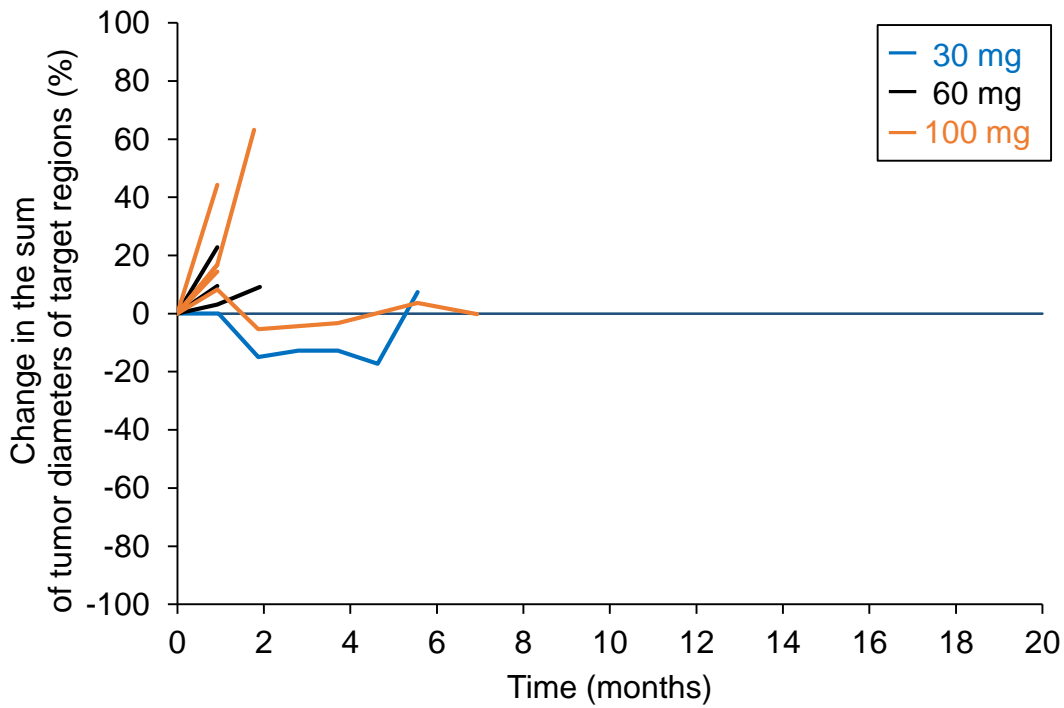


Supporting Information

First-in-human study of ONO-4578, an antagonist of prostaglandin E₂ receptor 4, alone and with nivolumab in solid tumors

Satoru Iwasa, Takafumi Koyama, Makoto Nishino, Shunsuke Kondo, Kazuki Sudo, Kan Yonemori, Tatsuya Yoshida, Kenji Tamura, Toshio Shimizu, Yutaka Fujiwara, Shigehisa Kitano, Akihiko Shimomura, Jun Sato, Fumiharu Yokoyama, Hiroyuki Iida, Maki Kondo, and Noboru Yamamoto

A. monotherapy cohorts



B. combination therapy cohorts

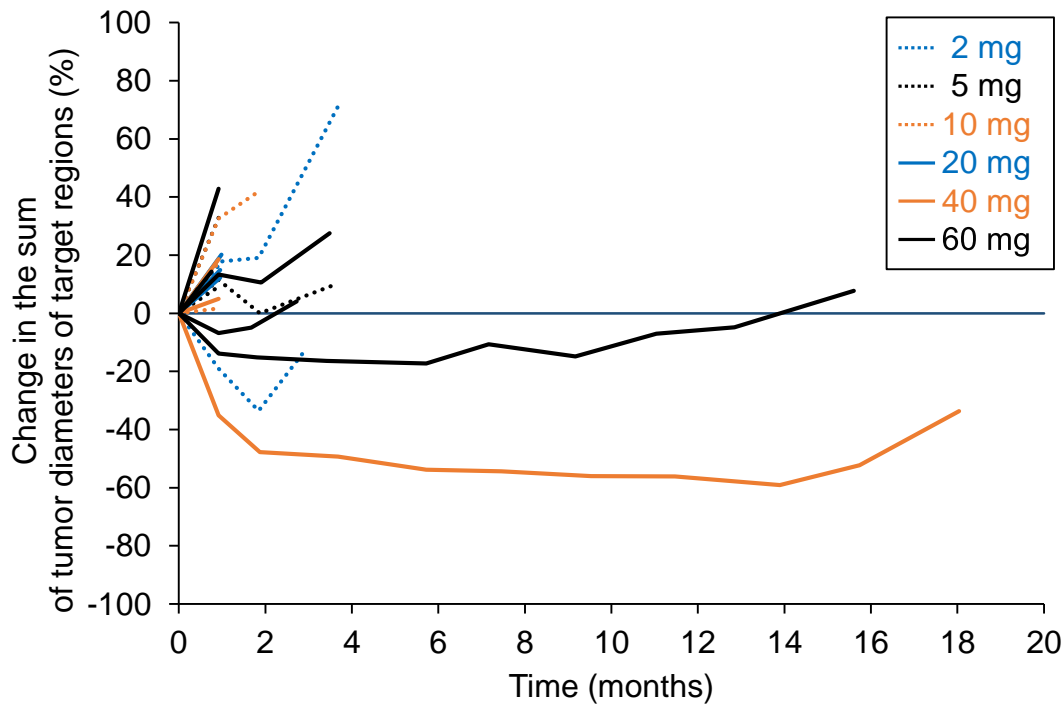
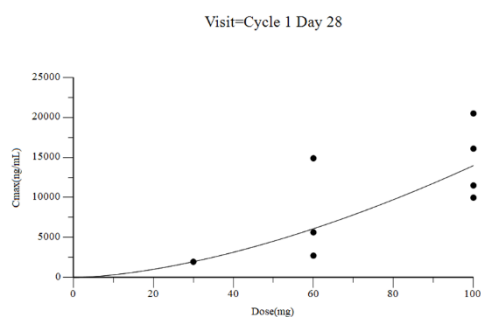


Figure S1. Tumor response

The sum of tumor diameters of target legions was periodically measured, and the percent change from that at the enrollment was plotted over time.

A. monotherapy cohorts

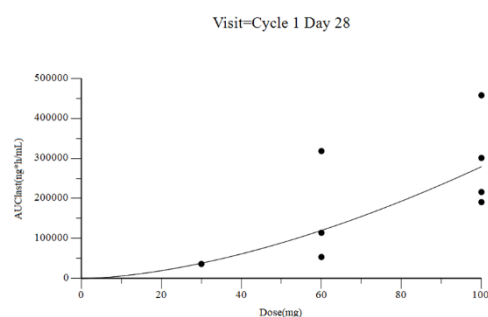
C_{max}



$$C_{max} = 7.81 \cdot \text{Dose}^{1.63}$$

95% CI of the exponent = 0.459 – 2.79

AUC_{24h}

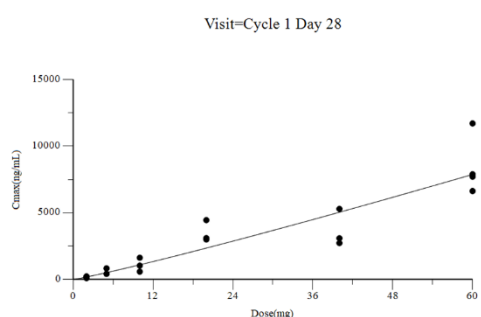


$$AUC_{24h} = 138 \cdot \text{Dose}^{1.65}$$

95% CI of the exponent = 0.392 – 2.91

B. combination therapy cohorts

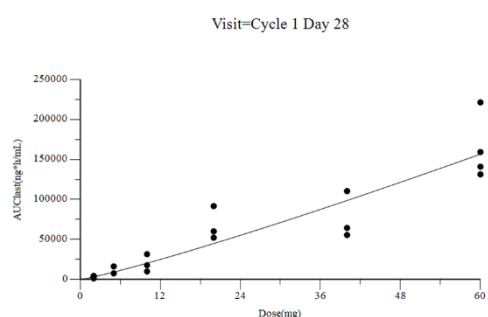
C_{max}



$$C_{max} = 87.5 \cdot \text{Dose}^{1.10}$$

95% CI of the exponent = 0.930 – 1.27

AUC_{24h}



$$AUC_{24h} = 1480 \cdot \text{Dose}^{1.14}$$

95% CI of the exponent = 0.950 – 1.33

Figure S2. Dose proportionality plot for pharmacokinetic parameters of ONO-4578 on day 28 of cycle 1

The maximum concentration (C_{max}) of ONO-4578 and the area under the concentration-time curve (AUC) for 24 hours in the monotherapy cohorts (A) and combination therapy cohorts (B).

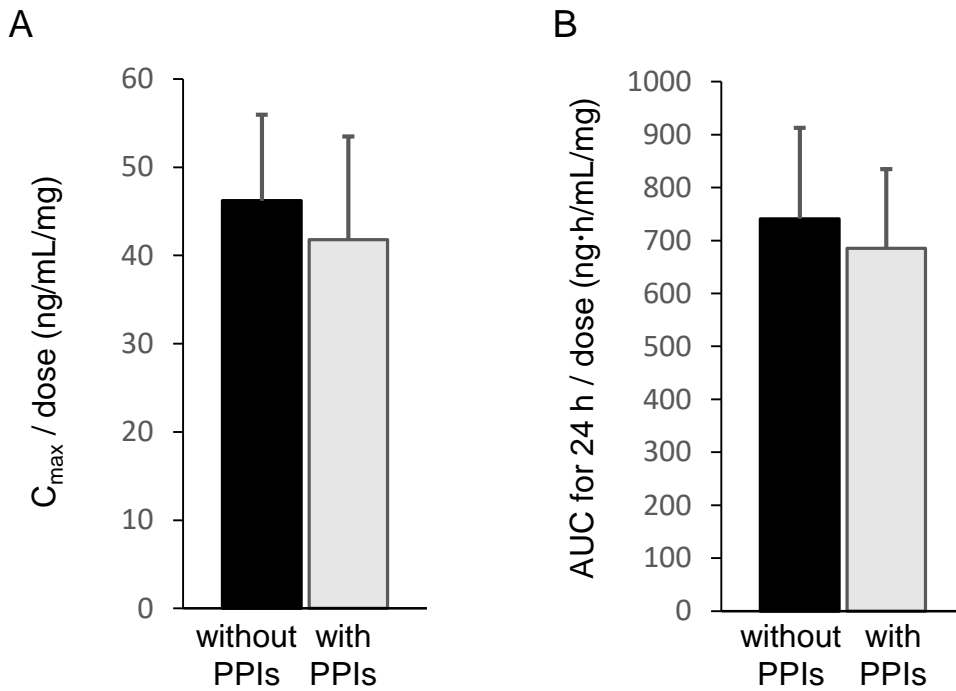


Figure S3. Pharmacokinetics in patients with and without PPIs
The C_{max} (A) and the AUC for 24 hours (B) of ONO-4578 on day 1 were divided by each administration dose. The mean values with standard deviation are shown.

Table S1. Administration status

Monotherapy, <i>N</i> = 10			Combination therapy, <i>N</i> = 21					
30 mg	60 mg	100 mg	2 mg	5 mg	10 mg	20 mg	40 mg	60 mg
<i>N</i> = 1	<i>N</i> = 3	<i>N</i> = 6	<i>N</i> = 3	<i>N</i> = 3	<i>N</i> = 3	<i>N</i> = 3	<i>N</i> = 3	<i>N</i> = 6
Median duration of ONO-4578 (range), d								
168	28	41	83	29	56	28	28	51.5
(168–168)	(28–57)	(20–210)	(28–113)	(28–112)	(28–56)	(28–28)	(28–548)	(5–278)
Median duration of nivolumab (range), d								
NA	NA	NA	70	15	42	15	15	37
			(15–98)	(15–99)	(15–45)	(15–16)	(15–535)	(1–468)

NA, not applicable

Table S2. Descriptive pharmacokinetics parameters of ONO-4578 during cycle 1

ONO-4578 dose	Monotherapy			Combination therapy					
	30 mg	60 mg	100 mg	2 mg	5 mg	10 mg	20 mg	40 mg	60 mg
Day 1									
<i>N</i>	1	3	6	3	3	3	3	3	6
<i>C</i> _{max} , µg/mL	1.18 (NC)	2.35 (0.667)	5.00 (0.959)	0.0662 (0.00644)	0.217 (0.0266)	0.477 (0.0962)	1.04 (0.213)	1.45 (0.403)	3.00 (0.642)
<i>AUC</i> _{24h} , µg·h/mL	23.1 (NC)	39.2 (14.6)	84.6 (9.86)	1.00 (0.288)	3.20 (0.238)	7.42 (1.53)	15.9 (1.60)	24.0 (5.90)	48.3 (9.48)
<i>T</i> _{max} , h	3.85 (3.85– 3.85)	4.10 (4.02– 4.18)	3.51 (2.00– 7.35)	1.95 (1.83– 2.97)	3.00 (3.00– 7.83)	2.05 (2.00– 4.02)	3.95 (3.93– 7.40)	2.98 (2.07– 7.60)	2.88 (1.92– 7.33)
<i>T</i> _{1/2} , h	53.4 (NC)	43.1 (39.5)	31.1 (11.7)	24.5 (8.99)	22.3 (5.07)	22.4 (3.33)	33.9 (21.3)	22.9 (3.60)	30.5 (12.9)
Day 28									
<i>N</i>	1	3	4	3	2	3	3	3	4
<i>C</i> _{max} , µg/mL	1.96 (NC)	7.76 (6.36)	14.5 (4.76)	0.181 (0.0715)	0.628 (NC)	1.09 (0.523)	3.52 (0.810)	3.70 (1.39)	8.48 (2.22)
<i>AUC</i> _{24h} , µg·h/mL	36.3 (NC)	162 (139)	292 (121)	3.29 (1.67)	12.0 (NC)	19.8 (10.9)	68.0 (20.9)	76.8 (29.5)	163 (40.4)
<i>T</i> _{max} , h	0.00 (0.00– 0.00)	3.93 (2.98– 3.97)	4.41 (0.917– 7.98)	2.08 (2.00– 3.98)	5.02 (4.00– 6.03)	1.95 (1.85– 2.00)	7.53 (4.12– 11.6)	6.00 (4.07– 11.8)	3.97 (2.88– 7.27)
<i>T</i> _{1/2} , h	38.9 (NC)	70.6 (55.3)	56.9 (42.0)	54.2 (31.5)	20.4 (NC)	26.3 (6.65)	36.7* (NC)	35.4* (NC)	48.5 (29.0)

Mean (standard deviation) for *C*_{max}, *AUC*_{24h}, and *T*_{1/2}, and median (range) for *T*_{max} is shown.

* *N* = 2

*AUC*_{24h}, area under the concentration-time curve for 24 h; *C*_{max}, maximum plasma concentration; NC, not calculated; *T*_{1/2}, terminal half-life time; *T*_{max}, time to maximum plasma concentration.