2016 年 5 月药物快讯

癌症 CANCER

2016 年 5 月 30 日，FDA 批准 AXUMIN 用于检测前列腺癌的复发

FDA 已经批准 Axumin（[18 F] fluciclovine）用于疑为前列腺癌复发男性患者的 PET 成像。Axumin 是 Blue Earth Diagnostics 公司推出上市的一种注射用放射性诊断剂，可在治疗前根据前列腺特异性抗原（PSA）水平诊断前列腺癌是否复发。目前已进行两项研究来评估 Axumin 在疾病复发患者上进行前列腺癌成像的安全性和有效性。第一项研究比较了 105 个男性疑似前列腺癌复发病例的 Axumin 扫描结果和前列腺穿刺活检和可疑成像病灶活检的组织病理学结果。扫描结果最初由放射科医师现场解读，接着由三个放射科医师在盲态研究中进行独立解读。第二项研究评估了 Axumin 和胆碱 C11（已批准用于 PET 扫描成像试验）患者 96 次扫描结果的一致性，平均 PSA 数值为 1.44ng/mL。放射科医师现场解读，接着由与第一项研究相同的三个放射科医师在第二次盲态研究中进行独立解读。独立解读结果基本一致，同时还确认了现场解读结果。这两项研究结果支持 Axumin 用于 PSA 值升高男性患者在治疗前进行前列腺癌成像的安全性和有效性。患者最常见的不良反应为注射部位疼痛、发红和口中有金属味（FDA 新闻稿）。

MAY 30, 2016
FDA APPROVES AXUMIN TO DETECT RECURRENT PROSTATE CANCER

The FDA has approved Axumin ([18F]fluciclovine), a radioactive diagnostic agent for injection marketed by Blue Earth Diagnostics, for PET imaging in men with suspected prostate cancer recurrence based on elevated prostate-specific antigen (PSA) levels following prior treatment. Two studies evaluated the safety and efficacy of Axumin for imaging prostate cancer in patients with recurrent disease. The first compared 105 Axumin scans in men with suspected recurrence of prostate cancer to the histopathology obtained by prostate biopsy and by biopsies of suspicious imaged lesions. The scans were initially read by radiologists on-site, and were subsequently read by three independent radiologists in a blinded study. The second study evaluated the agreement between 96 scans with Axumin and C11 choline, an approved PET scan imaging test, in patients with median PSA values of 1.44 ng/mL. Radiologists on-site read the scans, and the same three independent radiologists who read the scans in the first study read the Axumin scans in this second blinded study. The results of the independent scan readings were generally consistent with one another, and confirmed the results of the on-site scan readings. Both studies supported the safety and efficacy of Axumin for imaging prostate cancer in men with elevated PSA levels following prior treatment. The most commonly reported adverse reactions in patients were injection site pain, redness and a metallic taste in the mouth (FDA News Release).

2016 年 5 月 24 日，日本批准阿瓦斯汀治疗宫颈癌

日本已批准 Chugai 制药的阿瓦斯汀（R）（贝伐单抗）治疗晚期或复发性宫颈癌，去年九月获得孤儿药和优先审查权。批准是基于国外的 III 期临床研究结果（GOG-0240；ClinicalTrials.gov 标识符 NCT00803062）和日本的 II 期临床研究（JO29569 研究）。GOG-0240 研究评估了贝伐珠单抗标准或不标准化疗（紫杉醇、顺铂或紫杉醇以及拓扑替康）治疗 452 例持续复发或转移性宫颈癌患者的有效性和安全性。该研究达到了

主要终点，与仅接受化疗的患者相比，总体生存率提高，死亡风险统计学显著降低 26%，平均存活增加 3.9 个月（16.8 个月比 12.9 个月）。与仅接受化疗的患者相比，接受贝伐单抗与化疗联合治疗患者的无进展生存期的显著改善（8.3 个月对 6.0 个月）。研究表明，接受贝伐单抗与化疗联合治疗患者与仅接受化疗的患者相比，肿瘤缩小率（客观缓解率）显著增加（45.4%对 33.8%）。研究的安全性与早期报道的贝伐单抗治疗结果一致，仅接受贝伐单抗联合化疗治疗的患者与仅接受化疗的患者相比，前者胃肠阴道瘘的发生率增加（8.3%对 0.9%）。所有胃肠阴道瘘患者具有盆腔放疗病史。JO29569 研究评估了贝伐单抗联合紫杉醇+顺铂治疗的耐受性、安全性和有效性。在 8 名参加试验的晚期或复发宫颈癌日本患者中，7 名患者进行了评估，1 名患者在研究开始前排除。贝伐单抗联合化疗的耐受性已进行确认，有害现象不会成为问题并且没有观察到新安全问题。阿瓦斯汀已在日本上市销售，用于治疗不能手术切除的晚期或复发性结直肠癌、不能手术切除的晚期或复发性非鳞状非小细胞肺癌（NSCLC）、不能手术或复发性乳腺癌、恶性胶质瘤和卵巢癌（Chugai 制药新闻稿）。

MAY 24, 2016
AVASTIN APPROVED IN JAPAN FOR CERVICAL CANCER

Chugai Pharmaceutical has obtained Japanese approval for Avastin(R) (bevacizumab) for advanced or recurrent cervical cancer. This followed the granting of orphan drug designation and priority review in September last year. Approval was based on the results of an overseas phase III study (GOG-0240; ClinicalTrials.gov Identifier NCT00803062) and a Japanese phase II study (JO29569 study). The GOG-0240 study evaluated the efficacy and safety profile of bevacizumab with or without standard chemotherapies (paclitaxel and cisplatin or paclitaxel and nogitecan) in 452 patients with persistent, recurrent or metastatic cervical cancer. The study met its primary endpoint of improving overall survival with a statistically significant 26% reduction in the risk of death, representing a median gain in survival of 3.9 months, compared with those who received chemotherapy alone (16.8 months vs. 12.9 months). Patients who received bevacizumab plus chemotherapy had a significant improvement of progression free survival compared with those who received chemotherapy alone (8.3 months vs. 6.0 months). The study showed that patients who received bevacizumab plus chemotherapy had a significantly higher rate of tumor shrinkage (objective response rate) compared with those who received chemotherapy alone (45.4% vs. 33.8%). The safety profile in the study was consistent with previous reports of bevacizumab, except for an increase in gastrointestinal-vaginal fistulas observed in patients who received bevacizumab plus chemotherapy compared to those who received chemotherapy alone (8.3% vs. 0.9% respectively). All patients with gastrointestinal-vaginal fistulas had a history of prior pelvic radiation. The JO29569 study evaluated the tolerability, safety and efficacy of bevacizumab plus paclitaxel and cisplatin. Within eight Japanese patients with advanced or recurrent cervical cancer enrolled in the study, seven patients were evaluated, and one patient was excluded before the start of the study. The tolerability of bevacizumab plus chemotherapy was confirmed, and the harmful phenomenon to become the problem was not accepted, and no new safety finding were observed. Avastin is already marketed in Japan for unresectable advanced or recurrent colorectal cancer, unresectable advanced or recurrent non-squamous non-small cell lung cancer (NSCLC), inoperable or recurrent breast cancer, malignant glioma and ovarian cancer (Chugai Pharmaceutical News Release).

2016 年 5 月 19 日，FDA 批准 TECENTRIQ 及互补诊断用于诊断转移性尿路上皮癌

FDA 已授予加速批准 Genentech 公司的 Tecentriq（TM）（atezolizumab）用于局部晚期或转移性尿路上皮癌，适用于铂类化疗仍有疾病进展，或手术前后以铂类化疗为基础治疗 12 个月仍恶化的患者。Tecentriq 是 FDA 批准的第一个程序性细胞死亡 1 配体 1（PD-L1）抑制剂。该机构还批准了罗氏组织诊断的互补诊断 PD-L1（SP142）分析来提供考虑采用 atezolizumab 治疗转移性尿路上皮癌患者的 PD-L1 状态。这个试验是首个使用免疫细胞染色和肿瘤微环境评分来评估临床患者的 PD-L1 状态并向临床医生提供可以指导免疫决定的信息。Tecentriq 预计 1-2 周内在美国上市。Atezolizumab 加速批准是基于 II 期 IMvigor 210 研究（ClinicalTrials.gov 标识符 NCT02108652）的肿瘤反应率和观察到的反应持续时间，该适应症的批准可能根据验证试验中临床获益的验证和描述。在所有患者中， 14.8％的参与者至少出现肿瘤局部收缩，在反应分析时该效应持续超过 2.1 至 13.8 个月。在 PD-L1 表达阳性的患者中，26％的参与者出现肿瘤反应，而 PD-L1 表达阴性的参与者则为 9.5％。在疾病出现进展并接受新辅助或含铂治疗辅助的患者子集中（n = 59），atezolizumab 可使 22.0％患者的肿瘤缩小。最常见的 3-4 级不良反应（2％以上）为：尿路感染（9％）、贫血（8％）、疲劳（6％）、脱水、肠梗阻、尿路梗阻、血尿（3％）、呼吸困难（4％）、急性肾损伤、腹痛（4％）、静脉血栓栓塞、脓毒症和肺炎。3 名（0.9％）患者出现败血症或者肺炎或肠梗阻而导致死亡。3.2％（10/310）患者因不良反应而停止使用 atezolizumab。Genentech 公司（罗氏子公司）在 III 期研究 IMvigor 211 中对 atezolizumab 进行了评估，该研究比较了 atezolizumab 与化疗治疗含铂疗法仍出现恶化的膀胱癌（ClinicalTrials.gov 标识符 NCT02302807）。Ventana PD-L1（SP142）为 Tecentriq 的伴随诊断检测，由 Ventana Medical Systems 开发上市。罗氏将继续努力，使 PD-L1（SP142）法与 atezolizumab 联合使用适用于其他癌症适应症获得监管部门批准（Genentech 公司新闻稿；FDA 新闻发布; 罗氏公司新闻稿）。

MAY 19, 2016
FDA APPROVES TECENTRIQ AND COMPLEMENTARY DIAGNOSTIC FOR METASTATIC UROTHELIAL CARCINOMA

The FDA has granted accelerated approval to Genentech's Tecentriq(TM) (atezolizumab) for the treatment of people with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-based chemotherapy, or whose disease has worsened within 12 months of receiving platinum-based chemotherapy before surgery or after surgery. Tecentriq is the first programmed cell death 1 ligand 1 (PD-L1) inhibitor approved by the FDA. The agency also approved Roche Tissue Diagnostics' complementary diagnostic Ventana PD-L1 (SP142) Assay to provide PD-L1 status on patients who are considering treatment with atezolizumab for metastatic urothelial carcinoma. This test is the first to evaluate patient PD-L1 status using immune cell staining and scoring within the tumor microenvironment, providing clinicians with information that may guide immunotherapy decisions. Tecentriq is expected to be available in the U.S. within 1-2 weeks. Accelerated approval of atezolizumab was based on tumor response rate and duration of response observed in the phase II IMvigor 210 study (ClinicalTrials.gov Identifier NCT02108652), however continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. In all patients, 14.8% of participants experienced at least a partial shrinkage of their tumors, an effect that lasted from more than 2.1 to more than 13.8 months at the time of the response analysis. In patients who were classified as positive for PD-L1 expression, 26% of participants experienced a tumor response, compared to 9.5% of participants who were classified as negative for PD-L1 expression. In a subset of people with disease

progression following neoadjuvant or adjuvant platinum-containing therapy (n = 59), atezolizumab shrank tumors in 22.0% of people. The most common Grade 3-4 adverse reactions (2% or more) were: urinary tract infection (9%), anemia (8%), fatigue (6%), dehydration, intestinal obstruction, urinary obstruction, hematuria (3%), dyspnea (4%), acute kidney injury, abdominal pain (4%), venous thromboembolism, sepsis and pneumonia. Three people (0.9%) experienced either sepsis, pneumonitis or intestinal obstruction, which led to death. Atezolizumab was discontinued for adverse reactions in 3.2% (10) of the 310 patients. Genentech, a member of the Roche group, is also evaluating atezolizumab in the confirmatory phase III study IMvigor 211, which compares atezolizumab to chemotherapy in people whose bladder cancer has progressed on at least one prior platinum-containing regimen (ClinicalTrials.gov Identifier NCT02302807). The Ventana PD-L1 (SP142) assay companion diagnostic for Tecentriq is marketed by Ventana Medical Systems. Roche will continue to pursue regulatory approval for the PD-L1 (SP142) assay in combination with atezolizumab in other cancer indications (Genentech News Release; FDA News Release; Roche News Release).

2016 年 5 月 19 日，新型双重 IDO1/ TDO 抑制剂 RG-70099 在体内有效

罗氏已经报道吲哚胺 2,3 双加氧酶 1（IDO1）和色氨酸 2,3-双加氧酶（TDO）的小分子双重抑制剂 RG7-0099 在体外细胞测定和体内均可抑制两种酶（两者均 IC50<100nM）。IDO1/TDO 抑制抑制犬尿氨酸的形成并产生免疫抑制作用。在 IDO1+肿瘤模型（B16F10 小鼠黑色素瘤）中，RG-70099 治疗组的犬尿氨酸生成减少 81％。在 TDO+肿瘤模型（U87MG 胶质母细胞瘤）中，犬尿氨酸生成减少 95％。 RG-70099 还具有较好的口服生物利用度和安全性。IDO1 和 TDO 在肺腺癌细胞上共表达，但是这两种酶也在不同类型的肿瘤细胞上表达（Gyulveszi, G. et al. 107th Annu Meet Am Assoc Cancer Res (AACR) (April 16-20, New Orleans) 2016, Abst LB-0855）。

MAY 19, 2016
NOVEL, DUAL IDO1/TDO INHIBITOR RG-70099 IS ACTIVE IN VIVO

Roche has shown that their small-molecule dual inhibitor of indoleamine 2,3-dioxygenase 1 (IDO1) and tryptophan 2,3-dioxygenase (TDO), RG7-0099, inhibits both enzymes in cell-based assays (IC50 < 100 nM for both) and in vivo. Inhibition of IDO1/TDO suppresses the formation of kynurenine and leads to immunosuppressive effects. In an IDO1+ tumor model (B16F10 murine metastatic melanoma) kynurenine formation was reduced 81% with RG-70099. In a TDO+ tumor model (U87MG glioblastoma) kynurenine formation was reduced 95% with the agent. RG-70099 has also demonstrated oral bioavailability and safety. IDO1 and TDO are coexpressed on lung adenocarcinoma cells but the enzymes have also been detected on different types of tumor cells (Gyulveszi, G. et al. 107th Annu Meet Am Assoc Cancer Res (AACR) (April 16-20, New Orleans) 2016, Abst LB-085).

2016 年 5 月 18 日，韩国批准勃林格殷格翰的 OLMUNITIB

勃林格殷格翰公司报告 olmutinib 在韩国已批准用于治疗局部晚期或转移性表皮生长因子受体（EGFR）T790M 突变阳性的非小细胞肺癌，适用于早期使用 EGFR 酪氨酸激酶抑制剂治疗的患者。该化合物在韩国将由韩美药业分销（勃林格殷格翰公司新闻稿）。

MAY 18, 2016

BOEHRINGER INGELHEIM'S OLMUNITIB RECEIVES APPROVAL IN SOUTH KOREA

Boehringer Ingelheim reports that olmutinib has been approved in South Korea for the treatment of patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small-cell lung cancer, who had been previously treated with an EGFR tyrosine kinase inhibitor. The compound will be distributed in South Korea by Hanmi Pharmaceutical (Boehringer Ingelheim News Release).

2016 年 5 月 18 日，GVK BIOSCIENCES 公司报道开发选择性抑制剂 PI3KBETA

GVK Biosciences 公司的研究者已经开发了选择性的磷脂酰肌醇 4,5-二磷酸 3-激酶催化 β 亚基同型（PI3Kbeta）抑制剂，用于治疗 PTEN 缺失的肿瘤。一系列化合物的效力范围低至 2.5nM， PI3Kdelta 选择性>100 倍。化合物不降低胰岛素敏感性或 T 细胞增殖。先导化合物（GVK-01406）对 PI3Kdelta 表型的选择性得到改善，而未表现出激酶、安全问题、细胞色素 P450（CYP）或钾电压门控通道亚族 H 成员 2（hERG）的缺点。该化合物的进一步优化正在进行中。这些结果表明，该类化合物对通过 PTEN 突变或通过 PI3Kbeta 功能增益突变而产生耐药的肿瘤也可能具有一定的治疗潜力。此外，该类化合物还可能用于治疗罕见疾病，如错构瘤（Chowdhury, A.R. et al. 107th Annu Meet Am Assoc Cancer Res (AACR) (April 16-20, New Orleans) 2016, Abst 373）。

MAY 18, 2016

GVK BIOSCIENCES REPORTS DEVELOPMENT OF SELECTIVE PI3KBETA INHIBITORS

Investigators from GVK Biosciences have developed selective phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit beta isoform (PI3Kbeta) inhibitors reported to be useful for PTEN-deficient tumors. A chemical series with potency ranging as low as 2.5 nM for PI3Kbeta with >100-fold selectivity for PI3Kdelta was identified. Compounds did not reduce either insulin sensitivity or T-cell proliferation. The lead compound (GVK-01406) showed improved PI3Kdelta phenotypic selectivity. It showed no kinase panel, safety panel, cytochrome P450 (CYP) or potassium voltage-gated channel subfamily H member 2 (hERG) liabilities. Further optimization of the compound is ongoing. These findings suggest that these compounds have potential for tumors resistant to treatment via PTEN mutation or via PI3Kbeta gain-of-function mutation. In addition, they may be useful for the treatment of rare diseases such as hamartoma (Chowdhury, A.R. et al. 107th Annu Meet Am Assoc Cancer Res (AACR) (April 16-20, New Orleans) 2016, Abst 373).

2016 年 5 月 18 日，新 CDC7 抑制剂在体内具有广泛的抗肿瘤活性

美国礼来公司的科学家开发出一种强效的选择性细胞分裂周期 7 有关的蛋白激酶（CDC7）抑制剂，命名为 LY-3177833。该化合物的 CDC7/ DBF4 IC50=3.3 nM，pMCM2（S53）IC50=290 nM 和 IVTI TEC70=1.6 mcM。LY-3177833 的体内 MED= 5 mg/kg（口服）。该化合物可强烈影响染色体的动态。在小鼠异种移植模型，广泛的抗肿瘤活性与稳定的剂量/暴露依赖性体内靶抑制有关。此外，该化合物的临床前结果与非选择性 CDC7 抑制剂和细胞毒性剂不同，支持其采用连续给药方案进行临床研发（Ye, X.S. et al. 107th

Annu Meet Am Assoc Cancer Res (AACR) (April 16-20, New Orleans) 2016, Abst）。该化合物在专利文献（WO2014143601）中进行描述。

MAY 18, 2016
NEW CDC7 INHIBITOR SHOWS BROAD ANTITUMOR ACTIVITY IN VIVO

Scientists from Eli Lilly and Company have developed a potent and selective cell division cycle 7-related protein kinase (CDC7) inhibitor, named LY-3177833. The compound had CDC7/DBF4 IC50 = 3.3 nM, pMCM2 (S53) IC50 = 290 nM and IVTI TEC70 = 1.6 mcM. LY-3177833 showed MED = 5 mg/kg (p.o.) in vivo. The compound strongly impacted chromosome dynamics. In mouse xenograft models, broad antitumor activity was associated with robust dose/exposure-dependent in vivo target inhibition. In addition, the preclinical profile of the compound was different from nonselective CDC7 inhibitors and cytotoxic agents, something that supports its clinical development with a continuos dosing regimen (Ye, X.S. et al. 107th Annu Meet Am Assoc Cancer Res (AACR) (April 16-20, New Orleans) 2016, Abst).
The compound is described in the patent literature (WO 2014143601).

2016 年 5 月 6 日，SORRENTO 的抗 C-MET 抗体-药物缀合物进入 IND 研究

Sorrento Therapeutics 公司已经开发了一种抗体-药物缀合物（ADC），靶向肝细胞生长因子受体（c-Met）的单克隆抗体 STI-A0602 通过 C-lock（TM）缀合方法连接微管蛋白抑制剂或 DNA 损伤剂。该 ADC CBT-161 与裸抗体具有类似的结合亲和力和药代动力学特性。在多个非小细胞肺癌（NSCLC）异种移植物模型中，CBT-161 显著抑制肿瘤生长，有效剂量为 1 mg/kg，每周给药一次，连续 3 周给药，至少持续 3 周。疗效与肿瘤表面 c-Met 表达相关。此外，在非小细胞肺癌异种移植模型中，CBT-161 和表皮生长因子受体抑制剂组合可显著抑制肿瘤生长，CBT-161 单剂量给药、厄洛替尼每日给药或西妥昔单抗的每周给药两次的药效持续超过 3 周。在动物中未见体重显著降低。CBT-161 治疗非小细胞肺癌和其他癌症的潜在效果促进了 IND 研究的进行（Li, L. et al. 107th Annu Meet Am Assoc Cancer Res (AACR) (April 16-20, New Orleans) 2016, Abst 3897）。

MAY 06, 2016
ANTI-C-MET ANTIBODY-DRUG CONJUGATE FROM SORRENTO TO ENTER IND-ENABLING STUDIES

Sorrento Therapeutics has developed antibody-drug conjugate (ADCs) consisting of a monoclonal antibody targeting hepatocyte growth factor receptor (c-Met), STI-A0602, conjugated to tubulin inhibitors or a DNA damaging agent through the C-lock(TM) conjugation method. The ADC CBT-161 showed a similar binding affinity and pharmacokinetic profile as the naked antibody. In multiple non-small cell lung cancer (NSCLC) xenograft models, CBT-161 significantly inhibited tumor growth, with the effects of a dose of 1 mg/kg given once a week for 3 weeks lasting at least 3 weeks after dosing. Efficacy was correlated with c-Met expression on the tumor surface. Also in NSCLC xenografts, the combination of CBT-161 and epidermal growth factor receptor inhibitors significantly inhibited tumor growth, with efficacy lasting over 3 weeks with a single CBT-161 dose and a daily dose of erlotinib or a twice-weekly dose of cetuximab. No significant weight loss was observed in the animals. The potential of CBT-161 in treating NSCLC and other cancer led to its selection for IND-enabling studies (Li, L. et al. 107th Annu Meet Am Assoc Cancer Res (AACR) (April 16-20, New Orleans) 2016, Abst 3897).

眼部疾病 EYE DISORDERS

2016 年 5 月 17 日，新型小分子给视网膜疾病的治疗带来希望

Clearside 生物医学与 Covance 实验室的研究人员已经开发出一种可结合抗血管内皮细胞生长因子受体（VEGFR）和抗血小板生长因子受体（PDGFR）的新颖小分子（CLS-011A）。化合物的药代动力学和眼组织分布情况在荷兰兔上进行了测试。为期 91 天的脉络膜给药结果表明，CLS-011A（4 mg /眼；100 mL/注射）耐受性良好并且未见毒性迹象。CLS-011A 仅在玻璃体、视网膜和巩膜/脉络膜-RPE（SCR）可进行量化。在注射 3 个月后，60％以上的该化合物仍残留在 SRC。消除半衰期为 102 天。总结可得，CLS-011A 在最小全身暴露下具有较好的耐受性（Kissner, J. et al. Annu Meet Assoc Res Vis Ophthalmol (ARVO) (May 1-5, Seattle) 2016, Abst 4002）。

MAY 17, 2016
NOVEL SMALL MOLECULE SHOWS PROMISE FOR THE TREATMENT OF RETINAL DISEASE

Investigators from Clearside Biomedical and Covance Laboratories have developed a novel small molecule with anti-vascular endothelial growth factor receptor (VEGFR) and anti-platelet-derived growth factor receptor (PDGFR) binding properties (CLS-011A). The pharmacokinetics and ocular tissue distribution of the compound were tested in Dutch Belted rabbits. Suprachoroidal administration of CLS-011A (at 4 mg/eye; 100 mL/injection) was well tolerated through day 91. There were no signs of toxicity. CLS-011A was only quantifiable in the vitreous humor, retina and sclera/choroid-RPE (SCR). More than 60% of the compound remained in the SRC at 3 months after injection. The elimination half-life was 102 days. Taken together, these results show that CLS-011A was well tolerated with minimal systemic exposure (Kissner, J. et al. Annu Meet Assoc Res Vis Ophthalmol (ARVO) (May 1-5, Seattle) 2016, Abst 4002).

2016 年 5 月 11 日，OHR 制药开发可生物降解微球 AMD 治疗 OHR-3031

Ohr 制药的科学家报道 9 只雄性新西兰白兔使用可生物降解的微球给药系统给药抗血管生成化合物 OHR-3031 玻璃体制剂的研究。治疗开发用于年龄相关性的黄斑变性（AMD）。在第 0 天，双侧注射 2.6 mg OHR-3031（使用制剂 201412003）。注射后，化合物在眼组织中梯度可见（玻璃体>巩膜> =脉络膜>视网膜虹膜睫状体>房水）。持续给药后，玻璃体浓度恒定超过 42 日：浓度未见下降，因此，预计药物维持超过 42 天。视网膜和脉络膜可见治疗浓度的 OHR-3031 和活性代谢物，表明活性代谢物可在靶组织连续形成。值得注意的是，血浆浓度无法量化。药代动力学数据表明，玻璃体、视网膜、脉络膜、巩膜、眼房水、虹膜、睫状体和血浆中 OHR-3031 的 Cmax 值分别为 1,105,000、265,000，285,000、335,000、12,000、32300 和<2.5 ng/g；tmax 值分别为 14、3、28、28、1、0.17 天和 NC；AUC 值分别为 33,200,000、188000、2,190,000、258,00、220,000 ng.hg 和 NC。视网膜中代谢产物的 Cmax、tmax 和 AUC 数值分别为 2600 ng/g,、28 天和 1520 ng.hg。血浆 Cmax 为<1.0 ng/g。靶组织单次注射生物降解微粒制剂至少 6 周后，可见持续超治疗浓度的 OHR = 3031（Modi, M.W. et al. Annu Meet Assoc Res Vis Ophthalmol (ARVO) (May 1-5, Seattle) 2016, Abst 770）。

MAY 11, 2016
OHR PHARMACEUTICAL DEVELOPS BIODEGRADABLE MICROPARTICLE AMD TREATMENT OHR-3031

Ohr Pharmaceutical scientists have described a study of an intravitreal formulation of the antiangiogenic compound OHR-3031 delivered in a biodegradable microparticle drug delivery system to nine male New Zealand white rabbits. The treatment is being developed for age-related macular degeneration (AMD). Bilateral injections of 2.6 mg OHR-3031 (using formulation 201412003) were administered on day 0. Following injection an ocular tissue gradient of the compound was seen (vitreous > sclera >= choroid > retina iris-ciliary body > aqueous humor). Sustained delivery was seen, with constant vitreous concentrations seen over 42 days: concentrations were not seen to decline so it was expected that these were maintained beyond the 42 days. Therapeutic concentrations of OHR-3031 and active metabolite were seen in retina and choroid, which suggest the active metabolite is continuously formed in target tissues. It was noted that plasma concentrations were not quantifiable. Pharmacokinetic data showed Cmax values of OHR-3031 in vitreous humor, retina, choroid, sclera, aqueous humor, iris-ciliary body and plasma of 1,105,000, 265,000, 285,000, 335,000, 12,000, 32,300 and < 2.5 ng/g; tmax values were 14, 3, 28, 28, 1 , 0.17 day and NC, respectively; for AUC values results were 33, 200, 000, 188,000, 2,190,000, 258,00, 220,000 ng.hg and NC, respectively. For the metabolite the Cmax, tmax and AUC values for retina were 2600 ng/g, 28 days and 1520 ng.hg, respectively. Cmax for plasma was < 1.0 ng/g. Sustained supratherapeutic concentrations of OHR=3031 were achieved in the target tissue with a single injection of this biodegradable microparticle formulation for at least 6 weeks (Modi, M.W. et al. Annu Meet Assoc Res Vis Ophthalmol (ARVO) (May 1-5, Seattle) 2016, Abst 770).

2016 年 5 月 10 日，拜耳 ALK-1 抑制剂进行体内眼新血管形成试验

拜耳在西雅图举行的视觉与眼科研究协会年会（ARVO）上公布了关于 ALK-1 抑制剂 BAY-754 的数据。化合物体外研究结果显示，ALK-1 的生物化学 IC50 值为 1.6 nM，而细胞水平上 SMAD7 和 VEGFR-2 分别为 10 和 4400 nM。大鼠激光脉络膜新生血管形成（CNV）模型的体内结果表明，BAY-754 眼药水对血管渗漏呈现剂量依赖性抑制，剂量范围为 2.5 至 20 mg/mL，激光损伤后直接给药 23 天（早期研究方案）。该药对新血管形成也呈现一定的效果。在一项延迟方案中，手术后第 7 天给药，20 mg/ mL 的剂量下，药物对血管渗漏和新生血管面积（P <0.001）显著减少。在另一项延迟方案中，血管渗漏值按照激光损伤后 7 天基线值进行标准化，BAY-754 以 20 mg/mL/天剂量每日给药，给药 14 天，结果显示，单周给药后血管渗漏和新生血管面积减少。眼睛前部的药代动力学数据表明，Cmax.norm、AUC norm 和 t1/2 值分别为 4.7 kg/L、12 kg•h/L 和 2.3 h。眼睛后部的玻璃体/透镜和血浆的结果分别为 4.9、0.54 和 0.003 kg/L，17、1.2、0.014 kg•h/L 以及 6.8、3.4 和 1.7 h，（Boettger, M.K. et al. Annu Meet Assoc Res Vis Ophthalmol (ARVO) (May 1-5, Seattle) 2016, Abst 1115）。
BAY-754 已在专利文献（WO 2013004551）中进行描述。

MAY 10, 2016
BAYER'S ALK-1 INHIBITOR TESTED IN VIVO FOR OCULAR NEOVASCULARIZATION

Bayer presented data on BAY-754, an inhibitor of ALK-1, at the Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO) in Seattle.
In vitro the compound showed a biochemical IC50 value of 1.6 nM for ALK-1, compared to 10 and 4400

for cellular SMAD7 and VEGFR-2, respectively. In vivo results were presented showing that in a rat laser choroidal neovascularization (CNV) model there was dose-dependent inhibition of vascular leakage with BAY-754 eye drops for 23 days at doses ranging 2.5 to 20 mg/mL as administered directly after laser injury (early protocol). The effect was also seen on neovascularization. In a delayed protocol, in which treatment was administered 7 days after surgery, a 20 mg/mL dose showed significant reduction in vascular leakage and neovascular area ($P < 0.001$). In a different delayed protocol, in which vascular leakage values were normalized to baseline values 7 days after laser injury, BAY-754 still showed reduction in vascular leakage and neovascular areas after a single week of daily treatment at 20 mg/mL/day for 14 days. Pharmacokinetic data showed Cmax.norm, AUC norm and t1/2 values in the front of the eye to be 4.7 kg/L, 12 kg•h/L and 2.3 h, respectively. In the back of the eye, vitreous/lens and plasma results were 4.9, 0.54 and 0.003 kg/L, 17, 1.2 and 0.014 kg•h/L and 6.8, 3.4 and 1.7 h, respectively (Boettger, M.K. et al. Annu Meet Assoc Res Vis Ophthalmol (ARVO) (May 1-5, Seattle) 2016, Abst 1115).
BAY-754 has been described in the patent literature (WO 2013004551).

胃肠道疾病 GASTROINTESTINAL DISORDERS

2016 年 5 月 30 日，FDA 加速 OCALIVA 治疗原发性胆汁性胆管炎的审批

FDA 已经加速审批 Intercept 制药公司的 Ocaliva（商标）（奥贝胆酸），奥贝胆酸是一种法尼酯 X 受体（FXR）激动剂，与熊去氧（UDCA）联合用药后可治疗原发性胆汁性胆管炎（PBC），适用于 UDCA 反应不足或者 UDCA 单一疗法无法耐受的患者。加速批准是基于碱性磷酸酶（ALP）的减少因素。存活或疾病相关症状的改善尚未确定。该适应症的继续批准可能根据验证试验中临床获益的确定和描述。在 Intercept 的Ⅲ期临床试验 POISE 中，46％患者达到奥贝胆酸与熊去氧胆酸（UDCA 单药治疗不耐受的患者）联合用药的主要复合终点，相比之下，而熊去氧胆酸安慰剂组为 10％（ClinicalTrials.gov 标识符 NCT01473524）。瘙痒是 PBC 的常见症状，与疾病阶段或者结果无关，该不良反应是奥贝胆酸治疗患者中观察到的最常见副作用。但是在剂量滴定方案中（5 mg，每日一次增加至 10 mg，每日一次），奥贝胆酸治疗相关的皮肤瘙痒一般较少；滴定组的一名患者（1％）因搔痒而中止研究。在试验过程中观察到的其他副作用包括乏力、腹痛和不适、皮疹、口咽部疼痛、头晕、便秘、关节痛、甲状腺功能异常和湿疹。Ocaliva 预计将在 7-10 天内在美国上市，并通过专业药房网进行分销（Intercept 制药新闻稿）。

MAY 30, 2016
FDA GRANTS ACCELERATED APPROVAL TO OCALIVA FOR PRIMARY BILIARY CHOLANGITIS

The FDA has granted accelerated approval to Intercept Pharmaceuticals' Ocaliva(TM) (obeticholic acid), a farnesoid X receptor (FXR) agonist, for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA. Accelerated approval was granted based on a reduction in alkaline phosphatase (ALP). An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. In Intercept's phase III trial POISE, obeticholic acid administration in combination with UDCA (or as monotherapy in UDCA-intolerant patients) met the primary composite

endpoint in 46% of patients in the titration group, as compared to 10% of those receiving placebo added to UDCA (ClinicalTrials.gov Identifier NCT01473524). Pruritus, a common symptom of PBC that is unrelated to disease stage or outcomes, was the most common side effect observed in obeticholic acid-treated patients. However, pruritus associated with obeticholic acid treatment was generally less in patients who were on the dose titration regimen (5 mg once-daily increasing to 10 mg once-daily); one patient (1%) in the titration group discontinued from the study due to pruritus. Additional side effects observed during the trial included fatigue, abdominal pain and discomfort, rash, oropharyngeal pain, dizziness, constipation, arthralgia, thyroid function abnormality and eczema. Ocaliva is expected to be available in the U.S. within 7-10 days and will be distributed through a specialty pharmacy network (Intercept Pharmaceuticals News Release).

血液和凝血障碍 HEMATOLOGICAL & BLOOD COAGULATION DISORDERS

2016 年 5 月 27 日，FDA 批准 CSL 的 LONOCTOCOG ALPHA

CSL Behring 的 Afstyla（R）（lonoctocog alpha；抗血友病因子[重组]，单链）已经获得 FDA 批准，长效重组因子 VIII 单链疗法用于治疗成人和儿童血友病。该疗法的适应症为常规预防或减少出血事件的频率；按需治疗和控制出血事件；围手术期出血处理。Afstyla 预计在美国今年夏初上市（CSL Behring 新闻稿）。

MAY 27, 2016
CSL GAINS FDA APPROVAL FOR LONOCTOCOG ALPHA

CSL Behring has gained FDA approval for Afstyla(R) (lonoctocog alfa; antihemophilic factor [recombinant], single chain), a long-lasting recombinant factor VIII singlechain therapy for adults and children with hemophilia A. The therapy is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes; for on-demand treatment and control of bleeding episodes; and for the perioperative management of bleeding. Afstyla is expected to be available in the U.S. early this summer (CSL Behring News Release).

感染 INFECTIONS

2016 年 5 月 25 日，FDA 批准 FLUCELVAX QUADRIVALENT

FDA 已经批准 Seqirus 的 Flucelvax Quadrivalent（TM），Flucelvax Quadrivalent 是首个细胞培养产生的四联灭活季节性流感疫苗，适用于 4 周岁及以上人群。疫苗有助于预防由世界卫生组织（WHO）和美国 FDA 在流感季节推荐的两种甲型流感病毒和两个 B 型流感病毒。Flucelvax Quadrivalent 在美国将于 2016

- 2017 年流感季节可用。Flucelvax Quadrivalent 是基于细胞的三价流感疫苗 Flucelvax 的新产品。由于这两种疫苗使用的工艺制造相同并具有重叠组成部分，Flucelvax 临床试验的临床有效性和安全性数据与 Flucelvax Quadrivalent 有关。在年龄为 18-49 岁成年人上进行的临床研究中，Flucelvax 已被证明对疫苗状株（83.8％）和所有流行的流感毒株（69.5％）有效。其四价配方也在年龄 18 岁以上成人（研究 1）和 4-17 岁儿童（研究 2）上证明对流感具有免疫原性。Flucelvax Quadrivalent 可对 B 型流感病毒株产生更强的抗体反应，该病毒株未包含在三价流感疫苗中。Flucelvax Quadrivalent 耐受性较好并且其安全性与疫苗对照相似。它还利用了前身 Flucelvax 超过 11000 人的安全数据库。去年七月，CSL 集团及其附属公司收购诺华公司的流感疫苗业务。美国以前由诺华公司拥有的流感疫苗业务已经整合至 CSL 的流感疫苗业务，目前名为 Seqirus（Seqirus 新闻稿）。

MAY 25, 2016
FDA APPROVES FLUCELVAX QUADRIVALENT

The FDA has approved Seqirus' Flucelvax Quadrivalent(TM), the first four-strain, cell culture-derived, inactivated seasonal influenza vaccine for people age 4 years and older. The vaccine helps protect against the two influenza A viruses and two B viruses recommended by the World Health Organization (WHO) and the FDA for the current influenza season. Flucelvax Quadrivalent will be available in the U.S. during the 2016-2017 influenza season. Flucelvax Quadrivalent is an evolution of Flucelvax, a cell-based trivalent influenza vaccine. Because both vaccines are manufactured using the same process and have overlapping compositions, the clinical efficacy and safety data from clinical trials with Flucelvax is relevant to Flucelvax Quadrivalent. In clinical studies of adults aged 18-49 years, Flucelvax has been shown to be efficacious against influenza caused by vaccine-like strains (83.8%) and by all circulating influenza strains (69.5%). Its quadrivalent formulation was also shown to be immunogenic against influenza in adults age 18 years and older (Study 1) and children aged 4-17 years (Study 2). Flucelvax Quadrivalent produced stronger antibody responses to the influenza B virus strain, which was not contained in the trivalent comparator flu vaccine, and is well tolerated with a safety profile similar to its comparator vaccines. It also leverages the safety database demonstrated by its predecessor Flucelvax in more than 11,000 people. In July last year, the CSL Group and its affiliates acquired the influenza vaccines business of Novartis in the U.S. The influenza vaccines business previously owned by Novartis has been integrated into CSL's influenza vaccine business and now operates as Seqirus (Seqirus News Release).

代谢性疾病 METABOLIC DISORDERS

2016 年 5 月 30 日，欧盟委员会批准 STRIMVELIS 治疗 ADA-SCID

欧盟委员会已经批准 Strimvelis（TM）（GSK-2696273），Strimvelis 是治疗腺苷脱氨酶缺乏症导致的严重联合免疫缺陷（ADA-SCID）的首个体外干细胞基因疗法。Strimvelis 为自体 CD34 +细胞转导以表达 ADA 的疗法，是世界各地监管部门批准的首个儿童纠正基因治疗，适用于治疗无合适人类白细胞抗原（HLA）相关干细胞供体的 ADA-SCID 患者。Strimvelis 在欧洲批准后，需要进行治疗的患者可在意大利 Ospedale San Raffaele (OSR)接受基因治疗。批准是基于 Strimvelis 治疗的 18 名儿童数据。Strimvelis 治疗 3 年后，关键性研究的所有 12 名儿童呈现 100％的存活率，92％为无干预生存率（即治疗后>3 个月无需酶替代治

疗或造血干细胞移植）。Strimvelis 治疗并向 MAA 提供数据的所有 18 名儿童仍在世，随访平均时间约 7 年，首名患者在 13 年前接受该基因治疗。在评估人群（n = 17）范围内的无干预生存率为 82％。总体安全性研究结果与已进行的低剂量化疗和免疫治疗 ADA-SCID 儿童患者的预期结果一致。严重感染的显著减少已记录在案并且目前未见白血病事件。ADA-SCID 基因治疗最初由 OSR 和 Fondazione Telethon 通过 San Raffaele Telethon Institute for Gene Therapy (SR-Tiget)联合开发，并与葛兰素史克公司开展战略合作以及由 MOLMED 推进研发（葛兰素史克新闻稿）。

MAY 30, 2016
EUROPEAN COMMISSION APPROVES STRIMVELIS FOR ADA-SCID

The European Commission has approved Strimvelis(TM) (GSK-2696273), the first ex-vivo stem cell gene therapy to treat patients with severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID). Strimvelis, autologous CD34+ cells transduced to express ADA, is the first corrective gene therapy for children to be awarded regulatory approval anywhere in the world. It is indicated for the treatment of patients with ADA-SCID for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available. Following European approval, patients with the condition who are referred for treatment will be able to receive the gene therapy at Ospedale San Raffaele (OSR) in Italy. Approval was based on data collected from 18 children treated with Strimvelis. A 100% survival rate at 3 years post-treatment with Strimvelis was observed for all 12 children in the pivotal study, with 92% having intervention-free survival (i.e., did not require enzyme replacement therapy for a period of > 3 months post-treatment or hematopoietic stem cell transplantation). All 18 children treated with Strimvelis who contributed data to the MAA are alive today with a median follow-up duration of approximately 7 years, with the first of these having received this gene therapy over 13 years ago. Intervention-free survival within the evaluable population (n = 17) was 82%. Overall the safety findings are in line with those expected in children with ADA-SCID who have undergone treatment with low-dose chemotherapy and who are undergoing immune recovery. A significant reduction in severe infections has been documented and no leukemic events have been observed to date. The gene therapy for the treatment of ADA-SCID was originally developed by OSR and Fondazione Telethon, through their joint San Raffaele Telethon Institute for Gene Therapy (SR-Tiget), and was taken forward by GlaxoSmithKline through a strategic collaboration, which also saw it working with MolMed (GlaxoSmithKline News Release).

精神疾病 PSYCHIATRIC DISORDERS

2016 年 5 月 2 日，FDA 批准 NUPLAZID 治疗帕金森氏症相关的幻觉和妄想精神病

FDA 已经批准 ACADIA 制药公司的 Nuplazid（TM）（酒石酸匹莫范色林）治疗帕金森氏症相关的精神病幻觉和妄想。Nuplazid 是美国 FDA 批准的首个和唯一用于治疗该适应症的药物，预计将于下个月在美国正式上市。批准是基于关键性 III 期研究（研究-020）和其他支持性研究的数据。在研究-020 中，根据帕金森病阳性症状的评估标准（SAPS-PD），与安慰剂相比，pimavanserin 可显著减少精神病症状的发生频率和

严重程度（ClinicalTrials.gov 标识符 NCT01174004）。患者可获益而不损害运动功能。在这项研究中，最常见的不良反应（5%或以上，为安慰剂发生率的两倍）为外周性水肿（pimavanserin 为 7%，安慰剂为 3%）和混乱状态（pimavanserin 为 6%，安慰剂为 3%）。Nuplazid 为 FDA 批准的唯一药物，优先靶向 5-HT 2A 受体，该受体在帕金森氏症等疾病治疗上具有重要作用。Pimavanserin 独特的药理作用使之成为一类新药，可选择性作用于血清素反向激动剂，而不是优先作用于 5-HT 2A 受体，也可避免作用于多巴胺等抗精神病药的常见目标受体。Nuplazid 于 2014 年获得突破性指定疗法（见汤森路透药品新闻，2014 年 9 月 3 日）（ACADIA 制药新闻稿）。

MAY 02, 2016
FDA APPROVES NUPLAZID FOR HALLUCINATIONS AND DELUSIONS ASSOCIATED WITH PARKINSON'S DISEASE PSYCHOSIS

The FDA has approved ACADIA Pharmaceuticals' Nuplazid(TM) (pimavanserin tartrate) for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis. Nuplazid, the first and only medicine to be approved by the FDA for this indication, is expected to be launched commercially in the U.S. next month. Approval was based on data from a pivotal phase III study (Study-020) and other supportive studies. In Study-020, pimavanserin significantly reduced the frequency and severity of psychotic symptoms compared to placebo on the Scale for Assessment of Positive Symptoms - Parkinson's Disease (SAPS-PD) (ClinicalTrials.gov Identifier NCT01174004). This benefit was achieved without impairing motor function. The most common adverse reactions (5% or more and twice the rate of placebo) in this study were peripheral edema (7% pimavanserin vs. 3% placebo) and confusional state (6% pimavanserin vs. 3% placebo). Nuplazid is also the only drug approved by the FDA that preferentially targets 5-HT2A receptors, which are thought to play an important role in Parkinson's disease psychosis. The unique pharmacology of pimavanserin establishes a new class of drug, selective serotonin inverse agonists, by not only preferentially targeting 5-HT2A receptors but also avoiding activity at dopamine and other receptors commonly targeted by antipsychotics. Nuplazid was awarded breakthrough therapy designation for this condition in 2014 (see Thomson Reuters Drug News, September 3, 2014) (ACADIA Pharmaceuticals News Release).

来源：汤森路透癌症 CANCER

2016 年 5 月 30 日，FDA 批准 AXUMIN 用于检测前列腺癌的复发

FDA 已经批准 Axumin（[18 F] fluciclovine）用于疑为前列腺癌复发男性患者的 PET 成像。Axumin 是 Blue Earth Diagnostics 公司推出上市的一种注射用放射性诊断剂，可在治疗前根据前列腺特异性抗原（PSA）水平诊断前列腺癌是否复发。目前已进行两项研究来评估 Axumin 在疾病复发患者上进行前列腺癌成像的安全性和有效性。第一项研究比较了 105 个男性疑似前列腺癌复发病例的 Axumin 扫描结果和前列腺穿刺活检和可疑成像病灶活检的组织病理学结果。扫描结果最初由放射科医师现场解读，接着由三个放射科医师在盲态研究中进行独立解读。第二项研究评估了 Axumin 和胆碱 C11（已批准用于 PET 扫描成像试验）患者 96 次扫描结果的一致性，平均 PSA 数值为 1.44ng/mL。放射科医师现场解读，接着由与第一项研究相同的三个放射科医师在第二次盲态研究中进行独立解读。独立解读结果基本一致，同时还确认了现场解读结果。这两项研究结果支持 Axumin 用于 PSA 值升高男性患者在治疗前进行前列腺癌成像的安全性和有效性。患者最常见的不良反应为注射部位疼痛、发红和口中有金属味（FDA 新闻稿）。

MAY 30, 2016
FDA APPROVES AXUMIN TO DETECT RECURRENT PROSTATE CANCER

The FDA has approved Axumin ([18F]fluciclovine), a radioactive diagnostic agent for injection marketed by Blue Earth Diagnostics, for PET imaging in men with suspected prostate cancer recurrence based on elevated prostate-specific antigen (PSA) levels following prior treatment. Two studies evaluated the safety and efficacy of Axumin for imaging prostate cancer in patients with recurrent disease. The first compared 105 Axumin scans in men with suspected recurrence of prostate cancer to the histopathology obtained by prostate biopsy and by biopsies of suspicious imaged lesions. The scans were initially read by radiologists on-site, and were subsequently read by three independent radiologists in a blinded study. The second study evaluated the agreement between 96 scans with Axumin and C11 choline, an approved PET scan imaging test, in patients with median PSA values of 1.44 ng/mL. Radiologists on-site read the scans, and the same three independent radiologists who read the scans in the first study read the Axumin scans in this second blinded study. The results of the independent scan readings were generally consistent with one another, and confirmed the results of the on-site scan readings. Both studies supported the safety and efficacy of Axumin for imaging prostate cancer in men with elevated PSA levels following prior treatment. The most commonly reported adverse reactions in patients were injection site pain, redness and a metallic taste in the mouth (FDA News Release).

2016 年 5 月 24 日，日本批准阿瓦斯汀治疗宫颈癌

日本已批准 Chugai 制药的阿瓦斯汀（R）（贝伐单抗）治疗晚期或复发性宫颈癌，去年九月获得孤儿药和优先审查权。批准是基于国外的 III 期临床研究结果（GOG-0240；ClinicalTrials.gov 标识符 NCT00803062）和日本的 II 期临床研究（JO29569 研究）。GOG-0240 研究评估了贝伐珠单抗标准或不标准化疗（紫杉醇、顺铂或紫杉醇以及拓扑替康）治疗 452 例持续复发或转移性宫颈癌患者的有效性和安全性。该研究达到了主要终点，与仅接受化疗的患者相比，总体生存率提高，死亡风险统计学显著降低 26%，平均存活增加 3.9 个月（16.8 个月比 12.9 个月）。与仅接受化疗的患者相比，接受贝伐单抗与化疗联合治疗患者的无进展生存期的显著改善（8.3 个月对 6.0 个月）。研究表明，接受贝伐单抗与化疗联合治疗患者与仅接受化疗的患者相比，肿瘤缩小率（客观缓解率）显著增加（45.4%对 33.8%）。研究的安全性与早期报道的贝伐单抗治疗结果一致，仅接受贝伐单抗联合化疗治疗的患者与仅接受化疗的患者相比，前者胃肠阴道瘘的发生率增加（8.3%对 0.9%）。所有胃肠阴道瘘患者具有盆腔放疗病史。JO29569 研究评估了贝伐单抗联合紫杉醇+顺铂治疗的耐受性、安全性和有效性。在 8 名参加试验的晚期或复发宫颈癌日本患者中，7 名患者进行了评估，1 名患者在研究开始前排除。贝伐单抗联合化疗的耐受性已进行确认，有害现象不会成为问题并且没有观察到新安全问题。阿瓦斯汀已在日本上市销售，用于治疗不能手术切除的晚期或复发性结直肠癌、不能手术切除的晚期或复发性非鳞状非小细胞肺癌（NSCLC）、不能手术或复发性乳腺癌、恶性胶质瘤和卵巢癌（Chugai 制药新闻稿）。

MAY 24, 2016
AVASTIN APPROVED IN JAPAN FOR CERVICAL CANCER

Chugai Pharmaceutical has obtained Japanese approval for Avastin(R) (bevacizumab) for advanced or recurrent cervical cancer. This followed the granting of orphan drug designation and priority review in September last year. Approval was based on the results of an overseas phase III study (GOG-0240; ClinicalTrials.gov Identifier NCT00803062) and a Japanese phase II study (JO29569 study). The

GOG-0240 study evaluated the efficacy and safety profile of bevacizumab with or without standard chemotherapies (paclitaxel and cisplatin or paclitaxel and nogitecan) in 452 patients with persistent, recurrent or metastatic cervical cancer. The study met its primary endpoint of improving overall survival with a statistically significant 26% reduction in the risk of death, representing a median gain in survival of 3.9 months, compared with those who received chemotherapy alone (16.8 months vs. 12.9 months). Patients who received bevacizumab plus chemotherapy had a significant improvement of progression free survival compared with those who received chemotherapy alone (8.3 months vs. 6.0 months). The study showed that patients who received bevacizumab plus chemotherapy had a significantly higher rate of tumor shrinkage (objective response rate) compared with those who received chemotherapy alone (45.4% vs. 33.8%). The safety profile in the study was consistent with previous reports of bevacizumab, except for an increase in gastrointestinal-vaginal fistulas observed in patients who received bevacizumab plus chemotherapy compared to those who received chemotherapy alone (8.3% vs. 0.9% respectively). All patients with gastrointestinal-vaginal fistulas had a history of prior pelvic radiation. The JO29569 study evaluated the tolerability, safety and efficacy of bevacizumab plus paclitaxel and cisplatin. Within eight Japanese patients with advanced or recurrent cervical cancer enrolled in the study, seven patients were evaluated, and one patient was excluded before the start of the study. The tolerability of bevacizumab plus chemotherapy was confirmed, and the harmful phenomenon to become the problem was not accepted, and no new safety finding were observed. Avastin is already marketed in Japan for unresectable advanced or recurrent colorectal cancer, unresectable advanced or recurrent non-squamous non-small cell lung cancer (NSCLC), inoperable or recurrent breast cancer, malignant glioma and ovarian cancer (Chugai Pharmaceutical News Release).

2016 年 5 月 19 日，FDA 批准 TECENTRIQ 及互补诊断用于诊断转移性尿路上皮癌

FDA 已授予加速批准 Genentech 公司的 Tecentriq（TM）（atezolizumab）用于局部晚期或转移性尿路上皮癌，适用于铂类化疗仍有疾病进展，或手术前后以铂类化疗为基础治疗 12 个月仍恶化的患者。Tecentriq 是 FDA 批准的第一个程序性细胞死亡 1 配体 1（PD-L1）抑制剂。该机构还批准了罗氏组织诊断的互补诊断 PD-L1（SP142）分析来提供考虑采用 atezolizumab 治疗转移性尿路上皮癌患者的 PD-L1 状态。这个试验是首个使用免疫细胞染色和肿瘤微环境评分来评估临床患者的 PD-L1 状态并向临床医生提供可以指导免疫决定的信息。Tecentriq 预计 1-2 周内在美国上市。Atezolizumab 加速批准是基于 II 期 IMvigor 210 研究（ClinicalTrials.gov 标识符 NCT02108652）的肿瘤反应率和观察到的反应持续时间，该适应症的批准可能根据验证试验中临床获益的验证和描述。在所有患者中， 14.8％的参与者至少出现肿瘤局部收缩，在反应分析时该效应持续超过 2.1 至 13.8 个月。在 PD-L1 表达阳性的患者中，26％的参与者出现肿瘤反应，而 PD-L1 表达阴性的参与者则为 9.5％。在疾病出现进展并接受新辅助或含铂治疗辅助的患者子集中（n = 59），atezolizumab 可使 22.0％患者的肿瘤缩小。最常见的 3-4 级不良反应（2％以上）为：尿路感染（9％）、贫血（8％）、疲劳（6％）、脱水、肠梗阻、尿路梗阻、血尿（3％）、呼吸困难（4％）、急性肾损伤、腹痛（4％）、静脉血栓栓塞、脓毒症和肺炎。3 名（0.9％）患者出现败血症或者肺炎或肠梗阻而导致死亡。3.2％（10/310）患者因不良反应而停止使用 atezolizumab。Genentech 公司（罗氏子公司）在 III 期研究 IMvigor 211 中对 atezolizumab 进行了评估，该研究比较了 atezolizumab 与化疗治疗含铂疗法仍出现恶化的膀胱癌（ClinicalTrials.gov 标识符 NCT02302807）。Ventana PD-L1（SP142）为 Tecentriq 的伴随诊断检测，由 Ventana Medical Systems 开发上市。罗氏将继续努力，使 PD-L1（SP142）法与

atezolizumab 联合使用适用于其他癌症适应症获得监管部门批准（Genentech 公司新闻稿；FDA 新闻发布; 罗氏公司新闻稿）。

MAY 19, 2016
FDA APPROVES TECENTRIQ AND COMPLEMENTARY DIAGNOSTIC FOR METASTATIC UROTHELIAL CARCINOMA

The FDA has granted accelerated approval to Genentech's Tecentriq(TM) (atezolizumab) for the treatment of people with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-based chemotherapy, or whose disease has worsened within 12 months of receiving platinum-based chemotherapy before surgery or after surgery. Tecentriq is the first programmed cell death 1 ligand 1 (PD-L1) inhibitor approved by the FDA. The agency also approved Roche Tissue Diagnostics' complementary diagnostic Ventana PD-L1 (SP142) Assay to provide PD-L1 status on patients who are considering treatment with atezolizumab for metastatic urothelial carcinoma. This test is the first to evaluate patient PD-L1 status using immune cell staining and scoring within the tumor microenvironment, providing clinicians with information that may guide immunotherapy decisions. Tecentriq is expected to be available in the U.S. within 1-2 weeks. Accelerated approval of atezolizumab was based on tumor response rate and duration of response observed in the phase II IMvigor 210 study (ClinicalTrials.gov Identifier NCT02108652), however continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. In all patients, 14.8% of participants experienced at least a partial shrinkage of their tumors, an effect that lasted from more than 2.1 to more than 13.8 months at the time of the response analysis. In patients who were classified as positive for PD-L1 expression, 26% of participants experienced a tumor response, compared to 9.5% of participants who were classified as negative for PD-L1 expression. In a subset of people with disease progression following neoadjuvant or adjuvant platinum-containing therapy (n = 59), atezolizumab shrank tumors in 22.0% of people. The most common Grade 3-4 adverse reactions (2% or more) were: urinary tract infection (9%), anemia (8%), fatigue (6%), dehydration, intestinal obstruction, urinary obstruction, hematuria (3%), dyspnea (4%), acute kidney injury, abdominal pain (4%), venous thromboembolism, sepsis and pneumonia. Three people (0.9%) experienced either sepsis, pneumonitis or intestinal obstruction, which led to death. Atezolizumab was discontinued for adverse reactions in 3.2% (10) of the 310 patients. Genentech, a member of the Roche group, is also evaluating atezolizumab in the confirmatory phase III study IMvigor 211, which compares atezolizumab to chemotherapy in people whose bladder cancer has progressed on at least one prior platinum-containing regimen (ClinicalTrials.gov Identifier NCT02302807). The Ventana PD-L1 (SP142) assay companion diagnostic for Tecentriq is marketed by Ventana Medical Systems. Roche will continue to pursue regulatory approval for the PD-L1 (SP142) assay in combination with atezolizumab in other cancer indications (Genentech News Release; FDA News Release; Roche News Release).

2016 年 5 月 19 日，新型双重 IDO1/ TDO 抑制剂 RG-70099 在体内有效

罗氏已经报道吲哚胺 2,3 双加氧酶 1（IDO1）和色氨酸 2,3-双加氧酶（TDO）的小分子双重抑制剂 RG7-0099 在体外细胞测定和体内均可抑制两种酶（两者均 IC50<100nM）。IDO1/TDO 抑制抑制犬尿氨酸的形成并产生免疫抑制作用。在 IDO1+肿瘤模型（B16F10 小鼠黑色素瘤）中，RG-70099 治疗组的犬尿氨酸生成减少 81％。在 TDO+肿瘤模型（U87MG 胶质母细胞瘤）中，犬尿氨酸生成减少 95％。 RG-70099 还具有较好的口服生物利用度和安全性。IDO1 和 TDO 在肺腺癌细胞上共表达，但是这两种酶也在不同类型的

肿瘤细胞上表达（Gyulveszi, G. et al. 107th Annu Meet Am Assoc Cancer Res (AACR) (April 16-20, New Orleans) 2016, Abst LB-0855）。

MAY 19, 2016
NOVEL, DUAL IDO1/TDO INHIBITOR RG-70099 IS ACTIVE IN VIVO

Roche has shown that their small-molecule dual inhibitor of indoleamine 2,3-dioxygenase 1 (IDO1) and tryptophan 2,3-dioxygenase (TDO), RG7-0099, inhibits both enzymes in cell-based assays (IC50 < 100 nM for both) and in vivo. Inhibition of IDO1/TDO suppresses the formation of kynurenine and leads to immunosuppressive effects. In an IDO1+ tumor model (B16F10 murine metastatic melanoma) kynurenine formation was reduced 81% with RG-70099. In a TDO+ tumor model (U87MG glioblastoma) kynurenine formation was reduced 95% with the agent. RG-70099 has also demonstrated oral bioavailability and safety. IDO1 and TDO are coexpressed on lung adenocarcinoma cells but the enzymes have also been detected on different types of tumor cells (Gyulveszi, G. et al. 107th Annu Meet Am Assoc Cancer Res (AACR) (April 16-20, New Orleans) 2016, Abst LB-085).

2016 年 5 月 18 日，韩国批准勃林格殷格翰的 OLMUNITIB

勃林格殷格翰公司报告 olmutinib 在韩国已批准用于治疗局部晚期或转移性表皮生长因子受体（EGFR）T790M 突变阳性的非小细胞肺癌，适用于早期使用 EGFR 酪氨酸激酶抑制剂治疗的患者。该化合物在韩国将由韩美药业分销（勃林格殷格翰公司新闻稿）。

MAY 18, 2016
BOEHRINGER INGELHEIM'S OLMUNITIB RECEIVES APPROVAL IN SOUTH KOREA

Boehringer Ingelheim reports that olmutinib has been approved in South Korea for the treatment of patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small-cell lung cancer, who had been previously treated with an EGFR tyrosine kinase inhibitor. The compound will be distributed in South Korea by Hanmi Pharmaceutical (Boehringer Ingelheim News Release).

2016 年 5 月 18 日，GVK BIOSCIENCES 公司报道开发选择性抑制剂 PI3KBETA

GVK Biosciences 公司的研究者已经开发了选择性的磷脂酰肌醇 4,5-二磷酸 3-激酶催化 β 亚基同型（PI3Kbeta）抑制剂，用于治疗 PTEN 缺失的肿瘤。一系列化合物的效力范围低至 2.5nM， PI3Kdelta 选择性>100 倍。化合物不降低胰岛素敏感性或 T 细胞增殖。先导化合物（GVK-01406）对 PI3Kdelta 表型的选择性得到改善，而未表现出激酶、安全问题、细胞色素 P450（CYP）或钾电压门控通道亚族 H 成员 2（hERG）的缺点。该化合物的进一步优化正在进行中。这些结果表明，该类化合物对通过 PTEN 突变或通过 PI3Kbeta 功能增益突变而产生耐药的肿瘤也可能具有一定的治疗潜力。此外，该类化合物还可能用于治疗罕见疾病，如错构瘤（Chowdhury, A.R. et al. 107th Annu Meet Am Assoc Cancer Res (AACR) (April 16-20, New Orleans) 2016, Abst 373）。

MAY 18, 2016

GVK BIOSCIENCES REPORTS DEVELOPMENT OF SELECTIVE PI3KBETA INHIBITORS

Investigators from GVK Biosciences have developed selective phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit beta isoform (PI3Kbeta) inhibitors reported to be useful for PTEN-deficient tumors. A chemical series with potency ranging as low as 2.5 nM for PI3Kbeta with >100-fold selectivity for PI3Kdelta was identified. Compounds did not reduce either insulin sensitivity or T-cell proliferation. The lead compound (GVK-01406) showed improved PI3Kdelta phenotypic selectivity. It showed no kinase panel, safety panel, cytochrome P450 (CYP) or potassium voltage-gated channel subfamily H member 2 (hERG) liabilities. Further optimization of the compound is ongoing. These findings suggest that these compounds have potential for tumors resistant to treatment via PTEN mutation or via PI3Kbeta gain-of-function mutation. In addition, they may be useful for the treatment of rare diseases such as hamartoma (Chowdhury, A.R. et al. 107th Annu Meet Am Assoc Cancer Res (AACR) (April 16-20, New Orleans) 2016, Abst 373).

2016 年 5 月 18 日，新 CDC7 抑制剂在体内具有广泛的抗肿瘤活性

美国礼来公司的科学家开发出一种强效的选择性细胞分裂周期 7 有关的蛋白激酶（CDC7）抑制剂，命名为 LY-3177833。该化合物的 CDC7/ DBF4 IC50=3.3 nM，pMCM2（S53）IC50=290 nM 和 IVTI TEC70=1.6 mcM。LY-3177833 的体内 MED= 5 mg/kg（口服）。该化合物可强烈影响染色体的动态。在小鼠异种移植模型，广泛的抗肿瘤活性与稳定的剂量/暴露依赖性体内靶抑制有关。此外，该化合物的临床前结果与非选择性 CDC7 抑制剂和细胞毒性剂不同，支持其采用连续给药方案进行临床研发（Ye, X.S. et al. 107th Annu Meet Am Assoc Cancer Res (AACR) (April 16-20, New Orleans) 2016, Abst）。该化合物在专利文献（WO2014143601）中进行描述。

MAY 18, 2016

NEW CDC7 INHIBITOR SHOWS BROAD ANTITUMOR ACTIVITY IN VIVO

Scientists from Eli Lilly and Company have developed a potent and selective cell division cycle 7-related protein kinase (CDC7) inhibitor, named LY-3177833. The compound had CDC7/DBF4 IC50 = 3.3 nM, pMCM2 (S53) IC50 = 290 nM and IVTI TEC70 = 1.6 mcM. LY-3177833 showed MED = 5 mg/kg (p.o.) in vivo. The compound strongly impacted chromosome dynamics. In mouse xenograft models, broad antitumor activity was associated with robust dose/exposure-dependent in vivo target inhibition. In addition, the preclinical profile of the compound was different from nonselective CDC7 inhibitors and cytotoxic agents, something that supports its clinical development with a continuos dosing regimen (Ye, X.S. et al. 107th Annu Meet Am Assoc Cancer Res (AACR) (April 16-20, New Orleans) 2016, Abst). The compound is described in the patent literature (WO 2014143601).

2016 年 5 月 6 日，SORRENTO 的抗 C-MET 抗体-药物缀合物进入 IND 研究

Sorrento Therapeutics 公司已经开发了一种抗体-药物缀合物（ADC），靶向肝细胞生长因子受体（c-Met）的单克隆抗体 STI-A0602 通过 C-lock（TM）缀合方法连接微管蛋白抑制剂或 DNA 损伤剂。该 ADC CBT-161 与裸抗体具有类似的结合亲和力和药代动力学特性。在多个非小细胞肺癌（NSCLC）异种移植物模型中，CBT-161 显著抑制肿瘤生长，有效剂量为 1 mg/kg，每周给药一次，连续 3 周给药，至少持续 3 周。疗效

与肿瘤表面 c-Met 表达相关。此外，在非小细胞肺癌异种移植模型中，CBT-161 和表皮生长因子受体抑制剂组合可显著抑制肿瘤生长，CBT-161 单剂量给药、厄洛替尼每日给药或西妥昔单抗的每周给药两次的药效持续超过 3 周。在动物中未见体重显著降低。CBT-161 治疗非小细胞肺癌和其他癌症的潜在效果促进了 IND 研究的进行（Li, L. et al. 107th Annu Meet Am Assoc Cancer Res (AACR) (April 16-20, New Orleans) 2016, Abst 3897）。

MAY 06, 2016
ANTI-C-MET ANTIBODY-DRUG CONJUGATE FROM SORRENTO TO ENTER IND-ENABLING STUDIES

Sorrento Therapeutics has developed antibody-drug conjugate (ADCs) consisting of a monoclonal antibody targeting hepatocyte growth factor receptor (c-Met), STI-A0602, conjugated to tubulin inhibitors or a DNA damaging agent through the C-lock(TM) conjugation method. The ADC CBT-161 showed a similar binding affinity and pharmacokinetic profile as the naked antibody. In multiple non-small cell lung cancer (NSCLC) xenograft models, CBT-161 significantly inhibited tumor growth, with the effects of a dose of 1 mg/kg given once a week for 3 weeks lasting at least 3 weeks after dosing. Efficacy was correlated with c-Met expression on the tumor surface. Also in NSCLC xenografts, the combination of CBT-161 and epidermal growth factor receptor inhibitors significantly inhibited tumor growth, with efficacy lasting over 3 weeks with a single CBT-161 dose and a daily dose of erlotinib or a twice-weekly dose of cetuximab. No significant weight loss was observed in the animals. The potential of CBT-161 in treating NSCLC and other cancer led to its selection for IND-enabling studies (Li, L. et al. 107th Annu Meet Am Assoc Cancer Res (AACR) (April 16-20, New Orleans) 2016, Abst 3897).

眼部疾病 EYE DISORDERS

2016 年 5 月 17 日，新型小分子给视网膜疾病的治疗带来希望

Clearside 生物医学与 Covance 实验室的研究人员已经开发出一种可结合抗血管内皮细胞生长因子受体（VEGFR）和抗血小板生长因子受体（PDGFR）的新颖小分子（CLS-011A）。化合物的药代动力学和眼组织分布情况在荷兰兔上进行了测试。为期 91 天的脉络膜给药结果表明，CLS-011A（4 mg /眼；100 mL/注射）耐受性良好并且未见毒性迹象。CLS-011A 仅在玻璃体、视网膜和巩膜/脉络膜-RPE（SCR）可进行量化。在注射 3 个月后，60％以上的该化合物仍残留在 SRC。消除半衰期为 102 天。总结可得，CLS-011A 在最小全身暴露下具有较好的耐受性（Kissner, J. et al. Annu Meet Assoc Res Vis Ophthalmol (ARVO) (May 1-5, Seattle) 2016, Abst 4002）。

MAY 17, 2016
NOVEL SMALL MOLECULE SHOWS PROMISE FOR THE TREATMENT OF RETINAL DISEASE

Investigators from Clearside Biomedical and Covance Laboratories have developed a novel small molecule with anti-vascular endothelial growth factor receptor (VEGFR) and anti-platelet-derived growth factor receptor (PDGFR) binding properties (CLS-011A). The pharmacokinetics and ocular tissue distribution of the compound were tested in Dutch Belted rabbits. Suprachoroidal administration of CLS-011A (at 4 mg/eye; 100 mL/injection) was well tolerated through day 91. There were no signs of

toxicity. CLS-011A was only quantifiable in the vitreous humor, retina and sclera/choroid-RPE (SCR). More than 60% of the compound remained in the SRC at 3 months after injection. The elimination half-life was 102 days. Taken together, these results show that CLS-011A was well tolerated with minimal systemic exposure (Kissner, J. et al. Annu Meet Assoc Res Vis Ophthalmol (ARVO) (May 1-5, Seattle) 2016, Abst 4002).

2016 年 5 月 11 日，OHR 制药开发可生物降解微球 AMD 治疗 OHR-3031

Ohr 制药的科学家报道 9 只雄性新西兰白兔使用可生物降解的微球给药系统给药抗血管生成化合物 OHR-3031 玻璃体制剂的研究。治疗开发用于年龄相关性的黄斑变性（AMD）。在第 0 天，双侧注射 2.6 mg OHR-3031（使用制剂 201412003）。注射后，化合物在眼组织中梯度可见（玻璃体>巩膜> =脉络膜>视网膜虹膜睫状体>房水）。持续给药后，玻璃体浓度恒定超过 42 日：浓度未见下降，因此，预计药物维持超过 42 天。视网膜和脉络膜可见治疗浓度的 OHR-3031 和活性代谢物，表明活性代谢物可在靶组织连续形成。值得注意的是，血浆浓度无法量化。药代动力学数据表明，玻璃体、视网膜、脉络膜、巩膜、眼房水、虹膜、睫状体和血浆中 OHR-3031 的 Cmax 值分别为 1,105,000、265,000，285,000、335,000、12,000、32300 和<2.5 ng/g；tmax 值分别为 14、3、28、28、1、0.17 天和 NC；AUC 值分别为 33,200,000、188000、2,190,000、258,00、220,000 ng.hg 和 NC。视网膜中代谢产物的 Cmax、tmax 和 AUC 数值分别为 2600 ng/g,、28 天和 1520 ng.hg。血浆 Cmax 为<1.0 ng/g。靶组织单次注射生物降解微粒制剂至少 6 周后，可见持续超治疗浓度的 OHR = 3031（Modi, M.W. et al. Annu Meet Assoc Res Vis Ophthalmol (ARVO) (May 1-5, Seattle) 2016, Abst 770）。

MAY 11, 2016
OHR PHARMACEUTICAL DEVELOPS BIODEGRADABLE MICROPARTICLE AMD TREATMENT OHR-3031

Ohr Pharmaceutical scientists have described a study of an intravitreal formulation of the antiangiogenic compound OHR-3031 delivered in a biodegradable microparticle drug delivery system to nine male New Zealand white rabbits. The treatment is being developed for age-related macular degeneration (AMD). Bilateral injections of 2.6 mg OHR-3031 (using formulation 201412003) were administered on day 0. Following injection an ocular tissue gradient of the compound was seen (vitreous > sclera >= choroid > retina iris-ciliary body > aqueous humor). Sustained delivery was seen, with constant vitreous concentrations seen over 42 days: concentrations were not seen to decline so it was expected that these were maintained beyond the 42 days. Therapeutic concentrations of OHR-3031 and active metabolite were seen in retina and choroid, which suggest the active metabolite is continuously formed in target tissues. It was noted that plasma concentrations were not quantifiable. Pharmacokinetic data showed Cmax values of OHR-3031 in vitreous humor, retina, choroid, sclera, aqueous humor, iris-ciliary body and plasma of 1,105,000, 265,000, 285,000, 335,000, 12,000, 32,300 and < 2.5 ng/g; tmax values were 14, 3, 28, 28, 1 , 0.17 day and NC, respectively; for AUC values results were 33, 200, 000, 188,000, 2,190,000, 258,00, 220,000 ng.hg and NC, respectively. For the metabolite the Cmax, tmax and AUC values for retina were 2600 ng/g, 28 days and 1520 ng.hg, respectively. Cmax for plasma was < 1.0 ng/g. Sustained supratherapeutic concentrations of OHR=3031 were achieved in the target tissue with a single injection of this biodegradable microparticle formulation for at least 6 weeks (Modi, M.W. et al. Annu Meet Assoc Res Vis Ophthalmol (ARVO) (May 1-5, Seattle) 2016, Abst 770).

2016 年 5 月 10 日，拜耳 ALK-1 抑制剂进行体内眼新血管形成试验

拜耳在西雅图举行的视觉与眼科研究协会年会（ARVO）上公布了关于 ALK-1 抑制剂 BAY-754 的数据。化合物体外研究结果显示，ALK-1 的生物化学 IC50 值为 1.6 nM，而细胞水平上 SMAD7 和 VEGFR-2 分别为 10 和 4400 nM。大鼠激光脉络膜新生血管形成（CNV）模型的体内结果表明，BAY-754 眼药水对血管渗漏呈现剂量依赖性抑制，剂量范围为 2.5 至 20 mg/mL，激光损伤后直接给药 23 天（早期研究方案）。该药对新血管形成也呈现一定的效果。在一项延迟方案中，手术后第 7 天给药，20 mg/ mL 的剂量下，药物对血管渗漏和新生血管面积（P <0.001）显著减少。在另一项延迟方案中，血管渗漏值按照激光损伤后 7 天基线值进行标准化，BAY-754 以 20 mg/mL/天剂量每日给药，给药 14 天，结果显示，单周给药后血管渗漏和新生血管面积减少。眼睛前部的药代动力学数据表明，Cmax.norm、AUC norm 和 t1/2 值分别为 4.7 kg/L、12 kg•h/L 和 2.3 h。眼睛后部的玻璃体/透镜和血浆的结果分别为 4.9、0.54 和 0.003 kg/L，17、1.2、0.014 kg•h/L 以及 6.8、3.4 和 1.7 h，（Boettger, M.K. et al. Annu Meet Assoc Res Vis Ophthalmol (ARVO) (May 1-5, Seattle) 2016, Abst 1115）。

BAY-754 已在专利文献（WO 2013004551）中进行描述。

MAY 10, 2016

BAYER'S ALK-1 INHIBITOR TESTED IN VIVO FOR OCULAR NEOVASCULARIZATION

Bayer presented data on BAY-754, an inhibitor of ALK-1, at the Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO) in Seattle.

In vitro the compound showed a biochemical IC50 value of 1.6 nM for ALK-1, compared to 10 and 4400 for cellular SMAD7 and VEGFR-2, respectively. In vivo results were presented showing that in a rat laser choroidal neovascularization (CNV) model there was dose-dependent inhibition of vascular leakage with BAY-754 eye drops for 23 days at doses ranging 2.5 to 20 mg/mL as administered directly after laser injury (early protocol). The effect was also seen on neovascularization. In a delayed protocol, in which treatment was administered 7 days after surgery, a 20 mg/mL dose showed significant reduction in vascular leakage and neovascular area (P < 0.001). In a different delayed protocol, in which vascular leakage values were normalized to baseline values 7 days after laser injury, BAY-754 still showed reduction in vascular leakage and neovascular areas after a single week of daily treatment at 20 mg/mL/day for 14 days. Pharmacokinetic data showed Cmax.norm, AUC norm and t1/2 values in the front of the eye to be 4.7 kg/L, 12 kg•h/L and 2.3 h, respectively. In the back of the eye, vitreous/lens and plasma results were 4.9, 0.54 and 0.003 kg/L, 17, 1.2 and 0.014 kg•h/L and 6.8, 3.4 and 1.7 h, respectively (Boettger, M.K. et al. Annu Meet Assoc Res Vis Ophthalmol (ARVO) (May 1-5, Seattle) 2016, Abst 1115).

BAY-754 has been described in the patent literature (WO 2013004551).

胃肠道疾病 GASTROINTESTINAL DISORDERS

2016 年 5 月 30 日，FDA 加速 OCALIVA 治疗原发性胆汁性胆管炎的审批

FDA 已经加速审批 Intercept 制药公司的 Ocaliva（商标）（奥贝胆酸），奥贝胆酸是一种法尼酯 X 受体（FXR）激动剂，与熊去氧（UDCA）联合用药后可治疗原发性胆汁性胆管炎（PBC），适用于 UDCA 反应不足或者 UDCA 单一疗法无法耐受的患者。加速批准是基于碱性磷酸酶（ALP）的减少因素。存活或疾病相关症状的改善尚未确定。该适应症的继续批准可能根据验证试验中临床获益的确定和描述。在 Intercept 的Ⅲ期临床试验 POISE 中，46％患者达到奥贝胆酸与熊去氧胆酸（UDCA 单药治疗不耐受的患者）联合用药的主要复合终点，相比之下，而熊去氧胆酸安慰剂组为 10％（ClinicalTrials.gov 标识符 NCT01473524）。瘙痒是 PBC 的常见症状，与疾病阶段或者结果无关，该不良反应是奥贝胆酸治疗患者中观察到的最常见副作用。但是在剂量滴定方案中（5 mg，每日一次增加至 10 mg，每日一次），奥贝胆酸治疗相关的皮肤瘙痒一般较少；滴定组的一名患者（1％）因搔痒而中止研究。在试验过程中观察到的其他副作用包括乏力、腹痛和不适、皮疹、口咽部疼痛、头晕、便秘、关节痛、甲状腺功能异常和湿疹。Ocaliva 预计将在 7-10 天内在美国上市，并通过专业药房网进行分销（Intercept 制药新闻稿）。

MAY 30, 2016
FDA GRANTS ACCELERATED APPROVAL TO OCALIVA FOR PRIMARY BILIARY CHOLANGITIS

The FDA has granted accelerated approval to Intercept Pharmaceuticals' Ocaliva(TM) (obeticholic acid), a farnesoid X receptor (FXR) agonist, for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA. Accelerated approval was granted based on a reduction in alkaline phosphatase (ALP). An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. In Intercept's phase III trial POISE, obeticholic acid administration in combination with UDCA (or as monotherapy in UDCA-intolerant patients) met the primary composite endpoint in 46% of patients in the titration group, as compared to 10% of those receiving placebo added to UDCA (ClinicalTrials.gov Identifier NCT01473524). Pruritus, a common symptom of PBC that is unrelated to disease stage or outcomes, was the most common side effect observed in obeticholic acid-treated patients. However, pruritus associated with obeticholic acid treatment was generally less in patients who were on the dose titration regimen (5 mg once-daily increasing to 10 mg once-daily); one patient (1%) in the titration group discontinued from the study due to pruritus. Additional side effects observed during the trial included fatigue, abdominal pain and discomfort, rash, oropharyngeal pain, dizziness, constipation, arthralgia, thyroid function abnormality and eczema. Ocaliva is expected to be available in the U.S. within 7-10 days and will be distributed through a specialty pharmacy network (Intercept Pharmaceuticals News Release).

血液和凝血障碍 HEMATOLOGICAL & BLOOD COAGULATION DISORDERS

2016 年 5 月 27 日，FDA 批准 CSL 的 LONOCTOCOG ALPHA

CSL Behring 的 Afstyla（R）（lonoctocog alpha：抗血友病因子[重组]，单链）已经获得 FDA 批准，长效重组因子 VIII 单链疗法用于治疗成人和儿童血友病。该疗法的适应症为常规预防或减少出血事件的频率；按需治疗和控制出血事件；围手术期出血处理。Afstyla 预计在美国今年夏初上市（CSL Behring 新闻稿）。

MAY 27, 2016
CSL GAINS FDA APPROVAL FOR LONOCTOCOG ALPHA

CSL Behring has gained FDA approval for Afstyla(R) (lonoctocog alfa; antihemophilic factor [recombinant], single chain), a long-lasting recombinant factor VIII singlechain therapy for adults and children with hemophilia A. The therapy is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes; for on-demand treatment and control of bleeding episodes; and for the perioperative management of bleeding. Afstyla is expected to be available in the U.S. early this summer (CSL Behring News Release).

感染 INFECTIONS

2016 年 5 月 25 日，FDA 批准 FLUCELVAX QUADRIVALENT

FDA 已经批准 Seqirus 的 Flucelvax Quadrivalent（TM），Flucelvax Quadrivalent 是首个细胞培养产生的四联灭活季节性流感疫苗，适用于 4 周岁及以上人群。疫苗有助于预防由世界卫生组织（WHO）和美国 FDA 在流感季节推荐的两种甲型流感病毒和两个 B 型流感病毒。Flucelvax Quadrivalent 在美国将于 2016 - 2017 年流感季节可用。Flucelvax Quadrivalent 是基于细胞的三价流感疫苗 Flucelvax 的新产品。由于这两种疫苗使用的工艺制造相同并具有重叠组成部分，Flucelvax 临床试验的临床有效性和安全性数据与 Flucelvax Quadrivalent 有关。在年龄为 18-49 岁成年人上进行的临床研究中，Flucelvax 已被证明对疫苗状株（83.8％）和所有流行的流感毒株（69.5％）有效。其四价配方也在年龄 18 岁以上成人（研究 1）和 4-17 岁儿童（研究 2）上证明对流感具有免疫原性。Flucelvax Quadrivalent 可对 B 型流感病毒株产生更强的抗体反应，该病毒株未包含在三价流感疫苗中。Flucelvax Quadrivalent 耐受性较好并且其安全性与疫苗对照相似。它还利用了前身 Flucelvax 超过 11000 人的安全数据库。去年七月，CSL 集团及其附属公司收购诺华公司的流感疫苗业务。美国以前由诺华公司拥有的流感疫苗业务已经整合至 CSL 的流感疫苗业务，目前名为 Seqirus（Seqirus 新闻稿）。

MAY 25, 2016

FDA APPROVES FLUCELVAX QUADRIVALENT

The FDA has approved Seqirus' Flucelvax Quadrivalent(TM), the first four-strain, cell culture-derived, inactivated seasonal influenza vaccine for people age 4 years and older. The vaccine helps protect against the two influenza A viruses and two B viruses recommended by the World Health Organization (WHO) and the FDA for the current influenza season. Flucelvax Quadrivalent will be available in the U.S. during the 2016-2017 influenza season. Flucelvax Quadrivalent is an evolution of Flucelvax, a cell-based trivalent influenza vaccine. Because both vaccines are manufactured using the same process and have overlapping compositions, the clinical efficacy and safety data from clinical trials with Flucelvax is relevant to Flucelvax Quadrivalent. In clinical studies of adults aged 18-49 years, Flucelvax has been shown to be efficacious against influenza caused by vaccine-like strains (83.8%) and by all circulating influenza strains (69.5%). Its quadrivalent formulation was also shown to be immunogenic against influenza in adults age 18 years and older (Study 1) and children aged 4-17 years (Study 2). Flucelvax Quadrivalent produced stronger antibody responses to the influenza B virus strain, which was not contained in the trivalent comparator flu vaccine, and is well tolerated with a safety profile similar to its comparator vaccines. It also leverages the safety database demonstrated by its predecessor Flucelvax in more than 11,000 people. In July last year, the CSL Group and its affiliates acquired the influenza vaccines business of Novartis in the U.S. The influenza vaccines business previously owned by Novartis has been integrated into CSL's influenza vaccine business and now operates as Seqirus (Seqirus News Release).

代谢性疾病 METABOLIC DISORDERS

2016 年 5 月 30 日，欧盟委员会批准 STRIMVELIS 治疗 ADA-SCID

欧盟委员会已经批准 Strimvelis（TM）（GSK-2696273），Strimvelis 是治疗腺苷脱氨酶缺乏症导致的严重联合免疫缺陷（ADA-SCID）的首个体外干细胞基因疗法。Strimvelis 为自体 CD34 +细胞转导以表达 ADA 的疗法，是世界各地监管部门批准的首个儿童纠正基因治疗，适用于治疗无合适人类白细胞抗原（HLA）相关干细胞供体的 ADA-SCID 患者。Strimvelis 在欧洲批准后，需要进行治疗的患者可在意大利 Ospedale San Raffaele (OSR)接受基因治疗。批准是基于 Strimvelis 治疗的 18 名儿童数据。Strimvelis 治疗 3 年后，关键性研究的所有 12 名儿童呈现 100％的存活率，92％为无干预生存率（即治疗后>3 个月无需酶替代治疗或造血干细胞移植）。Strimvelis 治疗并向 MAA 提供数据的所有 18 名儿童仍在世，随访平均时间约 7 年，首名患者在 13 年前接受该基因治疗。在评估人群（n = 17）范围内的无干预生存率为 82％。总体安全性研究结果与已进行的低剂量化疗和免疫治疗 ADA-SCID 儿童患者的预期结果一致。严重感染的显著减少已记录在案并且目前未见白血病事件。ADA-SCID 基因治疗最初由 OSR 和 Fondazione Telethon 通过 San Raffaele Telethon Institute for Gene Therapy (SR-Tiget)联合开发，并与葛兰素史克公司开展战略合作以及由 MOLMED 推进研发（葛兰素史克新闻稿）。

MAY 30, 2016

EUROPEAN COMMISSION APPROVES STRIMVELIS FOR ADA-SCID

The European Commission has approved Strimvelis(TM) (GSK-2696273), the first ex-vivo stem cell gene therapy to treat patients with severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID). Strimvelis, autologous CD34+ cells transduced to express ADA, is the first corrective gene therapy for children to be awarded regulatory approval anywhere in the world. It is indicated for the treatment of patients with ADA-SCID for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available. Following European approval, patients with the condition who are referred for treatment will be able to receive the gene therapy at Ospedale San Raffaele (OSR) in Italy. Approval was based on data collected from 18 children treated with Strimvelis. A 100% survival rate at 3 years post-treatment with Strimvelis was observed for all 12 children in the pivotal study, with 92% having intervention-free survival (i.e., did not require enzyme replacement therapy for a period of > 3 months post-treatment or hematopoietic stem cell transplantation). All 18 children treated with Strimvelis who contributed data to the MAA are alive today with a median follow-up duration of approximately 7 years, with the first of these having received this gene therapy over 13 years ago. Intervention-free survival within the evaluable population (n = 17) was 82%. Overall the safety findings are in line with those expected in children with ADA-SCID who have undergone treatment with low-dose chemotherapy and who are undergoing immune recovery. A significant reduction in severe infections has been documented and no leukemic events have been observed to date. The gene therapy for the treatment of ADA-SCID was originally developed by OSR and Fondazione Telethon, through their joint San Raffaele Telethon Institute for Gene Therapy (SR-Tiget), and was taken forward by GlaxoSmithKline through a strategic collaboration, which also saw it working with MolMed (GlaxoSmithKline News Release).

精神疾病 PSYCHIATRIC DISORDERS

2016 年 5 月 2 日，FDA 批准 NUPLAZID 治疗帕金森氏症相关的幻觉和妄想精神病

FDA 已经批准 ACADIA 制药公司的 Nuplazid（TM）（酒石酸匹莫范色林）治疗帕金森氏症相关的精神病幻觉和妄想。Nuplazid 是美国 FDA 批准的首个和唯一用于治疗该适应症的药物，预计将于下个月在美国正式上市。批准是基于关键性 III 期研究（研究-020）和其他支持性研究的数据。在研究-020 中，根据帕金森病阳性症状的评估标准（SAPS-PD），与安慰剂相比，pimavanserin 可显著减少精神病症状的发生频率和严重程度（ClinicalTrials.gov 标识符 NCT01174004）。患者可获益而不损害运动功能。在这项研究中，最常见的不良反应(5%或以上，为安慰剂发生率的两倍)为外周性水肿（pimavanserin 为 7%，安慰剂为 3%）和混乱状态（pimavanserin 为 6%，安慰剂为 3%）。Nuplazid 为 FDA 批准的唯一药物，优先靶向 5-HT 2A 受体，该受体在帕金森氏症等疾病治疗上具有重要作用。Pimavanserin 独特的药理作用使之成为一类新药，可选择性作用于血清素反向激动剂，而不是优先作用于 5-HT 2A 受体，也可避免作用于多巴胺等抗

精神病药的常见目标受体。Nuplazid 于 2014 年获得突破性指定疗法（见汤森路透药品新闻，2014 年 9 月 3 日）（ACADIA 制药新闻稿）。

MAY 02, 2016
FDA APPROVES NUPLAZID FOR HALLUCINATIONS AND DELUSIONS ASSOCIATED WITH PARKINSON'S DISEASE PSYCHOSIS

The FDA has approved ACADIA Pharmaceuticals' Nuplazid(TM) (pimavanserin tartrate) for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis. Nuplazid, the first and only medicine to be approved by the FDA for this indication, is expected to be launched commercially in the U.S. next month. Approval was based on data from a pivotal phase III study (Study-020) and other supportive studies. In Study-020, pimavanserin significantly reduced the frequency and severity of psychotic symptoms compared to placebo on the Scale for Assessment of Positive Symptoms - Parkinson's Disease (SAPS-PD) (ClinicalTrials.gov Identifier NCT01174004). This benefit was achieved without impairing motor function. The most common adverse reactions (5% or more and twice the rate of placebo) in this study were peripheral edema (7% pimavanserin vs. 3% placebo) and confusional state (6% pimavanserin vs. 3% placebo). Nuplazid is also the only drug approved by the FDA that preferentially targets 5-HT2A receptors, which are thought to play an important role in Parkinson's disease psychosis. The unique pharmacology of pimavanserin establishes a new class of drug, selective serotonin inverse agonists, by not only preferentially targeting 5-HT2A receptors but also avoiding activity at dopamine and other receptors commonly targeted by antipsychotics. Nuplazid was awarded breakthrough therapy designation for this condition in 2014 (see Thomson Reuters Drug News, September 3, 2014) (ACADIA Pharmaceuticals News Release).