周T细胞淋巴瘤（peripheral T-cell lymphomas, PTCL）是一组起源于胸腺后成熟T细胞或NK细胞，且具有高度异质性的非霍奇金淋巴瘤（NHL），占所有NHL病例的7%[83]。PTCL除ALK阳性间变大细胞淋巴瘤（ALK^+ALCL）外，一线治疗尚无标准方案，仍以CHOP为基础的化疗方案为主，针对CD30阳性可以联合BV治疗。但患者总体反应率低，易出现复发进展，且挽救治疗疗效差，急需对患者进行个性化治疗。

Iqbal等[84]通过分析PTCL病例的基因表达谱，并结合免疫组织化学和细胞因子、转录因子的检测，将PTCL分成GATA3、TBX21以及细胞毒性基因亚组。而在2022年WHO分型中[85]，将淋巴结滤泡辅助性T细胞淋巴瘤（nodal T-follicular helper cell lymphoma, nTFHL）进行单独分类，其中主要包括nTFHL血管免疫母细胞型、nTFHL滤泡型和nTFHL非特指型，它们具有相似的基因改变（TET2、IDH2、DNMT3A、RHOA突变），并具有表观遗传学异常富集和免疫微环境异常等特点[86-87]。随着基因诊断技术的不断进步，对PTCL复杂的致癌机制和表观遗传变化的认识得到进一步的深化，结合患者分子特征进行个性化治疗。在2023年中国血液学科发展大会上，来自上海瑞金医院赵维莅教授分享了其团队采用基因组学、转录组学和代谢组学等系统生物学新技术对PTCL进行了分子分型研究，并针对不同分子亚型提出了相应的靶向治疗选择，为PTCL的分子分型及治疗提供思路。我科针对复发/难治性（R/R）PTCL进行了一项阿扎胞苷联合西达本胺在复发/难治性T细胞淋巴瘤患者中的安全性、耐受性、药代动力学及疗效的Ⅰ期临床研究，结果显示在PTCL-TFH亚型疾病控制率（DCR）达100%。结合该项研究结果，我们团队针对PTCL-TFH开展了多项研究，包括针对初治PTCL的一项阿扎胞苷、西达本胺联合CHOP方案（AC-CHOP）对比CHOP用于初治具有滤泡辅助T细胞表型外周T细胞淋巴瘤（PTCL-TFH）的前瞻性、多中心、随机对照Ⅲ期临床研究。2023年ASCO公布一项戈利昔替尼（JAK1特异性抑制剂）治疗R/R PTCL多中心研究[88]，80例可评估患者疗效达43.8%，完全缓解率为25%，证实戈利昔替尼有效。其他潜在的治疗靶点有PI3K抑制剂[89]、BCL2[90-91]、CD38[90]、CD52[92]和PDGFRα/β[93-95]。而免疫检查点抑制剂由于部分患者出现了超进展[96-97]，其应用目前仍在探索之中。基于PTCL的发生发展机制研究，联合靶向药物的个性化联合治疗将是未来改善PTCL患者预后的方向。

6 结语与展望

尽管淋巴瘤并非常见的恶性肿瘤，但是淋巴瘤的治疗却一直在引领着整个肿瘤领域的发展。

在新药时代，基于对淋巴瘤分子机制及肿瘤微环境的不断认识，越来越多的新药开发应用于临床，如ADC药物、免疫检查点抑制剂、小分子靶向药物、表观遗传学药物，以及CAR-T细胞疗法、双特异性抗体等，一些新药的组合甚至实现了无化疗（chemo-free），但目前化疗仍然是大部分亚型患者治疗的基石。根据不同亚型的分子机制，结合预测模型筛选高危患者，最终实现精准分层的个体化治疗模式将是恶性淋巴瘤未来的研究方向。

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] Wang HW, Balakrishna JP, Pittaluga S, *et al*. Diagnosis of Hodgkin lymphoma in the modern era[J]. Br J Haematol, 2019, 184(1): 45-59.

[2] Connors JM, Cozen W, Steidl C, *et al*. Hodgkin lymphoma[J]. Nat Rev Dis Primers, 2020, 6(1): 61.

[3] Meyer RM, Gospodarowicz MK, Connors JM, *et al*. ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma[J]. N Engl J Med, 2012, 366(5): 399-408.

[4] Abramson JS, Arnason JE, LaCasce AS, *et al*. Brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine for nonbulky limited-stage classical Hodgkin lymphoma[J]. Blood, 2019, 134(7): 606-613.

[5] Bröckelmann PJ, Goergen H, Keller U, *et al*. Efficacy of Nivolumab and AVD in Early-Stage Unfavorable Classic Hodgkin Lymphoma: The Randomized Phase 2 German Hodgkin Study Group NIVAHL Trial[J]. JAMA Oncol, 2020, 6(6): 872-880.

[6] Allen PB, Savas H, Evens AM, *et al*. Pembrolizumab followed by AVD in untreated early unfavorable and advanced-stage classical Hodgkin lymphoma[J]. Blood, 2021, 137(10): 1318-1326.

[7] Park SI, Shea TC, Olajide O, *et al*. ABVD followed by BV consolidation in risk-stratified patients with limited-stage Hodgkin lymphoma[J]. Blood Adv, 2020, 4(11): 2548-2555.

[8] Straus D, Radford J, Connors J, *et al*. HL-507 First-Line Brentuximab Vedotin Plus Chemotherapy Improves Overall Survival in Patients With Stage Ⅲ/Ⅳ Classical Hodgkin Lymphoma: An Updated Analysis of ECHELON-1[J]. Clin Lymphoma Myeloma Leuk, 2022, 22(suppl 2): S350.

[9] Herrera AF, LeBlanc ML, Castellino SM, *et al*. SWOG S1826, a randomized study of nivolumab(N)-AVD versus brentuximab vedotin(BV)-AVD in advanced stage(AS) classic Hodgkin lymphoma(HL)[J]. J Clin Oncol, 2023, 41(suppl 17): LBA4.

[10] Ramchandren R, Domingo-Domènech E, Rueda A, *et al*. Nivolumab for Newly Diagnosed Advanced-Stage Classic Hodgkin Lymphoma: Safety and Efficacy in the Phase Ⅱ CheckMate 205 Study[J]. J Clin Oncol, 2019, 37(23): 1997-2007.

[11] Yang Y, Yang H, Sun P, *et al*. Smart Start with Tislelizumab as the Front-line Treatment in Patients with High-risk Stage IIB and Advanced-stage Classical Hodgkin Lymphoma [J]. Hematol Oncol, 2023, 41(suppl 2): 114-115.

[12] Evens AM, Advani RH, Helenowski IB, *et al*. Multicenter Phase Ⅱ Study of Sequential Brentuximab Vedotin and Doxorubicin, Vinblastine, and Dacarbazine Chemotherapy for Older Patients With Untreated Classical Hodgkin Lymphoma[J]. J Clin Oncol, 2018, 36(30): 3015-3022.

[13] Cheson BD, Bartlett NL, Laplant B, *et al*. Brentuximab vedotin plus nivolumab as first-line therapy in older or chemotherapy-ineligible patients with Hodgkin lymphoma (ACCRU): a multicentre, single-arm, phase 2 trial[J]. Lancet Haematol, 2020, 7(11): e808-e815.

[14] Ansell SM. Hodgkin lymphoma: 2018 update on diagnosis, risk-stratification, and management[J]. Am J Hematol, 2018, 93(5): 704-715.

[15] Moskowitz CH, Nademanee A, Masszi T, *et al*. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial [J]. Lancet, 2015, 385(9980): 1853-1862.

[16] Armand P, Chen YB, Redd RA, *et al*. PD-1 blockade with pembrolizumab for classical Hodgkin lymphoma after autologous stem cell transplantation [J]. Blood, 2019, 134(1): 22-29.

[17] Younes A, Gopal AK, Smith SE, *et al*. Results of a pivotal phase Ⅱ study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma[J]. J Clin Oncol, 2012, 30(18): 2183-2189.

[18] Armand P, Engert A, Younes A, *et al*. Nivolumab for Relapsed/Refractory Classic Hodgkin Lymphoma After Failure of Autologous Hematopoietic Cell Transplantation: Extended Follow-Up of the Multicohort Single-Arm Phase Ⅱ CheckMate 205 Trial [J]. J Clin Oncol, 2018, 36(14): 1428-1439.

[19] Kuruvilla J, Ramchandren R, Santoro A, *et al*. Pembrolizumab versus brentuximab vedotin in relapsed or refractory classical Hodgkin lymphoma (KEYNOTE-204): an interim analysis of a multicentre, randomised, open-label, phase 3 study[J]. Lancet Oncol, 2021, 22(4): 512-524.

[20] Zhang HL, Yu JW, Li H. S216: CD47/PD-L1 bispecific antibody (IBI322) in anti-PD-1 or PD-L1 treatment-resistant classical Hodgkin lymphoma: A phase Ⅰ study[J]. Hemasphere, 2023, 7(suppl 3): e8102841.

[21] Zhang L, Li C, Marhaba A, *et al*. ITF2357 induces cell cycle arrest and apoptosis of meningioma cells via the PI3K-Akt pathway[J]. Med Oncol, 2022, 40(1): 21.

[22] Li Z, Mu W, Xiao M. Genetic lesions and targeted therapy in Hodgkin lymphoma[J]. Ther Adv Hematol, 2023, 14: 20406207221149245.

[23] Pasqualucci L, Dalla-Favera R. Genetics of diffuse large B-cell lymphoma[J]. Blood, 2018, 131(21): 2307-2319.

[24] Perry AM, Diebold J, Nathwani BN, *et al*. Non-Hodgkin lymphoma in the Far East: review of 730 cases from the international non-Hodgkin lymphoma classification project[J]. Ann Hematol, 2016, 95(2): 245-251.

[25] Wright GW, Huang DW, Phelan JD, *et al*. A Probabilistic Classification Tool for Genetic Subtypes of Diffuse Large B Cell Lymphoma with Therapeutic Implications[J]. Cancer Cell, 2020, 37(4): 551-568. e14.

[26] Schmitz R, Wright GW, Huang DW, *et al*. Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma[J]. N Engl J Med, 2018, 378(15): 1396-1407.

[27] Zhang H, Lu Y, Zhang T, *et al*. PIM1 genetic alterations associated with distinct molecular profiles, phenotypes and drug responses in diffuse large B-cell lymphoma[J]. Clin Transl Med, 2022, 12(4): e808.

[28] Zhang T, Lu Y, Liu X, *et al*. Comprehensive analysis of TP53 mutation characteristics and identification of patients with inferior prognosis and enhanced immune escape in diffuse large B-cell lymphoma[J]. Am J Hematol, 2022, 97(1): E14-E17.

[29] Poeschel V, Held G, Ziepert M, *et al*. Four versus six cycles of CHOP chemotherapy in combination with six applications of rituximab in patients with aggressive B-cell lymphoma with favourable prognosis (FLYER): a randomised, phase 3, non-inferiority trial[J]. Lancet, 2019, 394(10216): 2271-2281.

[30] Lenz G, Tilly H, Ziepert M, *et al*. Pola-R-CHP versus R-CHOEP in young patients with high-risk diffuse large B-cell lymphoma[J]. Hematol Oncol, 2023, 41(suppl 2): 420-421.

[31] Tilly H, Morschhauser F, Sehn LH, *et al*. Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma[J]. N Engl J Med, 2022, 386(4): 351-363.

[32] Dunleavy K, Fanale MA, Abramson JS, *et al*. Dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) in untreated aggressive diffuse large B-cell lymphoma with MYC rearrangement: a prospective, multicentre, single-arm phase 2 study[J]. Lancet Haematol, 2018, 5(12): e609-e617.

[33] Howlett C, Snedecor SJ, Landsburg DJ, *et al*. Front-line, dose-escalated immunochemotherapy is associated with a significant progression-free survival advantage in patients with double-hit lymphomas: a systematic review and meta-analysis[J]. Br J Haematol, 2015, 170(4): 504-514.

[34] Minson A, Verner E, Giri P, *et al*. Glofitamab plus R-CHOP or polatuzumab vedotin-R-CHP is deliverable with high overall response in patients ⩽65 years of age with high-risk DLBCL: Interim analysis of COALITION[J]. Hematol Oncol, 2023, 41(suppl 2): 421-422.

[35] Rutherford SC, Abramson JS, Bartlett NL, *et al*. Venetoclax with dose-adjusted EPOCH-R as initial therapy for patients with aggressive B-cell lymphoma: a single-arm, multicentre, phase 1 study[J]. Lancet Haematol, 2021, 8(11): e818-e827.

[36] Neelapu SS, Dickinson M, Munoz J, *et al*. Axicabtagene ciloleucel as first-line therapy in high-risk large B-cell lymphoma: the phase 2 ZUMA-12 trial [J]. Nat Med, 2022, 28(4): 735-742.

[37] Peyrade F, Jardin F, Thieblemont C, *et al*. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial[J]. Lancet Oncol, 2011, 12(5): 460-468.

[38] Oberic L, Peyrade F, Puyade M, *et al*. Subcutaneous Rituximab-MiniCHOP Compared With Subcutaneous Rituximab-MiniCHOP Plus Lenalidomide in Diffuse Large B-Cell Lymphoma for Patients Age 80 Years or Older[J]. J Clin Oncol, 2021, 39(11): 1203-1213.

[39] Fields PA, Townsend W, Webb A, *et al*. De novo treatment of diffuse large B-cell lymphoma with rituximab, cyclophosphamide, vincristine, gemcitabine, and prednisolone in patients with cardiac comorbidity: a United Kingdom National Cancer Research Institute trial[J]. J Clin Oncol, 2014, 32(4): 282-287.

[40] Moccia AA, Schaff K, Freeman C, *et al*. Long-term outcomes of R-CEOP show curative potential in patients with DLBCL and a contraindication to anthracyclines[J]. Blood Adv, 2021, 5(5): 1483-1489.

[41] Philip T, Guglielmi C, Hagenbeek A, *et al*. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma [J]. N Engl J Med, 1995, 333(23): 1540-1545.

[42] Kamdar M, Solomon SR, Arnason J, *et al*. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial[J]. Lancet, 2022, 399(10343): 2294-2308.

[43] Locke FL, Miklos DB, Jacobson CA, *et al*. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma [J]. N Engl J Med, 2022, 386(7): 640-654.

[44] Zhang HL,Cheng Y, Yang HY, *et al*. First interim analysis of a phase 1 study of zanubrutinib (zanu) plus lenalidomide (len) in patients (pts) with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL)[J]. J Clin Oncol, 2023, 41(suppl 16): 7557.

[45] Kalakonda N, Maerevoet M, Cavallo F, *et al*. Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicentre, open-label, phase 2 trial[J]. Lancet Haematol, 2020, 7(7): e511-e522.

[46] Salles G, Duell J, González Barca E, *et al*. Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study[J]. Lancet Oncol, 2020, 21(7): 978-988.

[47] Duell J, Maddocks KJ, González-Barca E, *et al*. Long-term outcomes from the Phase Ⅱ L-MIND study of tafasitamab (MOR208) plus lenalidomide in patients with relapsed or refractory diffuse large B-cell lymphoma[J]. Haematologica,

2021, 106(9): 2417-2426.

[48] Tan D, Horning SJ, Hoppe RT, *et al*. Improvements in observed and relative survival in follicular grade 1-2 lymphoma during 4 decades: the Stanford University experience[J]. Blood, 2013, 122(6): 981-987.

[49] Rimsza LM, Li H, Braziel RM, *et al*. Impact of histological grading on survival in the SWOG S0016 follicular lymphoma cohort [J]. Haematologica, 2018, 103(4): e151-e153.

[50] Koch K, Hoster E, Ziepert M, *et al*. Clinical, pathological and genetic features of follicular lymphoma grade 3A: a joint analysis of the German low-grade and high-grade lymphoma study groups GLSG and DSHNHL[J]. Ann Oncol, 2016, 27(7): 1323-1329.

[51] Horn H, Kohler C, Witzig R, *et al*. Gene expression profiling reveals a close relationship between follicular lymphoma grade 3A and 3B, but distinct profiles of follicular lymphoma grade 1 and 2[J]. Haematologica, 2018, 103(7): 1182-1190.

[52] Barraclough A, England JT, Villa D, *et al*. Outcomes in grade 3B follicular lymphoma: an international study led by the Australasian Lymphoma Alliance[J]. Haematologica, 2023, 108(9): 2444-2453.

[53] Gao F, Zhang T, Liu H, *et al*. Risk factors for POD24 in patients with previously untreated follicular lymphoma: a systematic review and meta-analysis[J]. Ann Hematol, 2022, 101(11): 2383-2392.

[54] Gao F, Zhang T, Liu X, *et al*. Clinical features and outcomes of patients with follicular lymphoma: A real-world study of 926 patients in China[J]. Front Oncol, 2022, 12: 863021.

[55] Lu Y, Yu J, Gong W, *et al*. An Immune-Clinical Prognostic Index (ICPI) for Patients With De Novo Follicular Lymphoma Treated With R-CHOP/CHOP Chemotherapy[J]. Front Oncol, 2021, 11: 708784.

[56] Lowry L, Smith P, Qian W, *et al*. Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: a randomised phase Ⅲ trial[J]. Radiother Oncol, 2011, 100(1): 86-92.

[57] Macmanus M, Fisher R, Roos D, *et al*. Randomized Trial of Systemic Therapy After Involved-Field Radiotherapy in Patients With Early-Stage Follicular Lymphoma: TROG 99.03[J]. J Clin Oncol, 2018, 36(29): 2918-2925.

[58] Marcus R, Davies A, Ando K, *et al*. Obinutuzumab for the First-Line Treatment of Follicular Lymphoma[J]. N Engl J Med, 2017, 377(14): 1331-1344.

[59] Hong X, Song Y, Shi Y, *et al*. Efficacy and safety of obinutuzumab for the first-line treatment of follicular lymphoma: a subgroup analysis of Chinese patients enrolled in the phase Ⅲ GALLIUM study[J]. Chin Med J (Engl), 2021, 135(4): 433-440.

[60] Hiddemann W, Barbui AM, Canales MA, *et al*. Immunochemotherapy With Obinutuzumab or Rituximab for Previously Untreated Follicular Lymphoma in the GALLIUM Study: Influence of Chemotherapy on Efficacy and Safety[J]. J Clin Oncol, 2018, 36(23): 2395-2404.

[61] Jacobsen E. Follicular lymphoma: 2023 update on diagnosis and management[J]. Am J Hematol, 2022, 97(12): 1638-1651.

[62] Zucca E, Rondeau S, Vanazzi A, *et al*. Short regimen of rituximab plus lenalidomide in follicular lymphoma patients in need of first-line therapy [J]. Blood, 2019, 134(4): 353-362.

[63] Morschhauser F, Fowler NH, Feugier P, *et al*. Rituximab plus Lenalidomide in Advanced Untreated Follicular Lymphoma[J]. N Engl J Med, 2018, 379(10): 934-947.

[64] Martin P, Jung SH, Pitcher B, *et al*. A phase Ⅱ trial of lenalidomide plus rituximab in previously untreated follicular non-Hodgkin's lymphoma (NHL): CALGB 50803 (Alliance)[J]. Ann Oncol, 2017, 28(11): 2806-2812.

[65] Sehn LH, Bartlett NL, Matasar M, *et al*. Mosunetuzumab demonstrates durable responses in patients with relapsed and/or refractory follicular lymphoma who have received ⩾2 prior therapies: updated analysis of a pivotal phase Ⅱ study[J]. Hematol Oncol, 2023, 41(suppl 2): 122-125.

[66] Merryman RW, Belada D, Sureda A, *et al*. Epcoritamab + R2 regimen and responses in patients with high-risk follicular lymphoma, regardless of POD24 status[J]. Clin Lymphoma Myeloma Leuk, 2023, 23(Suppl 1): S210.

[67] Chen W, Zheng R, Baade PD, *et al*. Cancer statistics in China, 2015[J]. CA Cancer J Clin, 2016, 66(2): 115-132.

[68] Ferrero S, Rossi D, Rinaldi A, *et al*. KMT2D mutations and TP53 disruptions are poor prognostic biomarkers in mantle cell lymphoma receiving high-dose therapy: a FIL study[J]. Haematologica, 2020, 105(6): 1604-1612.

[69] Lv H, Fei Y, Li W, *et al*. A novel clinical immune-related prognostic model predicts the overall survival of mantle cell lymphoma[J]. Hematol Oncol, 2022, 40(3): 343-355.

[70] Wu X, Lu H, Pang T, *et al*. Association of minimal residual disease levels with clinical outcomes in patients with mantle cell lymphoma: A meta-analysis[J]. Leuk Res, 2021, 108: 106605.

[71] Mckay P, Leach M, Jackson B, *et al*. Guideline for the management of mantle cell lymphoma[J]. Br J Haematol, 2018, 182(1): 46-62.

[72] Sarkozy C, Thieblemont C, Oberic L, *et al*. Very long-term follow-up of rituximab maintenance in young patients with mantle cell lymphoma included in the lyma trial, a lysa study[J]. Hematol Oncol, 2023, 41(suppl 2): 151-152.

[73] Wang ML, Jain P, Zhao S, *et al*. Ibrutinib-rituximab followed by R-HCVAD as frontline treatment for young patients (⩽65 years) with mantle cell lymphoma (WINDOW-1): a single-arm, phase 2 trial[J]. Lancet Oncol, 2022, 23(3): 406-415.

[74] Wang M, Jain P, Lee HJ, *et al*. Ibrutinib Plus Rituximab and Venetoclax (IRV) Followed By Risk-Stratified Observation or Short Course R-Hypercvad/MTX in Young Patients with Previously Untreated Mantle Cell Lymphoma- Phase-Ⅱ Window-2 Clinical Trial[J]. Blood, 2021, 138(suppl 1): 3525.

[75] Wang ML, Lee HJ, Fetooh A, *et al*. Ibrutinib-rituximab and venetoclax (IRV) followed by risk-stratified R-HyperCVAD/MTX in young patients with untreated mantle cell lymphoma-phase-Ⅱ WINDOW-2 trial[J]. Hematol Oncol, 2023, 41(suppl 2): 152-153.

[76] Dreyling M, Doorduijn JK, Gine E, *et al*. Efficacy and Safety of Ibrutinib Combined with Standard First-Line Treatment or As Substitute for Autologous Stem Cell Transplantation in Younger Patients with Mantle Cell Lymphoma: Results from the Randomized Triangle Trial By the European MCL Network[J]. Blood, 2022, 140(suppl 1): 1-3.

[77] Jain P, Zhao S, Lee HJ, *et al*. Ibrutinib With Rituximab in First-Line Treatment of Older Patients With Mantle Cell Lymphoma[J]. J Clin Oncol, 2022, 40(2): 202-212.

[78] Wang M, Jurczak W, Jerkeman M, *et al*. Primary results from the double-blind, placebo-controlled, phase Ⅲ SHINE study of ibrutinib in combination with bendamustine-rituximab (BR) and R maintenance as a first-line treatment for older patients with mantle cell lymphoma (MCL)[J]. J Clin Oncol, 2022,40(suppl 17): LBA7502.

[79] Cohen JB, Shah NN, Alencar AJ, *et al*. MCL-133 Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Previously Treated Mantle Cell Lymphoma: Updated Results From the Phase 1/2 BRUIN Study[J]. Clin Lymphoma Myeloma Leuk, 2022, 22 Suppl 2: S394-S395.

[80] Wang M, Munoz J, Goy A, *et al*. Three-Year Follow-Up of KTE-X19 in Patients With Relapsed/Refractory Mantle Cell Lymphoma, Including High-Risk Subgroups, in the ZUMA-2 Study[J]. J Clin Oncol, 2023, 41(3): 555-567.

[81] Toby A, Eyre CY, Wang ML. Therapeutic options for relapsed/refractory mantle cell lymphoma[J]. Blood, 2022, 139(5): 666-667.

[82] Wilson MR, Barrett A, Cheah CY, *et al*. How I manage mantle cell lymphoma: indolent versus aggressive disease[J]. Br J Haematol, 2023, 201(2): 185-198.

[83] Vose J, Armitage J, Weisenburger D. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes[J]. J Clin Oncol, 2008, 26(25): 4124-4130.

[84] Iqbal J, Wright G, Wang C, *et al*. Gene expression signatures delineate biological and prognostic subgroups in peripheral T-cell lymphoma[J]. Blood, 2014, 123(19): 2915-2923.

[85] Alaggio R, Amador C, Anagnostopoulos I, *et al*. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms[J]. Leukemia, 2022, 36(7): 1720-1748.

[86] Marchi E, O'Connor OA. The rapidly changing landscape in mature T-cell lymphoma (MTCL) biology and management[J]. CA Cancer J Clin, 2020, 70(1): 47-70.

[87] Swerdlow SH, Campo E, Pileri SA, *et al*. The 2016 revision of the World Health Organization classification of lymphoid neoplasms[J]. Blood, 2016, 127(20): 2375-2390.

[88] Cai QQ, Zhu J, Song Y, *et al*. Golidocitinib in treating refractory or relapsed peripheral T-cell lymphoma: Primary analysis of the multinational pivotal study results (JACKPOT8)[J]. J Clin Oncol, 2023, 41(suppl 16): 7503.

[89] Horwitz SM, Koch R, Porcu P, *et al*. Activity of the PI3K-δ,γ inhibitor duvelisib in a phase 1 trial and preclinical models of T-cell lymphoma[J]. Blood, 2018, 131(8): 888-898.

[90] Zaja F, Tabanelli V, Agostinelli C, *et al*. CD38, BCL-2, PD-1, and PD-1L expression in nodal peripheral T-cell lymphoma: Possible biomarkers for novel targeted therapies? [J]. Am J Hematol, 2017, 92(1): E1-E2.

[91] Rassidakis GZ, Jones D, Lai R, *et al*. BCL-2 family proteins in peripheral T-cell lymphomas: correlation with tumour apoptosis and proliferation[J]. J Pathol, 2003, 200(2): 240-248.

[92] Piccaluga PP, Agostinelli C, Righi S, *et al*. Expression of CD52 in peripheral T-cell lymphoma[J]. Haematologica, 2007, 92(4): 566-567.

[93] Lindauer M, Hochhaus A. Dasatinib[J]. Recent Results Cancer Res, 2014, 201: 27-65.

[94] Laimer D, Dolznig H, Kollmann K, *et al*. PDGFR blockade is a rational and effective therapy for NPM-ALK-driven lymphomas[J]. Nat Med, 2012, 18(11): 1699-1704.

[95] Piccaluga PP, Rossi M, Agostinelli C, *et al*. Platelet-derived growth factor alpha mediates the proliferation of peripheral T-cell lymphoma cells via an autocrine regulatory pathway[J]. Leukemia, 2014, 28(8): 1687-1697.

[96] Barta SK, Zain J, Macfarlane AW, *et al*. Phase Ⅱ Study of the PD-1 Inhibitor Pembrolizumab for the Treatment of Relapsed or Refractory Mature T-cell Lymphoma[J]. Clin Lymphoma Myeloma Leuk, 2019, 19(6): 356-364.e3.

[97] Bennani NN, Kim HJ, Pederson LD, *et al*. Nivolumab in patients with relapsed or refractory peripheral T-cell lymphoma: modest activity and cases of hyperprogression[J]. J Immunother Cancer, 2022, 10(6): e004984.

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