Supplementary Materials for

Overcoming hypoxia-induced tumor radioresistance in non-small cell lung cancer by targeting DNA-dependent protein kinase in combination with carbon ion irradiation

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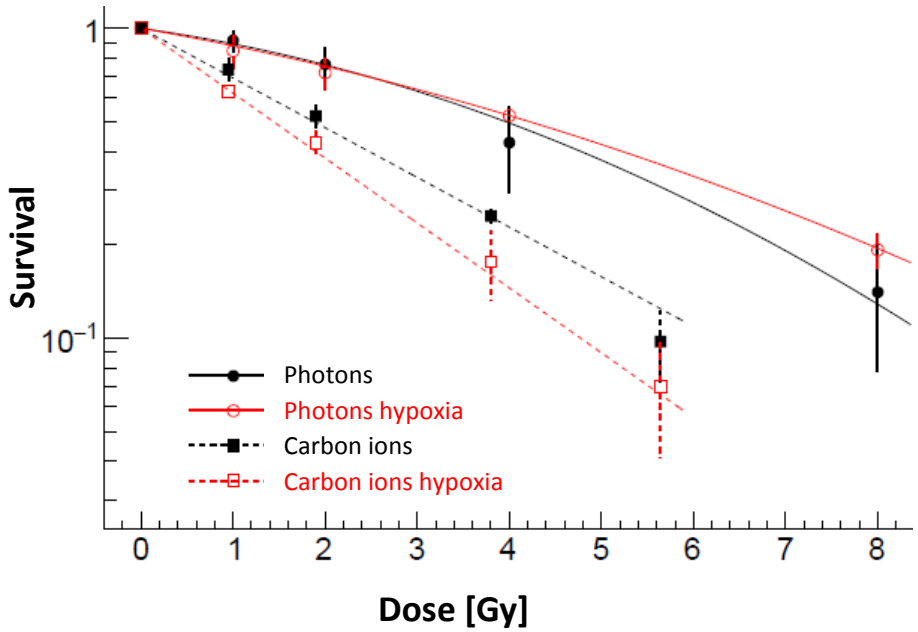

Figure S1. Clonogenic survival of the NSCLC cell line H1437 irradiated under normoxia (black) and hypoxia (1 % O_2, red) with photons (solid line) and carbon ions (dashed line). Bars represent mean ± SD of three independent experiments with n=4 technical replicates each.

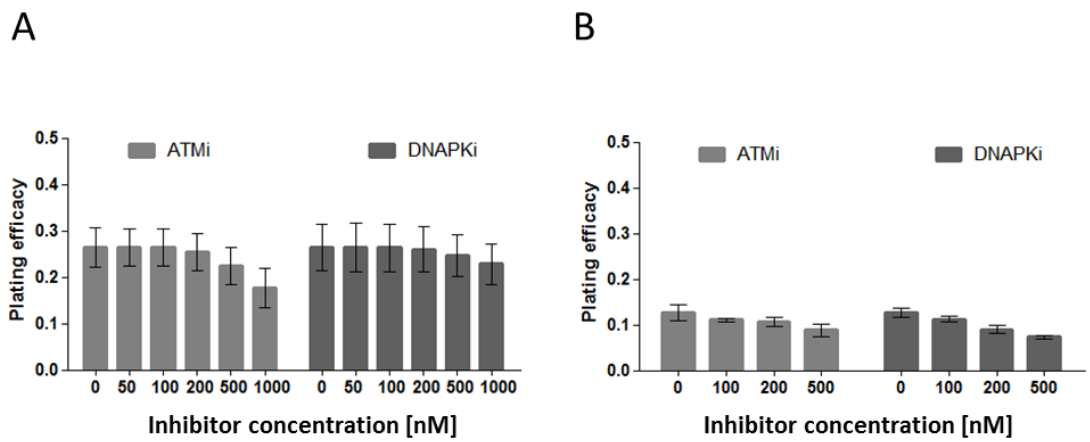

Figure S2. Plating efficacy (PE) of H1437 cells after treatment with dose series of ATMi (grey) or DNAPKi (black), respectively, under normoxia (**A**) and hypoxia (**B**). Bars represent mean ± SD of three independent experiments with n=4 technical replicates each.

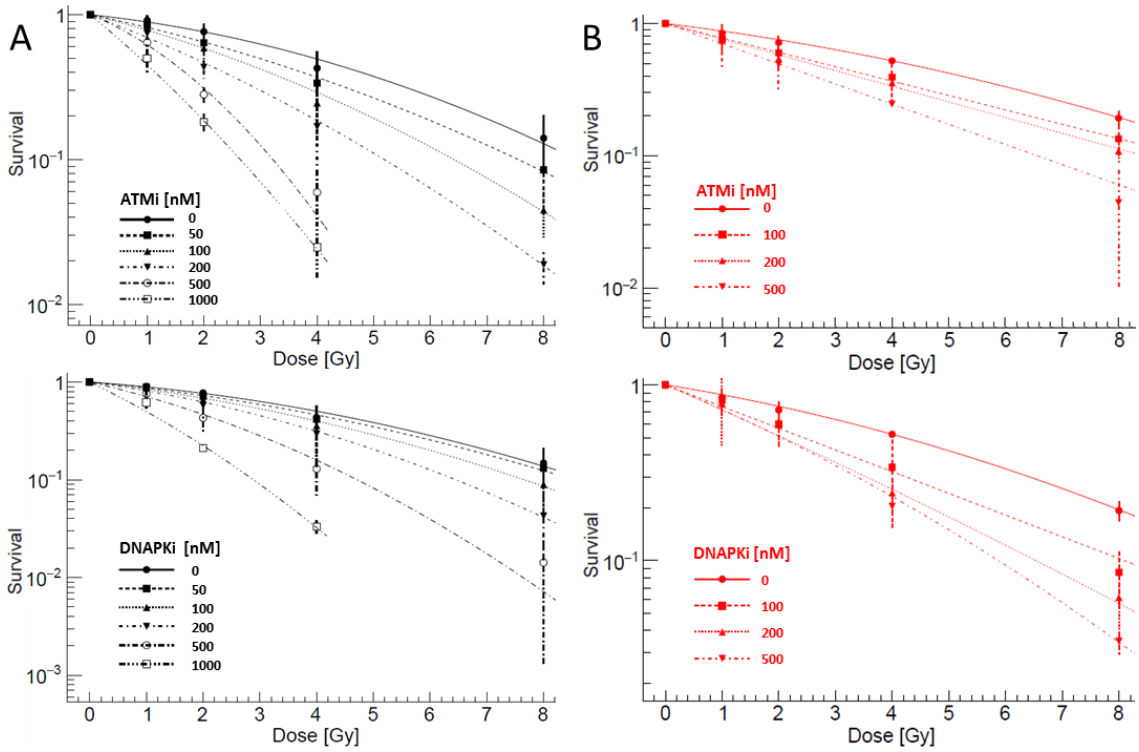

Figure S3. Clonogenic survival of H1437 cells irradiated with photons under normoxia (**A**) and hypoxia (**B**) in combination with increasing concentrations of ATMi (upper panel) or DNAPKi (lower panel), respectively. Data were normalized to non-irradiated samples at each corresponding baseline inhibitor concentration. Bars represent mean ± SD of three independent experiments with n=4 technical replicates each.

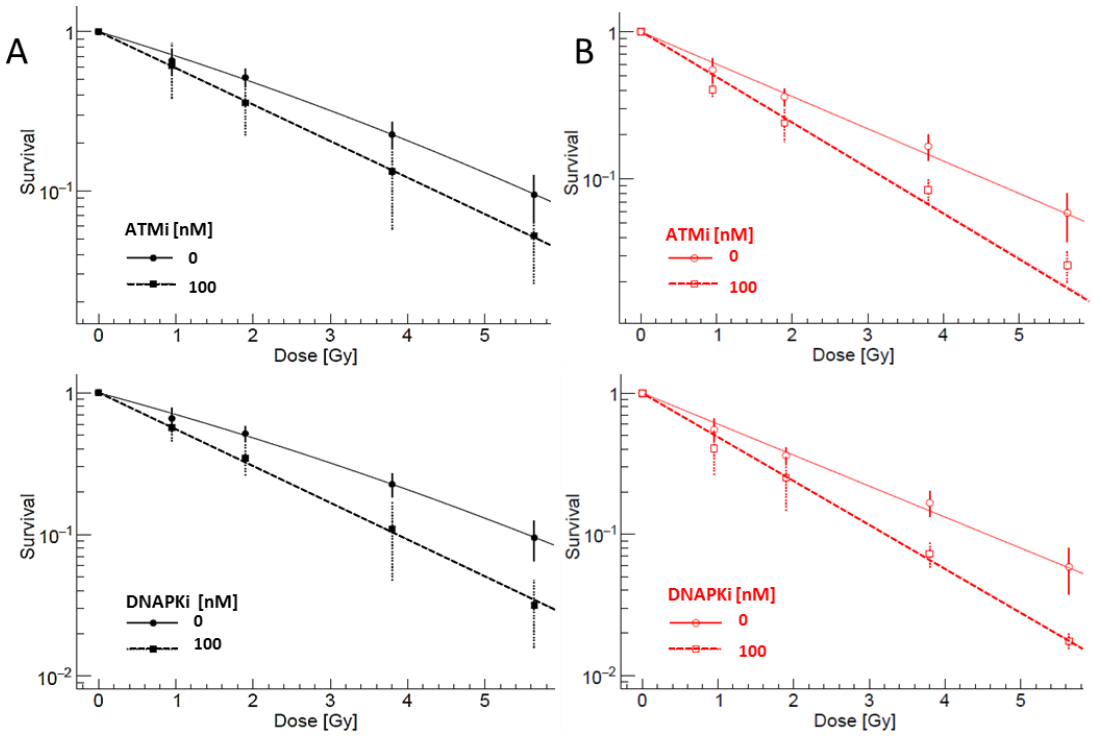

Figure S4. Clonogenic survival data for H1437 cells irradiated with carbon ions under normoxia (**A**) and hypoxia (**B**) in combination with 100 nM ATMi (upper panel) or DNAPKi (lower panel), respectively. Data were normalized to non-irradiated cells treated with 100 nM of the DDR inhibitors (baseline). Bars represent mean ± SD of three independent experiments with n=4 technical replicates each.

Table S5.

A. OER and RBE for A549 cells at 30 % survival fraction.

OER Photons	SEM	RBE Normoxia	SEM
1.39	**0.22**	**2.65**	**0.35**

OER Carbon ions	SEM	RBE Hypoxia	SEM
1.19	**0.02**	**3.1**	**0.3**

Abbreviations: OER: oxygen enhancement ratio; RBE: relative biological effectiveness; SEM: Standard error of the mean

B. SER for A549 cells at indicated ATM or DNAPK inhibitor concentrations in combination after photon and carbon ion irradiation under normoxic vs. hypoxic conditions.

Inhibitor conc. [nM]	SER ATMi Normoxia	SEM	SER ATMi Hypoxia	SEM	SER DNAPKi Normoxia	SEM	SER DNAPKi Hypoxia	SEM
Photons								
50	1.11	0.19			1.20	0.16		
100	1.31	0.52	1.64	0.15	1.40	0.19	2.70	0.24
200	1.87	0.39	2.16	0.19	1.89	0.25	4.60	0.41
500	2.54	0.34	3.63	0.33	2.13	0.28	9.75	0.94
1000	3.28	0.49			5.41	0.726		
Carbon ions								
100	1.50	0.03	1.50	0.06	1.66	0.03	1.86	0.03

Abbreviations: SER: Sensitization enhancement ratio; SEM: Standard error of the mean

Table S6.

A. OER and RBE for H1437 cells at 30 % survival fraction.

OER Photons	SEM	RBE Normoxia	SEM
1.09	**0.2136**	**1.92**	**0.2887**

OER Carbon ions	SEM	RBE Hypoxia	SEM
0.78	**0.0231**	**2.67**	**0.3522**

Abbreviations: OER: oxygen enhancement ratio; RBE: relative biological effectiveness; SEM: Standard error of the mean

B. SER for H1437 cells at indicated ATM or DNAPK inhibitor concentration in combination with photons and carbon ions under normoxic vs. hypoxic conditions.

Inhibitor conc. [nM]	SER ATMi Normoxia	SEM	SER ATMi Hypoxia	SEM	SER DNAPKi Normoxia	SEM	SER DNAPKi Hypoxia	SEM
Photons								
50	1.26	0.64			1.06	0.34		
100	1.50	0.62	1.32	0.18	1.20	0.42	1.50	0.20
200	1.95	1.24	1.44	0.19	1.42	0.47	1.82	0.24
500	2.86	0.72	1.85	0.24	2.02	1.36	1.88	2.09
1000	3.97	10.83			3.55	2.53		
Carbon ions								
100	1.34	0.06	1.51	0.06	1.40	0.04	1.41	0.03

Abbreviations: SER: Sensitization enhancement ratio; SEM: Standard error of the mean