Distinctive features of the main classes: mTOR, PI3K, dual inhibitors and AKT

Jordi Rodon
I have served in Advisory Boards for Novartis and Lilly
OUTLINE

1. Introductory notes to the Pharmacology of the Pi3K pathway: Family tree of PI3K-AKT-MTOR (PAM) inhibitors


3. Drugs with unique properties.
Family tree of PI3K-AKT-MTOR (PAM) inhibitors
Isophorm-specific PI3Ki

Catalytic

Allosteric

PanPI3Ki

PI3K/mTORi

PAMi

Catalytic

TORC1/2

Allosteric/Rapalogues

TORC1

AKTi

mTORi

ESMO Signalling Pathways 2014

Rodon, Nat Rev Clinca Oncol, 2013
Fruman, Nat Rev Drug Disc, 2014
mTOR inhibitors

- Rapamycin (Sirolimus)
- OSI-027
- INK-128
- PP-242
- CC-223
- CCI-779 (Temsirolimus)
- RAD001 (Everolimus)
- AP-23573 (Ridaforolimus)

Catalytic
TORC1/2

Allosteric/Rapalogues
TORC1

PAMi

ESMO Signalling Pathways 2014

Rodon, Nat Rev Clinical Oncol, 2013
Fruman, Nat Rev Drug Disc, 2014
Comparison of selectivity of some PI3K Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>p110α</th>
<th>p110β</th>
<th>p110δ</th>
<th>p110γ</th>
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<tr>
<td>BEZ235 (NVP-BEZ235, Dactolisib)</td>
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<tr>
<td>GDC-0941</td>
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<td>BKM120 (NVP-BKM120, Buparlisib)</td>
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GDC0032

"Isophorm selective"

PX-866: Irreversible PI3Ki

SF1126: Vascular Targeted Pan-PI3K/mTOR Inhibitor linked to an integrin-binding component

Isophorm-specific PI3Ki

PanPI3Ki

PI3K/mTORi

PAMi

Rodon, Nat Rev Clincal Oncol, 2013
Fruman, Nat Rev Drug Disc, 2014
AKT inhibitors

Dose-dependent increase in a non-signaling hyper phosphorylated AKT (S473 and T308), and subsequent decrease in phosphorylated downstream targets
New kids on the block

- Mutation specific
- Irreversible Isoform specific
- Isoform specific
- "Isophorm selective"/balanced
- Catalytic Isotorm specific
- Allosteric Rapalogues
- Isoform specific
- Irreversible Isoform specific
- "Isophorm selective"/balanced
- Catalytic TORC1/2
- Allosteric/ Rapalogues
- TORC1

- PanPI3Ki
- PI3K/mTORi
- Catalytic AKTi
- S6Ki
- PDK1i
- AKT/S6Ki
- Combo P/K-Alpha+ mTORi

ESMO Signalling Pathways 2014
Rodon, Nat Rev Clinical Oncol, 2013
Fruman, Nat Rev Drug Disc, 2014
YES
Predictors of sensitivity to pan-PI3K inhibitors

GDC-0941 Pan-PI3K inh – Breast cancer cell lines

Breast cancer types

<table>
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<tr>
<th>Subtype</th>
<th>( \alpha )</th>
<th>( \beta )</th>
<th>( \delta )</th>
<th>( \gamma )</th>
<th>mTOR</th>
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<td>GDC-0941</td>
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Predictors of sensitivity to PI3K-\(\alpha\) selective inhibitors

BYL719, PI3K alpha inhibitor

**PIK3CA** mutation and **PIK3CA** and **ERBB2** amplification associated with BYL719 sensitivity

74% mutant **PIK3CA** (26/35)
31% wild type **PIK3CA** (106/339)

Barretina et al. Nature 2012
Huang et al. Proc AACR 2012
Predictors of sensitivity to PI3K-β selective inhibitors

KIN-193, a PI3K beta inhibitor

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<th>IC50 (nmol/L)</th>
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<tr>
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<td>DNA-PK</td>
<td>53.7</td>
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<tr>
<td>hVPS34</td>
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35% mutant PTEN (20/57)
16% wild type PTEN (58/365)
Intertumoural heterogeneity between patients

Intratumoural heterogeneity between primary and metastatic sites

Intratumoural spatial heterogeneity

Space reliability

Time reliability

Progression after response
Intra-patient tumor heterogeneity

Gerlinger, Nat Gen, 2014
Temporal tumor heterogeneity and clonal evolution
I do not know (yet)
Conventional Drug Discovery Is Simplistic and Artificial
Conventional Drug Discovery Is Simplistic and Artificial
The Problem: Enormous Complexity of Real-Life Drug Action
GDC-0032, a panPI3K-beta sparing inhibitor in all solid tumors
The Devil is in the Details: Drugs with “unique” properties
The promise of PI3K irreversible inhibitors

PX866
Irreversible pan-PI3K inhibitor

• Preclinically: Inhibition of p-AKT (S473) was observed for up to 48 hours after PX-866 dosing in HT29 tumor models.

• Phase I trial:
  • DLTs of diarrhea
  • No hyperglycemia or skin toxicity
  • T 1/2+= 2.2-3.8 h
  • Inhibition of p-AKT was observed within 4 hours in 7 patients with p-AKT/T-AKT ratio decreases of 13% to 94%

<table>
<thead>
<tr>
<th></th>
<th>PX-866</th>
<th>17-OH 866</th>
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<td>PIK3CA WT</td>
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<td>C420R</td>
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<tr>
<td>mTOR</td>
<td>&gt;30,000</td>
<td>&gt;30,000</td>
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</tbody>
</table>

ESMO Signalling Pathways 2014
XL147 (panPI3Ki) and XL765 (PI3K/mTORi) and activity on MAPK.

BKM120 (panPi3Ki) and the antitubulin effect

Similar pERK reduction in:
• Mucinous breast carcinoma (74%) and rectal carcinoma (62%) treated with XL765
• Merckel Cell and Leiomiosarcoma treated with XL147

BKM120 causes more cell death than other PI3k in vitro, irrespective of their level of PI3K addiction.

It displays tubulin-binding and microtubule-estabilizing activities, but at concentrations that may not be reached in the clinic

Shapiro, CCR 2013
PI3K/PIM inhibitors

- PIM expression is regulated by JAK-STAT and NF-KB1 pathways
- Promote pro-survival signaling through regulation of BCL2 family
- Increased cap-dependent protein synthesis through phosphorylation and thus inhibition of translation repressor 4E-BP1 (By-pass Pi3K signaling)
- Cross-talk between PIM and PI3K.
- PIM Kinases are described as drivers of PI3k/AKT drug resistance

GSK690693, PI3K inhibitor

Pim-1

GAPDH

0 0.625 1.25 2.5 5 10 20 (µmol/L)

GDC-0941, panPI3K inhibitor

P-AKT (Ser473)

AKT

P-BAD (S112)

BAD

4E-BP1 (Ser65)

4E-BP1

IBL202, panPI3K/PIM inhibitor

EC_{50} (nM)

300

9350

2770

0 0.014 0.041 0.125 0.375 1.11 3.33 10 µM
Intravenous PI3K inhibitors
(PF-05212384 and BAY 80-6946)

PF-05212384 is an intravenous, ATP-competitive, highly selective pan-class I isoform PI3K and mTOR inhibitor.

The most common AEs (mucositis, hyperglycemia, and liver enzyme elevations) are known class-related effects of PI3K and mTOR inhibition.

Terminal $T_{1/2} = 30$-$37$ hours.

Paired tumor biopsies at MTD group revealed a $35.9\%$ reduction in pAkt S473.

Brain-Penetrant PI3K Inhibitors
(BKM120, GDC0084)

As per TCGA, $75\%$ of Glioblastoma cases have alterations that activate the PI3K pathway.

Most PAMi are substrates of Pgp and/or BCRP, and are likely to exert their effects only in areas where the BBB or blood–tumor barrier is permeable. Drugs designed to cross BB would be more efficient.

GNE-317 is a dual PI3K/mTOR inhibitor.
Many lessons yet to be learn with Pi3K inhibitors…

But remember…

It is the Pharmacology, stupid!*

*Adapted from the famous “It’s the economy, stupid” at the presidential campaign for Bill Clinton against George H. W. Bush.