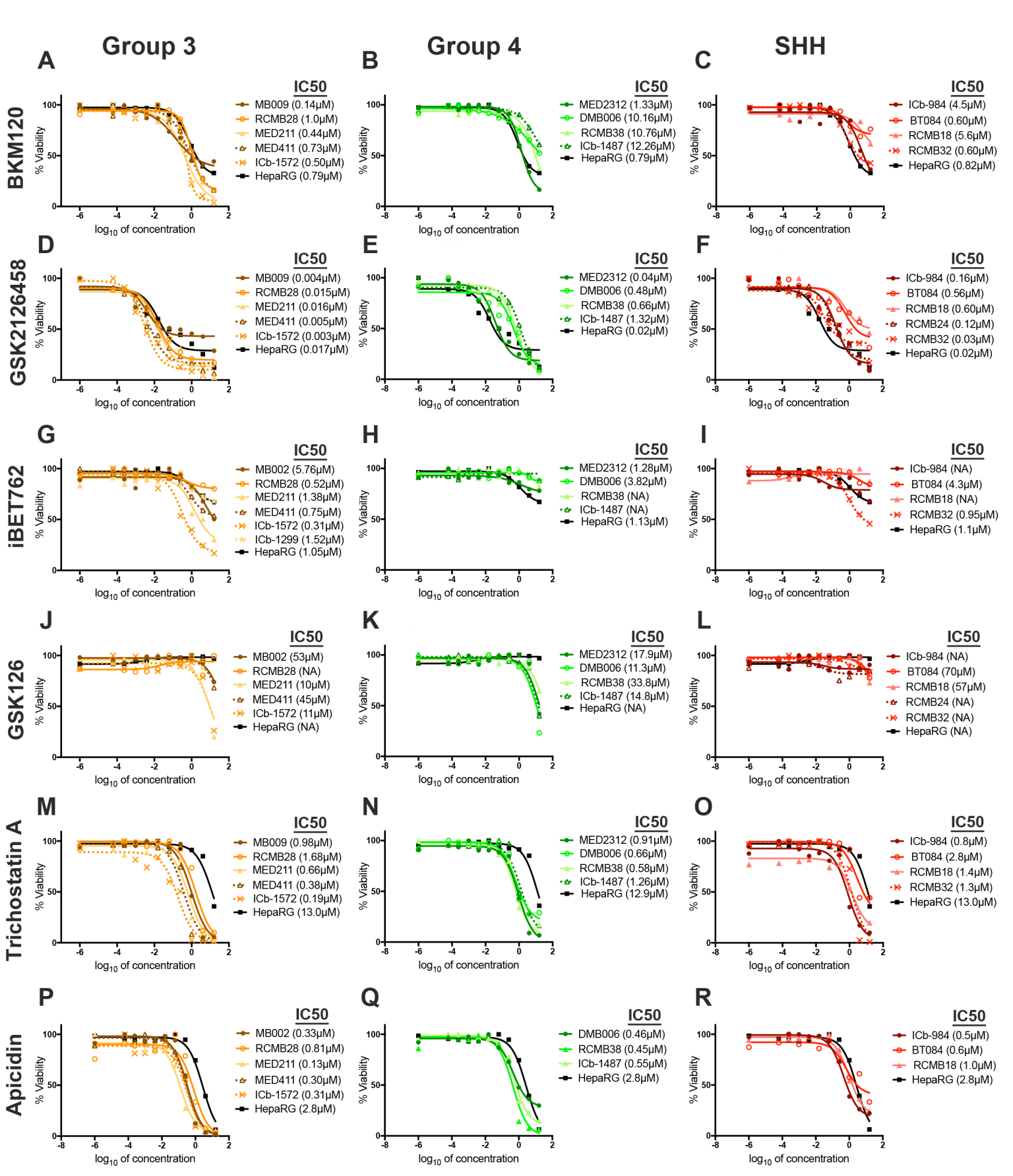
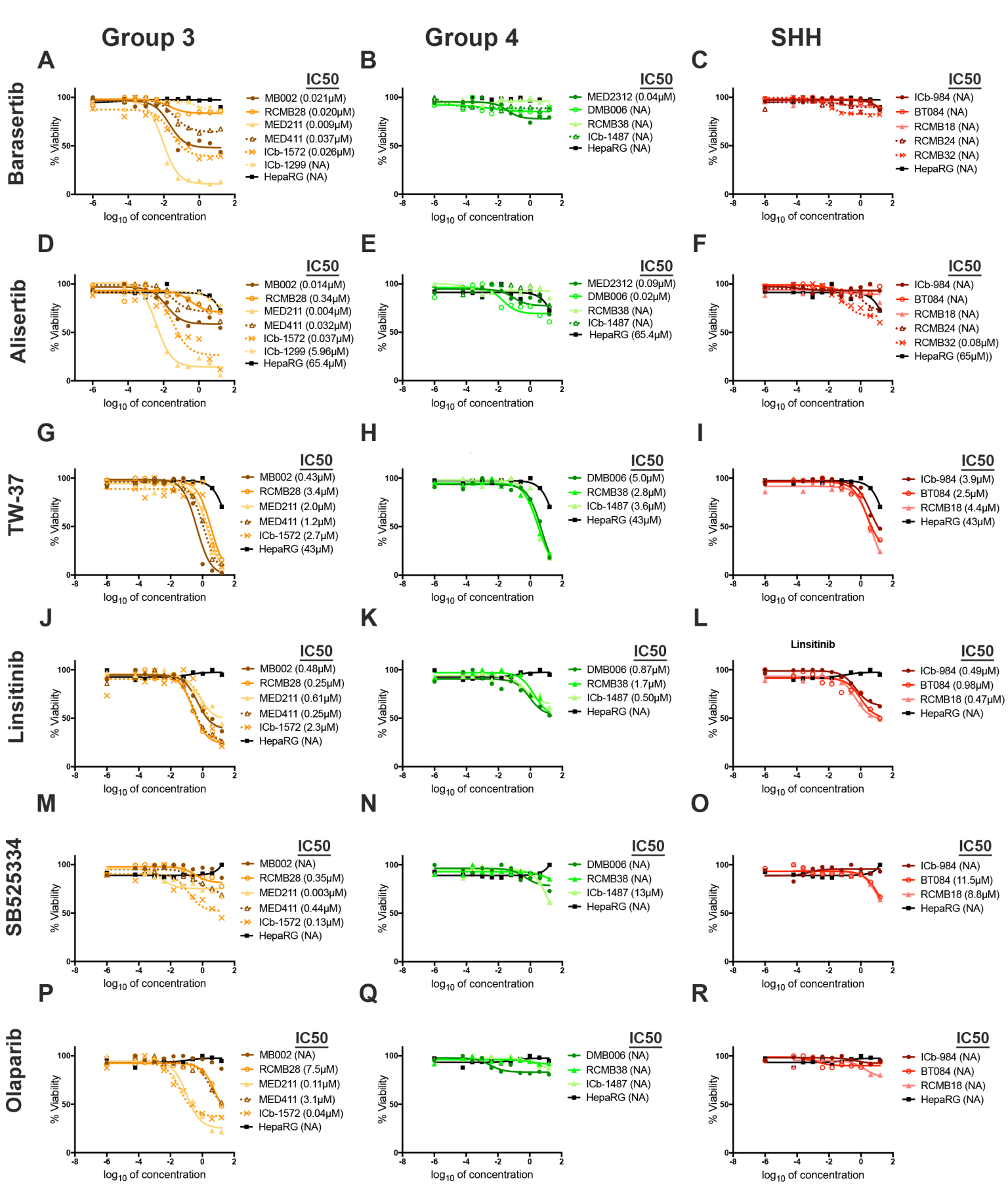


Supplementary Figure 1

Supplementary Figure 1: Mutation predicted drugs show variable response on PDX lines with each actionable lesion.

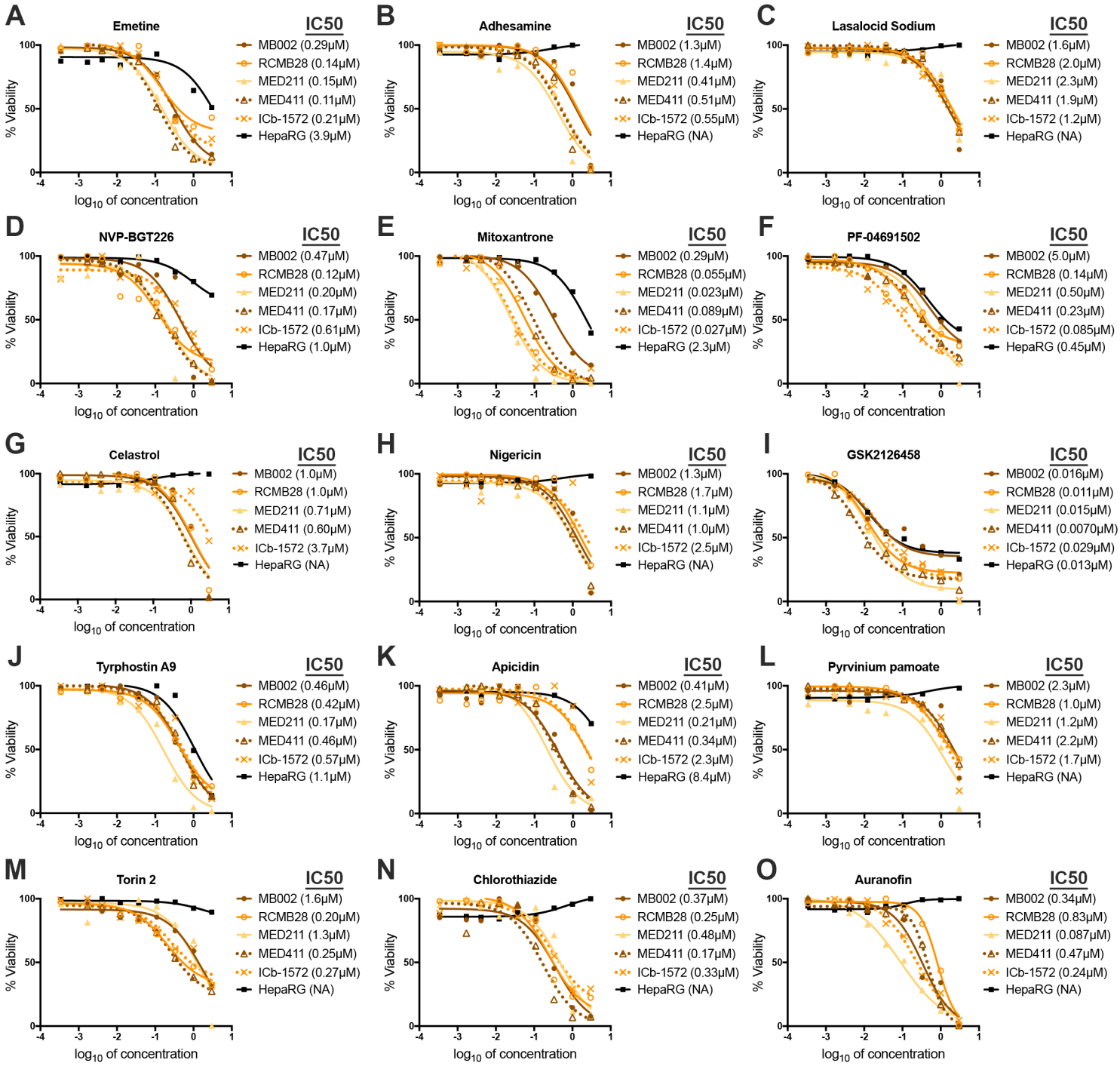
(A-R) Drugs predicted to work on genetic lesions described in Figure 2A were tested in dose response on PDX lines for effects on viability *in vitro* compared to HepaRG control cells and plotted against percent viability. IC50 values are listed after each PDX name. For each PDX, three biological replicates with three technical replicates each were performed. One biological replicate is shown for each PDX. The PI3K inhibitors BKM120 (A-C) and GSK2126458 (D-F), the BET inhibitor iBET762 (G-I), the EZH2 inhibitor GSK126 (J-L), and the HDAC inhibitors Trichostatin A (M-O) and Apicidin (P-R) were tested on Group 3 (A, D, G, J, M, P), Group 4 (B, E, H, K, N, Q), and SHH (C, F, I, L, O, R) PDX lines.



Supplementary Figure 2

Supplementary Figure 2: DiSCoVER predicted drug responses show variable concordance with predictions.

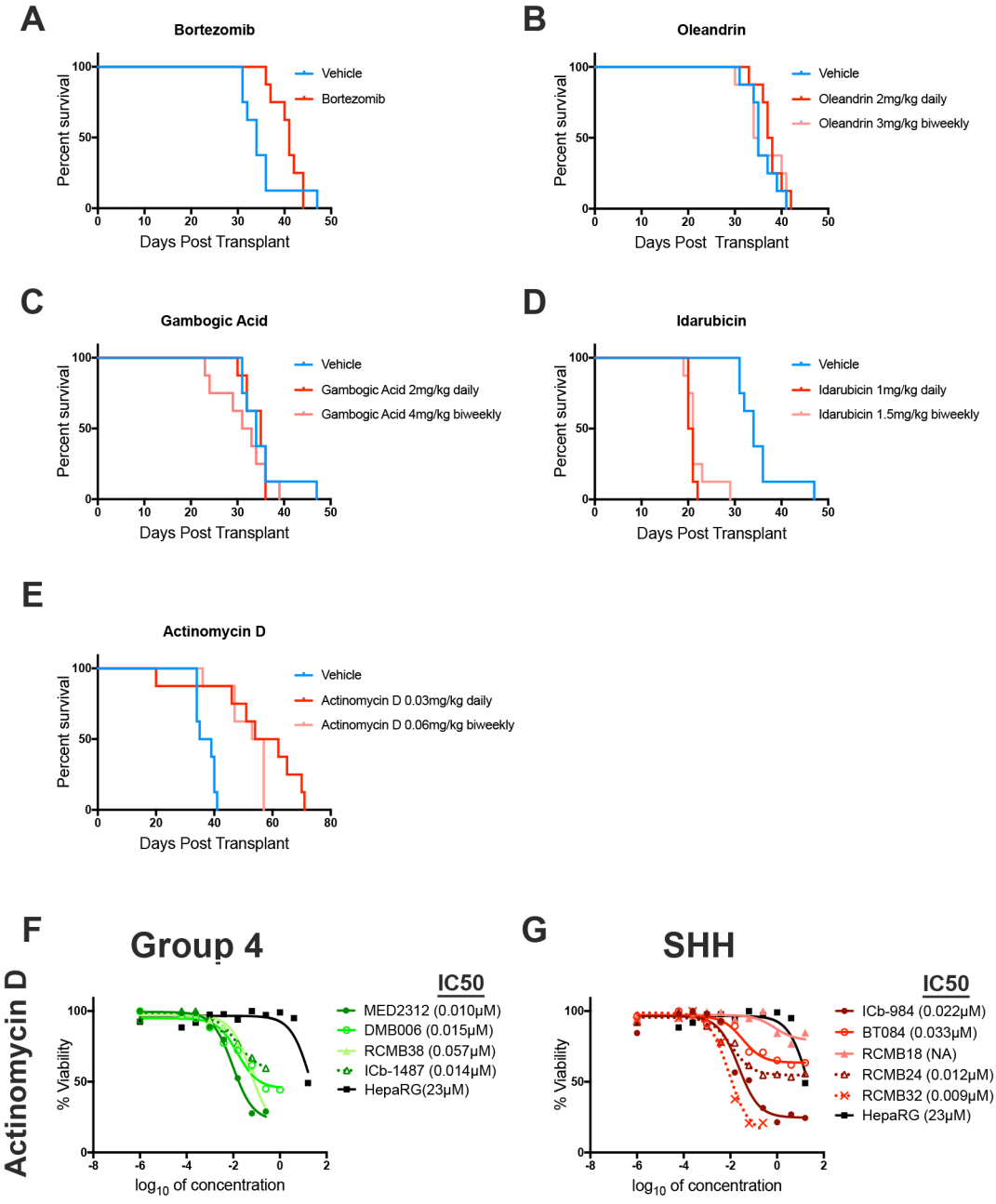
(A-R) Drugs suggested by DiSCoVER were tested in dose response on PDX lines for effects on viability *in vitro* compared to HepaRG control cells and plotted against percent viability. IC50 values are listed after each PDX name. For each PDX, three biological replicates with three technical replicates each were performed. One biological replicate is shown for each PDX. The Aurora kinase inhibitors Barasertib (A-B) and (D-F) Alisertib, the BCL2 inhibitor TW-37 (G-I), the IGFR1 inhibitor Linsitinib (J-L), the TGFbeta receptor I (ALK5) inhibitor SB525334 (M-O) and the PARP inhibitor Olaparib (P-R) were tested on Group 3 (A, D, G, J, M, P), Group 4 (B, E, H, K, N, Q), and SHH (C, F, I, L, O, R) PDX lines.



Supplementary Figure 3

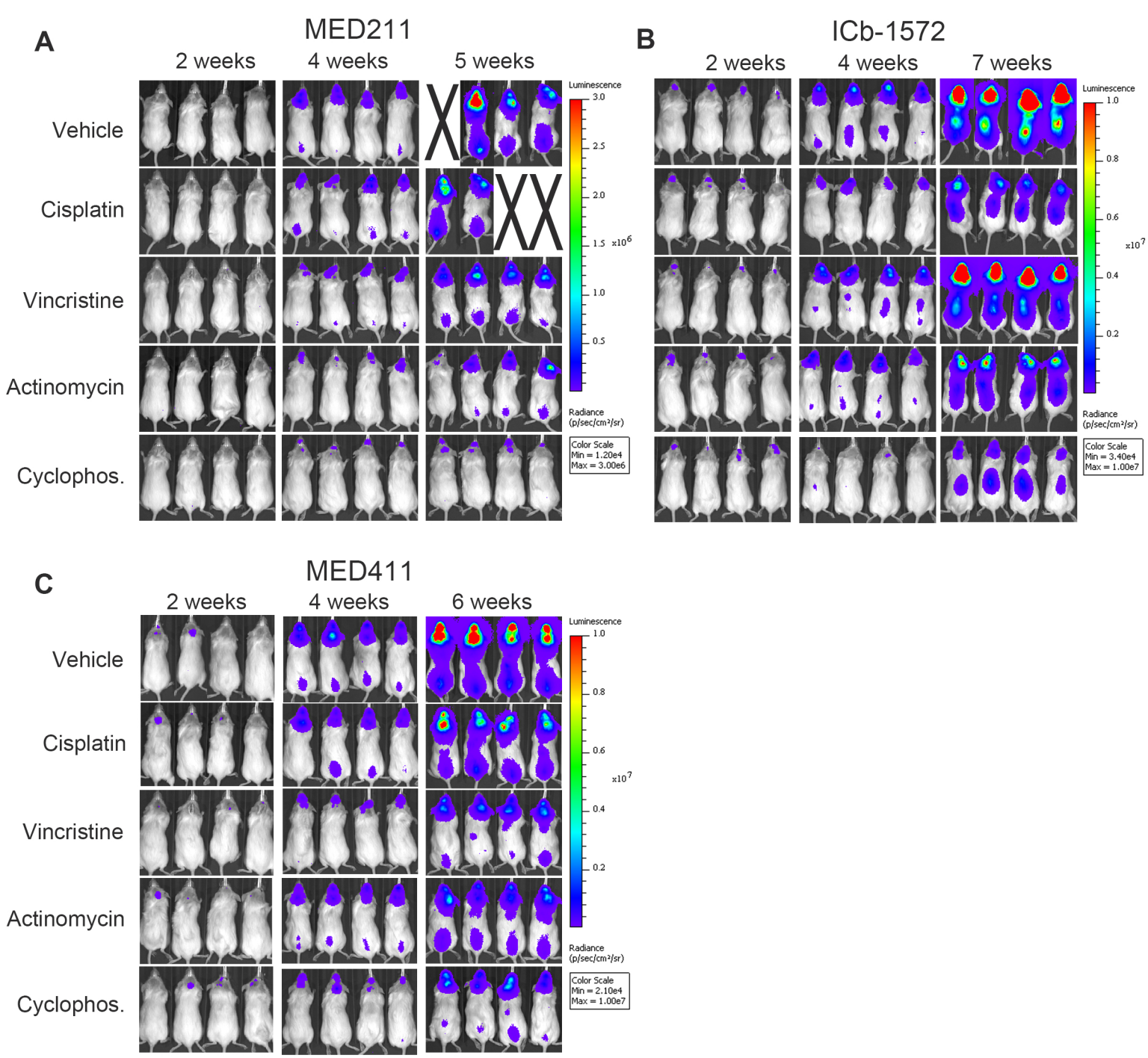
Supplementary Figure 3: Dose responses from 15 additional drug screening hits showed variable therapeutic windows.

(A-O) Drugs suggested by drug screening were tested in dose response on Group 3 PDX lines for effects on viability *in vitro* compared to HepaRG control cells and plotted against percent viability. IC50 values are listed after each PDX name. One biological replicate was performed for each PDX. The anti-protozoal Emetine (A), the glysosaminoglycan agonist Adhesamine (B), carboxylic polyether ionophore Lasalocid Sodium (C), the PI3K inhibitor NVP-GBT226 (D), the topoisomerase II inhibitor Mitoxantrone (E), the mTOR/PI3K inhibitor PF-04691502 (F), the multi-modal drug Celastrol (G), the potassium ionophore Nigericin (H), the Akt inhibitor GSK2126458 (I), the PDGF inhibitor Tyrphostin A9 (J), the HDAC inhibitor Apicidin (K), the anthelmintic Pyrvinium pamoate (L), the mTOR inhibitor Torin 2 (M), the thiazide diuretic Chlorothiazide (N), and the redox enzyme inhibitor Auranofin (O) are shown.



Supplementary Figure 4

Supplementary Figure 4: Actinomycin D is effective *in vitro* and *in vivo*.
(A-B) Actinomycin was tested in dose response on Group 4 (A) and SHH (B) PDX lines for effects on viability *in vitro* compared to HepaRG control cells and plotted against percent viability. IC50 values are listed after each PDX name. For each PDX, three biological replicates with three technical replicates each were performed. One biological replicate is shown for each PDX. (C-G) Mice with intracranial Group 3 PDX tumors (MED211) were treated with vehicle (10% DMSO, 10% Tween80, in sterile water i.p., n=8), (C) Bortezomib (1 mg/kg biweekly, i.p., n=8), (D) Oleandrin (2 mg/kg daily or 3 mg/kg biweekly, i.p., n=8 for each), (E) Gambogic acid (2 mg/kg daily or 4 mg/kg biweekly i.p., n=8 for each), (F) Idarubicin (1 mg/kg daily or 1.5 mg/kg biweekly, i.p., n=8 for each), or (G) Actinomycin D (0.03 mg/kg daily or 0.06 mg/kg biweekly, i.p., n=8 for each) starting 2 weeks post-transplant.



Supplementary Figure 5

Supplementary Figure 5: Actinomycin D slows Group 3 PDX tumor growth better than at least one of the three standard of care chemotherapies.

(A-C) Mice with intracranial Group 3 PDX tumors were treated weekly with vehicle (10% DMSO i.p.), cisplatin (4.5 mg/kg i.p.), vincristine (1 mg/kg i.p.), actinomycin D (0.3 mg/kg i.v.), or cyclophosphamide (130 mg/kg i.p.) starting 2 weeks post-transplant with weeks off described in the methods. Bioluminescent imaging of luciferase labeled tumor cells is shown at the initiation of treatment and different intervals thereafter in (A) MED211, (B) ICb-1572, and (C) MED411. Biological triplicates were carried out for each PDX, and representative images are shown.