Is there a role for dual PI3K/mTOR inhibitors for patients affected with lymphoma?

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Supplementary Material

Additional Dual PI3K/mTOR inhibitors

We discuss here the dual PI3K/mTOR inhibitors with no available clinical data in patients with lymphoma.

Dactolisib (BEZ235/NVP-BEZ235) is the most studied dual PI3K/mTOR inhibitor. It is a potent inhibitor of all the four PI3K isoforms (slightly less for the p110β), of TORC1/TORC2 and also of the PI3Kα mutants most commonly detected in solid tumors [1]. Dactolisib has preclinical anti-tumor activity in different models of B and T cell lymphomas [2-18]. The compound can also act as microtubule destabilizer [7] and it inhibits DNA damage response (DDR) kinases [12]. Indeed, Shortt and Coll. suggested that it is indeed the triple inhibition of PI3K, mTOR and DDR kinases playing a fundamental role in the higher activity seen with dactolisib in inducing apoptosis in Myc-driven mouse lymphoma models in comparison with single PI3K or mTOR inhibitors [12]. The clinical program for dactolisib has been stopped due to a high variable pharmacokinetic profile observed in the phase I studies [19]. Despite all the preclinical data available, to the best of our knowledge, no lymphoma patient has been treated with dactolisib.

BGT226/NVP-BGT226 inhibits p110α, p110β, p110δ, and p110γ, with a preference for p110α (wild type and mutated), and TORC1/TORC2 [20]. Besides showing activity in solid tumors, acute leukemia and multiple myeloma models [20-23], the compound has shown preclinical anti-lymphoma activity [16, 24]. Without enrolling any lymphoma patient, a phase I study performed in USA and Europe led to a stop in the clinical development of BGT226 due to the inability of reaching concentrations expected to properly inhibit PI3K signaling in the absence of dose-limiting toxicity [25]. Similar toxicity was observed in a parallel phase I study performed in Japanese patients with solid tumors, which stopped before reaching the dose-limiting toxicity based on the already available of the other study [26]. Resistance to BEZ235 and BGT226 is associated to higher expression of PAK1 gene, and combination of PI3K inhibition and PAK1 inhibition is synergistic [16].

PI103 is a strong inhibitor of p110α, p110β, p110δ L, p110γ, TORC1/TORC2 and also of DNA-PK with preclinical anti-tumor activity in solid tumors [27, 28] and mouse and human T-cell lymphoma models [29-31].

Apitolisib (GDC0980/RG7422/apitolisib) is a potent inhibitor of all the PI3K and of TORC1/TORC2 with anti-tumor activity in different solid tumor cell lines [32, 33]. Apitolisib has also strong *in vitro* activity in B cell lymphoma cell lines [34]. No patient with lymphoma was enrolled in the phase I (NCT00854152) [35], and no information on recruited patients is available from a second study (NCT00854126) [36], already closed.

PF04691502 inhibits the four PI3K isoforms, including mutant p110α, and TORC1/TORC2 and has preclinical activity in solid tumors [37], DLBCL, MCL [38] and cutaneous T cell lymphomas [39]. No study has been performed for patients with lymphoma.

Omipalisib (GSK2126458/GSK458) is an inhibitor of p110α (wild type and mutant), p110β, p110δ, p110γ, TORC1 and TORC2 with activity in cell lines derived from solid tumors [40], from BL [41] and T cell lymphomas [42]. Omipalisib has not been clinically evaluated in patients with lymphoma.

VS5584/SB2343 has shown activity in solid tumor, BL [43, 44] and MM cell lines [43]. No data are available of the phase I study (NCT01991938) that had already enrolled 75 patients and was terminated due to lack of recruitment and the company's decision to de-prioritize compound development.

Finally, **NU7441** is believed to mainly act as a DNA-PK inhibitor but it also targets PI3Ks and mTOR [45]. It has preclinical activity in cell lines derived from BL and from other lymphoma subtypes [46].

To the best of our knowledge, there are no reported data of activity in lymphoma models using **DS7423** [47], the GDC-0941 derivative **GNE-477** [48], the PF-04691502 derivative **PF-04979064** [49], **PKI-179** [50], **PKI-402** [51, 52]**, PQR530** [53], **PWT33597** (VDC-597 currently commercialized as veterinary anticancer drug) [54], **samotolisib** (LY3023414) [55, 56], **SN32976** [57, 58], **WJD008** [59], and for the multitarget PI3K/mTOR/ALK-1/DNA-PK inhibitor **Panulisib** (P7170) [60-62].

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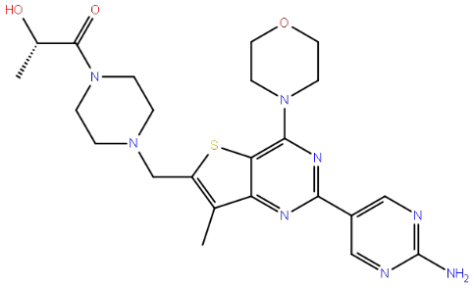
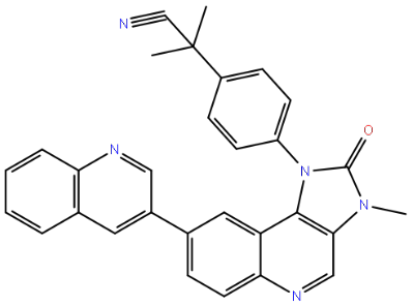
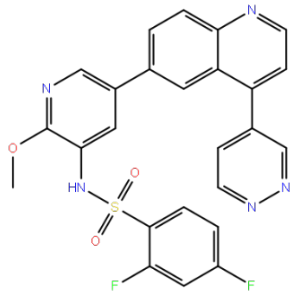
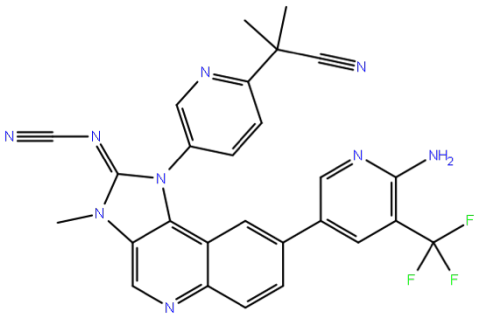
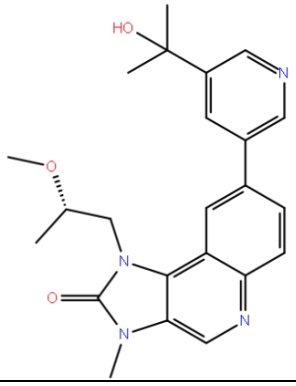
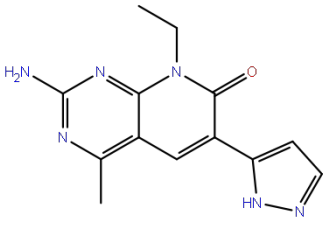
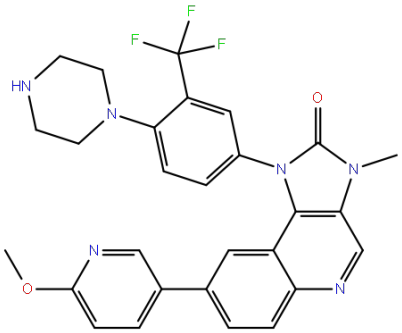
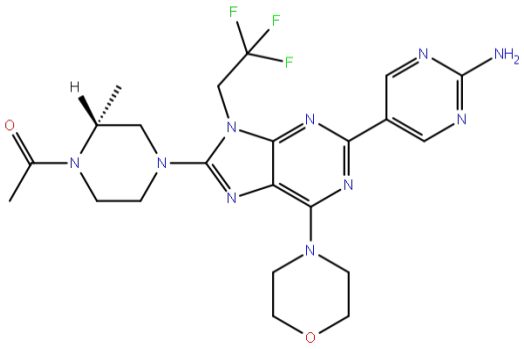
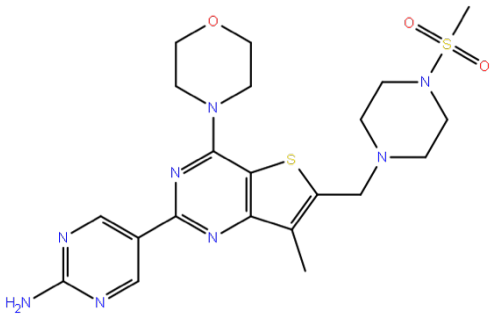
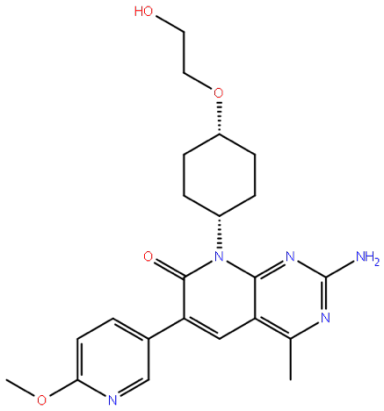
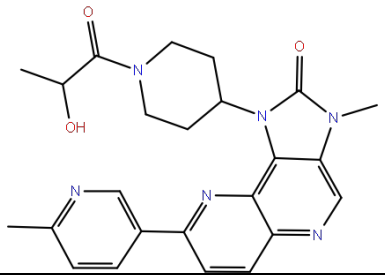
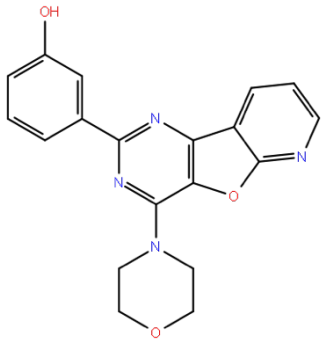
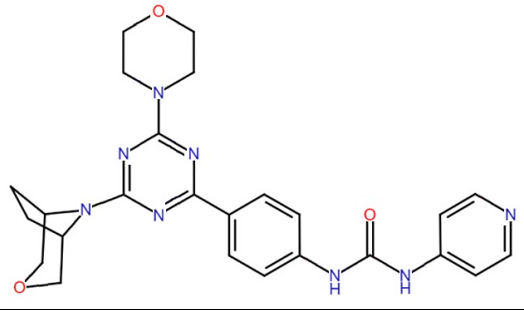
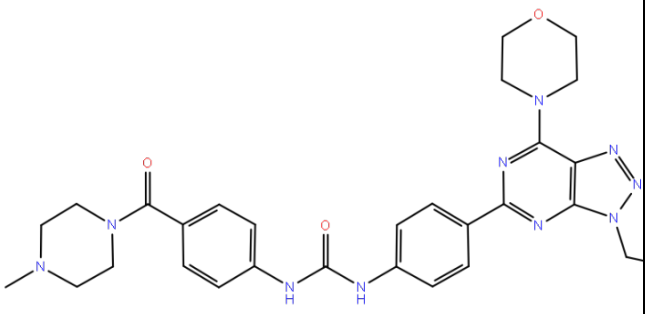
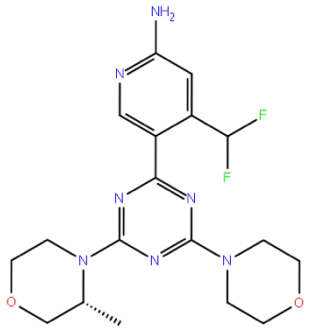
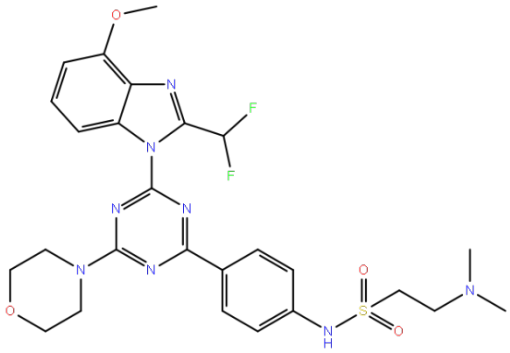
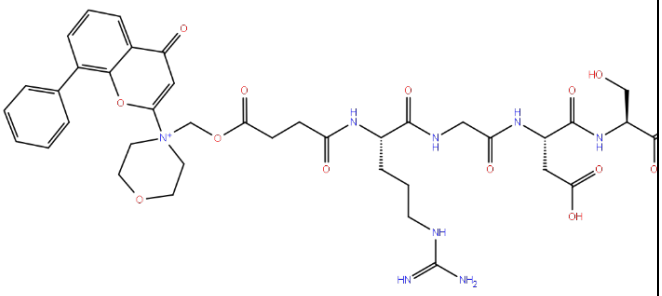
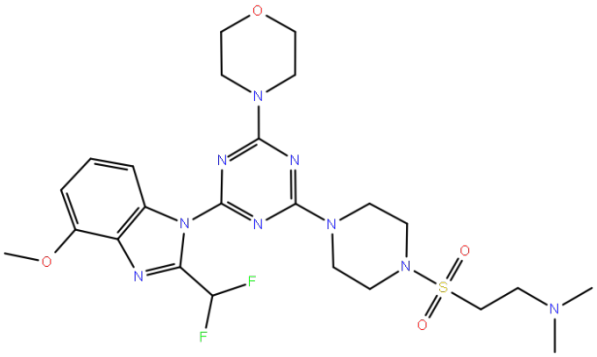
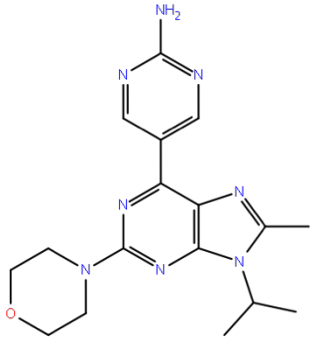
Supplementary Table 1. Chemical structures of dual PI3K/mTOR inhibitors that are not currently under clinical development. Data collected from https://www.ebi.ac.uk/chembl/ [63], http://zinc.docking.org/substances/home/ [64], https://pubchem.ncbi.nlm.nih.gov/ [65], https://www.drugbank.ca/ [66], https://fdasis.nlm.nih.gov/srs/. MW, molecular weight. IUPAC, International Union of Pure and Applied Chemistry. The three dual PI3K/mTOR inhibitors that are still in clinical development for humans (bimiralisib, GDC-0084 and gedatolisib) are presented in Table 1.

Official /Common/ Alternative name	3D-Structure	IUPAC Name	MW
Apitolisib, GDC-0980, RG7422		(2S)-1-(4-{[2-(2-aminopyrimidin-5-yl)-7-methyl-4-(morpholin-4-yl)thieno[3,2-d]pyrimidin-6-yl]methyl}piperazin-1-yl)-2-hydroxypropan-1-one	498.61
Dactolisib, BEZ235, NVP-BEZ235, RTB-101, NVP-BEZ235-NX		2-methyl-2-{4-[3-methyl-2-oxo-8-(quinolin-3-yl)-1H,2H,3H-imidazo[4,5-c]quinolin-1-yl]phenyl}propanenitrile	469.55
Omipalisib, GSK2126458, GSK458, GSK-212		2,4-difluoro-N-{2-methoxy-5-[4-(pyridazin-4-yl)quinolin-6-yl]pyridin-3-yl}benzene-1-sulfonamide	505.51
Panulisib, P7170, S9WA04F921		[8-[6-amino-5-(trifluoromethyl)pyridin-3-yl]-1-[6-(2-cyanopropan-2-yl)pyridin-3-yl]-3-methylimidazo[4,5-c]quinolin-2-ylidene]cyanamide	527.5

Official /Common/ Alternative name	3D-Structure	IUPAC Name	MW
Samotolisib, LY3023414, GTPL8918		8-[5-(2-hydroxypropan-2-yl)pyridin-3-yl]-1-[(2S)-2-methoxypropyl]-3-methylimidazo[4,5-c]quinolin-2-one	406.5
Voxtalisib, XL765, SAR245409		2-amino-8-ethyl-4-methyl-6-(1H-pyrazol-5-yl)-7H,8H-pyrido[2,3-d]pyrimidin-7-one	270.3
BGT226, NVP-BGT226		8-(6-methoxypyridin-3-yl)-3-methyl-1-[4-piperazin-1-yl-3-(trifluoromethyl)phenyl]imidazo [4,5-c] quinolin-2-one	534.54
DS7423, 70895382		1-{4-[2-(2-aminopyrimidin-5-yl)-6-(morpholin-4-yl)-9-(2,2,2-trifluoroethyl)-9H-purin-8-yl]-2-methylpiperazin-1-yl}ethan-1-one	520.5

Official /Common/ Alternative name	3D-Structure	IUPAC Name	MW
GNE-477		5-(7-methyl-6-((4-(methylsulfonyl)piperazin-1-yl)methyl)-4-morpholinothieno[3,2-d]pyrimidin-2-yl)pyrimidin-2-amine	504.64
PF-04691502		2-amino-6-(6-methoxypyridin-3-yl)-4-methyl-8-[(1r,4r)-4-(2-hydroxyethoxy)cyclohexyl]-7H,8H-pyrido[2,3-d]pyrimidin-7-one	425.49
PF-04979064		1-[1-[(2S)-2-hydroxypropanoyl]piperidin-4-yl]-3-methyl-8-(6-methylpyridin-3-yl)imidazo[4,5-c][1,5]naphthyridin-2-one	446.51
PI-103, 9884685		3-(6-morpholin-4-yl-8-oxa-3,5,10-triazatricyclo[7.4.0.02,7]trideca-1(9),2(7),3,5,10,12-hexaen-4-yl)phenol	348.36

Official /Common/ Alternative name	3D-Structure	IUPAC Name	MW
PKI-179		3-{4-[4-(morpholin-4-yl)-6-[(1R,5S)-3-oxa-8-azabicyclo[3.2.1]octan-8-yl]-1,3,5-triazin-2-yl]phenyl}-1-(pyridin-4-yl)urea	488.55
PKI-402, 44187953		1-[4-(3-ethyl-7-morpholin-4-yltriazolo[4,5-d]pyrimidin-5-yl)phenyl]-3-[4-(4-methylpiperazine-1-carbonyl)phenyl]urea	570.66
PQR530		4-(difluoromethyl)-5-[4-[(3S)-3-methylmorpholin-4-yl]-6-morpholin-4-yl-1,3,5-triazin-2-yl]pyridin-2-amine	407.4
PWT33597, VDC-597		3-{4-[3-ethyl-7-(morpholin-4-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-yl]phenyl}-1-[4-(4-methylpiperazine-1-carbonyl)phenyl]urea	684.74
SF-1126		(2S)-2-[[(2S)-3-carboxy-2-[[2-[[(2S)-5-(diaminomethylideneamino)-2-[[4-oxo-4-[[4-(4-oxo-8-phenylchromen-2-yl)morpholin-4-ium-4-yl]methoxy]butanoyl]amino]pentanoyl]amino]acetyl]amino]propanoyl]amino]-3-hydroxypropanoate	852.86

Official /Common/ Alternative name	3D-Structure	IUPAC Name	MW
			
SN32976, 1246202-11-8		2-[4-[4-[2-(difluoromethyl)-4-methoxybenzimidazol-1-yl]-6-morpholin-4-yl-1,3,5-triazin-2-yl]piperazin-1-yl]sulfonyl-N,N-dimethylethanamine	581.6
VS-5584, SB2343		5-(8-methyl-2-morpholin-4-yl-9-propan-2-ylpurin-6-yl)pyrimidin-2-amine	354.4