Sinergia tra meccanismi d'azione immunomodulanti

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NUOVI ORIZZONTI TERAPEUTICI nel MONDO dei "LINFOMI"

Lenalidomide-based combinations: preclinical rationale for association

Immunomodulatory property enhancers	Antiangiogenetic property enhancers	Direct antineoplastic effect enhancers
Monoclonal antibodies	**Agents targeting the VEGF/VEGFR signaling**	**Inhibitors of the unfolded protein response**
Targeting MM cell surface receptors (anti-CS1, CD40, CD38, CD138, CD74, CXCR4)	Bevacizumab	Proteasome inhibitors (Bortezomib, Carfilzomib, Ixazomib, Delanzomib, Marizomib)
Targeting MM cell surface ligands (anti-IL-6, IGF)	Pazopanib	Heat-shock-protein inhibitors (Tanespimycin)
Targeting immune cell surface receptors (KIR, PD-1/PD-L1 axis)		Aggresome formation inhibitors (Tubacin)
Immunotoxins	**Tyrosine kinase inhibitors**	**Agents inducing epigenetic modifications**
Targeting MM cell surface receptors (anti-CD56, CD138)	Sorafenib	Histone deacetylase inhibitors (Vorinostat, Panobinostat, Romidepsin)
	Sunitinib	Hypomethylating agents (Azacitidine)
Vaccine-based therapies	Vandetanib	**Agents interfering with intracellular signaling**
Whole-cell vaccine		mTOR inhibitors
Peptide vaccine		Akt/PI3K inhibitors
DNA vaccine		
Statins, Coxibs		**Agents interfering with the cell cycle**
		Aurora kinase inhibitors
		Polo-like kinase inhibitors
		Cyclin-dependent kinase inhibitors
		Agents targeting cancer stem cells
		Hedgehog pathway inhibitors

Cives M et al. Critical Reviews in Oncology/Hematology 85 (2013) 9–20

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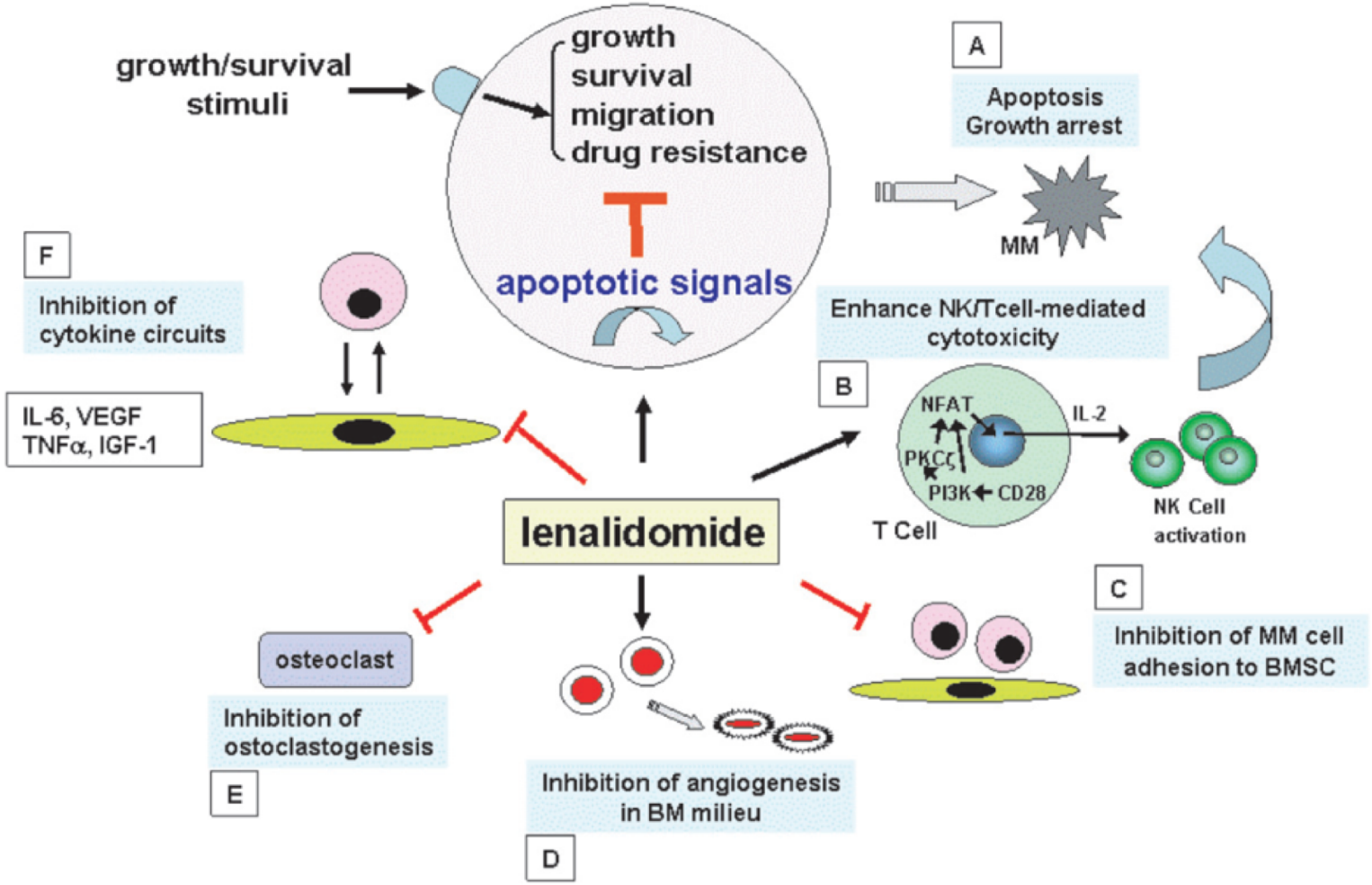
Potential mechanisms of action of lenalidomide and potential targets of drug combination



Hideshima T et al. Therapeutics and Clinical Risk Management 2008:4(1) 129–136

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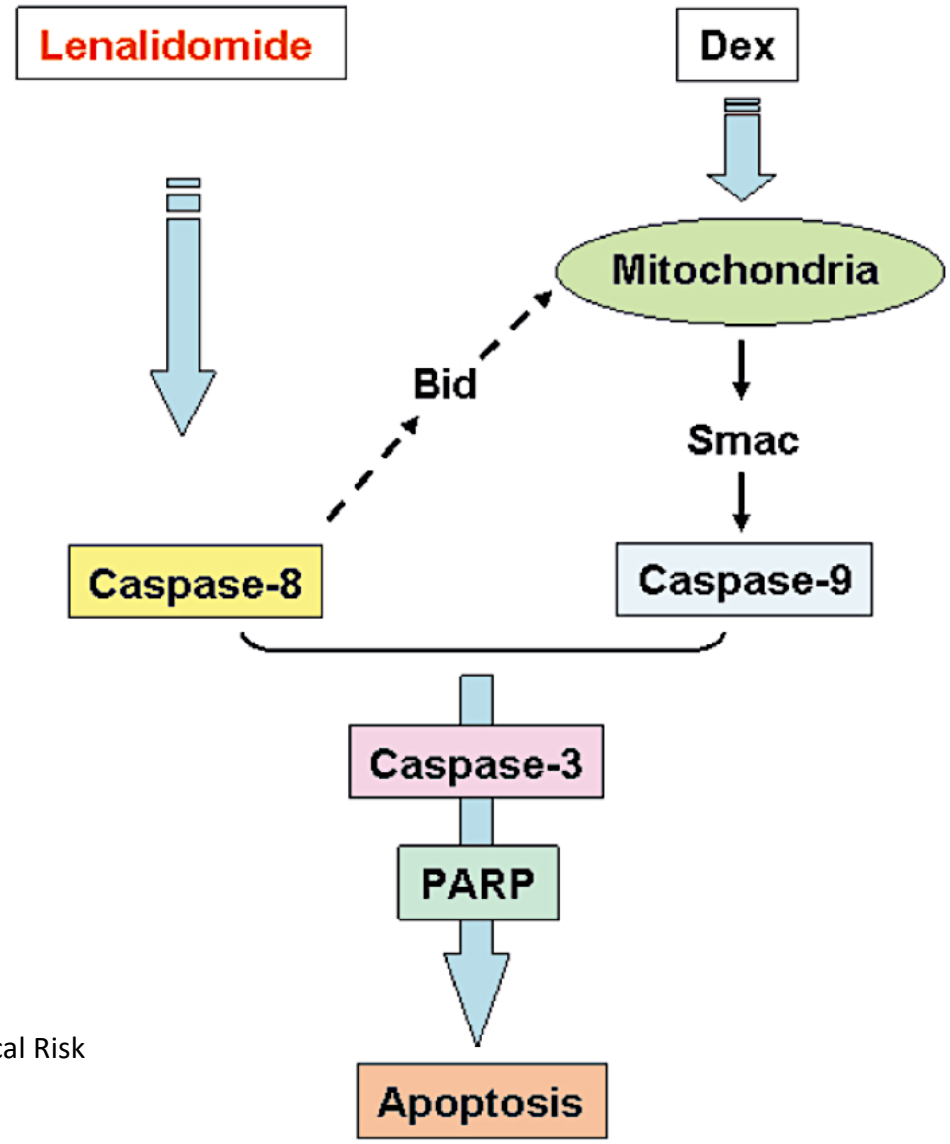
Potential mechanisms of synergistic cytotoxicity by lenalidomide plus **steroid** treatment



Hideshima T et al. Therapeutics and Clinical Risk Management 2008:4(1) 129–136

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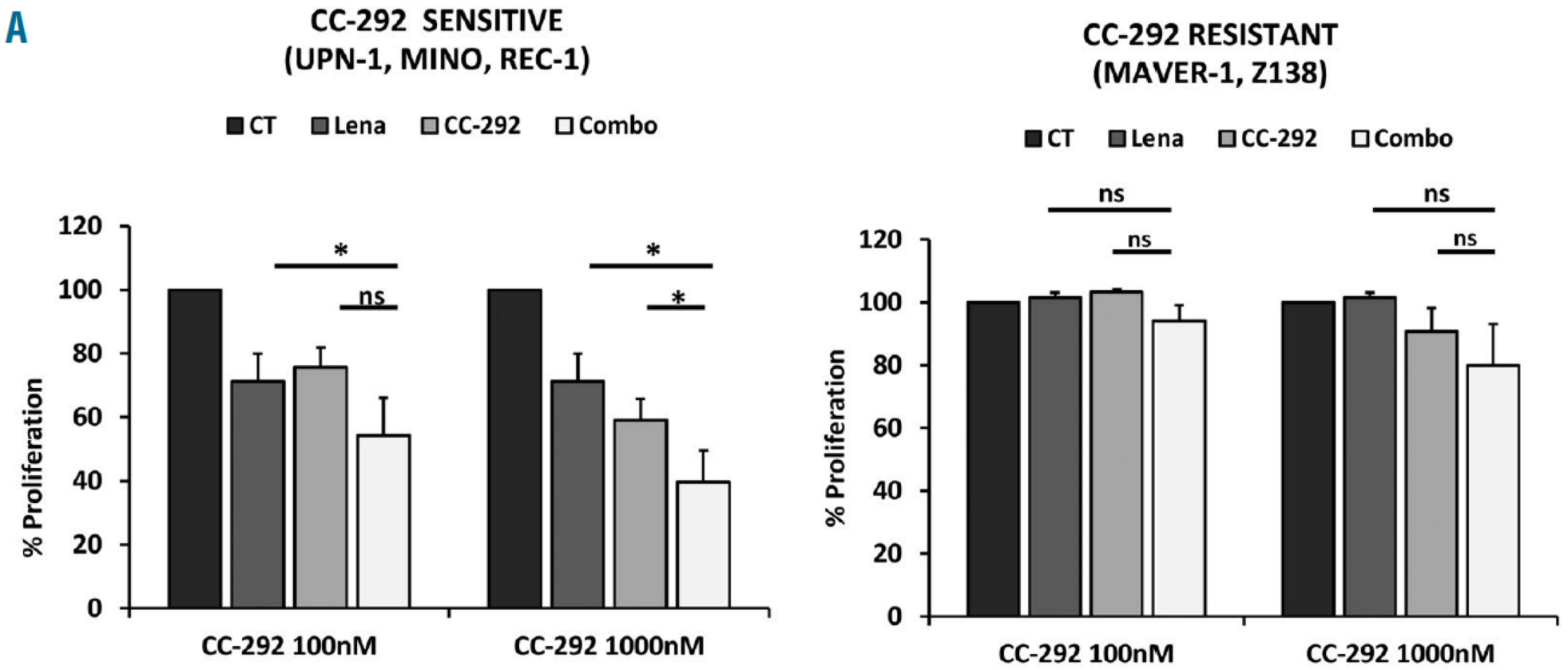
The **BTK inhibitor** CC-292 cooperates with lenalidomide in sensitive mantle cell lymphoma cells but not in CC-292 resistant



Vidal-Crespo A et al., Haematologica 2017; 102:e450

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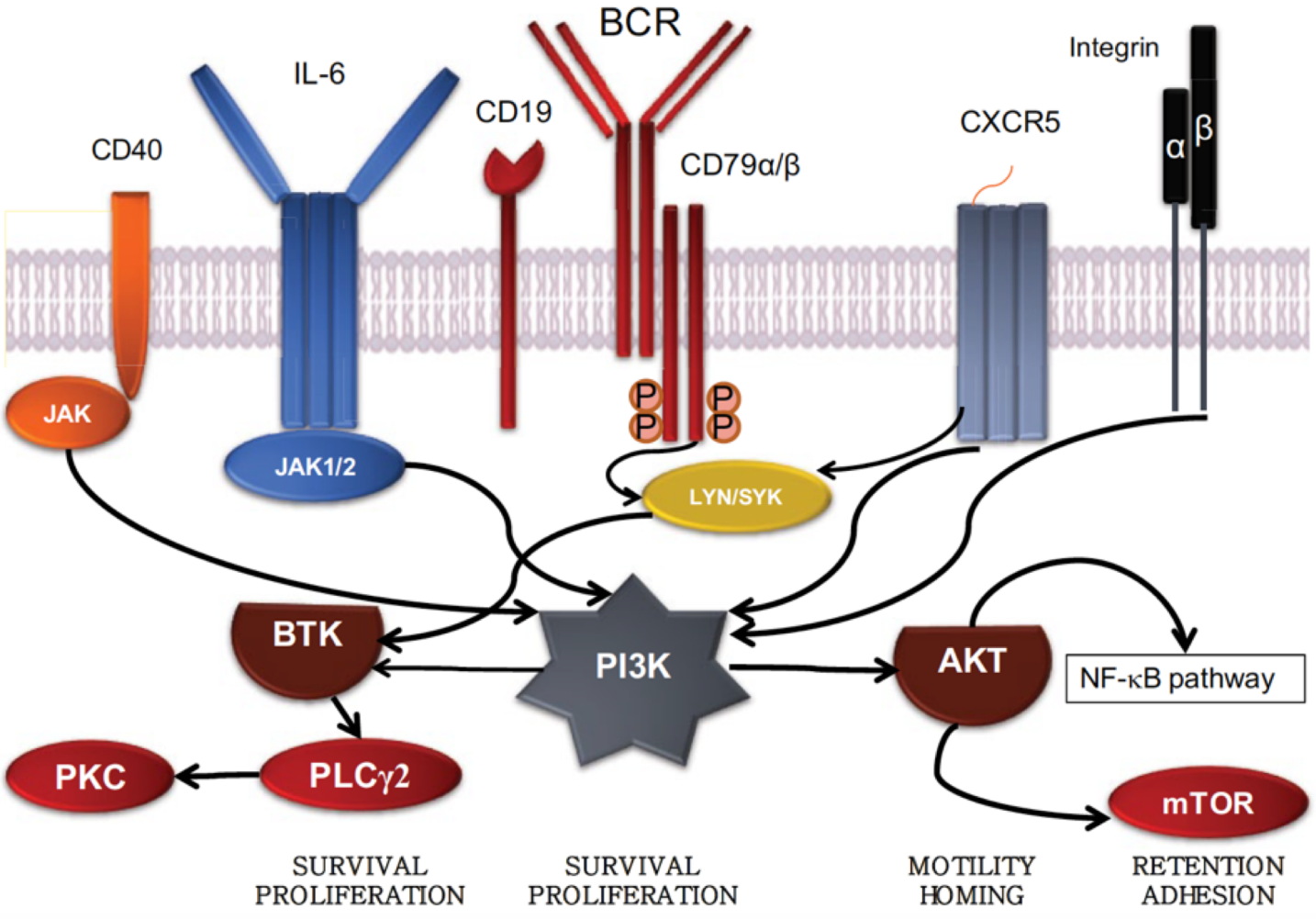
The role of PI3K in the biology of B cells



Ortiz-Maldonado V et al. Ther Adv Hematol 2015, Vol. 6(1) 25–36

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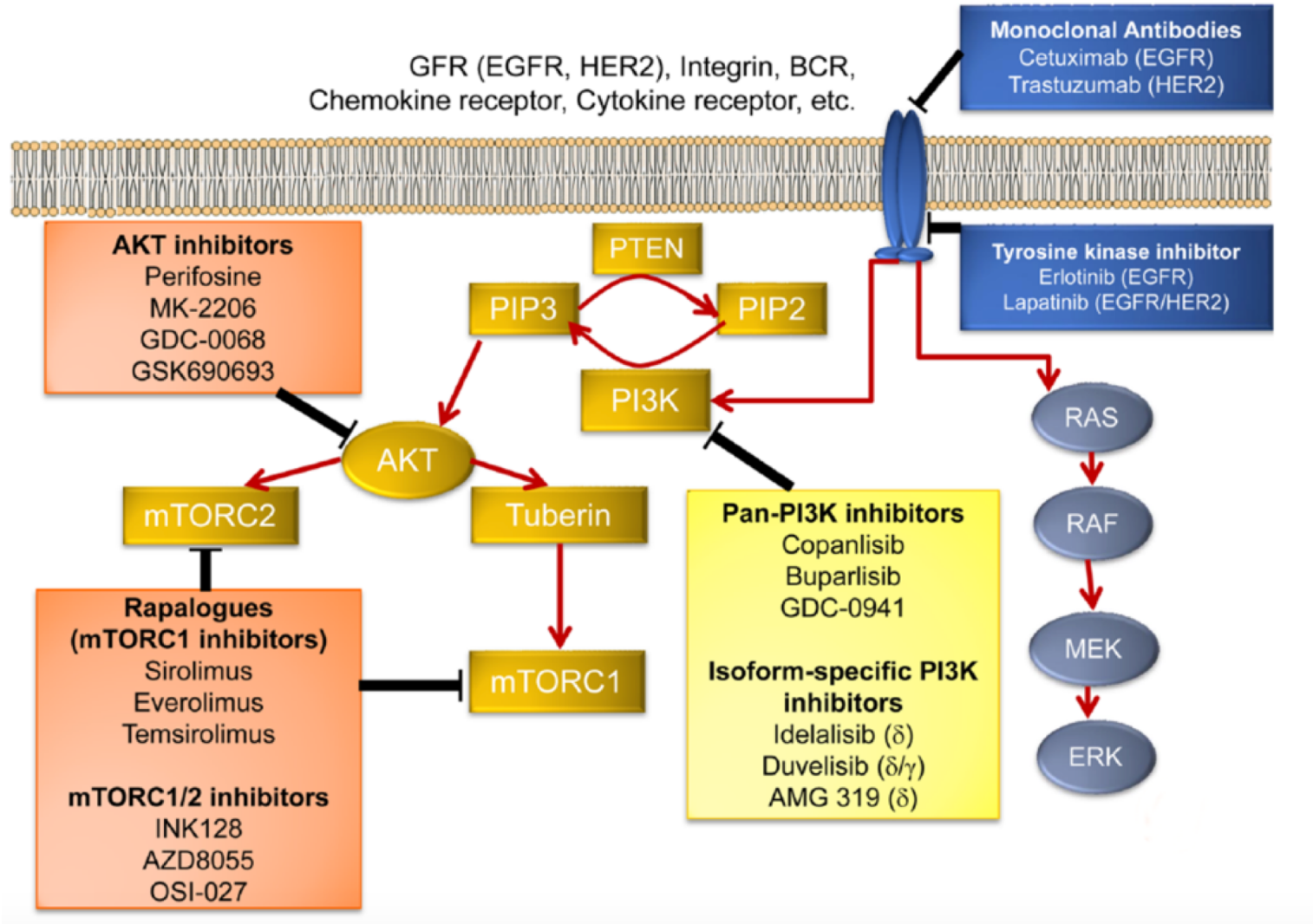
Signalling of the PI3K/AKT/mTOR pathway and relevant drugs that target each of the components of the pathway



Ortiz-Maldonado V et al. Ther Adv Hematol 2015, Vol. 6(1) 25–36

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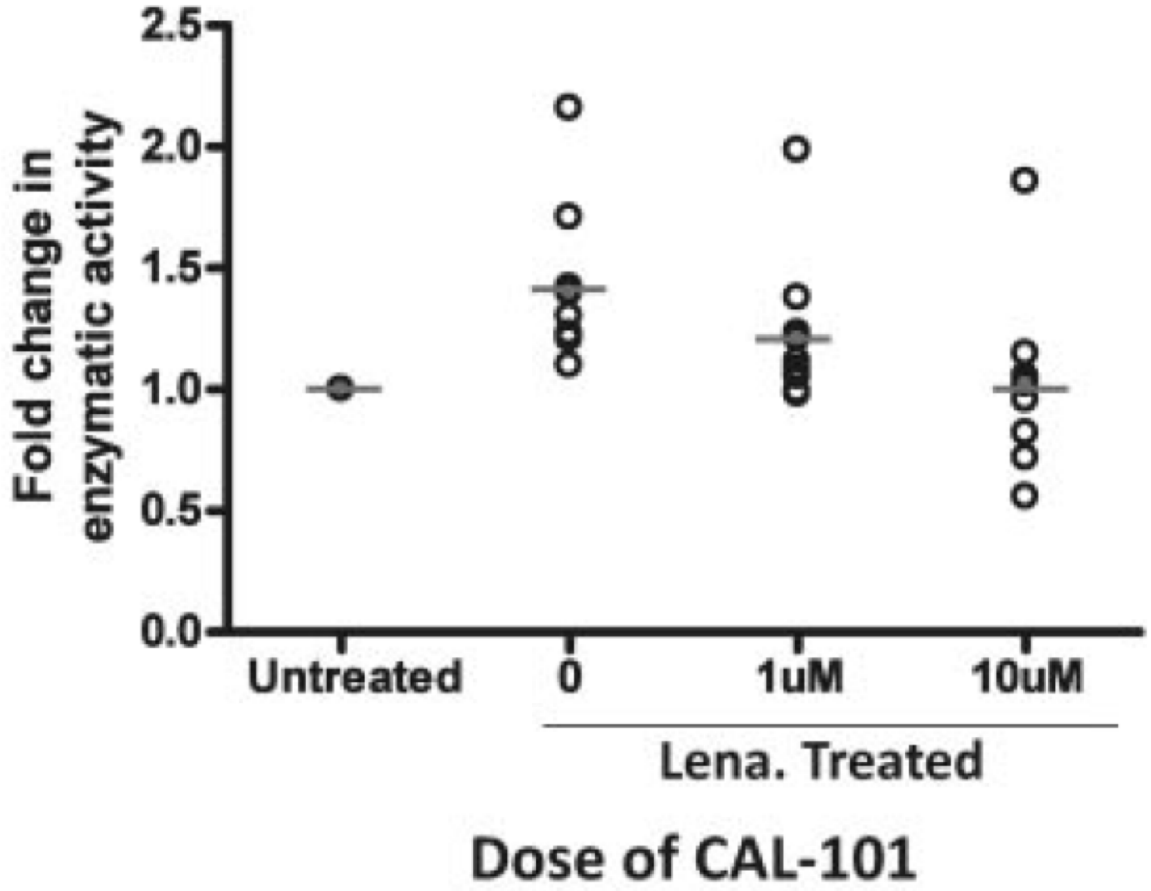
Lenalidomide leads to activation of the PI3K pathway via a **PI3K-**δ-dependent mechanism



Herman SEM et al. Blood 2011;117(16):4323-4327

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Conclusions

- IMDs have a complex mechanism of action and multiple pharmacological combinations are possible.
- Lenalidomide is currently gaining interest in both preclinical and clinical research for combinatory treatments with novel agents including monoclonal antibodies, immunotoxins, tyrosine kinase inhibitors, new proteasome inhibitors and epigenetic-interfering agents as well as with new compounds targeting the cancer stem cell niche.
- Preliminary data from clinical studies are encouraging and suggest a favorable safety profile, although the long-term tolerability of these combinatory regimens needs to be carefully evaluated since an increased incidence of new primary tumors has been documented.
- Thus, from bench to bedside studies are required to design clinical trials for new drug combination approval.