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preclinical
development of
crizotinib 6. Clinical
data 7. Acquired
resistance to crizotinib
8. Other diseases with
ALK activation 9.
Conclusion 10. Expert
opinion Drug Discovery
Case History The
preclinical profile of
crizotinib for the
treatment of non-small-
cell lung cancer and
other neoplastic
disorders

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disorders Article ·

Literature Review in
Expert Opinion on Drug
Discovery 8(9) · June ...

The preclinical profile of crizotinib

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The preclinical profile of crizotinib for the treatment of non-small-cell lung cancer and other neoplastic disorders. Roskoski R Jr. Roskoski R Jr. Expert Opin Drug Discov. 2013

Sep;8(9):1165-79. doi: 10.1517/17460441.2013.813015. Epub 2013 Jun 28. Expert ...

Preclinical Rationale
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**for Combination of
Crizotinib With ...**
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The combination of crizotinib with MMC appeared synergistic regardless of MSI or BRCA2 status. Using an in-vivo CRC xenograft model we found reduced tumor growth with combined crizotinib and MMC therapy ($p = 0.0088$). Our preclinical results support clinical testing of the combination of MMC and crizotinib in

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advanced CRC.

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for combination of
crizotinib with ...**

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Crizotinib. Crizotinib is a potent and specific small-molecule inhibitor of both ALK and c-MET tyrosine kinases. It is a 3-benzyl oxy-2-aminopyridine series inhibitor that

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was derived from a first-generation c-MET inhibitor, PHA-66752, using the cocrystal structure of this inhibitor with c-MET to further optimize active-site binding (). In a screen for kinase selectivity, crizotinib inhibited ...

Crizotinib for ALK- Rearranged Non-Small Cell Lung Cancer ...

DGIdb, The Drug Gene
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Interaction Database,
is a research resource
that can be used to
search candidate
genes or drugs against
the known and
potentially druggable
genome.

DGIdb - CRIZOTINIB Drug Record

small cell lung cancer
(NSCLC). Crizotinib is
an oral, ATP-
competitive small
molecule receptor
tyrosine kinase (RTK)

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inhibitor of ALK (including ALK oncogenic fusion variants) and of the c-Met/Hepatocyte growth factor receptor (c-Met/HGFR). Pre-clinical studies suggest activity against other targets such as RON.

202570Orig1s000 - Food and Drug Administration

The safety profile of crizotinib in this study was similar to that

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reported previously.

22,24 Treatment-
related adverse events
(as determined by the
investigators) ... In
preclinical studies, ...

**Crizotinib in
ROS1-Rearranged
Non-Small-Cell Lung
Cancer ...**

Suppliers, 15 Gangwal
Chemicals, 9 Roquette,
8 Sigachi Industries, 7
Microlex e.U, 4
Capsugel, 4 ACG
Worldwide, 3 Anhui

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Pharmaceutical
Excipients Co.,Ltd, 3
Kerry, 2 DFE Pharma, 2
Shanghai Shenmei
Pharmaceutical
Technology Co., Ltd, 2
Vasa Pharmachem, 1
BASF, 1 Finar, 1 Ideal
Cures Pvt Ltd, 1
Qualicaps, 1 Seppic

**Crizotinib API
Manufacturers |
Suppliers | Exporters**

...

Preclinical Activity of

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Crizotinib 0 10 30 100
300 1000 Crizotinib
(nM) pROS1 ROS1
pSTAT3 STAT3 pAKT
AKT pERK ERK Actin
Ryohei Katayama,
unpublished Crizotinib
(BaF3 cells) 0 50 100 0
1 10 100 1000 10000
CD74-ROS1 EML4-ALK
v1 Ba/F3 parental
(IL-3+) Concentration
(nM) rol) IC50 (nM) 4.2
20.8 839.3

**Crizotinib in Patients
with ROS1+ Non-**

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Preclinical work demonstrated that ensartinib was ... Phase II results showed promise in patients with crizotinib-resistant disease, and also carried a different toxicity profile than currently ...

Another ALK Drug Tops Crizotinib in First-Line NSCLC ...

D, Inhibitory profile of crizotinib (0, 0.01, 0.1,

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and 1 μ M). Results are displayed in bar columns with standard deviation (SD) in relation to cell viability. Treatment with dimethyl sulfoxide (indicated as a concentration of 0) was used as the standard for 100% cell viability in each cell line. * indicates a $p < 0.05$ (see text for exact p values) for erlotinib and crizotinib-treated cells.

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Preclinical Rationale
for Use of the
Clinically Available**

...

Crizotinib Synergizes
with Chemotherapy in
Preclinical Models of
Neuroblastoma

Kateryna Krytska 1 ,
Hannah T. Ryles 1 ,
Renata Sano 1 , Pichai
Raman 2 , Nicole R.
Infarinato 1 ,

**Crizotinib
Synergizes with**

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**Chemotherapy in
Preclinical ...**
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Brigatinib is a highly potent and selective ALK inhibitor. These findings provide the molecular basis for the promising activity being observed in ALK + , crizotinib-resistant patients with NSCLC being treated with brigatinib in clinical trials. Clin Cancer Res; 22(22); 5527-38.

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**The Potent ALK
Inhibitor Brigatinib
(AP26113)
Overcomes ...**

In preclinical studies, ceritinib is unable to overcome most ROS1 resistance mutations, including ROS1 G2032R. It has more severe side effects than crizotinib for many patients.

Ceritinib is approved for first line treatment of ALK+ metastatic non-small cell lung cancer

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in the USA and several
other countries.
The Treatment Of

**Drugs to Treat
ROS1+ Cancer - The
ROS1ders**

Ensartinib showed a significant improvement in progression-free survival (PFS) over crizotinib (Xalkori) with a favorable safety profile in patients with ALK-positive non-small cell lung cancer ...

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Significantly Prolongs PFS Over Crizotinib in ...

6. Preclinical
Pharmacology of
Crizotinib. Crizotinib is
a free base, anhydrous
crystalline compound
with a pH dependent
solubility profile.
Crizotinib showed
moderate metabolic
stability in human
hepatocytes, moderate
to high plasma protein
binding (92-97%) in

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human and animal
species, and low to
moderate permeability
in the Caco-2 cell
assay.

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