拾玉儿童公益 SHIYU CHILDREN FOUNDATION

向日葵儿童

儿童肿瘤创新药物手册

国外已注册、但中国尚未注册上市的药品总结

2026 年 6 月

提示

报告所有内容均来自美国食品药品管理局 (US FDA)、欧洲药品管理局 (EMA)、澳大利亚治疗用品管理局 (TGA) 等国际网站，中文部分为翻译，英文部分为原文。如有任何不一致之处，请以英文原文为准。希望这份报告能给大家带来启示和收获。

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该手册信息整理方旨在尽最大努力向儿童患者和家长提供正确、完整的健康资讯，但其中某些信息可能过时或者不完整，信息整理方不对因信息的不正确或遗漏导致的任何损失或损害承担责任。

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先后求学于三峡大学、中南大学，获临床医学学士、药理学硕士学位；目前取得副主任药师、心血管主治医师、心血管临床药师、执业药师、执业医师资格；先后在南方医科大学南方医院、意大利锡耶纳大学医院、复旦大学附属儿科医院进修访问；主要研究方向为临床试验、妊娠和哺乳期药物评价、药事管理，目前负责临床试验（GCP）、研究者发起的临床研究（IIT）、生物医学新技术、数字疗法基地，博鳌乐城真实世界研究。

目前在国内核心期刊发表多篇第一作者论文，有人民卫生出版社著作两部、科学出版社出版的译著一部，有多篇第一作者 SCI 论文在国际刊物发表，曾参与导师国家自然基金项目的研究，曾主持海南省卫生健康委员会、湖北省科技厅、荆州市科技局项目科研项目。

2012 年获荆州市自然科学优秀学术论文特等奖，2013 年获中国医院药学奖 - 青年药师优秀奖，2016 年获中华医学会临床药学分会优秀临床药师 - 提名奖，2017 获荆州区年度优秀政协委员，2018 年海南省刚性引进“好医生”。

钱晓文

复旦大学附属儿科医院，副主任医师，血液科副主任

主要关注儿童罕见病造血干细胞移植、儿童肿瘤创新治疗。近年来在海南博鳌医疗旅游先行区参与主持两项儿童神经母细胞瘤创新药物的临床急需进口药品先行先试，帮助推动儿童肿瘤及罕见病治疗创新药物在国内引进和上市应用。以原发免疫缺陷病、遗传代谢病和早发型炎症性肠病等儿童罕见病为主要研究对象，主攻造血干细胞移植，完成超过400 例的儿童罕见病移植治疗。在对上述罕见病和肿瘤患者的治疗管理中不断改进方案、完善流程，积累了丰富的经验，带出了一支优秀的医护团队。

担任国家卫生健康委员会儿童血液病恶性肿瘤专家委员会秘书长、中华医学会结核病学分会结核病相关疾病专业委员会委员、中国医师协会儿科专业委员会血液肿瘤学组委员、国家儿童医学中心血液 / 肿瘤专科联盟委员、上海市医学会儿科分会血液学组组员、上海市医学会血液学专科分会造血干细胞移植学组组员。

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编号	名称	原研药厂家	肿瘤分类	具体适应症	儿童临床试验	上市地区	信息来源
1	Tisagenlecleucel (Kymriah®) 详情页	诺华制药（瑞士）	血液肿瘤	复发或难治性 b 细胞急性淋巴母细胞白血病	ELIANA, NCT02435849	美国；欧盟	label(fda.gov) Tisagenlecleucel(EMA_Label)
2	Nelarabine 奈拉滨 (Arranon®) 详情页	诺华制药（瑞士）	血液肿瘤	1 岁及以上复发或难治性 T 淋巴细胞白血病 / T 淋巴细胞淋巴瘤	PGA2001, COG P9673	美国；澳大利亚	label(fda.gov) Arranon(TGA_Aprroval)
3	Gemtuzumab-Ozogamicin 吉妥单抗 (Mylotarg™) 详情页	辉瑞制药（美国）	血液肿瘤	2 岁及以上复发或难治性 CD33 阳性急性髓细胞白血病	0903A1-102-US phase I/II study	美国；澳大利亚（仅适用于 15 岁及以上）	label(fda.gov) Mylotarg(TGA_Approval)
4	Calaspargase Pegol-mknl 长效聚乙二醇化天冬酰胺酶 (Asparlas™) 详情页	施维雅（法国）	血液肿瘤	1 个月到 21 岁的急性淋巴细胞白血病	Study AALL07P4, Study DFCI 11-001	美国	label (fda.gov)
5	Asparaginase Erwinia Chrysanthemi (Recombinant)-rywn 菊欧文氏菌（重组）天冬酰胺酶 (Rylaze™) 详情页	爵士制药（爱尔兰）	血液肿瘤	1 个月及以上对大肠杆菌衍生的天冬氨酰胺酶过敏的急性淋巴细胞白血病和淋巴细胞淋巴瘤儿童	JZP458-201 (NCT04145531)	美国；澳大利亚；欧盟	label (fda.gov) Enrylaze(EMA_Label) Crisantaspase(TGA_Approval)
6	Brentuximab Vedotin 维布妥昔单抗 (Adcetris®) 详情页	武田（日本）和西雅图遗传学公司（美国）	血液肿瘤	2 岁及以上未经治疗的高危经典霍奇金淋巴瘤	AHOD1331(NCT02166463) (NCT02166463) AHOD1331(NCT02166463)	美国	label (fda.gov)

美国 FDA、欧盟 EMA、澳大利亚 TGA 已经获批上市、但中国还未获批上市的儿童肿瘤药物（信息更新截止到 2026 年 6 月）							
编号	名称	原研药厂家	肿瘤分类	具体适应症	儿童临床试验	上市地区	信息来源
7	Pembrolizumab 帕博利珠单抗 (Keytruda®) 详情页	默克药厂（美国）	血液肿瘤	小儿难治性经典霍奇金淋巴瘤，或经过 2 线或更多治疗后复发的慢性霍奇金淋巴瘤	将成人数据推断至小儿患者	美国；欧盟（仅适用于 3 岁及以上）	label (fda.gov) Pembrolizumab(EMA_Label)
			血液肿瘤	原发性纵隔大 B 细胞淋巴瘤		美国	
			实体肿瘤	梅克尔细胞癌		美国	
			实体肿瘤	卫星不稳定性高或错配修复缺陷癌		美国	
			实体肿瘤	肿瘤突变负高		美国	
			实体肿瘤	12 岁及以上患有晚期（不可切除或转移性）黑色素瘤		美国；欧盟	
8	Rituximab 利妥昔单抗 (Rituxan®) 详情页	基因泰克（美国）	血液肿瘤	6 个月及以上未治疗的晚期 CD20 阳性的弥漫大 B 细胞淋巴瘤 /Burkitt 淋巴瘤 / B 淋巴细胞白血病 / 急性 B 细胞白血病	Inter-B-NHL Ritux 2010, NCT01516580	美国	label (fda.gov)
9	Dasatinib 达沙替尼 (Sprycel®) 详情页	百时美施贵宝（美国）	血液肿瘤	1 岁及以上费城染色体阳性急性淋巴细胞白血病	CA180372 (NCT01460160)	美国；欧盟	SPRYCEL U.S. Prescribing Information (bms.com) Dasatinib(EMA_Label)
			血液肿瘤	1 岁及以上费城染色体阳性慢性骨髓性白血病	NCT00306202，NCT00777036	美国；欧盟	
10	Bosutinib 博苏替尼 (Bosulif®) 详情页	辉瑞制药（美国）	血液肿瘤	1 岁及以上费城染色体阳性慢性骨髓性白血病	The BCHILD trial(NCT04258943)	美国	Label (fda.gov)
11	Azacitidine 阿扎胞苷 (Vidaza) 详情页	百时美施贵宝（美国）	血液肿瘤	1 个月及以上幼年粒细胞白血病	AZA-JMML-001 (NCT02447666)	美国	label (fda.gov)

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编号	名称	原研药厂家	肿瘤分类	具体适应症	儿童临床试验	上市地区	信息来源
12	Crizotinib 克里唑替尼 (Xalkori®) 详情页	辉瑞制药（美国）	实体肿瘤	1 岁及以上 ALK 阳性儿童炎性肌纤维母细胞瘤	ADVL0912 (NCT00939770)	美国；欧盟（仅适用于 6 岁及以上）	XALKORI (fda.gov) Crizotinib (EMA_Label)
			血液肿瘤	1 岁及以上的 ALK 阳性复发或难治性系统性间变性大细胞淋巴瘤	ANHL12P1	美国；欧盟（仅适用于 6 岁及以上）	
13	Trecondi 曲奥舒凡 (Treosulfan) 详情页	林克医疗（澳大利亚）	血液肿瘤	1 个月及以上患有恶性和非恶性血液病的异基因造血干细胞移植前预处理治疗	Study MC-FludT.17/M	澳大利亚；欧盟	Trecondi(TGA Approval) Trecondi(EMA_Label)
14	Plerixafor 普乐沙福 (Mozobil®) 详情页	赛诺菲（法国）	实体肿瘤、血液肿瘤	与粒细胞集落刺激因子 (G-CSF) 联合使用，促使 1 岁至未满 18 岁患有淋巴瘤或实体恶性肿瘤的儿科患者的造血干细胞从骨髓进入外周血液中，以便进行收集和随后的自体干细胞移植。	DFI12860	欧盟	Plerixafor (EMA_Label)
15	Iobenguane I-131 碘苯胍 I-131 (Azedra®) 详情页	普罗基尼克斯制药（美国）	实体肿瘤	神经母细胞瘤的定位成像剂	/	美国	https: //www.ncbi.nlm.nih.gov/pmc/articles/PMC6678905/
			实体肿瘤	12 岁及以上儿童不可切除，局部晚期或转移性，嗜铬细胞瘤和副神经节瘤	Study IB12B (NCT00874614)	美国	Full Prescribing Information | AZEDRA® (iobenguane | 131)
16	Dinutuximab 地努图希单抗 (Unituxin™) 详情页	United Therapeutics（美国）	实体肿瘤	高危神经母细胞瘤	ANBL0032	美国	LABEL (fda.gov)
17	Avelumab 阿维鲁单 (Bavencio®) 详情页	默克制药（美国）	实体肿瘤	12 岁及以上儿童转移性默克尔细胞癌	将成人数据推断至小儿患者	美国	label (fda.gov)
18	Tagroxofusp-erzs (Elzonris™) 详情页	Stemline Therapeutics（美国）	实体肿瘤	2 岁及以上的儿童浆细胞样树突状细胞瘤	STML-401-0114 (NCT 02113982; Study 0114)	美国	LABEL (fda.gov)
19	Nivolumab and Relatlimab-rmbw (Opdualag™) 详情页	百时美施贵宝（美国）	实体肿瘤	12 岁及以上不可切除或转移性黑色素瘤	将成人数据推断至小儿患者	美国	label (fda.gov)

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编号	名称	原研药厂家	肿瘤分类	具体适应症	儿童临床试验	上市地区	信息来源
20	Ipilimumab 伊匹单抗 (Yervoy®) 详情页	百时美施贵宝（美国）	实体肿瘤	12 岁及以上儿童不可切除或转移性黑色素瘤	将成人数据推断至小儿患者	美国	Yervoy FDA Drug Label
21	Nivolumab 纳武单抗 (Opdivo®) 详情页	百时美施贵宝（美国）	实体肿瘤	12 岁及以上可切除或转移性黑色素瘤	将成人数据推断至小儿患者	美国	OPDIVO U.S. Prescribing Information (bms.com)
			实体肿瘤	12 岁及以上儿童高度微卫星不稳定 / 错配修复缺陷结直肠癌	SWOG 1826; NCT03907488	美国	
			实体肿瘤	12 岁及以上初治 III 或 IV 期经典霍奇金淋巴瘤（cHL）（+AVD chemotherapy）		美国	
22	Ipilimumab 伊匹单抗 (Yervoy®) + Nivolumab 纳武单抗 (Opdivo®) 详情页	百时美施贵宝（美国）	实体肿瘤	12 岁及以上转移性或不可切除的黑色素瘤	将成人数据推断至小儿患者	美国	label (fda.gov)
			实体肿瘤	12 岁以上儿童儿童高度微卫星不稳定 / 错配修复缺陷结直肠癌		美国	
23	Atezolizumab 阿替利珠单抗 (Tecentriq®) 详情页	基因泰克（美国）	实体肿瘤	2 岁及以上儿童肺泡软组织肉瘤	ML39345 (NCT03141684)	美国	label (fda.gov)
24	Trametinib Dimethyl Sulfoxide 异硫氰酸苯酯 (Mekinist) + Dabrafenib Mesylate 达拉菲尼甲磺酸盐 (Tafinlar®) 详情页	诺华制药（瑞士）	实体肿瘤	1 岁及以上儿童 BRAF_V600E 突变的不可切除或转移性实体瘤	TMT212X2101 (X2101) Study；CDRB436G2201 (G2201) Study – High-Grade Glioma Cohort	美国	label (fda.gov) Trametinib (EMA Label) Dabrafenib (EMA Label)
			实体肿瘤	1 岁及以上儿童 BRAF V600E 突变阳性的低级别胶质瘤	CDRB436G2201 (G2201) Study – Low-Grade Glioma Cohort	美国；欧盟	
			实体肿瘤	1 岁及以上儿童患有 BRAFV600E 突变的高级别胶质瘤，且至少接受过一次放疗和 / 或化疗	EudraCT 2015-004015-20	欧盟	
			实体肿瘤	≥ 12 岁青少年：BRAF V600 突变的不可切除 / 转移性黑色素瘤；以及完全切除后的 III 期黑色素瘤辅助治疗	从成人数据外推至青少	欧盟	
25	Eflornithine 依氟鸟氨酸 (IWILFIN ™) 详情页	US World -Meds（美国）	实体肿瘤	儿童高危神经母细胞瘤	Study 3b (NCT02395666)，ANBL0032	美国	label(fda.gov)
26	Tovorafenib 托沃拉非尼 (OJEMDA ™) 详情页	施维雅制药（法国）	实体肿瘤	6 个月及以上患有 BRAF 融合或重排或 BRAF V600 突变的复发性或难治性儿童低级别神经胶质瘤	FIREFLY-1; NCT0477548	美国	label(fda.gov) Tovorafenib（EMA Label）

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编号	名称	原研药厂家	肿瘤分类	具体适应症	儿童临床试验	上市地区	信息来源
27	Vorasidenib Citrate 沃拉西德尼 (VORANIGO®) 详情页	施维雅制药（法国）	实体肿瘤	12 岁及以上在手术（包括活检、次全切除或全切除）后具有易感异柠檬酸脱氢酶 1 或异柠檬酸脱氢酶 2 突变的 2 级星形细胞瘤或少突胶质细胞瘤	Study AG881-C-004	美国；澳大利亚	label(fda.gov) Vorasidenib (TGA_ Approval)
28	Repotrectinib 瑞普替尼 (Augtyro ™) 详情页	百时美施贵宝（美国）	实体肿瘤	12 岁及以上成人和儿童患者，患有以下特征的实体瘤：(1) 存在神经营养性酪氨酸受体激酶 (NTRK) 基因融合；(2) 局部晚期或转移性，或手术切除可能导致严重并发症；(3) 经治疗后疾病进展，或无其他令人满意的替代疗法	NCT03093116	美国	label(fda.gov)
29	Cabozantinib-S-Malate 卡博替尼 (Cabometyx®) 详情页	伊克力西斯（美国）	实体肿瘤	12 岁及以上患有局部晚期或转移性分化型甲状腺癌	COSMIC-311	美国	label(fda.gov)
30	Mifamurtide 米法莫肽 (Mepact®) 详情页	武田法国公司（法国）	实体肿瘤	高等级可切除的非转移性骨肉瘤，适用于通过手术将肿瘤全部切除，术后肉眼检查没有残留的肿瘤组织的儿科患者	/	欧盟	Mifamurtide (EMA_Label)
31	Vandetanib 凡德他尼 (Caprelsa®) 详情页	赛诺菲（法国）	实体肿瘤	5 岁及以上患有不可切除的局部晚期或转移性疾病的侵袭性和症状性的 RET 基因甲状腺髓样癌	IRUSZACT0098	欧盟	Vandetanib (EMA_Label)
32	Revumenib Citrate 瑞维美尼（Revufori®） 详情页	Syndax Pharma-ceuticals（美国）	血液肿瘤	1 岁及以上患有 KMT2A 基因易位复发或难治性急性白血病（ALL），急性淋巴细胞白血病（AML），混合表型急性白血病（MPAL）	SNDX-5613-0700 (NCT04065399)	美国	label (fda. gov)
33	Treosulfan 苏消安 (Grafapex®) 详情页	Medexus 制药（美国）	血液肿瘤	联合氟达拉滨（Fludarabine），为 1 岁及以上患有急性髓系白血病（AML）和骨髓增生异常综合征（MDS）的儿童进行同种异体造血干细胞移植（alloHSCT）前的预处理方案	将成人数据推断至小儿患者	美国	Label (fda.gov)

美国 FDA、欧盟 EMA、澳大利亚 TGA 已经获批上市、但中国还未获批上市的儿童肿瘤药物（信息更新截止到 2026 年 6 月）							
编号	名称	原研药厂家	肿瘤分类	具体适应症	儿童临床试验	上市地区	信息来源
34	Dordaviprone 多达维普隆 (Modeyso®) 详情页	爵士制药（爱尔兰）	实体肿瘤	1 岁及以上儿童患有 H3 K27M 突变弥漫性中线胶质瘤且在接受过先前治疗后病情出现进展	儿童与成人临床试验 ONC006, ONC013, ONC014, ONC016, and ONC0 (NCT02525692, NCT03295396, NCT03416530, NCT05392374, and NCT03134131)	美国	Label (fda.gov)
35	Selumentinib Sulfate 硫酸氢司美替尼 (Keselugo®) 详情页	阿斯利康制药（英国）	实体肿瘤	患有 1 型神经纤维瘤病（NF1）和无法手术切除并展现症状的丛状神经纤维瘤（PN）的成人和 1 岁以上儿童患者	SPRINKLE 研究	美国	Label (fda.gov)
36	Asparaginase 天冬酰胺酶 (Spectrila®) 详情页	Medac Gesell-schaft fuer klinische Spezial-praeparate mbH (德国)	血液肿瘤	作为抗肿瘤联合治疗的组成部分，用于治疗从出生至 18 岁的儿科患者及成人的急性淋巴细胞白血病	MC-ASP.5/ALL；MC-ASP.6/INF	欧盟	Asparaginase (Spectrila ®)
37	Nivolumab + Hyaluronidase 纳武单抗 + 透明质酸酶 (OPDIVO QVANTIG® 详情页	百时美施贵宝（美国）	实体肿瘤	12 岁及以上且体重 ≥ 30 kg 的不可切除或转移性黑色素瘤或黑色素瘤辅助治疗	将成人数据外推至小儿患者	美国	FDA Label
			实体肿瘤	12 岁及以上、体重至少 30 kg 的不可切除或转移性 MSI-H/dMMR 结直肠癌患者	将成人数据外推至小儿患者	美国	
38	Inotuzumab ozogamicin 奥加伊妥珠单抗 (Besponsa®) 详情页	辉瑞制药（美国）	血液肿瘤	欧盟于 2026 年上半年将 Besponsa 扩展至≥ 1 岁、特定复发 / 难治情形的 CD22+ BCP-ALL 儿童患者；美国同类但更宽的儿科适应症已于 2024 年批准。	ITCC-059 (WI203581; EudraCT 2016-000227-71)	美国；欧盟	Label(fda.gov) Label(EMA)

1 Tisagenlecleucel (KYMRIAH®)

label(fda.gov)
Tisagenlecleucel(EMA_Label)

- **药品类别 : 靶向疗法 (CAR-T 细胞疗法)**
- **原研药厂家 : 诺华制药 (瑞士)**
- **适应症 : 复发或难治性 b 细胞急性淋巴母细胞白血病 (ALL)**

  Indication: Relapsed or Refractory (r/r) B-cell Acute Lymphoblastic Leukemia (ALL)

- **儿童临床试验 (ELIANA, NCT02435849):** KYMRIAH 在复发或难治性 b 细胞急性淋巴母细胞白血病 (B-ALL) 的儿童和青少年中的疗效是通过一项开放标签、多中心、单臂试验进行评估的。这个试验总共筛选了 107 名患者，88 名被纳入研究，68 名接受了治疗，而 63 名患者情况用于疗效评估。治疗包括在接受一次 KYMRIAH 的单剂量后，进行淋巴清除条件化疗 (氟达拉滨每日 30 mg/m2 ，为期 4 天，和环磷酰胺每日 500mg/m2，为期 2 天)。在白血球 (WBC) 计数 <1000/μL 的 22 名患者中，有 20 名在接受 KYMRIAH 之前接受了淋巴减少化疗，而有 2 名在未经淋巴减少化疗的情况下接受了 KYMRIAH 注射。在入组和淋巴减少化疗之间，有 53 名患者接受了过渡 (bridging) 化疗。KYMRIAH 的疗效基于输注后 3 个月内实现完全缓解 (CR)，完全缓解持续时间，以及通过流式细胞术检测达到完全缓解和极小残余病变 (MRD)< 0.01% 的患者比例 (MRD 阴性)(见表 11)。在 63 名接受输注的患者中，52 名 (83%) 实现了完全缓解 / 完全缓解但血细胞计数不完全恢复，其中全部为 MRD 阴性。在从治疗反应开

始的中位随访时间为 4.8 个月的情况下，完全缓解 / 完全缓解但血细胞计数不完全恢复的中位持续时间尚未达到 (范围 : 1.2 至 14.1+ 个月)。完全缓解 / 完全缓解但血细胞计数不完全恢复的中位发生时间为 29 天，50 名 /52 名 (96%) 反应者的完全缓解 / 完全缓解但血细胞计数不完全恢复发生在 26 至 31 天之间。在实现完全缓解 / 完全缓解但血细胞计数不完全恢复的患者中，进行干细胞移植的比例为 12%(6/52)。

The efficacy of KYMRIAH in pediatric and young adults with r/r B-cell precursor ALL was evaluated in an open-label, multicenter single-arm trial. In total, 107 patients were screened, 88 were enrolled, 68 were treated, and 63 were evaluable for efficacy. Treatment consisted of lymphodepleting chemotherapy (fludarabine 30 mg/m2 daily for 4 days and cyclophosphamide 500 mg/m2 daily for 2 days) followed by a single dose of KYMRIAH. Of the 22 patients who had a WBC count <1000/μL, 20 received lymphodepleting chemotherapy prior to KYMRIAH while 2 received KYMRIAH infusion without lymphodepleting chemotherapy. Fifty-three patients received bridging chemotherapy between time of enrollment and lymphodepleting chemotherapy. The efficacy of KYMRIAH was established on the basis of complete remission (CR) within 3 months after infusion, the duration of CR, and proportion of patients with CR and minimal residual disease (MRD) < 0.01% by flow cytometry (MRD-negative) (Table 11). Among the 63 infused patients, 52 (83%) achieved CR/CRi, all of which were MRDnegative. With a median follow-up of 4.8 months from response, the median duration of CR/CRi was not reached (range: 1.2 to 14.1+ months). Median time to onset of CR/CRi was 29 days with onset of CR/CRi between 26 and 31 days for 50/52 (96%) responders. The stem cell transplantation rate among those who achieved CR/CRi was 12% (6/52).

2 Nelarabine 奈拉滨 (ARRANON®)

arranon (novartis.com)

Tisagenlecleucel(EMA_Label)

- **药品类别 : 细胞毒性药物 (化疗药)(2 线药)**
- **原研药厂家 : 诺华制药 (瑞士)**
- **适应症 : 1 岁及以上复发或难治性 T 淋巴母细胞白血病 /T 淋巴母细胞淋巴瘤**

  Indication: T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) in adult and pediatric patients age 1 year and older

- **儿童临床试验 PGA2001(COG P9673):** RRANON® 在儿科患者中的安全性和有效性是通过一项临床试验进行研究的 : 这是一项第二期、两阶段、开放标签的奈拉比林 (nelarabine) 研究，对象是在初次诊断时年龄 <=21 岁、患有复发性或难治性 T-ALL 或 T-NHL 的受试者。84 名患者中，有 39 名曾接受两个或更多次先前的诱导疗程，接受了每日 650 mg/m2 的 ARRANON，通过静脉注射，每天持续 1 小时，连续 5 天，每 21 天重复一次。如果患者在治疗过程中出现 2 级或更严重神经毒性的体征或症状，应停止继续使用 ARRANON 进行治疗。主要的有效性分析将是在治疗的第 21 天评估早期部分骨髓反应率 (或更好骨髓反应率)。早期部分骨髓反应要求在第 21 天时骨髓母细胞 <25%，而早期完全骨髓反应则要求在第 21 天时骨髓母细胞 <5%。

The safety and efficacy of ARRANON in pediatric patients were studied in a clinical trial: a phase II, two-stage, open label study of nelarabine in subjects with relapsed or refractory T-ALL or T-NHL who were <=21 years of age at initial diagnosis. Eighty-four (84) patients, 39 of whom had received two or more prior induction regimens, were treated with 650 mg/m2/day of ARRANON administered intravenously over 1 hour daily for 5 consecutive days repeated every 21 days. Patients who experienced signs or symptoms of Grade 2 or greater neurologic toxicity on therapy were to be discontinued from further therapy with ARRANON. The primary efficacy analysis would be the assessment of the early partial (or better) marrow response rate at day 21 of treatment. An early partial marrow response required<25% bone marrow blasts and an early complete marrow response required <5% bone marrow blasts at day 21.

- **海外仿制药：Nelarabine-Reach 奈拉滨 (nelarabine)**
- 药品使用说明书 : Nelarabine-Reach(nelarabine)
- 仿制药厂家 : 瑞奇制药 (澳大利亚)
- 适应症 : 与诺华制药的原研药 Nelarabine 奈拉滨 (ARRANON®) 一致。
- 海外仿制药 Nelarabine-Reach 和赛诺菲的原研药 Nelarabine(ARRANON®) 均未在中国上市并获批儿童肿瘤适应症。

3 Gemtuzumab-Ozogamicin 吉妥单抗 (MYLOTARG ™)

LABEL (fda.gov)
Population Pharmacokinetics of Gemtuzumab Ozogamicin in Pediatric Patients with Relapsed or Refractory Acute Myeloid Leukemia | Clinical Pharmacokinetics (springer.com)
Mylotarg(TGA_Approval)

- **药品类别 : 靶向疗法**
- **原研药厂家 : 辉瑞制药 (美国)**
- **适应症 : 2 岁及以上复发或难治性 _CD33_ 阳性急性髓细胞白血病**

  Indication: relapsed or refractory CD33-positive acute myeloid leukemia (AML)

- **儿童临床试验 0903A1-102-US phase I/II study：** 本试验研究了在 0903A1-102-US 第 I/II 期研究中，29 名年龄≤ 17 岁、患有复发或难治性急性髓细胞白血病的儿童患者经静脉给药 Gemtuzumab-Ozogamicin 后的人体药代动力学 (popPK)。总 hP67.6 抗体被用来代表 Gemtuzumab-Ozogamicin 药代动力学 (PK)，包括一个双室模型 : 包括线性清除 (CL1) 和包含衰减系数的时间依赖清除，被用来描述这一 Gemtuzumab-Ozogamicin 药代动力学 (PK)。一个包括线性清除和基于抗体清除速率的形成输入速率的双室模型被用来描述去配基卡黄霉素 (UC；荷载) 的 PK。两种模型都包括异速缩放，基线体重对 CL1 和中心容积有固定影响。hP67.6 和 UC 的 PK 参数不受任何可用的人口统计学因素和安全实验室值作为协变量 (基线体重除外) 的显著影响。试验进行了模

拟以比较 Gemtuzumab-Ozogamicin 的剂量方案 (在第 1 天和第 15 天分别为 6、7.5 和 9mg/m2，与在第 1、4 和 7 天分数剂量为 3 mg/m2 的方案相比)，结果显示在更频繁的给药方案下，总抗体和 UC 的低谷浓度在治疗期间保持在较高浓度。

This report describes the popPK of GO following intravenous administration in 29 pediatric patients aged ⩽ 17 years with relapsed or refractory AML who were enrolled in the 0903A1-102-US phase I/II study. The pharmacokinetics (PK) of GO, as represented by total hP67.6 antibody, were described by a two-compartment model with two clearance components: a linear clearance (CL1) and time-dependent clearance that includes a decay coefficient. The PK of unconjugated calicheamicin (UC; payload) were described by a two-compartment model with CL1 and an input rate of formation based on antibody rate of elimination. Allometric scaling was included in both models, with baseline body weight as a fixed effect on CL1 and central volume. PK parameters for hP67.6 and UC were not significantly affected by any of the available demographic factors and safety laboratory values tested as covariates (except baseline body weight). Simulations to compare GO dosing regimens (6, 7.5, and 9 mg/m2 on days 1 and 15 versus, 3 mg/m2 fractionated dosing on days 1, 4, and 7) were performed, showing that total antibody and UC trough concentrations were maintained at higher concentrations during treatment following the more frequent dosing than following the original regimen.

4 Calaspargase Pegol-mknl 长效聚乙二醇化天冬酰胺酶 (ASPARLAS ™)

LABEL (fda.gov)

- **药品类别 : 细胞毒性药物 (化疗药)**
- **原研药厂家 : 施维雅 (法国)**
- **适应症 : 1 个月到 21 岁的急性淋巴细胞白血病患者**

Indication: A component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia in pediatric and young adult patients age 1 month to 21 years.

- **儿童临床试验 (Study AALL07P4, Study DFCI 11-001) ：** 疗效的确定基于通过每 3 周静脉注射 ASPARLAS 2500 U/m2 来展示达到和维持最低血清天冬酶酶活性 (NSAA) 在 0.1 U/mL 以上的水平。在与多药化疗联合使用时，对 124 名 B 细胞系急性淋巴细胞白血病 (ALL) 患者的 ASPARLAS 药代动力学进行了研究。结果显示，在第 6、12、18、24 和 30 周，124 名患者中有 123 名 (99%，95% CI: 96% - 100%) 保持最低血清天冬酶酶活性 > 0.1 U/mL。

The determination of efficacy was based on a demonstration of the achievement and maintenance of nadir serum asparaginase activity (NSAA) above the level of 0.1 U/mL using ASPARLAS 2500 U/m2 intravenously every 3 weeks. The pharmacokinetics of ASPARLAS were studied when used in combination with multiagent chemotherapy in 124 patients with B cell lineage acute lymphoblastic

leukemia (ALL). The results showed that 123 (99%, 95% CI: 96% - 100%) of the 124 patients maintained NSAA > 0.1 U/mL at weeks 6, 12, 18, 24 and 30.

5 sparaginase Erwinia Chrysanthemi (Recombinant)-rywn 菊欧文氏菌 (重组) 天冬酰胺酶 (RYLAZE ™)

label (fda.gov)
Crisantaspase(TGA_Approval)
Enrylaze(EMA_Label)

- **药品类别 : 细胞毒性药物 (化疗药)(2 线药)**
- **原研药厂家 : 爵士制药 (爱尔兰)**
- **适应症 : 1 个月及以上对大肠杆菌衍生的天冬氨酰胺酶过敏的急性淋巴母细胞白血病 (ALL) 和淋巴母细胞淋巴瘤 (LBL) 儿童患者**

  Indication: acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) in pediatric patients 1 month or older who have developed hypersensitivity to E. coli-derived asparaginase

- **儿童试验 JZP458-201 (NCT04145531):** RYLAZE ™对于患有急性淋巴细胞白血病或淋巴母细胞性淋巴瘤且对大肠杆菌来源的天门冬酸天冬酰胺酶产生过敏反应的患者的治疗效果在研究中进行了评估。该研究为一项开放标签、多队列、多中心试验。治疗方案包括 RYLAZE ™以不同剂量，每周一、三和五肌肉注射，共 6 次，以替代每次泊加天冬酰胺酶的剂量。97 名 (94%) 患者曾对泊加天冬酰胺酶产生过敏反应，6 名患者 (7%) 报告了无症状的灭活情况。疗效的确定基于对达到和保持低谷血清天冬酸天冬酰胺酶活性 (NSAA) 高于 0.1

U/mL 水平的证明。建模和模拟结果显示，对于每 48 小时肌肉注射 25 mg/m2 的剂量，RYLAZE ™用药后 48 小时维持最低血清天冬酶酶活性 ⩾ 0.1 U/mL 的患者比例为 93.6%(95% CI: 92.6%, 94.6%)。

The efficacy of RYLAZE for the treatment of patients with acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LBL) who have developed hypersensitivity to E. coli-derived asparaginase as a component of a multi-agent chemotherapeutic regimen was evaluated in Study, an open-label, multi-cohort, multicenter trial. A treatment course consisted of RYLAZE at various dosages administered intramuscularly every Monday, Wednesday, and Friday for a total of 6 doses to replace each dose of pegaspargase. For the 102 patients treated, the median age was 10 years (range, 1-24 years). Ninety-seven (94%) patients had experienced a hypersensitivity reaction to pegaspargase, and 6 patients (7%) had reported silent inactivation. The determination of efficacy was based on a demonstration of the achievement and maintenance of nadir serum asparaginase activity (NSAA) above the level of 0.1 U/mL. The results of modeling and simulations showed that for a dosage of 25 mg/m2 administered intramuscularly every 48 hours, the proportion of patients maintaining NSAA ⩾ 0.1 U/mL at 48 hours after a dose of RYLAZE was 93.6% (95% CI: 92.6%, 94.6%) .

6 Brentuximab Vedotin 维布妥昔单抗 (ADCETRIS®)

label (fda.gov)

- **药品类别 : 抗体药物偶联物 (Antibody-Drug Conjugate, ADC)**
- **原研药厂家 : 武田 (日本) 和西雅图遗传学公司 (美国)**
- **适应症 : 2 岁及以上未经治疗的高危经典霍奇金淋巴瘤 (cHL)**

  Indication: 2 years and older with previously untreated high risk classical Hodgkin lymphoma (cHL), in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide

- **儿童临床试验 AHOD1331(NCT02166463):** 在一项随机、开放标签、主动对照试验中，评估了 ADCETRIS® 联合化疗治疗既往未治疗的高危经典霍奇金淋巴瘤儿科患者 (2 至 <22 岁) 的疗效。疗效是根据无事件生存期 (EFS) 确定的，定义为从随机分配到最早的疾病进展或复发、第二次恶性肿瘤或任何原因导致的死亡的时间。在随机分配的 600 例患者中，300 例随机分配到 ADCETRIS+ 阿霉素 [A]、长春新碱 [V]、依托泊苷 (E)、泼尼松 (P)、环磷酰胺 [C] (ADCETRIS+AVEPC) 组，300 例随机分配到 A+ 博莱霉素 [B]+V+E+P+C (ABVE-PC) 组。ADCETRIS+AVEPC 组的儿童中，事件无进展生存率为 23%，而 ABVE-PC 组为 52%。

  The efficacy of ADCETRIS in combination with chemotherapy for the treatment of pediatric patients (2 to <22 years of age) with previously untreated high

risk cHL was evaluated in a randomized, open-label, actively controlled trial. Efficacy was established based on event-free-survival (EFS), defined as the time from randomization to the earliest of disease progression or relapse, second malignancy, or death due to any cause. Of the 600 total patients randomized, 300 were randomized to ADevent-free survivalCETRIS + Doxorubicin [A], Vincristine [V], Etoposide [E], Prednisone [P], Cyclophosphamide [C] (ADCETRIS + AVEPC) arm and 300 patients were randomized to A+ Bleomycin [B]+V+E+P+C (ABVE-PC) arm.

7 Pembrolizumab 帕博利珠单抗 (KEYTRUDA®)

label (fda.gov)

Pembrolizumab(EMA_Label)

- **药品类别 : 免疫疗法**
- **原研药厂家 : 默克药厂 (美国)**
- **适应症 1: 小儿难治性经典霍奇金淋巴瘤 (cHL)，或经过 2 线或更多线治疗后复发的经典霍奇金淋巴瘤**

  Indication 1: refractory Classical Hodgkin Lymphoma (cHL), or Classical Hodgkin Lymphoma that has relapsed after 2 or more lines of therapy

- **儿童用药说明：** KEYTRUDA® 作为单药治疗小儿难治性经典霍奇金淋巴瘤患者的安全性和有效性已得到证实。在儿童患者中使用 KEYTRUDA® 治疗这些适应症得到了充分和良好对照的成人研究证据的支持，并提供了儿童患者额外的药代动力学和安全性数据。

  The safety and effectiveness of KEYTRUDA as a single agent have been established in pediatric patients with cHL. Use of KEYTRUDA in pediatric patients for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients.

- **成人试验 1 KEYNOTE-204 (NCT02684292)：** 一项在 304 例复发或难治性 cHL 患者中进行的随机、开放标签、积极对照试验。该试验招募了至少

一种多药化疗方案后复发或难治性疾病的成年人。患者被随机 (1: 1) 接受 : 1. KEYTRUDA 200mg 静脉注射，每 3 周一次或，2. 维布妥昔单抗 1.8 mg/kg 静脉注射，每 3 周一次。

A randomized, open label, active controlled trial conducted in 304 patients with relapsed or refractory cHL. The trial enrolled adults with relapsed or refractory disease after at least one multi-agent chemotherapy regimen. Patients were randomized (1: 1) to receive 1.KEYTRUDA 200 mg intravenously every 3 weeks or, 2.Brentuximab vedotin (BV) 1.8 mg/kg intravenously every 3 weeks.

- **适应症 2: 原发性纵隔大 B 细胞淋巴瘤**

Indication 2: Primary Mediastinal Large B-Cell Lymphoma, PMBCL

- **儿童用药说明：** KEYTRUDA® 作为单药治疗小儿原发性纵隔大 B 细胞淋巴瘤患者的安全性和有效性已经得到证实。在儿童患者中使用 KEYTRUDA® 治疗这些适应症得到了充分和良好对照的成人研究证据的支持，并提供了儿童患者额外的药代动力学和安全性数据。Keytruda 不推荐用于需要紧急细胞减灭手术的 PMBCL 患者。

The safety and effectiveness of KEYTRUDA as a single agent have been established in pediatric patients with PMBCL. Use of KEYTRUDA in pediatric patients for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients. Keytruda is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

- **成人试验 1 KEYNOTE-170 (NCT02576990)：** 一项多中心、开放标签、单臂试验，纳入了 53 名复发或难治性原发性纵隔大 B 细胞淋巴瘤患者。患者每 3 周静脉注 KEYTRUDA 200mg，直到不可接受的毒性或记录的疾病进展，或对没

有进展的患者进行长达 24 个月的治疗。客观缓解率为 45%(95%CI: 32，60)，包括 11% 的完全缓解和 34% 的部分缓解。随访期间未达到中位应答持续时间 (中位 9.7 个月)。首次客观缓解 (完全缓解或部分缓解) 的中位时间为 2.8 个月；不建议将 pembrolizumab 用于治疗需要紧急细胞减灭治疗的 PMBCL 患者。

A multicenter, openlabel, single-arm trial in 53 patients with relapsed or refractory PMBCL. Patients were treated with KEYTRUDA 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression, or for up to 24 months for patients who did not progress. For the 24 responders, the median time to first objective response (complete or partial response) was 2.8 months (range 2.1 to 8.5 months).

- **适应症 3：梅克尔细胞癌**

Indication 3: Merkel Cell Carcinoma, MCC

- **儿童用药说明：** KEYTRUDA 作为单药治疗小儿梅克尔细胞癌患者的安全性和有效性已经得到证实。在儿童患者中使用 KEYTRUDA 治疗这些适应症得到了充分和良好对照的成人研究证据的支持，并提供了儿童患者额外的药代动力学和安全性数据。

The safety and effectiveness of KEYTRUDA as a single agent have been established in pediatric patients with MCC. Use of KEYTRUDA in pediatric patients for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients.

- **成人试验 KEYNOTE-017 (NCT02267603)：** 一项多中心、非随机、开放标签的试验，招募了 50 名复发性局部晚期或转移性梅克尔细胞癌患者，这些患者此前未接受过针对晚期疾病的全身治疗。主要疗效指标是客观缓解率 (ORR) 和反应持续时间，由独立的中央盲审机构根据 RECIST 1.1 进行评估。客

观缓解率为 56%(95% CI: 41, 70)，完全缓解率为 24%。在 28 例有缓解的患者中，96% 的反应持续时间超过 6 个月，54% 的反应持续时间超过 12 个月。

A multicenter, nonrandomized, open-label trial that enrolled 50 patients with recurrent locally advanced or metastatic MCC who had not received prior systemic therapy for their advanced disease. The primary efficacy measures were objective response rate (ORR) and duration of response, as assessed by an independent central blind review facility according to RECIST 1.1. The objective response rate was 56% (95% CI: 41, 70) and the complete response rate was 24%. Of the 28 patients who had a response, 96 percent had a response lasting longer than six months and 54 percent had a response lasting longer than 12 months.

- **适应症 4：微卫星高度不稳定性或错配修复缺陷癌**

  Indication 4: microsatellite instability-high (MSI-H) or mismatch repair deficient cancer

- **儿童用药说明：**KEYTRUDA 作为单药治疗卫星不稳定性高或错配修复缺陷癌患儿的安全性和有效性已经得到证实。在儿童患者中使用 KEYTRUDA 治疗这些适应症得到了充分和良好对照的成人研究证据的支持，并提供了儿童患者额外的药代动力学和安全性数据。

The safety and effectiveness of KEYTRUDA as a single agent have been established in pediatric patients with MSI-H cancer. Use of KEYTRUDA in pediatric patients for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients.

- **适应症 5：肿瘤突变负荷高**

  Indication 5 : Tumor Mutational Burden-High Cancer, TMB-H

- **儿童用药说明：**KEYTRUDA 作为单药治疗小儿肿瘤突变负荷高癌症的安全性和有效性已经得到证实。在儿童患者中使用 KEYTRUDA 治疗这些适应症得到了充分和良好对照的成人研究证据的支持，并提供了儿童患者额外的药代动力学和安全性数据。

  The safety and effectiveness of KEYTRUDA as a single agent have been established in pediatric patients with TMB-H cancer. Use of KEYTRUDA in pediatric patients for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients.

- **成人试验 KEYNOTE-158 (NCT02628067)：**一项多中心、非随机、开放标签试验。1050 例患者被纳入疗效分析人群。根据协议规定的检测要求，对 790 例有足够组织进行检测的患者进行肿瘤基因突变负荷 (TMB) 分析。在 790 例患者中，102 例 (13%) 的肿瘤被确定为 TMB- h，定义为 TMB ⩾ 10 个突变 / 兆碱基。

  A multicenter, non-randomized, open-label trial.1050 patients were included in the efficacy analysis population. TMB was analyzed in the subset of 790 patients with sufficient tissue for testing based on protocol-specified testing requirements. Of the 790 patients, 102 (13%) had tumors identified as TMB-H, defined as TMB ⩾ 10 mutations per mega base.

- **适应症 6:** KEYTRUDA 作为单药治疗 12 岁及以上患有晚期 (不可切除或转移性) 黑色素瘤的成人和青少年，以及适用于 12 岁及以上已接受完全切除的 II B 期、II C 期或 III 期黑色素瘤患者的辅助治疗。

  Indication 6 : KEYTRUDA as monotherapy is indicated for the treatment of adults and adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma, and for the adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB, IIC or III melanoma and who have undergone complete resection.

- **儿童临床试验 (KEYNOTE-051):**173 名患有晚期黑色素瘤或 PD-L1 阳性晚期、复发或难治性实体瘤或淋巴瘤的儿科患者 (65 名 6 个月至 12 岁以下的儿童和 108 名 12 岁至 17 岁的青少年) 每 3 周接受一次 2 毫克 / 千克体重的 pembrolizumab 治疗。所有患者接受的 pembrolizumab 剂量中位数为 4 剂 (范围 : 1-35 剂)，其中 138 名患者 (85.7%) 接受了 2 剂或 2 剂以上的 pembrolizumab 治疗。针对青少年黑色素瘤患者的临床研究数据非常有限，因此将成人数据推断至小儿患者来确定疗效。在接受 KEYNOTE-051 治疗的 5 名晚期黑色素瘤青少年参与者中，没有患者获得完全或部分缓解，1 名患者病情稳定。

  173 pediatric patients (65 children aged 6 months to less than 12 years and 108 adolescents aged 12 years to 17 years) with advanced melanoma or PD-L1 positive advanced, relapsed, or refractory solid tumours or lymphoma were administered pembrolizumab 2 mg/kg bw every 3 weeks. All patients received pembrolizumab for a median of 4 doses (range: 1-35 doses), with 138 patients (85.7%) receiving pembrolizumab for 2 doses or more. Data from clinical studies in adolescent melanoma patients is very limited and extrapolation from adult data has been used to establish efficacy. Among the 5 adolescent participants

with advanced melanoma treated on KEYNOTE-051, no patient had a complete or a partial response, and 1 patient had stable disease.

- **成人试验 (KEYNOTE-006):** KEYNOTE-006 是一项多中心、开放标签、对照 III 期研究，用于既往未接受伊匹单抗治疗的晚期黑色素瘤患者。834 名患者 (年龄范围 : 18-89 岁) 被随机分配 (1: 1: 1) 接受 pembrolizumab 10 mg/kg 体重，每 2 周 (n=279) 或 3 周 (n=277) 一次，或接受伊匹单抗 3 mg/kg 体重，每 3 周一次 (n=278)。BRAFV600E 突变型黑色素瘤患者无需既往接受过 BRAF 抑制剂治疗。主要疗效结果指标为无进展生存期 (PFS) 和总生存期 (OS)。次要疗效结果指标为客观缓解率 (ORR) 和缓解持续时间。

  The safety and efficacy of pembrolizumab were investigated in KEYNOTE-006, a multicentre, open-label, controlled, Phase III study for the treatment of advanced melanoma in patients who were naïve to ipilimumab. 834 Patients (age range: 18-89) were randomised (1: 1: 1) to receive pembrolizumab 10 mg/kg bw every 2 (n=279) or 3 weeks (n=277) or ipilimumab 3 mg/kg bw every 3 weeks (n=278). Patients with BRAFV600E mutant melanoma were not required to have received prior BRAF inhibitor therapy. The primary efficacy outcome measures were progression-free survival (PFS) and overall survival (OS). Secondary efficacy outcome measures were objective response rate (ORR) and response duration.

Table 3: Efficacy results in KEYNOTE-006

Endpoint	Pembrolizumab 10 mg/kg bw every 3 weeks n=277	Pembrolizumab 10 mg/kg bw every 2 weeks n=279	Ipilimumab 3 mg/kg bw every 3 weeks n=278
OS			
Number (%) of patients with event	119 (43%)	122 (44%)	142 (51%)
Hazard ratio* (95% CI)	0.68 (0.53, 0.86)	0.68 (0.53, 0.87)	---
p-Value†	< 0.001	< 0.001	---
Median in months (95% CI)	Not reached (24, NA)	Not reached (22, NA)	16 (14, 22)
PFS			
Number (%) of patients with event	183 (66%)	181 (65%)	202 (73%)
Hazard ratio* (95% CI)	0.61 (0.50, 0.75)	0.61 (0.50, 0.75)	---
p-Value†	< 0.001	< 0.001	---
Median in months (95% CI)	4.1 (2.9, 7.2)	5.6 (3.4, 8.2)	2.8 (2.8, 2.9)
Best objective response			
ORR % (95% CI)	36% (30, 42)	37% (31, 43)	13% (10, 18)
Complete response	13%	12%	5%
Partial response	23%	25%	8%
Response duration‡			
Median in months (range)	Not reached (2.0, 22.8+)	Not reached (1.8, 22.8+)	Not reached (1.1+, 23.8+)
% ongoing at 18 months	68%§	71%§	70%§

* Hazard ratio (pembrolizumab compared to ipilimumab) based on the stratified Cox proportional hazard model
† Based on stratified log-rank test
‡ Based on patients with a best objective response as confirmed complete or partial response
§ Based on Kaplan-Meier estimation
NA = not available

- **成人试验 (KEYNOTE-002):** 对曾接受过伊匹单抗治疗的黑色素瘤患者进行的对照研究。KEYNOTE-002 是一项治疗晚期黑色素瘤的多中心、双盲、对照研究，研究对象是 540 名曾接受过伊匹单抗治疗的患者 (年龄范围 : 15-89 岁)，如果 BRAF V600 突变阳性，则接受 BRAF 或 MEK 抑制剂治疗。患者被随机分配 (1: 1: 1) 接受每 3 周剂量为 2 毫克 / 千克体重 (180 人) 或 10 毫克 / 千克体重 (181 人) 的 pembrolizumab 或化疗 (179 人，包括达卡巴嗪、替莫唑胺、卡铂、紫杉醇或卡铂 + 紫杉醇)。主要疗效指标是由 IRO 使用 RECIST 1.1 版评估的无进展生存期 (PFS) 和总生存期 (OS)。

Controlled study in melanoma patients previously treated with ipilimumab. The safety and efficacy of pembrolizumab were investigated in KEYNOTE-002,

a multicentre, double-blind, controlled study for the treatment of advanced melanoma in 540 patients (age range: 15-89) previously treated with ipilimumab and if BRAF V600 mutation-positive, with a BRAF or MEK inhibitor. Patients were randomised (1: 1: 1) to receive pembrolizumab at a dose of 2 (n=180) or 10 mg/kg bw (n=181) every 3 weeks or chemotherapy (n=179; including dacarbazine, temozolomide, carboplatin, paclitaxel, or carboplatin+paclitaxel). The primary efficacy outcome measures were PFS as assessed by IRO using RECIST version 1.1 and OS.

Table 4: Efficacy results in KEYNOTE-002

Endpoint	Pembrolizumab 2 mg/kg bw every 3 weeks n=180	Pembrolizumab 10 mg/kg bw every 3 weeks n=181	Chemotherapy n=179
PFS			
Number (%) of patients with event	150 (83%)	144 (80%)	172 (96%)
Hazard ratio* (95% CI)	0.58 (0.46, 0.73)	0.47 (0.37, 0.60)	---
p-Value†	< 0.001	< 0.001	---
Median in months (95% CI)	2.9 (2.8, 3.8)	3.0 (2.8, 5.2)	2.8 (2.6, 2.8)
OS			
Number (%) of patients with event	123 (68%)	117 (65%)	128 (72%)
Hazard ratio* (95% CI)	0.86 (0.67, 1.10)	0.74 (0.57, 0.96)	---
p-Value†	0.1173	0.0106‡	---
Median in months (95% CI)	13.4 (11.0, 16.4)	14.7 (11.3, 19.5)	11.0 (8.9, 13.8)
Best objective response			
ORR % (95% CI)	22% (16, 29)	28% (21, 35)	5% (2, 9)
Complete response	3%	7%	0%
Partial response	19%	20%	5%
Response duration§			
Median in months (range)	22.8 (1.4+, 25.3+)	Not reached (1.1+, 28.3+)	6.8 (2.8, 11.3)
% ongoing at 12 months	73%¶	79%¶	0%¶

* Hazard ratio (pembrolizumab compared to chemotherapy) based on the stratified Cox proportional hazard model
† Based on stratified log-rank test
‡ Not statistically significant after adjustment for multiplicity
§ Based on patients with a best objective response as confirmed complete or partial response from the final analysis
¶ Based on Kaplan-Meier estimation

- **成人试验 (KEYNOTE-001):** 针对未接受过伊匹单抗治疗和曾接受过伊匹单抗治疗的黑色素瘤患者进行的开放标签研究。KEYNOTE-001 的无对照开放标签研究对 pembrolizumab 治疗晚期黑色素瘤患者的安全性和有效性进行了调查。该研究评估了来自两个确定队列的 276 名患者 (年龄范围 : 18-88 岁) 的疗效，其中一个队列包括既往接受过伊匹单抗治疗的患者 (如果 BRAF V600 突变阳性，则接受 BRAF 或 MEK 抑制剂治疗)，另一个队列包括未接受过伊匹单

抗治疗的患者。患者被随机分配接受 pembrolizumab 治疗，剂量为每 3 周 2 mg/kg 体重或每 3 周 10 mg/kg 体重。患者接受 pembrolizumab 治疗，直至疾病进展或出现不可接受的毒性反应。临床病情稳定但有初步疾病进展证据的患者可继续接受治疗，直至疾病进展得到确认。主要疗效结局指标是采用 RECIST 1.1 进行独立审查评估的 客观缓解率 (ORR)。次要疗效指标为疾病控制率 (DCR，包括完全缓解、部分缓解和疾病稳定)、缓解持续时间、无进展生存期 (PFS) 和总生存期 (OS)。

Open-label study in melanoma patients naïve and previously treated with ipilimumab. The safety and efficacy of pembrolizumab for patients with advanced melanoma were investigated in an uncontrolled, open-label study, KEYNOTE-001. Efficacy was evaluated for 276 patients (age range: 18-88) from two defined cohorts, one which included patients previously treated with ipilimumab (and if BRAF V600 mutation-positive, with a BRAF or MEK inhibitor) and the other which included patients naïve to treatment with ipilimumab. Patients were randomly assigned to receive pembrolizumab at a dose of 2 mg/kg bw every 3 weeks or 10 mg/kg bw every 3 weeks. Patients were treated with pembrolizumab until disease progression or unacceptable toxicity. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. The primary efficacy outcome measure was ORR as assessed by independent review using RECIST 1.1. Secondary efficacy outcome measures were disease control rate (DCR; including complete response, partial response and stable disease), response duration, PFS and OS.

Table 5: Efficacy results in KEYNOTE-001

Endpoint	Pembrolizumab 2 mg/kg bw every 3 weeks in patients previously treated with ipilimumab n=89	Pembrolizumab 2 mg/kg bw every 3 weeks in patients naïve to treatment with ipilimumab n=51
Best objective response* by IRO†		
ORR % (95% CI)	26% (17, 36)	35% (22, 50)
Complete response	7%	12%
Partial response	19%	24%
Disease control rate %‡	48%	49%
Response duration§		
Median in months (range)	30.5 (2.8+, 30.6+)	27.4 (1.6+, 31.8+)
% ongoing at 24 months¶	75%	71%
PFS		
Median in months (95% CI)	4.9 (2.8, 8.3)	4.7 (2.8, 13.8)
PFS rate at 12 months	34%	38%
OS		
Median in months (95% CI)	18.9 (11, not available)	28.0 (14, not available)
OS rate at 24 months	44%	56%

* Includes patients without measurable disease at baseline by independent radiology
† IRO = Integrated radiology and oncologist assessment using RECIST 1.1
‡ Based on best response of stable disease or better
§ Based on patients with a confirmed response by independent review, starting from the date the response was first recorded; n=23 for patients previously treated with ipilimumab; n=18 for patients naïve to treatment with ipilimumab
¶ Based on Kaplan-Meier estimation

8 Rituximab 利妥昔单抗 (RITUXAN®)

label (fda.gov)

- **药品类别 : 单克隆抗体**
- **原研药厂家 : 基因泰克 (美国)**
- **适应症 : 6 个月及以上未治疗的晚期 cd20 阳性 DLBCL(CD20 阳性的弥漫大 B 细胞淋巴瘤)/BL(Burkitt 淋巴瘤)/BLL(B 淋巴细胞白血病)/B-AL(急性 B 细胞白血病) 患者**

Indication: Previously untreated, advanced stage, CD20-positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), Burkitt-like lymphoma (BLL) or mature B-cell acute leukemia (B-AL) in pediatric patients aged 6 months and older

- **儿童临床试验 Inter-B-NHL Ritux 2010, NCT01516580：** 一项多中心、开放标签、随机试验，研究对象是 6 个月及以上的未治疗的晚期 cd20 阳性 DLBCL(CD20 阳性的弥漫大 B 细胞淋巴瘤)/BL(Burkitt 淋巴瘤)/BLL(B 淋巴细胞白血病)/B-AL(急性 B 细胞白血病) 患者。患者分为两组 : LMB 和 R-LMB (Rituxan®+LMB)。他们被随机分配到 Lymphome Malin B (LMB) 化疗组 (皮质类固醇，长春新碱，单用环磷酰胺、大剂量甲氨蝶呤、阿糖胞苷、阿霉素、依托泊苷和三联药物 [甲氨蝶呤 / 阿糖胞苷 / 皮质类固醇] 鞘内治疗) 或与 RITUXAN® 合用或非美国获得许可的利妥昔单抗，根据 LMB 方案，以 375 mg/m2 BSA 的剂量注射 6 次 RITUXAN® IV(两个诱导疗程各 2 次，两个巩固

疗程各 1 次)。研究发现，在 LMB 组中有 28 个事件 (Event)，而在利妥昔单抗—LMB 组中有 10 个 (Event),(风险比为 0.32；90% 可信区间 : 0.17，0.58；p=0.0012)。

RITUXAN® in combination with chemotherapy was evaluated in Inter-B-NHL Ritux 2010 (NCT01516580), a multicenter, open-label, randomized trial of patients with previously untreated, advanced stage, CD20-positive DLBCL/BL/BLL/B-AL aged 6 months and older. Patients are divided into two groups: LMB and R-LMB (Rituxan+LMB). They were randomized to Lymphome Malin B (LMB) chemotherapy (corticosteroids, vincristine, cyclophosphamide, high-dose methotrexate, cytarabine, doxorubicin, etoposide and triple drug [methotrexate/cytarabine/corticosteroid] intrathecal therapy) alone or in combination with RITUXAN® or non-U.S. licensed rituximab, administered as six infusions of RITUXAN® IV at a dose of 375 mg/ m2 BSA (two doses during each of the two induction courses and one during each of the two consolidation courses) as per the LMB scheme.

- **国产仿制药 : 利妥昔单抗注射液 (汉利康 ®)**
- 药品使用说明书 : 利妥昔单抗
- 仿制药厂家 : 上海复宏汉霖生物制药有限公司
- 适应症 1: 只适用于成人复发或耐药的滤泡性中央型淋巴瘤 (国际工作分类 B、C 和 D 亚型的 B 细胞非霍奇金淋巴瘤) 的治疗。
- 适应症 2: 只适用于成人先前未经治疗的 CD20 阳性 III-IV 期滤泡性非霍奇金淋巴瘤，患者应与化疗联合使用。
- 适应症 3: 只适用于成人 CD20 阳性弥漫大 B 细胞性非霍奇金淋巴瘤 (DLBCL) 应与标准 CHOP 化疗 (环磷酰胺、阿霉素、长春新碱、强的松)8 个周期联合治疗。
- **国产仿制药利妥昔单抗注射液 (汉利康 ®) 在中国上市但未获批儿童肿瘤适应症。**

9 Dasatinib 达沙替尼 (Sprycel®)

SPRYCEL U.S. Prescribing Information (bms.com)

Dasatinib(EMA_Label)

- **药品类别 : 蛋白激酶抑制剂**
- **原研药厂家 : 百时美施贵宝 (美国)**
- **适应症 1: 1 岁及以上费城染色体阳性 Ph+ 急性淋巴细胞白血病**

Indication 1: newly diagnosed Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL)

- **儿童临床试验 CA180372 (NCT01460160)：** Sprycel® 片剂联合化疗的疗效在 2 期、多中心、单组 CA180-372 研究的单队列中进行评估，该研究包括 78 名新诊断的 b 细胞前体 Ph+ ALL 的儿科患者。在 3 年的研究中，无事件生存 (EFS) 二元率为 64.1%(95%CI[CI]: 52.4 至 74.7)。无事件生存期定义为从 Sprycel® 开始到第三个高危期结束时无完全缓解、复发、继发恶性肿瘤或任何原因死亡的时间。在诱导结束时，75 名患者 (96%) 的骨髓中淋巴细胞含量为 5%，而在巩固结束时，76 名患者 (97%) 达到了这一水平。

The efficacy of Sprycel® tablets in combination with chemotherapy was evaluated in a single cohort of the Phase 2, multicenter, single-arm CA180-372 study, which included 78 pediatric patients with newly diagnosed B-cell precursor Ph+ ALL. Efficacy was established on the basis of 3-year event-free survival (EFS), defined as the time from the start of SPRYCEL to lack of complete response at the end of the third high risk block, relapse, secondary malignancy, or death from any cause. The

3-year EFS binary rate for patients on Study CA180372 was 64.1% (95% CI: 52.4, 74.7). At the end of induction, 75 patients (96%) had a bone marrow with <5% lymphoblasts, and 76 patients (97%) achieved this by the end of consolidation.

- **适应症 2：1 岁及以上费城染色体阳性 Ph+ 慢性骨髓性白血病**

Indication 2: newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase

- **儿童临床试验 (NCT00306202，NCT00777036)：**两项针对 97 例慢性粒细胞白血病患者的儿科研究评估了 SPRYCEL® 在儿科患者中的疗效。在一项开放标签、非随机剂量范围试验 (NCT00306202) 和一项开放标签、非随机、单臂试验 (NCT00777036) 中治疗的 97 例慢性期慢性骨髓性白血病患者中，51 例患者 (仅来自单臂试验) 新诊断为慢性期骨髓性白血病，46 例患者 (17 例来自剂量范围试验，29 例来自单臂试验) 对先前的伊马替尼治疗有耐药或不耐受。97 例儿童患者中有 91 例接受 SPRYCEL® 片 60mg/m2 每日 1 次治疗 (高 BSA 患者最大剂量为 100mg 每日 1 次)。患者接受治疗直至疾病进展或出现不可接受的毒性。

The efficacy of SPRYCEL in pediatric patients was evaluated in two pediatric studies of 97 patients with chronic phase CML. Among 97 patients with chronic phase CML treated in two pediatric studies, an open-label, non-randomized dose-ranging trial (NCT00306202) and an open-label, non-randomized, single-arm trial (NCT00777036), 51 patients (exclusively from the single-arm trial) had newly diagnosed chronic phase CML and 46 patients (17 from the dose-ranging trial and 29 from the single-arm trial) were resistant or intolerant to previous treatment with imatinib. Ninety-one of the 97 pediatric patients were treated with SPRYCEL tablets 60 mg/ m2 once daily (maximum dose of 100 mg once daily for patients with high BSA). Patients were treated until disease progression or unacceptable toxicity.

10 Bosutinib 博苏替尼 (BOSULIF®)

Label (fda.gov)

- **药品类别：酪氨酸激酶抑制剂**
- **原研药厂家：辉瑞制药 (美国)**
- **适应症：1 岁及以上新确诊或耐药或不耐受的慢性期费城染色体阳性慢性髓性白血病 (Ph+ CML)**

  Indication: pediatric patients 1 year of age and older with chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML), newly-diagnosed or resistant or intolerant to prior therapy

- **儿童临床试验 The BCHILD trial(NCT04258943）：**BCHILD 试验是一项多中心、非随机、开放标签的研究，旨在确定每天口服一次 BOSULIF® 的推荐剂量，用于患有新确诊的慢性期费城染色体阳性慢性髓性白血病的儿童患者和接受过至少一次 TKI 治疗的耐抗或不耐受慢性期费城染色体阳性慢性髓性白血病的儿童患者，以评估其安全性、耐受性和有效性，并评估 BOSULIF® 在该患者群体中的药物动力学。耐药或不耐受的慢性期费城染色体阳性慢性髓性白血病患者的主要 (MCyR) 和完全 (CCyR) 细胞遗传学应答分别为 82.1% (95% CI: 63.1, 93.9) 和 78.6% (95% CI: 59.0, 91.7)。耐药或不耐受的慢性期费城染色体阳性慢性髓性白血病患者的主要分子生物学缓解率 (Major Molecular Remission, MMR) 为 50.0% (95% CI: 30.6, 69.4)。MR4.5(定义为 BCR-ABL/ABL IS ⩽ 0.0032%) 为 17.9% (95% CI: 6.1,36.9)。在 14 例获得 MMR 的患者中，有

2 例患者在治疗 13.6 个月和 24.7 个月后失去了 MMR。耐药或不耐受的慢性期费城染色体阳性慢性髓性白血病患者患者的中位总生存期随访时间为 23.2 个月 (范围 : 1.0 个月，61.5 个月)。

The BCHILD trial is a multicenter, non-randomized, open-label study conducted to identify a recommended dose of bosutinib administered orally once daily in pediatric patients with ND CP Ph+ CML (Newly-Diagnosed Chronic Phase Philadelphia Chromosome-Positive CML)and pediatric patients with R/I(Resistance or Intolerance) CP Ph+ CML who have received at least one prior TKI therapy, to estimate the safety and tolerability and efficacy, and to evaluate the PK of bosutinib in this patient population. The major (MCyR) and complete (CCyR) cytogenetic responses among patients with R/I CP Ph+ CML were 82.1% (95% CI: 63.1, 93.9) and 78.6% (95% CI: 59.0, 91.7), respectively. The MMR among patients with R/I CP Ph+ CML was 50.0% (95% CI: 30.6, 69.4). The MR4.5 (defined as BCR-ABL/ABL IS ⩽ 0.0032%) was 17.9% (95% CI: 6.1, 36.9). Among 14 patients who achieved MMR, two patients lost MMR after 13.6 months and 24.7 months on treatment. The median duration of follow-up for overall survival was 23.2 months (range: 1.0, 61.5 months) in patients with R/I CP Ph+CML.

11 Azacitidine 阿扎胞苷 (Vidaza)

label (fda.gov)

- **药品类别 : 细胞毒性药物 (化疗药)**
- **原研药厂家 : 百时美施贵宝 (美国)**
- **适应症 : 1 个月及以上新诊断为幼年粒细胞白血病**

  Indication: pediatric patients aged one month and older with newly diagnosed Juvenile Myelomonocytic Leukemia (JMML)

- **儿童临床试验 AZA-JMML-001 (NCT02447666) :** 一项国际、多中心、开放标签研究，旨在评估 Vidaza 在造血干细胞移植前的药代动力学、药效学、安全性和活性，共 18 例儿科患者，伴幼年髓细胞白血病 (JMML)。3 个周期后，11 例患者 (61%) 仍在心肺复苏术中，7 例患者 (39%) 病情进展。需要输血小板的 16 例患者中有 6 例 (38%) 在 3 个周期后无输血。在全基因组 DNA 甲基化研究中，所有 7 例具有中等或低甲基化特征的患者都实现临床部分反应 (clinical partial remission, cPR)。17 例患者接受造血干细胞移植 ;14 例 (82%) 在造血干细胞移植后中位随访 23.8 个月 (范围 7.0-39.3 个月) 无白血病。Vidaza 耐受性良好，血浆浓度 - 时间曲线与成人中观察到的相似。

  An international, multicenter, open-label study to evaluate the pharmacokinetics, pharmacodynamics, safety, and activity of VIDAZA prior to hematopoietic stem cell transplantation (HSCT) in a total of 18 pediatric patients with juvenile myelomonocytic leukemia (JMML). After 3 cycles, 11 patients (61%) were in cPR

and 7 (39%) had progressive disease. Six of 16 patients (38%) who needed platelet transfusions were transfusion-free after 3 cycles. All 7 patients with intermediate- or low-methylation signatures in genome-wide DNA-methylation studies achieved cPR. Seventeen patients received HSCT; 14 (82%) were leukemia-free at a median follow-up of 23.8 months (range, 7.0-39.3 months) after HSCT. Azacitidine was well tolerated and plasma concentration-–time profiles were similar to observed profiles in adults.

- **国产仿制药 : 注射用阿扎胞苷**
- 药品使用说明书 : 阿扎胞苷
- 仿制药厂家 : 齐鲁制药 (海南) 有限公司
- 适应症 : 骨髓增生异常综合 (MDS)，可治疗 5 种 MDS 亚型 (难治性贫血，难治性贫血伴环形铁粒幼细胞增多和同时伴有中性粒细胞减少症、血小板减少症或需要输血，难治性贫血伴有原始细胞增多，难治性贫血伴有原始细胞增多 - 转变型和慢性骨髓单核细胞性白血病) 中任何一种亚型的患者。
- **国产仿制药注射用阿扎胞苷在中国上市但未获批儿童肿瘤适应症。**

12 Crizotinib 克里唑替尼 (XALKORI®)

XALKORI (fda.gov)
Crizotinib(EMA_Label)

- **药品类别 : 酪氨酸激酶抑制剂**
- **原研药厂家 : 辉瑞制药 (美国)**
- **适应症 1: 1 岁及以上炎性肌纤维母细胞瘤 , ALK 阳性的儿童患者**

Indication 1: pediatric patients 1 year of age and older with unresectable, recurrent, or refractory inflammatory myofibroblastic tumor (IMT) that is ALK-positive

- **儿童临床试验 ADVL0912 (NCT00939770)：**一项多中心、单臂、开放标签的研究，研究对象为 1 至≤ 21 岁的患者，包括 14 例不可切除、复发或难治性 alk 阳性 IMT 的儿科患者。患者需要通过免疫组织化学或荧光原位杂交检测局部 ALK 融合。患者 (n=12) 每日两次接受 XALKORI 280 mg/m2 治疗，直至疾病进展或出现不可接受的毒性。

A multicenter, single-arm, open-label study in patients 1 to ≤ 21 years of age that included 14 pediatric patients with unresectable, recurrent, or refractory ALK-positive IMT. Patients were required to have an ALK fusion determined locally by immunohistochemistry or fluorescence in situ hybridization. Patients (n=12) received XALKORI 280 mg/ m2 twice daily until disease progression or unacceptable toxicity.

- **适应症 2：1 岁及以上复发或难治性系统性间变性大细胞淋巴瘤 (ALCL)，alk 阳性的儿童患者**

  Indication 2: pediatric patients 1 year of age with relapsed or refractory, systemic anaplastic large cell lymphoma (ALCL) that is ALK-positive

- **儿童临床试验 ANHL12P1(NCT01979536)：** 在一项评估 XALKORI® 联合化疗治疗新诊断 ALCL 小儿患者的研究中，2 年无事件生存率 (EFS) 为 76.8%(95% CI，68.5-88.1)，2 年总生存率为 95.2%(95% CI，85.7-98.4)。有 15 名患者复发，一名患者死亡；从诊断开始到复发的中位时间为 7.4 个月，复发发生在化疗完成后。66 名患者完成了 384 个化疗周期。66 名患者中有 13 名发生了 2 级或以上的血栓栓塞不良事件 (19.7%; 95% CI，11.1-31.3)。在接受强制性预防性抗凝的 25 名患者中，有两起血栓栓塞事件 (8.0%; 95% CI，0.01-26)。MDD 检测结果为阴性的患者具有更好的预后，其 EFS 为 85.6%(95% CI，68.6-93.8)；而 MDD 检测结果为阳性的患者 EFS 较低，为 58.1%(95% CI，33.4-76.4)。

  In a study that evaluated XALKORI® in combination with chemotherapy in pediatric patients with newly diagnosed ALCL. The 2-year event-free survival (EFS) is 76.8% (95% CI, 68.5 to 88.1) and the 2-year overall survival is 95.2% (95% CI, 85.7 to 98.4). Fifteen patients relapsed and one patient died; median time to relapse was 7.4 months from diagnosis, with relapses occurring after chemotherapy was complete. The 66 patients completed 384 cycles of chemotherapy. Thirteen of the 66 patients experienced a grade 2+ thromboembolic adverse event (19.7%; 95% CI, 11.1 to 31.3). In the 25 patients who received mandated prophylactic anticoagulation, there were two thromboembolic events (8.0%; 95% CI, 0.01 to 26). Patients with negative MDD had a superior outcome, with an EFS of 85.6% (95% CI, 68.6 to 93.8); positive MDD was associated with a lower EFS of 58.1% (95% CI, 33.4 to 76.4).

- **儿童临床试验 2 ADVL0912(NCT00939770)：** 一项多中心、单组、开放标签的研究，研究对象为 1 至≤ 21 岁的患者，包括 26 例经过至少一次全身治疗的复发或难治性全身 alk 阳性 ALCL 患者。ALK 阳性状态 (确认 ALK 融合) 通过免疫组织化学或荧光原位杂交在局部确定。患者接受 XALKORI® 280 mg/m2(20 例) 或 165 mg/m2(6 例) 口服，每日两次，直到疾病进展或不可接受的毒性。患者被允许停止 XALKORI®，接受造血干细胞移植 (HSCT)。

  The efficacy of XALKORI was evaluated In Study ADVL0912 (NCT00939770), a multicenter, single arm, open-label study in patients 1 to ⩽ 21 years of age that included 26 patients with relapsed or refractory, systemic ALK-positive ALCL after at least one systemic treatment. ALK-positive status (confirmation of an ALK fusion) was determined locally by immunohistochemistry or fluorescence in situ hybridization. Patients received XALKORI 280 mg/m2 (20 patients) or 165 mg/m2 (6 patients) orally twice daily until disease progression or unacceptable toxicity. Patients were permitted to discontinue XALKORI to undergo hematopoietic stem cell transplantation (HSCT).

13 Trecondi 曲奥舒凡 (Treosulfan)

Trecondi(TGA_Approval)
Trecondi(EMA_Label)

- **药品类别 : 靶向疗法**
- **原研药厂家 : 林克医疗 (澳大利亚)**
- **适应症 : 1 个月及以上患有恶性和非恶性血液病的儿童患者。Trecondi (treosulfan) 与氟达拉滨联合使用，无论是否使用塞替派，均可用于异基因造血干细胞移植前预处理治疗。**

Indication: Paediatric patients aged 1 month and older with malignant and non-malignant haematological diseases. Trecondi (treosulfan) is indicated in combination with fludarabine, with or without thiotepa, as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in paediatric patients older than one month with malignant and non-malignant diseases.

- **儿童临床试验 (Study MC-FludT.17/M)：** 在 70 名患者中进行了 Treosulfan 的预处理治疗方案的疗效和安全性评估，这些患者包括患有急性淋巴细胞白血病、急性髓性白血病、骨髓增生异常综合征或幼年型单核髓细胞白血病的患者。这些患者接受了含 Treosulfan 和氟达拉滨的预处理方案，其中 65 名患者同时使用了塞替派，而 5 名患者未使用。总共有 37 名患者 (52.9%) 年龄小于 12 岁。没有患者发生原发性移植失败，但有一名急性淋巴细胞白血病患者发生了继发性移

植失败。关于完全供体型嵌合的发生率 : 在异基因造血干细胞移植后第 28 天的随访中为 94.2%(90%CI: 87.2%-98.0%)；在异基因造血干细胞移植后第 100 天的随访中为 91.3%(90%CI: 83.6%-96.1%)；在第 12 个月的随访中为 91.2%(90%CI: 82.4%-96.5%)。24 个月的总体生存率为 85.7%(90%CI: 77.1%-91.2%)。70 名患者中共有 12 名 (17.1%) 死亡，其中 8 名因复发 / 病程进展死亡，4 名因移植相关原因死亡。在异基因造血干细胞移植后 100 天内的移植相关死亡率为 98.6%(90%CI: 93.4%-99.9%)，因为 70 名患者中有 1 名在异基因造血干细胞移植后 100 天内因移植 / 治疗相关原因死亡。24 个月的移植相关死亡率为 4.6%(90%CI: 1.8%-11.4%)。共有 16 名患者出现复发 / 病程进展。在异基因造血干细胞移植后第 24 个月，复发 / 病程进展的累积发生率为 23.0%(90%CI14.7%-31.3%)。大多数试验受试者接受了强化的预处理方案，其中噻替哌以每公斤体重 5 毫克的单剂量在异基因造血干细胞移植前两天分两次给药。大多数患者年龄在 28 天至 11 岁之间 (Treosulfan 组占 88.2%)。在异基因造血干细胞移植后 100 天内，Treosulfan 组的患者在移植后的第 100 天仍然存活且没有因移植或治疗而死亡的比例 (主要临床终点指标) 为 100.0%(90%CI: 94.3%-100.0%)。Treosulfan 组的 1 年总体生存率为 96.1%(90%CI: 88.0%-98.8%)。

The efficacy and safety of treosulfan-based conditioning was evaluated in 70 patients with acute lymphoblastic leukaemia (ALL), AML, MDS, or juvenile myelomonocytic leukaemia (JMML) who received a conditioning regimen with treosulfan and fludarabine with (n = 65) or without (n = 5) thiotepa. A total of 37 patients (52.9%) were younger than 12 years. No patient experienced a primary graft failure but one patient with ALL experienced a secondary graft failure. The incidence of complete donor-type chimerism was 94.2% (90% CI 87.2-98.0%) at day +28 visit, 91.3% (90% CI 83.6-96.1%) at day +100 visit and 91.2% (90% CI 82.4-96.5%) at month 12 visit. The overall survival at 24 months is 85.7% (90% CI 77.1-91.2%). A total of 12 of the 70 patients (17.1%) died, 8 patients because of relapse/progression and 4 patients transplant-related. The freedom from transplant-

related mortality until day +100 after HSCT (primary endpoint) is 98.6% (90% CI 93.4–99.9%) because one of the 70 patients died due to transplantation/ treatment-related cause until day +100 after HSCT. Transplant-related mortality at 24 months is 4.6% (90% CI 1.8 – 11.4%). Sixteen patients had a relapse/ progression. The cumulative incidence of relapse/progression is 23.0% (90% CI 14.7-31.3%) at month +24. Most trial subjects received the intensified regimen with thiotepa given in 2 single doses of 5 mg/kg/body weight on day -2. Most patients were 28 days to 11 years of age (88.2% in the treosulfan arm). The incidence of freedom from transplantation (treatment) related mortality until day +100 (primary endpoint) was 100.0% (90% CI 94.3%-100.0%) in the treosulfan arm. Overall survival at 1 year was 96.1% (90% CI 88.0%-98.8%) with treosulfan.

14 Plerixafor 普乐沙福 (Mozobil®)

Plerixafor(Mozobil®)

- 药品类别 : 靶向疗法
- 原研药厂家 : 赛诺菲 (法国)
- 适应症 : 对于患有淋巴瘤或实体恶性肿瘤的儿科患者 (1 岁至未满 18 岁)，Mozobil® 与粒细胞集落刺激因子 (G-CSF) 联合使用，用于促使造血干细胞从骨髓进入外周血液中，以便进行收集和随后的自体干细胞移植。适用于以下情况之一 : 1) 预防性使用 : 当通过粒细胞集落刺激因子 (G-CSF)(可结合或不结合化疗) 充分动员造血干细胞后，患者在预定收集日的外周血液中流动的干细胞数量不足以达到预期的造血干细胞收集量时；2) 如果患者曾经尝试收集干细胞但未能成功 (即没有足够的干细胞收集量)。

Indication: For paediatric patients (1 to less than 18 years), Mozobil® is indicated in combination with G-CSF to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in children with lymphoma or solid malignant tumours, either: - pre-emptively, when circulating stem cell count on the predicted day of collection after adequate mobilization with G-CSF (with or without chemotherapy) is expected to be insufficient with regards to desired hematopoietic stem cells yield, or who previously failed to collect sufficient haematopoietic stem cells.

- **儿童临床试验 (DFI12860):** Mozobil® 的疗效和安全性在一项随机 (2: 1)、开放标签、多中心、对照研究中进行了评估，研究对象为患有实体瘤 (包括神经母细胞瘤、肉瘤、尤文氏肉瘤) 或淋巴瘤且适合接受自体造血干细胞移植的儿科患者。患有白血病、在进行干细胞动员之前，骨髓中有较高比例的病理性细胞 (如癌细胞或其他异常细胞) 浸润的患者或曾接受过干细胞移植的患者被排除在外。45 名儿科患者 (1 岁至未满 18 岁) 按 2: 1 的比例随机分配到实验组 : 使用 0.24 mg/kg Mozobil® 与标准动员法 (G-CSF 结合或不结合化疗) 的联合治疗，和对照组 : 仅接受标准动员法。疗效结果 : 初步分析显示，Mozobil® 组中 80% 的患者在计划的首次单采前一天早晨至单采前早晨期间，外周血 CD34+ 细胞计数至少翻倍，而对照组中仅有 28.6% 的患者达到了相同的效果 (p=0.0019)。Mozobil® 组患者从基线到单采当天外周血 CD34+ 细胞计数的中位增加了 3.2 倍，而对照组为 1.4 倍。

  The efficacy and safety of Mozobil® were evaluated in a randomized (2: 1), open label, multi-center, controlled study in paediatric patients with solid tumors (including neuroblastoma, sarcoma, Ewing sarcoma) or lymphoma who were eligible for autologous hematopoietic stem cell transplantation (DFI12860). Patients with leukemia, persistent high percentage marrow involvement prior to mobilization, or previous stem cell transplantation were excluded. Forty-five paediatric patients (1 to less than 18 years) were randomised, 2: 1, using 0.24 mg/kg of Mozobil® plus standard mobilisation (G-CSF plus or minus chemotherapy) versus control (standard mobilisation alone). Efficacy results: The primary analysis showed that 80% of patients in the Mozobil® arm experienced at least a doubling of the PB CD34+ count, observed from the morning of the day preceding the first planned apheresis to the morning prior to apheresis, versus, 28.6 % of patients in the control arm (p=0.0019). The median increase in PB CD34+ cell counts from baseline to the day of apheresis was by 3.2 fold in the Mozobil® arm versus by 1.4 fold in the control arm.

- **海外仿制药 : Plerixafor Accord 普乐沙福 (仿制)**
- 药品使用说明书 : Plerixafor(Plerixafor Accord)
- 仿制药厂家 : 雅阁 (西班牙)
- 适应症 : 与赛诺菲的原研药 Plerixafor 普乐沙福 (Mozobil®) 一致。
- **海外仿制药 Plerixafor Accord 未在中国获批儿童肿瘤适应症。**
- **国产仿制药 : 普乐沙福注射液**
- 药品使用说明书 : 普乐沙福
- 仿制药厂家 : 湖南五洲通药业股份有限公司
- 适应症 : 与粒细胞集落刺激因子 (G-CSF) 联用，适用于非霍奇金淋巴瘤 (NHL) 和多发性骨髓瘤 (MM) 患者动员造血干细胞 (HSC) 进入外周血，以便于完成 HSC 采集与自体移植。
- **国产仿制药普乐沙福注射液在中国上市但未获批儿童肿瘤适应症。**

15 Iobenguane I-131 碘苯胍 I-131 (AZEDRA®)

Full Prescribing Information | AZEDRA® (iobenguane | 131)
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6678905/

- **药品类别：放射性药物疗法**
- **原研药厂家：普罗基尼克斯制药（美国）**
- **适应症：12 岁及以上 iobenguane I 131 扫描阳性不可切除，局部晚期或转移性，嗜铬细胞瘤和副神经节瘤**

  Indication: pediatric patients 12 years and older with iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy

- **儿童临床试验 Study IB12B (NCT00874614)：** 该研究是一项开放标签、单臂、多中心的临床试验 (NCT00874614)。主要疗效结果指标是持续至少六个月 (每月 28 天) 的 50% 或更多的所有抗高血压药物减少的患者的比例。试验还评估了根据 RECIST(实体肿瘤反应评估标准第 1.0 版) 测得的总体肿瘤反应。在最后的 12 个月评估后，患者进入长期随访阶段，最多为 4 年。共有 74 名患者接受了 AZEDRA 的剂量测定剂。在剂量测定后，68 名患者接受了至少一次治疗剂量，其中 50 名患者在至少 90 天的时间间隔内接受了两次治疗剂量。剂量测定剂为 185 mBq 至 222 MBq(对于体重 >50 kg 的患者) 和 3.7 MBq/kg(对于体重≤ 50 kg 的患者)。治疗剂量为 18,500 MBq(对于体重 >62.5 kg 的患者)

和 296 MBq/kg(对于体重≤ 62.5 kg 的患者)。在 68 名患者中，中位年龄为 55 岁 (16 至 72 岁)。根据 RECIST 的所有确认的反应均为部分反应。

An open-label, single-arm, multicenter clinical trial (NCT00874614). The major efficacy outcome measure was the proportion of patients who experienced a 50% or greater reduction of all antihypertensive medication(s) lasting for at least six months (28 days per month). Overall tumor response measured by RECIST (Response Evaluation Criteria in Solid Tumors version 1.0) was also evaluated. After the final 12-month assessment, patients entered into long-term follow-up for up to 4 additional years. A total of 74 patients received the dosimetric dose of AZEDRA. Following dosimetry, 68 patients received at least one therapeutic dose and 50 patients received two therapeutic doses administered at least 90 days apart. The dosimetric dose was 185 mBq to 222 MBq (5 mCi to 6 mCi) for patients weighing > 50 kg and 3.7 MBq/kg (0.1 mCi/kg) for patients weighing ⩽ 50 kg. The therapeutic dose was 18,500 MBq (500 mCi) for patients weighing >62.5 kg and 296 MBq/kg (8 mCi/kg) for patients weighing ⩽ 62.5 kg. Among the 68 patients, the median age was 55 years (16 to 72 years). All confirmed responses per RECIST were partial responses.

16 Dinutuximab 地努图希单抗 (UNITUXIN ™)

LABEL (fda.gov)
https://www.nmpa.gov.cn/datasearch/search-info.html?nmpa=aWQ9ZTE4NGE3YjYxZjYxMTExZjZhMTc0ZGNmYWFiYjQxNGEmaXRlbUlkPWZmODA4MDgxODNjYWQ3NTAwMTg0MDg4NjY1NzExODAw

- **药品类别：抗 GD2 免疫疗法**
- **原研药厂家：United Therapeutics (美国)**
- **适应症：对既往一线多药物、多模式治疗至少获得部分缓解的高危神经母细胞瘤儿童患者**

Indication: pediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line multiagent, multimodality therapy

- **儿童临床试验 ANBL0032：**一项随机、开放标签、多中心试验。该试验在高危神经母细胞瘤的小儿患者中进行。患者在自体干细胞移植后的第 50 天至第 77 天之间被随机分组。随机分配到 UNITUXIN ™ /RA 组的患者在 13-cis- 维甲酸 (RA) 独自使用一个周期后，接受了最多五个周期的 Dinutuximab(临床试验材料)，与粒细胞 - 巨噬细胞集落刺激因子或白细胞介素 -2 联合使用。而随机分配到 RA 组的患者接受了六个周期的 RA。

A randomized, open-label, multicenter trial conducted in pediatric patients with high-risk neuroblastoma. Patients were randomized between Day 50 and Day 77 post-autologous stem cell transplantation. Patients randomized to the Unituxin/

RA arm received up to five cycles of dinutuximab (clinical trials material) in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF) or interleukin-2 (IL-2) plus 13-cis-retinoic acid (RA), followed by one cycle of RA alone. Patients randomized to the RA arm received six cycles of RA. The efficacy results are summarized in Table 10.

Table 10: Efficacy Results

Efficacy Parameter		Unituxin/ RA arm n=113	RA arm n=113
EFS	No. of Events (%)	33 (29%)	50 (44%)
	Median (95% CI) (years)	NR (3.4 ,NR)	1.9 (1.3, NR)
	Hazard Ratio (95% CI)	0.57 (0.37, 0.89)	
	p-value (log-rank test)[1]	0.01	
OS[2]	No. of Events (%)	31 (27%)	48 (42%)
	Median (95% CI) (years)	NR (7.5,NR)	NR (3.9,NR)
	Hazard Ratio (95% CI)	0.58 (0.37,0.91)	

NR = not reached
[1] Compared to the allocated alpha of 0.01 pre-specified for the seventh interim analysis of EFS
[2] Based on an additional three years of follow up after the seventh interim analysis of EFS

17 Avelumab 阿维鲁单抗 (BAVENCIO®)

label (fda.gov)

- **药品类别：免疫疗法 (PD-L1)**
- **原研药厂家：默克制药（美国）**
- **适应症：12 岁及以上儿童转移性默克尔细胞癌**

Indication: pediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC).

- **儿童用药说明：**BAVENCIO® 在 12 岁及以上年龄的转移性默克尔细胞癌小儿患者中的安全性和有效性已得到确认。在这个年龄组使用 BAVENCIO 得到了充足和良好控制的 BAVENCIO 成人研究的证据支持，同时还有人口药代动力学数据证明年龄和体重对 avelumab 的稳态曝露没有临床意义的影响。对于单克隆抗体，成人和 12 岁及以上的小儿患者的药物曝露通常相似。而默克尔细胞癌病程在成人和小儿患者中足够相似，可以将成人数据推断至小儿患者。12 岁及以上小儿患者的推荐剂量与成人相同。

The safety and effectiveness of BAVENCIO have been established in pediatric patients aged 12 years and older for metastatic MCC. Use of BAVENCIO in this age group is supported by evidence from adequate and well-controlled studies of BAVENCIO in adults with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the steady state exposure of avelumab, that drug exposure is generally similar

between adults and pediatric patients age 12 years and older for monoclonal antibodies, and that the course of MCC is sufficiently similar in adult and pediatric patients to allow extrapolation of data in adults to pediatric patients. The recommended dose in pediatric patients 12 years of age or greater is the same as that in adults.

- **成人试验 JAVELIN Merkel 200 trial (NCT02155647)：**一项开放标签、单臂、多中心研究，纳入了组织学上确认的转移性默克尔细胞癌患者，其疾病在接受化疗治疗远程转移性疾病后进展。患者每 2 周接受一次 60 分钟的 BAVENCIO® 10 mg/kg 静脉输注，直到疾病进展或无法忍受的毒性发生。有放射性疾病进展但与明显临床恶化无关的患者，没有新的或加重的症状、2 周以上的表现状态无变化以及无需挽救治疗的患者，可以继续接受治疗。主要疗效终点包括由一个盲法独立中央审查委员会 (IRC) 评估的根据实体瘤反应评估标准 (RECIST)v1.1 确定的确诊总体反应率 (ORR) 和 IRC 评估的反应持续时间。

  An open-label, single-arm, multi-center study conducted in patients with histologically confirmed metastatic MCC whose disease had progressed on or after chemotherapy administered for distant metastatic disease. Patients received BAVENCIO® 10 mg/kg as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity. Patients with radiological disease progression not associated with significant clinical deterioration, defined as no new or worsening symptoms, no change in performance status for greater than 2 weeks, and no need for salvage therapy, could continue treatment. The major efficacy outcome measures were confirmed overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as assessed by a blinded independent central review committee (IRC) and IRC-assessed duration of response.

18 Tagroxofusp-erzs (ELZONRIS ™)

LABEL (fda.gov)

- **药品类别：靶向疗法**
- **原研药厂家：Stemline Therapeutics（美国）**
- **适应症： 2 岁及以上的儿童浆细胞样树突状细胞瘤**

Indication: blastic plasmacytoid dendritic cell neoplasm (BPDCN) in pediatric patients 2 years and older

- **儿童临床试验 1 STML-401-0114 (NCT 02113982; Study 0114)：**一项多中心、开放标签、单臂临床试验，纳入了 13 例未经治疗的浆细胞样树突状细胞瘤患者的前瞻性队列。治疗包括 ELZONRIS ™ 12mcg/kg 静脉注射，持续 15 分钟，每天 1 次，21 天周期的第 1 至第 5 天。

A multicenter, open-label, single-arm, clinical trial that included a prospective cohort of 13 patients with treatment-naive BPDCN. Treatment consisted of ELZONRIS ™ 12 mcg/kg intravenously over 15 minutes once daily on days 1 to 5 of a 21-day cycle.

- **儿童临床试验 2 STML-401-0114 (NCT 02113982; Study 0114)：**一项多中心、开放标签、单臂、包括 15 名复发或难治性浆细胞样树突状细胞瘤患者的临床试验。治疗方案包括 ELZONRIS ™，每个 21 天周期的第 1 天到第 5 天使用 12mcg/kg 的剂量。在 15 名复发 / 难治性浆细胞样树突状细胞瘤患者中，有一名患者达到了完全缓解 (持续时间 : 111 天)，另一名患者达到了完全缓解 (伴随继续性改善，持续时间 : 424 天)。

A multicenter, open-label, single-arm, clinical trial that included 15 patients with relapsed or refractory BPDCN. Treatment consisted of ELZONRIS ™ 12 mcg/kg on days 1 to 5 of each 21-day cycle. In the 15 patients with relapsed/refractory BPDCN, one patient achieved a CR (duration: 111 days) and one patient achieved a CRc (duration: 424 days).

19 Nivolumab and Relatlimab-rmbw (OPDUALAG ™)

label (fda.gov)

- **药品类别：免疫疗法**
- **原研药厂家：百时美施贵宝 (美国)**
- **适应症：12 岁及以上不可切除或转移性黑色素瘤**

Indication: pediatric patients 12 years of age or older with unresectable or metastatic melanoma

- **儿童用药说明：**OPDUALAG ™用于治疗不可切除或转移性黑色素瘤在 12 岁及以上、体重至少为 40 公斤的小儿患者的安全性和有效性已得到确认。OPDUALAG ™在这个适应症中的使用得到了充足和良好控制的成人研究的证据支持，并有额外的数据分析显示，12 岁及以上、体重至少为 40 公斤的小儿患者中 nivolumab 和 relatlimab 的接触量估计将得到类似于成人的安全性和有效性。单克隆抗体的药代动力学和不可切除或转移性黑色素瘤的病程在成人和 12 岁及以上、体重至少为 40 公斤的小儿患者中足够相似，可以将成人患者的数据推断至 12 岁及以上、体重至少为 40 公斤的小儿患者。

  The safety and effectiveness of OPDUALAG for the treatment of unresectable or metastatic melanoma have been established in pediatric patients 12 years of age or older who weigh at least 40 kg. Use of OPDUALAG for this indication is supported by evidence from an adequate and well-controlled study in adults and additional data analyses that suggest that nivolumab and relatlimab exposures

in pediatric patients 12 years of age who weigh at least 40 kg are expected to result in similar safety and efficacy to that of adults. The pharmacokinetics of monoclonal antibodies and the course of unresectable or metastatic melanoma are sufficiently similar in adults and pediatric patients 12 years of age or older to allow extrapolation of data from adult patients to pediatric patients 12 years of age or older (who weigh at least 40 kg).

- **成人试验 RELATIVITY-047 (NCT03470922)：** 一项随机 (1: 1)、双盲试验，纳入了 714 名未曾治疗过的转移性或不可切除的 III 期或 IV 期黑色素瘤患者。患者被随机分配接受每 4 周一次的静脉输注 OPDUALAG ™ (nivolumab 480mg 和 relatlimab 160mg)(n=355) 或每 4 周一次的静脉输注 nivolumab 480mg(n=359)，直到疾病进展或无法忍受的毒性出现。主要疗效终点是由独立的盲法中央评审 (BICR) 使用实体瘤反应评估标准 (RECIST v1.1) 确定的无进展生存期 (PFS)。其他疗效终点包括由 BICR 使用 RECIST v1.1 确定的总生存期 (OS) 和总体反应率 (ORR)。

  A randomized (1: 1), double-blinded trial in 714 patients with previously untreated metastatic or unresectable Stage III or IV melanoma. Patients were randomized to receive OPDUALAG ™ (nivolumab 480 mg and relatlimab 160 mg) by intravenous infusion every 4 weeks (n=355) or nivolumab 480 mg by intravenous infusion every 4 weeks (n=359) until disease progression or unacceptable toxicity. The major efficacy outcome measure was progression-free survival (PFS) determined by Blinded Independent Central Review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Additional efficacy outcome measures were overall survival (OS) and overall response rate (ORR) determined by BICR using RECIST v1.1.

20 ipilimumab 伊匹单抗 (YERVOY®)

Yervoy FDA Drug Label

- **药品类别：免疫疗法**
- **原研药厂家：百时美施贵宝 (美国)**
- **适应症：12 岁及以上儿童不可切除或转移性黑色素瘤**

Indication: unresectable or metastatic melanoma in pediatric patients 12 years and older

- **儿童用药说明：**YERVOY® 的安全性和有效性已经在 12 岁及以上的儿童患者中得到证实，用于治疗不可切除或转移性黑色素瘤。YERVOY® 在该年龄组的使用得到了充分和良好对照的成人 YERVOY® 研究的证据的支持，人群药代动力学数据表明，3mg/kg 和 1mg/kg 剂量在儿科和成人人群中的暴露具有可比性。此外，晚期黑色素瘤在成人和 12 岁及以上儿童患者中的肿瘤生物学和病程非常相似，因此可以将成人患者的数据外推至儿童患者。

  The safety and effectiveness of YERVOY® have been established in pediatric patients 12 years and older for the treatment of unresectable or metastatic melanoma. Use of YERVOY® in this age group is supported by evidence from adequate and well-controlled studies of YERVOY® in adults and population pharmacokinetic data demonstrating that the exposure at doses of 3 mg/kg and 1 mg/kg in the pediatric and adult populations are comparable. In addition, the tumor biology and course of advanced melanoma are sufficiently similar in adults and pediatric patients 12 years and older to allow extrapolation of data from

adults to pediatric patients.

- **儿童临床试验 (NCT01445379,NCT01696045):** YERVOY® 在两项临床试验中共评估了 45 名小儿患者。在这两项研究中，17 名年龄≥ 12 岁的患有黑色素瘤的患者接受了 YERVOY® 治疗，其中 2 名患者出现了客观反应，包括一个部分缓解，持续了 16 个月。在患有非黑色素瘤实体瘤的患者中未观察到任何反应。在这两项研究中，未观察到小儿患者出现新的安全信号。

  YERVOY® was evaluated in a total of 45 pediatric patients across two clinical trials. Of the 17 patients ≥ 12 years of age with melanoma treated with YERVOY® across both studies, 2 patients experienced objective responses including one partial response that was sustained for 16 months. There were no responses in patients with nonmelanoma solid tumors. No new safety signals were observed in pediatric patients in these two studies.

21 nivolumab 纳武单抗 (OPDIVO®)

OPDIVO U.S. Prescribing Information (bms.com)
https://www.nmpa.gov.cn/datasearch/search-info.html?nmpa=aWQ9ZWEzMThjNzJjZWI3ZmNkNzc4OGEzMzljYzgwZTlkZGUmaXRlbUlkPWZmODA4MDgxODNjYWQ3NTAwMTg0MDg4NjY1NzExODAw

- **药品类别：靶向疗法**
- **原研药厂家：百时美施贵宝 (美国)**
- **适应症 1：12 岁及以上可切除或转移性黑色素瘤**

Indication 1: unresectable or metastatic melanoma in pediatric (12 years and older) patients

- **儿童用药说明：** OPDIVO® 的安全性和有效性已经在 12 岁及以上的儿童患者中得到建立，用于治疗不可切除或转移性黑色素瘤，辅助治疗完全切除的 IIB 期、IIC 期、III 期或 IV 期黑色素瘤。OPDIVO® 用于这些适应症的证据来自对成年黑色素瘤患者进行的充分和良好对照的研究，以及儿科患者的额外药代动力学数据。

The safety and effectiveness of OPDIVO® have been established in pediatric patients aged 12 years and older for the treatment of unresectable or metastatic melanoma, adjuvant treatment of completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma. Use of OPDIVO® for these indications is supported by evidence from adequate and well-controlled studies in adults with melanoma or MSI-H or dMMR mCRC and additional pharmacokinetic data in pediatric patients.

- **成人试验 CHECKMATE-066 (NCT01721772):** 一项多中心、双盲、随机(1: 1)试验，纳入了 418 例 BRAF V600 野生型不可切除或转移性黑色素瘤患者。患者随机

接受每 2 周静脉输注 OPDIVO® 3mg/kg 或每 3 周静脉输注达卡巴嗪 1000 mg/m2，直到疾病进展或不可接受的毒性。

A multicenter, double-blind, randomized (1: 1) trial in 418 patients with BRAF V600 wild-type unresectable or metastatic melanoma. Patients were randomized to receive either OPDIVO 3 mg/kg by intravenous infusion every 2 weeks or dacarbazine 1000 mg/m2 intravenously every 3 weeks until disease progression or unacceptable toxicity.

- **适应症 2：12 岁及以上儿童高度微卫星不稳定 / 错配修复缺陷结直肠癌**

Indication 2: microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC) in pediatric (12 years and older) patients

- **儿童用药说明：**OPDIVO® 作为单药的安全性和有效性已经在 12 岁及以上的患有微卫星不稳定性高 (MSI-H) 或错配修复缺陷 (dMMR) 转移性结直肠癌 (mCRC) 的儿童患者中得到证实，这些转移性结直肠癌在氟嘧啶、奥沙利铂和伊立替康治疗后病情进展。在患有微卫星不稳定性高或错配修复缺陷转移性结直肠癌的成人患者中，OPDIVO® 用于这一适应症的证据得到了充分和良好对照的研究的支持，更多的人群药代动力学数据表明，年龄和体重对纳武单抗的稳定状态暴露没有临床意义的影响，成人和 12 岁及以上的儿童患者的单克隆抗体药物暴露通常相似。并且微卫星不稳定性高或错配修复缺陷转移性结直肠癌在成人和儿童患者中的病程足够相似，可以将成人的数据外推到儿童患者中。

The safety and effectiveness of OPDIVO as a single agent have been established in pediatric patients age 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin,

and irinotecan. Use of OPDIVO for this indication is supported by evidence from adequate and well-controlled studies of OPDIVO in adults with MSI-H or dMMR mCRC with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the steady-state exposure of nivolumab, that drug exposure is generally similar between adults and pediatric patients age 12 years and older for monoclonal antibodies, and that the course of MSI-H or dMMR mCRC is sufficiently similar in adults and pediatric patients to allow extrapolation of data in adults to pediatric patients.

- **成人试验 CHECKMATE-142 (NCT02060188)：** 一项多中心、非随机、多平行队列、开放标签试验，研究对象为局部确定的微卫星不稳定性高或错配修复缺陷转移性结直肠癌患者，这些患者在接受氟嘧啶、奥沙利铂或伊立替康化疗期间或之后出现疾病进展。纳入单药 OPDIVO® 微卫星不稳定性高转移性结直肠癌队列的患者每 2 周接受 OPDIVO® 3mg/kg 静脉输注 (IV)。纳入 OPDIVO® 和伊匹单抗治疗微卫星不稳定性高转移性结直肠癌队列的患者接受 OPDIVO® 3mg/kg 和伊匹单抗 1mg/kg 静脉注射，每 3 周给药 4 次，随后每 2 周静脉输注 OPDIVO® 作为单一药物，剂量为 3mg/kg。两组患者均持续治疗，直至出现不可接受的毒性或影像学进展。

  A multicenter, non-randomized, multiple parallel-cohort, open-label trial conducted in patients with locally determined dMMR or MSI-H metastatic CRC (mCRC) who had disease progression during or after prior treatment with fluoropyrimidine-, oxaliplatin-, or irinotecan-based chemotherapy. Patients enrolled in the single agent OPDIVO® MSI-H mCRC cohort received OPDIVO® 3 mg/kg by intravenous infusion (IV) every 2 weeks. Patients enrolled in the OPDIVO® and ipilimumab MSI-H mCRC cohort received OPDIVO 3 mg/kg and ipilimumab 1 mg/kg intravenously every 3 weeks for 4 doses, followed by OPDIVO® as a single agent at a dose of 3 mg/kg as intravenous infusion every 2 weeks. Treatment in both cohorts continued until unacceptable toxicity or radiographic progression.

- **适应症 3: 12 岁及以上初治 III 或 IV 期经典霍奇金淋巴瘤（cHL）（+AVD chemotherapy）**

  Indication 3: In combination with AVD chemotherapy for the treatment of patients aged 12 years and older with previously untreated Stage III or IV classical Hodgkin lymphoma (cHL).

- **儿童临床试验 SWOG 1826（NCT03907488）：**纳武利尤单抗联合 AVD 方案的疗效在 CA209-8UT 研究（SWOG 1826；NCT03907488）中进行了评估。该研究是一项随机、开放标签、多中心临床试验，纳入既往未经治疗的 III 期或 IV 期经典型霍奇金淋巴瘤（cHL）患者，年龄均为 12 岁及以上。共 994 例患者按 1:1 比例随机接受以下方案之一，共治疗 6 个周期：纳武利尤单抗联合 AVD； 维布妥昔单抗联合 AVD。 主要疗效终点为研究者评估的无进展生存期（PFS）。结果显示，纳武利尤单抗联合 AVD 组的 PFS 显著优于维布妥昔单抗联合 AVD 组，风险比为 0.42（95% CI：0.27–0.67；p<0.0001）。中位随访 13.7 个月时，两组均未达到中位 PFS。中位随访 36.7 个月时，纳武利尤单抗联合 AVD 组和维布妥昔单抗联合 AVD 组的死亡患者比例分别为 1.8% 和 3.4%。在纳武利尤单抗联合 AVD 组中，39% 的患者发生严重不良反应，9% 的患者发生免疫介导的不良反应，其中 2.7% 为 3–4 级。纳武利尤单抗的推荐剂量为：成人及体重≥ 40 kg 的儿童患者：240 mg； 体重 <40 kg 的儿童患者：3 mg/kg。 纳武利尤单抗采用静脉输注，在每个 28 天周期的第 1 天和第 15 天与 AVD 联合给药，最多治疗 6 个周期。建议从第 1 个治疗周期开始预防性使用粒细胞集落刺激因子（G-CSF）。

  Efficacy of nivolumab in combination with AVD was evaluated in Study CA209-8UT (SWOG 1826; NCT03907488), a randomized, open-label, multicenter trial in patients 12 years and older with previously untreated, Stage III and IV cHL. A total of 994 patients were randomized (1:1) to receive either nivolumab plus AVD or brentuximab vedotin plus AVD for 6 cycles.The primary efficacy outcome measure was progression-free survival (PFS) per investigator. The study demonstrated

superiority of PFS in the nivolumab plus AVD arm, with a hazard ratio of 0.42 (95% CI: 0.27, 0.67; p-value <0.0001). The median PFS was not reached in either arm, after a median follow-up of 13.7 months. After a median follow-up of 36.7 months, there were 1.8% deaths in the nivolumab plus AVD arm and 3.4% in the brentuximab vedotin plus AVD arm.In the nivolumab plus AVD arm, serious adverse reactions occurred in 39% and immune-mediated adverse reactions occurred in 9% of patients (Grade 3-4, 2.7%).The recommended dosing of nivolumab is 240 mg (for adults and pediatric patients weighing ⩾ 40 kg) or 3 mg/kg (for pediatric patients weighing <40 kg), administered intravenously in combination with AVD on Days 1 and 15 of each 28-day cycle for up to 6 cycles. Primary G-CSF prophylaxis is recommended starting in Cycle 1.

22 ipilimumab 伊匹单抗 (YERVOY®) + nivolumab 纳武单抗 (OPDIVO®)

label (fda.gov)

- **药品类别：靶向疗法 （CAR-T 细胞疗法)**
- **原研药厂家：诺华制药（瑞士）**
- **适应症 1：12 岁及以上转移性或不可切除的黑色素瘤**

  Indication 1: unresectable or metastatic melanoma in pediatric patients aged 12 years and older

- **儿童用药说明：** OPDIVO® 联合 ipilimumab 治疗不可切除或转移性黑色素瘤的安全性和有效性已经在 12 岁及以上的儿科患者中得到证实。

  The safety and effectiveness of OPDIVO® in combination with ipilimumab for the treatment of unresectable or metastatic melanoma have been established in pediatric patients aged 12 years and older.

- **适应症 2： 12 岁以上儿童儿童高度微卫星不稳定 / 错配修复缺陷结直肠癌**

  Indication 2: microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC)

- **成人试验 1 CHECKMATE-142 (NCT02060188)：** 一项多中心、非随机、

多平行队列、开放标签试验，研究对象为局部确定的微卫星不稳定性高或错配修复缺陷转移性结直肠癌患者，这些患者在接受氟嘧啶、奥沙利铂或伊立替康化疗期间或之后出现疾病进展。纳入单药 OPDIVO® 微卫星不稳定性高转移性结直肠癌队列的患者每 2 周接受 OPDIVO® 3mg/kg 静脉输注 (IV)。纳入 OPDIVO® 和 ipilimumab 微卫星不稳定性高转移性结直肠癌队列的患者接受 OPDIVO® 3mg/kg 和 ipilimumab 1mg/kg 静脉注射，每 3 周给药 4 次，随后每 2 周静脉输注 OPDIVO® 作为单一药物，剂量为 3mg/kg。两组患者均持续治疗，直至出现不可接受的毒性或影像学进展。

A multicenter, non-randomized, multiple parallel-cohort, open-label trial conducted in patients with locally determined dMMR or MSI-H metastatic CRC (mCRC) who had disease progression during or after prior treatment with fluoropyrimidine-, oxaliplatin-, or irinotecan-based chemotherapy. Patients enrolled in the single agent OPDIVO® MSI-H mCRC cohort received OPDIVO® 3 mg/kg by intravenous infusion (IV) every 2 weeks. Patients enrolled in the OPDIVO® and ipilimumab MSI-H mCRC cohort received OPDIVO® 3 mg/kg and ipilimumab 1 mg/kg intravenously every 3 weeks for 4 doses, followed by OPDIVO® as a single agent at a dose of 3 mg/kg as intravenous infusion every 2 weeks. Treatment in both cohorts continued until unacceptable toxicity or radiographic progression.

23 Atezolizumab 阿替利珠单抗 (TECENTRIQ®)

label (fda.gov)

- **药品类别：免疫疗法 (PD-L1)**
- **原研药厂家：基因泰克 (美国)**
- **适应症：2 岁及以上儿童肺泡软组织肉瘤**

Indication:Alveolar Soft Part Sarcoma, ASPS in pediatric patients aged 2 years and older

- **儿童用药说明：**在 2 岁及以上的儿科患者中，TECENTRIQ® 治疗不可切除或转移性肺泡软组织肉瘤的安全性和有效性已经得到证实。TECENTRIQ® 用于这一适应症的证据来自一项充分且对照良好的研究，该研究在成人和 2 名青少年肺泡软组织肉瘤患者 (≥ 12 岁) 中进行，并在 2 岁至 17 岁的儿科患者中获得了额外的药代动力学和安全性数据。这些数据表明，2 岁及以上儿童患者的 atezolizumab 暴露与成人相当，并且有望产生与成人相似的安全性和有效性。2 - 11 岁儿童患者不可切除或转移性肺泡软组织肉瘤的病程与成人和青少年患者非常相似，因此可以推断 2 岁及以上儿童患者的疗效和安全性。

  The safety and effectiveness of TECENTRIQ® for unresectable or metastatic ASPS have been established in pediatric patients aged 2 years and older. Use of TECENTRIQ® for this indication is supported by evidence from an adequate and well controlled study of TECENTRIQ® in adults and 2 adolescent pediatric patients

(⩾ 12 years of age) with ASPS with additional pharmacokinetic and safety data in pediatric patients 2 years to <17 years. These data suggest that atezolizumab exposure in pediatric patients aged 2 years and older is comparable with that of adults and is expected to result in similar safety and efficacy to that of adults. The course of unresectable or metastatic ASPS is sufficiently similar between pediatric patients 2 to 11 years old and that of adults and adolescent patients to allow extrapolation of efficacy and safety to pediatric patients 2 years and older.

- **儿童与成人临床试验 ML39345 (NCT03141684)：**TECENTRIQ® 的疗效在 ML39345 (NCT03141684) 研究中进行了评估，该研究是一项开放标签的单臂研究，纳入了 49 名 2 岁及以上不可切除或转移性肺泡软组织肉瘤的成人和儿童患者。成人患者静脉注射 1200mg，儿科患者静脉注射 15mg/kg(最多 1200mg)，每 21 天一次，直到疾病进展或出现不可接受的毒性。

  The efficacy of TECENTRIQ® was evaluated in study ML39345 (NCT03141684), an open-label, single-arm study, in 49 adult and pediatric patients aged 2 years and older with unresectable or metastatic ASPS. Adult patients received 1200 mg intravenously and pediatric patients received 15 mg/kg (up to a maximum of 1200 mg) intravenously once every 21 days until disease progression or unacceptable toxicity.

24 Trametinib Dimethyl Sulfoxide 异硫氰酸苯酯 (Mekinist / Spexotras®) + Dabrafenib Mesylate 达拉菲尼甲磺酸盐 (TAFINLAR® / Finlee®)

Dabrafenib+Trametinib(FDA label)
Trametinib Spexotras(EMA Label)
Dabrafenib Finlee(EMA Label)

- **药品类别：蛋白激酶抑制剂 / BRAF 激酶抑制剂**
- **原研药厂家：诺华制药（瑞士）**
- **适应症 1： 1 岁及以上患有不可切除或转移性实体瘤且携带 BRAF V600E 突变的儿童，这些患者在经过既往治疗后病情进展，且无其他理想治疗选择**

  Indication 1: pediatric patients 1 years of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options

- **儿童临床试验 1 TMT212X2101 (X2101) Study:** 一项针对难治性或复发性实体瘤儿童患者的多中心、开放标签、多队列研究。C 部分是 Mekinist 联合 Dabrafenib 的在 BRAF V600E 突变患者中进行剂量递增。客观缓解率 (ORR) 为 25% (95% CI: 12%, 42%)。在有应答的 9 例患者中，78% 的患者 DoR ≥ 6 个月，44% 的患者 DoR ≥ 24 个月。

A multi-center, open-label, multi-cohort study in pediatric patients with refractory or recurrent solid tumors. The ORR was 25% (95% CI: 12%, 42%). Part C was a dose escalation of MEKINIST in combination with dabrafenib in patients with a BRAFV600E mutation. For the 9patients who responded, DoR was ⩾ 6months for 78% of patients and ⩾ 24 months for 44% of patients.

- **儿童临床试验 2 CDRB436G2201 (G2201) Study – High-Grade Glioma Cohort:** 研究 G2201(NCT02684058) 是一项多中心、随机、开放标签的 II 期研究，研究 dabrafenib 和 trametinib 在 BRAF V600E 突变型低级别胶质瘤 (LGG) 和复发或进行性 BRAF V600E 突变型高级别胶质瘤 (HGG) 患儿化疗 naïve 中的应用。客观缓解率 (ORR) 为 56% (95% CI: 40,72)。中位 DoR 未达到 (95% CI: 9.2, NE)。在高级别胶质瘤队列中有应答的 23 例患者中，78% 的患者 DoR ⩾ 6 个月，48% 的患者 DoR ⩾ 12 个月，22% 的患者 DoR ⩾ 24 个月。

  Study G2201 (NCT02684058) CDRB436 was a multi-center, randomized, open-label, Phase II study of dabrafenib and trametinib in chemotherapy naïve pediatric patients with BRAF V600E mutant low-grade glioma (LGG) and patients with relapsed or progressive BRAF V600E mutant high-grade glioma (HGG). Patients with HGG were enrolled in a single arm cohort. The efficacy of TAFINLAR in combination with trametinib was evaluated in 41 pediatric patients with relapsed or progressive HGG.The ORR was 56% (95% CI: 40, 72). The median DoR was not reached(95%CI: 9.2,NE). For the 23 patients who responded in the HGG cohort, DoR was ⩾ 6 months for 78% of patients, ⩾ 12 months for 48% of patients, and ⩾ 24 months for 22% of patients.

- **适应症 2：1 岁及以上 BRAF V600E 突变阳性的低级别胶质瘤 (LGG) 且需要系统治疗的儿童**

  Indication 2: BRAF V600E Mutation-Positive Low-Grade Glioma aged 1 years and older who require systemic therapy

- **儿童临床试验 CDRB436G2201 (G2201) Study – Low-Grade Glioma Cohort:** 一项多中心开放标签试验 (Study CDRB436G2201; NCT02684058)。在 LGG 队列中，110 名患者随机分配到 D+T(n=73) 或 C+V(n=37)。G2201 研究显示，与随机分配到 C+V 组相比，随机分配到 D+T 组的 LGG 患者的 ORR 和 PFS 有统计学意义的改善。

  A multi-center, open-label trial (Study CDRB436G2201; NCT02684058). In the LGG cohort, 110 patients were randomized to D + T (n=73) or C + V (n=37). Study G2201 showed a statistically significant improvement in ORR and PFS in LGG patients randomized to D + T compared to those randomized to C + V.

- **适应症 3: 1 岁及以上儿童患有 BRAFV600E 突变的高级别胶质瘤 (HGG)，且至少接受过一次放疗和 / 或化疗**

  Indication 3: aged 1 year and older with high-grade glioma (HGG) with a BRAF V600E mutation who have received at least one prior radiation and/or chemotherapy treatment

- **儿童临床试验 EudraCT 2015-004015-20:** Dabrafenib 联合 Trametinib 治疗 1 至小于 18 岁携带 BRAF V600E 突变阳性胶质瘤的儿科患者的临床疗效和安全性在一项多中心、开放标签的 II 期临床研究中得到了评估。患有复发或难

治性高级别胶质瘤 (WHO 2016 年 3 级和 4 级) 的患者被纳入单组 Dabrafenib 联合 Trametinib 治疗队列。在该临床研究中，Dabrafenib 和 Trametinib 的剂量依年龄和体重而定 : 12 岁以下患者口服 Dabrafenib 的剂量为 2.625 mg/kg，每日两次；12 岁及以上患者的剂量为 2.25mg/kg，每日两次；6 岁以下患者口服 Trametinib 的剂量为 0.032mg/kg，每日一次；6 岁及以上患者的剂量为 0.025mg/kg，每日一次。Dabrafenib 的剂量上限为每日两次，每次 150mg，Trametinib 的剂量上限为每日一次，2mg。主要疗效终点是根据神经肿瘤反应评价 RANO(2010) 标准对 HGG 队列进行独立审查后得出的客观缓解率 (ORR)。主要分析在所有患者完成至少 32 周治疗后进行。在单组高级别胶质瘤队列中，共有 41 名复发或难治性 HGG 患者入组并接受 Dabrafenib 联合 Trametinib 治疗，治疗的中位持续时间为 72.7 周。患者的中位年龄为 13.0 岁，其中 5 名患者 (12.2%) 年龄为 12 个月至 <6 岁，10 名患者 (24.4%) 年龄为 6 至 <12 岁，26 名患者 (63.4%) 年龄为 12 至 <18 岁；56% 为女性。在初始诊断时的组织学分级中，20 名患者 (48.8%) 为 4 级，13 名患者 (31.7%) 为 3 级，4 名患者 (9.8%) 为 2 级，3 名患者 (7.3%) 为 1 级，1 名患者 (2.4%) 未报告分级。最常见的病理类型包括多形性胶质母细胞瘤 (31.7%)、间变性多形性黄色星形细胞瘤 (14.6%)、HGG NOS(9.8%) 和多形性黄色星形细胞瘤 (9.8%)。40 名患者 (97.6%) 报告曾接受过手术治疗，其中 24 名患者 (58.5%) 的最后一次手术为切除术。33 名患者 (80.5%) 曾接受过抗肿瘤化疗。37 名患者 (90.2%) 曾接受过放疗。21 名患者 (51.2%) 在接受研究治疗期间使用过全身性皮质类固醇。该队列的客观缓解率 (ORR) 为 56.1%(23/41)，95% CI(39.7%, 71.5%): 其中完全缓解 (CR) 患者 12 例 (29.3%)，部分缓解 (PR) 患者 11 例 (26.8%)。中位反应持续时间 (DOR) 为 22.2 个月 (95% CI: 7.6 - NE)，其中 15 名患者 (65.2%) 在进行主要分析时被剔除。

The clinical efficacy and safety of dabrafenib plus trametinib combination therapy in paediatric patients aged 1 to <18 years with BRAF V600 mutation-positive glioma was evaluated in a multicentre, open-label, Phase II clinical

study (EudraCT 2015-004015-20). Patients with relapsed or refractory high-grade glioma (WHO 2016 Grades 3 and 4) were enrolled into a single-arm dabrafenib plus trametinib cohort. Dabrafenib and trametinib dosing in the clinical study was age- and weight-dependent, with dabrafenib dosed orally at 2.625 mg/kg twice daily for ages <12 years and at 2.25 mg/kg twice daily for ages 12 years and older; trametinib was dosed orally at 0.032 mg/kg once daily for ages <6 years and at 0.025 mg/kg once daily for ages 6 years and older. Dabrafenib doses were capped at 150 mg twice daily and trametinib doses at 2 mg once daily. The primary efficacy endpoint was overall response rate (ORR, sum of confirmed complete/CR and partial responses/PR) by independent review based on RANO (2010) criteria for the HGG cohort. The primary analysis was performed when all patients had completed at least 32 weeks of therapy. In the single-arm high-grade glioma cohort, 41 patients with relapsed or refractory HGG were enrolled and treated with dabrafenib plus trametinib for a median duration of 72.7 weeks. Median age was 13.0 years, with 5 patients (12.2%) aged 12 months to <6 years, 10 patients (24.4%) aged 6 to <12 years and 26 patients (63.4%) aged 12 to <18 years; 56% were female. The histological grade at initial diagnosis was Grade 4 in 20 patients (48.8%), Grade 3 in 13 patients (31.7%), Grade 2 in 4 patients (9.8%), Grade 1 in 3 patients (7.3%) and missing in 1 patient (2.4%). The most common pathologies were glioblastoma multiforme (31.7%), anaplastic pleomorphic xanthoastrocytoma (14.6%), HGG NOS (9.8%) and pleomorphic xanthoastrocytoma (9.8%). Prior surgery was reported in 40 patients (97.6%), among those patients the procedure at last surgery was resection in 24 patients (58.5%). Prior antineoplastic chemotherapy was reported for 33 patients (80.5%). Prior radiotherapy was reported for 37 patients (90.2%). Systemic corticosteroid use while on study treatment was reported in 21 patients (51.2%). The ORR in this cohort was 56.1% (23/41), 95% CI (39.7%, 71.5%): CR in 12 patients (29.3%) and PR in 11 patients (26.8%). The median duration of response (DOR) was 22.2 months (95% CI: 7.6 – NE), with 15 patients (65.2%) censored at the time of the primary analysis.

- **适应症 4：≥ 12 岁青少年：BRAF V600 突变的不可切除 / 转移性黑色素瘤；以及完全切除后的III期黑色素瘤辅助治疗**

  Indication 4: For adolescents aged 12 years and older with BRAF V600 mutation-positive unresectable or metastatic melanoma, or as adjuvant treatment following complete resection of Stage III melanomaFor adolescents aged 12 years and older with BRAF V600 mutation-positive unresectable or metastatic melanoma, or as adjuvant treatment following complete resection of Stage III melanoma.

- **儿童用药说明：**基于一份采用建模与模拟方法、旨在证明达拉非尼和曲美替尼在青少年患者中的药代动力学（PK）、药效学（PD）及疗效的外推报告，将 TAFINLAR（达拉非尼）和 MEKINIST（曲美替尼） 的适应症扩展至：用于治疗 12 岁及以上、携带 BRAF V600 突变的不可切除或转移性黑色素瘤青少年患者，以及用于 12 岁及以上、携带 BRAF V600 突变的III期黑色素瘤青少年患者的辅助治疗。

  Extension of indication to include treatment of unresectable or metastatic melanoma with a BRAF V600 mutation and adjuvant treatment of Stage III melanoma with a BRAF V600 mutation for adolescents aged 12 years and older for TAFINLAR and MEKINIST, based on an extrapolation report using a modelling and simulation approach to demonstrate PK, PD and efficacy of dabrafenib and trametinib in adolescent patients.

- **成人临床试验 1 COMBI-d（NCT01584648）：**COMBI-d 是一项随机、双盲、安慰剂对照的III期试验，评价达拉非尼联合曲美替尼与达拉非尼单药相比，用于既往未经治疗、携带 BRAF V600E 或 V600K 突变的不可切除III C 期或转移性IV期皮肤黑色素瘤成 人患者的疗效和安全性。共有 423 例患者按 1:1 随机接

受达拉非尼 150 mg 每日两次联合曲美替尼 2 mg 每日一次（n=211），或达拉非尼 150 mg 每日两次联合安慰剂（n=212）。主要疗效终点为研究者评估的无进展生存期（PFS），关键次要终点为总生存期（OS）。主要分析显示，联合治疗组与达拉非尼单药组的中位 PFS 分别为 9.3 个月和 8.8 个月，疾病进展或死亡风险比（HR）为 0.75（95% CI：0.57，0.99；p=0.035）。在更新分析中，中位 PFS 分别为 11.0 个月和 8.8 个月（HR 0.67；95% CI：0.53，0.84）。成熟 OS 分析显示，中位 OS 分别为 25.1 个月和 18.7 个月（HR 0.71；95% CI：0.55，0.92；p=0.011）。

COMBI-d (NCT01584648) was a randomized, double-blind, placebo-controlled, Phase III trial evaluating the efficacy and safety of dabrafenib plus trametinib compared with dabrafenib monotherapy in treatment-naïve adult patients with unresectable Stage IIIC or metastatic Stage IV cutaneous melanoma harboring a BRAF V600E or V600K mutation. A total of 423 patients were randomized 1:1 to receive dabrafenib 150 mg twice daily plus trametinib 2 mg once daily (n=211), or dabrafenib 150 mg twice daily plus placebo (n=212). The primary efficacy endpoint was investigator-assessed progression-free survival (PFS), and the key secondary endpoint was overall survival (OS). At the primary analysis, median PFS was 9.3 months in the combination arm and 8.8 months in the dabrafenib monotherapy arm, with a hazard ratio (HR) for disease progression or death of 0.75 (95% CI: 0.57, 0.99; p=0.035). At an updated analysis, median PFS was 11.0 months versus 8.8 months, respectively (HR 0.67; 95% CI: 0.53, 0.84). In the mature OS analysis, median OS was 25.1 months with dabrafenib plus trametinib and 18.7 months with dabrafenib alone (HR 0.71; 95% CI: 0.55, 0.92; p=0.011).

- **成人临床试验 2 COMBI-v（NCT01597908）：**COMBI-v 是一项随机、开放标签、阳性对照的III期试验，评价达拉非尼联合曲美替尼与维莫非尼单药相比，用于既往未经治疗、携带 BRAF V600E 或 V600K 突变的不可切除或转移性皮肤黑色素瘤成人患者的疗效和安全性。共有 704 例患者按 1:1 随机接受达拉

非尼 150 mg 每日两次联合曲美替尼 2 mg 每日一次（n=352），或维莫非尼 960 mg 每日两次（n=352）。主要疗效终点为 OS，关键次要终点为研究者评估的 PFS。更新分析显示，联合治疗组与维莫非尼组的中位 OS 分别为 25.6 个月和 18.0 个月，死亡风险比为 0.66（95% CI：0.53，0.81；p<0.001）。主要 PFS 分析显示，中位 PFS 分别为 11.4 个月和 7.3 个月（HR 0.56；95% CI：0.46，0.69；p<0.001）；客观缓解率分别为 64% 和 51%。在 5 年随访分析中，两组中位 OS 分别为 26.0 个月和 17.8 个月，5 年 OS 率分别为 36% 和 23%。

COMBI-v (NCT01597908) was a randomized, open-label, active-controlled, Phase III trial evaluating the efficacy and safety of dabrafenib plus trametinib compared with vemurafenib monotherapy in treatment-naïve adult patients with unresectable or metastatic cutaneous melanoma harboring a BRAF V600E or V600K mutation. A total of 704 patients were randomized 1:1 to receive dabrafenib 150 mg twice daily plus trametinib 2 mg once daily (n=352), or vemurafenib 960 mg twice daily (n=352). The primary efficacy endpoint was OS, and the key secondary endpoint was investigator-assessed PFS. At an updated analysis, median OS was 25.6 months in the dabrafenib-plus-trametinib arm and 18.0 months in the vemurafenib arm, with an HR for death of 0.66 (95% CI: 0.53, 0.81; p<0.001). At the primary PFS analysis, median PFS was 11.4 months and 7.3 months, respectively (HR 0.56; 95% CI: 0.46, 0.69; p<0.001), and the objective response rates were 64% and 51%, respectively. At the 5-year analysis, median OS was 26.0 months versus 17.8 months, and the estimated 5-year OS rates were 36% versus 23%.

- **成人临床试验 3 COMBI-AD（NCT01682083）：**COMBI-AD 是一项多中心、随机、双盲、安慰剂对照的III期试验，评价达拉非尼联合曲美替尼用于 BRAF V600E 或 V600K 突变、完全切除后的III期皮肤黑色素瘤成人患者辅助治疗的疗效和安全性。符合条件的患者为完全切除的III A 期（淋巴结转移灶 >1 mm）、III B 期或III C 期黑色素瘤，并在随机分组前 12 周内完成包括完全淋

巴结清扫在内的手术治疗。共有 870 例患者按 1:1 随机接受达拉非尼 150 mg 每日两次联合曲美替尼 2 mg 每日一次（n=438），或两种匹配安慰剂（n=432），治疗持续 12 个月。主要疗效终点为研究者评估的无复发生存期（RFS），定义为从随机分组至首次疾病复发或任何原因死亡的时间；关键次要终点为 OS。主要分析显示，联合治疗组的中位 RFS 尚未达到，安慰剂组为 16.6 个月，复发或死亡风险比为 0.47（95% CI：0.39，0.58；$p=1.53\times10^{-14}$）。两组 3 年 RFS 率分别为 58% 和 39%。在增加约 29 个月随访后的更新分析中，RFS 获益仍然维持（HR 0.51；95% CI：0.42，0.61），5 年 RFS 率分别为 52% 和 36%。最终 OS 分析显示，两组 OS 差异未达到统计学显著性（HR 0.80；95% CI：0.62，1.01）；估计 5 年 OS 率分别为 79% 和 70%，10 年 OS 率分别为 66% 和 63%。

COMBI-AD (NCT01682083) was a multicenter, randomized, double-blind, placebo-controlled, Phase III trial evaluating adjuvant dabrafenib plus trametinib in adult patients with completely resected Stage III cutaneous melanoma harboring a BRAF V600E or V600K mutation. Eligible patients had completely resected Stage IIIA melanoma with lymph-node metastasis greater than 1 mm, Stage IIIB melanoma, or Stage IIIC melanoma, and were required to have undergone complete surgical resection, including complete lymphadenectomy, within 12 weeks before randomization. A total of 870 patients were randomized 1:1 to receive dabrafenib 150 mg twice daily plus trametinib 2 mg once daily (n=438), or two matching placebos (n=432), for 12 months. The primary efficacy endpoint was investigator-assessed relapse-free survival (RFS), defined as the time from randomization to disease recurrence or death from any cause. The key secondary endpoint was OS. At the primary analysis, median RFS was not reached in the combination arm and was 16.6 months in the placebo arm, with an HR for recurrence or death of 0.47 (95% CI: 0.39, 0.58; $p=1.53\times10^{-14}$). The estimated 3-year RFS rates were 58% and 39%, respectively. At an updated analysis incorporating approximately 29 additional months of follow-up, the RFS benefit

was maintained (HR 0.51; 95% CI: 0.42, 0.61), with estimated 5-year RFS rates of 52% and 36%, respectively. At the final OS analysis, the difference in OS was not statistically significant (HR 0.80; 95% CI: 0.62, 1.01). The estimated 5-year OS rates were 79% and 70%, and the estimated 10-year OS rates were 66% and 63%, respectively.

- 注 : Trametinib Dimethyl Sulfoxide(美国商品名为 Mekinst、欧盟商品名为 Spexotras®) 和 Dabrafenib(美国商品名为 TAFINLAR®、欧盟商品名为 Finlee®) 联合使用于治疗儿童肿瘤在美国食品药品管理局 (FDA) 和欧洲药品管理局 (EMA) 均获批上市，其中，上述适应症 1 和 2 为美国批准的儿科适应症，适应症 3 和 4 为欧盟批准的儿科适应症。

25 Eflornithine 依氟鸟氨酸 (IWILFIN ™)

label(fda.gov)

- **药品类别：鸟氨酸脱羧酶抑制剂**
- **原研药厂家： US WorldMeds(美国)**
- **适应症：降低患有高危神经母细胞瘤 (HRNB) 的成人和儿童患者的复发风险，这些患者对先前的多药物、多模式治疗 (包括抗 GD2 免疫治疗) 至少有部分反应。**

Indication: reduce the risk of relapse in pediatric patients with high-risk neuroblastoma (HRNB) who have demonstrated at least a partial response to prior multiagent, multimodality therapy including anti-GD2 immunotherapy.

- **儿童临床试验 Study 3b (NCT02395666) 和 ANBL0032:** IWILFIN ™的安全性和有效性已通过一项有两个队列的多中心、开放标签、非随机试验得到证实。在一个队列中，符合条件的患者是患有高危神经母细胞瘤的儿科患者，他们对先前的多药、多模式治疗 (包括诱导、巩固和抗 gd2 免疫治疗) 至少有部分反应。共有 105 名符合条件的患者口服 IWILFIN ™，每日两次，剂量基于体表面积 (BSA)，直到疾病进展，不可接受的毒性，或最长 2 年。肿瘤评估分别在治疗结束后 3、6、9、12、18 个月及出现临床指征时进行。完成 IWILFIN ™治疗后，对患者进行了为期 7 年的随访。主要疗效指标是无事件生存期 (EFS)，定义为从随机化开始 (或单臂试验中治疗开始) 到首次发生以下任何事件的时间 : 疾病进展、复发、继发性癌症或任何原因导致的死亡。另一个疗效指标是总生存期 (OS)，定义指从随机化开始 (或单臂试验中治疗开始) 到任何原因导致死亡的时间。该实验主要分析人群 (N=360) 中

59% 为男性；诊断时的中位年龄为 3 岁 (范围 : 0.1 - 20.1)；88% 是白人，6% 是黑人，4% 是亚洲人，7% 是西班牙人。大多数患者 (86%) 为 4 期疾病，44% 的肿瘤中观察到 MYCN 基因扩增。免疫治疗结束反应为完全缓解 (CR;87%)，非常好的部分反应 (VGPR;8%) 或部分缓解 (PR;5%)。在方案指定的初步分析中，EFS 风险比 (HR) 为 0.48 (95% CI: 0.27, 0.85)，OS 风险比 (HR) 为 0.32 (95% CI: 0.15, 0.70)。用于 EFS 初步分析的 Kaplan-Meier 图，每条曲线的阴影带代表逐点的 95%CI。

The safety and effectiveness of IWILFIN have been established through a multi-center, open label, non-randomized trial with two cohorts. Eligible patients in one cohort (Stratum 1) were pediatric patients with high-risk neuroblastoma (HRNB) who demonstrated at least a partial response to prior multiagent, multimodality therapy, including induction, consolidation, and anti-GD2 immunotherapy. A total of 105 eligible patients received IWILFIN orally twice daily, dosage based on body surface area (BSA) until disease progression, unacceptable toxicity, or for a maximum of 2 years. Tumor assessments were performed at 3, 6, 9, 12, 18 months, completion of treatment, and as clinically indicated. Following completion of IWILFIN ™ therapy, patients were followed for a total duration of 7 years. The major efficacy outcome measure was event free survival (EFS), defined as disease progression, relapse, secondary cancer, or death due to any cause. An additional efficacy outcome measure was overall survival (OS), defined as death due to any cause.

The demographic characteristics of the primary analysis population (N=360) were 59% male; median age at diagnosis 3 years (range: 0.1 to 20.1); 88% White, 6% Black, 4% Asian, 7% Hispanic. The majority of patients had Stage 4 disease (86%) and MYCN amplification was observed in 44% of tumors. End of immunotherapy responses were complete response (CR; 87%), very good partial response (VGPR; 8%), or partial response (PR; 5%). In the protocol-specified primary analysis, the EFS hazard ratio (HR) was 0.48 (95% CI: 0.27, 0.85) and OS HR was 0.32 (95% CI: 0.15, 0.70). The Kaplan-Meier plot for the primary analysis of EFS, with shaded bands for each curve representing the point-wise 95% confidence intervals.

26 Tovorafenib 托沃拉非尼 (OJEMDA™)

label(fda.gov)

- **药品类别 : 靶向疗剂**
- **原研药厂家 : Day One Biopharmaceuticals(美国)**
- **适应症 : 6 个月及以上患有复发性或难治性儿童低级别神经胶质瘤 (LGG) 的患者，这些患者含有 BRAF 融合或重排或 BRAF V600 突变。**

Indication: 6 months of age and older with relapsed or refractory pediatric low-grade glioma (LGG) harboring a BRAF fusion or rearrangement, or BRAF V600 mutation.

- **儿童临床试验 (FIREFLY-1; NCT0477548):** OJEMDA™的疗效在一项多中心、开放标签、单臂临床试验中进行了评估。符合条件的患者 (N=76) 需患有复发或难治性、携带 BRAF 激活突变的儿童低级别胶质瘤 (LGG)。患者还需至少有一个可测量病灶 (符合神经肿瘤反应评价 RANO 2010 标准)。患者每周口服一次 OJEMDA™，剂量约为 420mg/m^2，直至疾病进展或出现不可接受的毒性。肿瘤评估每 12 周进行一次。疗效结局指标包括客观缓解率 (ORR)，定义为根据 RAPNO-LGG(儿童神经肿瘤缓解评估) 标准，由独立评审判定的完全缓解 (CR)、部分缓解 (PR) 或轻微缓解 (MR) 的患者比例；缓解时长。疗效结果显示，76 名患者的客观缓解率 (ORR) 为 51%(95%CI: 41%，63%)，缓解时长为 13.8 个月 (95%CI: 11.3 个月，无)。

The efficacy of OJEMDA ™ was evaluated in a multicenter, open-label, single-arm he efficacy of OJEMDA ™ was evaluated in a multicenter, open-label, single-arm clinical trial. Eligible patients (N=76) were required to have a relapsed or refractory pediatric low-grade glioma (LGG) harboring an activating BRAF alteration. Patients were also required to have at least one measurable lesion as defined by RANO 2010 criteria. Patients received OJEMDA ™ approximately 420 mg/m2 orally once weekly until disease progression or unacceptable toxicity. Tumor assessments were performed every 12 weeks. The major efficacy outcome measure was overall response rate (ORR), defined as the proportion of patients with complete response (CR), partial response (PR), or minor response (MR) by independent review based on RAPNO-LGG (Response Assessment in Pediatric Neuro-Oncology) criteria. Efficacy results showed that the overall response rate of the 76 patients was 51% (95% CI: 41%, 63%), and the duration of response was 13.8 months (95% CI: 11.3 months, not reached).

Table 10 Efficacy Results Based on Independent Review in FIREFLY-1 (Arm-1)

Efficacy Parameter	**RAPNO-LGG N=76***
Overall Response Rate	
ORR (95% CI)[a]	51% (40, 63)
Complete Response (CR), n (%)	0 (0)
Partial Response (PR), n (%)	28 (37)
Minor Response (MR), n (%)	11 (14)
Duration of Response (DoR)	**N=39**
Median (95% CI)[b], Months	13.8 (11.3, NE)
% with observed DoR ≥ 6 months	85%
% with observed DoR ≥ 12 months	23%

Abbreviations: LGG = low-grade glioma; RAPNO = Response Assessment in Pediatric Neuro-Oncology; CI = confidence interval; NE = not estimable.
*At least one measurable lesion at baseline based on RAPNO-LGG criteria.
[a]Based on Clopper-Pearson exact confidence interval.
[b]Based on Kaplan-Meier estimate.

27 Vorasidenib Citrate 沃拉西德尼 (VORANIGO®)

label(fda.gov)

Vorasidenib(TGA_Approval)

- **药品类别 : 靶向疗法**
- **原研药厂家 : 施维雅制药 (法国)**
- **适应症 : 患有 2 级星形细胞瘤或少突胶质细胞瘤的成人和 12 岁及以上的儿童患者，这些患者在手术 (包括活检、次全切除或全切除) 后具有易感异柠檬酸脱氢酶 1 (IDH1) 或异柠檬酸脱氢酶 2 (IDH2) 突变**

Indication: 12 years and older with Grade 2 astrocytoma or oligodendroglioma with a susceptible IDH1 or IDH2 mutation following surgery including biopsy, sub-total resection, or gross total resection

- **儿童临床试验 (Study AG881-C-004):** VORANIGO® 的疗效在 INDIGO 试验中得到了评估，INDIGO 试验是一项随机、多中心、双盲、安慰剂对照的研究。符合条件的患者 (N=331) 需要有 IDH1 或 IDH2 突变的 2 级星形细胞瘤或少突胶质细胞瘤，并接受过包括活检、部分切除或完全切除在内的手术。患者需要有可测量的、非增强的疾病；经中心确认的最小、非结节性、非可测量增强的患者也有资格。患者被随机分组，168 名进入 VORANIGO® 组，163 名进入安慰剂组。患者每天口服一次 VORANIGO® 40 毫克或每天口服一次安慰剂，直至疾病进展或出现不可接受的毒性。肿瘤评估每 12 周进行一次。主要疗效结果是无进展

生存期 (PFS)。VORANIGO® 组患者的下一次干预的中位时间未达到，而安慰剂组患者的中位时间为 17.8 个月 (HR=0.26；95% CI: [0.15, 0.43]，p<0.0001)。

The efficacy of VORANIGO® was evaluated in the INDIGO trial, a randomized, multicenter, double-blind, placebo-controlled study. Eligible patients (N=331) were required to have IDH1- or IDH2-mutant Grade 2 astrocytoma or oligodendroglioma with prior surgery including biopsy, sub-total resection, or gross total resection. Patients were required to have measurable, non-enhancing disease; patients with centrally confirmed minimal, non-nodular, non-measurable enhancement were eligible. Patients were randomized, 168 to the VORANIGO® arm and 163 to the placebo arm. The median age was 40 years (range: 16 to 71); Patients received either VORANIGO® 40 mg orally once daily or placebo orally once daily until disease progression or unacceptable toxicity. Tumor assessments were performed every 12 weeks. The major efficacy outcome was progression-free survival (PFS). The median time to the next intervention was not reached for patients in the VORANIGO® arm and 17.8 months for patients in the placebo arm (HR=0.26; 95% CI: [0.15, 0.43], p<0.0001)

Table 7: Efficacy Results for the INDIGO Trial (Study AG881-C-004)

Efficacy Parameter	VORANIGO 40 mg daily (n=168)	Placebo (n=163)
Progression-Free Survival (PFS)		
Number of Events, n (%)		
Progressive disease	47 (28)	88 (54)
Death	0	0
Hazard ratio (95% CI)[a]	0.39 (0.27, 0.56)	
p-value[b]	<0.0001	

CI = Confidence Interval
[a] Stratified Cox proportional hazard model, stratified by 1p19q status and baseline tumor size.
[b] Based on one-sided stratified log-rank test compared to the pre-specified α of 0.000359 (one-sided).

IDH1 或 IDH2 突变的星形细胞瘤或少突胶质瘤在成人和儿童患者中的病程具有足够的相似性，可以将成人患者的药代动力学数据外推至儿童患者。

In addition, the course of IDH1- or IDH2-mutant astrocytoma or oligodendroglioma is sufficiently similar between adults and pediatric patients to allow extrapolation of pharmacokinetic data in adults to pediatric patients.

28 Repotrectinib 瑞普替尼 (Augtyro ™)

- **药品类别 : 靶向疗法**
- **原研药厂家 : 百时美施贵宝 (美国)**
- **适应症 : 12 岁及以上成人和儿童患者，患有以下特征的实体瘤 : (1) 存在神经营养性酪氨酸受体激酶 (NTRK) 基因融合；(2) 局部晚期或转移性，或手术切除可能导致严重并发症；(3) 经治疗后疾病进展，或无其他令人满意的替代疗法。**

  Indication: adult and pediatric patients 12 years of age and older with solid tumors that: 1) have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, 2) are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity, and 3) have progressed following treatment or have no satisfactory alternative therapy.

- **儿童临床试验 (NCT03093116):** AUGTYRO ™ 的疗效在 TRIDENT-1 中进行了评估，这是一项多中心、单臂、开放标签、多队列临床试验，在 88 例局部晚期或转移性 NTRK 基因融合阳性 (NTRK1/2/3) 实体瘤成年患者中进行了评估，这些患者既往接受过酪氨酸激酶抑制剂 (TKI) 治疗 (48 名) 或未接受过酪氨酸激酶抑制剂 (TKI) 治疗 (40 名)。患者接受 AUGTYRO™ 160 mg 口服，每天一次，持续 14 天，然后增加到 160 mg，每天两次，直到疾病进展或出现不可接受的毒性。每 8 周进行一次肿瘤评估。主要疗效结局指标是客观缓解率 (ORR) 和缓解持续时间 (DOR)。疗效结果显示，酪氨酸激酶抑制剂初治患者的客观缓解率

(ORR) 为 58%(95%CI: 41%，73%)，酪氨酸激酶抑制剂预处理患者的客观缓解率 (ORR) 为 50%(95%CI: 35%，65%)；酪氨酸激酶抑制剂初治患者的缓解持续时间时长 Ne，酪氨酸激酶抑制剂 (TKI) 预处理患者的环节持续时间为 9.9 个月 (95%CI: 7.4 个月，13 个月)。

The efficacy of AUGTYRO ™ was evaluated in TRIDENT-1 (NCT03093116), a multi-center, single-arm, open-label, multi-cohort clinical trial in 88 adult patients with locally advanced or metastatic NTRK gene fusion-positive (NTRK1/2/3) solid tumors who had either received a prior TKI treatment (48) or were TKI-naïve (40). Patients received AUGTYRO ™ 160 mg orally once daily for 14 days, then increased to 160 mg twice daily until disease progression or unacceptable toxicity. Tumor assessments were performed every 8 weeks. The major efficacy outcome measures were ORR and DOR. Efficacy results showed that the overall response rate was 58% (95%CI: 41%, 73%) in patients treated with TKI and 50% (95%CI: 35%, 65%) in patients treated with TKI. The duration of remission was Ne in patients treated with TKI and 9.9 months in patients treated with TKI (95%CI: 7.4 months, 13 months).

AUGTYRO ™用于治疗局部晚期或转移性 NTRK 阳性实体瘤的安全性和有效性已在 12 岁及以上的儿童患者中得到验证。支持在该年龄组使用 AUGTYRO ™，是基于一项充分且经过良好控制的成人患者研究的证据，并辅以 12 岁及以上儿童患者的药代动力学和安全性数据。这些数据表明，在 12 岁及以上儿童患者中，Repotrectinib 的药物暴露预计会与成人患者相似，且其安全性和疗效也预计与成人相似。此外，局部晚期或转移性 NTRK 阳性实体瘤在成人和 12 岁及以上儿童患者中的病程足够相似，因此可以将成人患者数据外推至 12 岁及以上的儿童患者。

The safety and effectiveness of AUGTYRO ™ for the treatment of locally advanced or metastatic NTRK-positive solid tumors have been established in pediatric patients 12 years of age or older. Use of AUGTYRO ™ in this age group is supported

by evidence from an adequate and well-controlled study in adult patients with additional pharmacokinetic and safety data in pediatric patients aged 12 years and older. This includes data demonstrating that the exposure of repotrectinib in pediatric patients 12 years of age and older is expected to result in similar safety and efficacy to that of adults, and that the course of locally advanced or metastatic NTRK-positive solid tumors is sufficiently similar in adults and pediatric patients 12 years of age or older to allow extrapolation of data in adult to pediatric patients 12 years of age or older.

Table 6: Efficacy Results for Patients with NTRK Gene Fusion-Positive Tumors in TRIDENT-1

Efficacy Parameters	TKI-Naïve Patients (n=40)	TKI-Pretreated Patients (n=48)
Confirmed Overall Response Rate, % (95% CI)	58 (41, 73)	50 (35, 65)
Complete Response, %	15	0
Partial Response, %	43	50
Median Duration of Response (mDOR)[a], in Months (95% CI)	NE (NE, NE)	9.9 (7.4, 13.0)
Range (months)	3.7+, 43.9+	1.8, 26.5+
% with DOR ≥ 6 months[b]	87	71
% with DOR ≥ 9 months[b]	83	63
% with DOR ≥ 12 months[b]	83	42

NE = not evaluable; "+" indicates ongoing response

[a] Median DOR (95% CI) are based on Kaplan-Meier estimates.

[b] DOR landmark analysis is based on the observed DOR.

29 Cabozantinib-S-Malate 卡博替尼 (Cabometyx®)

Cabozantinib (Cabometyx®)

- **药品类别 : 靶向疗法**
- **原研药厂家 : 伊克力西斯 (美国)**
- **适应症 : 12 岁及以上患有局部晚期或转移性分化型甲状腺癌 (DTC)**

Indication: CABOMETYX® is indicated for the treatment of adult and pediatric patients 12 years of age and older with locally advanced or metastatic differentiated thyroid cancer (DTC).

- **儿童临床试验 (COSMIC-311):** CABOMETYX® 的疗效在 COSMIC-311 中进行了评估，这是一项随机 (2: 1)、双盲、安慰剂对照、多中心试验，受试者为局部晚期或转移性分化型甲状腺癌患者，这些患者在既往 VEGFR 靶向治疗后进展且放射性碘难治性或不合格。患者被随机分配接受 CABOMETYX® 60 mg 口服，每日一次或安慰剂联合支持治疗，直至疾病进展或出现不可接受的毒性。主要疗效结局指标是 意向治疗 (ITT) 人群的无进展生存期 (PFS) 和前 100 名随机化患者的客观缓解率 (ORR)。每 8 周进行一次肿瘤评估。疗效结果显示 : 接受 CABOMETYX® 组的无进展生存期 (PFS) 中位数为 11.0 个月 (95%CI: 7.4 个月，13.8 个月)，客观缓解率 (ORR) 为 18%(95%CI: 10%，29%)CABOMETYX® 用于治疗 12 岁及以上儿童分化型甲状腺癌的依据来自针对成人的充分且严格对照研究，并辅以群体药代动力学数据，这些数据显示，在推荐剂量下，CABOMETYX ® 在 12 岁及以上儿童患者中的暴露水平与成人处于相同范围内。

The efficacy of CABOMETYX® was evaluated in COSMIC-311, a randomized (2:1), double-blind, placebo-controlled, multicenter trial in patients with locally advanced or metastatic differentiated thyroid cancer (DTC) that had progressed following prior VEGFR-targeted therapy and were radioactive iodine-refractory or ineligible. Patients were randomized to receive CABOMETYX® 60 mg orally once daily or placebo with supportive care until disease progression or unacceptable toxicity. The multiple primary efficacy outcome measures were progression-free survival (PFS) in the ITT population, and overall response rate (ORR) in the first 100 randomized patients. Tumor assessments were conducted every 8 weeks. Efficacy results: Median PFS in the CABOMETYX® group was 11.0 months (95%CI: 7.4 months, 13.8 months), and overall response rate was 18% (95%CI: 10%, 29%).

Use of CABOMETYX® in pediatric patients aged 12 years and older with DTC is supported by evidence from adequate and well-controlled studies of CABOMETYX® in adults with additional population pharmacokinetic data demonstrating that cabozantinib exposure is within the same range between adults and pediatric patients aged 12 years and older at the recommended dosages.

30 Mifamurtide 米法莫肽 (Mepact®)

Mifamurtide(Mepact®)

- **药品类别 : 靶向疗法**
- **原研药厂家 : 武田法国公司 (法国)**
- **适应症 : 高等级可切除的非转移性骨肉瘤儿童、青少年和年轻成人患者，适用于通过手术将肿瘤全部切除，术后肉眼检查没有残留的肿瘤组织的患者。与术后多药化疗联合使用，该药物的安全性和疗效已在初诊年龄为 2 至 30 岁的患者研究中进行了评估。**

Indication: Mepact® is indicated in children, adolescents and young adults for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection. It is used in combination with post-operative multi-agent chemotherapy. Safety and efficacy have been assessed in studies of patients 2 to 30 years of age at initial diagnosis

- **儿童及成人临床试验 :** Mifamurtide 的疗效和安全性在一项随机的 III 期临床试验中进行了评估，通过 678 例 (年龄范围为 1.4 至 30.6 岁) 新诊断等级可切除的非转移性骨肉瘤患者，在辅助化疗 (阿霉素顺铂和甲氨蝶呤联合或不联合异环磷酰胺) 基础上加用 Mifamurtide，评估了 Mifamurtide 的疗效和安全性。疗效结果 : 该治疗显著提高了 6 年总生存率，并使死亡风险相对降低了 28%(p = 0.0313，风险比 (HR) = 0.72 [95% CI: 0.53, 0. 97])。

The efficacy and safety of mifamurtide were evaluated in a randomised phase III study of 678 patients(age range from 1.4 to 30.6 years) with newly-diagnosed resectable high-grade osteosarcoma, the addition of adjuvant mifamurtide to chemotherapy (either doxorubicin cisplatin and methotrexate with or without ifosfamide). Efficacy results: This treatment significantly increased the 6-year overall survival and resulted in a relative reduction in the risk of death by 28% (p = 0.0313, hazard ratio (HR) = 0.72 [95% confidence interval (CI): 0.53, 0. 97]).

31 Vandetanib 凡德他尼 (Caprelsa®)

Vandetanib(EMA_Label)

- **药品类别 : 靶向疗法**
- **原研药厂家 : 赛诺菲 (法国)**
- **适应症： 5 岁及以上患有不可切除的局部晚期或转移性疾病的侵袭性和症状性的 RET 基因甲状腺髓样癌的儿童及青少年患者。**

Indication: Caprelsa® is indicated for the treatment of aggressive and symptomatic Rearranged during Transfection (RET) mutant medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease for adults, children and adolescents aged 5 years and older.

- **儿童临床试验 (IRUSZACT0098):** 一项 I/II 期单中心开放标签单臂研究评估了 Caprelsa® 在 16 例不可切除的局部晚期或转移性遗传性甲状腺髓样癌患者中的有效性。研究开始时患者的特征如下 : 平均年龄 14.2 岁 (9-17 岁)，50% 为女性，50% 为男性，93.8% 为白人，26.7% 为西班牙裔，6.3% 为黑人。大多数患者 (81.3%) 在进入研究前已接受部分或全部甲状腺切除术。除一名患者以 150 mg/m2/ 天开始剂量外，所有患者的起始 Caprelsa® 剂量均为 100mg/m2/ 天。在对前 1 或 2 个治疗周期 (1 个周期 =28 天) 耐受良好后，其余患者继续以 100mg/m2 剂量治疗。根据实体瘤反应评价标准 RECIST v 1.0，主要疗效结果为客观缓解率 (ORR)，观察到的客观缓解率为 43.8%，均为部分缓解。31.3% 的患者病情稳定至少 8 周。疾病控制率 (包括病情保持稳定或有正面反

应持续超过 24 周) 为 75.0%。这项研究中没有囊括 5-8 岁儿童患者。

A Phase I/II single-center open-label, single-arm study (Study IRUSZACT0098) assessed the activity of vandetanib in 16 patients with unresectable locally advanced or metastatic hereditary MTC. Characteristics of the patients at study entry were the following: mean age 14.2 years (range 9-17 years), 50% female, 50% male, 93.8% White, 26.7% Hispanic and 6.3% were Black. Most patients (81.3%) had undergone partial or total thyroidectomy prior to study entry. Starting vandetanib dose was 100mg/ m2/day for all patients except for one who started at 150mg/ m2/day. After having well tolerated the first 1 or 2 cycles of therapy (1 cycle = 28 days), the remaining patients continued on 100 mg/ m2 of treatment. The primary efficacy outcome was ORR according to RECIST v 1.0. The objective response rate observed was 43.8%, all of which were partial responses. 31.3% of patients had stable disease for at least 8 weeks. Disease Control Rate including best response or Stable Disease >24 weeks was 75.0%. There is no experience with Caprelsa® in patients 5-8 years of age in this study.

32 Revumenib Citrate 瑞维美尼 (Revuforj®)

Vandetanib(EMA_Label)

- **药品类别 : 梅嫩（Menin）蛋白抑制剂**
- **原研药厂家 : Syndax 制药 (美国)**
- **适应症 : 1 岁及以上儿童患有 KMT2A 基因易位复发或难治性急性白血病（ALL）**

Indication: REVUFORJ is indicated for the treatment of relapsed or refractory acute leukemia with a lysine methyltransferase 2A gene (KMT2A) translocation in adult and pediatric patients 1 year and older.

- **儿童用药说明 :** 在 1 岁及以上患有 KMT2A 易位复发或难治性急性白血病的儿科患者中 , REVUFORJ 的安全性和有效性已得到证实。REVUFORJ 用于该适应症已从一项充分且对照良好的成人，儿童试验组数据中得到支持。此外，儿科的药代动力学和安全性数据也支持 REVUFORJ 用于该适应症。该研究在 13 名婴儿患者（年龄 < 2 岁）、41 名儿童患者（年龄 2 至 < 12 岁）和 16 名青少年患者（年龄 12 至 < 17 岁）中进行。对于体重低于 40 公斤的患者，推荐剂量以 体表面积（BSA） 为基础。

REVUFORJ 在 1 岁以下的儿科患者中的安全性和有效性尚未确定。

The safety and efficacy of REVUFORJ have been established in pediatric patients 1 year and older with relapsed or refractory acute leukemia with a KMT2A translocation. Use of REVUFORJ for this indication is supported by evidence

from adequate and well-controlled trials in adults and pediatric and additional pharmacokinetic and safety data in pediatric. The patients included 13 infants (age < 2 years), 41 children (age 2 to < 12 years) and 16 adolescents (age 12 to < 17 years). The recommended dosage in patients weighing less than 40 kg is BSA-based. The safety and efficacy of REVUFORJ in pediatric patients less than 1 year old have not been established.

- **儿童与成人临床试验 SNDX-5613-0700(NCT04065399):** REVUFORJ 的疗效在一项开放标签、多中心试验 (SNDX-5613-0700, NCT04065399; AUGMENT-101) 的单臂临床试验中评估。该试验的参与对象由至少 30 天大的复发或难治性 (R/R) 急性白血病 (伴有 KMT2A 基因易位) 的成人及儿童患者组成。此试验排除了具有 11 号染色体长臂（q）23 区域部分串联重复（partial tandem duplication, PTD）的患者。入选的必要条件条件为 QTc 间隔监控 <450 毫秒。治疗方案为：成人每日两次口服剂量约为 160 毫克的 REVUFORJ，联合强效 CYP3A4 抑制剂，直至病情进展、出现不可接受的毒性反应、4 个疗程后仍未达到形态学上无白血病的状态，或接受造血干细胞移植 (HSCT)。接受治疗的 104 中，有 24 名（23%）患者在接受 REVUFORJ 治疗后接受了造血干细胞移植。

  疗效评估基于完全缓解（CR）+CR 部分血液学恢复（CRh）的比例、CR+CRh 持续时间以及从输血依赖转为输血不依赖的比例。该试验的中位随访时间为 5.73 个月（范围：0.3 至 28.9 个月）。疗效结果如表 11 所示。亚组分析显示，86 例急性髓系白血病患者中 18 例（21%）达到 CR+CRh，16 例急性淋巴细胞白血病患者中 3 例（19%）达到 CR+CRh，2 例混合表型急性白血病患者中 1 例（50%）达到 CR+CRh。

  在 22 例达到 CR 或 CRh 的患者中，达到 CR 或 CRh 的中位时间为 1.9 个月（范围：0.9 至 5.6 个月）。

在 83 例基线时依赖红细胞（RBC）和 / 或血小板输注的患者中，有 12 例（14%）在基线后 56 天内不再依赖红细胞和血小板输注。在 21 例基线时不依赖红细胞和血小板输注的患者中，有 10 例（48%）在基线后 56 天内不再依赖输血。

The efficacy of REVUFORJ was evaluated in a single-arm cohort of an open-label, multicenter trial (SNDX-5613-0700, NCT04065399; AUGMENT-101) in adult and pediatric patients at least 30 days old with relapsed or refractory (R/R) acute leukemia with a KMT2A translocation. Patients with an 11q23 partial tandem duplication were excluded. Eligibility required a QTcF < 450 msec at study baseline. Treatment consisted of REVUFORJ at a dose approximately equivalent to 160 mg in adults orally twice daily with a strong CYP3A4 inhibitor until disease progression, unacceptable toxicity, failure to achieve morphological leukemia-free state by 4 cycles of treatment, or hematopoietic stem cell transplantation (HSCT). Twenty-four (23%) patients underwent HSCT following treatment with REVUFORJ。

Efficacy was established on the basis of the rate of complete remission (CR) plus CR with partial hematologic recovery (CRh), the duration of CR+CRh, and the rate of conversion from transfusion dependence to transfusion independence. The median follow-up was 5.73 months (range, 0.3 to 28.9 months). The efficacy results are shown in Table 11. On subgroup analysis, CR+CRh was achieved by 18/86 (21%) of patients with AML, 3/16 (19%) of patients with ALL, and 1/2 (50%) of patients with MPAL.

Of the 22 patients who achieved a CR or CRh, the median time to CR or CRh was 1.9 months (range: 0.9, 5.6 months).

Among the 83 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 12 (14%) became independent of RBC and platelet transfusions during any 56-day postbaseline period. Of the 21 patients who were independent of both RBC and platelet transfusions at baseline, 10 (48%) remained transfusion independent during any 56-day post-baseline period.

Table 11. Efficacy Results in Patients with Relapsed or Refractory Acute Leukemia with KMT2A translocation (Study SNDX-5613-0700)

Endpoint	REVUFORJ N=104
CR[1]+CRh[2] n (%)	22 (21.2)
95% CI	(13.8, 30.3)[6]
Median DOCR+CRh[3] (months)	6.4[6]
95% CI	(2.7, NE)
CR n (%)	13 (12.5)
95% CI	(6.8, 20.4)[6]
Median DOCR[4] (months)	4.3[6]
95% CI	(1.0, NE)
CRh n (%)	9 (8.7)
95% CI	(4.0, 15.8)[6]
Median DOCRh[5] (months)	6.4[6]
95% CI	(1.9, NE)

CI: confidence interval; NE = not estimable; DOCR = duration of CR; DOCRh = duration of CRh.
1. CR is defined as bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC ≥1.0 × 10^9/L and platelet count ≥100 × 10^9/L.
2. CRh is defined as bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; residual neutropenia (>0.5 × 10^9/L) and thrombocytopenia (>50 × 10^9/L), but the count recovery criteria for CR are not met.
3. Duration of CR+CRh is defined as the time from first CR or CRh to the first documented relapse or death, whichever occurs first.
4. Duration of CR is defined as the time from first CR to the first documented relapse or death, whichever occurs first.
5. Duration of CRh is defined as the time from first CRh to the first documented relapse or death, whichever occurs first.
6. The 95% CI of the response rate is derived using the exact method based on binomial distribution. The median of the response duration is derived using

33 Treosulfan 苏消安 (Grafapex®)

Label (fda.gov)

- **药品类别 : 烷化剂（化疗）**
- **原研药厂家 : Medexus 制药 (美国)**
- **适应症 : 联合氟达拉滨（Fludarabine），为 1 岁及以上患有急性髓系白血病（AML）和骨髓增生异常综合征（MDS）的儿童进行同种异体造血干细胞移植（alloHSCT）前的预处理方案**

Indication: 1) Use in combination with fludarabine as a preparative regimen for allogeneic hematopoietic stem cell transplantation (alloHSCT) in adult and pediatric patients 1 year of age and older with acute myeloid leukemia (AML). 2) Use in combination with fludarabine as a preparative regimen for allogeneic hematopoietic stem cell transplantation in adult and pediatric patients 1 year of age and older with myelodysplastic syndrome(MDS).

- **儿童用药说明 :** 基于一项充分且有良好控制组的成人研究，现已确定将 GRAFAPEX 作为异体造血干细胞移植前准备方案的一部分，用于治疗 1 岁及以上患有急性髓系白血病（AML）或骨髓增生异常综合征（MDS）的儿科患者。该研究还获得了 111 名儿科患者的药代动力学和安全性数据，其中包括 22 名婴儿（1 个月至 2 岁）、54 名儿童（2 岁至 12 岁）和 35 名青少年（12 岁至 17 岁）。儿科患者的肝脏和胃肠道不良反应发生率高于成人。对于 1 岁以下患有 AML 或 MDS 的儿科患者，GRAFAPEX 作为异体造血干细胞移植前准备方案的安全性和有效性尚未确定。

The safety and efficacy of GRAFAPEX as part of a preparative regimen prior to allogeneic hematopoietic stem cell transplant in pediatric patients 1 year of age and older with AML or MDS have been established based on evidence from an adequate and well-controlled study in adults, with additional pharmacokinetic and safety data in 111 pediatric patients, including 22 infants (1 month to < 2 years), 54 children (2 to < 12 years), and 35 adolescents (12 to < 17 years). The incidence of hepatic and gastrointestinal adverse reactions was higher in pediatric patients than in adults. Safety and effectiveness of GRAFAPEX as part of a preparative regimen prior to allogeneic hematopoietic stem cell transplant in pediatric patients with AML or MDS younger than 1 year of age have not been established.

- **成人临床试验 MC-FludT.14/L Trial II(NCT00822393):** 一项随机活性对照试验对 GRAFAPEX 的疗效进行了评估，该试验将 GRAFAPEX 与白消安（Busulfan）联合氟达拉滨作为同种异体移植的准备方案进行了比较。符合条件的患者包括患有急性髓系白血病 (AML) 或骨髓增生异常综合征 (MDS) 的 18 至 70 岁成年人，卡诺夫斯基表现评分 > 60%，年龄 ⩾ 50 岁或造血细胞移植合并症指数 [HCT-CI] 评分 > 2。患者随机分配接受 GRAFAPEX 10 g/m^2（第 -4、-3 和 -2 天）或白消安 0.8 mg/kg（第 -4 和 -3 天，每 6 小时一次）联合氟达拉滨 30 mg/m2（第 -6、-5、-4、-3 和 -2 天），并在第 0 天进行造血干细胞移植。有 570 名患者随机分配接受 GRAFAPEX（n = 280）或白消安（n = 290）。疗效人群包括 365 例 AML 患者和 205 例 MDS 患者：536 例患者接受外周血干细胞治疗，15 例患者接受骨髓干细胞治疗，19 例患者未接受移植。

  疗效基于总生存期 (OS) 确定，OS 定义为从随机分组至因任何原因死亡的时间。与白消安相比，OS 的风险比 (HR)（按供体类型和风险组分层）在随机分组人群中为 0.67（95%），在急性髓系白血病患者中为 0.73（95%），在骨髓增生异常综合征患者中为 0.64（95%）。

与成人相比，体表面积 (BSA) < 0.7 平方米和体表面积 (BSA) 0.7 至 < 1.1 平方米的儿科患者的苏消安暴露量分别高出 11% 和 5%。儿科患者与成人之间苏消安的中位终末半衰期无显著临床差异。在儿科患者中，活性单环氧中间体的中位终末半衰期为 1.6 小时。

The efficacy of GRAFAPEX was evaluated in a randomized active-controlled trial comparing GRAFAPEX to busulfan in combination with fludarabine as a preparative regimen for allogeneic transplantation. Eligible patients included adults 18 to 70 years old with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS), Karnofsky performance status > 60%, and age ⩾ 50 years or hematopoietic cell transplantation comorbidity index [HCT-CI] score > 2. The patients were randomized to receive GRAFAPEX 10 g/m^2 daily on day -4, -3 and -2 or to busulfan 0.8 mg/kg every 6 hours on day -4 and -3 in combination with fludarabine 30 mg/m2 daily on day -6, -5, -4, -3 and -2, and hematopoietic stem cell transplantation on day 0. There were 570 patients randomized to GRAFAPEX (n = 280) or busulfan (n = 290). The efficacy population included 365 patients with AML and 205 patients with MDS: 536 patients received peripheral blood stem cells, 15 patients received marrow stem cells, and 19 patients were not transplanted.

Efficacy was established on the basis of overall survival (OS), defined as the time from randomization until death from any cause. The hazard ratio (HR) for OS (stratified by donor type and risk group) compared to busulfan was 0.67 (95% CI: 0.51, 0.90) in the randomized population, 0.73 (95% CI: 0.51, 1.06) in patients with AML, and 0.64 (95% CI: 0.40, 1.02) in patients with MDS.

Treosulfan exposure in pediatric patients with BSA < 0.7 m2 and with BSA 0.7 to < 1.1 m2 are 11% and 5% higher, respectively, compared to adults. No clinically significant difference in treosulfan median terminal half-life was observed between pediatric patients and adults. The median terminal half-life of the active monoepoxide intermediate was 1.6 hrs in pediatric patients.

34 Dordaviprone 多达维普隆 (Modeyso®)

Label (fda.gov)

- **药品类别 : 蛋白酶激活剂**
- **原研药厂家 : 爵士制药 (爱尔兰)**
- **适应症 : 1 岁及以上儿童患有 H3 K27M 突变弥漫性中线胶质瘤且在接受过先前治疗后病情出现进展。本适应症基于临床试验中总体缓解率和缓解持续时间结果获 USA FDA 加速批准，其未来持续批准可能取决于在确认性试验中验证并说明其临床获益。**

MODEYSO is indicated for the treatment of adult and pediatric patients 1 year of age and older with diffuse midline glioma harboring an H3 K27M mutation with progressive disease following prior therapy.

This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

- **儿童用药说明 :**MODEYSO 在治疗携带 H3 K27M 突变且患有弥漫性中线胶质瘤的 1 岁及以上儿童患者中的安全性和有效性已得到证实。该试验在 4 名 9 至 17 岁、患有 H3 K27M 突变的弥漫性中线胶质瘤的儿童患者中评估 MODEYSO 的疗效。在四项开放标签临床研究（ONC006、ONC013、ONC014 和 ONC018）中，对 154 名 3 至 17 岁、按推荐剂量接受 MODEYSO 治疗的儿童胶

质瘤患者进行了安全性评估。在这 154 名患者中，73% 为 3 至 11 岁，27% 为 12 至 17 岁。在儿童患者中未观察到其他安全性信号。成人患者的推荐剂量为每周口服一次，每次 625 毫克；体重≥ 10 公斤的儿科患者的推荐剂量基于体重，如下表 1 所示。

MODEYSO 对于 1 岁以下儿科患者的安全性和有效性尚未确定。

The safety and effectiveness of MODEYSO has been established in pediatric patients aged 1 year and older for the treatment of diffuse midline glioma harboring an H3 K27M mutation. The efficacy of MODEYSO was evaluated in 4 pediatric patients aged 9 to 17 years with diffuse midline glioma harboring an H3 K27M mutation. Safety was evaluated in 154 pediatric patients with glioma aged 3 to 17 years who received MODEYSO at the recommended dose across four open-label clinical studies (ONC006, ONC013, ONC014, and ONC018). Of these 154 patients, 73% were 3 to 11 years of age and 27% were 12 to 17 years of age. No additional safety signals were observed in pediatric patients. The recommended dose in adult patients is 625 mg orally once weekly, while The recommended dose in pediatric patients weighing ⩾ 10 kg is based on body weight and shown in Table 1 below.

The safety and effectiveness of MODEYSO have not been established in pediatric patients less than 1 year of age.

The recommended dosage of MODEYSO in pediatric patients aged 1 to <17 years who weigh at least 10 kg is based on body weight (Table 1). A recommended dosage of MODEYSO has not been established in pediatric patients who weigh less than 10 kg.

Table 1: Recommended Body Weight-Based Dosage for Pediatric Patients

Body Weight (kg)	Recommended Dosage
10 kg to <12.5 kg	125 mg Once Weekly
12.5 kg to <27.5 kg	250 mg Once Weekly
27.5 kg to <42.5 kg	375 mg Once Weekly
42.5 kg to <52.5 kg	500 mg Once Weekly
≥52.5 kg	625 mg Once Weekly

- **儿童与成人临床试验 ONC006, ONC013, ONC014, ONC016, and ONC0（NCT02525692, NCT03295396, NCT03416530, NCT05392374, and NCT03134131)：**预先设定的标准旨在建立综合疗效人群；符合条件的患者需接受过 MODEYSO 单药治疗，患有携带 H3 K27M 突变的弥漫性中线胶质瘤，且根据神经肿瘤学 - 高级别胶质瘤疗效评估 (RANO-HGG) 标准，病变进展且可测量， 在放疗≥ 90 天后，既往抗癌疗法已充分清除，卡氏体能状态 / 兰斯基体能状态 (KPS/LPS) 评分≥ 60，且皮质类固醇使用量稳定或减少。患有弥漫性内在性脑桥胶质瘤 (DIPG)、原发性脊髓肿瘤、组织学异常或脑脊液播散的患者被排除在试验之外。患者接受基于体重的 MODEYSO 剂量给药，直至病情进展或出现不可接受的毒性反应。

综合疗效人群包括 50 例符合这些标准的患者。主要疗效结论指标是采用由盲法独立中心审查 (BICR) 根据 RANO 2.0 标准评估而得来的总体缓解率 (ORR)。其他疗效结局指标包括采用 BICR 根据 RANO-HGG 标准和神经肿瘤低级别胶质瘤疗效评估 (RANO-LGG) 标准评估的 ORR、缓解持续时间和达到缓解时间。

试验中的基线人口统计数据为：中位年龄 31 岁（范围：9 至 70 岁），其中 6% 小于 17 岁；46% 为女性；80% 为白人、6% 为黑人或非裔美国人、2% 为亚裔、10% 为其他种族、2% 为种族不明；8% 为西班牙裔或拉丁裔；72% 的 KPS/LPS 为 80 至 100。相关疾病特征包括在第一次复发时接受治疗的 72% 的患者，28% 复发 2 次或 2 次以上的；原发肿瘤位置为丘脑（52%）和非丘脑中线区域（48%）；88% 曾接受替莫唑胺治疗；62% 在基线时接受皮质类固醇治疗。距离上次放疗结束的中位时间为 7.4 个月（范围: 3.0 至 102.1）。疗效如图 8 所示。

在对药物有反应的应答患者中，中位应答时间为 3.6 个月（范围：1.6-15.6）。根据 BICR 评估的 RANO 2.0 标准，综合应答评估结果显示，另有 1 例应答者，该评估考虑了皮质类固醇使用情况和体能状态。根据 BICR 评估的 RANO-HGG 标准（n=50），ORR 为 20%（95% CI: 10-34），其中 1 例完全应答，9 例部

分应答。根据 BICR 评估的 RANO-LGG 标准（n=50），ORR 为 20%（95% CI: 10-34），其中 5 例部分应答，5 例轻微应答。

Pre-specified criteria were defined to establish an integrated efficacy population; eligible patients were required to have received single-agent MODEYSO, have diffuse midline glioma harboring an H3 K27M mutation with progressive and measurable disease per Response Assessment in Neuro-Oncology-High Grade Glioma (RANO-HGG) criteria, be ⩾ 90 days post-radiation therapy, have adequate washout from prior anticancer therapies, have a Karnofsky Performance Status/ Lansky Performance Status (KPS/LPS) score ⩾ 60, and have stable or decreasing corticosteroid use. Patients with diffuse intrinsic pontine glioma (DIPG), primary spinal tumors, atypical histologies, or cerebrospinal fluid dissemination were excluded. Patients received weight-based dosing of MODEYSO until disease progression or unacceptable toxicity.

The integrated efficacy population included 50 patients who met these criteria. The major efficacy outcome measure was overall response rate (ORR) assessed by blinded independent central review (BICR) according to RANO 2.0 criteria. Additional efficacy outcome measures were BICR-assessed ORR according to RANO-HGG criteria and Response Assessment in Neuro-Oncology-Low Grade Glioma (RANO-LGG) criteria, duration of response, and time to response.

Baseline demographics were: median age 31 years (range: 9 to 70) with 6% younger than 17 years of age; 46% female; 80% White, 6% Black or African American, 2% Asian, 10% other races, and 2% race unknown; 8% were of Hispanic or Latino ethnicity; 72% had KPS/LPS 80 to 100. Relevant disease characteristics included 72% treated at first recurrence, 28% had 2 or more recurrences; primary tumor location was thalamic in 52% and non-thalamic midline region in 48%; 88% received prior temozolomide; 62% were receiving corticosteroids at baseline; median time from end of prior radiation was 7.4 months (range: 3.0 to 102.1). Efficacy are shown in Table 8 below.

Among responders, the median time to response was 3.6 months (range 1.6, 15.6). Using BICR-assessed RANO 2.0 criteria, there was one additional responder based on the integrated response assessment, which takes into account corticosteroid use and performance status. Based on BICR-assessed RANO-HGG criteria (n=50), the ORR was 20% (95% CI: 10, 34), with 1 complete and 9 partial responses. Based on BICR-assessed RANO-LGG criteria (n=50), the ORR was 20% (95% CI: 10, 34), with 5 partial and 5 minor responses

Table 8: Efficacy Results for Patients with Diffuse Midline Glioma Harboring an H3 K27M Mutation in Studies ONC006, ONC013, ONC014, ONC016, and ONC018 per RANO 2.0

Efficacy Parameter	MODEYSO N=50
Overall Response Rate (95% CI)[a]	22% (12, 36)
Partial response (PR)	16%
Minor response (MR)	6%
Duration of Response	N=11
Median (95% CI)[b], months	10.3 (7.3, 15.2)
% with observed DOR ≥6 months[c]	73%
% with observed DOR ≥12 months[c]	27%

Abbreviations: BICR=blinded independent central review; CI=confidence interval; RANO=Response Assessment in Neuro-Oncology.
[a] Confirmed overall response rate assessed by BICR; CI based on Clopper-Pearson method.
[b] Based on Kaplan-Meier estimate.
[c] Based on observed time.

35 Selumentinib Sulfate 硫酸氢司美替尼 (Keselugo®)

Label (fda.gov)

- **药品类别 : 蛋白激酶抑制剂**
- **原研药厂家 : 阿斯利康制药 (英国)**
- **适应症 : 适用于治疗患有 1 型神经纤维瘤病（NF1）和无法手术切除并展现症状的丛状神经纤维瘤（PN）的成人和 1 岁以上儿童患者。**

  KOSELUGO 在 1 岁以下儿童患者中的安全性和有效性尚未证实。

Indication: Keselugo is indicated for the treatment of adult and pediatric patients 1 year of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).

The safety and effectiveness of KOSELUGO have not been established in pediatric patients younger than 1 year of age.

中国 NMPA 批准本品胶囊剂型用于 3 岁及以上伴有症状、无法手术的 1 型神经纤维瘤病相关丛状神经纤维瘤的儿童及成人患者；12 岁对应的口服颗粒剂国内尚未申报上市。

- **儿童临床试验 SPRINKLE（NCT05309668）：**

1 岁以上儿童使用 KOSELUGO 颗粒剂（SPRINKLE 研究）：

SPRINKLE 研究（NCT05309668）是一项单臂、多中心剂量探索和活性评估研究，旨在评估 KOSELUGO 口服颗粒剂的安全性。该研究包含了 36 名年龄在 1 岁至小于 7 岁，临床诊断为 1 型神经纤维瘤病（NF1）相关症状性且患有手术无法消除的周围神经病变（PN）的儿童患者。研究评估了 KOSELUGO 口服颗粒剂的药代动力学（PK）、安全性、疗效和耐受性。研究患者将接受 2 粒 KOSELUGO 口服颗粒剂，每日两次，每次 2 粒，剂量相当于 25 mg/m² 体表面积（BSA），共 25 个疗程，直至疾病进展或出现不可耐受的毒性反应。研究对象的中位年龄约为 4 岁（范围：1 至 7 岁）—— 其中，61% 为男性，61% 为白人，14% 为亚裔，3% 为黑人或非裔美国人。

在 SPRINKLE 研究中，使用 KOSELUGO 口服颗粒剂治疗的患有 1 型神经纤维瘤病 (NF1) 丛状神经纤维瘤 (PN) 患儿的中位治疗持续时间为 11 个月（范围：3-25 个月）。在接受 KOSELUGO 口服颗粒剂治疗的患者中，6% 发生了严重不良反应。以下严重不良反应各发生 1 例：包括发热、胃肠炎和上呼吸道感染。共有 31% 的患者因不良反应而中断用药。发生率 ≥ 5% 的不良反应包括发热、呕吐、腹泻、上呼吸道感染、胃肠炎和湿疹。其中，最常见的不良反应（≥ 40%）是发热、皮肤干燥和甲沟炎。

SPRINKLE 研究中观察到的 KOSELUGO 口服颗粒剂的安全性与 KOSELUGO 胶囊剂的已知安全性一致。

Pediatrics > 1 year of Age on KOSELUGO Granules (SPRINKLE)：

The safety of KOSELUGO oral granules was evaluated in SPRINKLE (NCT05309668), a dose-finding and activity estimating, single-arm, multicenter study in 36 pediatric patients ages 1 year to less than 7 years with a clinical diagnosis of NF1-related symptomatic, inoperable PN. The study evaluated the pharmacokinetics (PK), safety,efficacy, and tolerability of KOSELUGO oral granules. Study patients were to receive 2 KOSELUGO oral granules for 25 cycles at a dose equivalent to 25 mg/m BSA twice daily until disease progression or unacceptable toxicity. The

median age was approximately 4 years (range: 1 to 7 years), 61% were male, 61% were White, 14% were Asian and 3% were Black or African American.

In the SPRINKLE study, the median duration of KOSELUGO oral granules treatment in pediatric patients with neurofibromatosis type 1 (NF1) plexiform neurofibromas (PN) was 11 months (range: 3-25 months). Serious adverse reactions occurred in 6% of patients who received KOSELUGO oral granules. Serious adverse reactions occurred in 1 patient each and included pyrexia, gastroenteritis and upper respiratory infection. A total of 31% of patients had an adverse reaction leading to a dosage interruption. Adverse reactions requiring a dosage interruption in ⩾ 5% of patients were pyrexia, vomiting, diarrhea, upper respiratory infection, gastroenteritis and eczema. The most common adverse reactions (⩾ 40%) were pyrexia, dry skin, and paronychia.

The observed safety profile of KOSELUGO oral granules in the SPRINKLE study was consistent with the known safety profile of KOSELUGO capsules.

36 Asparaginase 天冬酰胺酶 (Spectrila®)

- **药品类别 : 抗肿瘤剂**
- **原研药厂家： Medac Gesellschaft fuer klinische Spezialpraeparate mbH（德国）**
- **适应症： Spectrila 适用于作为抗肿瘤联合治疗的组成部分，用于治疗从出生至 18 岁的儿科患者及成人的急性淋巴细胞白血病。**

  Indication: Spectrila is indicated as a component of antineoplastic combination therapy for the treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years and adults.

- **儿童及成人临床试验 :**

  1 至 18 岁新发急性淋巴细胞白血病儿童 / 青少年的研究：

  在一项随机双盲临床试验（研究 MC-ASP.5/ALL；基于 ALL 治疗方案 DCOG ALL10）中，比较了 Spectrila 与原生大肠杆菌天冬酰胺酶（参考药品）的有效性和安全性。该试验纳入 199 名年龄为 1–18 岁的新诊断急性淋巴细胞白血病（ALL）儿童及青少年患者。患者在诱导治疗的第 12、15、18、21、24、27、30 和 33 天接受 5,000 U/m^2 的天冬酰胺酶治疗（Spectrila 与参考大肠杆菌天冬酰胺酶组）。诱导治疗结束后，患者继续接受包含进一步天冬酰胺酶治疗的化疗方案。

  主要终点为诱导治疗期间血清完全天冬酰胺耗竭患者的比率（定义为从第

12 天至第 33 天所有检测时间点的血清天冬酰胺水平均低于定量下限 [< 0.5 μM]）。本研究旨在证明 Spectrila 在主要终点方面相对于参考大肠杆菌天冬酰胺酶的非劣效性。

在新发急性淋巴细胞白血病婴儿中的研究：

在一项非对照临床试验（研究 MC-ASP.6/INF）中，12 例新发急性淋巴细胞白血病（de novo ALL）婴儿（首次输注时的中位年龄 [范围] 为 6 个月 [0.5–12.2 个月]）根据 INTERFANT-06 方案接受 Spectrila 治疗。患者在诱导治疗的第 15、18、22、25、29 和 33 天接受门冬酰胺酶治疗，剂量根据给药时患者的当前年龄调整（<6 个月：6,700 U/m^2；6–12 个月：7,500 U/m^2；>12 个月：10,000 U/m^2）。12 例患者中有 11 例（92%）血清中门冬酰胺完全耗竭。诱导治疗后，12 例患者（100%）均达到完全缓解（CR）。

Study in children/adolescents aged 1–18 years with de novo ALL:

The efficacy of dinutuximab beta has been evaluated in a randomised controlled trial comparing the administration of dinutuximab beta with or without IL-2 in the first-line treatment of patients with high-risk neuroblastoma and in two single-arm studies in the relapsed/refractory setting. Efficacy and safety of Spectrila was compared to a native E. coli-asparaginase (reference medicinal product) in a randomised double-blinded clinical trial (study MC-ASP.5/ALL; based on ALL treatment protocol DCOG ALL10) in 199 children/adolescents aged 1–18 years with de novo ALL. Patients received 5,000 U/m^2 asparaginase (Spectrila versus a reference E.coli- asparaginase) at days 12, 15, 18, 21, 24, 27, 30, and 33 of induction treatment. After induction treatment, patients continued treatment with chemotherapy regimens which included further treatment with asparaginases.

The primary endpoint was the rate of patients with complete asparagine depletion in serum (defined as asparagine serum levels below the lower limit of

quantification (< 0.5 µM) at all time points measured from day 12 up to day 33) during induction treatment. The objective of the study was to demonstrate the non-inferiority of Spectrila to the reference E. coli-asparaginase with regard to the primary endpoint.

Study in infants with de novo ALL:

In an uncontrolled clinical trial (study MC-ASP.6/INF), 12 infants (median age [range] at time of first infusion: 6 months [0.5–12.2 months]) with de novo ALL were treated with Spectrila within the INTERFANT-06 protocol. Patients received asparaginase at a dose of 10,000 U/m^2, adjusted to the current age of the patient at the time of administration (< 6 months: 6,700 U/m^2; 6–12 months: 7,500 U/m^2; > 12 months: 10,000 U/m^2) on days 15, 18, 22, 25, 29, and 33 of induction treatment. Asparagine depletion in serum was complete in 11 of 12 patients (92%). All 12 patients (100%) were in CR after induction treatment.

37 nivolumab 纳武单抗 + hyaluronidase 透明质酸酶 (OPDIVO QVANTIG®)

FDA Label

- **药品类别 : 免疫疗法（PD-1 抑制剂与透明质酸酶组成的固定剂量复方皮下注射制剂）**
- **原研药厂家 : 百时美施贵宝（美国）**
- **适应症 1：不可切除或转移性黑色素瘤及黑色素瘤辅助治疗**

  Indication1 : Unresectable or metastatic melanoma and adjuvant treatment of melanoma.

- **儿童用药说明 :**OPDIVO QVANTIG 作为单药，可用于治疗 12 岁及以上且体重≥ 30 kg 的不可切除或转移性黑色素瘤儿童成人患者。OPDIVO QVANTIG 也可作为单药辅助治疗，用于肿瘤已完全切除的 IIB 期、IIC 期、III 期或 IV 期黑色素瘤的 12 岁以上、体重≥ 30 kg 的儿童及成人患者。

  OPDIVO QVANTIG, as monotherapy, is indicated for adult and pediatric patients 12 years of age and older who weigh 30 kg or greater with unresectable or metastatic melanoma. OPDIVO QVANTIG, as monotherapy, is indicated for the adjuvant treatment of adult and pediatric patients 12 years of age and older who weigh 30 kg or greater with completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma.

  OPDIVO QVANTIG 用于上述黑色素瘤适应症的安全性和有效性已在 12 岁及以上、体重≥ 30 kg 的儿童患者中得到确立。模型预测显示，儿童接受推荐剂量

OPDIVO QVANTIG 后的纳武单抗暴露量处于成人观察或预测的暴露范围内。OPDIVO QVANTIG 用于 12 岁以下或体重不足 30 kg 的黑色素瘤儿童患者的安全性和有效性尚未确立。

The safety and effectiveness of OPDIVO QVANTIG for the above melanoma indications have been established in pediatric patients 12 years of age and older who weigh 30 kg or greater. Nivolumab exposure following the recommended pediatric dosage of OPDIVO QVANTIG is predicted to be within the range observed or predicted in adults. The safety and effectiveness of OPDIVO QVANTIG have not been established in patients younger than 12 years of age or weighing less than 30 kg with melanoma.

OPDIVO QVANTIG 不适用于与伊匹木单抗联合治疗不可切除或转移性黑色素瘤。需要联合纳武利尤单抗和伊匹木单抗时，应使用静脉用制剂；完成联合治疗后可按照标签转换为 OPDIVO QVANTIG 单药治疗。

OPDIVO QVANTIG is not indicated in combination with ipilimumab for unresectable or metastatic melanoma. Intravenous nivolumab should be used during combination treatment with ipilimumab; patients may subsequently receive OPDIVO QVANTIG as monotherapy in accordance with the label.

- **适应症 2：微卫星高度不稳定或错配修复缺陷转移性结直肠癌**

Indication2 : Microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer.

- **儿童用药说明 :**OPDIVO QVANTIG 作为单药，可用于在使用静脉用纳武单抗和伊匹木单抗联合治疗后的 12 岁及以上、体重至少 30 kg 的不可切除或转移性 MSI-H/dMMR 结直肠癌患者。OPDIVO QVANTIG 作为单药，也用于治疗 12 岁及以上、体重至少 30 kg 且在氟嘧啶、奥沙利铂和伊立替康治疗后有疾病进

展的 MSI-H/dMMR 转移性结直肠癌患者。

OPDIVO QVANTIG, as monotherapy, is indicated for adult and pediatric patients 12 years of age and older who weigh 30 kg or greater with unresectable or metastatic MSI-H or dMMR colorectal cancer following treatment with intravenous nivolumab and ipilimumab combination therapy. OPDIVO QVANTIG, as monotherapy, is indicated for adult and pediatric patients 12 years of age and older who weigh 30 kg or greater with MSI-H or dMMR metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

OPDIVO QVANTIG 用于上述 MSI-H/dMMR 转移性结直肠癌适应症的安全性和有效性已在 12 岁及以上、体重至少 30 kg 的儿童患者中得到确立。该儿童适应症由静脉用纳武单抗成人临床研究，以及儿童药代动力学和安全性资料支持。OPDIVO QVANTIG 尚未在专门的儿童随机疗效试验中进行评价。OPDIVO QVANTIG 用于 12 岁以下或体重不足 30 kg 的 MSI-H/dMMR 转移性结直肠癌儿童患者的安全性和有效性尚未确立。

The safety and effectiveness of OPDIVO QVANTIG for the above MSI-H/dMMR metastatic colorectal cancer indications have been established in pediatric patients 12 years of age and older who weigh 30 kg or greater. Pediatric use is supported by adult clinical studies of intravenous nivolumab and additional pediatric pharmacokinetic and safety data. OPDIVO QVANTIG has not been evaluated in a dedicated randomized pediatric efficacy trial. The safety and effectiveness of OPDIVO QVANTIG have not been established in patients younger than 12 years of age or weighing less than 30 kg with MSI-H or dMMR metastatic colorectal cancer.

- **成人试验 1 CHECKMATE-8HW (NCT03143153):** 是一项随机、三组、开放标签试验，纳入既往未接受免疫治疗、经当地标准方法确认患有不可切除或转移性 MSI-H/dMMR 结直肠癌的患者。患者接受静脉用纳武单抗联合伊匹

木单抗、纳武单抗单药或研究者选择的化疗。在一线治疗人群中，与化疗相比，纳武单抗联合伊匹木单抗显著提高了无进展生存期。在所有治疗线数人群中，，纳武单抗联合伊匹木单抗的中位无进展生存期未达到仅用纳武单抗单药的 39.3 个月，风险比为 0.62（95% CI：0.48–0.81）；客观缓解率分别为 71% 和 58%。

CHECKMATE-8HW was a randomized, three-arm, open-label trial in immunotherapy-naive patients with unresectable or metastatic MSI-H/dMMR colorectal cancer. Patients received intravenous nivolumab plus ipilimumab, intravenous nivolumab monotherapy, or investigator’s choice of chemotherapy. In the first-line population, intravenous nivolumab plus ipilimumab significantly improved BICR-assessed PFS compared with chemotherapy. Across all treatment lines, median PFS was not reached with nivolumab plus ipilimumab and was 39.3 months with nivolumab monotherapy; the hazard ratio was 0.62 (95% CI: 0.48–0.81). Objective response rates were 71% and 58%, respectively.

- **成人试验 2 CHECKMATE-142 (NCT02060188):** CHECKMATE-142 是一项多中心、非随机、多平行队列、开放标签试验，纳入纳入既往治疗期间或治疗后有疾病进展的有局部检测 MSI-H/dMMR 转移性结直肠癌，结直肠癌患者。试验中 74 名患者接受静脉用纳武单抗单药，119 名患者接受静脉用纳武单抗联合伊匹木单抗。审评确认的客观缓解率分别为 38% 和 60%；完全缓解率分别为 11% 和 14%。在既往接受氟嘧啶、奥沙利铂及伊立替康治疗的患者中，客观缓解率分别为 32% 和 56%。

  CHECKMATE-142 was a multicenter, non-randomized, multiple parallel-cohort, open-label trial in patients with locally determined MSI-H or dMMR metastatic colorectal cancer whose disease progressed during or after prior therapy. Seventy-four patients received intravenous nivolumab monotherapy and 119 received intravenous nivolumab plus ipilimumab. BICR-assessed objective response rates were 38% and 60%, respectively, and complete response rates were 11% and

14%. Among patients previously treated with a fluoropyrimidine, oxaliplatin, and irinotecan, objective response rates were 32% and 56%, respectively.

38 Inotuzumab ozogamicin 奥加伊妥珠单抗 (Besponsa®)

Label(fda.gov)
Label(EMA)

- **药品类别 : 靶向疗法（抗体偶联细胞毒药物）**
- **原研药厂家 : 辉瑞制药 (美国)**
- **适应症 : 用于治疗成人及 1 岁及以上儿童复发或难治性 CD22 阳性 B 细胞前体急性淋巴细胞白血病（ALL）。**

  Indication1: BESPONSA is indicated for the treatment of relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukemia (ALL) in adult and pediatric patients 1 year and older.

- **儿童用药说明 :**BESPONSA 用于 1 岁及以上复发或难治性 CD22 阳性 B 细胞前体 ALL 儿童患者的安全性和有效性已经确立，其儿童适应症主要由 WI203581（ITCC-059）研究的疗效和安全性数据支持。尚未确立该药在 1 岁以下患者中的安全性和有效性。与成人相比，接受 BESPONSA 治疗的儿童患者肝功能检查异常发生率较高：儿童患者 3 ～ 4 级 AST 升高、ALT 升高及总胆红素升高的发生率分别为 21%、21% 和 9%，成人患者分别为 4%、4% 和 5%。

  SPediatric use: The safety and effectiveness of BESPONSA in pediatric patients 1 year and older with relapsed or refractory CD22-positive B-cell precursor ALL have been established. Use in this population is supported by evidence of safety and effectiveness from Study WI203581 (ITCC-059). The safety and effectiveness of

BESPONSA in patients younger than 1 year have not been established. Compared with adults, pediatric patients had a higher incidence of liver test abnormalities, with Grade 3–4 increases in AST, ALT, and total bilirubin occurring in 21%, 21%, and 9% of pediatric patients, respectively, compared with 4%, 4%, and 5% of adults.

- **儿童临床试验 WI203581（ITCC-059；EudraCT 2016-000227-71）:**BESPONSA 的儿童疗效在 WI203581（ITCC-059）研究中进行评价。该研究是一项国际多中心、单臂、开放标签的 I / II 期临床试验，在 53 例年龄≥ 1 岁且 <18 岁的复发或难治性 CD22 阳性 B 细胞前体 ALL 儿童患者中评价 BESPONSA 单药治疗。 I 期部分用于确定推荐 II 期剂量， II 期部分进一步评价所选剂量的疗效、安全性和耐受性。在 53 例患者中，12 例患者接受 1.4 mg/m^2/ 周期的初始剂量，41 例患者接受 1.8 mg/m^2/ 周期的初始剂量。1.8 mg/m^2/ 周期的剂量分 3 次静脉输注，分别于第 1 天给予 0.8 mg/m^2，第 8 天和第 15 天各给予 0.5 mg/m^2。患者接受治疗的中位周期数为 2 个周期，范围为 1 ～ 4 个周期。患者中位年龄为 9 岁，范围为 1 ～ 17 岁；55% 的患者处于第二次或以上复发。FDA 以完全缓解率（CR）、CR 持续时间以及达到微小残留病（MRD）阴性的 CR 患者比例作为主要疗效依据。CR 定义为骨髓原始细胞 <5%、外周血中无白血病原始细胞、外周血细胞计数完全恢复——血小板≥ 100×10^9/L 且中性粒细胞绝对计数≥ 1×10^9/L——并且所有髓外病灶消失。在全部 53 例患者中，22 例达到 CR，CR 率为 42%（95% CI：28.1%，55.9%）；中位 CR 持续时间为 8.2 个月（95% CI：2.6 个月，无法估计）。在 22 例达到 CR 的患者中，按流式细胞术评估，21 例达到 MRD 阴性，MRD 阴性率为 95.5%（95% CI：77.2%，99.9%）；按实时定量 PCR 评估，19 例达到 MRD 阴性，MRD 阴性率为 86.4%（95% CI：65.1%，97.1%）。安全性方面，62% 的患者发生严重不良反应；主要严重不良反应包括感染、发热性中性粒细胞减少、肝静脉闭塞性疾病（VOD）、发热和出血。VOD 发生率为 15%，致死性不良反应发生率为 8%。

The efficacy of BESPONSA in pediatric patients was evaluated in Study WI203581 (ITCC-059), an international, multicenter, single-arm, open-label Phase I/II trial of BESPONSA monotherapy in 53 pediatric patients ≥ 1 and <18 years of age with relapsed or refractory CD22-positive B-cell precursor ALL. The Phase I portion was designed to identify the recommended Phase II dose, and the Phase II portion further evaluated the efficacy, safety, and tolerability of the selected dose. Among the 53 patients, 12 received an initial dose of 1.4 mg/m^2 per cycle and 41 received an initial dose of 1.8 mg/m^2 per cycle. The 1.8 mg/m^2 dose was administered intravenously in three divided doses: 0.8 mg/m^2 on Day 1 and 0.5 mg/m^2 on Days 8 and 15. Patients received a median of 2 treatment cycles, with a range of 1 to 4 cycles. The median age was 9 years, with a range of 1 to 17 years, and 55% of patients had experienced a second or subsequent relapse. Efficacy was established on the basis of the complete remission (CR) rate, duration of CR, and the proportion of patients with MRD-negative CR. CR was defined as less than 5% blasts in the bone marrow, absence of leukemic blasts in peripheral blood, full recovery of peripheral blood counts—platelets ≥ $100 \times 10^9/L$ and absolute neutrophil count ≥ $1 \times 10^9/L$—and resolution of any extramedullary disease. Among all 53 patients, 22 achieved CR, corresponding to a CR rate of 42% (95% CI: 28.1%, 55.9%). The median duration of CR was 8.2 months (95% CI: 2.6 months, not estimable). Among the 22 patients who achieved CR, 21 were MRD-negative by flow cytometry, corresponding to an MRD-negativity rate of 95.5% (95% CI: 77.2%, 99.9%). Nineteen patients were MRD-negative by real-time quantitative PCR, corresponding to an MRD-negativity rate of 86.4% (95% CI: 65.1%, 97.1%). Serious adverse reactions occurred in 62% of patients. The principal serious adverse reactions included infection, febrile neutropenia, hepatic veno-occlusive disease (VOD), pyrexia, and hemorrhage. VOD occurred in 15% of patients, and fatal adverse reactions occurred in 8%.

拾玉儿童公益
SHIYU CHILDREN FOUNDATION

深圳市拾玉儿童公益基金会成立于 2018 年 7 月，登记注册单位为深圳市民政局。基金会秉承专业、科学、平等、坚持的价值观，旨在弘扬慈善和科学精神，促进中国儿童健康事业发展。2022 年 4 月获评“深圳市 4A 级社会组织”。基金会希望通过科普教育、舒缓安宁、转化科研三大模块，聚焦服务重症患儿家庭，提升患儿预后和生活质量，让孩子的每一天都是最好的一天！

向日葵儿童

「向日葵儿童」是拾玉儿童公益基金会旗下的公益项目，聚焦科普教育，从线上到线下，从文字到视频，致力于开创新型公益服务模式，帮助家长和基层医生了解疾病，避免误诊，少走弯路，提高中国患儿的生存预后和生活质量。同时，也唤起社会大众对肿瘤患儿群体的正确认识和支持，帮助康复患儿顺利回归学校和社会（www.curekids.cn）。

向日葵儿童公众号一直以来都致力于通过图文和视频等形式传播温暖、靠谱的儿童肿瘤科普知识，是目前国内最主要的儿童肿瘤垂直自媒体平台之一。

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