<SUPPLEMENT>

Table S1. Patient disposition in the single-agent arm

n (%)	GWN323 10 mg q3w	GWN323 30 mg q3w	GWN323 60 mg q3w	GWN323 150 mg q3w	GWN323 375 mg q3w	GWN323 750 mg q3w	GWN323 1500 mg q3w	All patients
	N=6	N=3	N=5	N=9	N=7	N=5	N=4	N=39
Treated	6 (100)	3 (100)	5 (100)	9 (100)	7 (100)	5 (100)	4 (100)	39 (100)
Discontinued from treatment	6 (100)	3 (100)	5 (100)	9 (100)	7 (100)	5 (100)	4 (100)	39 (100)
Reason for discontinuation								
Adverse event	0	0	0	1 (11.1)	0	1 (20.0)	0	2 (5.1)
Physician decision	0	0	0	1 (11.1)	0	0	0	1 (2.6)
Progressive disease	6 (100)	3 (100)	4 (80.0)	7 (77.8)	6 (85.7)	3 (60.0)	4 (100)	33 (84.6)
Patient/guardian decision	0	0	1 (20.0)	0	1 (14.3)	0	0	2 (5.1)
Death	0	0	0	0	0	1 (20.0)	0	1 (2.6)
Post-treatment follow-up for patients who discontinued from treatment								
Did not enter post-treatment follow-up	1 (16.7)	1 (33.3)	1 (20.0)	0	0	2 (40.0)	1 (25.0)	6 (15.4)
Entered post-treatment follow-up, discontinued	5 (83.3)	2 (66.7)	4 (80.0)	9 (100)	7 (100)	3 (60.0)	3 (75.0)	33 (84.6)
Reason for discontinuation								
Completed	2 (33.3)	1 (33.3)	1 (20.0)	2 (22.2)	4 (57.1)	0	2 (50.0)	12 (30.8)
Death	2 (33.3)	0	1 (20.0)	3 (33.3)	2 (28.6)	2 (40.0)	0	10 (25.6)
New therapy for study indication	1 (16.7)	1 (33.3)	2 (40.0)	3 (33.3)	1 (14.3)	1 (20.0)	1 (25.0)	10 (25.6)
Progressive disease	0	0	0	1 (11.1)	0	0	0	1 (2.6)

q3w, every 3 weeks.

Table S2. Patient disposition in the combination arm

n (%)	GWN323 10 mg + spartalizumab 100 mg q3w	GWN323 10 mg + spartalizumab 200 mg q3w	GWN323 30 mg + spartalizumab 100 mg q3w	GWN323 30 mg + spartalizumab 300 mg q3w	GWN323 75 mg + spartalizumab 300 mg q3w	GWN323 150 mg + spartalizumab 300 mg q3w	GWN323 300 mg + spartalizumab 300 mg q3w	GWN323 750 mg + spartalizumab 300 mg q3w	All patients
	N=6	N=4	N=4	N=5	N=5	N=17	N=7	N=5	N=53
Patients treated									
Treated	6 (100)	4 (100)	4 (100)	5 (100)	5 (100)	17 (100)	7 (100)	5 (100)	53 (100)
Discontinued from treatment	6 (100)	4 (100)	4 (100)	5 (100)	5 (100)	17 (100)	7 (100)	5 (100)	53 (100)
Reason for discontinuation									
Adverse event	0	1 (25.0)	1 (25.0)	0	0	0	0	0	2 (3.8)
Lost to follow-up	0	0	0	0	1 (20.0)	0	0	0	1 (1.9)
Physician decision	0	0	0	0	0	0	1 (14.3)	1 (20.0)	2 (3.8)
Progressive disease	4 (66.7)	3 (75.0)	3 (75.0)	4 (80.0)	2 (40.0)	15 (88.2)	6 (85.7)	4 (80.0)	41 (77.4)
Study terminated by sponsor	0	0	0	1 (20.0)	0	1 (5.9)	0	0	2 (3.8)
Patient/guardian decision	1 (16.7)	0	0	0	1 (20.0)	1 (5.9)	0	0	3 (5.7)
Death	1 (16.7)	0	0	0	1 (20.0)	0	0	0	2 (3.8)
Post-treatment follow-up for patients who discontinued from treatment									
Did not enter post-treatment follow-up	2 (33.3)	0	1 (25.0)	1 (20.0)	2 (40.0)	4 (23.5)	0	3 (60.0)	13 (24.5)
Entered post-treatment follow-up, discontinued	4 (66.7)	4 (100)	3 (75.0)	4 (80.0)	3 (60.0)	13 (76.5)	7 (100)	2 (40.0)	40 (75.5)
Reason for discontinuation									
Completed	1 (16.7)	1 (25.0)	0	0	0	3 (17.6)	1 (14.3)	0	6 (11.3)
Death	1 (16.7)	0	1 (25.0)	0	2 (40.0)	0	1 (14.3)	0	5 (9.4)
New therapy for study indication	2 (33.3)	3 (75.0)	2 (50.0)	4 (80.0)	1 (20.0)	9 (52.9)	5 (71.4)	2 (40.0)	28 (52.8)
Patient/guardian decision	0	0	0	0	0	1 (5.9)	0	0	1 (1.9)

q3w, every 3 weeks.

Table S3. Overview of AEs

	Single-agent arm															
n (%)	**GWN323 10 mg q3w N=6**		**GWN323 30 mg q3w N=3**		**GWN323 60 mg q3w N=5**		**GWN323 150 mg q3w N=9**		**GWN323 375 mg q3w N=7**		**GWN323 750 mg q3w N=5**		**GWN323 1500 mg q3w N=4**		**All patients N=39**	
	All grades	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
AEs	6 (100)	3 (50.0)	3 (100)	2 (66.7)	5 (100)	1 (20.0)	9 (100)	4 (44.4)	7 (100)	4 (57.1)	5 (100)	2 (40.0)	4 (100)	1 (25.0)	39 (100)	17 (43.6)
Treatment related	6 (100)	0	3 (100)	0	4 (80.0)	0	5 (55.6)	0	7 (100)	1 (14.3)	4 (80.0)	0	3 (75.0)	0	32 (82.1)	1 (2.6)
SAEs	2 (33.3)	2 (33.3)	2 (66.7)	2 (66.7)	0	0	3 (33.3)	3 (33.3)	2 (28.6)	2 (28.6)	2 (40.0)	2 (40.0)	1 (25.0)	1 (25.0)	12 (30.8)	12 (30.8)
Fatal SAEs	0	0	0	0	0	0	1 (11.1)	1 (11.1)	0	0	0	0	0	0	1 (2.6)	1 (2.6)
AEs leading to discontinuation	0	0	1 (33.3)	0	0	0	1 (11.1)	1 (11.1)	0	0	1 (20.0)	1 (20.0)	0	0	3 (7.7)	2 (5.1)
AEs leading to dose adjustment/interruption	0	0	1 (33.3)	1 (33.3)	0	0	0	0	1 (14.3)	1 (14.3)	2 (40.0)	1 (20.0)	0	0	4 (10.3)	3 (7.7)
AEs requiring additional therapy	6 (100)	2 (33.3)	3 (100)	2 (66.7)	5 (100)	0	9 (100)	4 (44.4)	7 (100)	3 (42.9)	4 (80.0)	2 (40.0)	3 (75.0)	1 (25.0)	37 (94.9)	14 (35.9)

	Combination arm															
n (%)	**GWN323 10 mg + spartalizumab 100 mg q3w**		**GWN323 10 mg + spartalizumab 200 mg q3w**		**GWN323 30 mg + spartalizumab 100 mg q3w**		**GWN323 30 mg + spartalizumab 300 mg q3w**		**GWN323 75 mg + spartalizumab 300 mg q3w**		**GWN323 150 mg + spartalizumab 300 mg q3w**		**GWN323 300 mg + spartalizumab 300 mg q3w**		**GWN323 750 mg + spartalizumab 300 mg q3w**		**All patients**	
	N=6		**N=4**		**N=4**		**N=5**		**N=5**		**N=17**		**N=7**		**N=5**		**N=53**	
	All grades	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
AEs	6 (100)	4 (66.7)	3 (75.0)	2 (50.0)	4 (100)	3 (75.0)	5 (100)	2 (40.0)	5 (100)	3 (60.0)	17 (100)	6 (35.3)	6 (85.7)	3 (42.9)	5 (100)	2 (40.0)	51 (96.2)	25 (47.2)
Treatment related	5 (83.3)	0	3 (75.0)	1 (25.0)	4 (100)	2 (50.0)	4 (80.0)	0	4 (80.0)	0	15 (88.2)	2 (11.8)	3 (42.9)	1 (14.3)	3 (60.0)	0	41 (77.4)	6 (11.3)
SAEs	3 (50.0)	3 (50.0)	0	0	3 (75.0)	3 (75.0)	1 (20.0)	1 (20.0)	3 (60.0)	3 (60.0)	4 (23.5)	3 (17.6)	2 (28.6)	2 (28.6)	2 (40.0)	2 (40.0)	18 (34.0)	17 (32.1)

Treatment related	0	0	0	0	1 (25.0)	1 (25.0)	0	0	0	0	3 (17.6)	2 (11.8)	0	0	0	0	4 (7.5)	3 (5.7)
Fatal SAEs	1 (16.7)	1 (16.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (1.9)	1 (1.9)
AEs leading to discontinuation	0	0	0	0	1 (25.0)	1 (25.0)	0	0	1 (20.0)	1 (20.0)	0	0	1 (14.3)	1 (14.3)	0	0	3 (5.7)	3 (5.7)
Treatment related	0	0	0	0	1 (25.0)	1 (25.0)	0	0	0	0	0	0	0	0	0	0	1 (1.9)	1 (1.9)
AEs leading to dose adjustment/interruption	1 (16.7)	1 (16.7)	1 (25.0)	0	1 (25.0)	0	0	0	2 (40.0)	0	5 (29.4)	3 (17.6)	0	0	1 (20.0)	0	11 (20.8)	4 (7.5)
AEs requiring additional therapy	5 (83.3)	3 (50.0)	3 (75.0)	2 (50.0)	4 (100)	3 (75.0)	5 (100)	2 (40.0)	5 (100)	3 (60.0)	15 (88.2)	5 (29.4)	5 (71.4)	3 (42.9)	4 (80.0)	2 (40.0)	46 (86.8)	23 (43.4)

AE, adverse event; q3w, every 3 weeks; SAE, serious AE.

Table S4. Serious adverse events reported in ≥5% of patients

	Single-agent arm															
n (%)	**GWN323 10 mg q3w N=6**		**GWN323 30 mg q3w N=3**		**GWN323 60 mg q3w N=5**		**GWN323 150 mg q3w N=9**		**GWN323 375 mg q3w N=7**		**GWN323 750 mg q3w N=5**		**GWN323 1500 mg q3w N=4**		**All patients N=39**	
	All grades	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Patients with ≥1 event	2 (33.3)	2 (33.3)	2 (66.7)	2 (66.7)	0	0	3 (33.3)	3 (33.3)	2 (28.6)	2 (28.6)	2 (40.0)	2 (40.0)	1 (25.0)	1 (25.0)	12 (30.8)	12 (30.8)
Anaemia	0	0	2 (66.7)	2 (66.7)	0	0	0	0	0	0	0	0	0	0	2 (5.1)	2 (5.1)
Nausea	0	0	0	0	0	0	0	0	0	0	1 (20.0)	0	1 (25.0)	0	2 (5.1)	0
Pulmonary embolism	0	0	0	0	0	0	1 (11.1)	1 (11.1)	0	0	1 (20.0)	1 (20.0)	0	0	2 (5.1)	2 (5.1)
Small intestinal obstruction	1 (16.7)	1 (16.7)	0	0	0	0	0	0	0	0	0	0	1 (25.0)	1 (25.0)	2 (5.1)	2 (5.1)
Vomiting	0	0	0	0	0	0	0	0	0	0	1 (20.0)	0	1 (25.0)	0	2 (5.1)	0

	Combination arm															
n (%)	**GWN323 10 mg + spartalizumab 100 mg q3w N=6**		**GWN323 10 mg + spartalizumab 200 mg q3w N=4**		**GWN323 30 mg + spartalizumab 100 mg q3w N=4**		**GWN323 30 mg + spartalizumab 300 mg q3w N=5**		**GWN323 75 mg + spartalizumab 300 mg q3w N=5**		**GWN323 150 mg + spartalizumab 300 mg q3w N=17**		**GWN323 300 mg + spartalizumab 300 mg q3w N=7**		**GWN323 750 mg + spartalizumab 300 mg q3w N=5**		**All patients N=53**	
	All grades	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Patients with ≥1 event	3 (50.0)	3 (50.0)	0	0	3 (75.0)	3 (75.0)	1 (20.0)	1 (20.0)	3 (60.0)	3 (60.0)	4 (23.5)	3 (17.6)	2 (28.6)	2 (28.6)	2 (40.0)	2 (40.0)	18 (34.0)	17 (32.1)
Abdominal pain	1 (16.7)	1 (16.7)	0	0	0	0	0	0	0	0	1 (5.9)	1 (5.9)	0	0	1 (20.0)	1 (20.0)	3 (5.7)	3 (5.7)
Sepsis	1 (16.7)	1 (16.7)	0	0	1 (25.0)	1 (25.0)	0	0	1 (20.0)	1 (20.0)	0	0	0	0	0	0	3 (5.7)	3 (5.7)
Vomiting	1 (16.7)	0	0	0	0	0	0	0	0	0	1 (5.9)	1 (5.9)	1 (14.3)	0	0	0	3 (5.7)	1 (1.9)

q3w, every 3 weeks.

Table S5. Adverse events suspected to be related to the study drug reported in ≥10% of patients

	Single-agent arm															
n (%)	**GWN323 10 mg q3w N=6**		**GWN323 30 mg q3w N=3**		**GWN323 60 mg q3w N=5**		**GWN323 150 mg q3w N=9**		**GWN323 375 mg q3w N=7**		**GWN323 750 mg q3w N=5**		**GWN323 1500 mg q3w N=4**		**All patients N=39**	
	All grades	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Patients with ≥1 event	6 (100)	0	3 (100)	0	4 (80.0)	0	5 (55.6)	0	7 (100)	1 (14.3)	4 (80.0)	0	3 (75.0)	0	32 (82.1)	1 (2.6)
Pyrexia	2 (33.3)	0	1 (33.3)	0	1 (20.0)	0	1 (11.1)	0	5 (71.4)	0	0	0	0	0	10 (25.6)	0
Chills	1 (16.7)	0	0	0	1 (20.0)	0	2 (22.2)	0	0	0	1 (20.0)	0	2 (50.0)	0	7 (17.9)	0
Myalgia	2 (33.3)	0	0	0	0	0	2 (22.2)	0	1 (14.3)	0	0	0	1 (25.0)	0	6 (15.4)	0
Diarrhoea	1 (16.7)	0	1 (33.3)	0	1 (20.0)	0	1 (11.1)	0	0	0	1 (20.0)	0	0	0	5 (12.8)	0
Rash	0	0	2 (66.7)	0	1 (20.0)	0	0	0	0	0	0	0	1 (25.0)	0	4 (10.3)	0

	Combination arm															
n (%)	**GWN323 10 mg + spartalizumab 100 mg q3w N=6**		**GWN323 10 mg + spartalizumab 200 mg q3w N=4**		**GWN323 30 mg + spartalizumab 100 mg q3w N=4**		**GWN323 30 mg + spartalizumab 300 mg q3w N=5**		**GWN323 75 mg + spartalizumab 300 mg q3w N=5**		**GWN323 150 mg + spartalizumab 300 mg q3w N=17**		**GWN323 300 mg + spartalizumab 300 mg q3w N=7**		**GWN323 750 mg + spartalizumab 300 mg q3w N=5**		**All Patients N=53**	
	All grades	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Patients with ≥1 event	5 (83.3)	0	3 (75.0)	1 (25.0)	4 (100)	2 (50.0)	4 (80.0)	0	4 (80.0)	0	15 (88.2)	2 (11.8)	3 (42.9)	1 (14.3)	3 (60.0)	0	41 (77.4)	6 (11.3)
Fatigue	2 (33.3)	0	0	0	0	0	1 (20.0)	0	3 (60.0)	0	3 (17.6)	0	1 (14.3)	0	0	0	10 (18.9)	0
Pyrexia	1 (16.7)	0	1 (25.0)	0	0	0	0	0	1 (20.0)	0	5 (29.4)	0	1 (14.3)	0	1 (20.0)	0	10 (18.9)	0
Chills	0	0	0	0	0	0	1 (20.0)	0	1 (20.0)	0	4 (23.5)	0	1 (14.3)	0	1 (20.0)	0	8 (15.1)	0
Nausea	2 (33.3)	0	2 (50.0)	0	1 (25.0)	0	1 (20.0)	0	0	0	1 (5.9)	0	0	0	1 (20.0)	0	8 (15.1)	0
Rash	2 (33.3)	0	0	0	1 (25.0)	0	0	0	0	0	3 (17.6)	0	1 (14.3)	0	0	0	7 (13.2)	0
Pruritus	0	0	0	0	1 (25.0)	0	2 (40.0)	0	0	0	3 (17.6)	0	0	0	0	0	6 (11.3)	0

q3w, every 3 weeks.

Table S6. Pharmacokinetic parameters for the GWN323 single-agent arm

Parameter	Statistics	GWN323 10 mg q3w N=6	GWN323 30 mg q3w N=3	GWN323 60 mg q3w N=5	GWN323 150 mg q3w N=6	GWN323 375 mg q3w N=3	GWN323 750 mg q3w N=5	GWN323 1500 mg q3w N=4	All patients N=32
				Cycle 1 day 1					
AUC_{last} (h*µg/mL)	Mean (SD)	669 (263)	1830 (406)	3820 (1160)	5740 (2270)	15 000 (4610)	43 700 (16 100)	82 600 (34 200)	20 400(31 000)
	CV%	39.3	22.2	30.4	39.5	30.8	36.7	41.4	151.9
	Geo-mean	630	1810	3680	5360	14 400	41 800	77 100	6320
	Geo-CV%	38.8	22.6	31.8	42.3	34.8	34.8	45.9	392.2
AUC_{inf} (h*µg/mL)	Mean (SD)	660 (176)	2390 (NA)	NA	5870 (3180)	NA	39 200 (NA)	NA	6290 (12 600)
	CV%	26.6	NA	NA	54.1	NA	NA	NA	200.0
	Geo-mean	640	2390	NA	5430	NA	39 200	NA	1880
	Geo-CV%	28.1	NA	NA	62.0	NA	NA	NA	290.4
C_{max} (ng/mL)	Mean (SD)	5470 (2960)	9320 (3700)	20 000 (6400)	37 600 (9290)	127 000 (37 000)	248 000 (21 500)	474 000 (221 000)	122 000 (174 000)
	CV%	54.2	39.7	31.9	24.7	29.2	8.7	46.6	142.9
	Geo-mean	4880	8820	19300	36 500	123 000	247 000	438 000	40 900
	Geo-CV%	54.3	43.5	31.5	27.8	32.6	8.6	47.6	365.4
t_{max} (h)	Median	0.583	0.583	0.5	0.583	0.583	0.583	0.625	0.583
	Min-max	0.5-1.58	0.5-0.583	0.5-0.567	0.550-0.750	0.583-0.750	0.5-0.833	0.567-0.750	0.5-1.58
$t_{½}$ (h)	Median	171	169	NA	198	NA	136	NA	175
	Min-Max	140-227	169-169	NA	191-206	NA	136-136	NA	136-227
CL (L/h))	Mean (SD)	0.0161 (0.004 45)	0.0125 (NA)	NA	0.0299 (0.0162)	NA	0.0191 (NA)	NA	0.0191(0.0091)
	CV%	27.7	NA	NA	54.1	NA	NA	NA	47.6
V_z (L)	Mean (SD)	4.06 (1.09)	3.06 (NA)	NA	8.43 (4.17)	NA	3.76 (NA)	NA	4.89 (2.63)
	CV%	26.7	NA	NA	49.5	NA	NA	NA	53.7
				Cycle 4 day 1					
AUC_{last} (h*µg/mL)	Mean (SD)	1420 (546)	NA	5140 (2000)	12 300 (4520)	NA	102 000 (NA)	115 000 (29 200)	29 100 (47 300)
	CV%	38.4	NA	39.0	36.9	NA	NA	25.5	162.8
	Geo-mean	1310	NA	4820	11 800	NA	102 000	113 000	6890
	Geo-CV%	52.1	NA	48.8	39.1	NA	NA	26.3	502.4

AUC_{inf} (h*µg/mL)	Mean (SD)	1740 (326)	NA	NA	16 000 (NA)	NA	NA	NA	5310 (7150)
	CV%	18.8	NA	NA	NA	NA	NA	NA	134.7
	Geo-mean	1720	NA	NA	16 000	NA	NA	NA	3000
	Geo-CV%	20.2	NA	NA	NA	NA	NA	NA	160.6
C_{max} (ng/mL)	Mean (SD)	6670 (1740)	NA	25 400 (4450)	52 000 (6010)	NA	304 000 (NA)	699 000 (291 000)	147 000 (271 000)
	CV%	26.2	NA	17.5	11.6	NA	NA	41.6	183.7
	Geo-mean	6450		25 200	51 800		304 000	668 000	33 400
	Geo-CV%	30.3		17.9	11.6		NA	44.9	467.8
t_{max} (h)	Median	0.583	NA	0.550	0.550	NA	1.13	0.5	0.550
	Min-max	0.5-0.6	NA	0.5-0.783	0.550-0.550	NA	1.13-1.13	0.5-0.5	0.5-1.13
$t_{½}$ (h)	Median	256	NA	NA	341	NA	NA	NA	272
	Min-max	233-288	NA	NA	341-341	NA	NA	NA	233-341
V_z (L)	Mean (SD)	3.12 (0.976)	NA	NA	6.95 (NA)	NA	NA	NA	4.08 (2.07)
	CV%	31.3	NA	NA	NA	NA	NA	NA	50.9

AUC_{last}, area under the curve from time = 0 to last measurable concentration; AUC_{inf}, area under the plasma concentration-time curve extrapolated to infinity; CL, total clearance uncorrected for absolute bioavailability; C_{max}, maximum concentration; CV, Coefficient of variation; Geo, geometric; Min-max, minimum-maximum; q3w, every 3 weeks; SD, standard deviation; $t_{½}$, elimination half-life; t_{max}, time to reach C_{max}; V_z, apparent volume of distribution during terminal elimination phase.

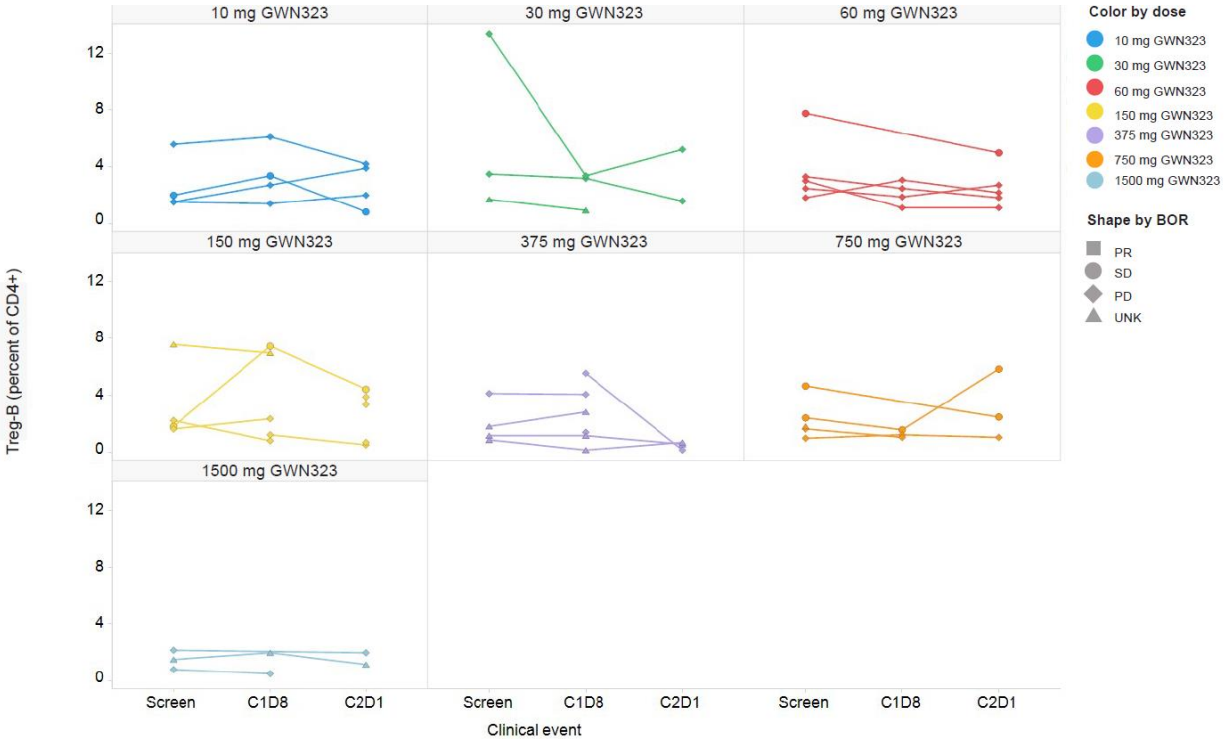
Table S7. Pharmacokinetic parameters for GWN323 (cycle 1 day 1): combination arm

		Cycle 1 day 1							
Parameter	**Statistics**	**GWN323 10 mg + spartalizumab 100 mg q3w N=5**	**GWN323 10 mg + spartalizumab 200 mg q3w N=4**	**GWN323 30 mg + spartalizumab 100 mg q3w N=4**	**GWN323 30 mg + spartalizumab 300 mg q3w N=5**	**GWN323 75 mg + spartalizumab 300 mg q3w N=5**	**GWN323 150 mg + spartalizumab 300 mg q3w N=12**	**GWN323 300 mg + spartalizumab 300 mg q3w N=6**	**GWN323 750 mg + spartalizumab 300 mg q3w N=1**
AUC_{last} (h*µg/mL)	Mean (SD)	395 (95.9)	524 (210)	1210 (586)	1310 (268)	4870 (1450)	6680 (2100)	23 500 (10 600)	NA
	CV%	24.3	40.1	48.3	20.5	29.8	31.4	44.9	NA
	Geo-mean	385	491	1100	1290	4700	6400	22100	
	Geo-CV%	26.3	43.9	64.6	21.5	32.7	34.8	45.8	
AUC_{inf} (h*µg/mL)	Mean (SD)	456 (149)	390 (NA)	NA	1500 (405)	4830 (1860)	9690 (528)	30300 (18200)	NA
	CV%	32.7	NA	NA	26.9	38.4	5.5	60.0	NA
	Geo-mean	437	390	NA	1480	4650	9680	27400	NA
	Geo-CV%	35.2	NA	NA	27.7	41.0	5.5	71.2	NA
C_{max} (ng/mL)	Mean (SD)	2690 (509)	2690 (974)	7240 (1070)	8300 (2100)	24100 (8540)	39000 (11800)	109000 (36600)	NA
	CV%	18.9	36.3	14.7	25.3	35.5	30.3	33.7	NA
	Geo-mean	2650	2550	7190	8090	22900	37000	104000	NA
	Geo-CV%	20.3	39.3	15.5	27.1	37.5	40.1	36.2	NA
t_{max} (h)	Median	1.58	1.71	1.52	1.70	11.7	2.17	2.09	NA
	Min-max	0.5-1.85	0.5-1.92	0.550-1.75	1.50-2.53	1.50-25.9	1.98-2.37	1.58-21.8	NA
$t_{½}$ (h)	Median	181	213	NA	150	182	273	203	NA
	Min-max	124-220	213-213	NA	110-191	147-218	244-303	180-227	NA
CL (L/h))	Mean (SD)	0.0239 (0.0083)	0.0256 (NA)	NA	0.0207 (0.00557)	0.0168 (0.00643)	0.00805 (0.0114)	0.0121 (0.00725)	NA
	CV%	34.7	NA	NA	26.9	38.4	141.4	60.0	NA
V_z (L)	Mean (SD)	5.80 (1.40)	7.86 (NA)	NA	4.26 (0.493)	4.64 (2.91)	3.52 (4.97)	3.37 (1.55)	NA
	CV%	24.1	NA	NA	11.6	62.7	141.4	46.0	NA
		Cycle 4 day 1							
AUC_{last} (h*µg/mL)	Mean (SD)	915 (644)	2160(790)	3730 (2130)	2480 (366)	33100 (24900)	15300 (NA)	NA	NA
	CV%	70.4	36.5	57.1	14.8	75.3	NA	NA	NA
	Geo-mean	771	2090	3310	2470	28000	15300	NA	NA
	Geo-	82.4	38.7	67.7	14.6	101.2	NA	NA	NA

	CV%								
AUC_{inf} (h*µg/mL)	Mean (SD)	1230 (676)	3090 (NA)	6520 (NA)	2700 (288)	35600 (25000)	NA	NA	NA
	CV%	55.0	NA	NA	10.7	70.3	NA	NA	NA
	Geo-mean	1130	3090	6520	2690	30900	NA	NA	NA
	Geo-CV%	63.3	NA	NA	10.7	90.2	NA	NA	NA
C_{max} (ng/mL)	Mean (SD)	2890(1280)	5770(2470)	10500(3290)	10600(1880)	60000(16300)	47800(13000)	NA	NA
	CV%	44.4	42.8	31.3	17.7	27.2	27.2	NA	NA
	Geo-mean	2700	5490	10100	10500	58800	46900	NA	NA
	Geo-CV%	47.1	46.4	34.4	18.8	28.1	28.1	NA	NA
t_{max} (h)	Median	1.52	11.0	1.67	2.15	230	0.842	NA	NA
	Min-max	0.767-1.55	0.517-21.6	1.58-23.6	1.57-2.57	2.17-458	0.667-1.02	NA	NA
$t_{½}$ (h)	Median	355	751	598	209	465	NA	NA	NA
	Min-max	354-356	751-751	598-598	203-215	356-575	NA	NA	NA
V_z (L)	Mean (SD)	8.36(5.34)	10.3(NA)	8.36(NA)	4.22(0.321)	3.11(0.658)	NA	NA	NA
	CV%	63.9	NA	NA	7.6	21.2	NA	NA	NA

AUC_{last}, area under the curve from time = 0 to last measurable concentration; AUC_{inf}, area under the plasma concentration-time curve extrapolated to infinity; CL, total clearance uncorrected for absolute bioavailability; C_{max}, maximum concentration; CV, Coefficient of variation; Geo, geometric; Min-max, minimum-maximum; q3w, every 3 weeks; SD, standard deviation; $t_{½}$, elimination half-life; t_{max}, time to reach C_{max}; V_z, apparent volume of distribution during elimination phase

Figure S1: Peripheral effector Treg cells in patients treated with single-agent GWN323

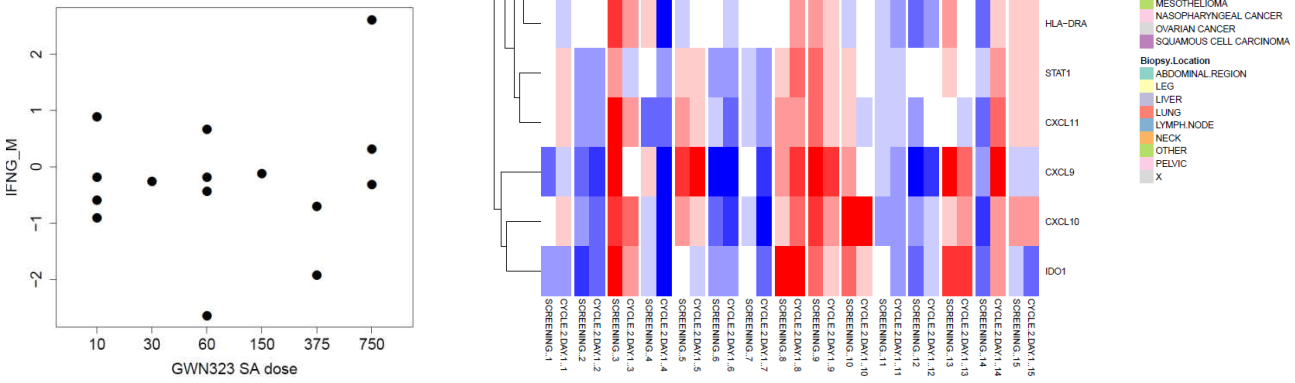


Blood was collected and PBMCs isolated at screening, C1D8 and C2D1. PBMCs were stained to identify the percentages of peripheral effector Treg cells. BOR categories are indicated by shape and doses of GWN323 +/- spartalizumab are colour coded. Immune cell identification markers were: Proliferating T cells: CD8+Ki67+ % of CD8+, proliferating NK cells: CD56+Ki67+ % of CD56+Total Tregs: (CD4+ CD127lo $CD25^{hi}$ Foxp3+ (% of CD4+ $CD127^{lo}$ $CD25^{hi}$)* CD4+ CD127lo CD25hi (% of CD4+))/100, eTregs: CD4+ $CD127^{lo}$ $CD25^{hi}$ $Foxp3^{hi}$ CD45RA-% of CD4+ and nTregs: CD4+ $CD127^{lo}$ $CD25^{hi}$ $Foxp3^{lo}$ CD45RA+% of CD4+.

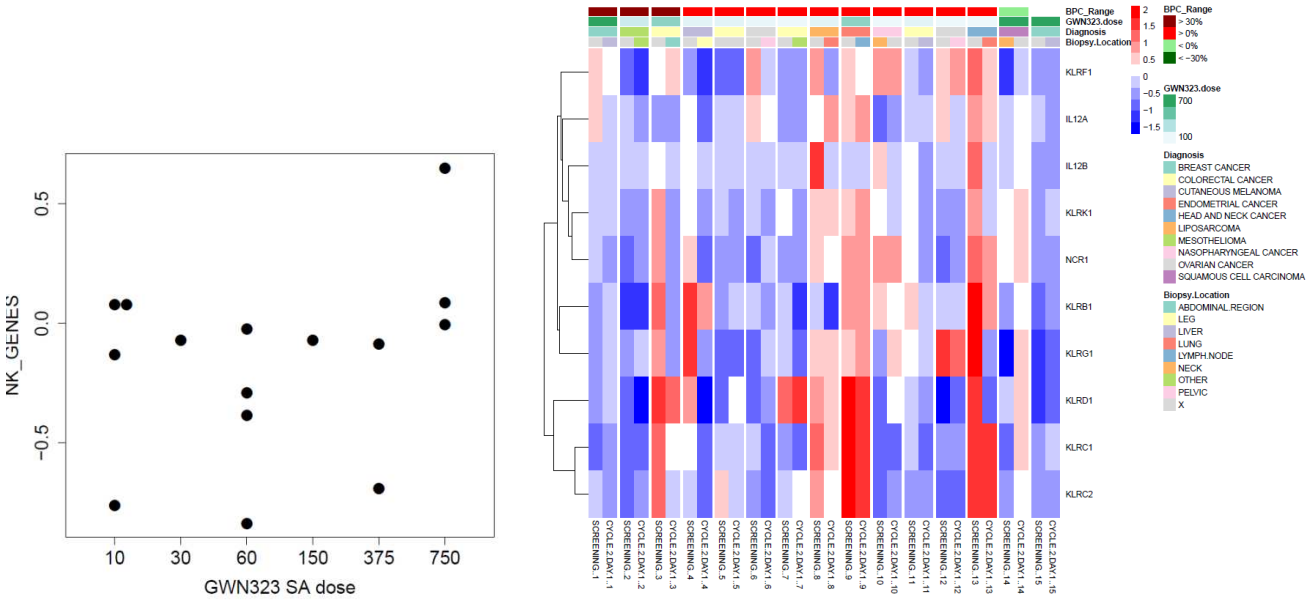
BOR, best overall response; C, cycle; D, day; PBMC, peripheral blood mononuclear cell; PD, progressive disease; SD, stable disease; Treg, regulatory T; UNK, unknown.

Figure S2: Combined RNA sequencing data from all single-agent patients: (A) effect of treatment on IFNγ and (B) NK cell signature

(A)



(B)

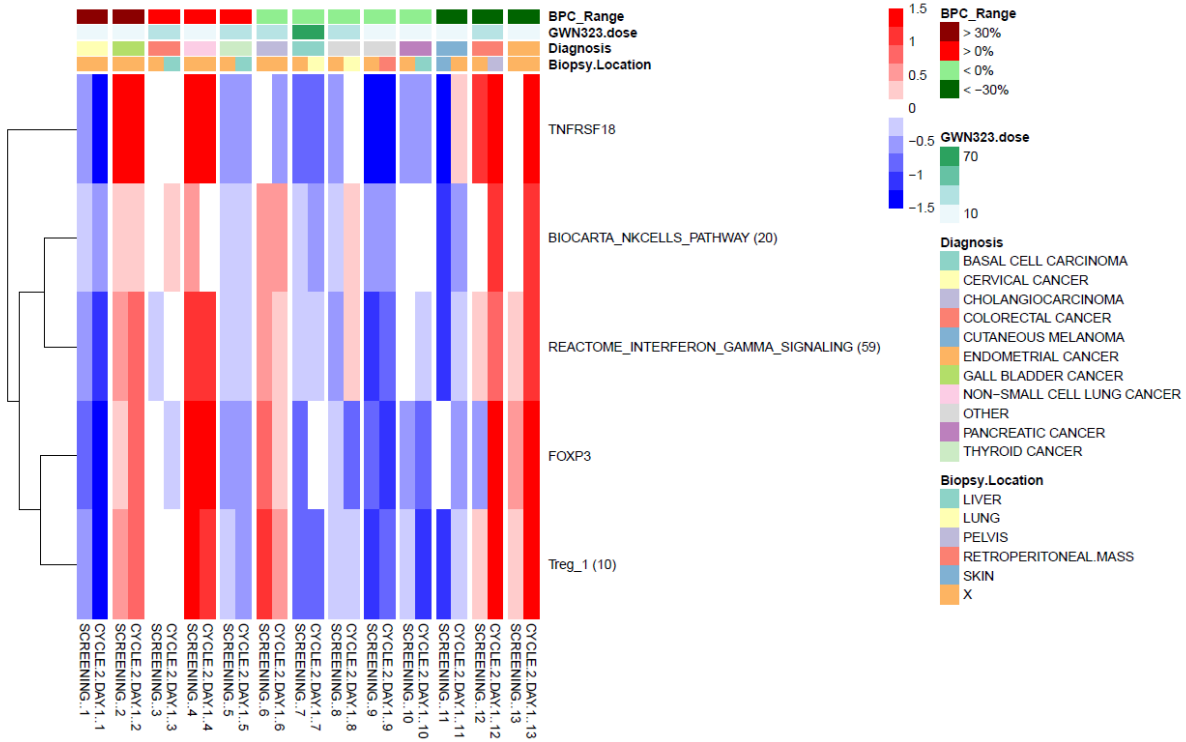


RNA sequencing analysis was performed on paraffin-embedded sections of tumour collected at screening and cycle 2 day 1 for the single-agent treatment patients. Gene expression heatmaps and correlation plots between GWN323 dose and IFNɣ gene signatures (A) and NK cell gene signatures (B) are shown. The heatmaps on the right show the gene expression values for the screening/cycle 2 day 1 pairs. The GWN323 dose, diagnosis and biopsy locations are colour coded and sorted on the range of BPC (BPC_Range) in tumour size. Biopsy location is important as normal cells from nearby tissue can impact differential gene expression differently. The boxplots on the left show the distribution of fold change for the signatures for all the sets of GWN323 doses. The gene signature expression levels in the single arm indicate no significant correlations between the GWN323 dosing and changes in T-cell expression. A single outlier in the 750

mg dosage arm is likely owing to difference in biopsy location between the screening and on-treatment samples, the on-treatment sample being sourced from the lymph node resulting in higher gene expression levels in general.

BPC, best percent change; IFN, interferon; NK, natural killer; RNA, Ribonucleic acid; SA, single agent

Figure S3: Combined RNA sequencing data from patients treated with GWN323 and spartalizumab



RNA sequencing analysis was performed on paraffin-embedded sections of tumour collected at screening and cycle 2 day 1 for the combination arm. Gene signature expression heatmaps for the screening/cycle 2 day 1 pairs are shown for a number of IFNɣ, Treg and NK cell gene signatures and more. The GWN323 dose, diagnosis and biopsy locations are colour coded and sorted on the range of BPC (BPC_Range) in tumour size. Biopsy location is important as normals cells from nearby tissue can impact differential gene expression differently. Analysis of the paired samples in the combination arm in patients with a 30% on-treatment

decrease in tumour volume show upregulation of multiple IFN-γ signatures and Treg signatures. The numbers next to each signature name indicate the number of genes contained in the respective signature.

BPC, best percent change; IFN, interferon; NK, natural killer; RNA, Ribonucleic acid; Treg, T regulatory. TNFRSF, tumor necrosis factor receptor superfamily

SUPPLEMENTAL METHODS

Biomarker assessments

Assessments were performed on archival or newly obtained tumour biopsies via immunohistochemistry and ribonucleic acid (RNA) sequencing. Immunohistochemistry staining for spartalizumab was performed on the Dako Autostainer Link 48 system with the 22C3 mouse monoclonal primary antibody and EnVision FLEX visualisation system, as described in the spartalizumab immunohistochemistry 22C3 pharmDx package insert. The percentage of tumour cells with partial or complete membranous staining of spartalizumab was assessed. Immunohistochemistry staining for CD8 was performed on the Ventana Benchmark XT system with the Dako CD8 mouse monoclonal primary antibody (clone C8/144B). Images of whole tumour sections were captured using a Mirax scanner (Zeiss) and Meso Scale Discovery (MSD) with Definiens (Definiens AG, Munich, Germany). DAB (3,3′-Diaminobenzidine) intensity was quantified as percent positive pixels. For RNA sequencing, RNA was extracted from formalin-fixed paraffin-embedded tissue biopsies. To enrich for messenger RNA (mRNA), ribosomal RNA (rRNA) was depleted using RNase H digestion. The rRNA-depleted RNA was fragmented, converted to complementary DNA and constructed into sequencing libraries with the TruSeq RNA Library Preparation Kit v2 (Illumina #RS-122-2001 and #RS-122-2002). The resulting libraries were sequenced with 100-base pair (bp) paired-end reads to a target depth of 50 million total reads per sample on an Illumina HiSeq sequencing system. Next-generation sequencing data processing sequencing reads were aligned to the human reference genome (hg19) using STAR. HTSeq was used to quantify the number of reads aligned to each gene in the RefSeq transcriptome. Sequencing data were evaluated for quality, and low complexity libraries with <2 million estimated unique read pairs were excluded from the downstream analysis. Gene count

data were normalised using the trimmed mean of M values method as implemented in edgeR. All downstream gene signature analyses were performed on the log2 of the normalised gene count data. Flow cytometry (using a BD Fortessa) was performed on peripheral blood mononuclear cell samples taken before treatment and at several on-treatment timepoints to quantify immune cell subsets. Immune cell identification markers were as follows: Proliferating T cells: CD8+Ki67+ % of CD8+, proliferating NK cells: CD56+Ki67+ % of CD56+Total Tregs: (CD4+ CD127lo $CD25^{hi}$ Foxp3+ (% of CD4+ $CD127^{lo}$ $CD25^{hi}$)* CD4+ $CD127^{lo}$ $CD25^{hi}$ (% of CD4+))/100, eTregs: CD4+ $CD127^{lo}$ $CD25^{hi}$ $Foxp3^{hi}$ CD45RA-% of CD4+ and nTregs: CD4+ $CD127^{lo}$ $CD25^{hi}$ $Foxp3^{lo}$ CD45RA+% of CD4+.