儿童肿瘤
创新药物手册

美国已经上市，但中国大陆尚未注册上市或尚未获批儿童适应症的药品总结

2024 年 3 月

提示

此版本报告仅参考美国食品药品管理局（US FDA）官方发布的药物文件（Prescription Information），并将其与国家药品监督管理局批准上市的儿童肿瘤药进行对比，总结目前国外已经上市，但中国大陆尚未注册上市或尚未获批儿童适应症的药品信息。此版本报告暂未囊括其他国家儿童肿瘤药物注册情况，后续更新的报告将覆盖更多国家地区的儿童肿瘤药物注册情况。报告所有内容均来自国际网站，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。如果您有任何意见或问题，欢迎发送邮件至 hnetzl@163.com，后续将有专人与您联系。

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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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信息整理方

加强海南省儿童肿瘤诊疗体系建设项目办公室：由海南省妇女儿童医学中心和克林顿健康发展组织（CHAI）的人员共同合作组成。

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审阅专家

邹俊

海南省妇女儿童医学中心临床药学科主任、临床试验机构办公室主任，副主任药师

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药学药物临床试验、妊娠和哺乳期药物评价、药事管理。

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，有三篇第一作者 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各一项。

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

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	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 (ALL)	ELIANA, NCT02435849	https://www.fda.gov/
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 淋巴母细胞白血病 /T 淋巴母细胞淋巴瘤	PGA2001, COG P9673	arranon (novartis.com)
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	PGA2001, COG P9673	https://www.accessdata.fda.gov/drugsatfda_docs/
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患者	0903A1-102-US phase I/II study	LABEL (fda.gov)
5	Asparaginase Erwinia Chrysanthemi 菊欧文氏菌天冬酰胺酶 (Erwinaze®) 详情页	爵士制药（爱尔兰）	血液肿瘤	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	Study AALL07P4, Study DFCI 11-001	ERWINAZE
6	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母细胞白血病 (ALL) 和淋巴母细胞淋巴瘤 (LBL) 儿童患者	A pediatric clinical trail patients treated on enrolled National Cancer Institute (NCI)-sponsored cooperative group ALL protocols	label (fda.gov)
7	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 (cHL)	AHOD1331 (NCT02166463)	label (fda.gov)

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8	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	label (fda.gov)
			血液肿瘤	原发性纵隔大 B 细胞淋巴瘤		
			实体肿瘤	梅克尔细胞癌		
			实体肿瘤	卫星不稳定性高或错配修复缺陷癌		
			实体肿瘤	肿瘤突变负高		
9	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 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	Inter-B-NHL Ritux 2010, NCT01516580	label (fda.gov)
10	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 Ph+ 急性淋巴细胞白血病	CA180372 (NCT01460160)	SPRYCEL U.S. Prescribing Information (bms.com)
			血液肿瘤	1 岁及以上费城染色体阳性 Ph+ 慢性骨髓性白血病	(NCT00306202，NCT00777036)	
11	Bosutinib 博苏替尼 (Bosulif®) 详情页	辉瑞制药（美国）	血液肿瘤	1 岁及以上新诊断的慢性期费城染色体阳性慢性髓性白血病 (CML) 及耐药或不耐受的慢性期费城染色体阳性慢性髓性白血病（CML）	The BCHILD trial (NCT04258943)	Label (fda.gov)
12	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	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	信息来源
13	Crizotinib 克里唑替尼 (Xalkori®) 详情页	辉瑞制药（美国）	实体肿瘤	1 岁及以上儿童炎性肌纤维母细胞瘤	ADVL0912 (NCT00939770)	XALKORI (fda.gov)
			血液肿瘤	1 岁及以上的儿童患复发或难治性系统性间变性大细胞淋巴瘤 (ALCL)， alk 阳性	ANHL12P1 (NCT01979536)	
14	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	/	https://www.ncbi.nlm.nih.gov/pmc/articles/
			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)	Full Prescribing Information | AZEDRA®
15	Dinutuximab 地努图希单抗 (Unituxin ™) 详情页	United Therap -eutics（美国）	实体肿瘤	高危神经母细胞瘤	ANBL0032	LABEL (fda.gov)
16	Avelumab 阿维鲁单 (Bavencio®) 详情页	默克药厂（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	label (fda.gov)
17	Tagroxofusp-erzs (Elzonris ™) 详情页	Stemline Therap -eutics（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)	LABEL (fda.gov)
18	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	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	信息来源
19	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	Yervoy FDA Drug Label
20	Nivolumab 纳武单抗 (Opdivo®) 详情页	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	OPDIVO U.S. Prescribing Information (bms.com)
			实体肿瘤	12 岁及以上可切除或转移性黑色素瘤		
21	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	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		
22	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)	label (fda.gov)
23	Everolimus 依维莫司 (Afinitor®) 详情页	诺华制药（瑞士）	实体肿瘤	1 岁及以上儿童结节性硬化症 - 相关室管膜下巨细胞星形细胞瘤	EXIST-1 (NCT00789828)；Study 2485 (NCT00411619)	DailyMed - AFINITOR- everolimus tablet AFINITOR DISPERZ (nih.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	label (fda.gov)
			实体肿瘤	1 岁及以上儿童 BRAF V600E 突变阳性的低级别胶质瘤（LGG）	CDRB436G2201 (G2201) Study – Low-Grade Glioma Cohort	
25	Eflornithine 依氟鸟氨酸 (IWILFIN ™) 详情页	US WorldMeds	实体肿瘤	儿童高危神经母细胞瘤（HRNB）	Study 3b (NCT02395666) ,ANBL0032	label(fda.gov)

本文件仅参考美国 FDA 药物文件（prescription information），未囊括其他国家儿童肿瘤药物注册情况

1 Tisagenlecleucel (KYMRIAH®)

https://www.fda.gov/media/107296/download

- **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，进行淋巴减少（lymphodepleting）化疗（fludarabine 每日 30 mg/m^2 ，为期 4 天，和 cyclophosphamide 每日 500mg/m^2 ，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），CR 持续时间，以及通过流式细胞术检测达到 CR 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 CR/CRi，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，CR/CRi 的中位持续时间尚未达到（范围：1.2 至 14.1+ 个月）。CR/CRi 的中位发生时间为 29 天，50 名 /52 名（96%）反应者的 CR/CRi 发生在 26 至 31 天之间。在实现 CR/CRi 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/m^2 daily for 4 days and cyclophosphamide 500 mg/m^2 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)

- **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)：**ARRANON® 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/m^2 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/m^2/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.

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)

- **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 AML 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 CL1 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 9 mg/m^2，与在第 1、4 和 7 天分数剂量为 3 mg/m^2 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/m^2 on days 1 and 15 versus, 3 mg/m^2 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/m^2 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 NSAA > 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/m^2 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 Asparaginase Erwinia Chrysanthemi 菊欧文氏菌天冬酰胺酶 (Erwinaze®)

ERWINAZE (asparaginase Erwinia chrysanthemi) Label (fda.gov)

- **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：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患者**

  Indication: patients with acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to E. coli-derived asparaginase

- **儿童临床试验 1：**研究 1 是一项单臂、多中心、开放标签、安全性和临床药理学试验。研究纳入了在美国国家癌症研究所（NCI）赞助的合作组 ALL 方案中接受治疗但由于过敏反应无法继续接受聚丙酰天冬酶（pegaspargase）的患者。主要的研究结果指标是确定实现血清谷物天冬酶水平≥ 0.1 国际单位 / ml 的患者比例。研究已经证明，血清谷物天冬酶活性≥ 0.1 国际单位 /ml 与天冬酶耗尽（天冬酶 <0.4mcg/ml 或 3μM）以及预测临床疗效的血清水平相关。患者在原始治疗方案上剩余的每次预定聚丙酰天冬酶剂量中，用 ERWINAZE 25,000 国际单位 /m^2 肌肉注射两周（总共 6 剂）替代。研究 1 纳入了 58 名患者，其中 48 名根据第 1 疗程中药代动力学样本的可用性评估了主要研究结果指标。中位年龄为 11 岁（2 至 18 岁）；研究 1 达到了其主要研究结果指标，即超过 50% 的患者在第三剂后 48 或 72 小时内达到了预定的谷物天冬酶活性水平≥ 0.1

国际单位 /ml。

A single-arm, multi-center, open-label, safety and clinical pharmacology trial. Study 1 enrolled patients treated on National Cancer Institute (NCI)-sponsored cooperative group ALL protocols who were unable to continue to receive pegaspargase due to hypersensitivity reactions. The main outcome measure was determination of the proportion of patients who achieved a serum trough asparaginase level greater than or equal to 0.1 International Units/mL. Serum trough asparaginase activity ≥ 0.1 International Units/mL has been demonstrated to correlate with asparagine depletion (asparagine <0.4 mcg/mL or 3 μM) and to serum levels that predict clinical efficacy. Patients received ERWINAZE 25,000 International Units/m^2 intramuscularly for two weeks (total 6 doses) as a replacement for each scheduled dose of pegaspargase remaining on their original treatment protocol. Fifty-eight patients were enrolled in Study 1, of these 48 were evaluable for the main outcome measure based on availability of pharmacokinetic samples in Course 1. The median age was 11 years (2 to 18 years); Study 1 met its main outcome measure of demonstrating that greater than 50% of the patients achieved the prespecified trough asparaginase activity level of ≥ 0.1 International Units/mL at 48 or 72 hours following the third dose.

- **儿童临床试验 1：**一项开放标签、单臂、多中心的药代动力学研究纳入了 30 名患者。主要的研究结果指标是在 ERWINAZE® 治疗的前两周内，确定在第五次剂量后（48 小时剂量）血清谷底天冬酶酶活性（NSAA）水平≥ 0.1 国际单位 /ml 的患者比例。其中 30 名患者中，有 24 名根据第 1 疗程的药代动力学样本对主要研究结果指标进行了评估。在研究 2 中，对 24 名可评估的患者（年龄≥ 1 岁至≤ 17 岁）进行了 ERWINAZE® 25,000 国际单位 /m^2 静脉给药后，测定了曲霉腔青霉素天冬酶的血清天冬酶活性。在第 1 疗程中 60 分钟注射后 5 分钟，第 1 剂后的平均天冬酶活性水平为 12.65 ± 3.16 国际单位 /ml，第 4 剂后为 12.11 ± 3.11 国际单位 /ml。主要的研究目标在第五次剂量后 48 小时

内观察到 83% 的患者的天冬酶活性水平≥ 0.1 国际单位 /ml 时达成。第 6 次剂量后 72 小时的天冬酶活性水平≥ 0.1 国际单位 /ml 是次要终点，43% 的患者达到了这个终点。

An open-label, single-arm, multicenter PK study enrolled 30 patients. The main outcome measure was determination of the proportion of patients with 2-day NSAA levels (48-hour levels taken after the fifth dose) ⩾ 0.1 International Units/mL in the first 2 weeks of ERWINAZE treatment. Of the thirty patients enrolled, 24 were evaluable for the main outcome measure based on the pharmacokinetic samples in Course 1. In Study 2, serum asparaginase activity of asparaginase Erwinia chrysanthemi was determined in 24 evaluable patients (aged ⩾ 1 year to ⩽ 17 years) following intravenous administration of ERWINAZE 25,000 International Units/m^2. Five minutes after the 60-minute infusion in Course 1, the mean asparaginase activity level was 12.65 ± 3.16 International Units/mL post-dose 1 and 12.11 ± 3.11 International Units/mL post dose 4. The main study objective was met with an asparaginase activity level of ⩾ 0.1 International Units/mL 48 hours after the fifth dose observed in 83% of patients. The 72-hour post dose 6 asparaginase activity level of ⩾ 0.1 International Units/mL was the secondary endpoint, with 43% of patients achieving this endpoint.

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

label (fda.gov)

- **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%）报告了无声失活。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/m^2 的剂量，RYLAZE ™用药后 48 小时维持 NSAA ⩾ 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/m^2 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%) .

7 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 cHL 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.

8 Pembrolizumab 帕博利珠单抗 (KEYTRUDA®)

label (fda.gov)

- **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 线或更多治疗后复发的慢性霍奇金淋巴瘤**

  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 cHL 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 PMBCL 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 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.

- **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 PMBCL 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修复疗法的 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 MCC 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 MCC 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：卫星不稳定性高或错配修复缺陷癌**

  Indication 4: microsatellite instability-high (MSI-H)

- **儿童用药说明：**KEYTRUDA 作为单药治疗 MSI-H 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 TMB-H 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 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 / 兆酶。

  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.

9 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/m^2 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/m^2 BSA (two doses during each of the two induction courses and one during each of the two consolidation courses) as per the LMB scheme.

10 Dasatinib 达沙替尼 (Sprycel®)

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

- **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% 置信区间 [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 CML 患者中，51 例患者 (仅来自单臂试验) 新诊断为慢性期 CML, 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 /m^2 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/m^2 once daily (maximum dose of 100 mg once daily for patients with high BSA). Patients were treated until disease progression or unacceptable toxicity.

11 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.

12 12. 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.

13 Crizotinib 克里唑替尼 (XALKORI®)

XALKORI (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 1：1 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/m^2 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/m^2 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/m^2(20 例) 或 165 mg/m^2(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/m^2 (20 patients) or 165 mg/m^2 (6 patients) orally twice daily until disease progression or unacceptable toxicity. Patients were permitted to discontinue XALKORI to undergo hematopoietic stem cell transplantation (HSCT).

14 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）。疗效结果总结在表 7 中。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). The efficacy results are summarized in Table 7. All confirmed responses per RECIST were partial responses.

15 Dinutuximab 地努图希单抗 (UNITUXIN ™)

LABEL (fda.gov)

- **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)

(Table 8) or interleukin-2 (IL-2) (Table 9) 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

16 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 MCC 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 MCC 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 MCC 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.

17 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 BPDCN 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 BPDCN 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 BPDCN 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).

18 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.

19 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.

20 nivolumab 纳武单抗 (OPDIVO®)

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

- **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 dacarbazine1000 mg/

m^2，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/m^2 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 (mCRC) 在氟嘧啶、奥沙利铂和伊立替康治疗后病情进展。在患有 MSI-H 或 dMMR mCRC 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 MSI-H 或 dMMR mCRC 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 dMMR 或 MSI-H 转移性 CRC (mCRC) 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® MSI-H mCRC 队列的患者每 2 周接受 OPDIVO® 3mg /kg 静脉输注 (IV)。纳入 OPDIVO® 和 ipilimumab MSI-H mCRC 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.

21 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 dMMR 或 MSI-H 转移性 CRC (mCRC) 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® MSI-H mCRC 队列的患者每 2 周接受 OPDIVO® 3mg /kg 静脉输注 (IV)。纳入 OPDIVO® 和 ipilimumab MSI-H mCRC 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.

22 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 ASPS 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 ASPS 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 ASPS 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 ASPS 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.

23 Everolimus 依维莫司 (AFINITOR®)

Novartis_AfinitoR®

- **药品类别：蛋白激酶抑制剂**
- **原研药厂家：诺华制药（瑞士）**
- **适应症：的 1 岁及以上患有结节性硬化症复合体（TSC）的儿科患者的需要治疗干预但无法根治性切除的室管膜下巨细胞星形细胞瘤 （SEGA）**

  Indication: pediatric patients aged 1 year and older with tuberous sclerosis complex (TSC) for the treatment of Subependymal Giant Cell Astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected.

- **儿童临床试验 1 EXIST-1 (NCT00789828)：** 一项随机 (2:1)、双盲、安慰剂对照试验 (exist1, NCT00789828) 在 117 例儿童和成人 SEGA 和 TSC 患者中进行了 AFINITOR®。在纳入的 117 名患者中，78 名随机分配到 AFINITOR 组，39 名随机分配到安慰剂组。经 AFINITOR® 治疗的患者 SEGA 反应率有统计学意义上的显著提高。在 AFINITOR® 组中有 27 例 (35%) 患者出现 SEGA 反应，而在安慰剂组中没有 SEGA 反应。

  A randomized (2:1), double-blind, placebo-controlled trial of AFINITOR® was conducted in 117 pediatric and adult patients with SEGA and TSC. Of the 117 patients enrolled, 78 were randomized to AFINITOR® and 39 to placebo. The SEGA response rate was statistically significantly higher in AFINITOR®-treated patients.

There were 27 (35%) patients with SEGA responses in the AFINITOR® arm and no SEGA responses in the placebo arm.

- **儿童临床试验 2 Study 2485 (NCT00411619)：**一项开放标签单臂试验，旨在评估 AFINITOR® 在 SEGA 和 TSC 患者中的安全性和有效性。总共有 28 名患者接受了 AFINITOR® 治疗。6 个月时，28 例患者中有 9 例 (32%，95% CI: 16% 至 52%) 最大 SEGA 病变的肿瘤体积减小≥ 50%。这 9 例患者的中位缓解持续时间为 11.8 个月 (范围为 3.2 至 39.1 个月)。在数据截止时，9 例患者中有 7 例的容量持续减少≥ 50%。在初步分析中，28 例患者中有 32% (95% CI: 16%， 52%) 在 6 个月时客观缓解，定义为最大的 SEGA 病变体积至少减少 50%。在研究结束时，持续缓解的中位持续时间为 12 个月 (3 个月至 6.3 年)。在最后一名患者入组 60 个月后，28 名患者中有 11% 的人出现了疾病进展。在使用阿替尼托期间，没有患者出现新的 SEGA 病变。另外 9 名患者在开始使用 AFINITOR® 后的 1 至 4 年内，其最大的 SEGA 病变体积缩小≥ 50%，其中 3 名患者在接受 AFINITOR® 之前进行了手术切除并随后再生。

  An open-label, single-arm trial was conducted to evaluate the safety and efficacy of AFINITOR® in patients with SEGA and TSC. In total, 28 patients received treatment with AFINITOR. At 6 months, 9 out of 28 patients (32%, 95% CI: 16% to 52%) had a ≥ 50% reduction in the tumor volume of their largest SEGA lesion. The median duration of response for these 9 patients was 11.8 months (range 3.2 to 39.1 months). Seven of these 9 patients had an ongoing volumetric reduction of ≥ 50% at the data cutoff. At the primary analysis, 32% of the 28 patients (95% CI: 16%, 52%) had an objective response at 6 months, defined as at least a 50% decrease in volume of the largest SEGA lesion. At the completion of the study, the median duration of durable response was 12 months (3 months to 6.3 years). By 60 months after the last patient was enrolled, 11% of the 28 patients had documented disease progression. No patient developed a new SEGA lesion while on AFINITOR®. Nine additional patients were identified as having a ≥ 50% volumetric reduction in their largest SEGA lesion between 1 to 4 years

after initiating AFINITOR®, including 3 patients who had surgical resection with subsequent regrowth prior to receiving.

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

label (fda.gov)

- **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 1：6 岁及以上儿童 BRAF_V600E 突变的不可切除或转移性实体瘤**

  Indication 1: pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation

- **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 BRAFV600E 突变患者中进行剂量递增。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 9 patients who responded, DoR was ⩾ 6 months

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 HGG 患儿化疗 naïve 中的应用。ORR 为 56% (95% CI: 40,72)。中位 DoR 未达到 (95% CI: 9.2, NE)。在 HGG 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) 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 singlearm 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 岁及以上儿童 BRAF V600E 突变阳性的低级别胶质瘤 (LGG)**

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

- **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.

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**
- **适应症：适用于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 (HRNB) 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% 置信区间。

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.

加强海南省儿童肿瘤诊疗体系建设项目

海南省妇女儿童医学中心在海南省卫健委的大力支持下，正在开展加强海南省儿童肿瘤（实体肿瘤及血液瘤）诊疗体系建设项目。项目旨在提高海南省儿童肿瘤的早期发现率、纳入治疗率与规范化的诊疗水平，从而最终提升儿童肿瘤患者的生存率。项目重点工作之一是通过博鳌乐城政策推动进口新型儿童肿瘤药物在海南的有效应用，以更广泛地惠及全国患儿。

项目由海南省卫健委指导，海南省妇女儿童医学中心与克林顿健康发展组织（CHAI）等多方合作。

向日葵儿童

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