药渡 Pharmacodia | 决策基于数据 Decision Making Based On Data

药渡数据库介绍

全球一流的药物研发情报系统

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~20,000
Drugs & Biologics

~200,000
Global Approvals

~280,000
Clinical Trials

~1,500
Targets

~6,500
Companies

~1,800
Indications

服务于药物研发的不同阶段

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同靶点竞争药物

同适应症竞争药物

药理、药代、毒理数据

动物实验模型

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数据解决方案：

https://data.pharmacodia.com

解决新药研发的6大难题

为药物研发提供数据支撑

药物结构	合成路线	试验数据	市场销售	药渡报告	专利信息
高清呈现	清晰明确	独家权威	真实可观	专业独家	精准详细

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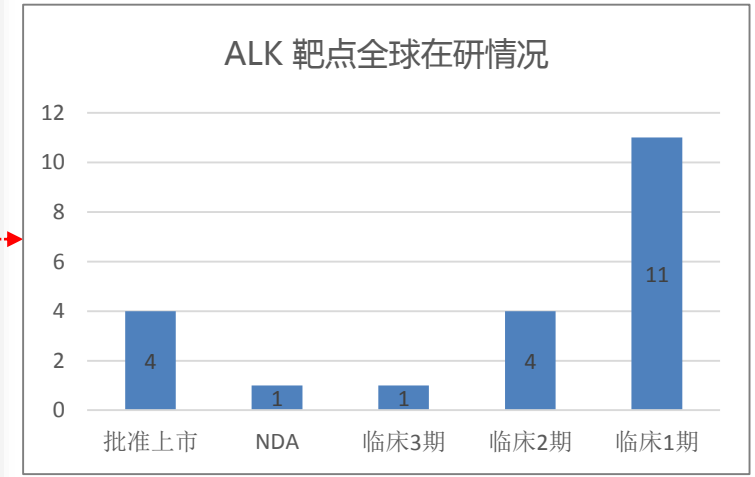
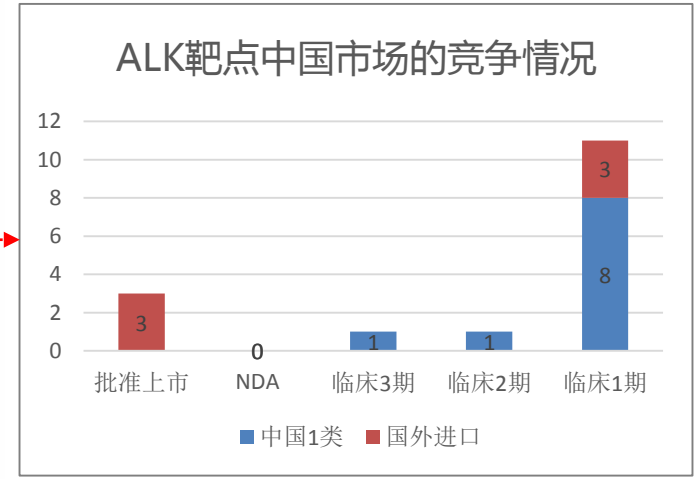
以ALK靶点为例基于药渡数据的产出结果

ALK 靶点药物 全球 市场竞争情况

【靶点】精准搜索：**ALK**



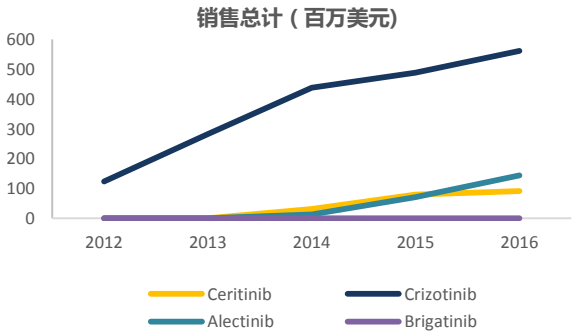
ALK 靶点药物在 中国 市场竞争情况



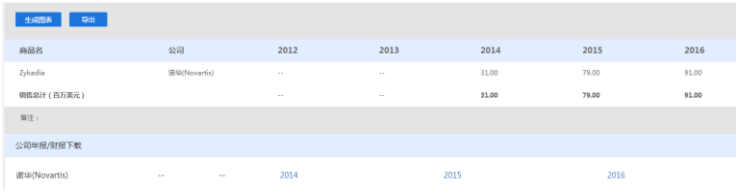
ALK靶点上市药物市场销售情况

ALK靶点上市药物销售额

全球销售额	销售总计（百万美元）				
药物/年份	**2012**	**2013**	**2014**	**2015**	**2016**
Ceritinib	-	-	31.00	79.00	91.00
Crizotinib	123.00	282.00	438.00	488.00	561.00
Alectinib	-	-	12.74	70.75	143.42
Brigatinib	-	-	-	-	-



企业年报



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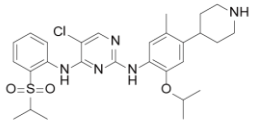
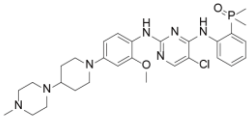
ALK靶点药物化学结构（已经公开的）

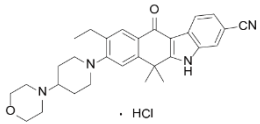
已上市药物：4个



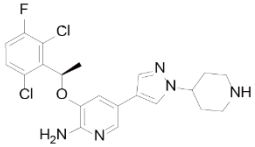
Ceritinib 2014批准
（诺华）



Brigatinib 2017批准
（Ariad）

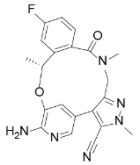


Alectinib Hydrochloride 2014批准
（中外）



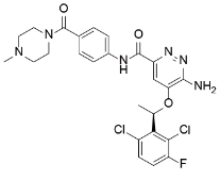
Crizotinib 2011批准
（辉瑞）

NDA：1个



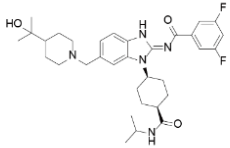
Lorlatinib
（辉瑞）

临床III期药物：1个

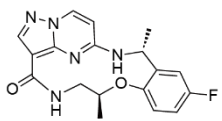


Ensartinib 中国1类
（贝达药业）

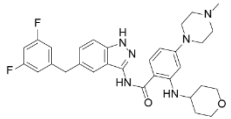
临床II期药物：3个



Belizatinib（终止）
（安进）



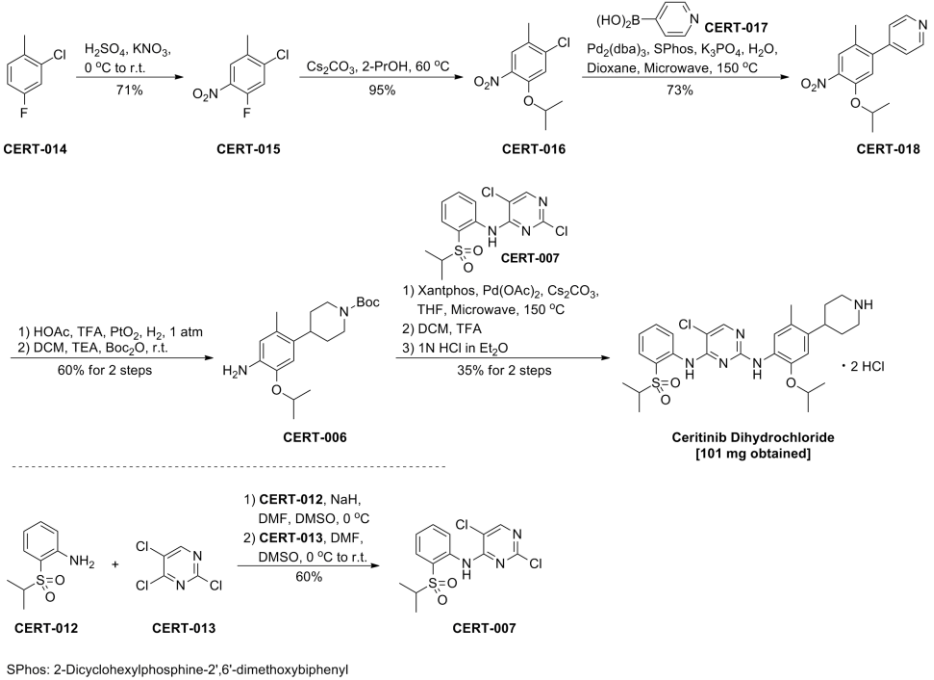
Ropotrectinib
(洛普替尼)



Entrectinib
（Nerviano Medical Sciences）

Ceritinib合成工艺路线

Route 1



SPhos: 2-Dicyclohexylphosphine-2',6'-dimethoxybiphenyl

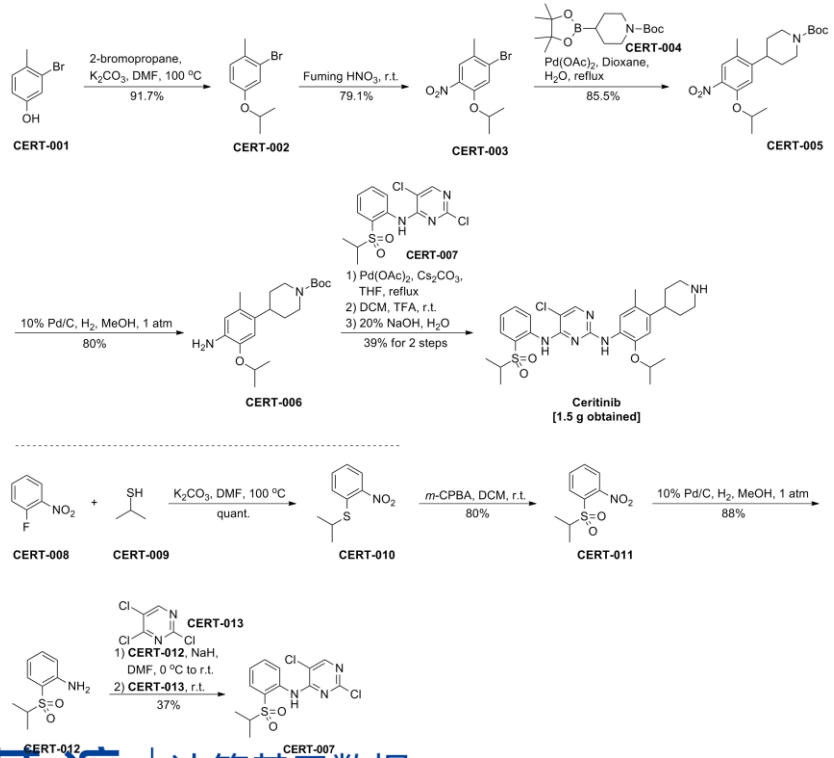
合成路线及中间体信息

步骤数：8	总产量：101 mg	总收率：6.2%	原研路线

中间体编号	CAS 号	供应商
CERT-014	452-73-3	MERCK
CERT-015	112108-73-3	
CERT-016	1032903-50-6	
CERT-017	1692-15-5	MERCK
CERT-006	1032903-63-1	
CERT-007	761440-16-8	
CERT-012	76697-50-2	
CERT-013	5750-76-5	MERCK

Ceritinib合成工艺路线

Route 2



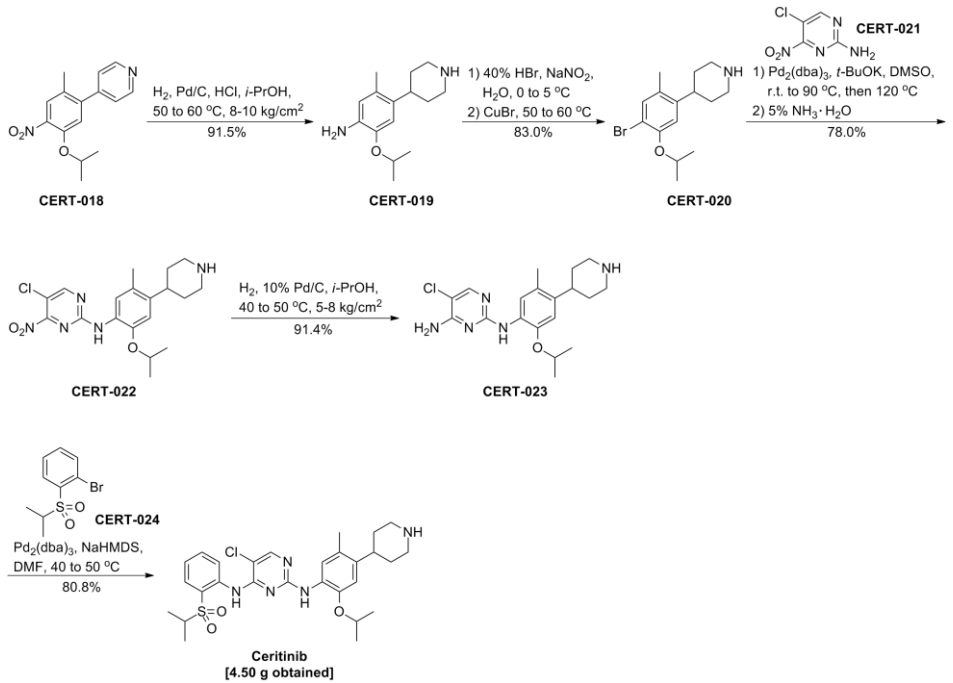
合成路线及中间体信息

步骤数：10	总产量：1.5g	总收率：4%	优化路线

中间体编号	CAS 号	供应商
CERT-001	60710-39-6	
CERT-002	1254062-68-4	
CERT-003	1202858-68-1	
CERT-004	1048970-17-7	MERCK
CERT-005	1663471-00-8	
CERT-006	1032903-63-1	
CERT-007	761440-16-8	
CERT-008	1493-27-2	MERCK
CERT-009	75-33-2	MERCK
CERT-010	70415-85-9	
CERT-011	70415-86-0	
CERT-012	76697-50-2	
CERT-013	5750-76-5	MERCK

Ceritinib合成工艺路线

Route 3



合成路线及中间体信息

步骤数：5	总产量：4.5 g	总收率：43.7%	优化路线

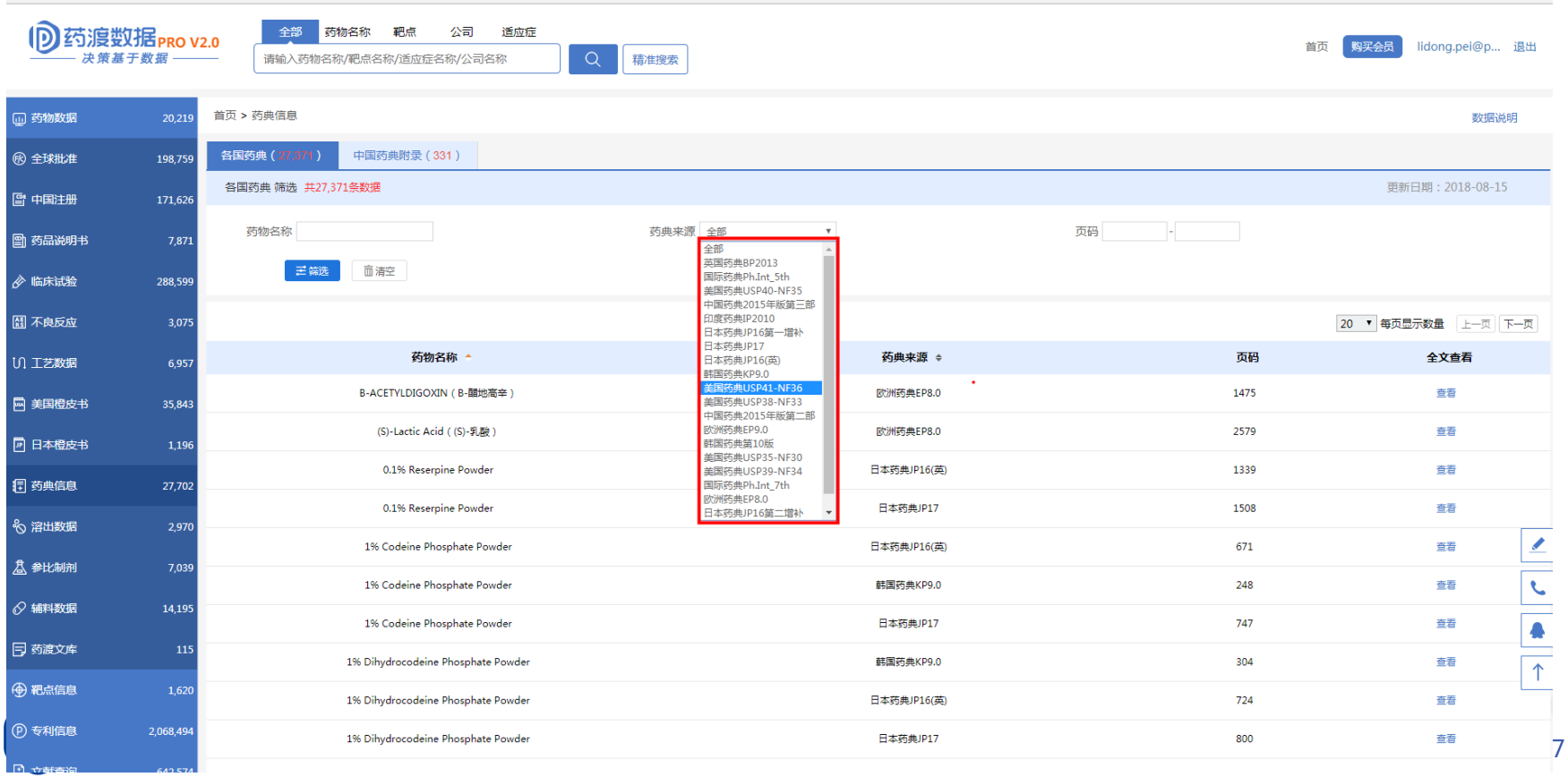
中间体编号	CAS 号	供应商
CERT-018	1032903-62-0	
CERT-019	1035230-24-0	
CERT-020	1622997-09-4	
CERT-021	1622997-13-0	
CERT-022	1622997-11-8	
CERT-023	1622997-12-9	
CERT-024	900174-43-8	

Ceritinib合成工艺路线

关键路线对比

路线名称	Route 1	Route 2	Route 3
路线总收率	5.0%	6.2%	43.7%
步骤数目	10	8	5
生产规模	1.5 g (Ceritinib)	101 mg (Ceritinib Dihydrochloride)	4.50 g (Ceritinib)
原料是否市售	Yes	Yes	Yes
是否使用高毒试剂	/	/	NaNO2 (CERT-020)
是否使用昂贵试剂	Pd(OAc)2 (CERT-005, Ceritinib)	Pd2(dba)3 (CERT-018); PtO2 (CERT-006); Pd(OAc)2 (Ceritinib Dihydrochloride)	Pd2(dba)3 (CERT-022, Ceritinib)
是否使用重金属试剂	Pd(OAc)2 (CERT-005, Ceritinib) Pd/C (CERT-012)	Pd2(dba)3 (CERT-018); PtO2 (CERT-006); Pd(OAc)2 (Ceritinib Dihydrochloride)	CuBr (CERT-020); Pd2(dba)3 (CERT-022, Ceritinib)
其他不适合工业化生产的试剂	/	/	/
其他不适合工业化生产的手段	/	Microwave (CERT-018, Ceritinib Dihydrochloride)	NaHMDS (Ceritinib)
是否使用柱层析纯化产物	/	CERT-015; CERT-016; CERT-018; CERT-006; Ceritinib Dihydrochloride	/
是否涉及手性拆分(重结晶or Chiral-HPLC)	/	/	/
重结晶	MeCN (Ceritinib)	MeCN (CERT-007)	EtOAc / n-Hexane (CERT-019); EtOH (CERT-022); EtOH (CERT-022); MeCN (Ceritinib)
是否需要高温(≥100℃)	100 ℃ (CERT-010)	150 ℃ (CERT-018, Ceritinib Dihydrochloride)	120 ℃ (CERT-022)
是否需要低温(＜0℃)	/	/	/
高压反应	/	/	8-10 kg/cm2 (CERT-019); 5-8 kg/cm2 (CERT-022)

质量标准 —— 各国最新药典


药渡数据 PRO V2.0
决策基于数据
全部 药物名称 靶点 公司 适应症
请输入药物名称/靶点名称/适应症名称/公司名称
精准搜索
首页 购买会员 lidong.pei@p... 退出
药物数据 20,219
全球批准 198,759
中国注册 171,626
药品说明书 7,871
临床试验 288,599
不良反应 3,075
工艺数据 6,957
美国橙皮书 35,843
日本橙皮书 1,196
药典信息 27,702
溶出数据 2,970
参比制剂 7,039
辅料数据 14,195
药渡文库 115
靶点信息 1,620
专利信息 2,068,494
首页 > 药典信息
数据说明
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中国药典附录（331）
各国药典 筛选 共27,371条数据
更新日期：2018-08-15
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药典来源 全部
全部
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国际药典Ph.Int_5th
美国药典USP40-NF35
中国药典2015年版第三部
印度药典IP2010
日本药典JP16第一增补
日本药典JP17
日本药典JP16(英)
韩国药典KP9.0
美国药典USP41-NF36
美国药典USP38-NF33
中国药典2015年版第二部
欧洲药典EP9.0
韩国药典第10版
美国药典USP35-NF30
美国药典USP39-NF34
国际药典Ph.Int_7th
欧洲药典EP8.0
日本药典JP16第二增补
页码
筛选
清空
20 每页显示数量
上一页
下一页
药物名称
药典来源
页码
全文查看
B-ACETYLDIGOXIN（B-醋地高辛） 欧洲药典EP8.0 1475 查看
(S)-Lactic Acid（(S)-乳酸） 欧洲药典EP8.0 2579 查看
0.1% Reserpine Powder 日本药典JP16(英) 1339 查看
0.1% Reserpine Powder 日本药典JP17 1508 查看
1% Codeine Phosphate Powder 日本药典JP16(英) 671 查看
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1% Dihydrocodeine Phosphate Powder 日本药典JP16(英) 724 查看
1% Dihydrocodeine Phosphate Powder 日本药典JP17 800 查看

Ceritinib临床前 PD

Mechanism of Action

As an ALK kinase inhibitor, ceritinib was approximately 50-fold more specific for ALK (IC_{50} = 0.15 nM) than insulin receptor (InsR, IC_{50} = 7 nM) and insulin-like growth factor 1 receptor (IGF-1R, IC_{50} = 8 nM), and other members of the insulin receptor superfamily.Ceritinib inhibited autophosphorylation of ALK, ALK-mediated phosphorylation of the down-stream signaling protein STAT3, and the proliferation of ALK-dependent cancer cells.

***In Vitro* Efficacy**

Phosphorylation of ceritinib in Karpas299 cells:

- ALK protein: IC_{50} = 46 nM.
- STAT3 protein: IC_{50} = 150 nM.

Anti-proliferative activity in tumor cells:

- Ba/F3 cells containing ALK fusion protein: IC_{50} = 26-56 nM.
- Ba/F3 cells containing EMLA-ALK mutation: IC_{50} = 37.6-940 nM.
- Ba/F3 cells containing other fusion proteins: IC_{50} = 180-400 nM.
- Human NSCLC cell lines: IC_{50} = 3.8-14.6 nM.
- Other human cell lines containing wild type and fusion ALK: IC_{50} = 24-45 nM.
- Cells from crizotinib-resistant patients with ALK mutation: IC_{50} = 25-230 nM.
- Cells from crizotinib-resistant patients without ALK mutation: IC_{50} = 2.6 nM.
- JFCR013-2 cells (from ceritinib-resistant patient): IC_{50} = 192 nM.

***In Vivo* Efficacy**

H2228 cells xenograft models:

- In SCID mouse:

v Tumor growth inhibition: 41% T/C at 3.125 mg/kg.
v Complete tumor regression at 25 mg/kg after 14 days treatment.

- In nude rat:

v Tumor growth inhibition 2% T/C at 10 mg/kg.
v Complete tumor regression at 25 mg/kg.

Crizotinib-resistant H2228 cells carrying the ALK-mutation xenograft model in SCID mouse:

- Non-ALK-mutation:

v Tumor growth inhibition: T/C% = -15.97% at 50 mg/kg and complete tumor regression at 100 mg/kg.

- I1171T ALK-mutation:

v Tumor growth inhibition T/C% = 44% at 25 mg/kg and complete tumor regression at 50 mg/kg.

- C1156Y ALK-mutation:

v Tumor growth inhibition T/C% = 11.7% at 50 mg/kg and complete tumor regression at 100 mg/kg.

Karpas299 cells xenograft models:

- In SCID mouse:

v Tumor growth inhibition T/C% = 18% at 12.5 mg/kg.
v Significant tumor regression at 25 mg/kg after 14 days treatment.

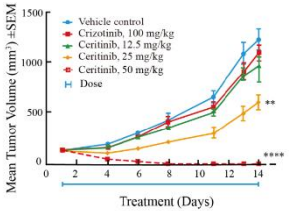
- In nude rat:

v Tumor growth inhibition T/C% = 30% at 12.5 mg/kg.
v Significant tumor regression at 25 mg/kg after 14 days treatment.

Table 3 *In Vitro* Inhibition of Ceritinib and Crizotinib on Human Protein Kinases[5,6]

Kinase	Type	IC_{50} (nM)		Kinase	Type	IC_{50} (nM)	
		Ceritinib	Crizotinib			Ceritinib	Crizotinib
EML4-ALK	Y[a]	31	160	EML4-ALK L1196M	Y	69	1460
EML4-ALK C1156Y	Y	160	440	EML4-ALK G1202R	Y	940	1370
EPK CE ALK (1066-1459)	Y	0.15	3	EPK ROCK2	S/T	450	2500
EPK CE IGF-1R (980-1369)	Y	8	400	EPK EPHB4 (566-987)	Y	2600	150
EPK CE INSR (871-1343)	Y	7	290	EPK LCK	Y	600	80
EPK AURORA_A	S/T[b]	110	60	EPK MET (956-1390)	Y	3200	8
EPK cABLT315	Y	130	6	EPK JAK2	Y	600	60
EPK CE AXL (515-885)	Y	180	13	EPK CE FGFR3 (411-K650E-806)	Y	430	1700
EPK CE RET (658-1072)	Y	400	2200				

The applicant evaluated the selectivity of ceritinib and crizotinib by testing its *in vitro* activity against 36 recombinant human protein kinases using the caliper mobility shift assay, table 3 showed the potency kinases for ceritinib (IC_{50} <500 nM) and crizotinib (IC_{50} < 200 nM). [a] Y: Tyrosine-specific protein kinases. [b] S/T: Serine/Threonine-specific protein kinases.



Study: Antitumor activities in crizotinib-resistant ALK I1171T mutant H2228 cells xenograft models.

Animal: SCID beige mouse (female, n = 6/group).

Model: Crizotinib-resistant H2228 NSCLC cells with ALK I1171T mutations were implanted s.c. into SCID mouse.

Administration: Ceritinib: 12.5, 25, or 50 mg/kg/day, p.o.; Crizotinib: 100 mg/kg/day, p.o.. Vehicle control: 0.5% MC/0.5% Tween 80.

Starting: Mice bearing established tumors (mean ~130 mm^3).

Test: Mean tumors volumes were ~130 mm^3.

Result: Treatment with 50 mg/kg ceritinib resulted in complete tumor regression after 14 days of treatment. ($^{**}P \leq 0.05$; $^{****}P \leq 0.0001$).

Figure B Effect of Ceritinib on Crizotinib-Resistant with ALK I1171T Mutations Human H2228 NSCLC Xenografts in SCID Mouse Models[5]

Ceritinib临床前 PK

Absorption

Exhibited non-linear pharmacokinetics in humans after oral administrations. The increase in AUC appeared to be greater than dose-proportional in the dose range of 50 to 750 mg ceritinib.
Had moderate bioavailability in rats (48.3%), but high in mice (54.6%) and monkeys (58%).
Was observed slowly (T_{max} = 3.98-15 h) in humans, mice (7 h), rats (12 h) and monkeys (13-18.3 h).
Showed a half-life ranging between 19.4-40.6 h in humans, much longer than those in rats (13.2 h) and monkeys (12.1-16 h), after oral administrations.
Had moderate system clearance in mice (26.6 mL/min/kg), rats (1.49 L/h/kg), but low to moderate in monkeys (0.366-0.78 L/h/kg), in contrast to liver blood flow, after intravenous administrations. The Cl/F in humans was 44.5-147 L/h after oral administration.
Exhibited an extensive distribution in mice, rats and monkeys, with the apparent volumes of distribution at 9.7, 19.9 and 6.53-13.5 L/kg, after intravenous administrations. The V_z/F in humans was 1880-6230 L after oral administration.
Was classified as a low passive permeability compound.

Efficacy Distribution

Exhibited high plasma protein binding in rats (97.9%-98.4%), dogs (98.3%-98.8%), monkeys (94.4%-95.2%) and humans (96.7%-98.8%). Note that ceritinib was mainly bound to HSA.
The binding to RBC was 56.9%-58.6% in humans, indicating the drug was distributed more to blood cells than to plasma.

Metabolism

Could be slightly metabolized in rat, monkey and human hepatocytes.
CYP3A was the major metabolizing enzyme, with CYP2C19, 1A2, 2C8, 2D6 and 2C9 involved in the metabolism of ceritinib.
The metabolism of ceritinib included mono-oxygenation, *O*-dealkylation, *S*-dealkylation, and *N*-formylation of ceritinib. Secondary biotransformation pathways involving the primary biotransformation products included glucuronidation, dehydrogenation and the addition of a thiol group to *O*-dealkylation ceritinib.
Overall, the parent drug was the most abundant component in plasma in humans. Eleven metabolites were found in the human plasma, each at levels ≤2.3% of the total drug-related AUC.
Five of these eleven metabolites were not detected in rat or monkey plasma. The remaining three unique human metabolites detected at low levels in plasma included M46.6 (1.7%), M48.8 (1.7%), and M52.0 (2%).

Excretion

Was predominantly eliminated in feces in rats, monkeys and humans, with the parent drug as the significant component in rat, monkey and human feces.
About 24.3% and 65.4% of ceritinib were recovered via biliary excretion in bile duct-cannulated (BDC) rats after oral and intravenous administration, respectively.

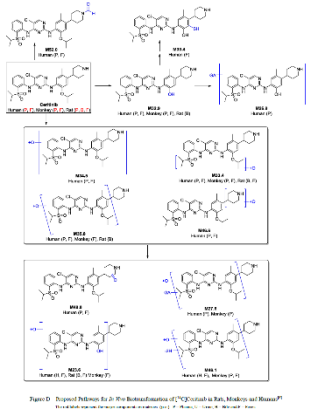
DDI

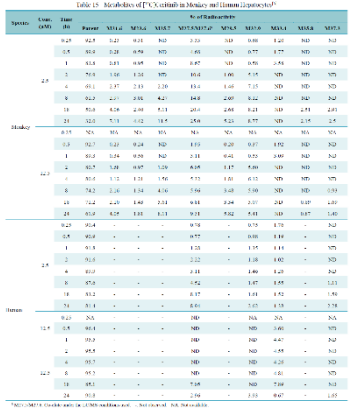
Ceritinib was a strong inhibitor of CYP3A4/5 (IC_{50} = 0.2 μM), moderate of CYP2A6 (IC_{50} = 5 μM), CYP2B6 (IC_{50} = 2 μM), CYP2C8 (IC_{50} = 2 μM, amodiaquine as substrate) and CYP2C9 (IC_{50} = 2 μM), but weak of CYP2C19 (IC_{50} = 70 μM), CYP2D6 (IC_{50} = 20 μM), CYP2E1 (IC_{50} = 30 μM) and CYP2C8 (IC_{50} = 25 μM, paclitaxel as substrate).
Ceritinib had no induction for CYP1A2, CYP2B6 or CYP2C9 mRNA/activities, but had concentration-dependent induction for CYP3A4 mRNA.

Table 7 *In Vivo* Pharmacokinetic Parameters of Ceritinib in Mice, Rats and Monkeys after Single Intravenous and Oral Doses of Certinib[5]

Species	Route	Dose (mg/kg)	T_{max} (h)	C_{max} (ng/mL)	AUC_{inf} (ng·h/mL)	AUC_{last} (ng·h/mL)	$T_{1/2}$ (h)	Cl or Cl/F (L/h/kg)	V_z (L/kg)	F (%)
Balb/c mouse (male)	i.v.	5	-	1753 ± 509 nM	5634 ± 441 nM·h	5366 ± 379 nM·h[a]	6.2 ± 0.5	26.6 ± 2.2 mL/min/kg	9.7 ± 0.6	-
	p.o.	20	7.0 ± 0.0	695 ± 31 nM	12296 ± 981 nM·h	10334 ± 963 nM·h[a]	-	-	-	54.6
Han Wistar rat (male)	i.v.	10	0.083 ± 0	975 ± 139	6950 ± 1470	6890 ± 1510	9.7 ± 1.2	1.49 ± 0.342	19.9 ± 0.49	-
	p.o.	25	12.0	363	8390	8330	13.2	NA	NA	48.3
Cynomolgus monkey (male)	i.v.	5	0.083	1410	6530	6450	29	0.78	13.5	-
	i.v.	10	0.083[b]	3190	27800	27400	14.5	0.366	6.53	-
	p.o.	30	18.3 ± 9.8	881 ± 12	35800 ± 3460	35500 ± 3520	12.1 ± 2.0	-	-	43.0
	p.o.	60	13 ± 9.2	947 ± 140	45300 ± 8860	45100 ± 8840	16 ± 0.61	-	-	58

[a] $AUC_{0\text{-}24}$. [b] First sampling time point.





Ceritinib临床前 TOX

Single-Dose Toxicity

Acute toxicity in monkeys: No lethality up to 250 mg/kg.

Repeated-Dose Toxicity

A series of oral repeat-dose toxicology studies were conducted with ceritinib in rats (up to 13 weeks) and monkeys (up to 13 weeks).

- By the 13-week studies, the NOAEL was 10 mg/kg/day in monkeys, but not established in rats.
- Target organ of species-concordance: Pancreas (atrophy and inflammation in both species), biliopancreatic and bile ducts (inflammation and dilatation in rats), GI tract and liver (elevation of liver enzymes in both species).

Safety Pharmacology

Both *in vitro* and *in vivo* safety pharmacology studies were conducted to assess the effects on cardiovascular, behavioral, general physiological, and respiratory function.

- Ceritinib was unlikely to interfere with vital functions of the respiratory and central nervous systems.
- It demonstrated sort of potential for causing QT prolongation (modest): Ceritinib inhibited the hERG current at all tested concentrations, with an estimated IC_{50} of 0.4 μM. The effects was confirmed by the monkey study at a single dose of 100 mg/kg.[6]

Genotoxicity

The micronucleus test in TK6 cells was considered positive, but no mutagenicity or clastogenicity was confirmed in other *in vitro* and *in vivo* genotoxicity studies with ceritinib. Therefore, genotoxic risk was not expected in humans.

Reproductive and Developmental Toxicity

No fertility, early embryonic development, pre-/postnatal or juvenile toxicology studies have been conducted, in line with ICH S9 for the advanced cancer indication.

Embryo-fetal development in rats and rabbits:

- No feototoxicity and teratotoxicity after dosing with ceritinib organogenesis. However, maternal plasma exposure was less than that at the clinical RHD of 50 mg.[6]

Carcinogenicity

No carcinogenicity studies were performed and are generally required for the cancer indication according to ICH S9.

Table 24 Genotoxicity Studies of Ceritinib[5,6]

Assay	Species/System	Metabolism Activity	Dose	Finding
In vitro reverse mutation assay (Ames)	*S. typhimurium*: TA97, TA98, TA100, TA1535, TA102	±S9	0-1000 μg/plate	Negative.
In vitro miniscreen Ames test	*S. typhimurium*: TA98, TA100	±S9	30-1000 μg/well	Negative[a].
In vitro chromosome aberration assay	HPBL	3 or 17 h: ±S9 20 h: -S9	0-16 μg/mL	Negative.
			0-22 μg/mL	Incomplete[b].
In vitro micronucleus assay	HPBL	3 or 20 h: -S9 3 h: +S9	0-18.6 μg/mL	Negative.
	TK6 cell	3 or 20 h: -S9 3 h: +S9	0-33 μg/mL	Positive for 20 h treatment[c].
In vivo micronucleus assay	Rat bone marrow	-	0-2000 mg/kg, p.o.× 2	Negative.

[a] Positive and negative control results were not provided for comparative purposes. [b] 2nd assay cancelled (-S9: 20h; +S9: 3 + 17h) by the Applicant. [c] Increased number of cells containing micronuclei after 20-h treatment –S9, but not after 3 h treatment ± S9.

Table 25 Reproductive and Developmental Toxicology Studies of Ceritinib by Oral (Gavage) Administration[5]

Study	Species	Dose (mg/kg/day)	Endpoint	Finding
Embryonic-fetal development	Wistar rat	0, 1, 10, 50	Maternal	Depressed gestational body weight at MD and HD.
			Fetal developmental	No embryo lethality or fetotoxicity.
	NZW rabbit	0, 2, 10, 25	Maternal	Mildly depressed gestational body weight and food consumption at HD.
			Fetal developmental	No significant embryo lethality or fetotoxicity. Significant incomplete ossification of sternebrae at all doses. Incidence of visceral anomalies in a small number of fetuses.

Vehicle: 0.5% (w/v) MC in RODI water.

Ceritinib及ALK靶点最新文献报道

首页 > 文献查询 > 关键词： ceritinib ×

文献筛选　共528条数据

首页 > 文献查询 > 关键词： ALK ×

文献筛选　共31,956条数据

注：靶点文献搜索含ALK字段的单词均显示

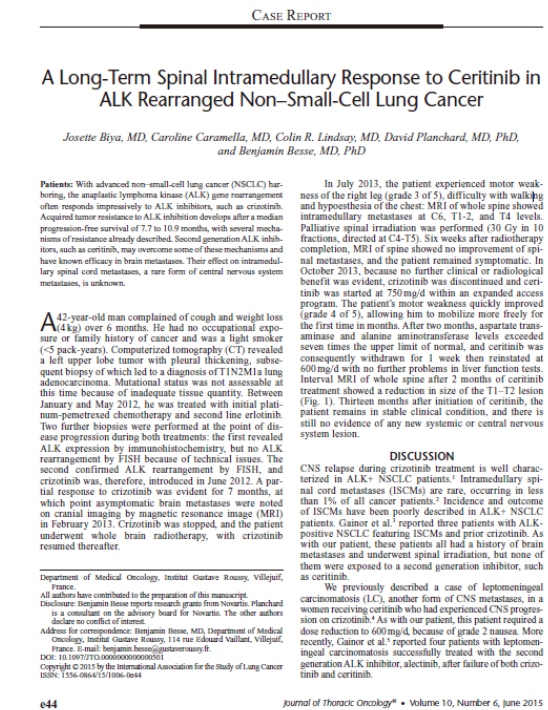
已下载文献示例：

1、A Long-Term Spinal Intramedullary Response to Ceritinib in ALK Rearranged Non-Small-Cell Lung Cancer

2、Treatment of ALK-Rearranged Non-Small Cell Lung Cancer: Recent Progress and Future Directions

Adobe Acrobat 文档

双击图标打开文件



CASE REPORT

A Long-Term Spinal Intramedullary Response to Ceritinib in ALK Rearranged Non–Small-Cell Lung Cancer

Josette Biya, MD, Caroline Caramella, MD, Colin R. Lindsay, MD, David Planchard, MD, PhD, and Benjamin Besse, MD, PhD

Patients: With advanced non–small-cell lung cancer (NSCLC) harboring, the anaplastic lymphoma kinase (ALK) gene rearrangement often responds impressively to ALK inhibitors, such as crizotinib. Acquired tumor resistance to ALK inhibition develops after a median progression-free survival of 7.7 to 10.9 months, with several mechanisms of resistance already described. Second generation ALK inhibitors, such as ceritinib, may overcome some of these mechanisms and have known efficacy in brain metastases. Their effect on intramedullary spinal cord metastases, a rare form of central nervous system metastases, is unknown.

A 42-year-old man complained of cough and weight loss (4 kg) over 6 months. He had no occupational exposure or family history of cancer and was a light smoker (<5 pack-years). Computerized tomography (CT) revealed a left upper lobe tumor with pleural thickening, subsequent biopsy of which led to a diagnosis of T1N2M1a lung adenocarcinoma. Mutational status was not assessable at this time because of inadequate tissue quantity. Between January and May 2012, he was treated with initial platinum-pemetrexed chemotherapy and second line erlotinib. Two further biopsies were performed at the point of disease progression during both treatments: the first revealed ALK expression by immunohistochemistry, but no ALK rearrangement by FISH because of technical issues. The second confirmed ALK rearrangement by FISH, and crizotinib was, therefore, introduced in June 2012. A partial response to crizotinib was evident for 7 months, at which point asymptomatic brain metastases were noted on cranial imaging by magnetic resonance image (MRI) in February 2013. Crizotinib was stopped, and the patient underwent whole brain radiotherapy, with crizotinib resumed thereafter.

In July 2013, the patient experienced motor weakness of the right leg (grade 3 of 5), difficulty with walking and hypoesthesia of the chest. MRI of whole spine showed intramedullary metastases at C6, T1-2, and T4 levels. Palliative spinal irradiation was performed (30 Gy in 10 fractions, directed at C4-T5). Six weeks after radiotherapy completion, MRI of spine showed no improvement of spinal metastases, and the patient remained symptomatic. In October 2013, because no further clinical or radiological benefit was evident, crizotinib was discontinued and ceritinib was started at 750 mg/d within an expanded access program. The patient's motor weakness quickly improved (grade 4 of 5), allowing him to mobilize more freely for the first time in months. After two months, aspartate transaminase and alanine aminotransferase levels exceeded seven times the upper limit of normal, and ceritinib was consequently withdrawn for 1 week then reinstated at 600 mg/d with no further problems in liver function tests. Interval MRI of whole spine after 2 months of ceritinib treatment showed a reduction in size of the T1–T2 lesion (Fig. 1). Thirteen months after initiation of ceritinib, the patient remains in stable clinical condition, and there is still no evidence of any new systemic or central nervous system lesion.

DISCUSSION

CNS relapse during crizotinib treatment is well characterized in ALK+ NSCLC patients.[1] Intramedullary spinal cord metastases (ISCMs) are rare, occurring in less than 1% of all cancer patients.[2] Incidence and outcome of ISCMs have been poorly described in ALK+ NSCLC patients. Gainor et al.[3] reported three patients with ALK-positive NSCLC featuring ISCMs and prior crizotinib. As with our patient, these patients all had a history of brain metastases and underwent spinal irradiation, but none of them were exposed to a second generation inhibitor, such as ceritinib.

We previously described a case of leptomeningeal carcinomatosis (LC), another form of CNS metastases, in a women receiving ceritinib who had experienced CNS progression on crizotinib.[4] As with our patient, this patient required a dose reduction to 600 mg/d, because of grade 2 nausea. More recently, Gainor et al.[5] reported four patients with leptomeningeal carcinomatosis successfully treated with the second generation ALK inhibitor, alectinib, after failure of both crizotinib and ceritinib.

Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France.
All authors have contributed to the preparation of this manuscript.
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Address for correspondence: Benjamin Besse, MD, Department of Medical Oncology, Institut Gustave Roussy, 114 rue Edouard Vaillant, Villejuif, France. E-mail: benjamin.besse@gustaveroussy.fr.
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DOI 10.1007/s40265-015-0415-9

LEADING ARTICLE

Treatment of *ALK*-Rearranged Non-Small Cell Lung Cancer: Recent Progress and Future Directions

Laird Cameron[1] · Benjamin Solomon[1,2]

Published online: 16 June 2015

Abstract Rearrangements of the anaplastic lymphoma kinase (*ALK*) gene originally discovered nearly 20 years ago in the context of anaplastic large cell lymphoma were identified as oncogenic drivers in a subset of non-small cell lung cancers (NSCLCs) in 2007. These *ALK* gene rearrangements are present in 3–5 % of NSCLC patients, typically younger, never or light smokers with adenocarcinomas. Crizotinib is a first-in-class ALK tyrosine kinase inhibitor with significant activity in *ALK*-positive NSCLC that received accelerated US Food and Drug Administration approval for treatment of *ALK*-positive NSCLC in 2011, just 4 years after identification of *ALK* rearrangements in this setting. Subsequently, two phase III trials have shown crizotinib to have a tolerable toxicity profile and to be superior to standard chemotherapy for the first- or second-line treatment of advanced *ALK*-positive lung cancer and numerous countries have approved its use. Despite initial responses, acquired resistance to crizotinib invariably leads to disease progression. Mechanisms of resistance have been described to include *ALK* tyrosine kinase mutations, activation of bypass signalling pathways and pharmacokinetic failure of crizotinib. Several next-generation ALK inhibitors, including ceritinib and alectinib, are in clinical development and show efficacy in both the crizotinib naïve and crizotinib refractory settings. Ongoing clinical trials will identify the optimal strategy to incorporate these novel agents in the treatment of patients with *ALK*-positive NSCLC.

Key Points

Anaplastic lymphoma kinase (*ALK*) gene rearrangements are found in 3–5 % of non-small cell lung cancer patients, typically, although not exclusively, in younger, never or light smokers with adenocarcinoma.

ALK-positive lung cancers are sensitive to crizotinib, an ALK tyrosine kinase inhibitor (TKI) that has been shown in two phase III studies to improve response rates, progression-free survival, lung cancer-related symptoms and quality of life in comparison to chemotherapy, in both the first- and second-line setting.

Disease progression on crizotinib reflects the development of acquired resistance, which can manifest through ALK pathway-dependent (*ALK* tyrosine kinase domain mutations or amplification) or ALK-independent mechanisms (activation of bypass signalling pathways) as well as pharmacokinetic failure (e.g. central nervous system metastases).

Multiple novel ALK TKIs are in clinical development that show increased potency against ALK, including *ALK* mutations that confer resistance to crizotinib, and demonstrate clinical efficacy in the crizotinib-resistant setting.

This article is part of the topical collection on Lung Cancer.

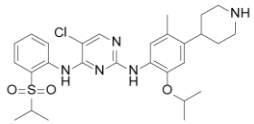
✉ Benjamin Solomon
ben.solomon@petermac.org

[1] Department of Medical Oncology, Peter MacCallum Cancer Centre, St Andrew's Place, East Melbourne, VIC 3002, Australia

[2] Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, VIC, Australia

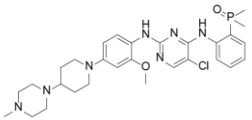
ALK靶点药物中国专利到期情况

已上市药物：4个



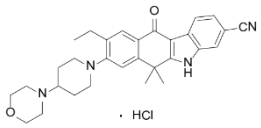
Ceritinib 2014批准
（诺华）

专利到期日（CN）：2027-11-20



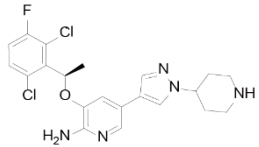
Brigatinib 2017批准
（Ariad）

专利到期日（CN）：2029-05-21



Alectinib Hydrochloride 2014批准
（中外）

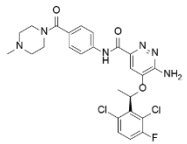
专利到期日（CN）：2030-06-09



Crizotinib 2011批准
（辉瑞）

专利到期日（CN）：2025-08-15

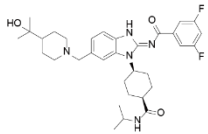
临床III期药物：1个



Ensartinib
（贝达药业）中国1类

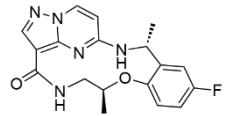
专利到期日（CN）：2029-06-18

临床II期药物：3个



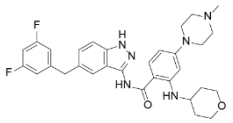
TSR-011
（安进）

专利到期日（CN）：2035-01-23



TPX-0005

专利到期日（CN）：2035-01-23

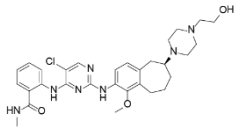


Entrectinib
（Nerviano Medical Sciences）

专利到期日（CN）：2028-07-08

ALK靶点药物中国专利到期情况

临床I期药物：10个



CEP-37440
（梯瓦）

专利到期日（CN）：2033-03-06

中国1类 Undisclosed

Frizotinib (氟卓替尼)
临床一期 进行中
适 应 症：非小细胞肺癌
靶　　点：ALK
研发公司：江苏豪森医药
研发代码：
其他介绍：

结构未公开，无专利信息

中国1类 Undisclosed

TQ-B3101
临床一期 进行中
适 应 症：胃癌，非小细胞肺癌，淋巴瘤
靶　　点：ALK
研发公司：正大天晴，东南大学
研发代码：TQ-B3101
其他介绍：

结构未公开，无专利信息

中国1类 Undisclosed

ZL-2302
临床一期 进行中
适 应 症：间变性淋巴瘤激酶（ALK）阳性非小细胞肺癌
靶　　点：ALK
研发公司：赛诺菲，再鼎医药
研发代码：ZL-2302
其他介绍：

结构未公开，无专利信息

中国1类 Undisclosed

PLB-1003
临床一期 进行中
适 应 症：非小细胞肺癌
靶　　点：ALK
研发公司：北京浦润奥
研发代码：PLB-1003
其他介绍：

结构未公开，无专利信息

中国1类 Undisclosed

EBI-215
临床一期 进行中
适 应 症：非小细胞肺癌
靶　　点：ALK
研发公司：Eternity Bioscience
研发代码：EBI-215; EBI-600215
其他介绍：

结构未公开，无专利信息

中国1类 Undisclosed

TQ-B3139
临床一期 进行中
适 应 症：成神经细胞瘤，弥漫大B细胞淋巴瘤，肺癌
靶　　点：ALK
研发公司：正大天晴，赛林泰
研发代码：TQ-B3139
其他介绍：

结构未公开，无专利信息

中国1类 Undisclosed

CT-707
临床一期 进行中
适 应 症：非小细胞肺癌
靶　　点：IGF1R，ALK，FAK1
研发公司：赛林泰
研发代码：CT-707
其他介绍：

结构未公开，无专利信息

中国1类 Undisclosed

APG-1252
临床一期 进行中
适 应 症：非小细胞肺癌
靶　　点：BCL2，ALK
研发公司：亚盛医药
研发代码：APG-1252
其他介绍：

结构未公开，无专利信息

中国1类 Undisclosed

Foritinib Succinate (丁二酸复瑞替尼)
临床一期 进行中
适 应 症：肺癌
靶　　点：ALK
研发公司：重庆复创医药，中国科学院上海药物研究所
研发代码：SAF-189s
其他介绍：

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衍生物（盐型、酯型）专利
新用途专利　制剂专利

每个药物都链接了研发及生产资源

药渡 Pharmacodia | 决策基于数据 Decision Making Based On Data

目录

大数据的三要素

药渡数据如何做到对医药大数据的深入洞察？

药渡数据

核心数据

~ 20,000 药物+生物制品
~ 2,000,000 全球批准
~ 280,000 临床试验
~ 1,500 靶点
~ 6,500 研发公司
~ 1,800 适应症

行业专家

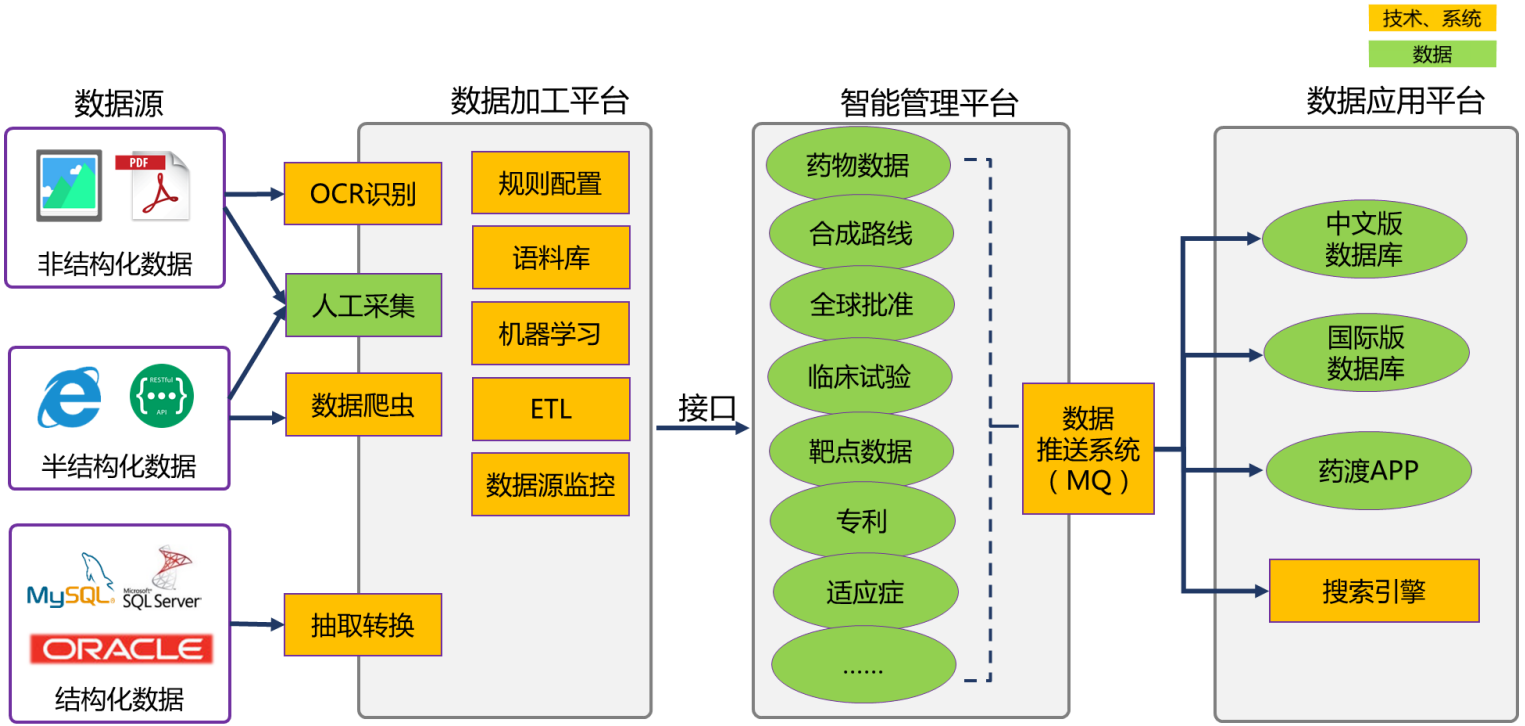
“千人计划”专家
上百人的数据整理团队
博士比例：30%
药学部门最低学历：硕士

算法（逻辑）

标准化体系：
药物名称、靶点、适应症、公司

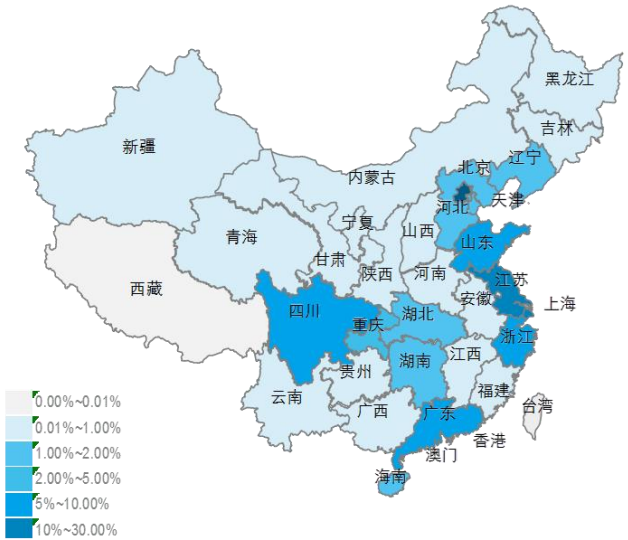
用户需求导向：
解决创新药、仿制药立项问题

数据更新及时、准确


技术、系统
数据
数据源
数据加工平台
智能管理平台
数据应用平台
非结构化数据
半结构化数据
结构化数据
OCR识别
人工采集
数据爬虫
抽取转换
规则配置
语料库
机器学习
ETL
数据源监控
接口
药物数据
合成路线
全球批准
临床试验
靶点数据
专利
适应症
.....
数据
推送系统
（MQ）
中文版
数据库
国际版
数据库
药渡APP
搜索引擎

行业地位：国内前100家药企都在用“药渡”

- 国内用户已基本覆盖全国，主要分布在北京、上海、江苏、广东等制药业发达的省市。
- 主要包括制药企业，高校科研院所，投资机构，政府机构等



国家食品药品监督管理总局药品审评中心
CENTER FOR DRUG EVALUATION, CFDA

振东制药 ZHENDONG PHARMACEUTICAL

科伦药业 KELUN PHARMACEUTICAL

正大天晴 CHIA TAI TIANQING

天士力控股集团

圣和药业 SANHOME

以岭药业 YILING PHARMACEUTICAL

京新药业

凯瑞康宁 XW Laboratories

和径医药 JING MEDICINE

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HG 领晟医药 LINK HEALTH GROUP

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中国科学院上海药物研究所 SIMM

天津药物研究院 Tianjin Institute of pharmaceutical research

投资机构版：5大问题，解决方案-药渡VC

以新药项目为中心，围绕全球新药搭建的药企、投资机构、生物医药园区的资源循环

Data is Powerful，Data is Beautiful！

联系人：丁红霞|　　手机：13810721280

地址：北京市海淀区上地五街7号昊海大厦105室

邮编：100193

电话：86-10-82826195

邮箱：sheryl.ding@pharmacodia.com