STATISTICAL PROPERTIES

Simulation setting

Simulation results were run to display the performance of the design characteristics, see Table S1. The following scenarios were chosen to display the operating characteristics with the optimal combination(s) indicated in bold type in Table S1: (1) all true DLT probabilities are safe (i.e. less toxic than 25%) and the highest Zone has the combination with the highest dRsp rate, (2) all true DLT probabilities are safe (i.e. less toxic than 25%) and the dRsp probabilities begin to plateau at arm C in Zone 2, (3) two combinations (C and D) have true DLT probabilities more toxic than 25% and combination B has the highest dRsp rate among safe combinations, (4) all true DLT probabilities are safe (i.e. less toxic than 25%) and equal dRsp for combination B and D, (5) two combinations (B and D) have true DLT probabilities more toxic than 25% and combination C has the highest dRsp rate among safe combinations, and (6) all combinations are too toxic (i.e. more toxic than 25%). For each scenario, 1000 simulated trials were run. Displayed in the table within each scenario for each arm is the true DLT probability, the true dRsp response rate, the percentage of trials in which the arm was recommended as the optimal combination, and the percentage of patients treated. Displayed in the last four columns is the average and selected percentiles for the trial size at study closure, the percentage of times in the simulations that the trial closed due to safety concerns, the percentage of simulated patients that had a DLT, and the percentage of simulated patients that had a dRsp.

Simulation results

It is clear from examining the results in Table S1 that the proposed design is performing well in terms of recommending optimal treatment regimens, as well as allocating patients to these regimens. In Scenario 1, the design selects, as the optimal treatment regimen, the target regimen in 75% of simulated trials, while assigning 50% of 48 patients on average to this regimen. In Scenario 2, recommendation of target regimens as the optimal treatment regimen

occurs in approximately 61% of simulated trials, while more than half (55%) of the patients enrolled are treated at these regimens. In Scenario 3, the design identifies the target regimens as the optimal treatment regimen in approximately 62% of simulated trials while allocating 43% of patients to one of these three regimens. In Scenario 4, the optimal regimens are selected in 84% of trials. Similar findings are obtained from Scenario 5, in which the method is able to locate the optimal regimen in 75% of simulated trials. Finally, in Scenario 6, all regimens are overly toxic. The method correctly terminates the trial in 99.7% of simulated trials, and treats 92% of the 8 accrued patients on average to Zone 1. Overall the simulation results indicate that the design outlined in this article is a practical Phase I/II adaptive method for use with combined immunotherapy agents.

Table S1: Design performance								
Maximum sample size set at 70, stop when a recommended arm has accrued 30 patients								
Scenario: / **Zone:** / **Regimen:**	True probabilities (DLT, dRsp) % optimal regimen recommended % patient allocation				Avg size, percentiles	% stop	% DLT	% dRsp
	1	**2**		**3**				
	A	**B**	**C**	**D**				
1:	(0.02, 0.19) 0.05 0.15	(0.07, 0.30) 0.09 0.17	(0.05, 0.40) 0.11 0.18	**(0.17, 0.70)** **0.75** **0.50**	48, 25th = 44 50th = 46 75th = 49 90th = 58 95th = 64	0.000	0.107	0.501
2:	(0.01, 0.35) 0.15 0.20	(0.03, 0.45) 0.24 0.25	**(0.05, 0.60)** **0.44** **0.34**	**(0.10, 0.60)** **0.17** **0.21**	50, 25th = 45 50th = 47 75th = 54 90th = 63 95th = 67	0.002	0.046	0.513
3:	(0.14, 0.19) 0.28 0.31	**(0.20, 0.40)** **0.62** **0.43**	(0.44, 0.50) 0.07 0.20	(0.44, 0.70) 0.02 0.06	49, 25th = 42 50th = 48 75th = 56 90th = 65 95th = 70	0.020	0.242	0.373
4:	(0.05, 0.15) 0.13 0.20	**(0.05, 0.40)** **0.67** **0.46**	(0.17, 0.20) 0.04 0.14	**(0.17, 0.40)** **0.17** **0.20**	48, 25th = 44 50th = 46 75th = 50 90th = 59 95th = 64	0.003	0.090	0.332
5:	(0.05, 0.20) 0.10 0.21	(0.40, 0.40) 0.12 0.22	**(0.20, 0.50)** **0.75** **0.47**	(0.45, 0.70) 0.03 0.10	52, 25th = 45 50th = 50 75th = 60 90th = 69 95th = 70	0.005	0.237	0.438
6:	(0.60, 0.20) 0.00 0.92	(0.70, 0.40) 0.00 0.04	(0.80, 0.50) 0.00 0.04	(0.90, 0.70) 0.00 0.01	8, 25th = 2 50th = 7 75th = 12 90th = 17 95th = 21	0.997	0.620	0.215