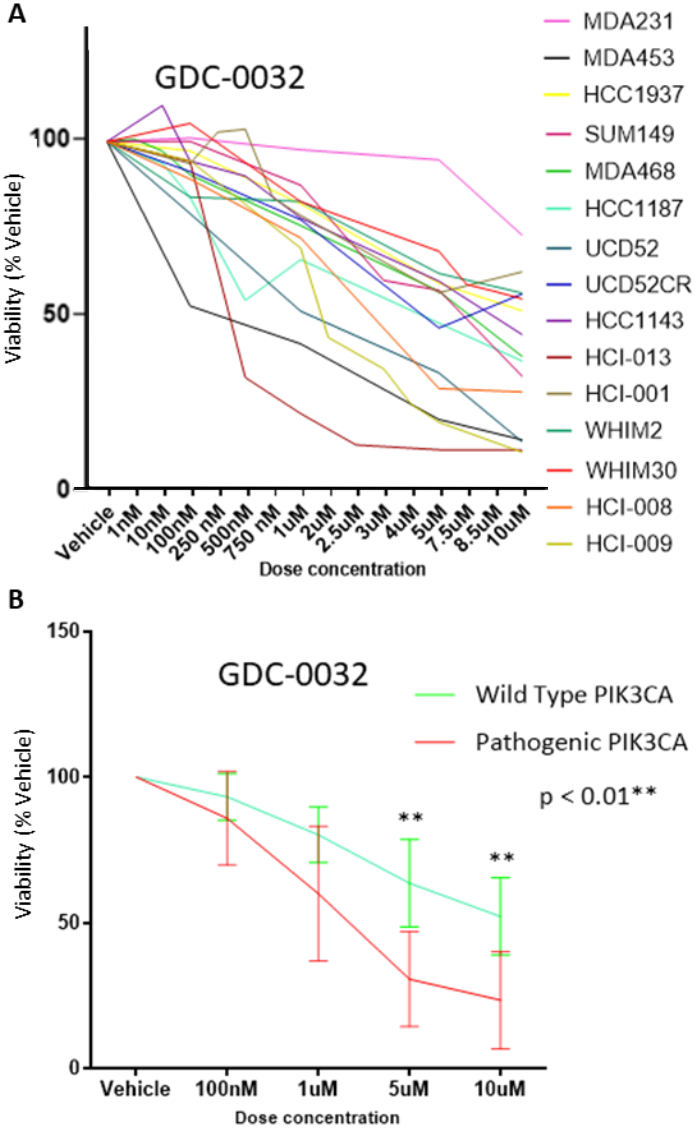
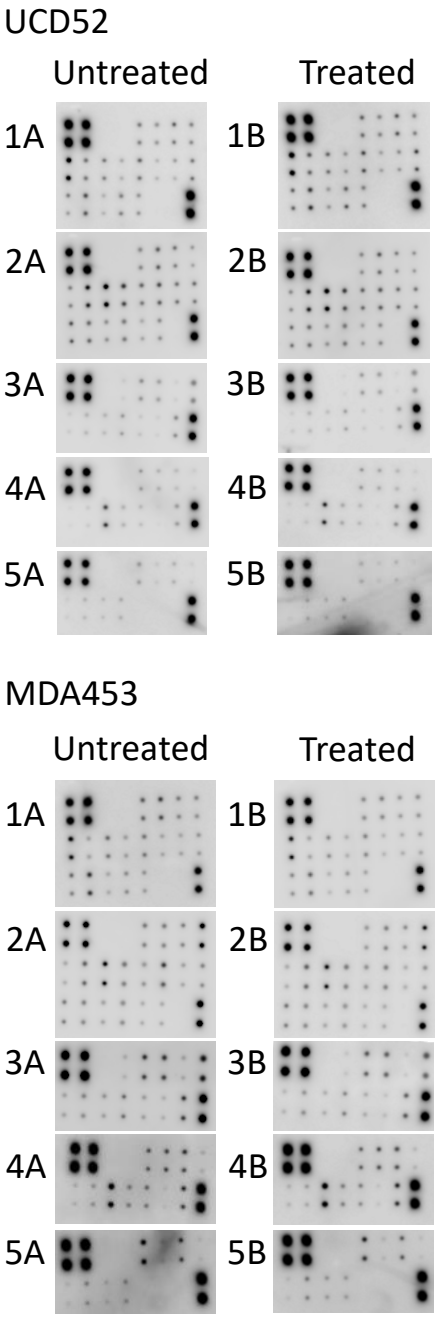
GSE	Samples (bulk)		GSE	Samples (sc)
GSE118942	HCI01.MGT.101020 HCI01.MGT.101021 HCI01.MGT.101022 HCI02.MGT.100945 HCI02.MGT.100946 HCI02.MGT.100948 HCI03.MGT.102031 HCI04.MGT.100763 HCI08.MGT.100879 HCI09.MGT.100241 HCI09.MGT.100508 HCI09.MGT.100511 HCI09.MGT.100512 HCI10.MGT.100276 HCI10.MGT.100277	HCI13.MGT.100822 PT52.MGT.100302 PT52.MGT.100303 PT52.MGT.100304 PT52.MGT.100775 PT52.MGT.100916 PT52.MGT.100917 WHIM2.MGT.100000 WHIM2.MGT.100027 WHIM2.MGT.100076 WHIM30.MGT.100431 WHIM30.MGT.175278A WHIM30.MGT.181040A WHIM30.MGT.182696A WHIM30.MGT.NSG21A	GSE174391	HCC1143 HCC1187 MDA468 SUM1493
GSE189325	WHIM2.107647 WHIM2.107647b	WHIM2.107668 WHIM2.107672	GSE189324	WHIM2_106305 WHIM2_106361
In process	BCM.0132.107564 BCM.15034.107894 BCM.15057.107957 BCM.15057.107968 BCM.2147.107741 BCM.2147.107744 BCM.2147.107745 BCM.2147CR2.107841 BCM.2147CR2.107842 BCM.2277.107573 BCM.3887.107696 BCM.5097.107568 BCM.5097.107931 HCI.001.107935 HCI.011.107898 HCI.013.107857 HCI.013.107939 UCD52CR21.107961 UCD52CR21.107964 UCD52CR21.107966 UCD52CR21.107967 WHIM30.107947	WHIM30CR6.107919 WHIM30CR6.107920 WHIM30CR7.107949 WHIM30CR7.107950 WHIM30CR7.107951 BCM.15034.107510 BCM.15057.107336 BCM.5097.107567 BCM.7482.107504 HCI.001.100097 HCI.011.107518 HCI.011.107522 HCI.013.102249 UCD52.100398 UCD52.100916 UCD52.107627 UCD52CR.107532 UCD52CR.107591 UCD52CR.107592 WHIM30.107661 WHIM30.107662 WHIM30CR.107502	In progress	BCM-2147_107007 BCM-2277_107010 BCM-3887_107156 BCM-7482_107157 HCI-001-105983 HCI-001-105984 UCD52 UCD52CR UC52CR_107080-107081 WHIM2_105940 WHIM30_105954

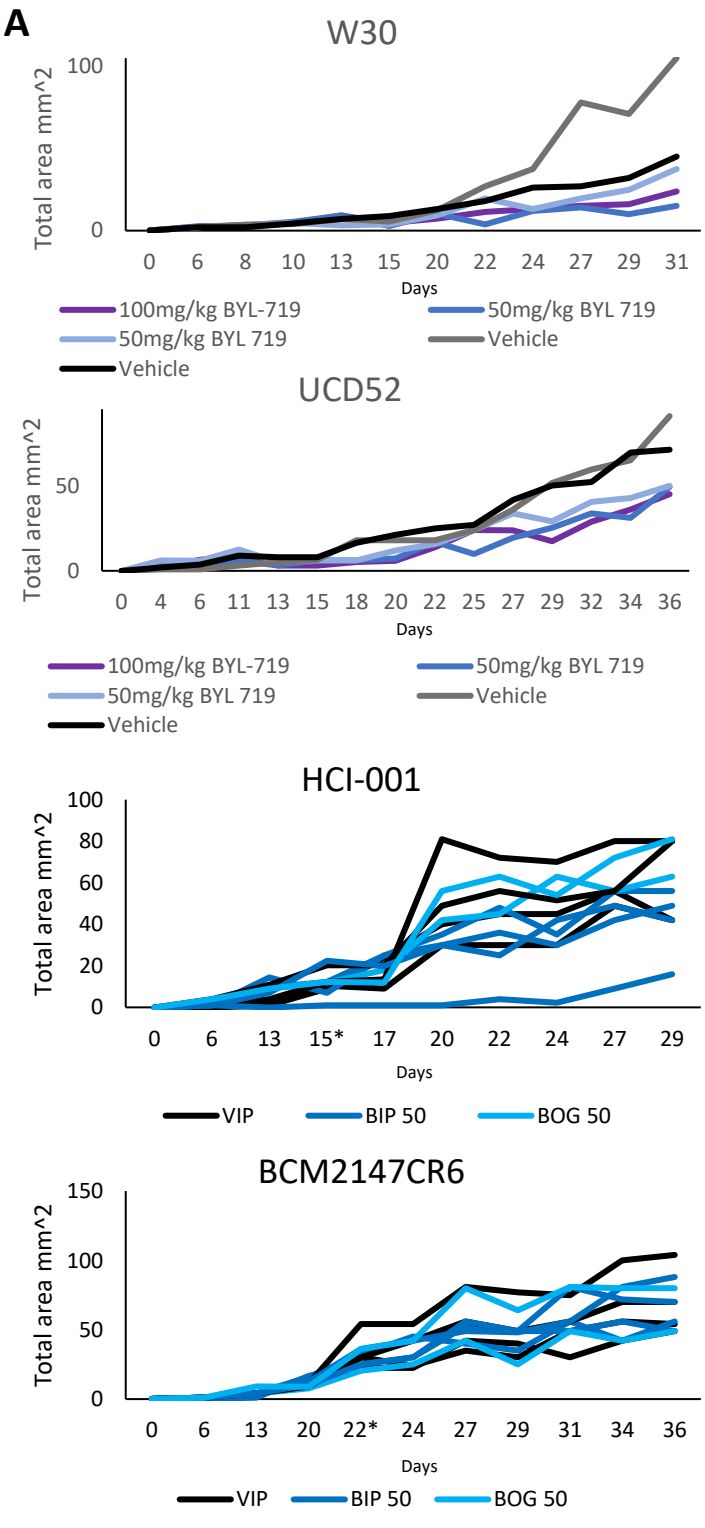
Supplemental Table S1. Bulk and scRNA samples used.



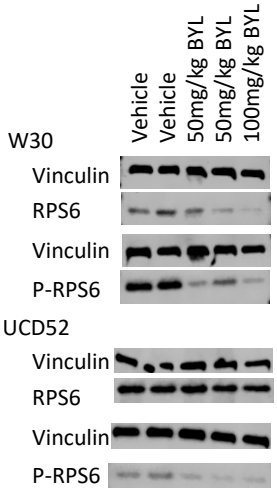
Supplemental Figure S1. Pathogenic PIK3CA containing models were more responsive to GDC- 0032. (A) Dose to viability by model *in vitro*. (B) Dose to viability by model, grouped by PIK3CA oncogenic status



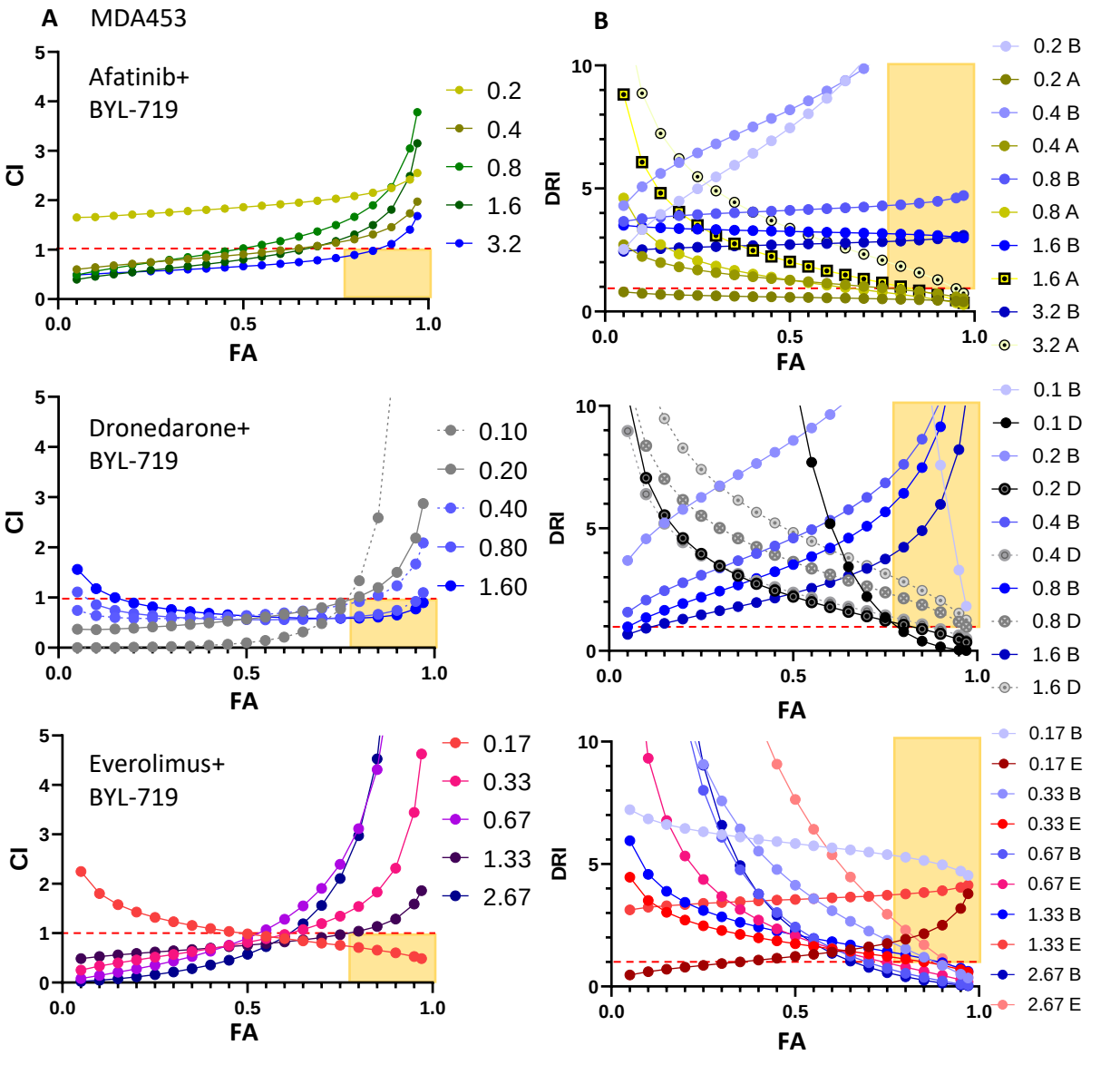
Supplemental Figure S2. Phospho-protein array membranes of (As) untreated and treated (Bs) from lysates made with UCD52 and MDA453 treated with BYL-719. Each number denotes the numbered membrane from the RayBiotech C55 phosphoprotein array.



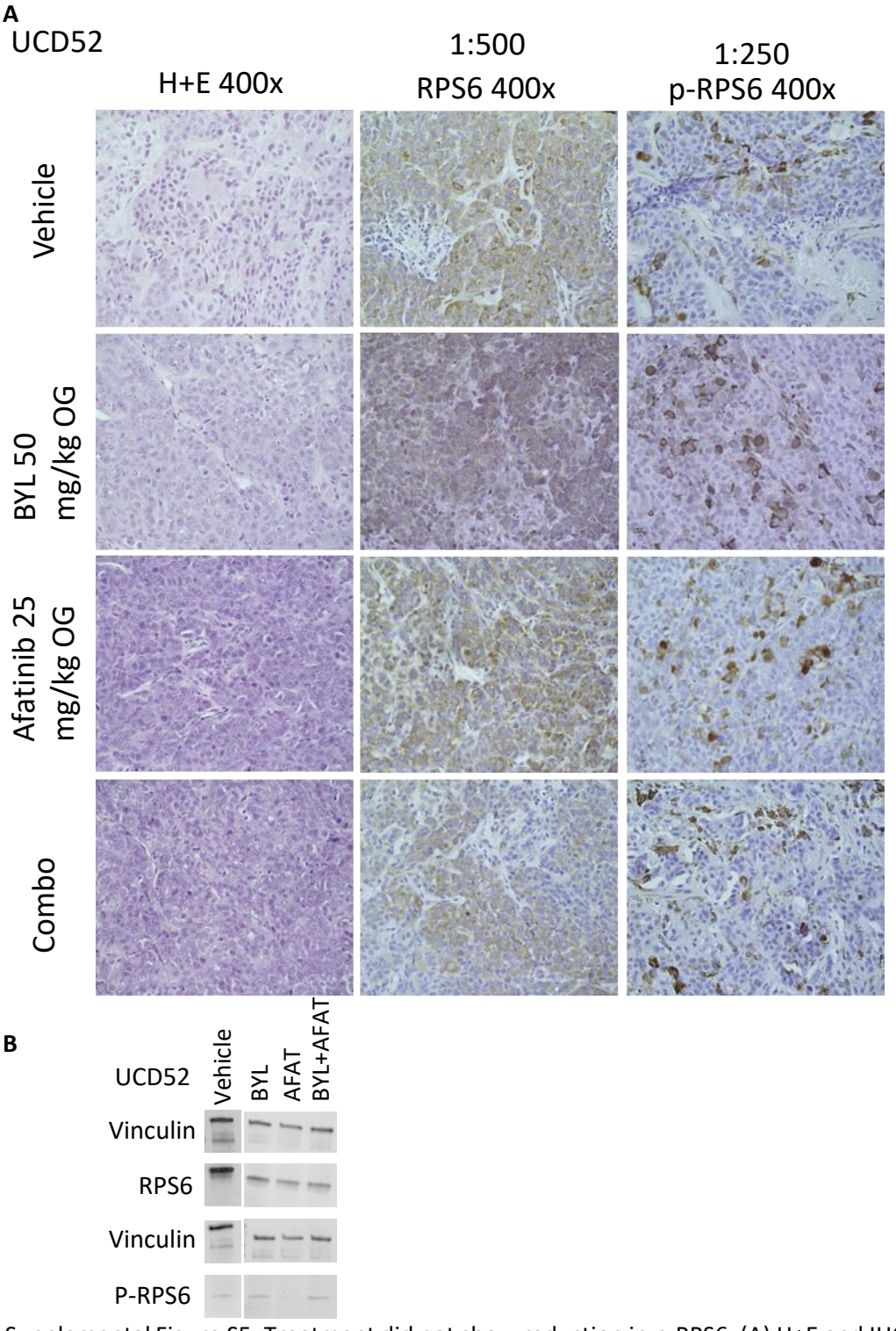
B



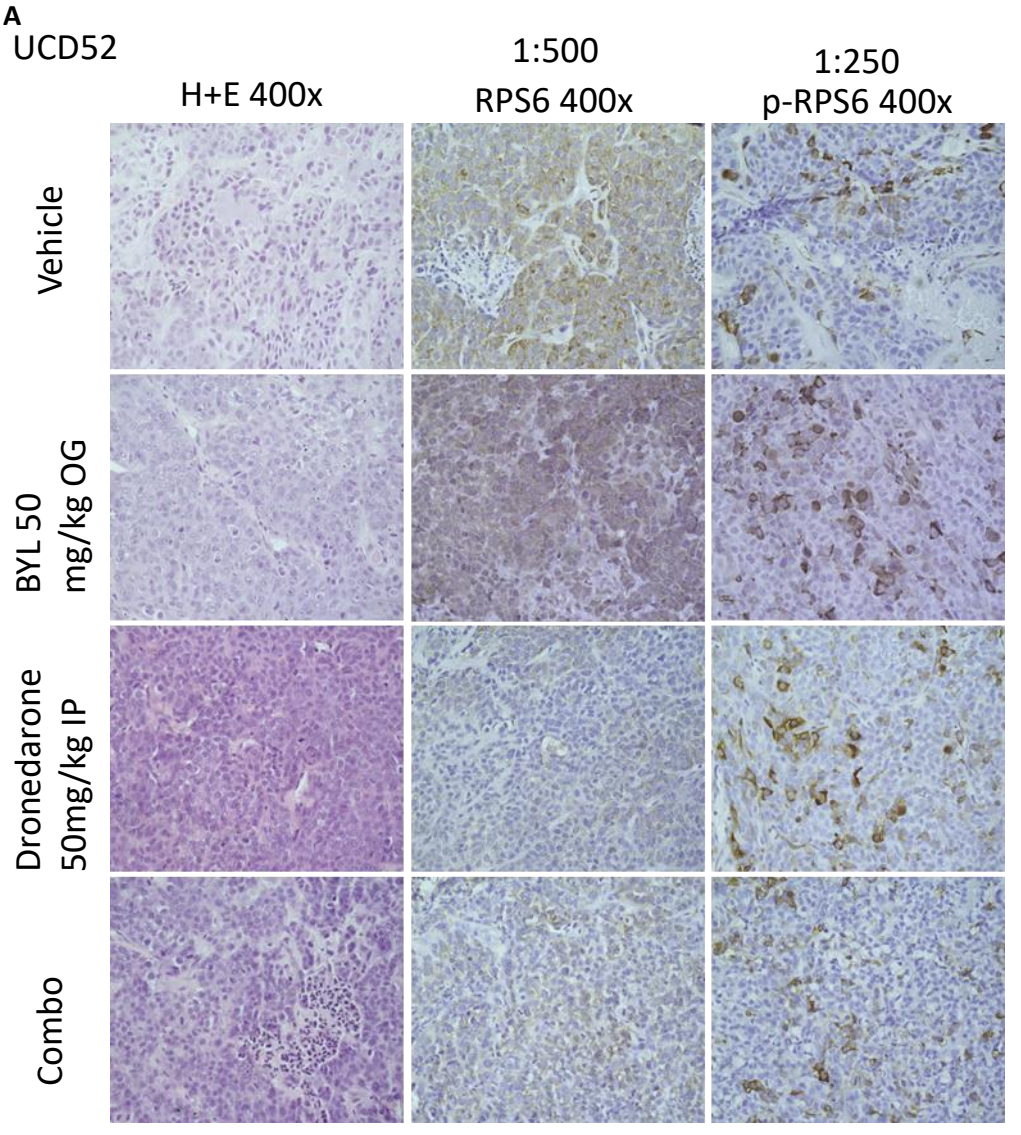
Supplemental Figure S3. Preliminary single agent trials of BYL-719 showed some efficacy in WHIM30 and UCD52, but resistance arose. In HCI-001 and BCM2147CR6, the drug preformed as well as vehicle.

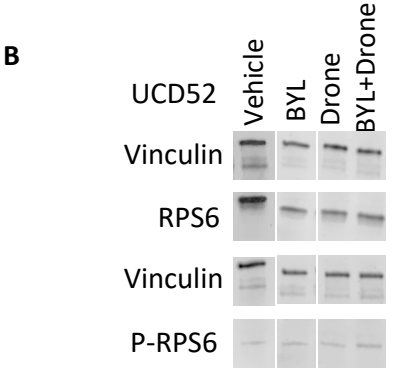


Supplemental Figure S4. Full output from CompuSyn shows multiple drug ratios which were effective in MDA453 for Combination Index (CI) and for Dose Reduction Index (DRI) and high Fraction Affacted (FA)

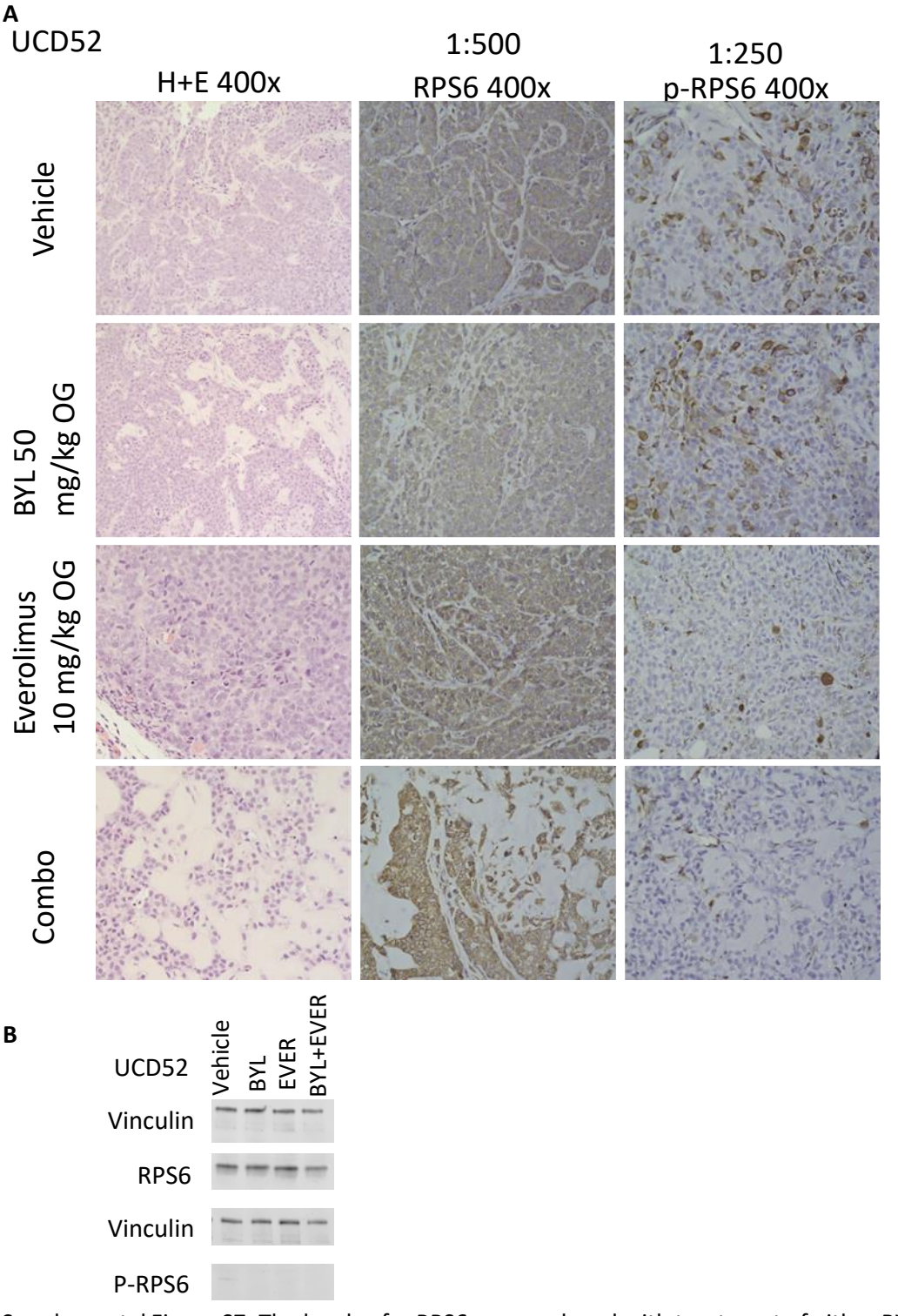


Supplemental Figure S5. Treatment did not show reduction in p-RPS6. (A) H+E and IHC of RPS6 and p-RPS6 of each treatment group in the BYL-719 with Afatinib trial in UCD52. (B) Western blots of Vinculin loading control and RPS6 and p-RPS6.

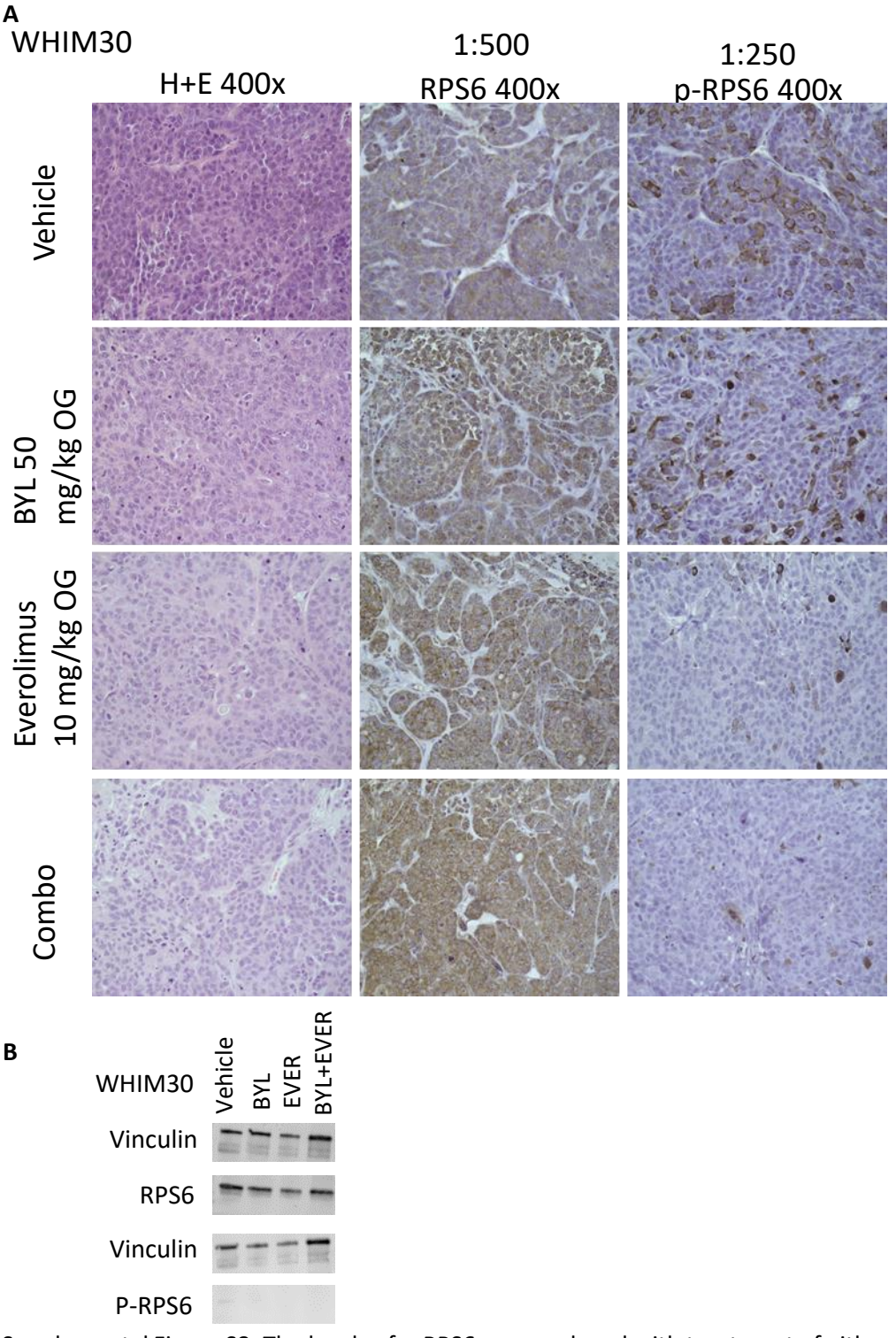




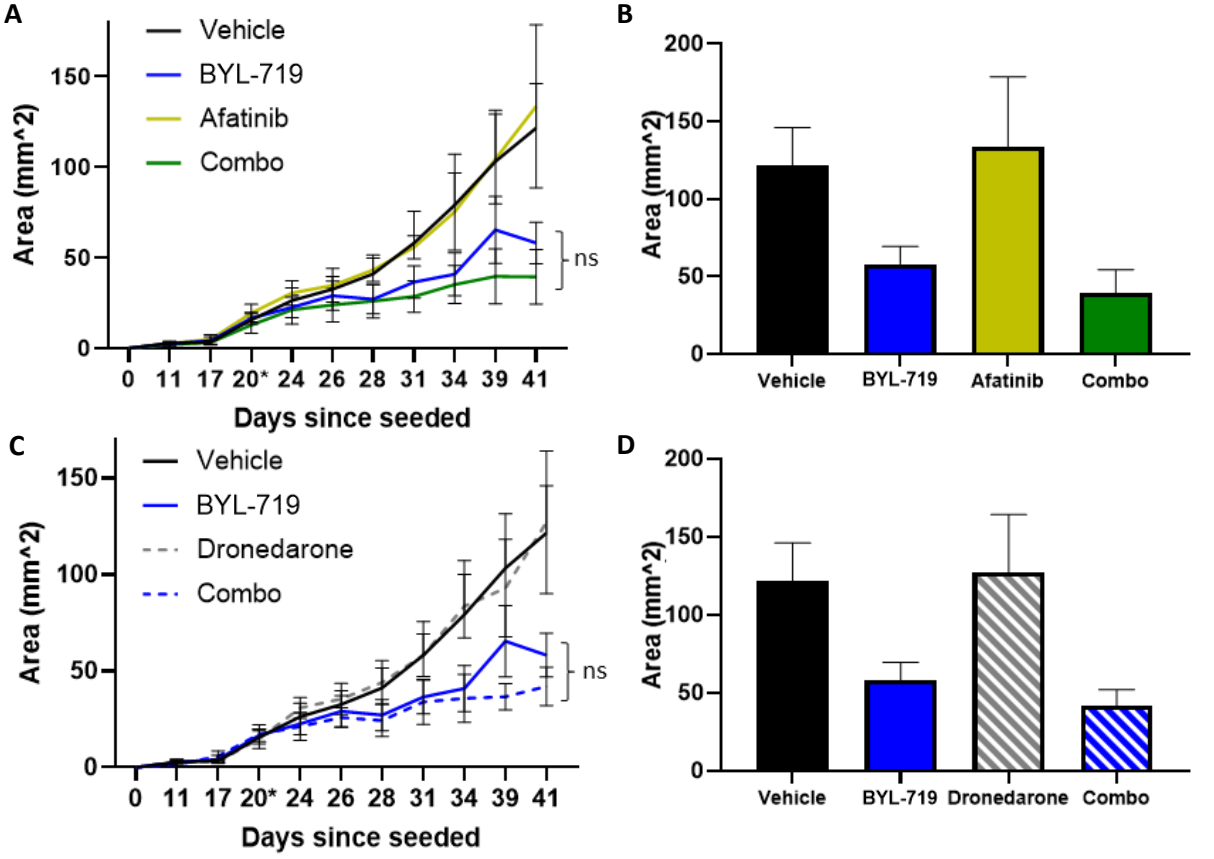
Supplemental Figure S6. Total RPS6 was reduced with dronedarone treatment in UCD52 in IHC but not in western. (A) H+E and IHC of RPS6 and p-RPS6 of each treatment group in the BYL-719 with Dronedarone trial in UCD52. (B) Western blots of Vinculin loading control and RPS6 and p-RPS6.



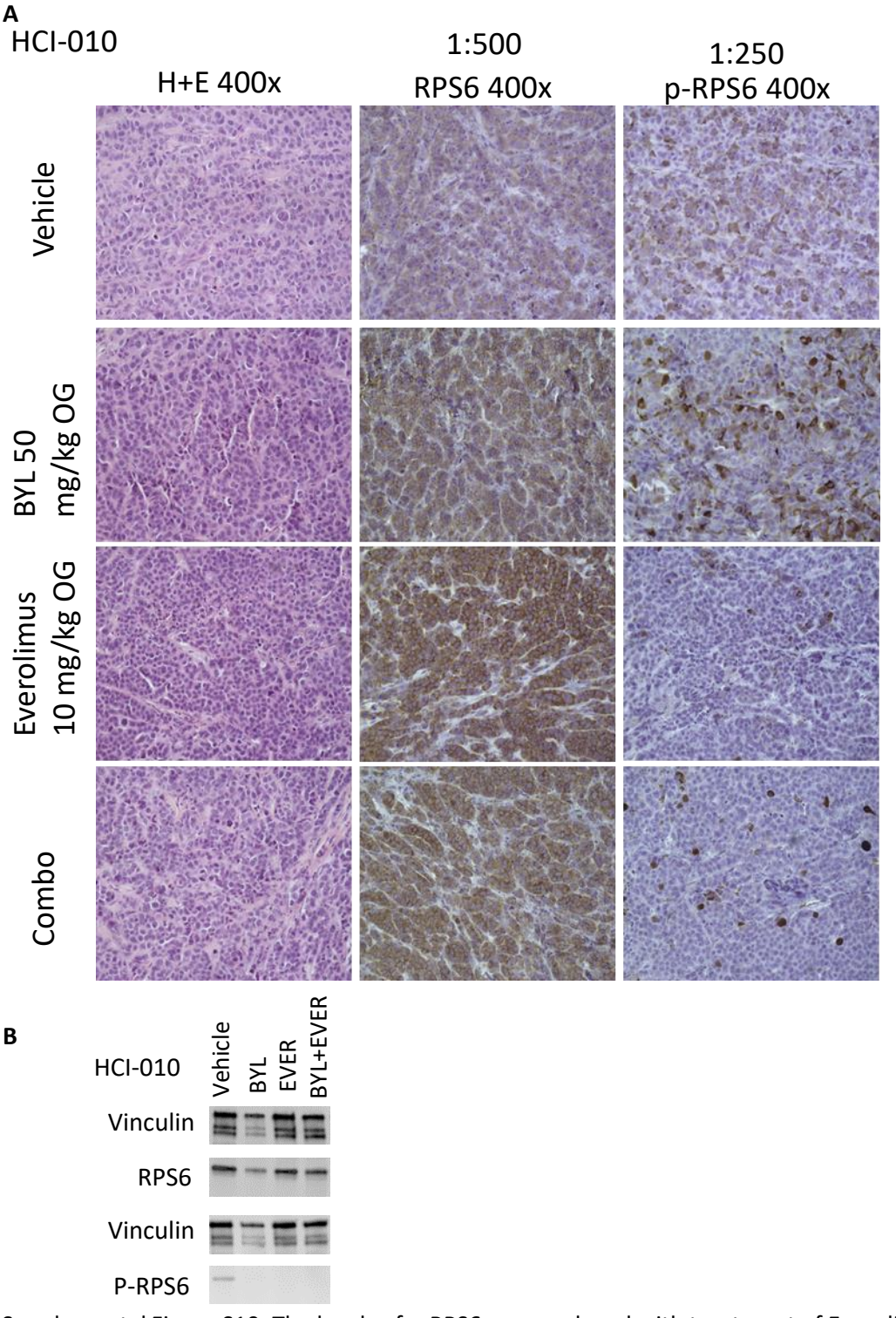
Supplemental Figure S7. The levels of p-RPS6 were reduced with treatment of either BYL-719 or Everolimus, and even further with combination therapy in UCD52. (A) H+E and IHC of RPS6 and p-RPS6 of each treatment group in the BYL-719 with Everolimus trial in UCD52. (B) Western blots of Vinculin loading control and RPS6 and p-RPS6.



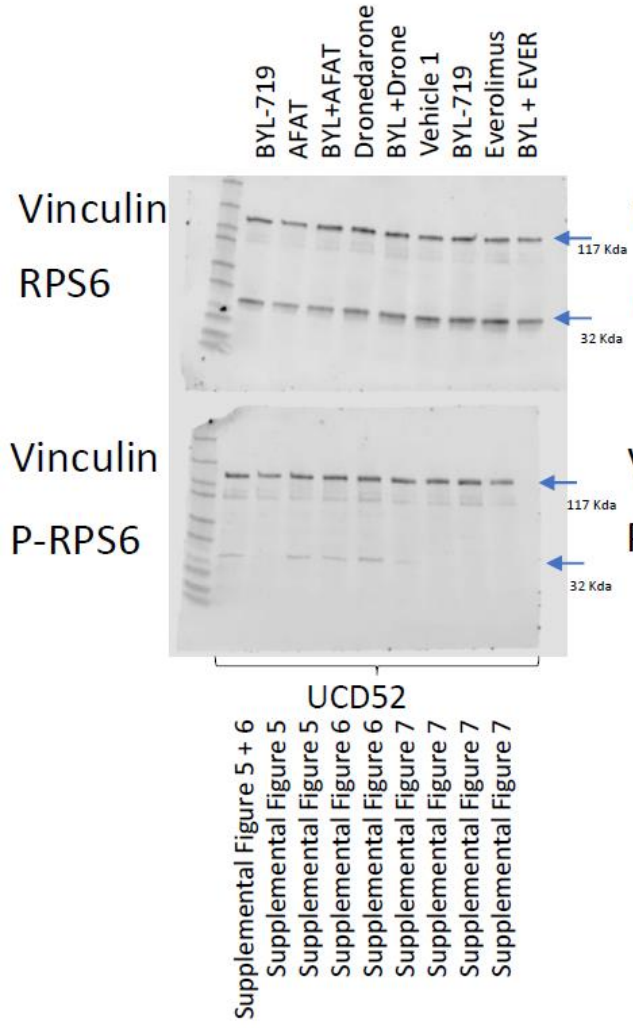
Supplemental Figure S8. The levels of p-RPS6 were reduced with treatment of either BYL-719 or Everolimus, and even further with combination therapy in WHIM30. (A) H+E and IHC of RPS6 and p-RPS6 of each treatment group in the BYL-719 with Everolimus trial in WHIM30. (B) Western blots of Vinculin loading control and RPS6 and p-RPS6.

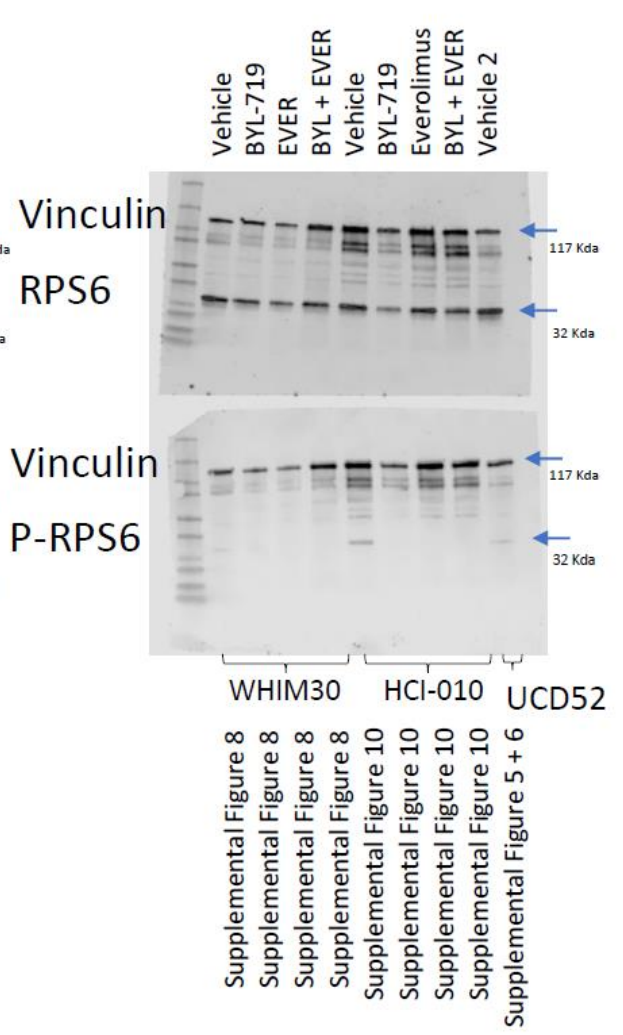


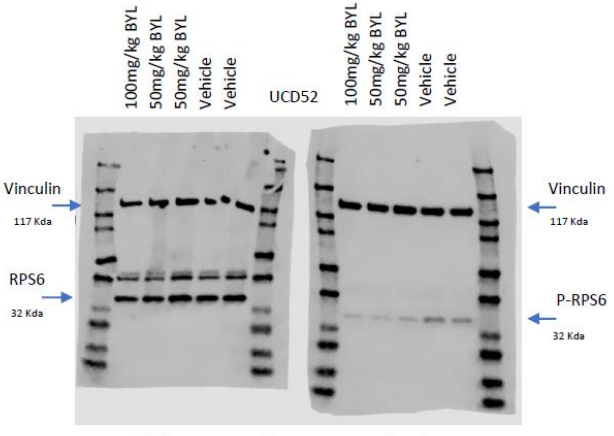
Supplemental Figure S9. Further combination therapies showed a trend of an effect in WHIM30. The final tumor area of the combinations of (A+B) Afatinib and (C+D) Dronedarone with BYL-719 was reduced relative to either treatment alone, but the effect of the combination was not significant relative to the effect of BYL-719 alone.



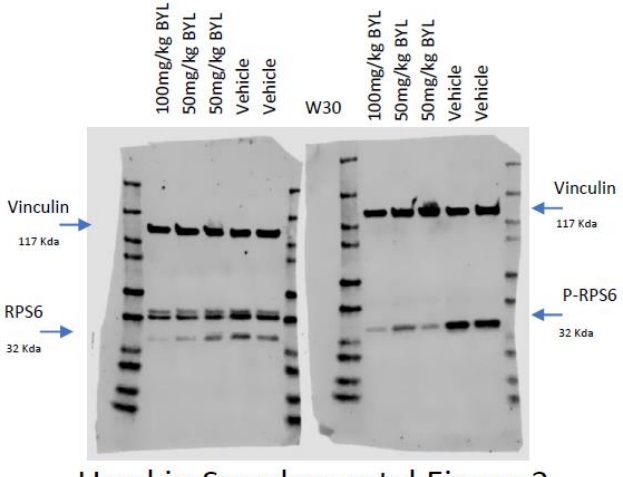
Supplemental Figure S10. The levels of p-RPS6 were reduced with treatment of Everolimus in HCI-010. (A) H+E and IHC of RPS6 and p-RPS6 of each treatment group in the BYL-719 with Everolimus trial in HCI-010. (B) Western blots of Vinculin loading control and RPS6 and p-RPS6.





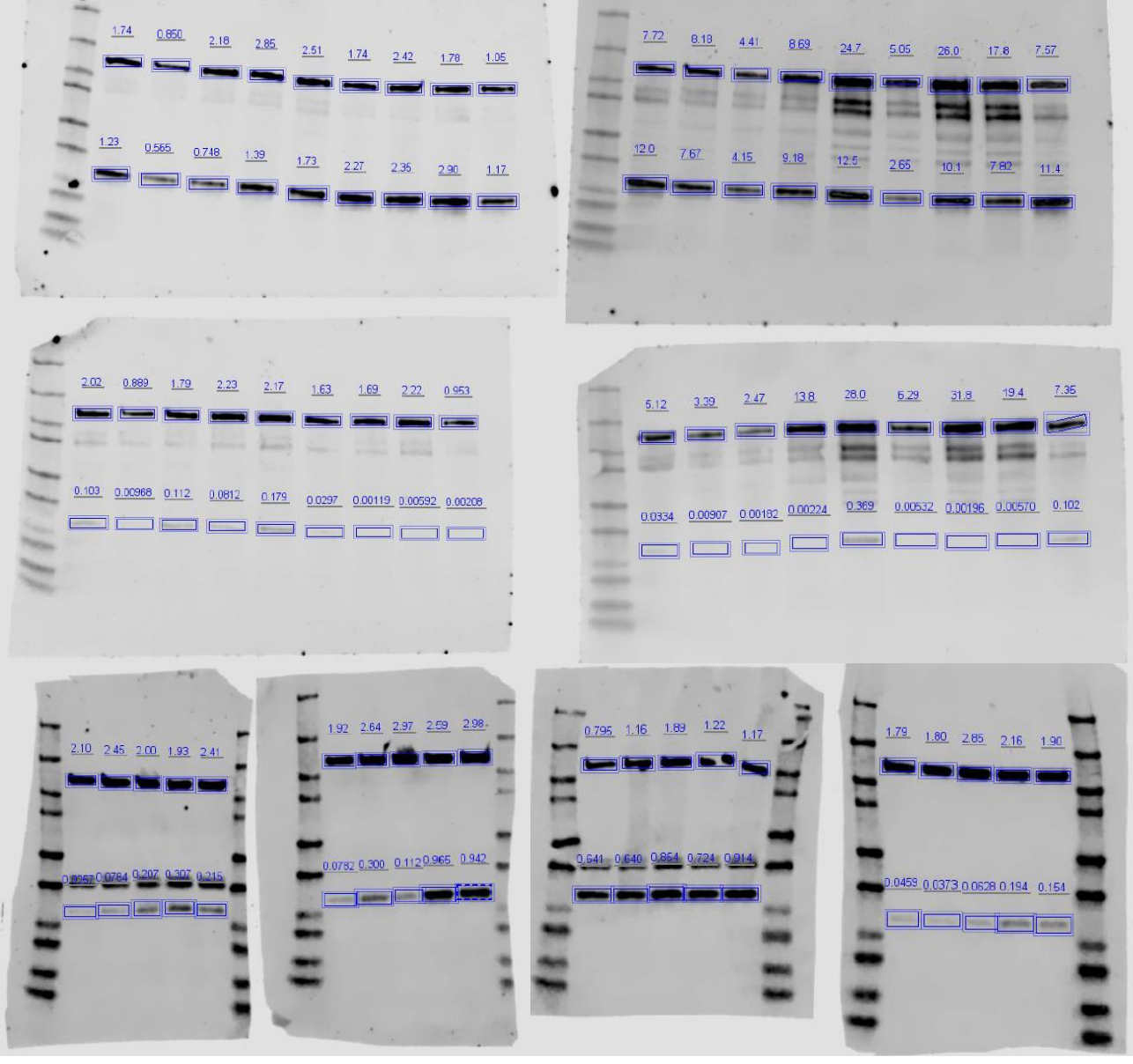


Used in Supplemental Figure 3



Used in Supplemental Figure 3

Supplemental Figure S11. Complete western blots of in vivo trials from tumors of the UCD52, WHIM30, and HCI-010 PDXs which were treated with vehicle, single agents, or combinations.



Supplemental Figure S12. Complete western blots of in vivo trials from tumors of the UCD52, WHIM30, and HCI-010 PDXs which were treated with vehicle, single agents, or combinations, values indicate densitometry.