Come si produce il farmaco target del gene mutato

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Treating AML

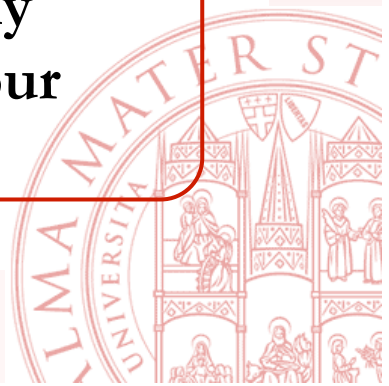
Cytotoxic agents

Small molecule targeted therapies

Monoclonal antibodies

- Major treatment is chemoterapy
- Sometimes followed by stem cell transplant
- Surgery and radiation therapy may also be used sometimes

The standard therapy for most subtypes of newly diagnosed AML was unchanged since the past four decades



Standard treatment AML

Remission induction therapy

intensive doses of chemotherapy drugs, aiming to achieve remission by destroying malignant cells

- idarubicin
- thioguanine
- daunorubicin, or mitoxantrone plus cytarabine

Post-remission therapy

high doses of chemotherapy, aiming to destroy any leukemic cells that may still linger

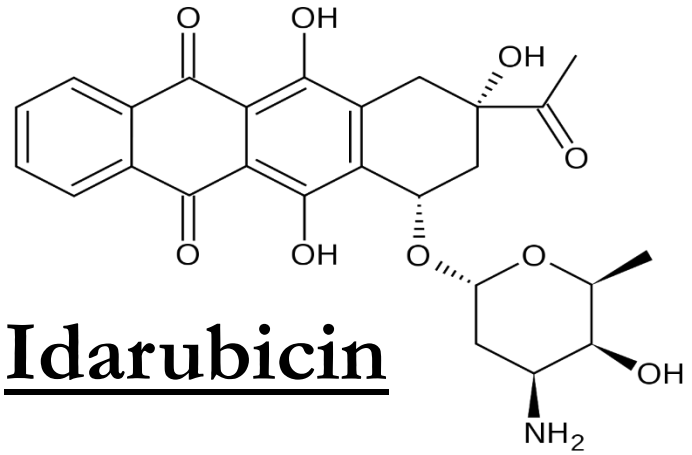
- mitoxantrone
- cyclophosphamide
- idarubicin
- daunorubicin
- etoposide
- cytarabine

Most patients with newly diagnosed AML are offered the combination of standard-dose cytarabine with an anthracycline (daunorubicin or idarubicin), the so-called 7 + 3 regimen.

Kadia, Annals of Oncology 2016 27: 770–778.

Treating AML

- ✓ The last Food and Drug Administration (FDA)-approved drug for AML (1990)
- ✓ oral administration
- ✓ in combination with cytarabine induces remission

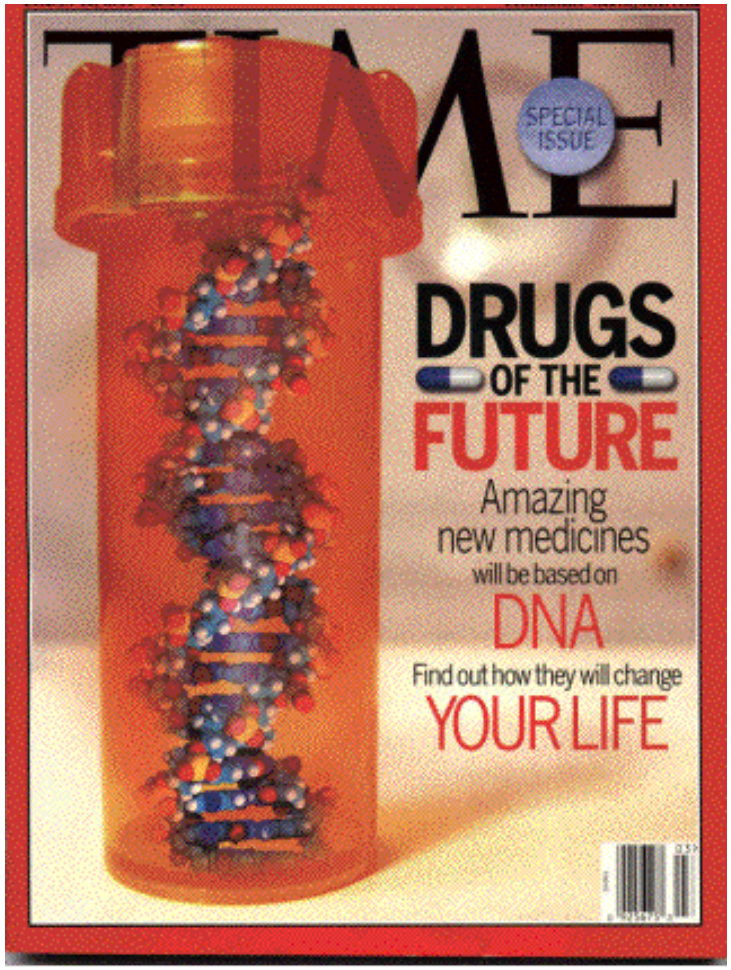


Idarubicin

- ✓ Bone marrow depression
- ✓ Cumulative, dose related, irreversible cardiotoxicity
- ✓ Total, severe alopecia

Clear need for newer therapies and a more personalized (targeted) approach

Personalized Medicine



The ability to offer

- ✓ **The Right Drug**
- ✓ **To The Right Patient**
- ✓ **For The Right Disease**
- ✓ **At The Right Time**
- ✓ **With The Right Dosage**

New approaches in the treatment of AML

Cytotoxic agents

Small molecule targeted therapies

Monoclonal antibodies

Inhibitors of Plk kinases

Isocitrate dehydrogenase inhibitors

FLT3 inhibitors

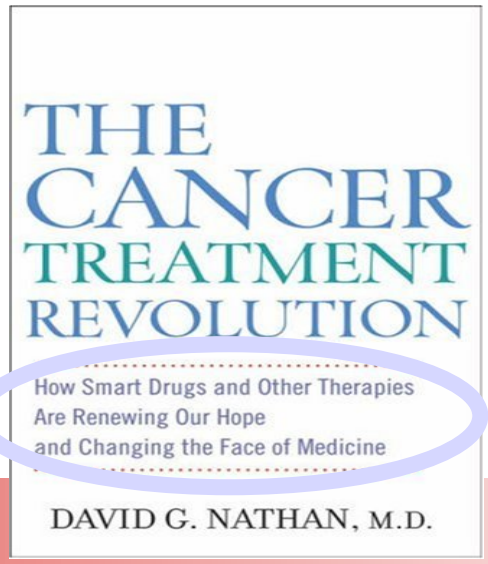
Activators of the intrinsic or mitochondrial pathway of apoptosis

Kinases inhibitors

Before Kinases as Drug Targets, cancer chemotherapy was not targeted at all!

Cytotoxic agents were directed to targets not specific to tumor cells (i.e. idarubicin and DNA)

BROAD SPECTRUM OF SIDE EFFECTS

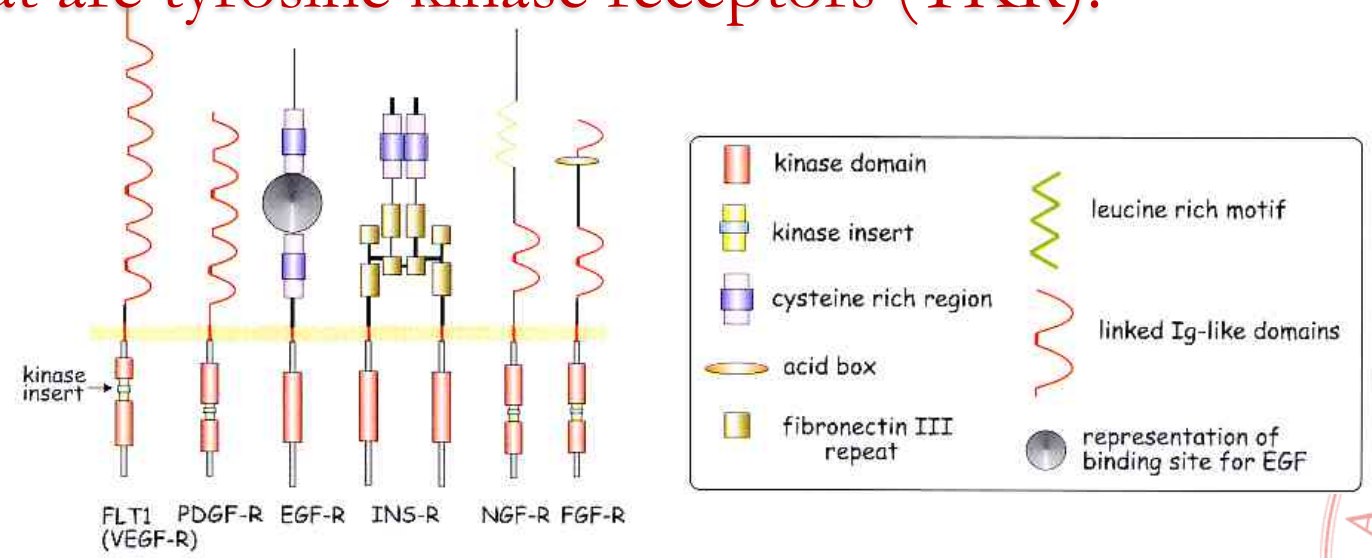


Targeting kinase FLT3 for the treatment of AML

FLT3 is a receptor tyrosine kinase with important roles in hematopoietic stem/ progenitor cell survival and proliferation

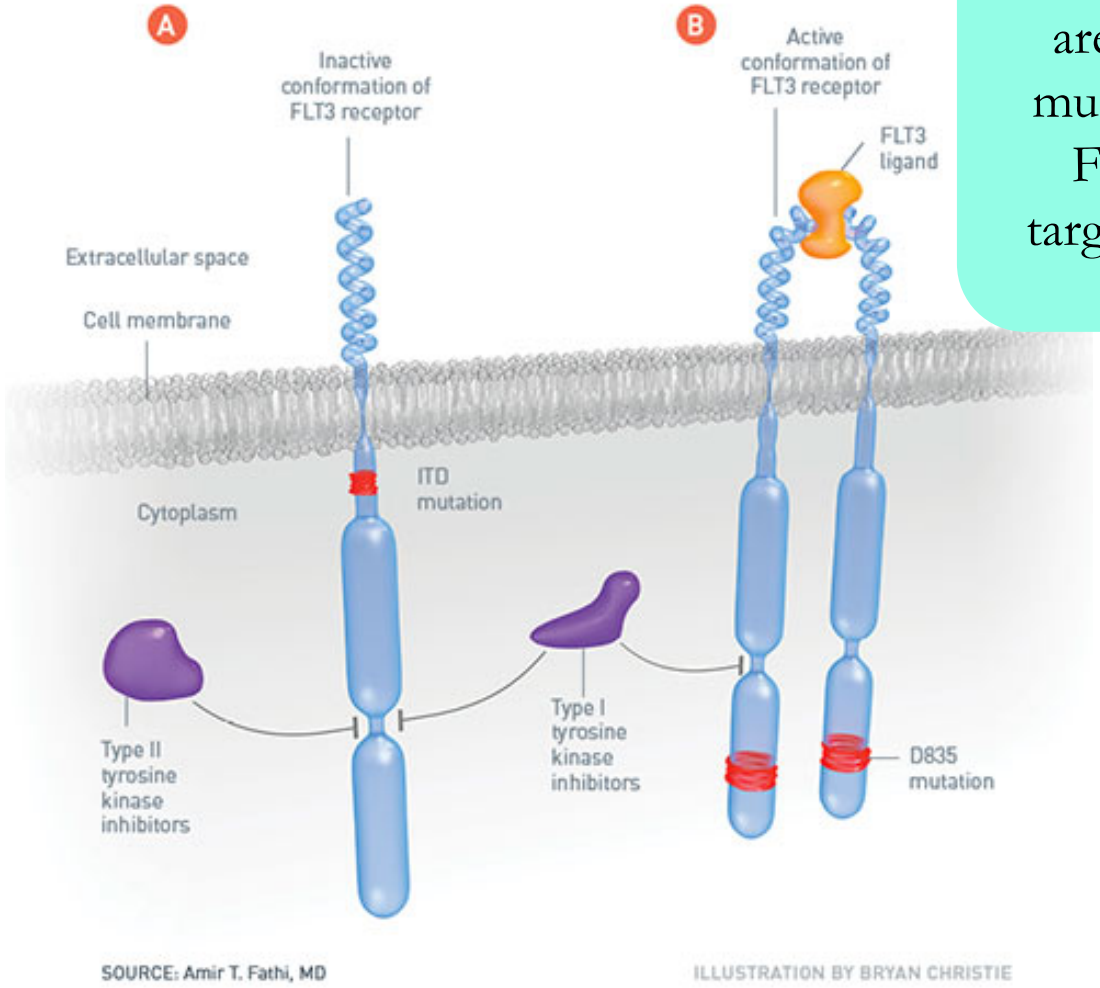
In AML, FLT3 is expressed at very high levels (~ 90% of patients)

What are tyrosine kinase receptors (TKR)?



Targeting FLT3 for the treatment of AML

The activation of FLT3 receptor

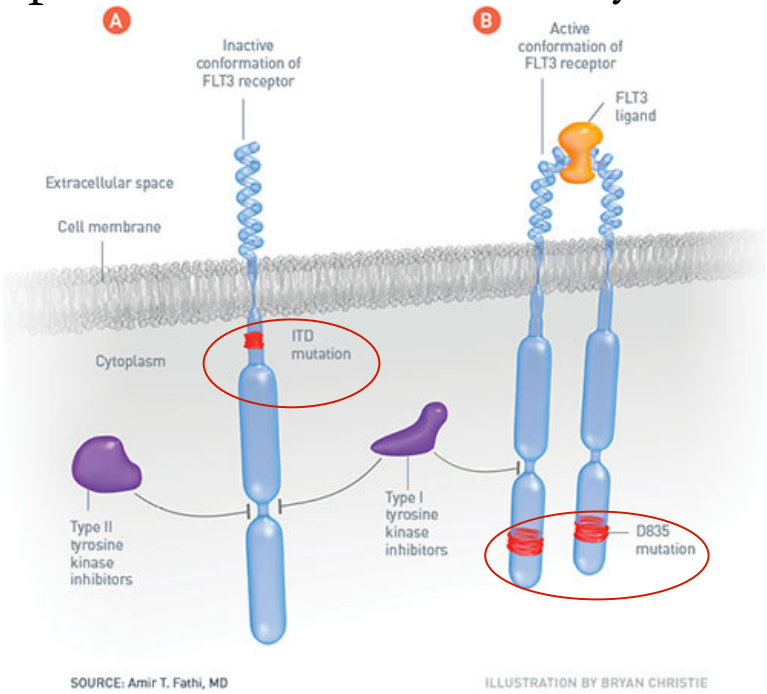


FLT3 activating mutations are the most common mutations in AML, thus FLT3 is a promising target for therapeutics in leukemia

Targeting FLT3 for the treatment of AML

30% of patients with AML carry FLT3 mutations

Internal tandem duplication (ITD) of the juxtamembrane domain



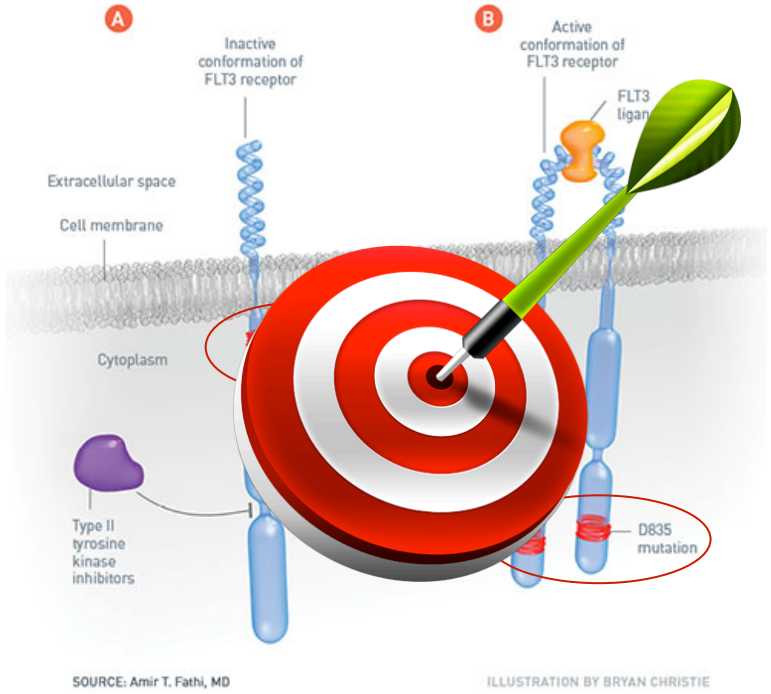
Point mutations in the tyrosine kinase domain

The kinase is always activated

→ PI3 kinase/AKT pathway
RAS/MAP kinase pathway
STAT 5 phosphorylation pathway

→ **Promotion of growth and survival of AML blasts**

Targeting FLT3 for the treatment of AML

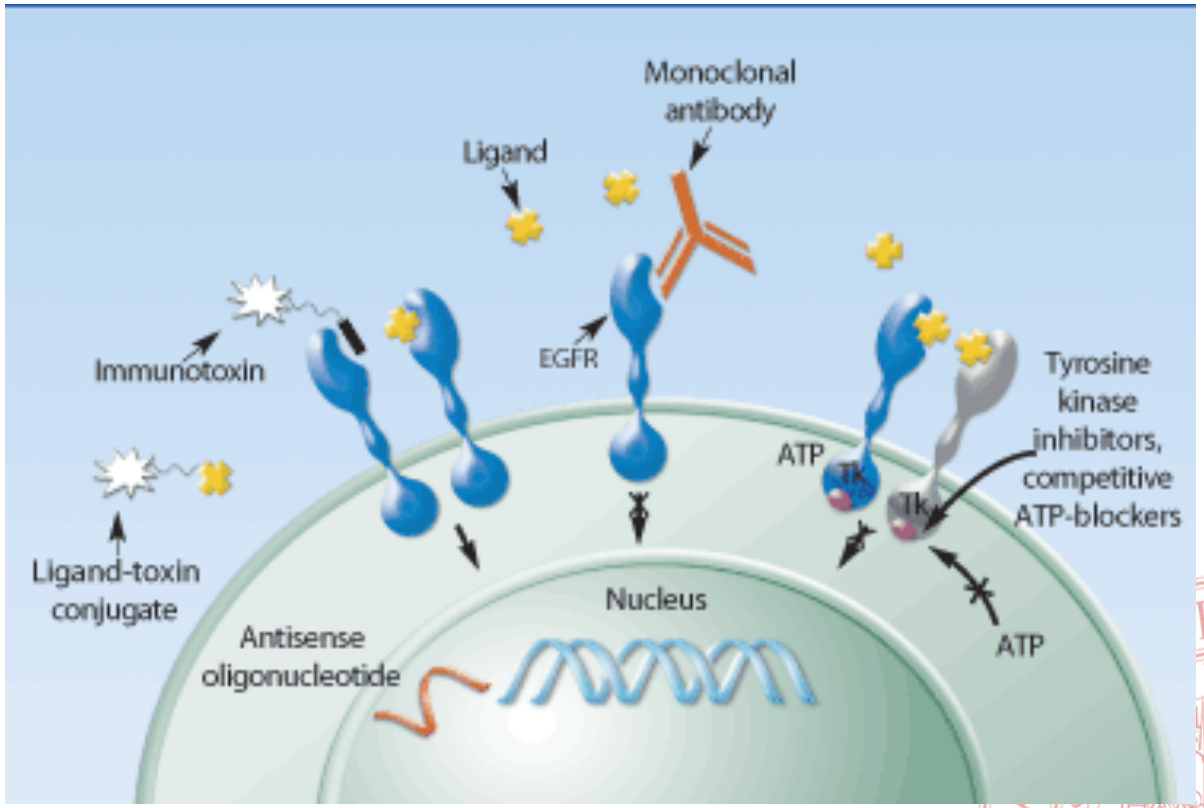


Development of FLT3 inhibitors

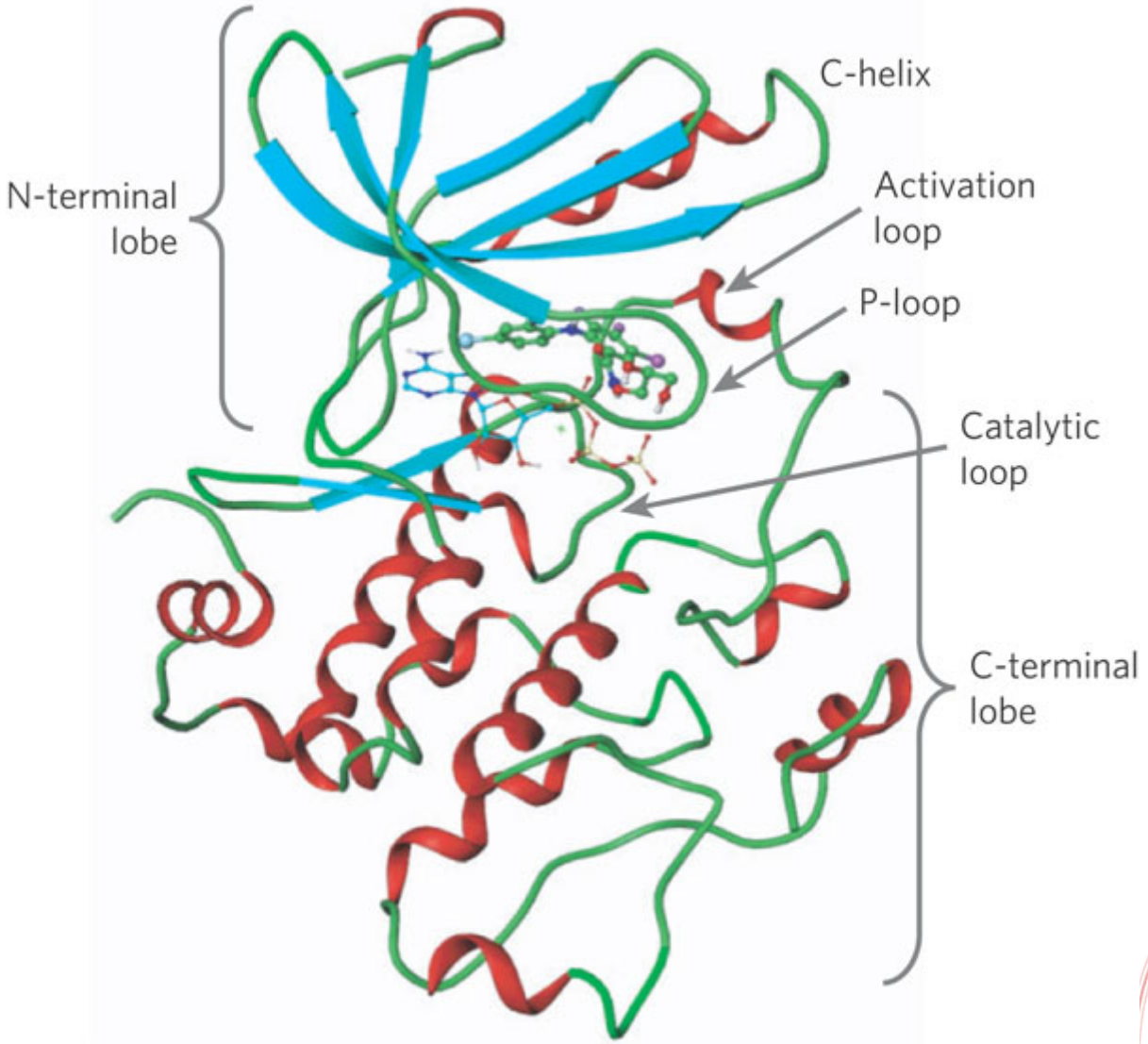
Pharmaceutical strategies targeting tyrosine kinase receptors :

1. **Monoclonal antibodies: directed against the extracellular domain**

2. **Small molecules: compete with ATP at ATP binding site**

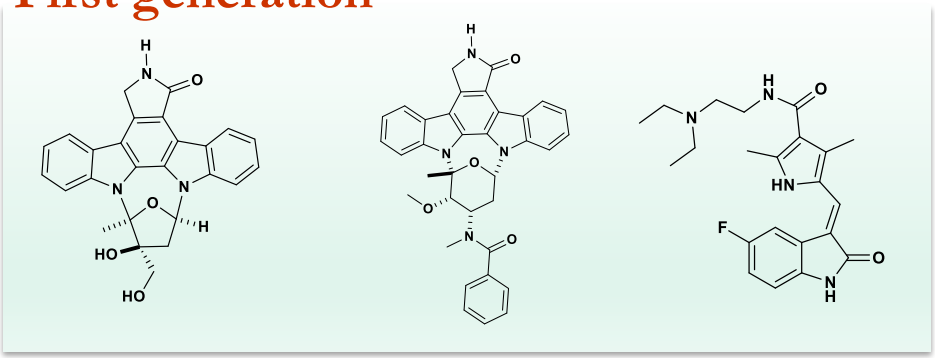


Kinase architecture



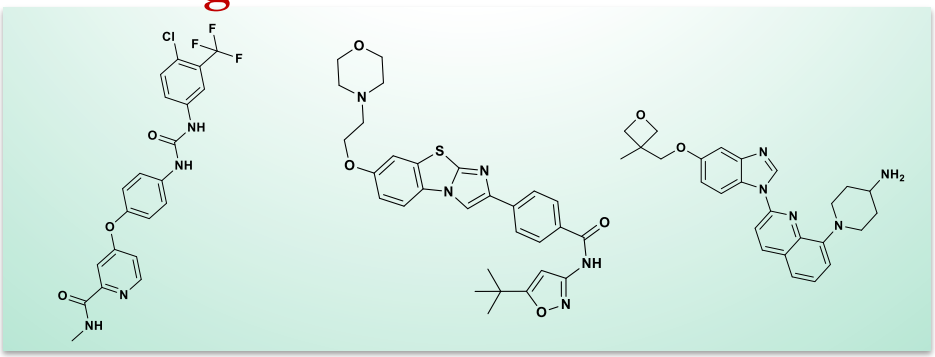
FLT3 inhibitors in AML

First generation



Lestaurtinib Midostaurin Sunitinib

Second generation

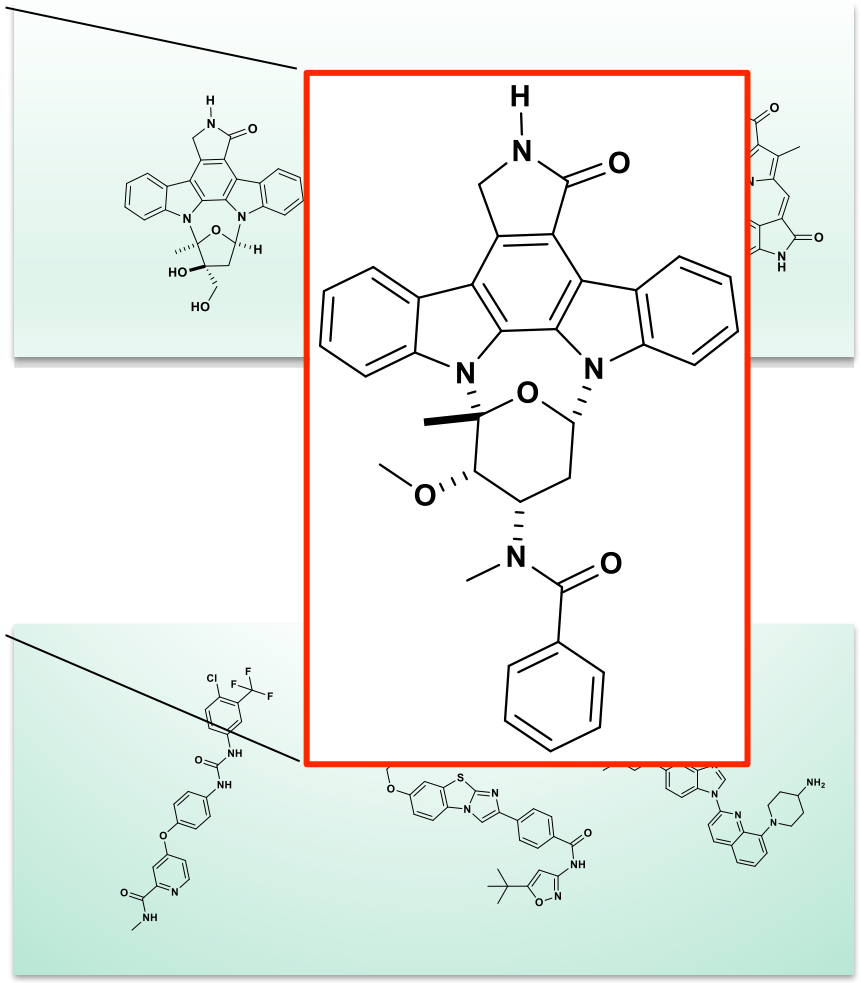


Sorafenib Quizartinib Crenolanib

"Typical" kinases inhibitors

Weisberg, Drug Resistance Updates 2009 12: 81–89.

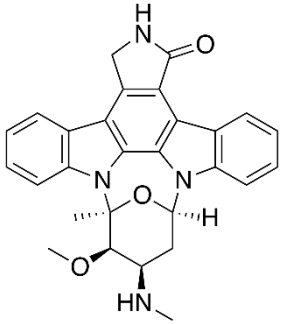
FLT3 inhibitors: Midostaurin



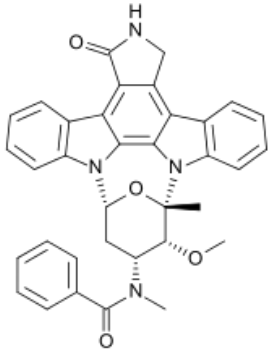
Midostaurin :

FDA approved (2017)

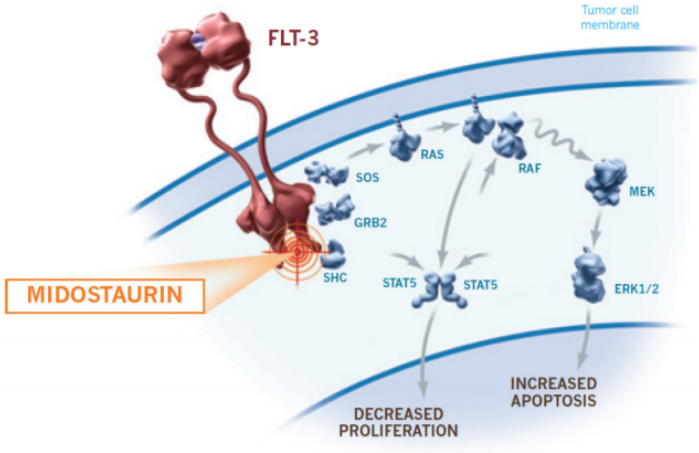
Midostaurin (PKC412): a case study



staurosporine
(alkaloid derived from
Streptomyces staurosporeus)



midostaurin



<u>Multikinase</u> inhibitor that blocks the activity of FLT3 and other kinases

Patnaik, Future Oncol. 2017 13(21), 1853–1871.

Midostaurin (PKC412): a case study

Pre-clinical studies:

Inhibitory activity toward FLT3 in cell models

2000 → 2002 → 2003

- ✓ Inhibition of protein kinase C
- ✓ Inhibition of multiple other kinases
- ✓ Antiproliferative activity toward multiple cancer cell lines and xenografts

Inhibitory activity toward FLT3 in a mouse model

Clinical pharmacology:

- ❖ Rapidly absorbed after oral administration
- ❖ Metabolized by cytochrome CYP3A4
- ❖ At therapeutic doses it reach micromolar concentrations during the first week and then decline, until a steady state is reached after approximately 28 days
- ❖ The elimination half-life is 24 hours

Patnaik, Future Oncol. 2017 13(21), 1853–1871.

Midostaurin (PKC412): a case study

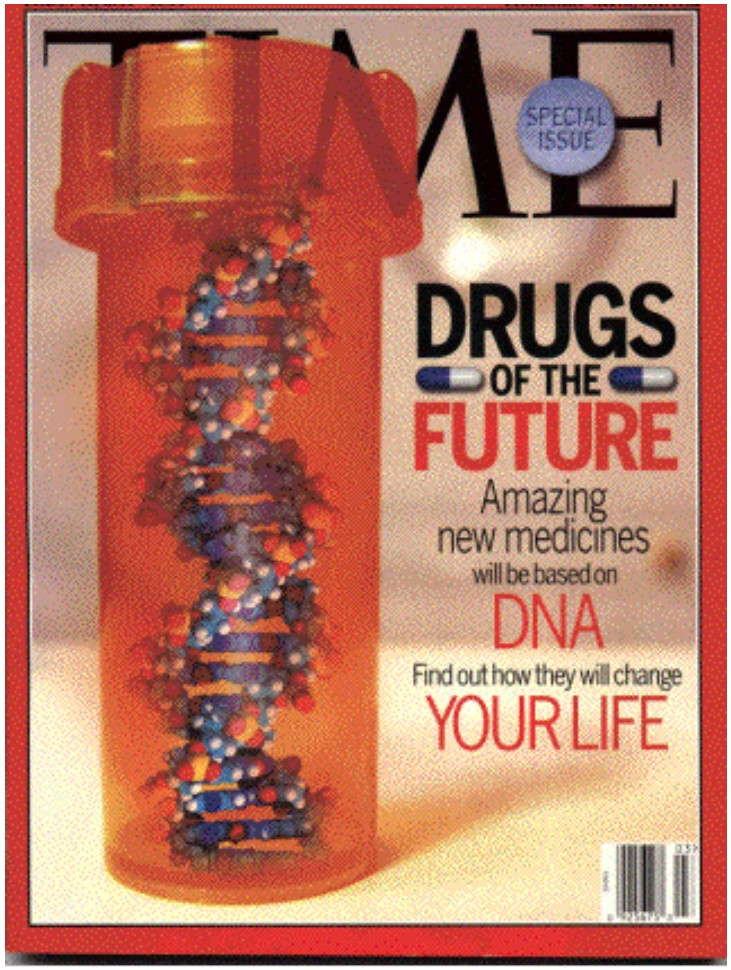
April 28, 2017

The U.S. Food and Drug Administration approved midostaurin for the treatment of adult patients with FLT3+ AML

July 20, 2017

The Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product midostaurin

Personalized Medicine



The ability to offer

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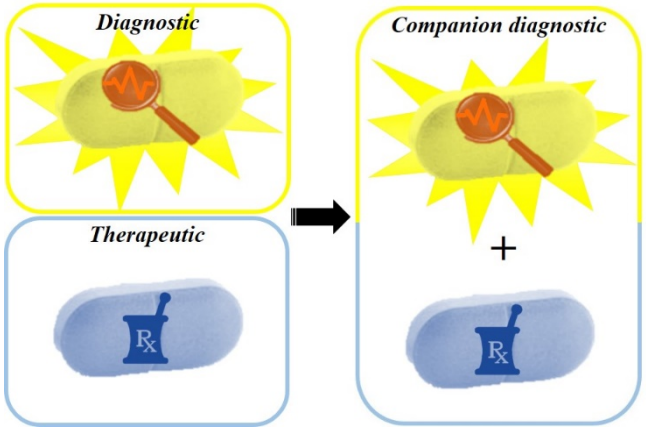
Diagnosis of AML

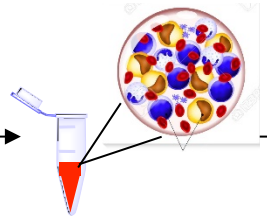
CDx FLT3 Mutation Assay

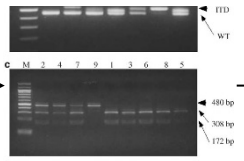
In vitro diagnostic test designed to detect mutations in the FLT3 gene in patients diagnosed with AML

Personalized approaches in AML



Patient gets diagnosed and tumor or blood sample taken

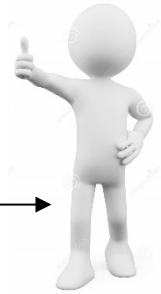




analysis marker

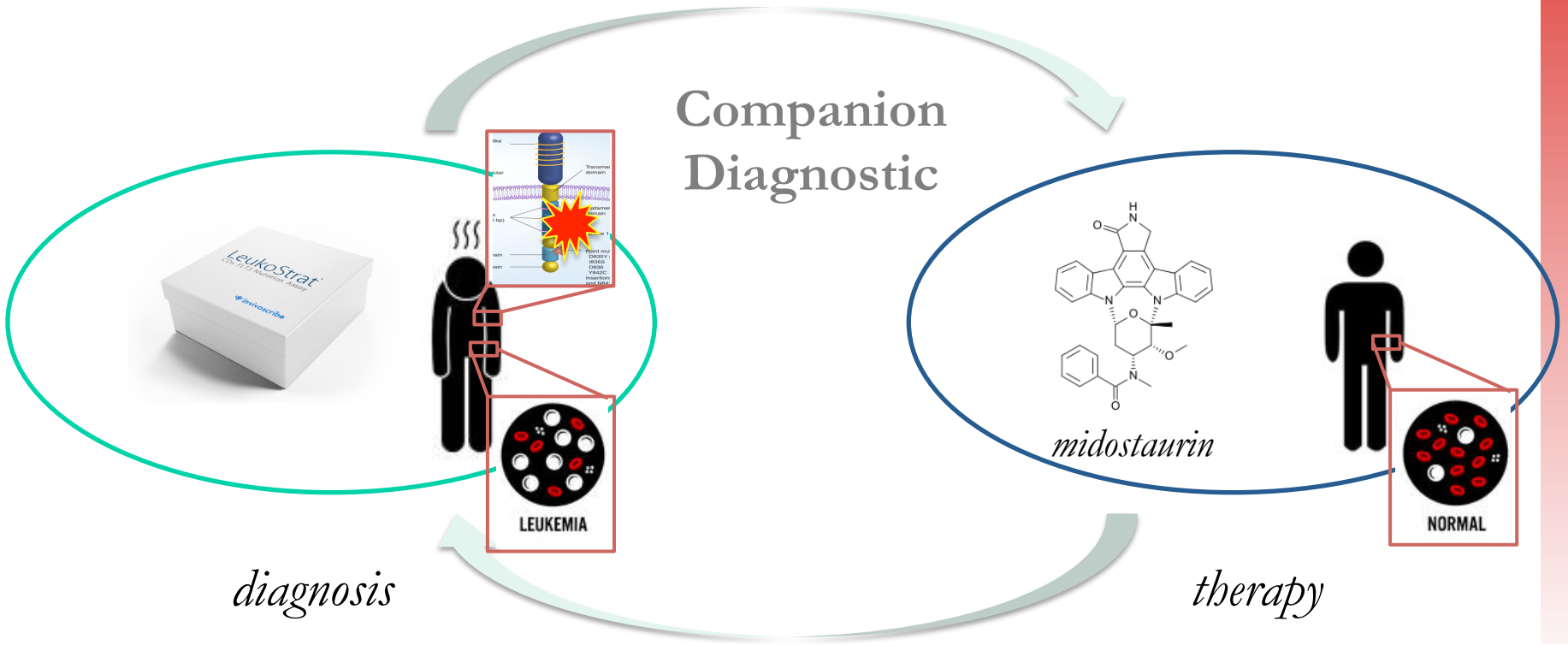
Positive test

patient is treated with drug



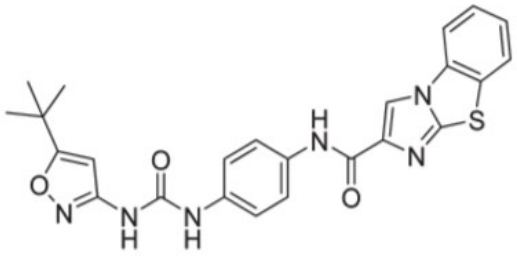
patient benefits

Personalized approaches in AML



Development of better FLT3 inhibitors (2° generation): from a good hit to a drug

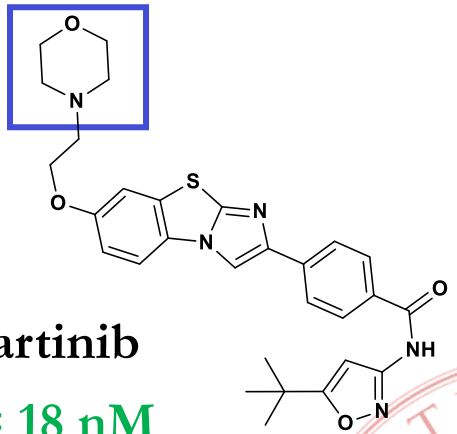
Chemistry is essential for transforming lead molecules into drugs. This requires optimizing the ADME properties as early as possible in the drug discovery cycle



1 (AB530)

- Low aqueous solubility
- Poor PK properties

Morpholine nucleus confers aqueous solubility and its salts are water soluble

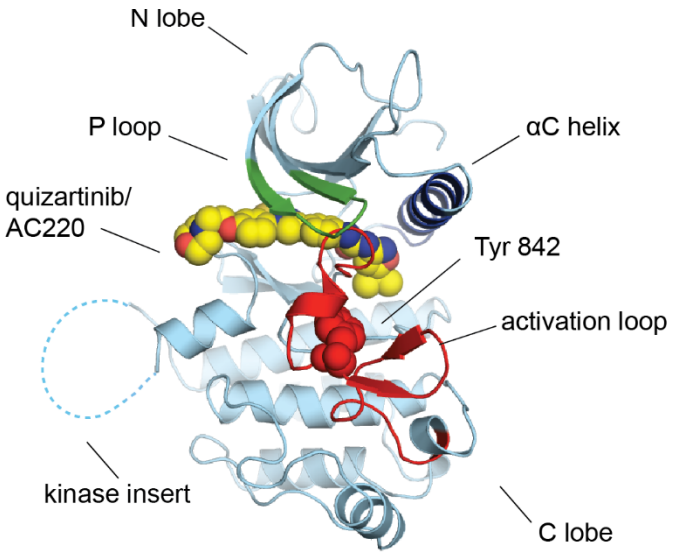


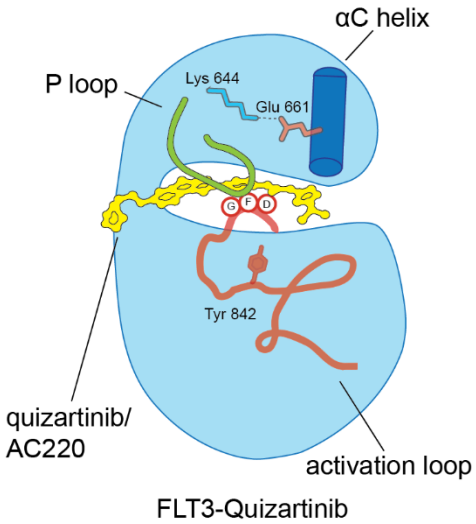
Quizartinib

IC_{50} = 18 nM

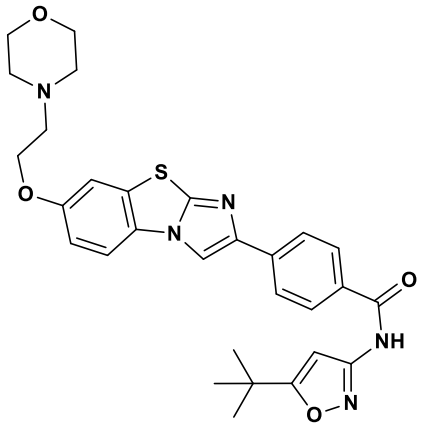
(QuANTUM-R)
Phase III Clinical Trial

Development of FLT3 inhibitors: from a good hit to a drug candidate





FLT3-Quizartinib


Quizartinib

Hinge region

- Selective targeting
- Higher inhibitory effect
- Optimal PK properties

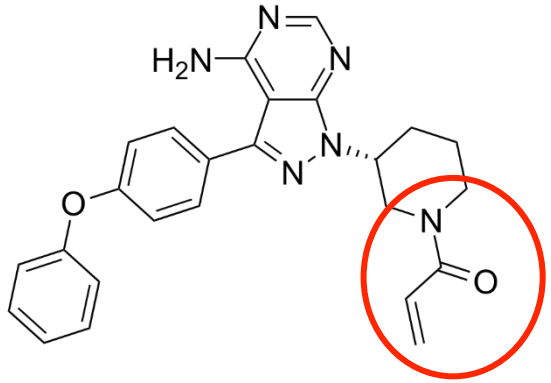
Grafone, Oncol Rev. 2012 6(1), e8.

Looking for selectivity…..
towards more targeted therapies
Development of irreversibile TKI inhibitors

Rationale:

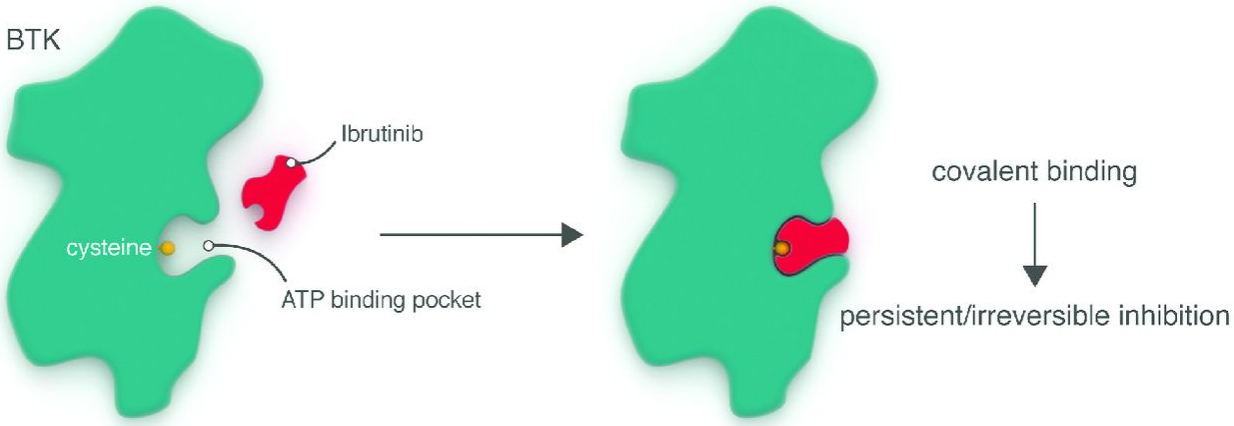
TKIs should compete with ATP ⇨ high dosage or *tight binding inhibitors*

Development of 3rd generation FLT3 inhibitors: from reversible to covalent inhibitors

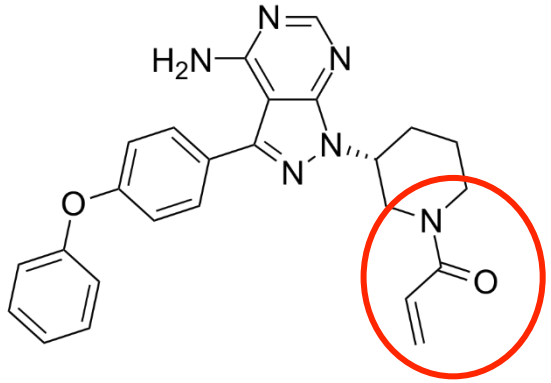


Michael acceptor moiety

Ibrutinib

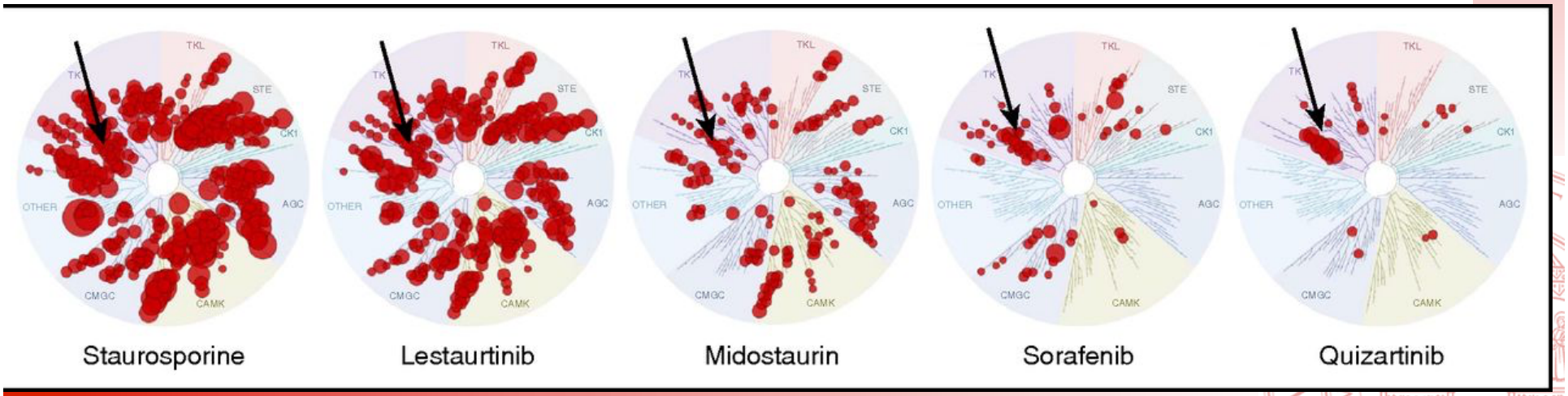


Development of 3rd generation FLT3 inhibitors: from reversible to covalent inhibitors



Ibrutinib

- Selective targeting
- Higher inhibitory effect
- No off-target toxicity



Levis, Blood 2017 129(26), 3403-3406.

Conclusions

Approximately 30% of patients with AML carry the FLT3 mutation, which is associated with aggressive disease, with poor prognosis and a high risk for relapse

"This is the first step in applying the theories of personalized medicine to patients with AML, specifically those patients with AML who have a FLT3 mutation, who we have shown are likely to benefit from the addition of this targeted agent, midostaurin, to standard therapy."

Richard M. Stone, MD, Director, Adult Leukemia Program, Dana-Farber Cancer Institute, Boston.