Patient demographics	Dose level 3/RP2D (n=41)
Age, years, median (range)	63 (42 – 85)
Sex, male/female (%)	17 (41) / 24 (59)
ECOG performance status, n (%)	
0	6 (15)
1	34 (83)
2	1 (2)
Prior lines of SCLC therapy, n (%)	
1	21 (51)
2	16 (39)
3	3 (7)
>3	1 (2)
Median (range)	1 (1-6)
Chemotherapy-free interval*	
≥ 90 days (“platinum sensitive”) (%)	30 (73)
< 90 days (“platinum resistant”) (%)	11 (27)
Baseline brain metastases present (%)	15 (37)
Treated	6 (15)
Untreated	9 (22)

Supplementary Table 1. Baseline patient demographics for patients enrolled to the RP2D (dose level 3) in both the phase I and II portions. Shown are data for the subset of patients enrolled to start at dose level 3 or RP2D. *Chemotherapy-free interval, defined as time from last date of first-line platinum-based chemotherapy to first date of second-line systemic therapy.

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	Phases 1 & 2 (n=50)					RP2D: Dose level 3 (n=41)				
Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1-4	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1-4
Thrombocytopenia	9 (18%)	12 (24%)	8 (16%)	5 (10%)	34 (68%)	8 (20%)	10 (24%)	7 (17%)	5 (12%)	30 (73%)
Anemia	12 (24%)	8 (16%)	14 (28%)	0	34 (68%)	8 (20%)	8 (20%)	13 (32%)	0	29 (71%)
Neutropenia	4 (8%)	4 (8%)	11 (22%)	8 (16%)	27 (54%)	4 (10%)	4 (10%)	9 (22%)	8 (20%)	25 (61%)
Fatigue	13 (26%)	10 (24%)	2 (4%)	0	25 (50%)	11 (27%)	9 (22%)	2 (5%)	0	22 (54%)
Nausea	14 (28%)	7 (14%)	0	0	21 (42%)	12 (29%)	4 (10%)	0	0	16 (39%)
Leukopenia	7 (14%)	4 (8%)	4 (8%)	5 (10%)	20 (40%)	6 (15%)	2 (5%)	4 (10%)	5 (12%)	17 (41%)
Vomiting	8 (16%)	2 (4%)	1 (2%)	0	11 (22%)	6 (15%)	2 (5%)	0	0	8 (20%)
Anorexia	4 (8%)	3 (6%)	2 (4%)	0	9 (18%)	4 (10%)	3 (7%)	2 (5%)	0	9 (22%)
Diarrhea	5 (10%)	2 (4%)	0	0	7 (14%)	4 (10%)	1 (2%)	0	0	5 (12%)
AST increase	5 (10%)	0	1 (2%)	0	6 (12%)	4 (10%)	0	1 (2%)	0	5 (12%)
Hyponatremia	4 (8%)	0	1 (2%)	0	5 (10%)	4 (10%)	0	1 (2%)	0	5 (12%)
Weight loss	3 (6%)	1 (2%)	0	0	4 (8%)	2 (5%)	1 (2%)	0	0	3 (7%)
ALT increase	2 (4%)	0	1 (2%)	0	3 (6%)	2 (5%)	0	1 (2%)	0	3 (7%)
Abdominal pain	2 (4%)	1 (2%)	0	0	3 (6%)	2 (5%)	0	0	0	2 (5%)
Hypomagnesemia	3 (6%)	0	0	0	3 (6%)	3 (7%)	0	0	0	3 (7%)
Hypoalbuminemia	3 (6%)	0	0	0	3 (6%)	2 (5%)	0	0	0	2 (5%)
Constipation	3 (6%)	0	0	0	3 (6%)	2 (5%)	0	0	0	2 (5%)
Lymphopenia	0	0	2 (4%)	0	2 (4%)	0	0	1 (2%)	0	1 (2%)
Weakness	1 (2%)	0	1 (2%)	0	2 (4%)	0	0	1 (2%)	0	1 (2%)
Creatinine increase	2 (4%)	0	0	0	2 (4%)	2 (5%)	0	0	0	2 (5%)
Dizziness	2 (4%)	0	0	0	2 (4%)	2 (5%)	0	0	0	2 (5%)
Heartburn	2 (4%)	0	0	0	2 (4%)	1 (2%)	0	0	0	1 (2%)
Lung infection	0	0	1 (2%)	0	1 (2%)	0	0	1 (2%)	0	1 (2%)
Febrile neutropenia	0	0	1 (2%)	0	1 (2%)	0	0	1 (2%)	0	1 (2%)
Pneumonitis	0	0	1 (2%)	0	1 (2%)	0	0	1 (2%)	0	1 (2%)
Mucositis	0	1 (2%)	0	0	1 (2%)	0	1 (2%)	0	0	1 (2%)
Dehydration	0	1 (2%)	0	0	1 (2%)	0	1 (2%)	0	0	1 (2%)
Fever	1 (2%)	0	0	0	1 (2%)	1 (2%)	0	0	0	1 (2%)
Hemorrhage, duod	1 (2%)	0	0	0	1 (2%)	1 (2%)	0	0	0	1 (2%)
Poor PO intake	1 (2%)	0	0	0	1 (2%)	1 (2%)	0	0	0	1 (2%)
Oral pain	1 (2%)	0	0	0	1 (2%)	0	0	0	0	0
Arthralgia	1 (2%)	0	0	0	1 (2%)	1 (2%)	0	0	0	1 (2%)
Headache	1 (2%)	0	0	0	1 (2%)	1 (2%)	0	0	0	1 (2%)
Balance impaired	1 (2%)	0	0	0	1 (2%)	0	0	0	0	0
Dyspnea	1 (2%)	0	0	0	1 (2%)	1 (2%)	0	0	0	1 (2%)
Pruritis/Rash m-p	1 (2%)	0	0	0	1 (2%)	1 (2%)	0	0	0	1 (2%)
Dry skin	1 (2%)	0	0	0	1 (2%)	1 (2%)	0	0	0	1 (2%)
Ear pain	1 (2%)	0	0	0	1 (2%)	1 (2%)	0	0	0	1 (2%)

Supplementary Table 2: Treatment related adverse events among all patients (left) and patients enrolled at the RP2D (right). Listed are grades 1-4 adverse events that were deemed by the investigator to be possibly, probably, or definitely related to study drug(s). For each patient, only the highest grade of each AE is included.

	Phases I & II (n=50), n (%)	Dose level 3/R2PD (n=41), n (%)
OT duration of treatment, all patients		
1-2 cycles	14 (28)	13 (32)
≥ 3 cycles	36 (72)	28 (68)
Dose Reduction		
None	29 (58)	23 (56)
At least one	21 (42)	18 (44)
Dose Reduction in patients with ≥ 3 cycles		
None	15 (42)	10 (36)
At least one	21 (58)	18 (64)
Reasons for dose reductions		
Cytopenias*	19 (38)	17 (41)
Fatigue	2 (4)	2 (5)
Nausea/Vomiting	1 (2)	0

Supplementary Table 3: OT duration of treatment and dose reductions. *Cytopenias: inclusive of anemia, thrombocytopenia, neutropenia, or leukopenia

Supplementary Figure S1

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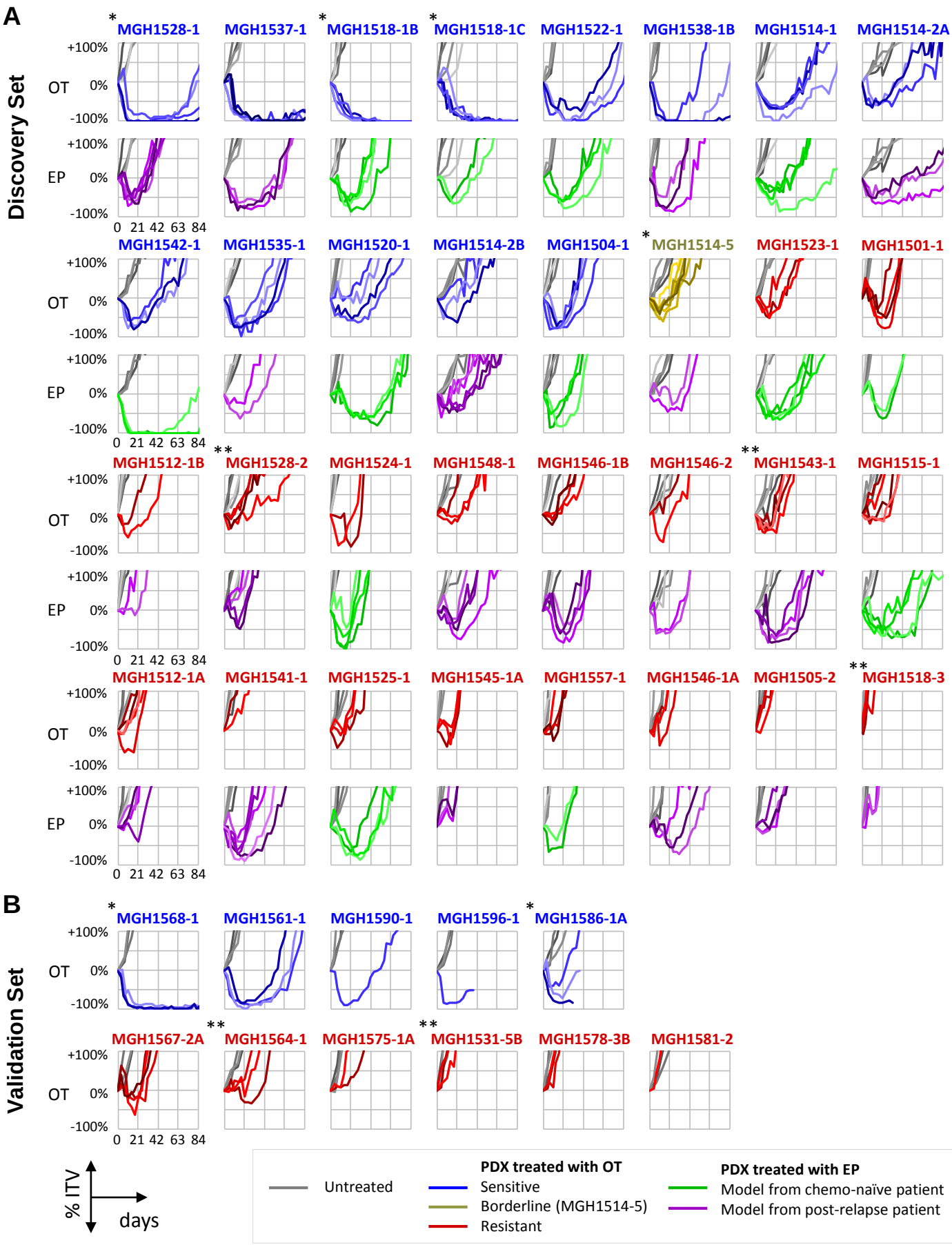
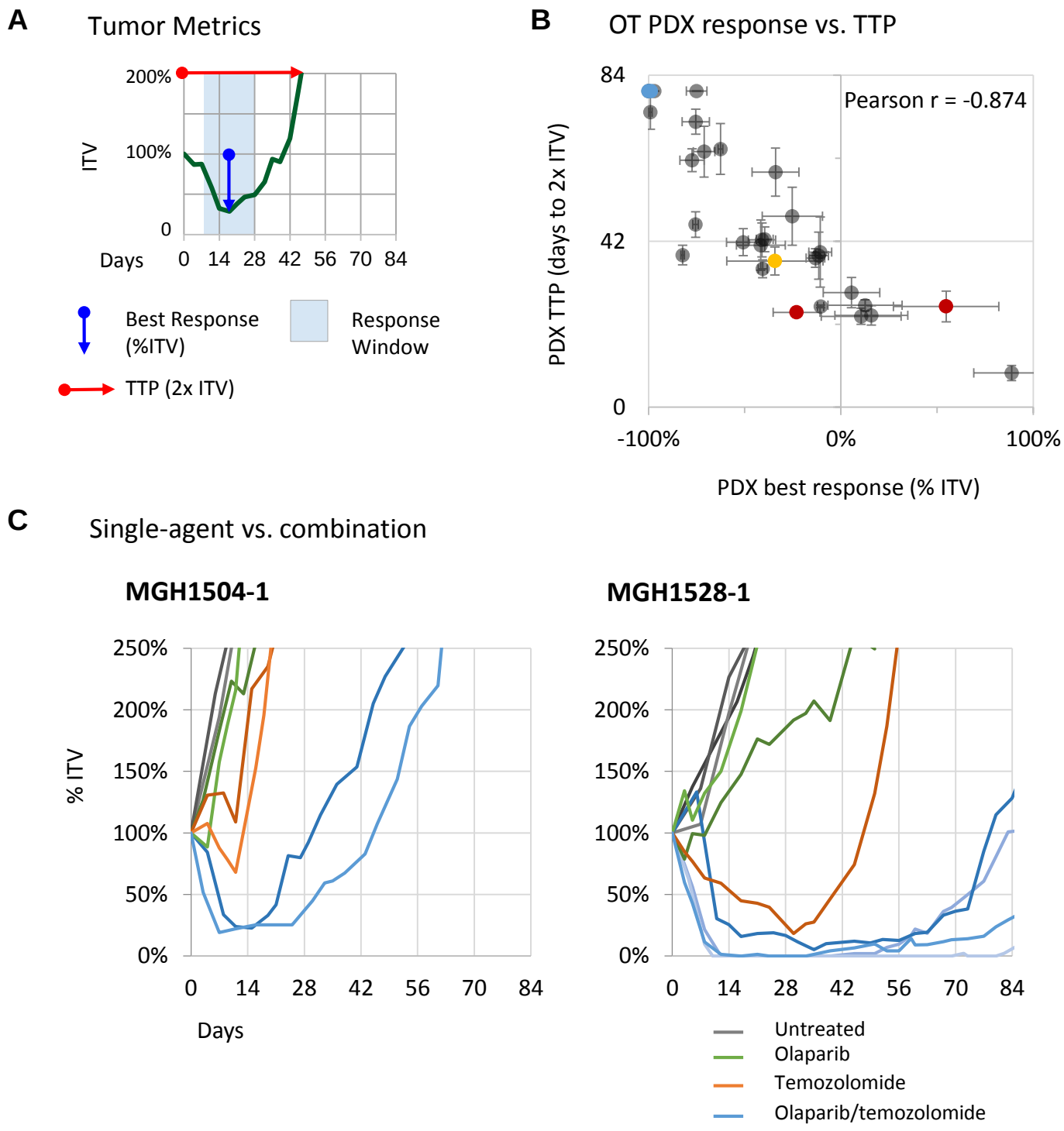


Supplementary Figure S1. Tumor volume curves following treatment with OT or EP for 32 SCLC PDX models. (**A**) 32-model discovery set. Tumor volume curves (colored) represent % initial tumor volume (ITV) versus time (days) after a single cycle of OT (row 1) or EP (row 2), with tumor volume curves for untreated xenografts in gray. 2-6 replicate xenografts are plotted per treatment per model. Models are arranged from left to right and top to bottom by decreasing time to progression (TTP, days to 2x ITV) following OT, with the most OT-sensitive models (longest TTP) in the upper left. Blue OT curves and titles denote models with longer TTP than the threshold model MGH1514-5 (yellow), and include the pre-treatment models from OT trial patients with durable partial responses, MGH1518-1 and MGH1528-1. Red OT curves denote models with shorter TTP than MGH1514-5, and include models derived at progression from OT trial patients: MGH1528-2, MGH1543-1, and MGH1518-3. (*) Denotes models derived from OT trial patients prior to therapy, and (**) denotes models derived post-relapse. For EP tumor volume curves, green represents models derived from chemo-naïve patients, and purple represents models derived from patients after at least one line of therapy. (**B**) 11-model validation set treated with a single cycle of OT as in (A). Blue curves and titles represent sensitive models with deeper average best response compared with threshold model MGH1514-5 (yellow, Figure S1A). Red curves represent resistant models with inferior average OT responses.



Supplementary Figure S2. Correlation between OT metrics, and single agent efficacy. (**A**) Tumor metrics. Response = minimum % ITV between days 7-28. TTP = time to 2x ITV. (**B**) Average best response versus time to progression (TTP) across 32 models treated with OT (r = Pearson correlation). Colored circles = models derived from OT trial patients: blue = pre-trial from durable partial responders, yellow = pre-trial from brief stable disease, red = post-progression models. Error bars = SEM for replicate xenografts treated with OT. (**C**) Tumor volume curves for single agent versus combination treatment with OT. Green = olaparib 50 mpk bid x 5 days. Orange = temozolomide 25 mpk bid x 5 days. Blue = combination OT x 5 days. Gray = vehicle control for OT.

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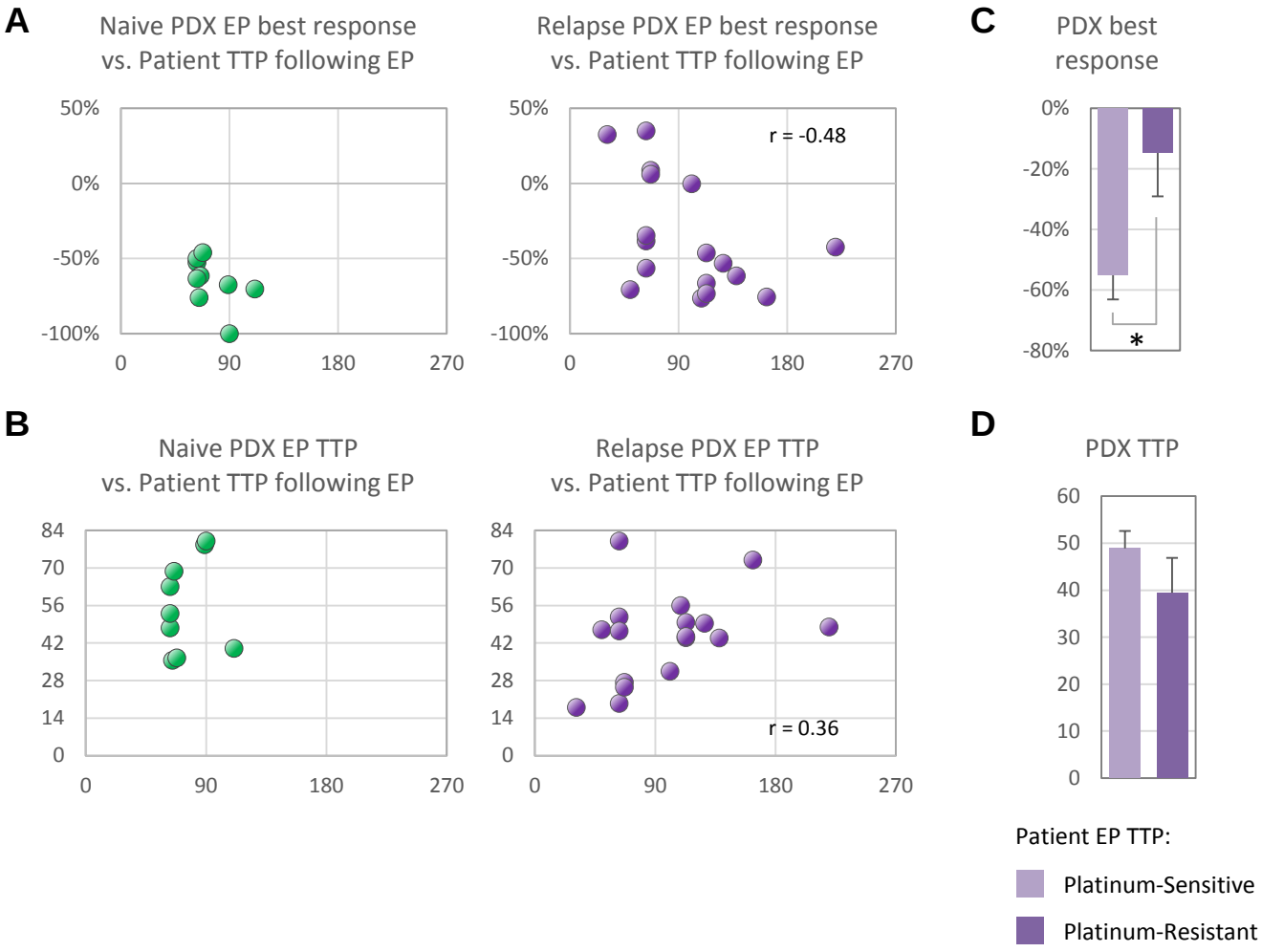
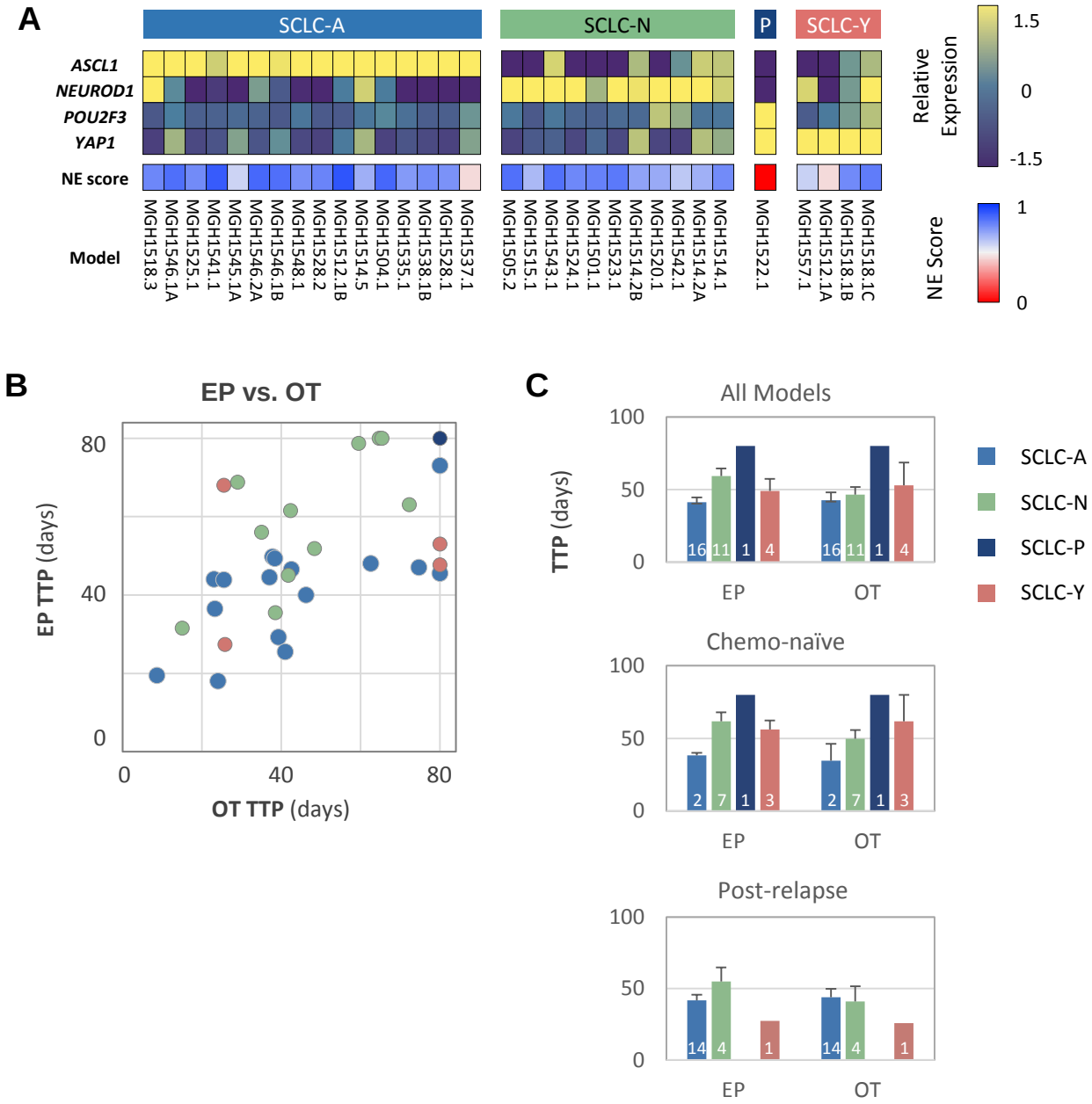


Supplementary Figure S3. Comparison of patient and PDX sensitivity to EP. (**A-B**) PDX model best response (A) and time to progression (days) (B) following treatment with EP versus the time to clinical progression for the donor patient following the last dose of first-line EP (days). (**C-D**) Average PDX model best response (C) and time to progression (D) for models derived post-relapse (≥ 1 line of therapy) from platinum sensitive (time to clinical progression < 90 days) versus platinum-resistant (time to clinical progression > 90 days) patients. *Significant unpaired 2-tailed T-test p-value = 0.02

Supplementary Table 4. Discovery set transcriptome sequencing for correlation with OT sensitivity. Paired-end RNA-seq performed on untreated replicate xenografts from 32 PDX models separately treated with OT (Supplementary Figure S1A). Average $\log_2$ (TPM+1) for each model. Models arranged from shortest to longest TTP (resistant to sensitive).

Supplementary Table 5. Differential expression of transcripts by OT sensitivity in the discovery set. Comparison of expression levels of transcripts between OT sensitive and resistant PDX cohorts in the 32-model discovery set, by fold-change and unpaired t-test. Expression biomarker features such as bimodal expression pattern and ROC curve AUC are quantified. Membership in the EP/OT cross-resistance signatures (Figure 5E, F) is annotated.

Supplementary Figure S4 Farago et al.



Supplementary Figure S4. Molecular subtype classification of PDX models. (**A**) Classification of PDX models by predominant expression of the transcriptional regulators ASCL1, NEUROD1, POU2F3 or YAP1 (ANPY), according to scheme described in Rudin, Poirier et al., Nature Reviews Cancer 2019. Log-fold expression versus the panel mean is depicted. Neuroendocrine (NE) score calculated according to method described in Zhang et al., Transl Lung Ca Res 2018. (**B**) Sensitivity of PDX models labeled by ANPY subclassification to EP versus OT (TTP after start of treatment). (**C**) Average model TTP for each regimen for each subclass, with SEM error bars and number of models in each subclass at column base. Models further subdivided by whether they were derived from chemo-naïve (middle panel) or post relapse patients (bottom panel).

Supplementary Figure S5

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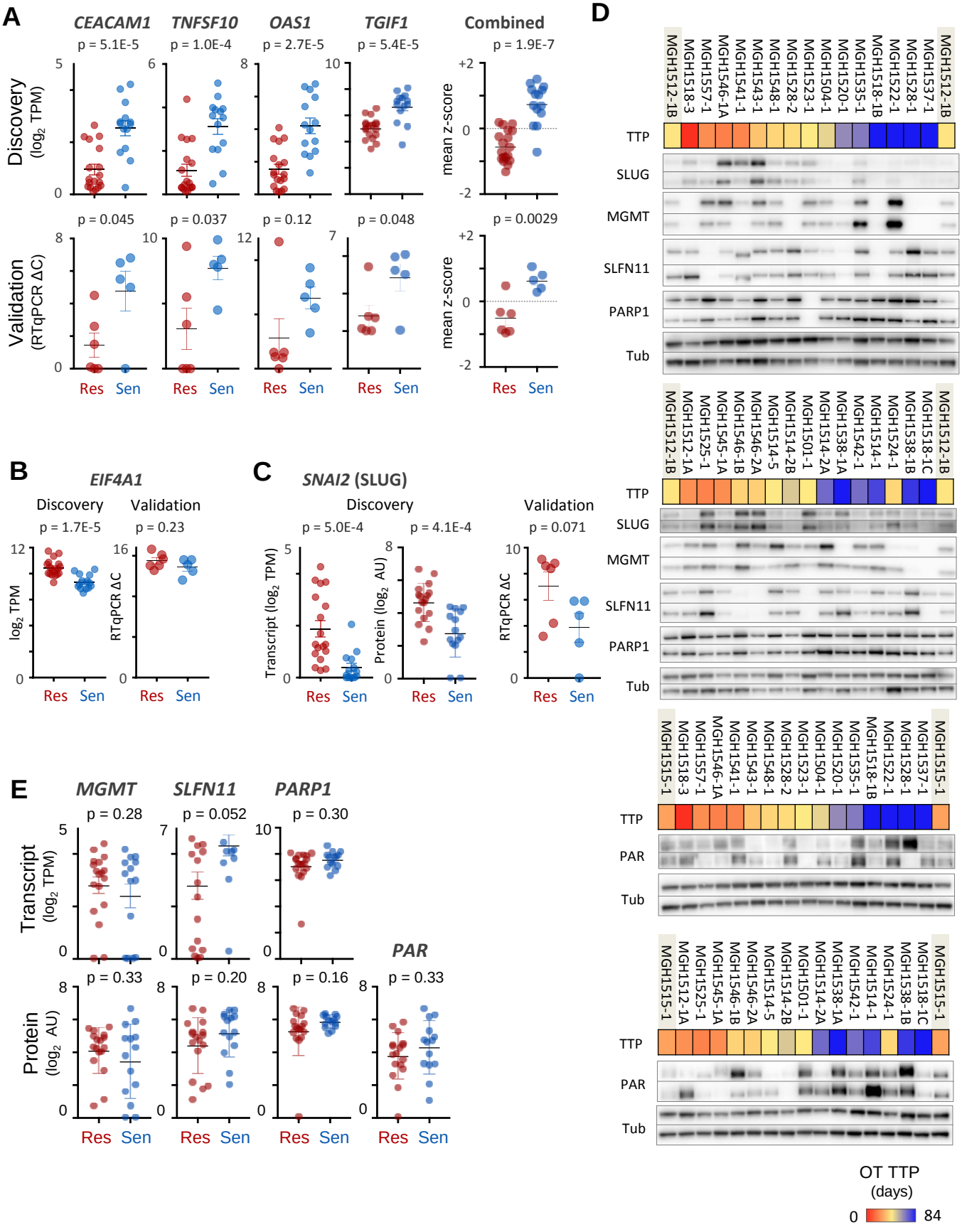

Supplementary Figure S5. Biomarker candidate quantification by transcript and protein levels. (A) Quantification of transcript levels within the discovery set (32 models, RNA-seq) and validation set (11 models, qRT-PCR) for four candidates from the inflammatory response signature, with the average z-scores of the four transcripts ("Combined"). **(B)** Quantification of transcript levels within the discovery and validation sets for *EIF4A1,* the most differentially expressed candidate from the MYC target signature. **(C)** Quantification of transcript and protein levels within the discovery set and transcript levels in the validation set for *SNAI2* (SLUG), a candidate marker for OT-resistance. (**D**) Immunoblots of protein lysates within the PDX discovery set (31 models) were probed for SLUG, MGMT, SLFN11, PARP1, PAR, and a tubulin loading control. Densitometry was performed on each band, and ratios of each protein to the tubulin loading control were calculated. To compare between blots, protein/tubulin ratios were calibrated to bridging lysate standards (ends of blot): MGH1512-1B for SLUG, MGMT, SLFN11 and PARP1, and MGH1515-1 for PAR. The same lysates standards were loaded for each blot for that antigen. Biologic replicate xenografts were probed and values were averaged, with top band = mouse #1 and bottom band = mouse #2, except for bridging lysates where on top blot left band = mouse #1 and right band = mouse #2, and the reverse on the bottom blot (left = mouse #2, right = mouse #1). Colorbar represents TTP as in Figure 6A. **(E)** Quantification of transcript (RNA-seq) and protein (quantitative immunoblot) levels within the PDX discovery set for hypothesis-driven biomarker candidates *MGMT, SLFN11, PARP1* and PAR.