"A potent class III PI3K inhibitor lead compound proposed for preclinical development as a glioblastoma therapeutic"

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Standard GBM treatment is toxic and is associated with a dismal prognosis

Maximal surgical resection

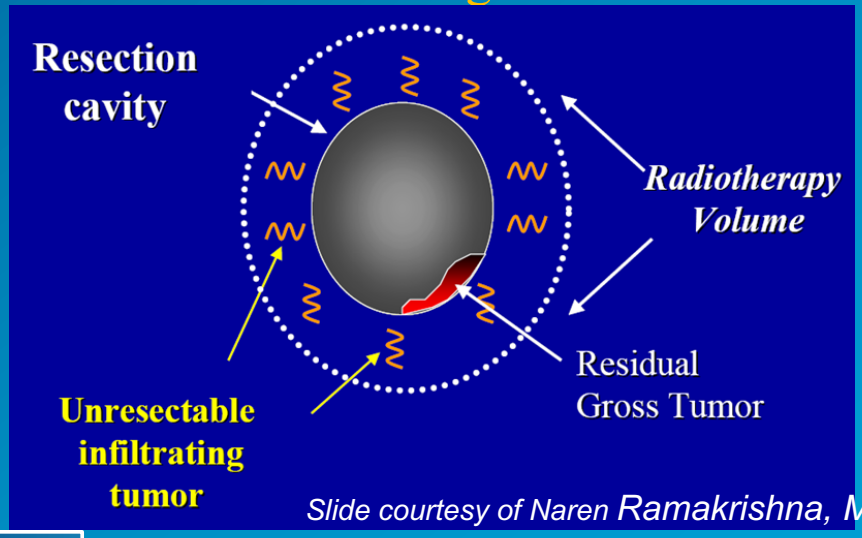
Many cells and masses are missed – disrupts normal tissue

Involved-field megavoltage radiation therapy
+
Concurrent temozolomide 75 mg/m^2

Brain tissue and stem cell niche *permanently* damaged in the very few survivors

6-12 cycles of temozolomide
150-200 mg/m^2

TMZ toxic systemically and to stem cell niches



Slide courtesy of Naren Ramakrishna, M.D.

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New therapeutics are urgently needed for GBM

PI3K inhibitors are often effective in GBM cultures but not *in vivo*

This is because of three problems:

1. Many compounds have poor brain penetrability
2. Enhanced PI3K signaling via feedback loops after initial PI3K blockade
3. GBM cell signaling redundancy

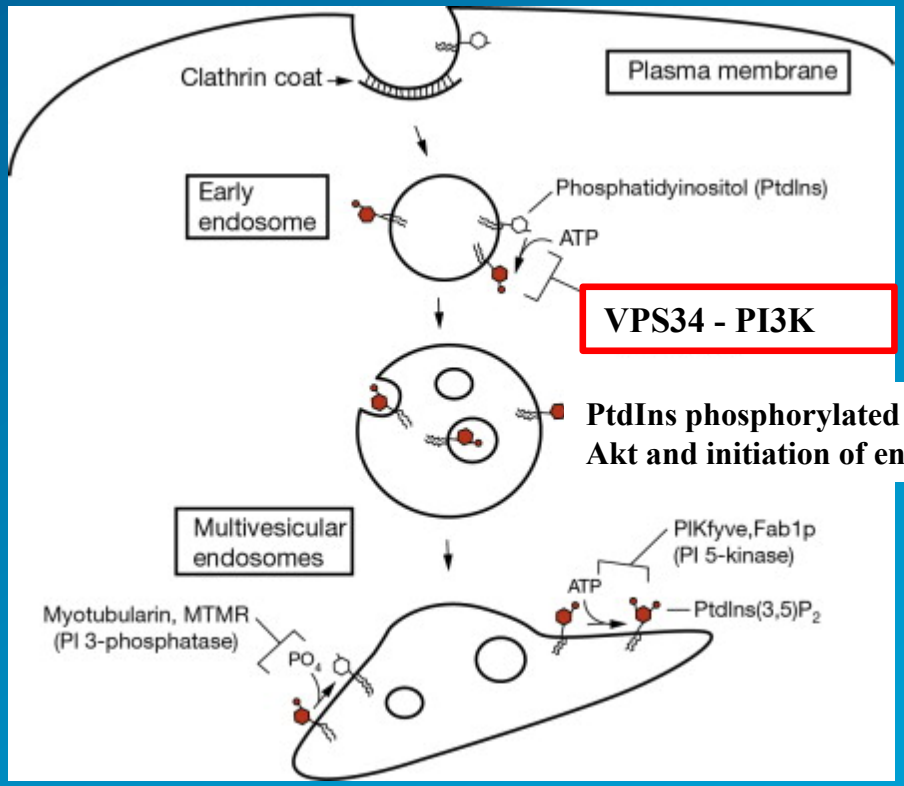
Potential solutions:

1. Good brain penetrance
2. Targeting a novel PI3K pathway – autophagy – VPS34 and more than one signaling protein; VPS34 & mTOR & PI3Ka, PI3Kb, PI3Kd, PI3Kg

A key target may also be autophagy, which is a PI3K mediated catabolic pathway that yields amino acids for tumor survival and proliferation, and modulates immunity

VPS34 is a phosphoinositide 3-kinase (PI3K) class III isoform that has a key role in autophagy and immunoregulation.

Autophagy cascade



PtdIns phosphorylated by VPS34-PI3K facilitate docking of Akt and initiation of endosomally mediated autophagy

Inhibition of Vps34 blocks autophagy and triggers inflammation to potentiate anti–PD-1/PD-L1 immunotherapy.

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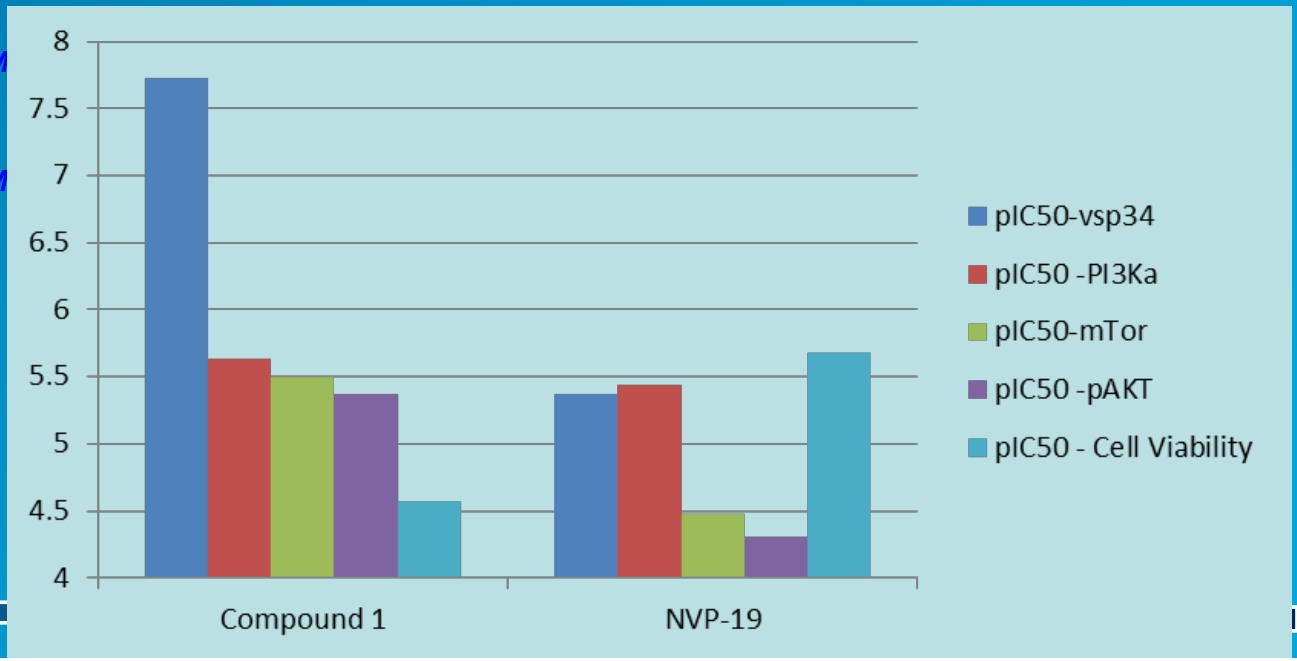
Potential Utility of a VPS34 (Class III PI3K) Inhibitor

Novartis developed the NVP-19 VPS inhibitor based on the following rationale:

- Autophagy may prolong the survival of tumor cells defective in apoptosis by protecting them from metabolic stress.
- Inhibiting autophagy and sensitizing apoptosis-resistant cells to metabolic stress represents a promising tumor therapy regimen. (Mathew et al. (2007) Nature Reviews)
- PTEN (phosphatase and tensin homologue detected in chromosome 10) is absent in a number of human cancers. Inhibiting VPS34 overcomes the absence of tumor suppressor PTEN, providing antitumor activity and increased tumor sensitivity to a wide variety of drugs. (Stein et al. (2001) Endocrine-Related Cancer)

In vitro data for GCT VPS34 inhibitor vs. Novartis compound

	Class III PI3K	Class I PI3K				Protein Kinases	Cell-based Assays		ADMET – In Vitro				PK- In vivo				
	VPS34 IC_{50} (uM)	PI3Ka IC_{50} (uM)	PI3Kb IC_{50} (uM)	PI3Kg IC_{50} (uM)	PI3Kd IC_{50} (uM)	mTOR IC_{50} (uM)	pAKT IC_{50} (uM)	Cell Viability IC_{50} (uM)	Plasma Protein Binding / Plasma stability @4h	HLM, DLM, RLM, MLM $t_{1/2}$ (min)	MDCK P_{app} A->B (R_E) %Recov	AUC_{inf} plasma (i.v.)	B/P ratio Cmax (i.v.)	$T_{1/2}$ (h) (i.v.)	Cl Plasma ml/min/ kg (i.v.)	Plasma Vss L/kg (i.v.)	Oral Bioavail %F
GCT-NPT 520-322	0.019	2.3	0.58	0.36	1.75	3.2	4.3	27	99%/ stable	49 27, 21, 21	45.6 (1.0) 103%	27068	0.38	1.3	6.16	1.40	68
NVP-19	4.3	3.6	-	-	-	>33 uM	>50	2.1	-	-	-	-	-	-	-	-	-



Key takeaways

1. GCT's VPS34 inhibitor is advanced, *i.e.*, at the lead stage.
2. Excellent oral bioavailability and BBB penetration.
3. Targets VSP34 in the low nanomolar range.
4. Next steps encompass *in vivo* orthotopic models of GBM to evaluate efficacy, tumor concentration, safety, etc., to provide a basis for pre-IND studies.