Suppl Table S1

	Testing Cohort	Validation Cohort
Patient Characteristics	**Value**	**Value**
Cases, n	117	137
Age, Years		
Mean (range)	54.8 (25-75)	70.3 (52-92)
Sex, n (%)		
Male	87 (74)	86 (63)
Female	30 (26)	51 (37)
Histology, n (%)		
Adenocarcinoma	54 (46)	67 (49)
Squamous cell carcinoma	63 (54)	71 (51)
Involved Lymph nodes, n (%)		
N0		99 (72)
N1-2		39 (28)
TNM Stage (7th Edition), n (%)		
IA	4 (3)	27 (20)
IB	44 (38)	49 (36)
II	29 (25)	31 (22)
IIB	21 (18)	9 (7)
IIIA	18 (15)	21 (15)
IV	1 (1)	

Supplementary Table S1. Clinical and pathologic characteristics of the testing and validation patient cohorts.

Suppl Table S2

Cohort	Diagnosis		# patients	% of patients showing Axl staining ≥ 1+ in ≥10% tumor cells	% of patients showing Axl staining ≥ 2+ in ≥10% tumor cells	% of patients showing Axl staining ≥ 3+ in ≥10% tumor cells
Testing Cohort	NSCLC	AC	54	66	11	0
		SCC	63	76	6	0
Validation cohort	NSCLC	AC	67	49	9	0
		SCC	70	66	7	0

Supplementary Table S2. AXL protein expression, as assessed by IHC, scored as % of patients with tumors containing at least 10% AXL positive cells at designated intensities, in two independent patient cohorts (testing and validation cohort).

Suppl Table S3

Parameters	AXL low	AXL high	p[a]
Age			
≤70.3	52	23	0.336
>70.3	48	13	
Histology			
Adenocarcinoma	49	21	0.447
Squamous cell carcinoma	51	16	
Tumor size			
≤43.2	57	13	0.153
>43.2	43	19	
Involved Lymph nodes			
N0	72	22	0.053
N1-2	23	15	
TNM Stage (7th Edition)			
I-II	87	29	0.2842
III	13	8	

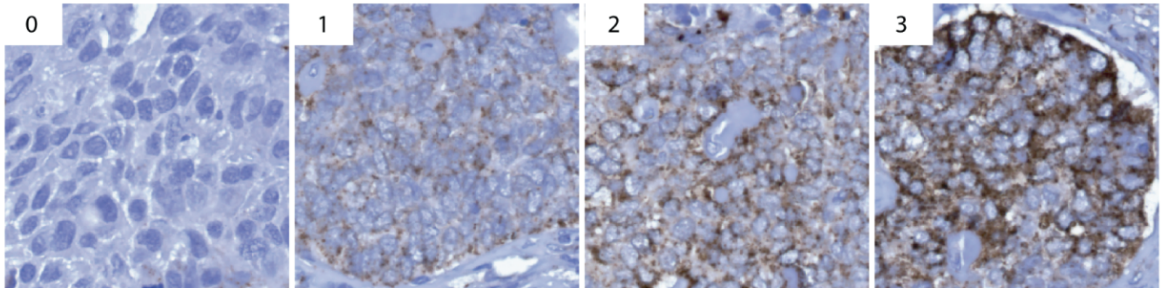
Supplementary Table S3. Clinical and pathologic characteristics of the AXL^{low}- and AXL^{high}-expressing patients in the validation patient cohort.

Suppl Table S4

	Cancer Specific Survival						Disease-Free Survival					
	Univariate			Multivariate			Univariate			Multivariate		
	Hazard Ratio	95% CI	P	Hazard Ratio	95% CI	P	Hazard Ratio	95% CI	P	Hazard Ratio	95% CI	P
Axl expression	1.79	1.08-2.99	0.024	1.76	1.03-2.95	0.037	1.60	1.07-2.40	0.022	1.59	1.05-2.41	0.028
Age (≤70.1 vs. >70.1)	0.49	0.29-0.79	0.004	0.43	0.26-0.70	0.001	0.66	0.44-0.94	0.022	0.59	0.41-0.87	0.008
Tumor size (≤43.2 vs. >43.2)	1.23	0.76-2.01	0.390				1.19	0.82-1.73	0.349			
Nodal status (Positive vs. negative	2.17	1.31-3.58	0.002	2.12	1.27-3.54	0.004	1.62	1.09-2.42	0.017	1.53	0.94-2.49	0.080
TNM stage Stage I vs. Stage II & III	1.61	0.86-3.02	0.135				1.53	0.94-2.49	0.083	1.03	0.57-1.84	0.917
Histology Adenoma vs. Squamous cell carcinoma	0.71	0.43-1.16	0.176				0.85	0.59-1.24	0.429			

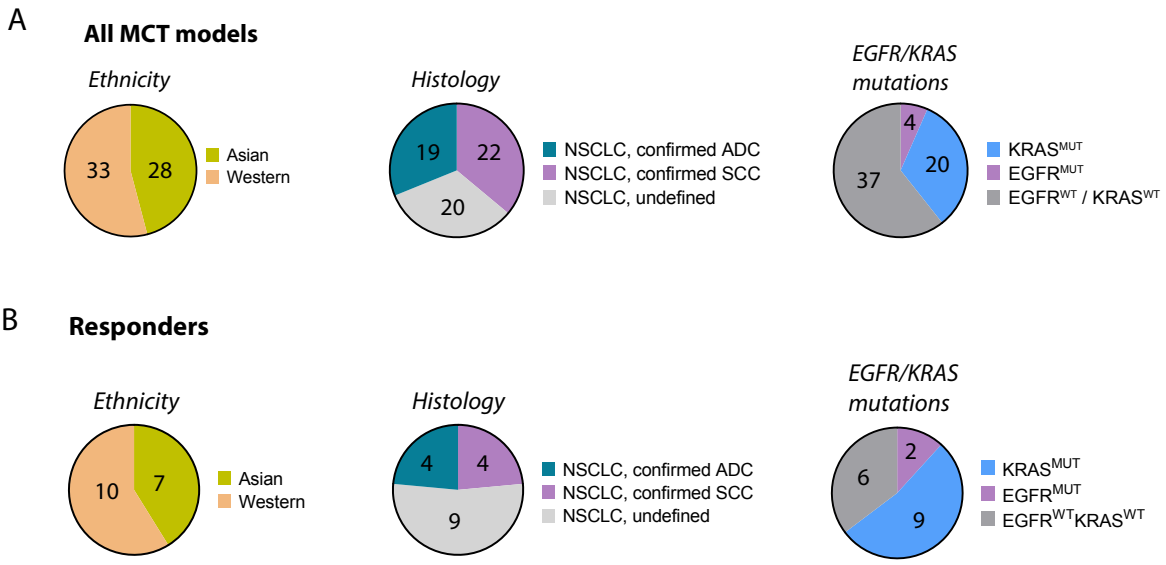
Supplementary Table S4. Statistical analyses of various parameters associated with cancer-specific and disease-free survival of NSCLC patients. Both univariate and multivariate analysis were performed.

Supplementary Figure 1



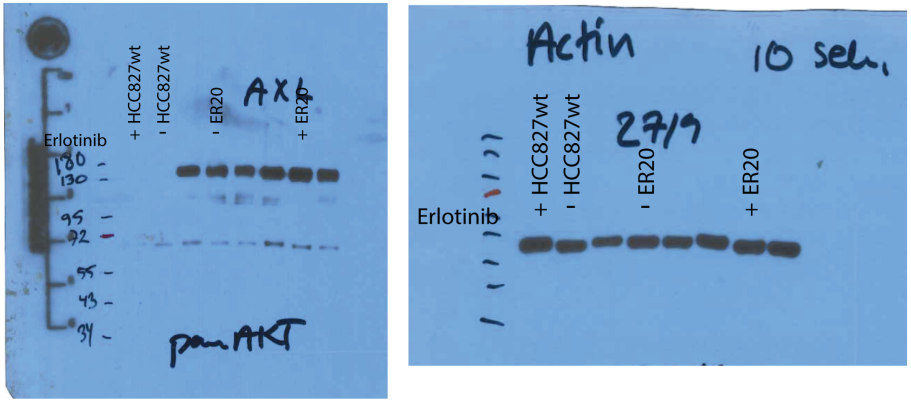
Supplementary figure S1. Representative immunohistochemical stainings of NSCLC sections showing no AXL staining (0) or AXL staining at increasing intensity (1–3).

Supplementary Figure 2



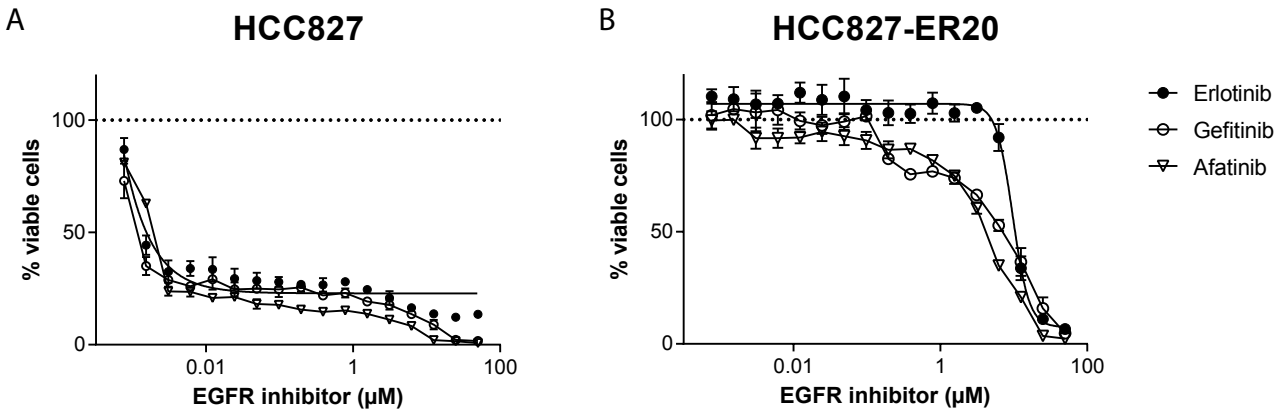
Supplementary Figure 2. (A) Ethnic, histological and mutational characteristics of the 61 NSCLC PDX models included in a mouse PDX clinical trial. (B) Idem for group of responders in mouse PDX clinical trial.

Supplementary Figure 3



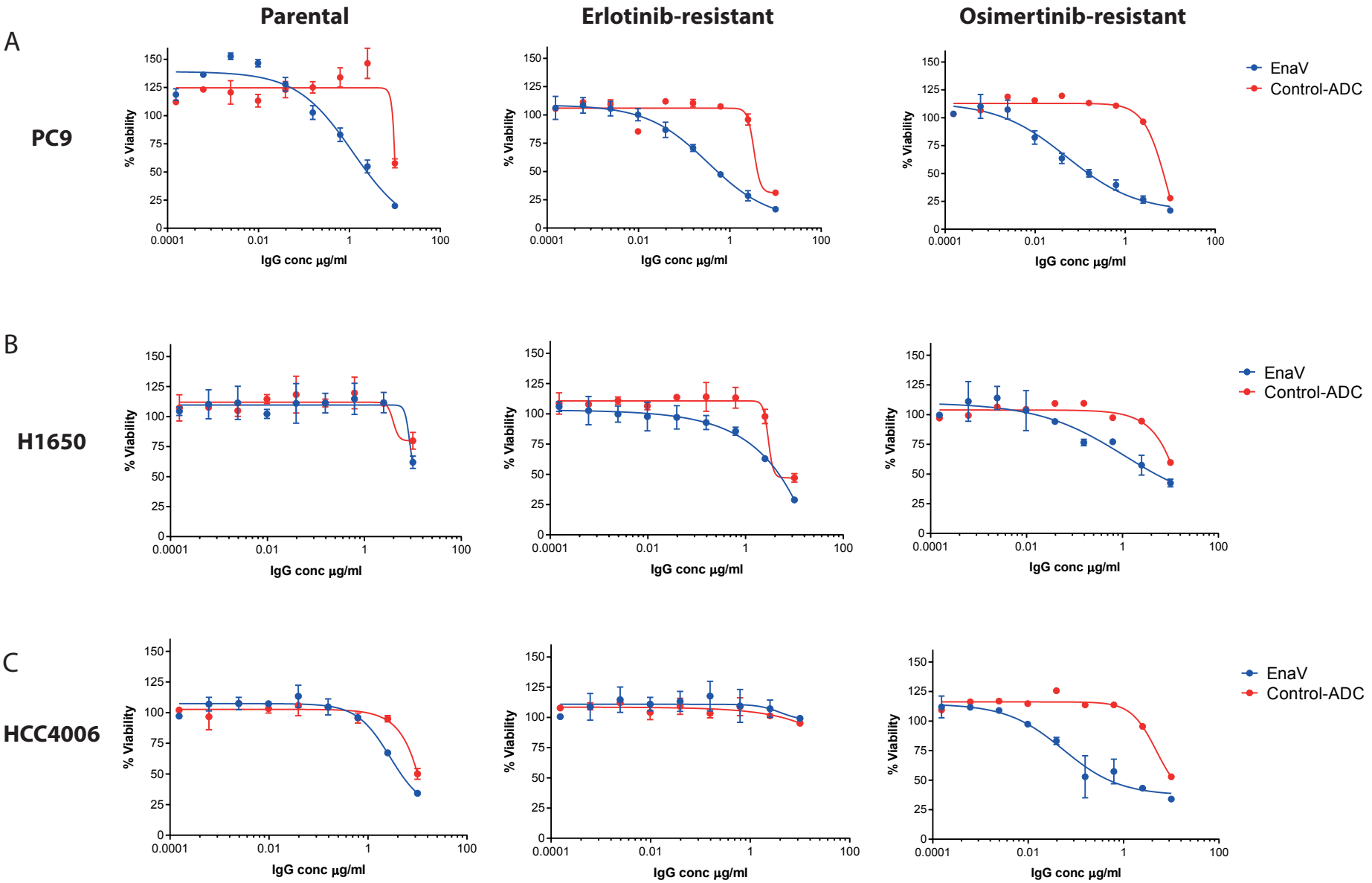
Supplementary figure S3. Full unedited gel for Figure 6B. Left: Western Blot of AXL expressed in the cell lines as indicated above each lane; right: Western Blot of actin expressed in the same cell lines as indicated above each lane.

Supplementary Figure 4



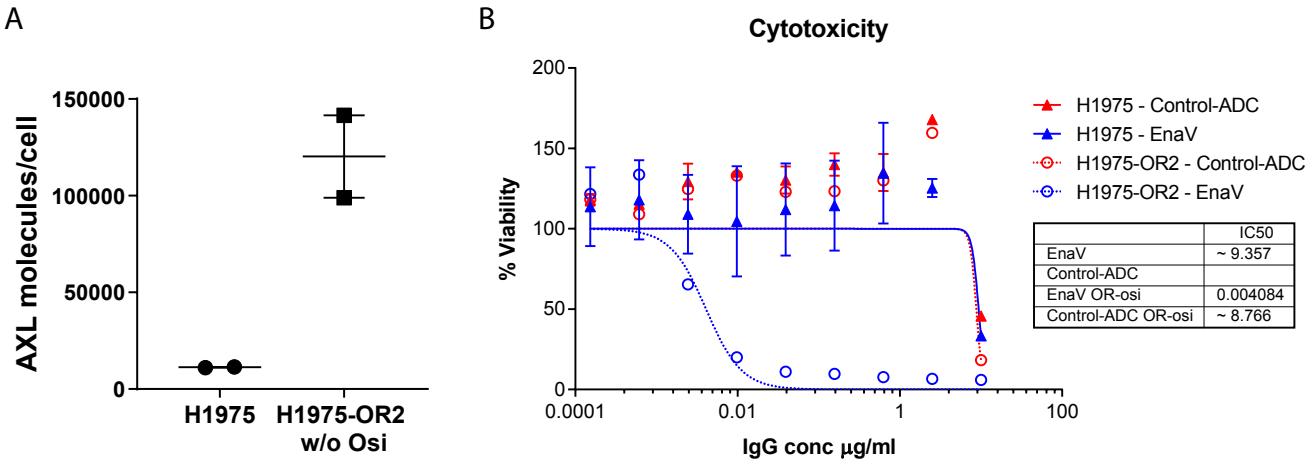
Supplementary figure S4. Sensitivity of NSCLC cell line HCC827 and resistant derivatives to EGFRi erlotinib, gefitinib and afatinib. Cell viability of (A) parental HCC827 cells or (B) erlotinib-resistant HCC827 cells upon exposure to the indicated EGFRi in vitro. Viability was calculated as follows:
% viability = (luminescence sample of interest – luminescence STAU) / (average luminescence of control vehicle treated – luminescence STAU), with STAU representing 1 μM staurosporin for 100% cell killing.

Supplementary Figure 5



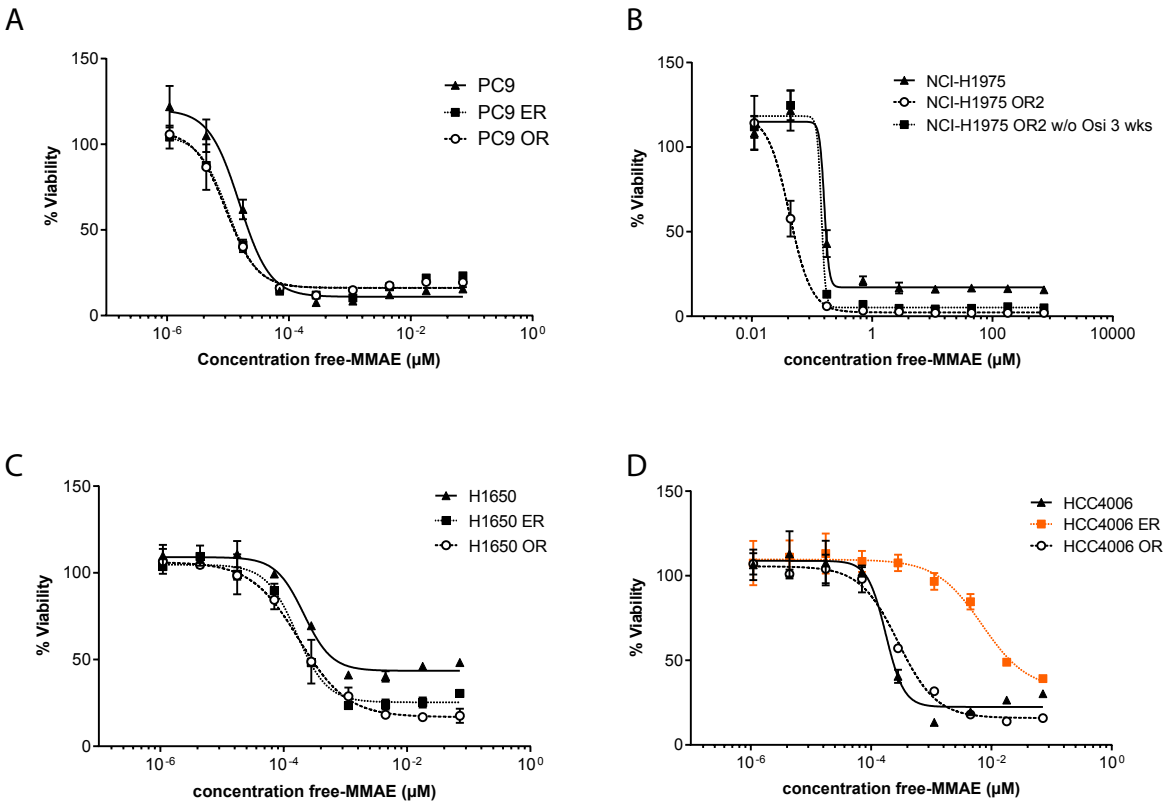
Supplementary figure S5. Sensitivity of NSCLC cell lines PC9, H1650 and HCC4006 and EGFRi-resistant derivatives to enapotamab vedotin (EnaV) *in vitro*. (A) Cell viability of parental, erlotinib-resistant or osimertinib-resistant PC9 NSCLC cells to EnaV or isotype-ADC. (B) Cell viability of parental, erlotinib-resistant or osimertinib-resistant H1650 NSCLC cells to EnaV or isotype-ADC. (C) Cell viability of parental, erlotinib-resistant or osimertinib-resistant HCC4006 NSCLC cells to EnaV or isotype-ADC. Viability was calculated as follows:
% viability = (luminescence sample of interest – luminescence STAU) / (average luminescence of control vehicle treated – luminescence STAU), with STAU representing 1 µM staurosporin for 100% cell killing.

Supplementary Figure 6



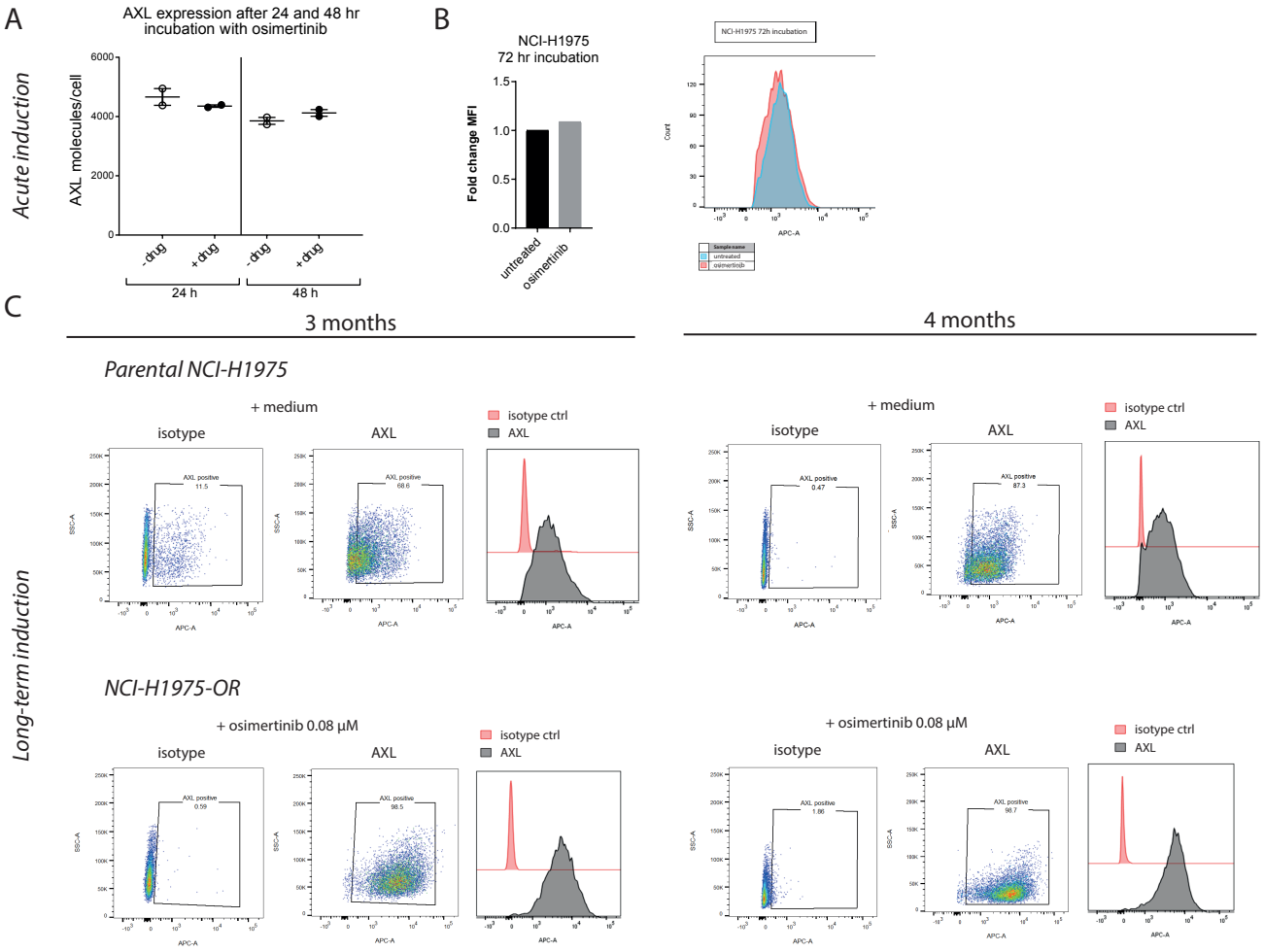
Supplementary figure S6. AXL expression and enapotamab vedotin (EnaV) sensitivity of NSCLC cell line H1975 in absence of EGFRi osimertinib. (A) Expression of AXL on parental H1975 NSCLC cells and osimertinib-resistant H1975 cells after osimertinib was omitted from culture for 3 weeks. (B) Cell viability of H1975 NSCLC cells and osimertinib-resistant H1975-OR2 NSCLC cells upon in vitro exposure to EnaV or isotype-ADC, while osimertinib was omitted from cell culture for 3 weeks. Viability was calculated as follows:
% viability = (luminescence sample of interest – luminescence STAU) / (average luminescence of control vehicle treated – luminescence STAU), with STAU representing 1 µM staurosporin for 100% cell killing.

Supplementary Figure 7



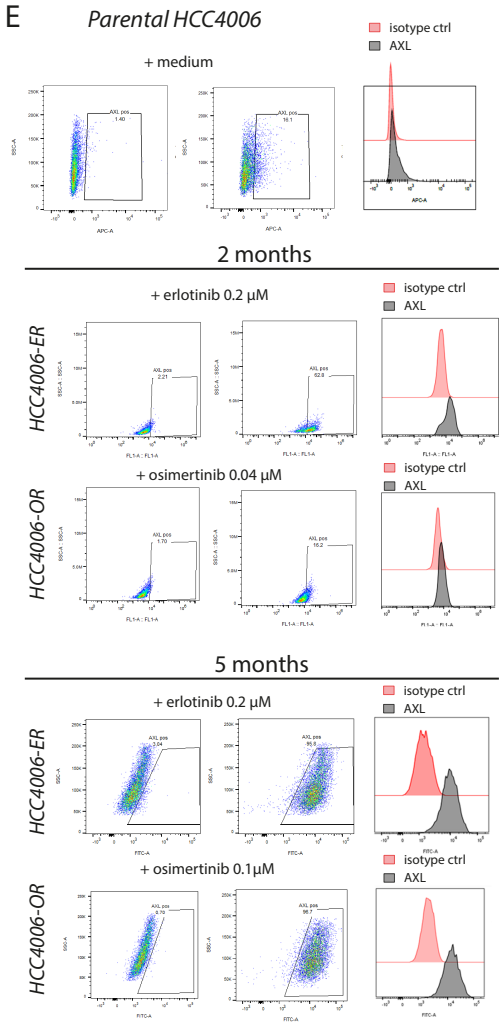
Supplementary figure S7. Sensitivity of NSCLC cell lines and resistant derivatives to free monomethyl auristatin E (MMAE). Cell viability of (A) PC9, (B) H1975, (C) H1650 and (D) HCC4006 NSCLC cells and erlotinib-resistant (ER) and osimertinib-resistant (OR) derivatives upon *in vitro* exposure to free MMAE. Viability was calculated as follows:
% viability = (luminescence sample of interest – luminescence STAU) / (average luminescence of control vehicle treated – luminescence STAU), with STAU representing 1 μM staurosporin for 100% cell killing.

Supplementary Figure 8



Supplementary Figure S8. *(A-D)* AXL expression on NSCLC cell line NCI-H1975 upon culture with medium or osimertinib. (A, B) Acute induction of AXL expression on NCI-H1975 cells as determined by flow cytometry upon exposure to osimertinib for (A) 24h and 48h, (B) determined upon exposure to osimertinib for 72h (fold change over medium control of mean fluorescence intensity; MFI). (C) AXL expression on parental (top row) and osimertinib-treated (bottom row) NCI-H1975 cells after 3 and 4 months of culture in the presence of either medium or osimertinib. (D) AXL expression measured as AXL molecules per cell as determined by QiFi analysis on NCI-H1975 cells after 3 or 5 months of exposure to either medium only (parental) or osimertinib (-OR).

Supplementary Figure 8; *continued*



Supplementary figure S8*(E-F)*. (E) AXL expression on parental (top row) and erlotinib- or osimertinib-treated HCC4006 cells after 2, 3 and 5 months of culture in the presence of either medium, erlotinib or osimertinib at the indicated concentrations. (F) AXL expression measured as AXL molecules per cell as determined by QiFi analysis on HCC4006 cells after 2, 3 and 5 months of exposure to either medium only (parental), osimertinib (-OR) or erlotinib (-ER).