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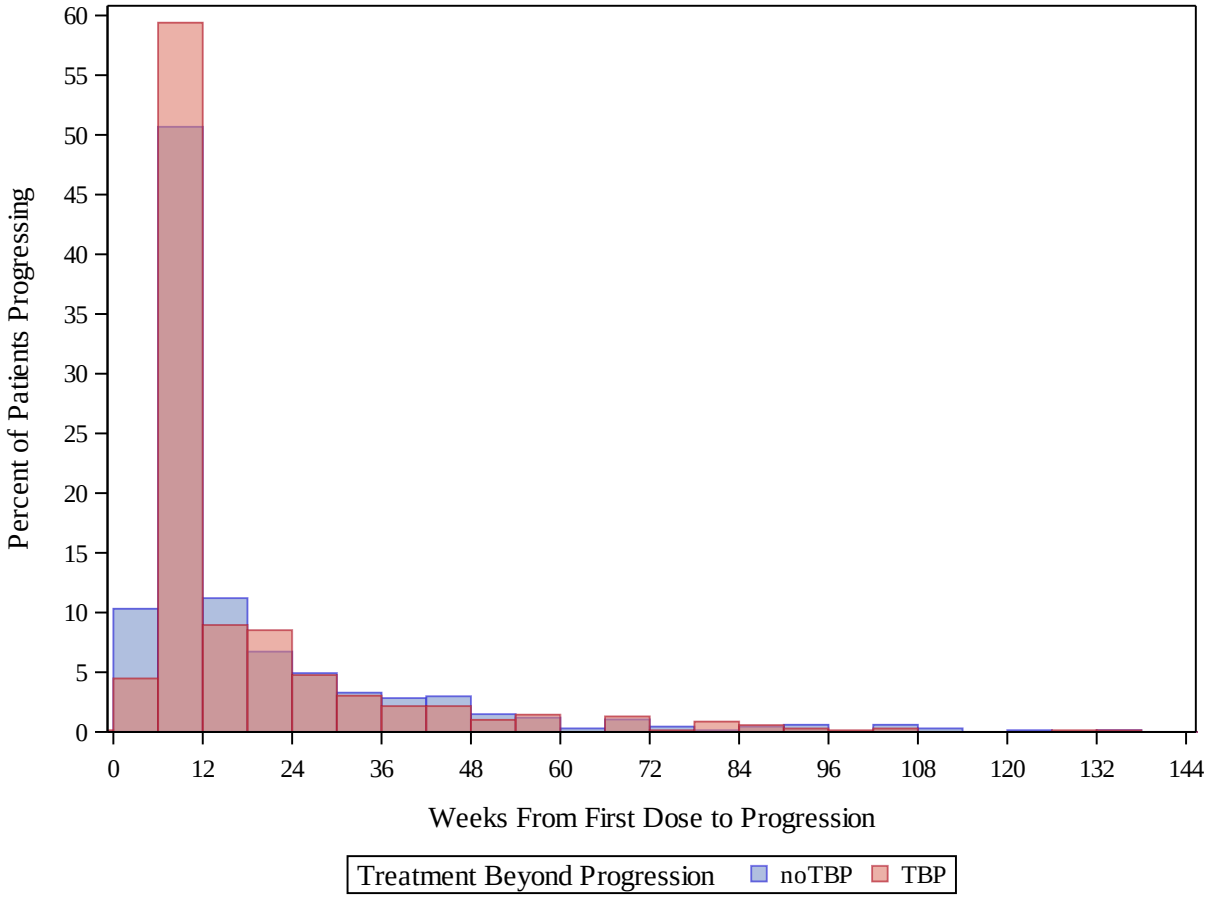
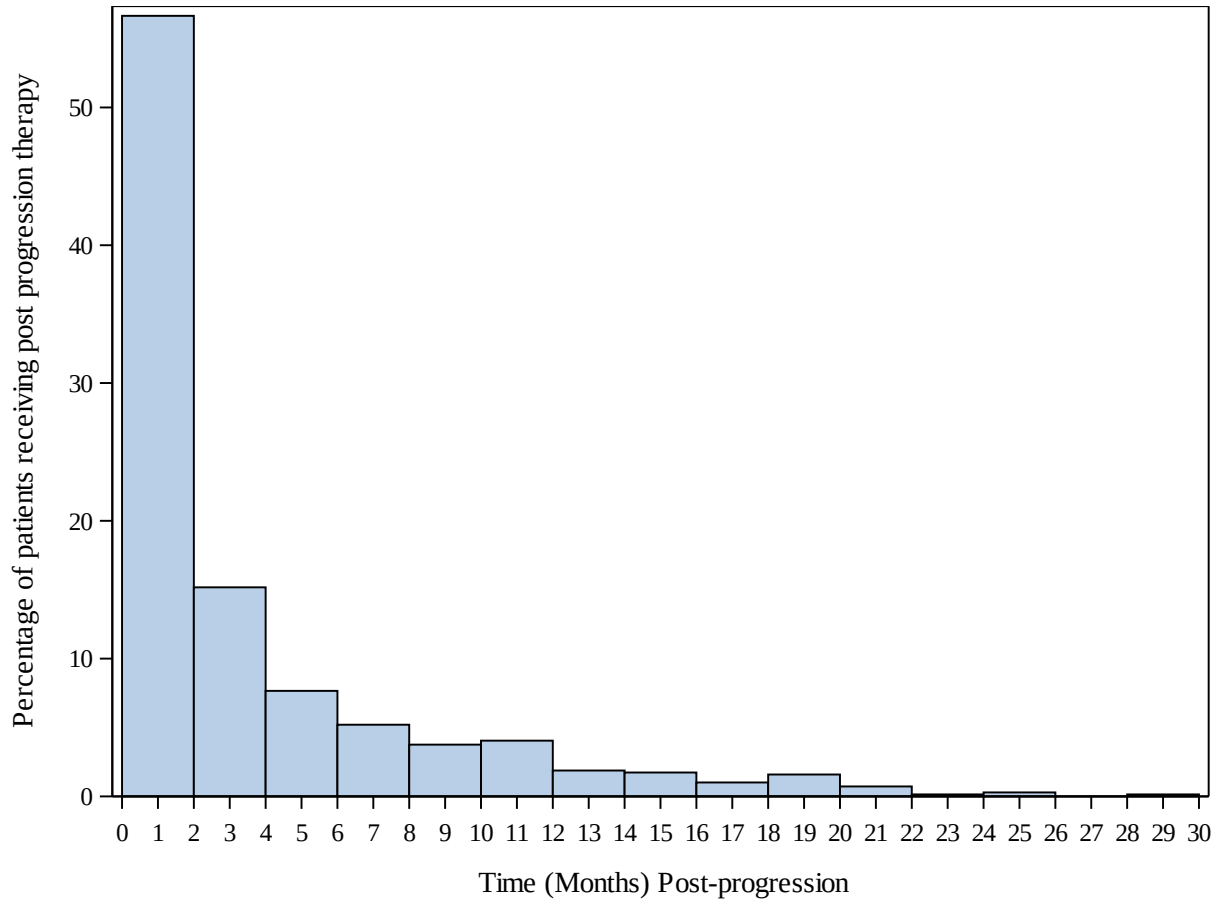
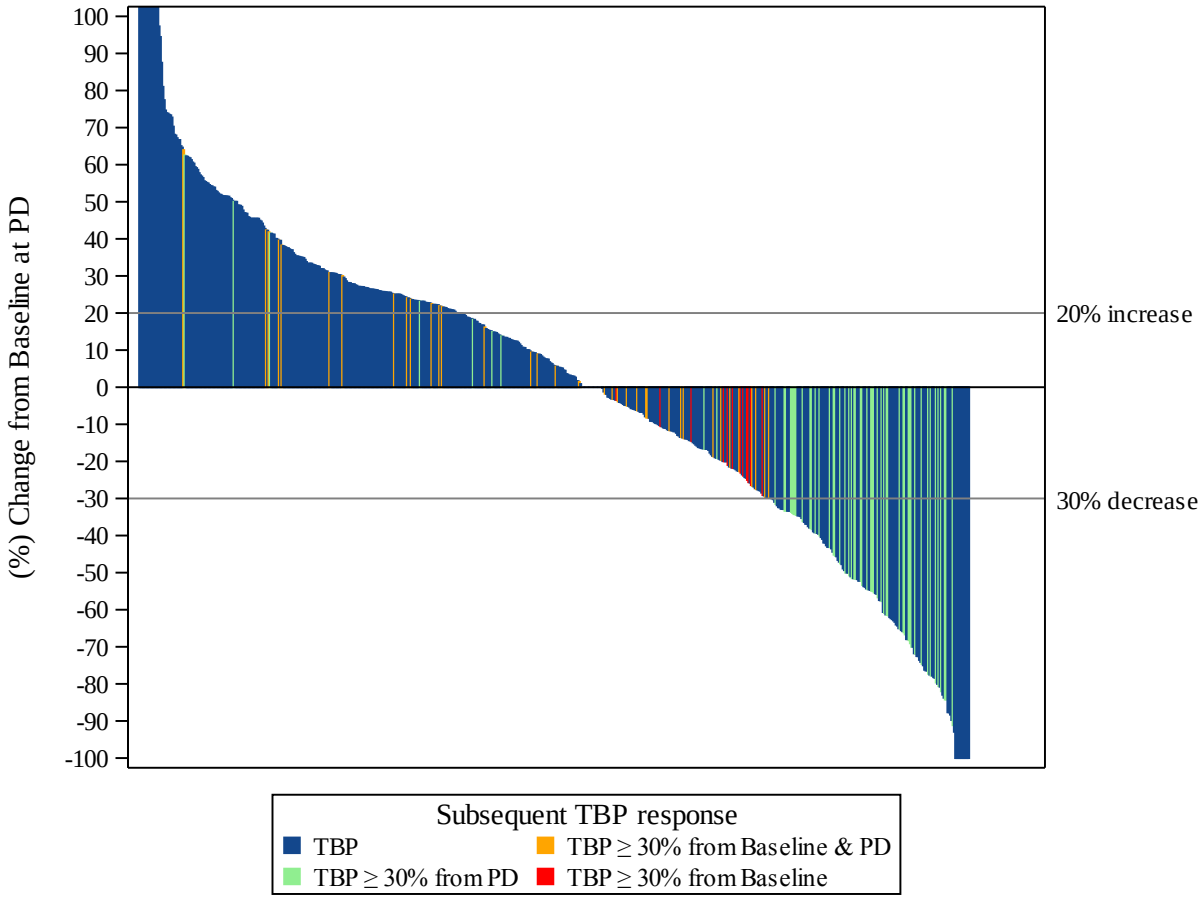
Appendix Figure S1: Time to Progression in Patients Treated with anti-PD1 Antibody



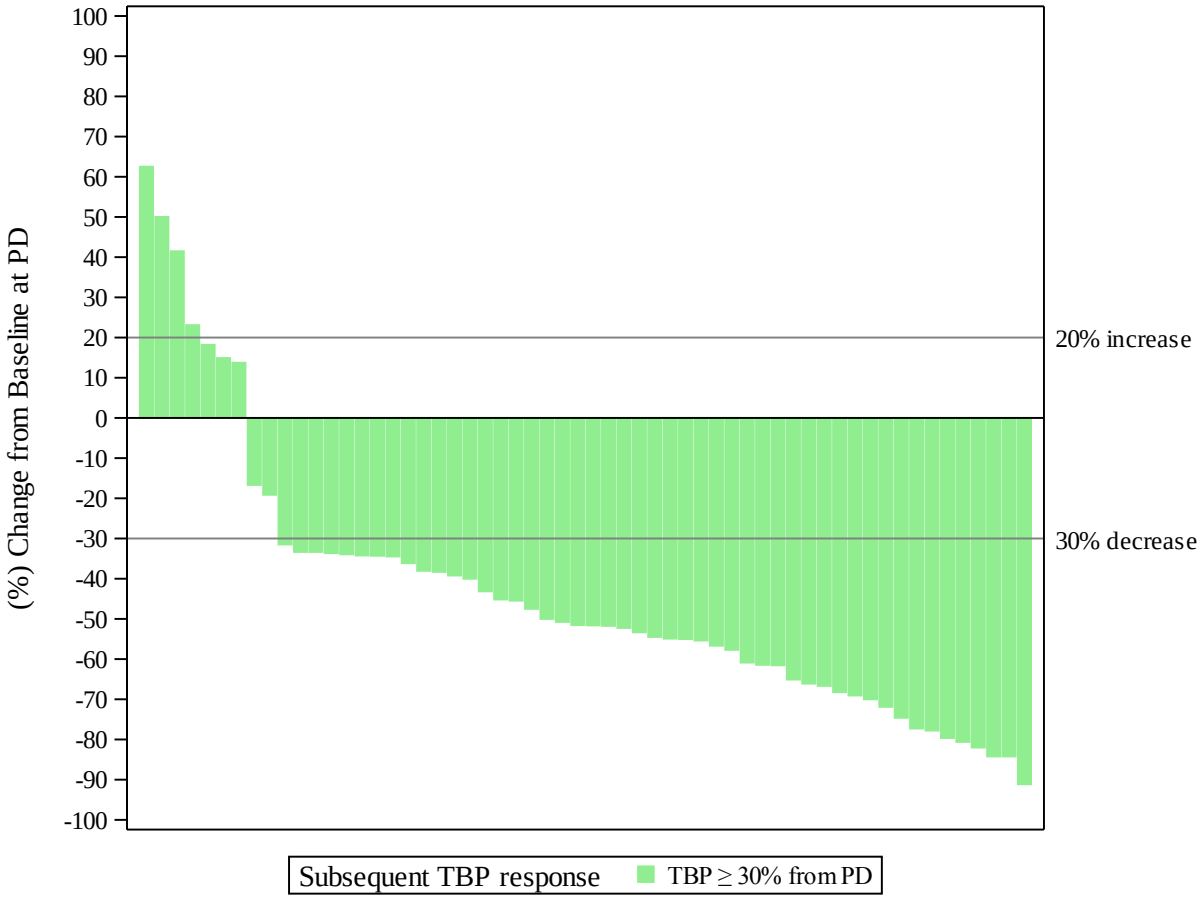
Appendix Figure S2: Duration of Treatment Beyond Progression



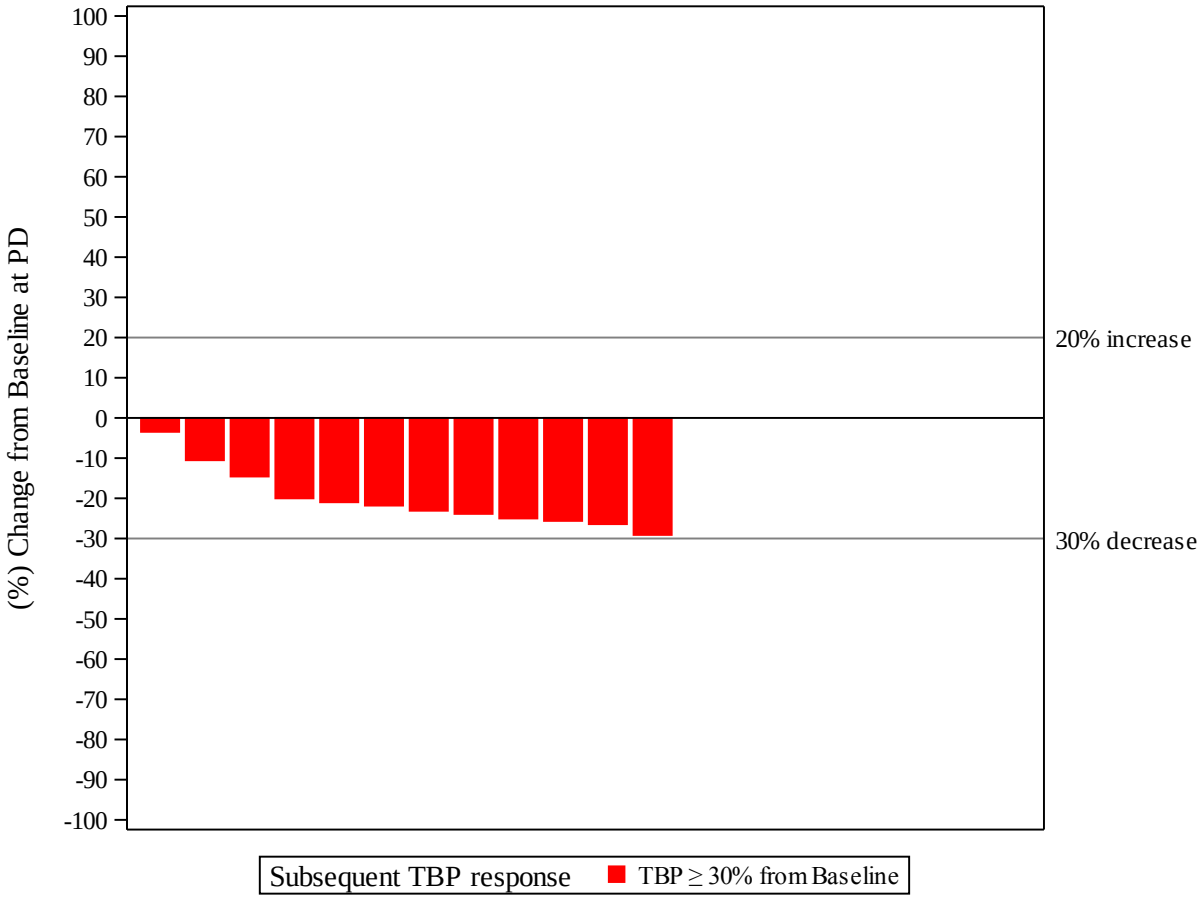
Appendix Figure S3: Waterfall Plot at time of Progressive Disease



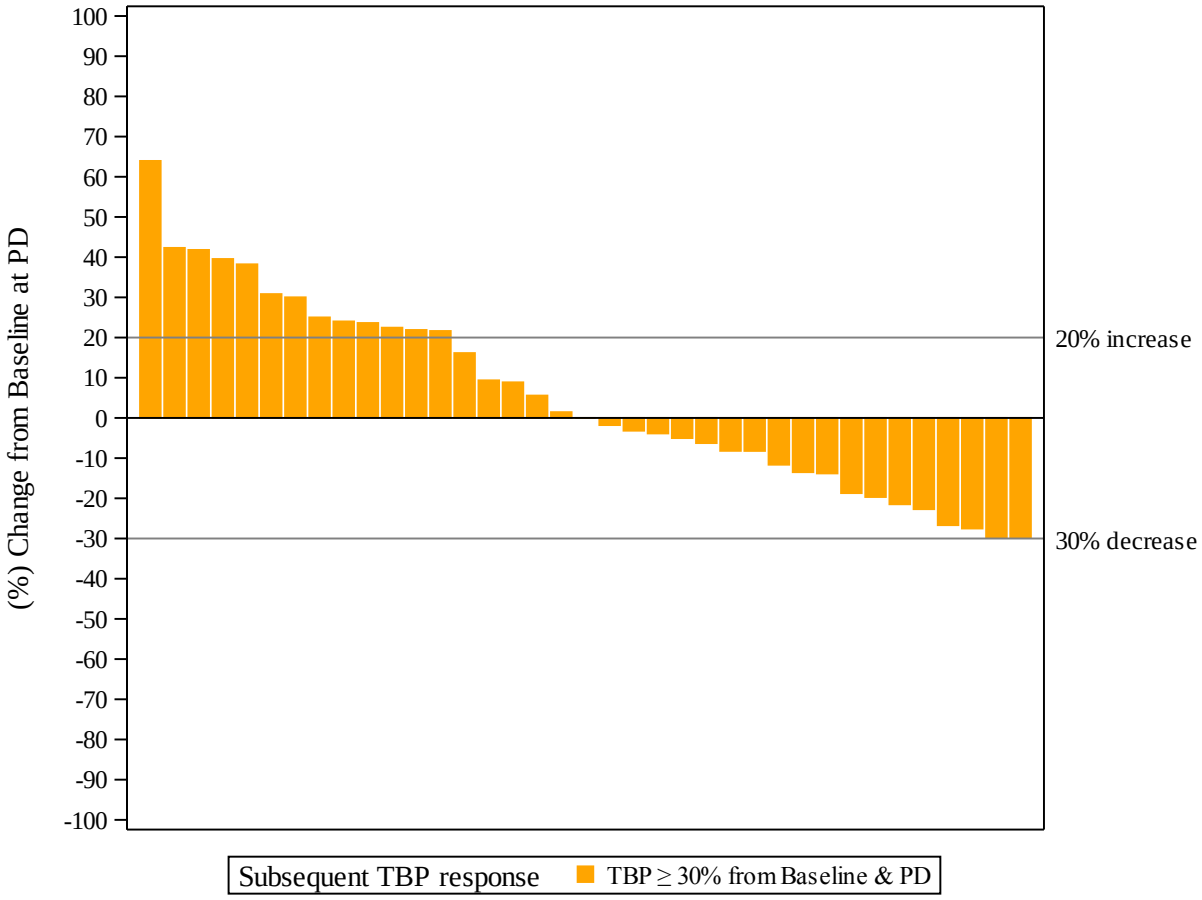
S3A: Waterfall plot for all patients TBP (n=692) at the time of progressive disease showing those in blue that did not have subsequent tumor response ≥30% from baseline during their TBP, those in red that had subsequent tumor response from baseline (n=20), those in green that had subsequent tumor response from PD (n=58), and those in orange that had both (n=37). Those with no assessed target tumor burden at time of progression are blank.



S3B: Waterfall plot of change from baseline at the time of progressive disease for TBP patients having subsequent tumor response ≥ 30% from PD level tumor burden (n=58).

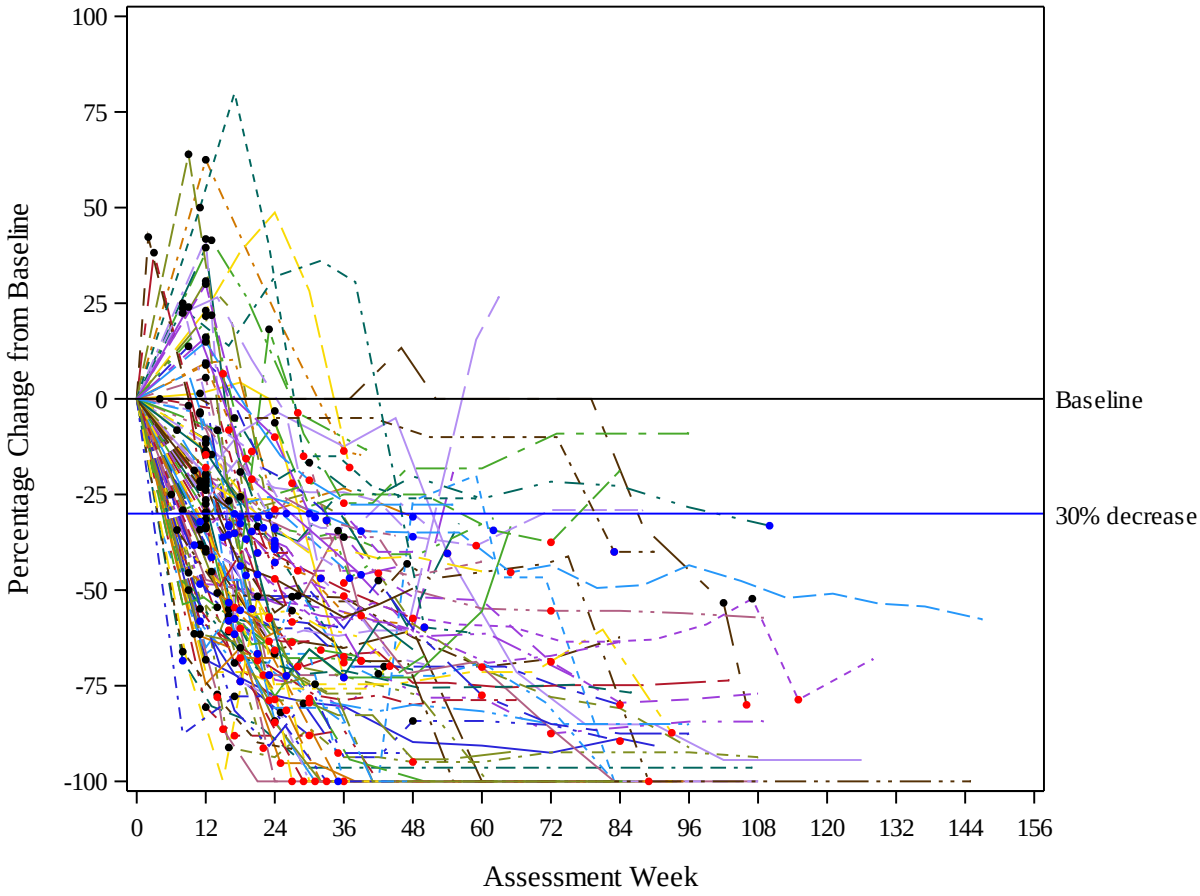


S3C: Waterfall plot of change from baseline at the time of progressive disease for TBP patients having subsequent tumor response ≥ 30% from baseline level tumor burden (n=20). Eight of these patients did not have PD level tumor burden assessed.

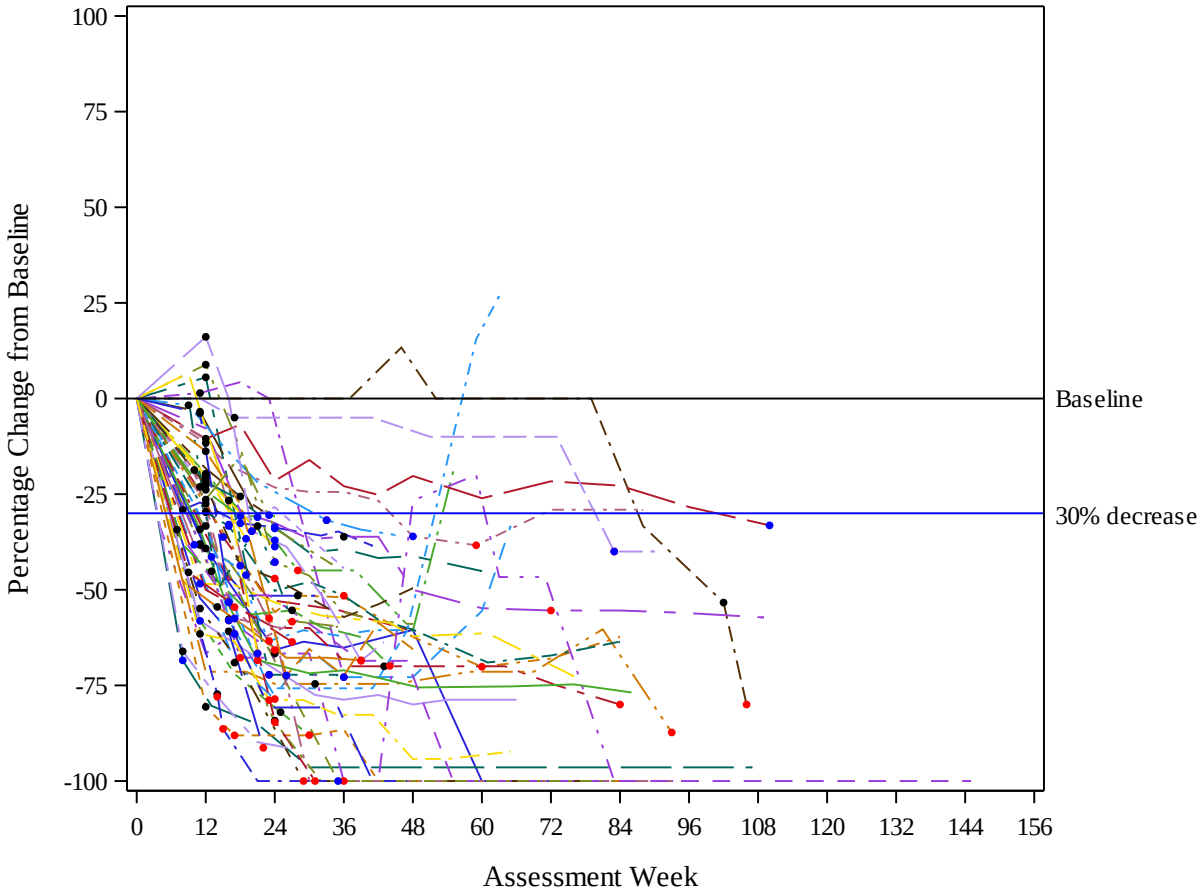


S3D: Waterfall plot of change from baseline at the time of progressive disease for TBP patients having subsequent tumor response ≥ 30% from both baseline and PD level tumor burden (n=37).

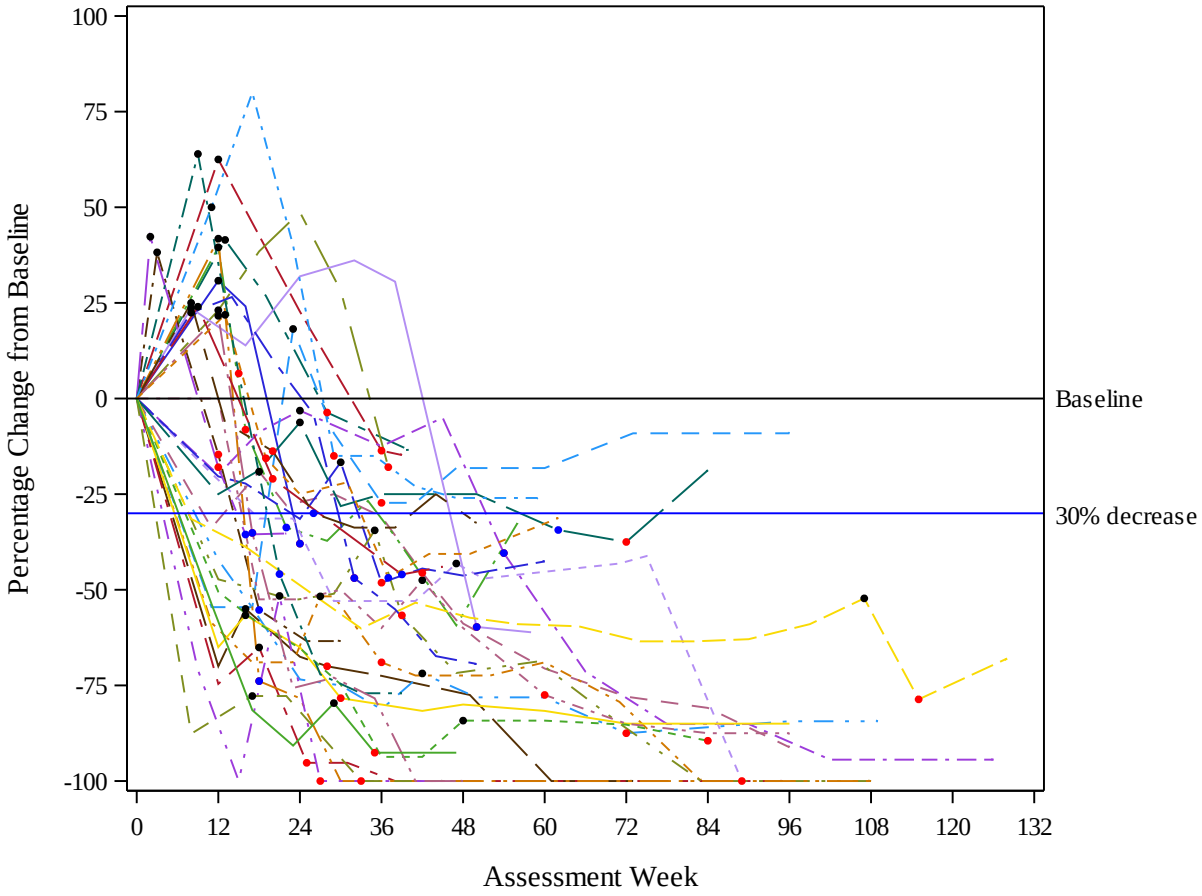
Appendix Figure S4: Patients Experiencing Target Tumor Response After Treatment Beyond Progression



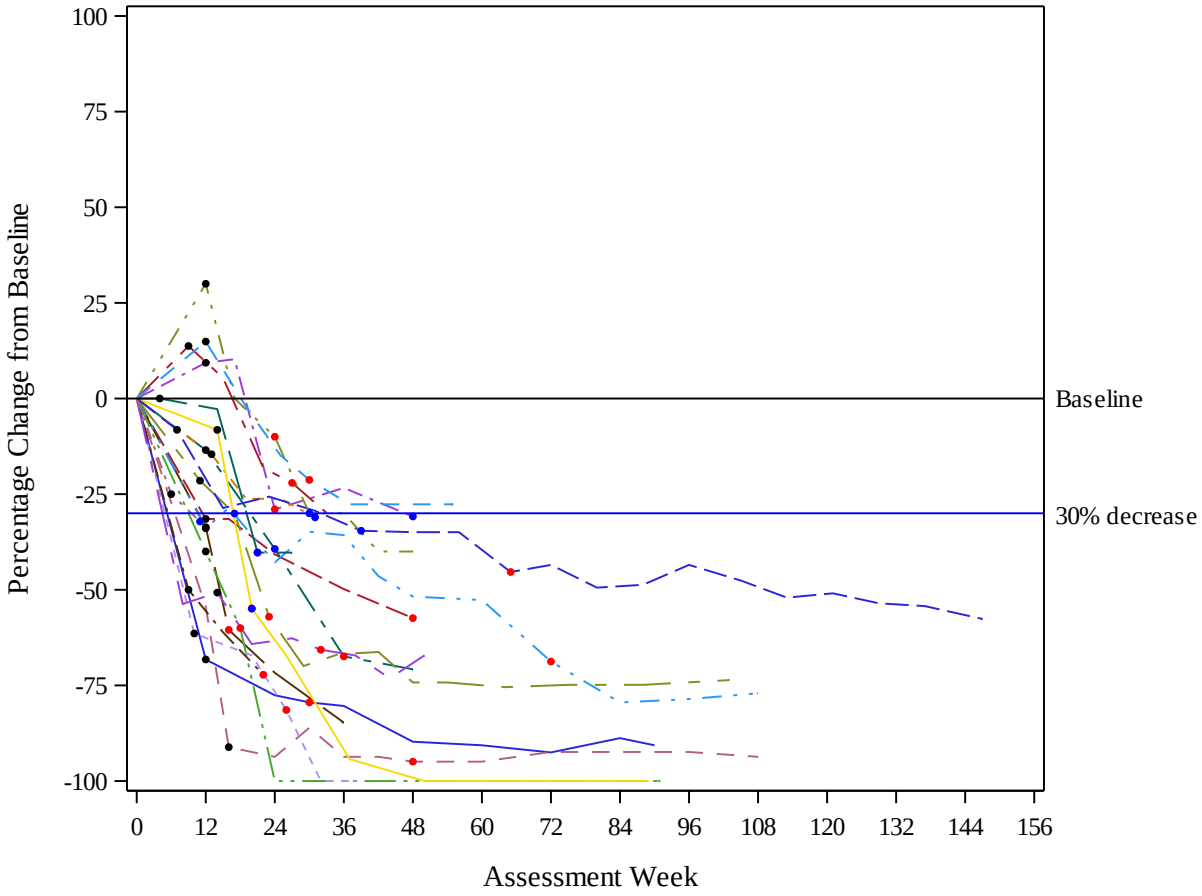
S4A: Spider plot for all n=115 patients who progressed per RECIST v1·1 (black circle) and exhibited subsequent response (≥30% reduction in tumor burden) in reference to baseline (blue circle) or in reference to Progressive Disease (red circle).



S4B: Spider plot for all n=61 patients who progressed solely by new lesion per RECIST v1·1 (black circle) and exhibited subsequent response (≥30% reduction in tumor burden) in reference to baseline (blue circle) or in reference to Progressive Disease (red circle).

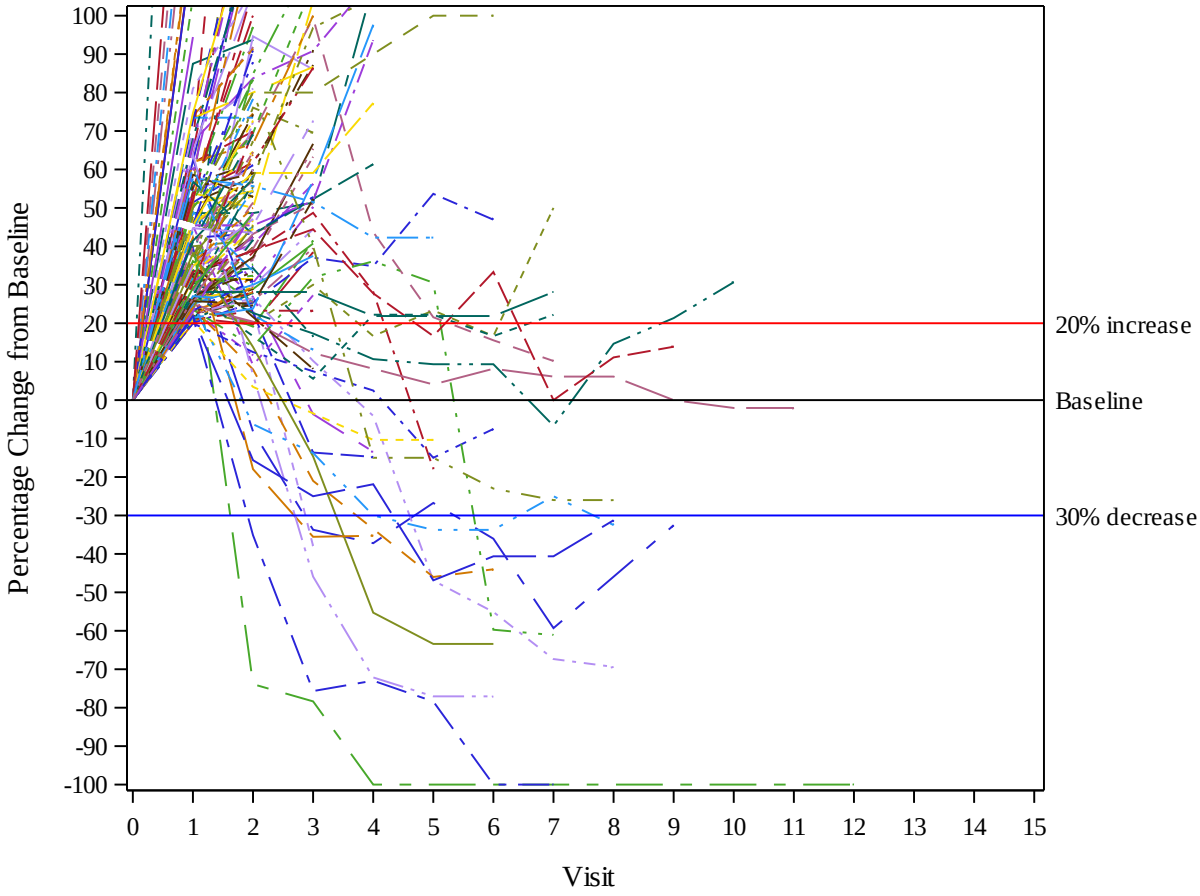


S4C: Spider plot for all n=34 patients who progressed by target tumor burden per RECIST v1·1 (black circle) and exhibited subsequent response (≥30% reduction in tumor burden) in reference to baseline (blue circle) or in reference to Progressive Disease (red circle). Four patients had combination progression (target/new (n=1), target/non-target (n=1), and target/non-target/new (n=2)).

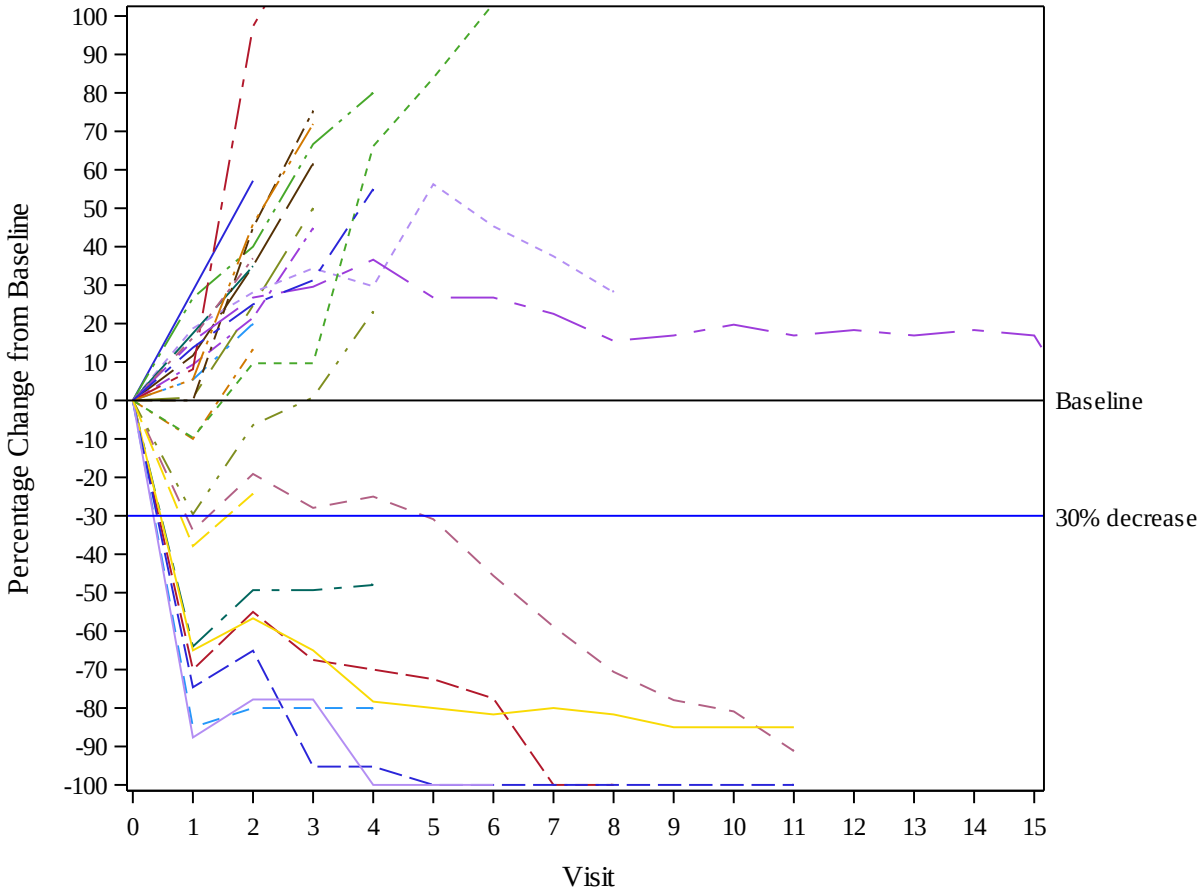


S4D: Spider plot for n=20 patients who progressed by non-target (n=10) or combination non-target/new lesion (n=10) per RECIST v1·1 (black circle) and exhibited subsequent response (≥30% reduction in tumor burden) in reference to baseline (blue circle) or in reference to Progressive Disease (red circle). The patient above the 20% threshold did not have an absolute increase of 5 mm but did have non-target unequivocal progression.

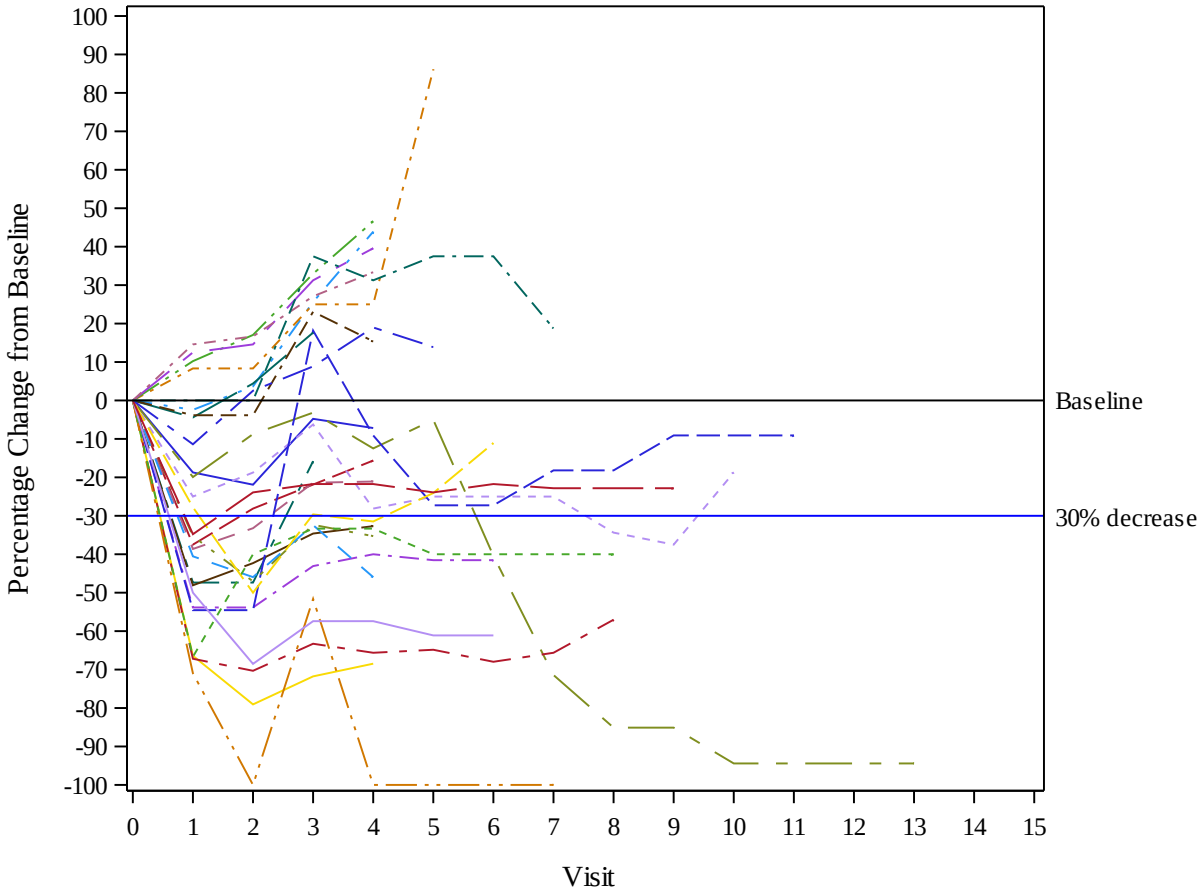
Appendix Figure S5: Percent Change in Tumor Burden from baseline by visit for Patients Progressing due to Target Lesion Increase and Continuing Treatment Beyond Progression



S5A: Spider plot demonstrating percentage change in tumor burden from baseline by visit number for all n=176 patients who progressed at first assessment due to target lesion progression and were continued on anti PD-1 agent with at least one subsequent assessment. Of those 176 patients, 133 had subsequent increased or unchanged target lesion tumor burden and 43 had exhibited any reduction in tumor burden, including 16 who had a decrease in tumor burden of ≥ 30% from their tumor burden at the time of RECIST-defined PD. Ten patients decreased tumor burden from the 20% PD level but not back to baseline, n=21 decreased below their baseline level and n=12 patients ultimately reduced tumor burden to ≥30% of baseline burden.



S5B: Spider plot for all n=25 patients who progressed at second assessment due to target lesion progression (some of these patients also experienced simultaneous progression with new lesions (n=1), in non-target lesions (n=6), and in target, new, and non-target lesions (n=2)) and were continued on anti PD-1 agent demonstrating percentage change in tumor burden from baseline by visit number



S5C: Spider plot for all n=27 patients who progressed at third assessment due to target lesion progression (some of these patient also experienced simultaneous progression with new lesions (n=3) and in non-target lesions (n=2)) and were continued on anti PD-1 agent demonstrating percentage change in tumor burden from baseline by visit number

Tables

Appendix Table S1: Classification of Site of New Lesion Progressive Disease by Mutually Exclusive Categories

Occurrence of visceral lesion (e.g. lung and/or liver)	Occurrence of CNS (or leptomeningeal) lesion	Occurrence of other lesion (e.g. lymph node)	Category
Yes	Yes	Yes or No	CNS and Visceral
No	Yes	Yes or No	CNS
Yes	No	Yes or No	Visceral
No	No	Yes	Non-Visceral

Abbreviations: CNS, central nervous system

Appendix Table S2: Location of New Lesion at Time of Progression*

	CNS n (%)	CNS and Visceral n (%)	Non-Visceral n (%)	Visceral n (%)	Not Reported n (%)	Total
noTBP	38 (21·2)	4 (2·2)	64 (35·8)	70 (39·1)	3 (1·7)	179
TBP	19 (7·7)	1 (0·4)	124 (50·0)	97 (39·1)	7 (2·8)	248
Total	57	5	188	167	10	427

Abbreviations: TBP, treatment beyond progression
*Among those patients who progressed due only to new lesion

Appendix Table S3: Patients Experiencing Target Tumor Response After Treatment Beyond Progression

Confirmed BOR prior to PD	Reason for Progression	Week of PD Assessment	% change from baseline at PD	Best % change from baseline post PD	Best % change from PD	Best % change from nadir	Weeks on treatment beyond progression
≥30% Reduction from Baseline during TBP							
PD	New Lesion	12	N/A	-100	N/A	-100	27
PD	New Lesion	12	N/A	-100	N/A	-100	16
PD	New Lesion	2	N/A	-96·43	N/A	-96·43	105
PD	New Lesion	0	N/A	-80	N/A	-80	66
PD	New Lesion	8	N/A	-72·61	N/A	-72·61	68
PD	New Lesion	0	N/A	-60·39	N/A	-60·39	46
PD	New Lesion	12	N/A	-51·56	N/A	-51·56	10
PD	New Lesion	12	-21·8	-45·12	-29·82	-29·82	72
PD	New Lesion	12	-23·86	-44·32	-26·87	-26·87	27
PD	New Lesion	12	-26·42	-43·4	-23·08	-23·08	20
PD	New Lesion	12	-20·97	-38·71	-22·45	-22·45	15
PD	New Lesion	8	-29·09	-38·5	-13·27	-13·27	32
PD	New Lesion	8	N/A	-38·24	N/A	-38·24	4
PD	New Lesion	12	-20	-36·67	-20·83	-20·83	9
PD	New Lesion	12	-10·51	-33·16	-25·32	-25·32	94
PD	Non-Target	6	-25	-32·14	-9·52	-9·52	1
PD	Non-Target and New Lesion	13	-14·56	-31·07	-19·32	-19·32	12
PD	New Lesion	11	-3·45	-31·03	-28·57	-28·57	7
PD	New Lesion	11	-23·08	-30·77	-10	-10	14
SD	New Lesion	18	-25·61	-30·49	-6·56	-6·56	8

Confirmed BOR prior to PD	Reason for Progression	Week of PD Assessment	% change from baseline at PD	Best % change from baseline post PD	Best % change from PD	Best % change from nadir	Weeks on treatment beyond progression
≥30% Reduction from Baseline and PD during TBP							
PD	Non-Target and New Lesion	14	-8·2	-100	-100	-100	6
PD	Target	12	41·79	-100	-100	-100	99
PD	Target	12	21·62	-100	-100	-100	38
PD	New Lesion	11	-3·85	-100	-100	-100	49
SD	Target	24	-3·17	-94·41	-94·23	-93·02	112
PD	New Lesion	12	-29·63	-77·78	-68·42	-68·42	51
PD	Target/New Lesion	9	63·93	-77·05	-86	-77·05	32
PD	Non-Target	11	-21·47	-75·46	-68·75	-68·75	56
PD	New Lesion	11	1·43	-72·86	-73·24	-72·86	22
PD	New Lesion	12	-13·79	-72·41	-68	-68	36
PD	New Lesion	12	5·56	-72·22	-73·68	-72·22	21
PD	Non-Target	12	-13·48	-70·79	-66·23	-66·23	42
PD	Target	8	22·45	-69·39	-75	-69·39	47
PD	New Lesion	12	-29·69	-69·01	-55·93	-55·93	81
PD	New Lesion	12	16·13	-68·55	-72·92	-68·55	25
SD	New Lesion	16	-26·67	-66·67	-54·55	-54·55	5
PD	Target	3	38·21	-63·41	-73·53	-63·41	30
PD	New Lesion	10	-18·69	-62·62	-54·02	-54·02	24
PD	Target	8	23·61	-61·11	-68·54	-61·11	57
PD	New Lesion	12	-19·66	-60·67	-51·05	-51·05	32
PD	New Lesion	12	-27·5	-60	-44·83	-44·83	22
PD	Target	12	39·53	-59·3	-70·83	-59·3	18
PD	New Lesion	12	8·85	-59	-62·33	-59	43
PD	Non-Target and New Lesion	7	-8·18	-57·62	-53·85	-53·85	88

Confirmed BOR prior to PD	Reason for Progression	Week of PD Assessment	% change from baseline at PD	Best % change from baseline post PD	Best % change from PD	Best % change from nadir	Weeks on treatment beyond progression
PD	New Lesion	12	-22·69	-57·14	-44·57	-44·57	44
PD	Target	13	21·88	-46·88	-56·41	-46·88	55
PD	Target/Non-Target/New Lesion	9	24	-46	-56·45	-46	39
PD	Non-Target and New Lesion	4	0	-40·28	-40·28	-40·28	25
SD	New Lesion	17	-5	-40	-36·84	-36·84	64
PD	Non-Target	12	30	-40	-53·85	-40	45
PD	New Lesion	12	-11·63	-38·37	-30·26	-30·26	81
PD	Target	12	30·8	-37·95	-52·56	-37·95	15
SD	Target	24	-6·25	-37·5	-33·33	-16·67	71
PD	New Lesion	9	-1·77	-35·69	-34·53	-34·53	32
PD	Target	2	42·3	-35·55	-54·71	-35·55	20
PD	Target/Non-Target	8	25	-33·75	-47	-33·75	46
PD	Non-Target	12	9·35	-30·84	-36·75	-30·84	36
≥30% Reduction from PD during TBP							
PD	New Lesion	12	-39·2	-100	-100	-100	69
SD	Target	16	-55	-100	-100	-100	63
PR	Target	27	-51·72	-100	-100	-100	56
PR	Target	47	-43·14	-100	-100	-100	28
SD	Target	18	-65·08	-100	-100	-100	79
PR	New Lesion	24	-66·67	-100	-100	-100	77
PR	Target	35	-34·46	-100	-100	-100	53
PD	New Lesion	12	-80·6	-100	-100	-100	81
SD	New Lesion	24	-84·21	-100	-100	-100	3

Confirmed BOR prior to PD	Reason for Progression	Week of PD Assessment	% change from baseline at PD	Best % change from baseline post PD	Best % change from PD	Best % change from nadir	Weeks on treatment beyond progression
PD	Non-Target	12	-40	-100	-100	-100	14
PD	Non-Target and New Lesion	10	-61·43	-100	-100	-100	26
PD	New Lesion	11	-54·9	-100	-100	-100	49
PD	New Lesion	7	-34·29	-100	-100	-100	87
PD	New Lesion	16	-57·69	-100	-100	-100	56
PD	New Lesion	14	-77·27	-100	-100	-100	22
PR	Target	21	-51·61	-100	-100	.	29
SD	Target	17	-77·78	-100	-100	-100	34
SD	Non-Target	16	-91·14	-94·94	-42·86	-42·86	19
PD	New Lesion	11	-61·54	-94·23	-85	-85	53
PR	Target	29	-79·63	-92·59	-63·64	-20	18
PD	Non-Target and New Lesion	12	-68·22	-92·52	-76·47	-76·47	80
PD	New Lesion	8	-66·1	-91·53	-75	-75	23
SD	New Lesion	16	-60·87	-91·3	-77·78	-77·78	6
SD	Target	18	-19·12	-91·18	-89·09	-86·67	87
PR	Target	48	-84·21	-89·47	-33·33	66·67	38
PR	New Lesion	25	-82	-88	-33·33	-33·33	2
PR	Target	42	-71·88	-87·5	-55·56	-33·33	63
PR	Target	42	-47·5	-87·5	-76·19	-68·75	54
PR	New Lesion	31	-74·6	-87·3	-50	-50	71
SD	Target	16	-56·67	-85	-65·38	-57·14	62
PD	Non-Target and New Lesion	12	-33·63	-84·72	-76·98	-76·98	33
PR	New Lesion	43	-70	-80	-33·33	-33·33	30

Confirmed BOR prior to PD	Reason for Progression	Week of PD Assessment	% change from baseline at PD	Best % change from baseline post PD	Best % change from PD	Best % change from nadir	Weeks on treatment beyond progression
SD	New Lesion	102	-53·33	-80	-57·14	-57·14	3
PD	Non-Target and New Lesion	12	-33·93	-79·46	-68·92	-68·92	72
PR	Target	107	-52·25	-78·65	-55·29	-41·54	57
PD	New Lesion	17	-69·05	-78·57	-30·77	-30·77	5
PD	New Lesion	11	-34·21	-76·84	-64·8	-64·8	64
PD	New Lesion	12	-33·33	-75·76	-63·64	-63·64	50
SD	Non-Target	14	-50·75	-73·13	-45·45	-41·94	40
PD	Non-Target	9	-50	-72·22	-44·44	-44·44	18
SD	New Lesion	28	-51·52	-70·13	-38·39	-32·35	63
PR	New Lesion	27	-55·38	-69·89	-32·53	-30·86	6
SD	New Lesion	14	-54·49	-68·44	-30·66	-30·66	27
PD	New Lesion	13	-45·16	-67·74	-41·18	-41·18	12
PD	New Lesion	9	-45·45	-63·64	-33·33	-33·33	18
PD	New Lesion	11	-38·03	-63·38	-40·91	-40·91	51
PD	New Lesion	11	-38·3	-59·57	-34·48	-34·48	19
SD	New Lesion	21	-33·33	-58·33	-37·5	-16·67	3
PD	Non-Target	12	-31·48	-57·41	-37·84	-37·84	45
PR	New Lesion	36	-36·14	-57·23	-33·02	-32·38	69
SD	Target	30	-16·67	-48·15	-37·78	-24·32	32
PD	Non-Target and New Lesion	9	13·73	-29·9	-38·36	-29·9	25
PD	Non-Target and New Lesion	12	14·89	-27·66	-37·04	-27·66	46
PR	Target	23	18·18	-27·27	-38·46	60	80
PD	Target	11	50	-26	-50·67	-26	49

Confirmed BOR prior to PD	Reason for Progression	Week of PD Assessment	% change from baseline at PD	Best % change from baseline post PD	Best % change from PD	Best % change from nadir	Weeks on treatment beyond progression
PD	Target	12	23·08	-17·95	-33·33	-17·95	129
PD	Target	12	62·5	-14·77	-47·55	-14·77	42
PD	Target/Non-Target/New Lesion	13	41·46	-13·41	-38·79	-13·41	39

Abbreviations: BOR, best overall response; PD, progressive disease; PR, partial response; SD, stable disease; N/A, Not available;

Appendix Table S4: Demographics and Disease Characteristics of Patients Treated with Anti PD-1 Antibody with Response from Baseline (n=57)

Variable	Category Value	TBP, Subsequent Response from Baseline (n=57) n (%)	TBP, No Subsequent Response from Baseline (n=635) n (%)
Prior to Anti-PD-1 Therapy			
Age	Median (IQR), years	62 (52, 68)	61 (50, 69)
Sex	Female	20 (35·1)	246 (38·7)
	Male	37 (64·9)	389 (61·3)
AJCC Stage at Study Entry	Stage III	4 (7·0)	24 (3·8)
	Stage IV	42 (73·7)	514 (80·9)
	Missing	11 (19·3)	97 (15·3)
M Stage at Study Entry	M0/M1A/M1B	13 (22·8)	161 (25·4)
	M1C	31 (54·4)	336 (52·9)
	Missing	13 (22·8)	138 (21·7)
Prior Lines of Systemic Therapy for Advanced Disease	0	29 (50·9)	303 (47·7)
	1	14 (24·6)	161 (25·4)
	2	11 (19·3)	105 (16·5)
	≥3	3 (5·3)	66 (10·4)
PD-L1 Expression	Negative/Indeterminate	15 (26·3)	197 (31·0)
	Positive	27 (47·4)	286 (45·0)
	Missing	15 (26·3)	152 (23·9)
BRAF V600 Mutation Status	Mutant	14 (24·6)	171 (26·9)
	Wild Type	43 (75·4)	443 (69·8)
	Missing	0 (0·0)	21 (3·3)
Baseline ECOG Performance Status	0	45 (78·9)	487 (76·7)
	1	12 (21·1)	147 (23·1)
	2	0 (0·0)	1 (0·2)
Baseline LDH > ULN Category	≤ULN	36 (63·2)	415 (65·4)
	>ULN	21 (36·8)	211 (33·2)
	Missing	0 (0·0)	9 (1·4)
At Time of RECIST-Defined Progression			
ECOG Status Within 28 Days Prior to Progression	0	39 (68·4)	423 (66·6)
	1	15 (26·3)	191 (30·1)
	2	0 (0·0)	7 (1·1)
	3	1 (1·8)	6 (0·9)
	Missing	2 (3·5)	8 (1·3)
	Improvement from baseline	3 (5·3)	36 (5·7)
	Worsening from baseline	7 (12·3)	101 (15·9)

Variable	Category Value	TBP, Subsequent Response from Baseline (n=57) N (%)	TBP, No Subsequent Response from Baseline (n=635) N (%)
LDH Category Within 28 Days Prior to Progression	≤ULN	38 (66·7)	397 (62·5)
	>ULN	17 (29·8)	215 (33·9)
	Missing	2 (3·4)	23 (3·6)
	Improvement to ≤ULN	7 (12·3)	65 (10·2)
	Worsening to >ULN	3 (5·3)	69 (10·9)
Reason for Progression	Target	11 (19·3)	197 (31·0)
	Non-Target	5 (8·8)	61 (9·6)
	New Lesion	34 (59·6)	214 (33·7)
	Non-Target and New Lesion	4 (7·0)	46 (7·2)
	Target + Other	3 (5·4)	117 (18·4)
	Target/Non-Target	1 (1·8)	39 (6·1)
	Target/New Lesion	1 (1·8)	38 (6·0)
	Target/Non-Target/New Lesion	1 (1·8)	40 (6·3)
Confirmed BOR Prior to Progression	CR	0 (0·0)	8 (1·3)
	PR	0 (0·0)	88 (13·9)
	SD	5 (8·8)	118 (18·6)
	PD	52 (91·2)	421 (66·3)
Duration of Response Prior to Progression	Median (IQR), months	--	5·5 (4·0-10·5)
Timing of RECIST PD	First Assessment (range week 0-24)	52 (91·2)	406 (63·9)
	Second Assessment (range week 6-27)	3 (5·3)	55 (8·7)
	Third Assessment (range week18-50)	2 (3·5)	55 (8·7)
	12 weeks or less	49 (86·0)	393 (61·9)
	13 to 16 weeks	4 (7·0)	39 (6·1)
	17 to 20 weeks	2 (3·5)	22 (3·5)
	21 to 24 weeks	2 (3·5)	53 (8·3)
	greater than 24 weeks	0 (0·0)	128 (20·2)

Abbreviations: IQR, interquartile range

Appendix Table S5: Demographics and Disease Characteristics of TBP and NoTBP Patients on Both Arms of Trial CA209066

Variable	Category Value	Nivolumab TBP n (%)	Dacarbazine TBP n (%)	Nivolumab noTBP n (%)	Dacarbazine noTBP n (%)
Prior to Anti-PD-1 Antibody Therapy					
Age	Median (IQR), years	63 (50, 69)	64·5 (57, 72)	64 (51, 70)	67 (57,73)
Sex	Female	31 (52·5)	21 (38·9)	19 (46·3)	35 (36·1)
	Male	28 (47·5)	33 (61·1)	22 (53·7)	62 (63·9)
AJCC Stage at Study Entry	Stage III	6 (10·2)	4 (7·4)	7 (17·1)	12 (12·4)
	Stage IV	53 (89·8)	50 (92·6)	34 (82·9)	85 (87·6)
M Stage at Study Entry	M0/M1A/M1B	22 (37·3)	20 (37·0)	19 (46·3)	38 (39·2)
	M1C	37 (62·7)	34 (63·0)	22 (53·7)	59 (60·8)
PD-L1 Expression	Negative/Indeterminate	39 (66·1)	37 (68·5)	29 (70·7)	64 (66·0)
	Positive	20 (33·9)	17 (31·5)	12 (29·3)	33 (34·0)
BRAF V600 Mutation Status	Wild Type	56 (94·9)	54 (100·0)	40 (97·6)	94 (96·9)
	Missing	3 (5·1)	0 (0·0)	1 (2·4)	3 (3·1)
Baseline ECOG Performance Status	0	45 (76·3)	37 (68·5)	26 (63·4)	64 (66·0)
	1	14 (23·7)	17 (31·5)	15 (36·6)	33 (34·0)
Baseline LDH > ULN Category	≤ULN	39 (66·1)	33 (61·1)	21 (51·2)	65 (67·0)
	>ULN	19 (32·2)	20 (37·0)	20 (48·8)	29 (29·9)
	Missing	1 (1·7)	1 (1·9)	0 (0·0)	3 (3·1)
At Time of RECIST-Defined Progression					
ECOG Status Within 28 Days Prior to Progression	0	41 (69·5)	30 (55·6)	16 (39·0)	47 (48·5)
	1	16 (27·1)	18 (33·3)	13 (31·7)	31 (32·0)
	2	0 (0·0)	1 (1·9)	1 (2·4)	3 (3·1)
	Missing	2 (3·4)	5 (9·3)	11 (26·8)	16 (16·5)
	Improvement from baseline	6 (10·2)	2 (3·7)	2 (4·9)	4 (4·1)
	Worsening from baseline	8 (13·6)	6 (11·1)	7 (17·1)	13 (13·4)
LDH Category Within 28 Days Prior to Progression	≤ULN	35 (59·3)	28 (51·9)	13 (31·7)	45 (46·4)
	>ULN	17 (28·8)	10 (18·5)	21 (51·2)	37 (38·1)
	Missing	7 (11·9)	16 (29·6)	7 (17·1)	15 (15·5)
	Improvement to >ULN	5 (8·5)	4 (7·4)	0 (0·0)	5 (5·2)
	Worsening of ≤ULN	4 (6·8)	1 (1·9)	5 (12·2)	17 (17·5)
Reason for Progression	Target	12 (20·3)	13 (24·1)	6 (14·6)	21 (21·6)
	Non-Target	4 (6·8)	8 (14·8)	1 (2·4)	4 (4·1)
	New Lesion	23 (39·0)	17 (31·5)	10 (24·4)	24 (24·7)
	Non-Target and New Lesion	4 (6·8)	3 (5·6)	4 (9·8)	12 (12·4)
	Target/Non-Target	3 (5·1)	4 (7·4)	0 (0·0)	11 (11·3)
	Target/New Lesion	6 (10·2)	5 (9·3)	5 (12·2)	14 (14·4)
	Target/Non-Target/New Lesion	7 (11·9)	4 (7·4)	15 (36·6)	11 (11·3)

Variable	Category Value	Nivolumab TBP n (%)	Dacarbazine TBP n (%)	Nivolumab noTBP n (%)	Dacarbazine noTBP n (%)
Confirmed BOR prior to PD	PR	7 (11·9)	5 (9·3)	2 (4·9)	3 (3·1)
	SD	14 (23·7)	11 (20·4)	9 (22·0)	31 (32·0)
	PD	38 (64·4)	38 (70·4)	30 (73·2)	63 (64·9)
Duration of Response Prior to Progression	Median (IQR), months	4·2 (2·8, 6·9)	3·0 (2·8, 4·4)	6·4 (2·8, 9·9)	5·6 (4·1, 7·2)
Timing of RECIST PD	First Assessment	37 (62·7)	38 (70·4)	29 (70·7)	62 (63·9)
	Second Assessment	8 (13·6)	6 (11·1)	5 (12·2)	13 (13·4)
	Third Assessment	8 (13·6)	6 (11·1)	4 (9·8)	10 (10·3)
	12 weeks or less	36 (61·0)	38 (70·4)	30 (73·2)	62 (63·9)
	13 to 16 weeks	7 (11·9)	6 (11·1)	3 (7·3)	12 (12·4)
	17 to 20 weeks	3 (5·1)	2 (3·7)	1 (2·4)	4 (4·1)
	21 to 24 weeks	8 (13·6)	4 (7·4)	4 (9·8)	5 (5·2)
	greater than 24 weeks	5 (8·5)	4 (7·4)	3 (7·3)	14 (14·4)

Abbreviations: IQR, interquartile range

Appendix Table S6: Safety Analysis: Adverse Reactions Experienced in >2% of Patients Treated Beyond Progression By Time Period

		Pre-Progression n (%)		Post-Progression n (%)	
Adverse Event		**All Grades**	**Grades 3-4**	**All Grades**	**Grades 3-4**
Blood And Lymphatic System Disorders	Anaemia	57 (8·2)	11 (1·6)	59 (8·5)	15 (2·2)
Endocrine Disorders	Hyperthyroidism	29 (4·2)	0 (0·0)	4 (0·6)	0 (0·0)
	Hypothyroidism	40 (5·8)	0 (0·0)	38 (5·5)	1 (0·1)
Gastrointestinal Disorders	Abdominal Distension	21 (3·0)	0 (0·0)	12 (1·7)	1 (0·1)
	Abdominal Pain	47 (6·8)	2 (0·3)	48 (6·9)	6 (0·9)
	Abdominal Pain Upper	26 (3·8)	1 (0·1)	18 (2·6)	1 (0·1)
	Constipation	84 (12·1)	0 (0·0)	67 (9·7)	4 (0·6)
	Diarrhoea	147 (21·2)	4 (0·6)	117 (16·9)	18 (2·6)
	Dry Mouth	44 (6·4)	0 (0·0)	18 (2·6)	0 (0·0)
	Dyspepsia	22 (3·2)	0 (0·0)	6 (0·9)	0 (0·0)
	Nausea	138 (19·9)	7 (1·0)	98 (14·2)	4 (0·6)
	Vomiting	75 (10·8)	7 (1·0)	60 (8·7)	7 (1·0)
General Disorders And Administration Site Conditions	Asthenia	75 (10·8)	3 (0·4)	47 (6·8)	2 (0·3)
	Chest Pain	18 (2·6)	1 (0·1)	12 (1·7)	1 (0·1)
	Chills	39 (5·6)	0 (0·0)	22 (3·2)	0 (0·0)
	Fatigue	238 (34·4)	8 (1·2)	121 (17·5)	7 (1·0)
	Influenza Like Illness	30 (4·3)	0 (0·0)	16 (2·3)	0 (0·0)
	Oedema Peripheral	40 (5·8)	2 (0·3)	30 (4·3)	3 (0·4)
	Pain	27 (3·9)	3 (0·4)	20 (2·9)	0 (0·0)
	Pyrexia	72 (10·4)	2 (0·3)	49 (7·1)	0 (0·0)
Infections And Infestations	Nasopharyngitis	41 (5·9)	0 (0·0)	51 (7·4)	0 (0·0)
	Upper Respiratory Tract Infection	26 (3·8)	0 (0·0)	19 (2·7)	0 (0·0)
	Urinary Tract Infection	27 (3·9)	0 (0·0)	33 (4·8)	3 (0·4)
Investigations	Alanine Aminotransferase Increased	35 (5·1)	5 (0·7)	26 (3·8)	4 (0·6)
	Aspartate Aminotransferase Increased	32 (4·6)	5 (0·7)	26 (3·8)	4 (0·6)
	Blood Alkaline Phosphatase Increased	15 (2·2)	0 (0·0)	15 (2·2)	1 (0·1)
	Blood Creatinine Increased	14 (2·0)	1 (0·1)	13 (1·9)	0 (0·0)
	Lipase Increased	17 (2·5)	12 (1·7)	11 (1·6)	5 (0·7)
	Weight Decreased	30 (4·3)	0 (0·0)	37 (5·3)	2 (0·3)
Metabolism And Nutrition Disorders	Decreased Appetite	78 (11·3)	1 (0·1)	72 (10·4)	0 (0·0)
	Dehydration	8 (1·2)	3 (0·4)	18 (2·6)	5 (0·7)
	Hyperglycaemia	17 (2·5)	4 (0·6)	19 (2·7)	6 (0·9)
	Hypertriglyceridaemia	14 (2·0)	4 (0·6)	7 (1·0)	1 (0·1)
	Hypokalaemia	21 (3·0)	2 (0·3)	15 (2·2)	2 (0·3)
	Hyponatraemia	21 (3·0)	8 (1·2)	21 (3·0)	11 (1·6)
Musculoskeletal And Connective Tissue Disorders	Arthralgia	92 (13·3)	0 (0·0)	56 (8·1)	2 (0·3)
	Back Pain	56 (8·1)	6 (0·9)	53 (7·7)	8 (1·2)
	Groin Pain	10 (1·4)	1 (0·1)	14 (2·0)	1 (0·1)
	Muscle Spasms	14 (2·0)	0 (0·0)	14 (2·0)	0 (0·0)
	Muscular Weakness	12 (1·7)	1 (0·1)	15 (2·2)	2 (0·3)
	Musculoskeletal Pain	43 (6·2)	3 (0·4)	28 (4·0)	5 (0·7)

Adverse Event		Pre-Progression n (%)		Post-Progression n (%)	
		All Grades	Grades 3-4	All Grades	Grades 3-4
	Myalgia	56 (8·1)	0 (0·0)	32 (4·6)	3 (0·4)
	Neck Pain	12 (1·7)	1 (0·1)	14 (2·0)	2 (0·3)
	Pain In Extremity	45 (6·5)	1 (0·1)	48 (6·9)	3 (0·4)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	Malignant Neoplasm Progression	6 (0·9)	3 (0·4)	29 (4·2)	12 (1·7)
	Tumour Pain	14 (2·0)	2 (0·3)	3 (0·4)	1 (0·1)
Nervous System Disorders	Dizziness	52 (7·5)	1 (0·1)	34 (4·9)	0 (0·0)
	Dysgeusia	20 (2·9)	0 (0·0)	7 (1·0)	0 (0·0)
	Headache	84 (12·1)	0 (0·0)	62 (9·0)	3 (0·4)
Psychiatric Disorders	Anxiety	23 (3·3)	0 (0·0)	17 (2·5)	1 (0·1)
	Depression	18 (2·6)	0 (0·0)	12 (1·7)	1 (0·1)
	Insomnia	44 (6·4)	0 (0·0)	35 (5·1)	0 (0·0)
Respiratory, Thoracic And Mediastinal Disorders	Cough	109 (15·8)	0 (0·0)	68 (9·8)	1 (0·1)
	Dyspnoea	55 (7·9)	3 (0·4)	45 (6·5)	3 (0·4)
	Dyspnoea Exertional	21 (3·0)	0 (0·0)	11 (1·6)	0 (0·0)
Skin And Subcutaneous Tissue Disorders	Dry Skin	42 (6·1)	0 (0·0)	17 (2·5)	0 (0·0)
	Eczema	14 (2·0)	0 (0·0)	10 (1·4)	0 (0·0)
	Erythema	27 (3·9)	0 (0·0)	18 (2·6)	0 (0·0)
	Pruritus	144 (20·8)	3 (0·4)	68 (9·8)	0 (0·0)
	Rash	154 (22·3)	4 (0·6)	84 (12·1)	4 (0·6)
	Vitiligo	34 (4·9)	0 (0·0)	55 (7·9)	1 (0·1)
Vascular Disorders	Hypertension	24 (3·5)	8 (1·2)	17 (2·5)	5 (0·7)

Abbreviations: Pre-Progression, time period during initial treatment prior to progressive disease; Post-Progression, time period after progression when therapy was continued including events up to 30 days after last dose

Appendix Table S7: ECOG Performance Status Evolution with Treatment Beyond Progression

ECOG PS n (%)	Baseline	w/in 28 days prior to PD	At Last dose Taken
0	533 (77·0)	463 (66·9)	398 (57·5)
1	158 (22·8)	205 (29·6)	213 (30·8)
2	1 (0·1)	7 (1·0)	19 (2·8)
3	0	7 (1·0)	5 (0·7)
Missing	0	10 (1·4)	57 (8·2)
Improvement from baseline	na	39 (5·6)	39 (5·6)
Worsening from baseline	na	108 (15·6)	143 (20·7)

Abbreviations: PD, Progressive Disease; PS, performance status

Appendix Table S8: Immune-Related Adverse Events within 90 days

Adverse Event		TBP n (%)		noTBP n (%)	
		All Grades	Grades 3-4	All Grades	Grades 3-4
Endocrine Disorders	Adrenal Insufficiency	5 (0·7)	3 (0·4)	4 (0·6)	0 (0·0)
	Hyperthyroidism	1 (0·1)	0 (0·0)	3 (0·4)	1 (0·1)
	Hypophysitis	6 (0·9)	2 (0·3)	6 (0·9)	2 (0·3)
	Hypothyroidism	5 (0·7)	1 (0·1)	2 (0·3)	0 (0·0)
	Thyroiditis	1 (0·1)	0 (0·0)	2 (0·3)	0 (0·0)
Gastrointestinal Disorders	Colitis	10 (1·4)	3 (0·4)	25 (3·7)	18 (2·7)
	Diarrhoea	25 (3·6)	12 (1·7)	28 (4·2)	14 (2·1)
	Pancreatitis	1 (0·1)	0 (0·0)	2 (0·3)	2 (0·3)
Hepatobiliary Disorders	Hepatitis	5 (0·7)	3 (0·4)	18 (2·7)	16 (2·4)
Investigations	Alanine Aminotransferase Increased	3 (0·4)	3 (0·4)	12 (1·8)	10 (1·5)
	Aspartate Aminotransferase Increased	2 (0·3)	1 (0·1)	9 (1·3)	6 (0·9)
Renal And Urinary Disorders	Nephritis	2 (0·3)	2 (0·3)	2 (0·3)	1 (0·1)
	Renal Failure	0 (0·0)	0 (0·0)	2 (0·3)	1 (0·1)
	Renal Failure Acute	0 (0·0)	0 (0·0)	3 (0·4)	2 (0·3)
Respiratory, Thoracic And Mediastinal Disorders	Pneumonitis	11 (1·6)	0 (0·0)	12 (1·8)	7 (1·0)
Skin And Subcutaneous Tissue Disorders	Pruritus	2 (0·3)	2 (0·3)	1 (0·1)	0 (0·0)
	Rash	10 (1·4)	3 (0·4)	11 (1·6)	6 (0·9)
	Vitiligo	1 (0·1)	0 (0·0)	1 (0·1)	0 (0·0)

Abbreviations: TBP, treatment beyond progression

Appendix Table S9: Safety Analysis: Adverse Reactions Experienced prior to initial RECIST v1·1 progression with a ≥ 2% difference between cohorts

		TBP n (%)		noTBP n (%)	
Adverse Event		**All Grades**	**Grades 3-4**	**All Grades**	**Grades 3-4**
Blood And Lymphatic System Disorders	Anaemia	57 (8·2)	11 (1·6)	93 (13·9)	20 (3·0)
Gastrointestinal Disorders	Abdominal Pain	47 (6·8)	2 (0·3)	88 (13·2)	11 (1·6)
	Colitis	6 (0·9)	0 (0·0)	35 (5·2)	24 (3·6)
	Constipation	84 (12·1)	0 (0·0)	121 (18·1)	1 (0·1)
	Diarrhoea	147 (21·2)	4 (0·6)	186 (27·8)	27 (4·0)
	Dry Mouth	44 (6·4)	0 (0·0)	21 (3·1)	0 (0·0)
	Nausea	138 (19·9)	7 (1·0)	195 (29·1)	12 (1·8)
	Vomiting	75 (10·8)	7 (1·0)	120 (17·9)	14 (2·1)
General Disorders And Administration Site Conditions	Fatigue	238 (34·4)	8 (1·2)	254 (38·0)	20 (3·0)
	Oedema Peripheral	40 (5·8)	2 (0·3)	61 (9·1)	3 (0·4)
	Pyrexia	72 (10·4)	2 (0·3)	116 (17·3)	7 (1·0)
Investigations	Alanine Aminotransferase Increased	35 (5·1)	5 (0·7)	48 (7·2)	18 (2·7)
	Aspartate Aminotransferase Increased	32 (4·6)	5 (0·7)	47 (7·0)	13 (1·9)
	Blood Alkaline Phosphatase Increased	15 (2·2)	0 (0·0)	35 (5·2)	4 (0·6)
	Weight Decreased	30 (4·3)	0 (0·0)	56 (8·4)	1 (0·1)
Metabolism And Nutrition Disorders	Decreased Appetite	78 (11·3)	1 (0·1)	158 (23·6)	5 (0·7)
	Dehydration	8 (1·2)	3 (0·4)	29 (4·3)	7 (1·0)
	Hypoalbuminaemia	7 (1·0)	0 (0·0)	27 (4·0)	6 (0·9)
Musculoskeletal And Connective Tissue Disorders	Back Pain	56 (8·1)	6 (0·9)	77 (11·5)	6 (0·9)
	Muscular Weakness	12 (1·7)	1 (0·1)	27 (4·0)	3 (0·4)
	Musculoskeletal Chest Pain	6 (0·9)	0 (0·0)	22 (3·3)	1 (0·1)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	Malignant Neoplasm Progression	6 (0·9)	3 (0·4)	31 (4·6)	16 (2·4)
Nervous System Disorders	Headache	84 (12·1)	0 (0·0)	104 (15·5)	8 (1·2)
Psychiatric Disorders	Insomnia	44 (6·4)	0 (0·0)	58 (8·7)	1 (0·1)
Respiratory, Thoracic And Mediastinal Disorders	Cough	109 (15·8)	0 (0·0)	123 (18·4)	0 (0·0)
	Dyspnoea	55 (7·9)	3 (0·4)	98 (14·6)	14 (2·1)
Skin And Subcutaneous Tissue Disorders	Night Sweats	12 (1·7)	0 (0·0)	30 (4·5)	0 (0·0)
	Pruritus	144 (20·8)	3 (0·4)	113 (16·9)	0 (0·0)

Abbreviations: TBP, treatment beyond progression