

Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

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Centre	Total Recruited	CHEMO-INTENSITY Pathway	CHEMO-BSC Pathway	PI name
Leeds Teaching Hospitals NHS FT Trust	58	55	3	Dr Daniel Swinson
East Kent Hospitals NHS Trust	33	32	1	Dr Justin Waters
Hull and East Yorkshire Hospitals NHS Trust	25	24	1	Dr Rajarshi Roy
University Hospitals Bristol NHS Foundation Trust	25	24	1	Dr Stephen Falk
Sheffield Teaching Hospitals NHS Trust	25	25	0	Dr Jonathan Wadsley
The Royal Wolverhampton NHS Trust	23	23	0	Dr Mano Joseph
Mid Yorkshire Hospitals NHS Trust	21	18	3	Dr Kostantinos-Vellios
North Cumbria University Hospitals NHS Trust	21	21	0	Dr Jonathan Nicoll
Royal United Hospital Bath NHS Trust	20	20	0	Dr Tania Tillett
Royal Surrey County Hospital NHS Foundation Trust	19	19	0	Dr Sebastian Cummins
The Dudley Group NHS Foundation Trust	18	16	2	Dr Simon Grumett
United Lincolnshire Hospitals NHS Trust	18	10	8	Dr Zuzana Stokes
The Christie NHS Foundation Trust	16	15	1	Dr Tom Waddell
The Shrewsbury and Telford Hospital NHS Trust	14	11	3	Dr Anirban Chatterjee
Betsi Cadwaldr University LHB	13	13	0	Dr Angel Garcia
York Teaching Hospital NHS Foundation Trust (Scarb)	13	4	9	Dr Mohammed Khan
Guys and St Thomas's NHS Foundation Trust	12	11	1	Dr Nick Maisey
Worcestershire Acute Hospitals NHS Trust	12	9	3	Dr Cheng Boon
Calderdale and Huddersfield NHS Foundation Trust	11	7	4	Dr Jo Dent
Sherwood Forest NHS Foundation Trust	9	9	0	Dr Eleanor James
NHS Tayside	9	9	0	Prof Russell Petty
Bradford Teaching Hospitals NHS Foundation Trust	9	8	1	Dr Sue Cheeseman
Norfolk and Norwich University Hospitals NHS Foundation Trust	8	8	0	Dr Tom Roques
Imperial College Healthcare NHS Trust	8	8	0	Dr Nick Reed
Gloucestershire Hospitals NHS Foundation Trust	7	7	0	Dr Charles Candish
University Hospitals of Morecambe Bay NHS Foundation Trust	7	7	0	Dr David Fyfe
York Teaching Hospital NHS Foundation Trust (York)	7	6	1	Dr Kim Last
Royal Cornwall NHS Trust	7	7	0	Dr Richard Ellis
NHS Grampian	7	7	0	Dr Leslie Samuel
Western Sussex Hospitals NHS Foundation Trust	7	7	0	Dr Rebecca Herbertson
South Devon Healthcare NHS Trust	6	6	0	Dr Louise Medley
Oxford University Hospitals NHS Trust	6	6	0	Dr Kinnari Patel

Plymouth Hospitals NHS Trust	6	6	0	Dr David Sherriff
East Sussex Healthcare NHS Trust	6	6	0	Dr Angus Robinson
Blackpool Teaching Hospitals NHS Trust	5	5	0	Dr Pavel Bezecky
Betsi Cadwaldr University LHB	5	5	0	Dr Duncan Wilkins
Hinchingbrooke Health Care NHS Trust	4	4	0	Dr Adam McGeoch
Barts Health NHS Trust	4	4	0	Dr David Propper
Ysbyty Gwynedd	4	3	1	Dr Rachel Williams
Weston Area Healthcare Trust	3	3	0	Dr Serena Hilman
Barking, Havering & Redbridge University Hospitals NHS Trust	3	3	0	Dr Sherif Raouf
Great Western Hospitals NHS Foundation Trust	3	3	0	Dr Claire Blesing
The Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust	3	3	0	Dr Joanne Parkinson
South Tees Hospitals NHS Foundation Trust	3	3	0	Dr Nick Wadd
Milton Keynes Hospital NHS Foundation Trust	2	2	0	Dr Wasiru Saka
Walsall Healthcare NHS Trust	2	2	0	Dr Victoria Kunene
Abertawe Bro Morgannwg University Local Health Board	2	2	0	Dr Colin Askill
Mid Cheshire Hospitals Foundation Trust	2	1	1	Dr Arshad Jamil
Taunton and Somerset NHS Foundation Trust	2	1	1	Dr Emma Cattell
Dorset County Hospital NHS Foundation Trust	2	2	0	Dr Lauren Gorf
Hywel Dda Health Board (Bronglais)	2	1	1	Dr Vallipuram Vigneswaran
Yeovil District Hospital NHS Foundation Trust	1	1	0	Dr Erica Beaumont
County Durham and Darlington NHS Foundation Trust	0	0	0	Dr Syed Zubair
Hywel Dda Health Board	0	0	0	Dr Elin Jones
Wye Valley NHS Trust	0	0	0	Dr Nick Reed
Salisbury NHS F Trust	0	0	0	Dr Alaeldon Shablak
Northern Lincolnshire and Goole NHS Foundation Trust	0	0	0	Dr Georgios Bozas

eTable 2: Baseline characteristics

Used in subgroup analysis and prognostic modelling. Frailty domains are summarised in Table S2.

	CHEMO-INTENSITY pathway				CHEMO-BSC pathway	
	Level A (n=170)	Level B (n=171)	Level C (n=173)	Total (n=514)	Level C (n=23)	BSC (n=22)
Age group (years)						
<75	73 (43%)	73 (43%)	72 (42%)	218 (42%)	6 (26·1%)	4 (18·2%)
≥75	97 (57%)	98 (57%)	101 (58%)	296 (58%)	17 (73·9%)	18 (81·8%)
Gender						
Male	131 (77%)	129 (75%)	125 (72%)	385 (75%)	14 (60·9%)	13 (59·1%)
Female	39 (23%)	42 (24%)	48 (28%)	129 (25%)	9 (39·1%)	9 (40·9%)
WHO PS						
0-1	117 (69%)	116 (68%)	120 (70%)	353 (69%)	10 (43·5%)	7 (31·8%)
2	49 (29%)	49 (29%)	50 (29%)	148 (29%)	10 (43·5%)	13 (59·1%)
>2	4 (2·4%)	6 (3·5%)	3 (1·7%)	13 (2·5%)	3 (13·0%)	2 (9·1%)
Distant metastases						
No	55 (32%)	53 (31%)	52 (30%)	160 (31%)	11 (47·8%)	10 (45·5%)
Yes	115 (68%)	118 (69%)	121 (70%)	354 (69%)	12 (52·2%)	12 (54·5%)
Tumour histology						
Squamous	20 (12%)	18 (11%)	20 (12%)	58 (11%)	4 (17·4%)	5 (22·7%)
Other	150 (88%)	153 (90%)	153 (88%)	456 (89%)	19 (82·6%)	17 (77·3%)
Dose reduction						
No	159 (94%)	159 (93%)	162 (94%)	480 (93%)	23 (100·0%)	20 (90·9%)
Yes	11 (6·5%)	12 (7·0%)	11 (6·4%)	34 (6·6%)	0 (0·0%)	2 (9·1%)
Trastuzumab						
No	163 (95·9%)	161 (94·2%)	163 (94·2%)	487 (94·7%)	22 (95·7%)	21 (95·5%)
Yes	7 (4·1%)	10 (5·8%)	10 (5·8%)	27 (5·3%)	1 (4·3%)	1 (4·5%)
Site of primary tumour						
Esophagus	55 (32%)	73 (42%)	69 (40%)	197 (38%)	13 (56·5%)	9 (40·9%)
GE junction	50 (29·4%)	34 (20%)	39 (23%)	123 (24%)	4 (17·4%)	4 (18·2%)
Gastric	64 (38%)	64 (37%)	64 (37%)	192 (37%)	6 (26·1%)	9 (40·9%)
Missing	1 (0·6%)	0 (0·0%)	1 (0·6%)	2 (0·4%)		
VAS <50 (EQ-5D)						
No	143 (84·1%)	141 (82·5%)	141 (81·5%)	425 (82·7%)	17 (73·9%)	16 (72·7%)
Yes	22 (13%)	26 (15%)	29 (17%)	77 (15%)	5 (21·7%)	4 (18·2%)
Missing	5 (2·9%)	4 (2·3%)	3 (1·7%)	12 (2·3%)	1 (4·3%)	2 (9·1%)
GHS/QoL <41·6 (C-30)						
No	128 (75·3%)	120 (70·2%)	129 (74·6%)	377 (73·3%)	13 (56·5%)	17 (77·3%)
Yes	36 (21%)	50 (29%)	38 (22%)	124 (24%)	8 (34·8%)	5 (22·7%)
Missing	6 (3·5%)	1 (0·6%)	6 (3·5%)	13 (2·5%)	2 (8·7%)	0 (0·0%)
Pain (EQ-5D)						
I have no pain or discomfort	53 (31%)	43 (25%)	58 (34%)	154 (30%)	9 (39·1%)	4 (18·2%)
I have moderate pain or discomfort	100 (58·8%)	114 (66·7%)	97 (56·1%)	311 (61%)	11 (47·8%)	16 (72·7%)
I have extreme pain or discomfort	11 (6·5%)	7 (4·1%)	14 (8·1%)	32 (6·2%)	2 (8·7%)	2 (9·1%)
Missing	6 (3·5%)	7 (4·1%)	4 (2·3%)	17 (3·3%)	1 (4·3%)	0 (0·0%)
Dysphagia (OG-25)						
No	57 (34%)	45 (26%)	45 (26%)	147 (29%)	6 (26·1%)	7 (31·8%)
Yes	108 (64%)	124 (73%)	124 (72%)	356 (69%)	16 (69·6%)	15 (68·2%)
Missing	5 (2·9%)	2 (1·2%)	4 (2·3%)	11 (2·1%)	1 (4·3%)	0 (0·0%)
Baseline Odynophagia (OG-25)						
No	65 (38%)	63 (37%)	64 (37%)	192 (37%)	10 (43·5%)	9 (40·9%)
Yes	99 (58%)	106 (62%)	105 (61%)	310 (60%)	12 (52·2%)	13 (59·1%)
Missing	6 (3·5%)	2 (1·2%)	4 (2·3%)	12 (2·3%)	1 (4·3%)	0 (0·0%)
Trouble with taste (OG-25)						
No	100 (59%)	108 (63%)	101 (58%)	309 (60%)	13 (56·5%)	14 (63·6%)
Yes	65 (38%)	61 (36%)	68 (39%)	194 (38%)	9 (39·1%)	7 (31·8%)
Missing	5 (2·9%)	2 (1·2%)	4 (2·3%)	11 (2·1%)	1 (4·3%)	1 (4·5%)

	CHEMO-INTENSITY pathway				CHEMO-BSC pathway	
	Level A (n=170)	Level B (n=171)	Level C (n=173)	Total (n=514)	Level C (n=23)	BSC (n=22)
Number of reported symptoms						
0	35 (21%)	23 (14%)	28 (16%)	86 (17%)	3 (13.0%)	6 (27.3%)
1	30 (18%)	40 (23%)	31 (18%)	101 (20%)	5 (21.7%)	3 (13.6%)
2	57 (34%)	67 (39%)	64 (37%)	188 (37%)	10 (43.5%)	6 (27.3%)
3	42 (25%)	39 (23%)	46 (27%)	127 (25%)	4 (17.4%)	6 (27.3%)
Missing	6 (3.5%)	2 (1.2%)	4 (2.3%)	12 (2.3%)	1 (4.3%)	1 (4.5%)
BNP > 100 or NT-Pro-BNP > 400						
No	96 (57%)	98 (57.0%)	102 (59%)	296 (58%)	11 (47.8%)	9 (40.9%)
Yes	55 (32%)	61 (36%)	56 (32%)	172 (34%)	11 (47.8%)	13 (59.1%)
Missing	19 (11%)	12 (7.0%)	15 (8.7%)	46 (8.9%)	1 (4.3%)	0 (0.0%)
Haemoglobin <12 g/dl						
No	94 (55%)	94 (55%)	90 (52%)	278 (54%)	12 (52.2%)	7 (31.8%)
Yes	75 (44%)	77 (45%)	82 (47%)	234 (46%)	11 (47.8%)	15 (68.2%)
Missing	1 (0.6%)	0 (0.0%)	1 (0.6%)	2 (0.4%)		
White Cell Count > 11(*10/l)						
No	141 (83%)	136 (80%)	141 (82%)	418 (81%)	14 (60.9%)	18 (81.8%)
Yes	29 (17%)	35 (21%)	31 (18%)	95 (19%)	9 (39.1%)	4 (18.2%)
Missing	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.2%)		
Neutrophil:lymphocyte ratio > 4.0						
No	74 (44%)	90 (53%)	85 (49%)	249 (48%)	9 (39.1%)	9 (40.9%)
Yes	96 (56.5%)	81 (47.4%)	87 (50.3%)	264 (51.4%)	14 (60.9%)	13 (59.1%)
Missing	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.2%)		
Platelets > 400(*10/l)						
No	142 (84%)	141 (83%)	138 (80%)	421 (82%)	17 (73.9%)	15 (68.2%)
Yes	28 (17%)	30 (18%)	34 (20%)	92 (18%)	6 (26.1%)	7 (31.8%)
Missing	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.2%)		
GFR (formula derived) <60ml/min						
No	136 (80%)	126 (74%)	127 (73%)	389 (76%)	19 (82.6%)	13 (59.1%)
Yes	32 (19%)	43 (25%)	42 (24%)	117 (23%)	4 (17.4%)	9 (40.9%)
Missing	2 (1.2%)	2 (1.2%)	4 (2.3%)	8 (1.6%)		
Bilirubin >21 umol/l						
No	164 (97%)	164 (96%)	167 (97%)	495 (96%)	23 (100.0%)	22 (100.0%)
Yes	6 (3.5%)	7 (4.1%)	5 (2.9%)	18 (3.5%)		
Missing	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.2%)		
Albumin <30 g/dl						
No	140 (82%)	139 (81%)	133 (77%)	412 (80%)	17 (73.9%)	18 (81.8%)
Yes	30 (18%)	32 (19%)	38 (22%)	100 (20%)	6 (26.1%)	4 (18.2%)
Missing	0 (0.0%)	0 (0.0%)	2 (1.2%)	2 (0.4%)		
Urea >6 mmol/l						
No	105 (62%)	101 (59%)	113 (65%)	319 (62%)	13 (56.5%)	13 (59.1%)
Yes	57 (34%)	64 (37%)	53 (31%)	174 (34%)	9 (39.1%)	8 (36.4%)
Missing	8 (4.7%)	6 (3.5%)	7 (4.0%)	21 (4.1%)	1 (4.3%)	1 (4.5%)
Sodium <135 mmol/l						
No	133 (78%)	132 (77%)	129 (75%)	394 (77%)	17 (73.9%)	17 (77.3%)
Yes	36 (21%)	39 (23%)	43 (25%)	118 (23%)	6 (26.1%)	5 (22.7%)
Missing	1 (0.6%)	0 (0.0%)	1 (0.6%)	2 (0.4%)		
CEA >3ug/ml or Ca19-9 >37ku/l						
No	60 (35%)	62 (36%)	62 (36%)	184 (36%)	11 (47.8%)	10 (45.5%)
Yes	104 (61%)	109 (64%)	107 (62%)	320 (62%)	12 (52.2%)	12 (54.5%)
Missing	6 (3.5%)	0 (0.0%)	4 (2.3%)	10 (1.9%)		

eTable 3: Baseline Frailty domains

Derived using the comprehensive health assessment (CHA).

	CHEMO-INTENSITY pathway			CHEMO-BSC pathway	
	Level A (n=170)	Level B (n=171)	Level C (n=173)	Level C (n=23)	BSC (n=22)
Weight Loss: BMI < 18.5 (kg/m²)					
Yes	7 (4.1%)	13 (7.6%)	11 (6.4%)	2 (8.7%)	6 (27%)
No	163 (96%)	157 (92%)	160 (93%)	21 (91%)	15 (68%)
Missing	0 (0.0%)	1 (0.6%)	2 (1.2%)	0 (0.0%)	1 (4.5%)
Weight Loss: 3kg or >5%					
Yes	92 (54%)	94 (55%)	85 (49%)	11 (48%)	10 (46%)
No	78 (46%)	75 (44%)	85 (49%)	12 (52%)	11 (50%)
Missing	0 (0.0%)	2 (1.2%)	3 (1.7%)	0 (0.0%)	1 (4.5%)
Mobility: >10 seconds or unable to complete test					
Yes	103 (61%)	91 (53%)	95 (55%)	19 (83%)	14 (66%)
No	64 (38%)	78 (46%)	75 (43%)	4 (17%)	7 (32%)
Missing	3 (1.8%)	2 (1.2%)	3 (1.7%)	0 (0.0%)	1 (4.5%)
Falls: Has had 2 or more falls in the past 6 months					
Yes	8 (4.7%)	9 (5.3%)	7 (4.0%)	2 (8.7%)	0 (0.0%)
No	162 (95%)	162 (95%)	166 (96%)	21 (91%)	22 (100%)
Cognition: Mild or severe dementia diagnosis					
Yes	22 (13%)	25 (15%)	26 (15%)	4 (17%)	3 (14%)
No	148 (87%)	145 (85%)	147 (85%)	19 (83%)	18 (82%)
Missing	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (4.5%)
Function: ADL/IADL					
0	73 (43%)	74 (43%)	73 (42%)	7 (30%)	3 (14%)
1	42 (25%)	32 (19%)	43 (25%)	4 (17%)	5 (23%)
2	30 (18%)	30 (18%)	23 (13%)	4 (17%)	4 (18%)
3	13 (7.6%)	17 (9.9%)	7 (4.0%)	2 (8.7%)	5 (22.7%)
4	7 (4.1%)	7 (4.1%)	11 (6.4%)	3 (13%)	2 (9.1%)
5	4 (2.4%)	7 (4.1%)	9 (5.2%)	1 (4.3%)	2 (9.1%)
6	1 (0.6%)	4 (2.3%)	6 (3.5%)	2 (8.7%)	0 (0.0%)
7	0 (0.0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	1 (4.5%)
Function: One or more impairment in ADL or IADL					
Yes	97 (57%)	97 (57%)	100 (58%)	16 (70%)	19 (86%)
No	73 (43%)	74 (43%)	73 (42%)	7 (30%)	3 (14%)
Social: Required 24 hour care					
Yes	0 (0.0%)	2 (1.2%)	1 (0.6%)		
No	168 (99%)	168 (98%)	171 (99%)	23 (100%)	21 (96%)
Missing	2 (1.2%)	1 (0.6%)	1 (0.6%)	0 (0.0%)	1 (4.5%)
Mood: Extremely anxious or depressed					
Yes	2 (1.2%)	4 (2.3%)	3 (1.7%)		
No	163 (96%)	160 (94%)	166 (96%)	21 (91%)	22 (100%)
Missing	5 (2.9%)	7 (4.1%)	4 (2.3%)	2 (8.7%)	0 (0.0%)
Fatigue: 'Very much for either needing to rest or was tired' or					

	CHEMO-INTENSITY pathway			CHEMO-BSC pathway	
	Level A (n=170)	Level B (n=171)	Level C (n=173)	Level C (n=23)	BSC (n=22)
'Quite a bit for both questions'					
Yes	42 (25%)	42 (25%)	42 (24%)	5 (22%)	7 (32%)
No	117 (69%)	126 (74%)	121 (70%)	15 (65%)	15 (68%)
Missing	11 (6.5%)	3 (1.8%)	10 (5.8%)	3 (13.0%)	0 (0.0%)
Polypharmacy: 5 or more prescribed regular medications					
Yes	127 (75%)	129 (75%)	116 (67%)	19 (83%)	14 (64%)
No	42 (25%)	41 (24%)	56 (32%)	4 (17%)	7 (32%)
Missing	1 (0.6%)	1 (0.6%)	1 (0.6%)	0 (0.0%)	1 (4.5%)

eTable 4a Summaries of missing data for quality of life questionnaires in CHEMO-INTENSITY pathway (Percentage out of total expected questionnaires)

QoL time point	EORTC-QLQ-C30			Fatigue			EQ-5D-3L		
	Number not missing	Number missing	Percentage missing	Number not missing	Number missing	Percentage missing*	Number not missing	Number missing	Percentage missing
Baseline	499	15	2.92	499	15	2.92	490	24	4.67
Cycle 1				279	213	43.3			
Cycle 2				227	243	51.7			
9 weeks / Cycle 3	230	121	34.5	314	121	27.8	297	138	31.7
Cycle 4				160	246	60.6			
Cycle 5				148	232	61.1			
18 weeks / Cycle 6				208	146	41.2	210	156	42.6
27 weeks				161	115	41.7	163	113	40.9
36 weeks				115	90	43.9	115	90	43.9
52 weeks				47	42	47.2	48	41	46.1

*Percentage out of total expected questionnaires

eTable 4b Summaries of missing data for quality of life questionnaires in the CHEMO-BSC pathway

QoL time point	Fatigue			EQ-5D-3L		
	Number not missing	Number missing	Percentage missing	Number not missing	Number missing	Percentage missing
Baseline	43	2	4.44	43	2	4.44
Cycle 1	4	28	87.5			
Cycle 2	2	25	92.6			
9 weeks / Cycle 3	14	9	39.1	12	11	47.8
Cycle 4	1	19	95.0			
Cycle 5	1	15	93.8			
18 weeks / Cycle 6	8	7	46.7	8	7	46.7
27 weeks	2	7	77.8	2	7	77.8
36 weeks	1	2	66.7	1	2	66.7
52 weeks	1	0	0	1	0	0

*Percentage out of total expected questionnaires

eTable 5: EORTC-QLQ-C30 Global health status in the CHEMO-INTENSITY pathway

(mean and 95% Confidence Intervals for baseline, adjusted mean and 95% Confidence Intervals for 9 weeks)

	Level A	Level B	Level C
Global health status			
Baseline	60 (57, 63)	57 (54, 61)	61 (58, 64)
9 weeks	60 (57, 64)	63 (59, 66)	66 (62, 69)

eTable 6: EORTC-QLQ-C30 Functional scales in the CHEMO-INTENSITY pathway

(mean and 95% Confidence Intervals for baseline, adjusted mean and 95% Confidence Intervals for 9 weeks)

	Level A	Level B	Level C
Physical functioning			
Baseline	76 (73, 79)	73 (70, 76)	74 (71, 77)
9 weeks	65 (62, 68)	67 (63, 70)	71 (68, 74)
Role functioning			
Baseline	7 (69, 77)	68 (63, 72)	68 (63, 73)
9 weeks	61 (57, 65)	66 (61, 70)	70 (66, 74)
Emotional functioning			
Baseline	79 (76, 81)	76 (73, 80)	77 (73, 80)
9 weeks	80 (77, 83)	78 (75, 81)	81 (78, 84)
Cognitive functioning			
Baseline	86 (83, 89)	84 (81, 88)	85 (82, 88)
9 weeks	80 (76, 83)	83 (80, 86)	83 (80, 86)
Social functioning			
Baseline	76 (71, 80)	71 (66, 75)	72 (67, 76)
9 weeks	68 (63, 72)	75 (70, 80)	77 (73, 82)

eTable 7: EORTC-QLQ-C30 Symptom scales in the CHEMO-INTENSITY pathway

(mean and 95% Confidence Intervals for baseline, adjusted mean and 95% Confidence Intervals for 9 weeks)

	Level A	Level B	Level C
Fatigue			
Baseline	38 (34, 42)	42 (38, 46)	39 (35, 43)
9 weeks	46 (42, 50)	45 (41, 49)	37 (33, 41)
Nausea / Vomiting			
Baseline	15 (11, 18)	17 (14, 21)	17 (14, 21)
9 weeks	17 (13, 20)	11 (7.5, 14)	11 (8, 14)
Pain			
Baseline	29 (24, 33)	24 (20, 28)	25 (21, 29)
9 weeks	17 (13, 21)	20 (16, 24)	17 (13, 20)

eTable 8: EORTC-QLQ-C30 Symptom scales - CHEMO-INTENSITY pathway

(mean and 95% Confidence Intervals for baseline, adjusted mean and 95% Confidence Intervals for 9 weeks)

	Level A	Level B	Level C
Dyspnoea			
Baseline	24 (20, 28)	27 (22, 31)	23 (18, 27)
9 weeks	25 (21, 30)	30 (26, 34)	20 (16, 24)
Insomnia			
Baseline	29 (24, 34)	28 (24, 33)	30 (25, 35)
9 weeks	24 (19, 29)	27 (22, 32)	27 (22, 31)
Appetite loss			
Baseline	41 (36, 47)	46 (41, 51)	43 (37, 48)
9 weeks	33 (28, 38)	32 (27, 37)	27 (22, 32)
Constipation			
Baseline	31 (26, 35)	28 (23, 32)	23 (19, 28)
9 weeks	22 (18, 26)	15 (11, 20)	17 (13, 21)
Diarrhoea			
Baseline	12 (8.3, 15)	6.1 (3.8, 8.4)	9.7 (6.5, 13)
9 weeks	15.1 (11, 19)	12 (8.3, 16)	11 (7.6, 14.9)
Financial Problems			
Baseline	7.6 (4.47, 10.8)	8.8 (5.5, 12)	8.9 (5.75, 12)
9 weeks	5.7 (3.33, 8.15)	4.9 (2.5, 7.3)	3.7 (1.3, 6.0)

eTable 9: EORTC-QLQ-C30 Fatigue scale in the CHEMO-INTENSITY pathway

(mean and 95% Confidence Intervals for baseline, adjusted mean and 95% Confidence Intervals for subsequent assessments)

	Level A	Level B	Level C
Baseline	38.4 (34.5, 42.3)	42.2 (38.5, 46.0)	38.8 (34.9, 42.7)
Cycle 1	44.8 (40.4, 49.2)	43.9 (39.6, 48.1)	43.8 (39.8, 47.9)
Cycle 2	48.2 (43.0, 53.4)	42.7 (37.4, 48.1)	41.9 (36.7, 47.0)
9 weeks / Cycle 3	47.0 (42.4, 51.5)	45.6 (41.1, 50.2)	38.3 (33.8, 42.7)
Cycle 4	44.7 (38.7, 50.7)	47.7 (41.7, 53.7)	48.8 (43.2, 54.4)
Cycle 5	43.8 (37.6, 50.0)	48.4 (42.2, 54.7)	45.0 (39.4, 50.6)
18 weeks / Cycle 6	46.7 (41.0, 52.3)	51.0 (45.5, 56.5)	48.0 (42.8, 53.1)
27 weeks	48.8 (42.0, 55.7)	56.0 (49.3, 62.6)	54.5 (48.0, 61.0)
36 weeks	46.1 (38.8, 53.5)	63.9 (56.9, 71.0)	49.4 (42.4, 56.3)
52 weeks	64.8 (53.6, 76.0)	63.0 (51.2, 74.8)	59.7 (48.6, 70.8)

eTable 10: EORTC-OG-25 Symptom scales in the CHEMO-INTENSITY pathway
 (mean and 95% Confidence Intervals for baseline, adjusted mean and 95% Confidence Intervals for subsequent assessments)

	Level A	Level B	Level C
Dysphagia			
Baseline	22.1 (18.5, 25.7)	22.5 (19.2, 25.8)	22.2 (19.0, 25.3)
9 weeks	11.4 (8.8, 14.0)	12.3 (9.7, 15.0)	9.7 (7.2, 12.3)
Odynophagia			
Baseline	22.5 (18.7, 26.2)	23.5 (19.4, 27.5)	23.6 (19.6, 27.6)
9 weeks	11.1 (8.2, 14.0)	10.9 (7.8, 13.8)	10.2 (7.3, 13.1)
Pain and discomfort			
Baseline	26.9 (22.7, 31.1)	27.0 (22.92, 31.05)	27.0 (22.78, 31.26)
9 weeks	15.8 (12.4, 19.1)	16.2 (12.82, 19.49)	18.4 (15.08, 21.65)
Trouble with taste			
Baseline	21.4 (16.6, 26.2)	18.7 (14.4, 23.1)	19.3 (15.2, 23.5)
9 weeks	26.5 (21.6, 31.3)	23.9 (19.0, 28.7)	20.2 (15.4, 25.0)

eTable 11: Summaries of best response

By allocated treatment and differences between standard and experimental groups with exact 90% confidence intervals.

	Level A (n=125)	Level B (n=112)	Level C (n=112)	Level A vs. Level B	Level A vs. Level C
RECIST response at week 9-52					
Responses: CR + PR	59 (47%) (40, 55)	32 (29%) (22, 36)	35 (31%) (24, 39)	19% (8 to 29)	16% (5 to 26)
Disease control: CR + PR + SD	86 (69%) (61, 76)	69 (62%) (53, 69)	70 (63%) (54, 70)	7.2% (-3.5 to 17.8)	6.3% (-4.4 to 17)
Complete response	6 (4.8%) (2, 9)	5 (4.5%) (2, 9)	5 (4.5%) (2, 9)	0.3% (-10.3 to 11.0)	0.3% (-10 to 11)
Partial response	53 (42%) (35, 50)	27 (24%) (18, 32)	30 (27%) (20, 35)	18% (7.6 to 29)	16% (4.9 to 26)
Stable disease	27 (22%) (16, 29)	37 (33%) (26, 41)	35 (31%) (24, 39)	-11% (-21.9 to -0.7)	-9.7% (-20 to 1.1)
Progressive disease	13 (10%) (6.3, 16)	18 (16%) (11, 23)	13 (12%) (7.0, 18)	-5.7% (-16.3 to 5.0)	-1.2% (-12 to 10)
Non measureable disease	1 (0.8%) (0.1, 3.7)	0 (0.0%) (0.0, 2.6)	2 (1.8%) (0.3, 5.5)	0.8% (-9.9 to 11.5)	-1.0% (-12 to 8)
No assessment	25 (20%) (14, 26)	25 (22%) (16, 30)	27 (24%) (18, 32)	-2.3% (-13.0 to 8.4)	-4.1% (-15 to 7)

eTable 12: Factors Associated with OTU outcome

(multivariable analysis)

	Odds of a worse outcome (95% CI)	Chi-sq	Degrees of freedom	p value
Frailty				
Severely frail (≥ 3) vs. Not/Slightly frail (0-2)	1.44 (1.03-2.02)	4.51	1	0.034
Baseline VAS <50 (EQ-5D)				
Yes vs. No	1.69 (1.06- 2.69)	4.87	1	0.027
Neutrophil:lymphocyte ratio > 4.0				
Yes vs. No	1.59 (1.14, 2.20)	7.65	1	0.006

Table 13: Lookup table for multivariable prognostic model

Baseline Frailty	Baseline QL (EQ-5D VAS)	Baseline NLR	Predicted class probabilities		
			probability of Good OTU	probability of Intermediate OTU	probability of Poor OTU
Not/Slightly frail (0-2)	VAS score ≥ 50	NLR ≤ 4.0	0.44	0.29	0.27
Not/Slightly frail (0-2)	VAS score ≥ 50	<i>NLR >4.0</i>	0.35	0.30	0.36
Not/Slightly frail (0-2)	<i>VAS score <50</i>	NLR ≤ 4.0	0.33	0.30	0.38
<i>Severely frail (≥ 3)</i>	VAS score ≥ 50	NLR ≤ 4.0	0.35	0.30	0.35
Not/Slightly frail (0-2)	<i>VAS score <50</i>	<i>NLR >4.0</i>	0.24	0.28	0.47
<i>Severely frail (≥ 3)</i>	VAS score ≥ 50	<i>NLR >4.0</i>	0.26	0.29	0.45
<i>Severely frail (≥ 3)</i>	<i>VAS score <50</i>	NLR ≤ 4.0	0.25	0.28	0.47
<i>Severely frail (≥ 3)</i>	<i>VAS score <50</i>	<i>NLR >4.0</i>	0.18	0.25	0.57

QL=quality of life; VAS=visual analogue scale (≥ 50 = better QL; <50 = worse QL); NLR=neutrophil:lymphocyte ratio; OTU=overall treatment utility

Adverse baseline characteristics shown in ***bold italics***

eTable 14: Predictive ability of the multivariable prognostic model evaluated at each variable combination

Normalised linear predictor	Linear predictor corresponds to:			Odds of a worse outcome (95% CI)		Predicted class probabilities			
	Baseline Frailty	Baseline QL (EQ-5D VAS)	Baseline NLR ratio	Level B vs. Level A	Level C vs. Level A	Allocation	P(Good OTU)	P(Intermediate OTU)	P(Poor OTU)
1	Not/Slightly frail (0-2)	VAS score \geq 50 (better QL)	NLR \leq 4.0	1.01 (0.50-2.00)	0.33 (0.16-0.68)	Level A	0.41	0.30	0.29
						Level B	0.41	0.30	0.29
						Level C	0.68	0.20	0.12
0.698	Severely frail (\geq 3)	VAS score \geq 50 (better QL)	NLR \leq 4.0	1.13 (0.74-1.73)	0.62 (0.40-0.94)	Level A	0.38	0.30	0.32
						Level B	0.35	0.30	0.35
						Level C	0.50	0.28	0.22
0.685	Not/Slightly frail (0-2)	VAS score \geq 50 (better QL)	NLR $>$ 4.0	1.14 (0.75-1.73)	0.63 (0.42-0.96)	Level A	0.38	0.30	0.32
						Level B	0.35	0.30	0.35
						Level C	0.49	0.30	0.23
0.617	Not/Slightly frail (0-2)	VAS score $<$ 50 (worse QL)	NLR \leq 4.0	1.17 (0.79-1.74)	0.73 (0.49-1.08)	Level A	0.37	0.30	0.33
						Level B	0.33	0.30	0.36
						Level C	0.45	0.29	0.26
0.383	Severely frail (\geq 3)	VAS score \geq 50 (better QL)	NLR $>$ 4.0	1.29 (0.78-2.13)	1.17 (0.72-1.90)	Level A	0.35	0.30	0.35
						Level B	0.29	0.30	0.41
						Level C	0.31	0.30	0.39
0.315	Severely frail (\geq 3)	VAS score $<$ 50 (worse QL)	NLR \leq 4.0	1.32 (0.75-2.33)	1.35 (0.78-2.33)	Level A	0.34	0.03	0.36
						Level B	0.28	0.30	0.42
						Level C	0.28	0.30	0.43
0.302	Not/Slightly frail (0-2)	VAS score $<$ 50 (worse QL)	NLR $>$ 4.0	1.33	1.38 (0.79-2.43)	Level A	0.34	0.30	0.36

Normalised linear predictor	Linear predictor corresponds to:			Odds of a worse outcome (95% CI)		Predicted class probabilities			
	Baseline Frailty	Baseline QL (EQ-5D VAS)	Baseline NLR ratio	Level B vs. Level A	Level C vs. Level A	Allocation	P(Good OTU)	P(Intermediate OTU)	P(Poor OTU)
				(0.74-2.38)		Level B	0.28	0.30	0.43
					Level C	0.27	0.30	0.44	
00	Severely frail (≥ 3)	VAS score < 50 (worse QL)	NLR > 4.0	1.50 (0.59-3.83)	2.56 (1.02-6.46)	Level A	0.31	0.30	0.39
						Level B	0.23	0.28	0.49
						Level C	0.15	0.23	0.62























eTable 15 Chemotherapy delivery and tolerability (CHEMO-INTENSITY randomisation)

[Note that participants who did not receive any treatment were excluded so only 492 participants were included in this table]

	Level A	Level B	Level C
n	170	171	173
Started treatment	161	163	168
Required dose-reduction for toxicity (cycle 1-3)	63 (39%)	39 (24%)	21 (13%)
Stopped for toxicity (cycle 1-3)	53 (33%)	47 (29%)	34 (20%)
Any of the above (dose-reduction <u>or</u> stop)	104 (65%)	79 (49%)	51 (30%)
Tolerated treatment but stopped before cycle 3 because of cancer progression or death	18 (11%)	31 (19%)	31 (19%)
Received 3 cycles at intended dose without delay (> 1 week)	51 (32%)	72 (44%)	97 (58%)

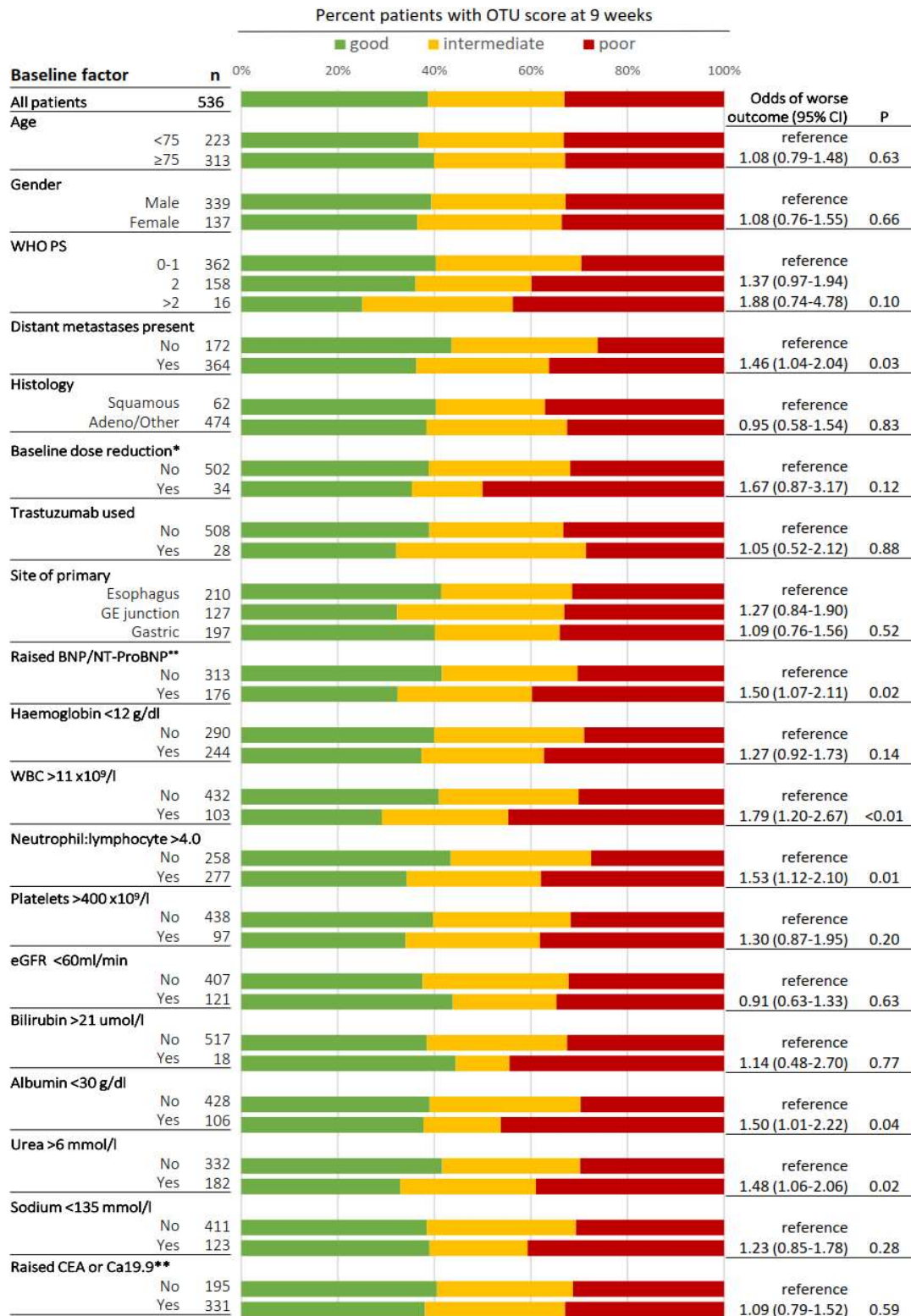
Supplementary Figures

eFigure 1. Influence of baseline factors and dose level on OTU

		n	0% 20% 40% 60% 80% 100%	odds of a worse OTU (95%CI)	main effect test
					
All patients	Level A	170		reference	
	Level B	171		1.15 (0.78-1.70)	0.49
	Level C	173		0.81 (0.54-1.19)	0.28
					interaction test
Age <75	Level A	73		reference	
	Level B	73		0.97 (0.53-1.75)	A vs. B 0.46
	Level C	72		0.75 (0.41-1.37)	
Age ≥75	Level A	97		reference	A vs. C 0.81
	Level B	98		1.30 (0.76-2.17)	
	Level C	101		0.83 (0.50-1.39)	
PS 0-1	Level A	117		reference	
	Level B	116		1.11 (0.69-1.79)	A vs. B 0.84
	Level C	120		0.66 (0.41-1.06)	
PS ≥2	Level A	53		reference	A vs. C 0.15
	Level B	55		1.22 (0.61-2.44)	
	Level C	53		1.23 (0.61-2.50)	
Non-frail or slightly frail	Level A	67		reference	
	Level B	75		0.96 (0.52-1.78)	A vs. B 0.42
	Level C	73		0.53 (0.28-1.00)	
Severely frail	Level A	103		reference	A vs. C 0.09
	Level B	96		1.34 (0.80-2.25)	
	Level C	100		1.06 (0.64-1.79)	

This analysis includes all 514 patients in the CHEMO-INTENSITY pathway. All odds ratios are adjusted for the minimisation stratification factors (age, PS, metastases, histology (squamous/other), renal function, planned use of trastuzumab). Tests for interaction are a one degree of freedom test for two-category subgroups which sought treatment effect heterogeneity.

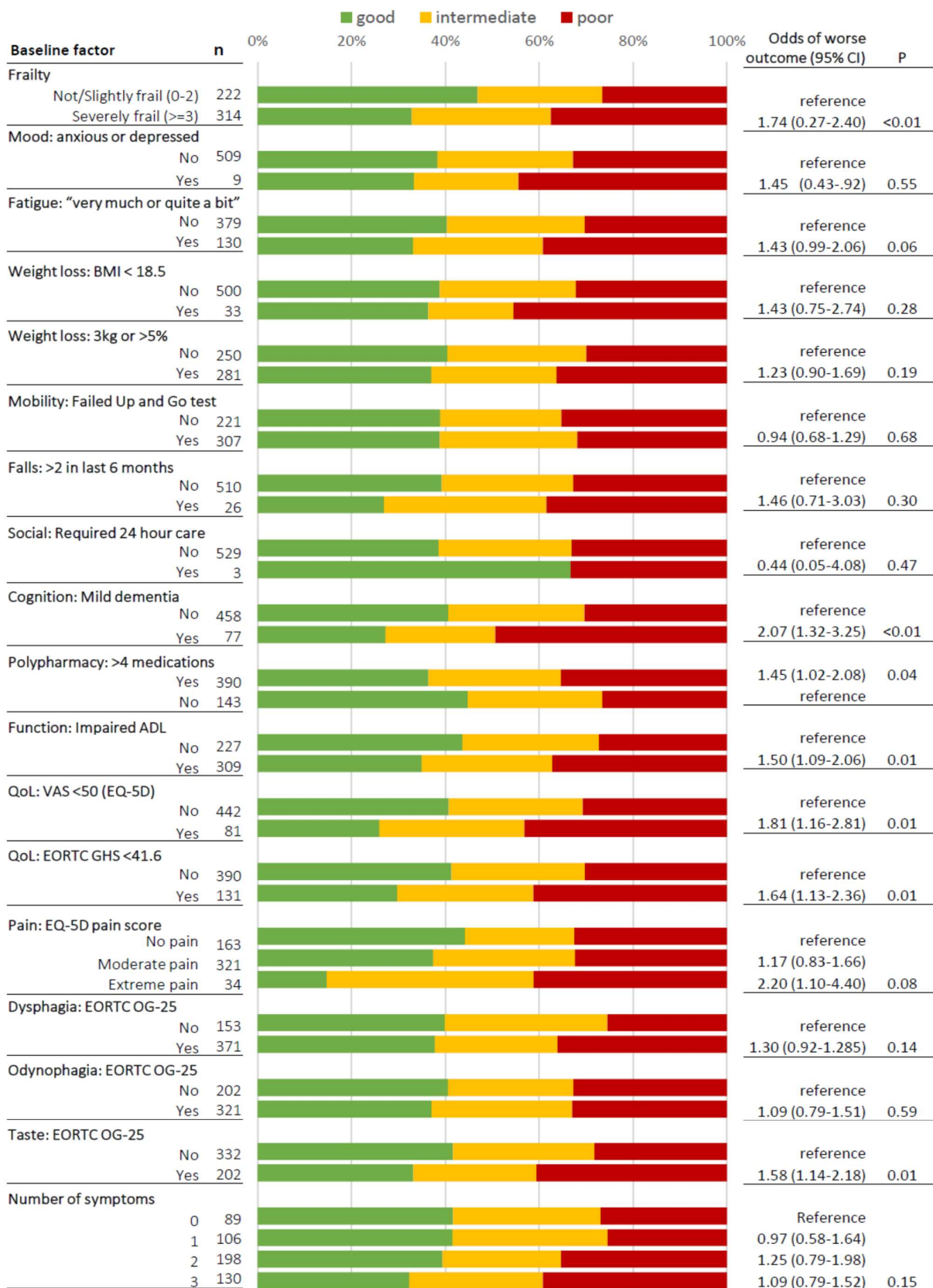
eFigure 2. Univariate analysis: impact of baseline variables Overall Treatment Utility



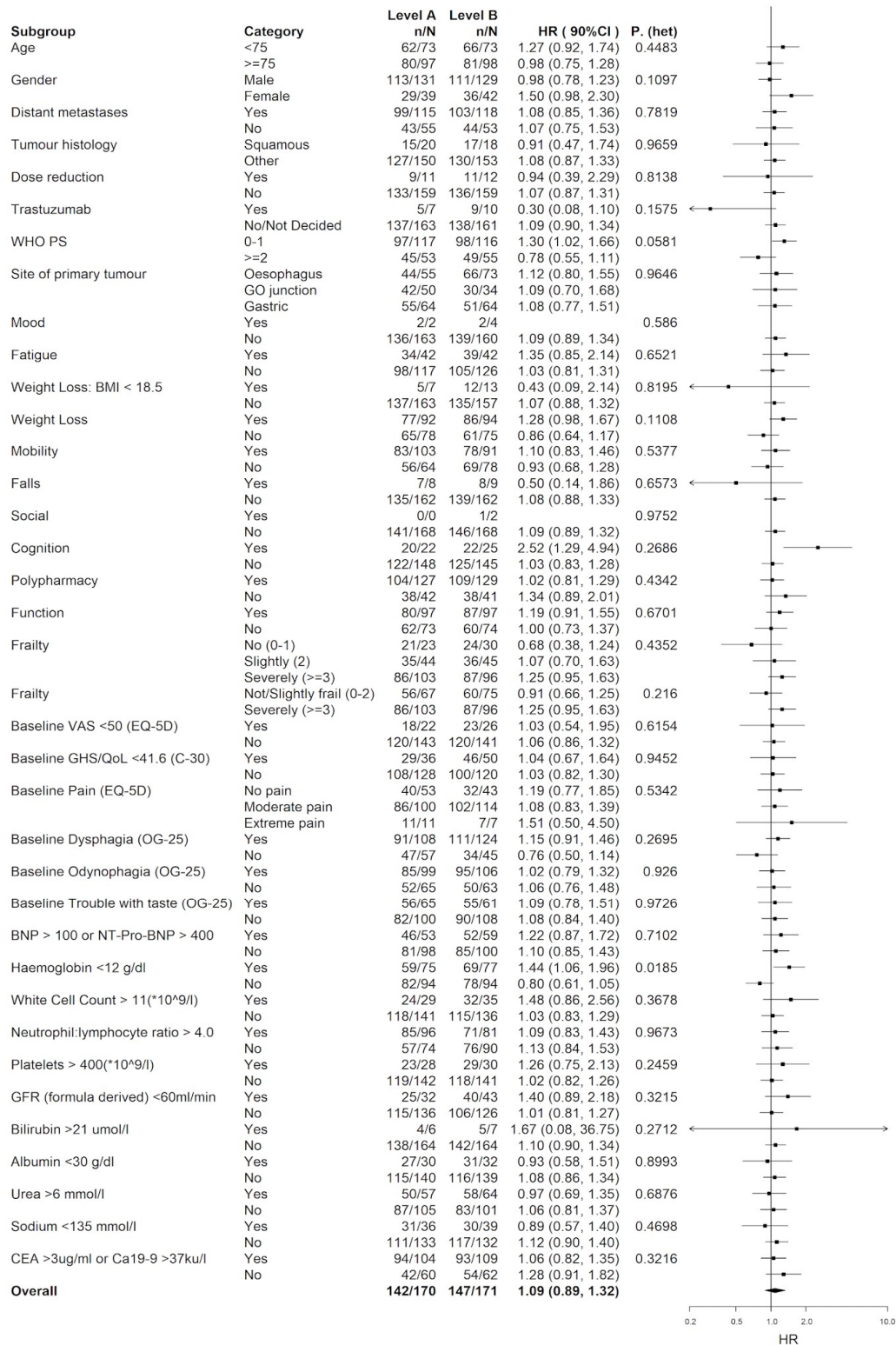
This analysis includes all patients allocated chemotherapy (all 514 in the CHEMO-INTENSITY plus 23 in the CHEMO-BSC pathway). Patients allocated BSC alone are not included as OTU cannot be scored in patients not allocated chemotherapy. *A baseline capecitabine dose reduction of 25% was mandated for patients with eGFR 30-50ml/min or bilirubin 1.5-2 xULN. Patients with eGFR <30 or bili >2xULN were not eligible. ** "Raised" defined as: BNP>100 pg/ml, NT-proBNP >400 pg/ml, CEA >3 ug/ml, Ca19.9 >37 kU/l

eFigure 3 Univariate analysis : Impact of baseline symptoms Overall Treatment Utility

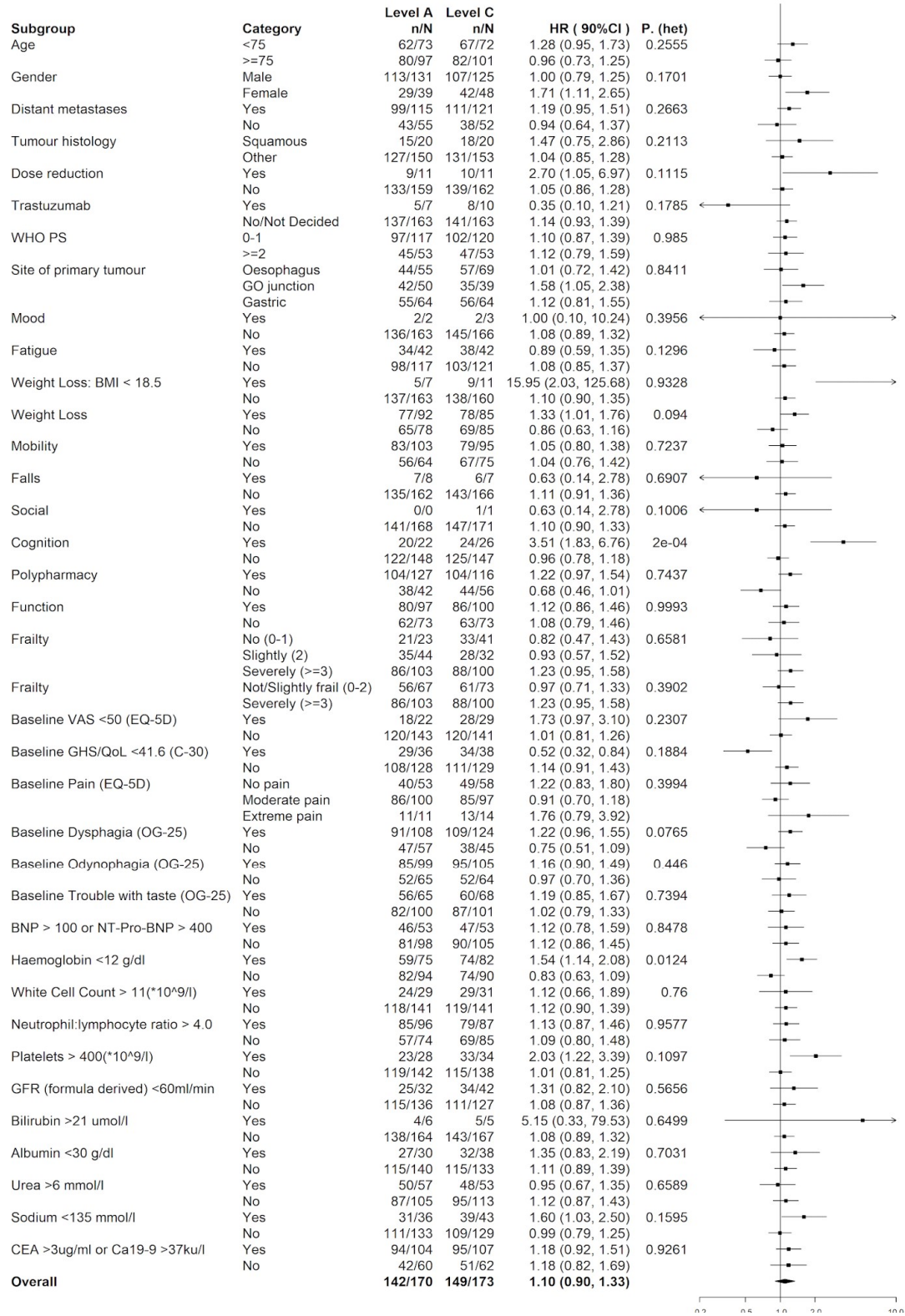
Percent patients with OTU score at 9 weeks



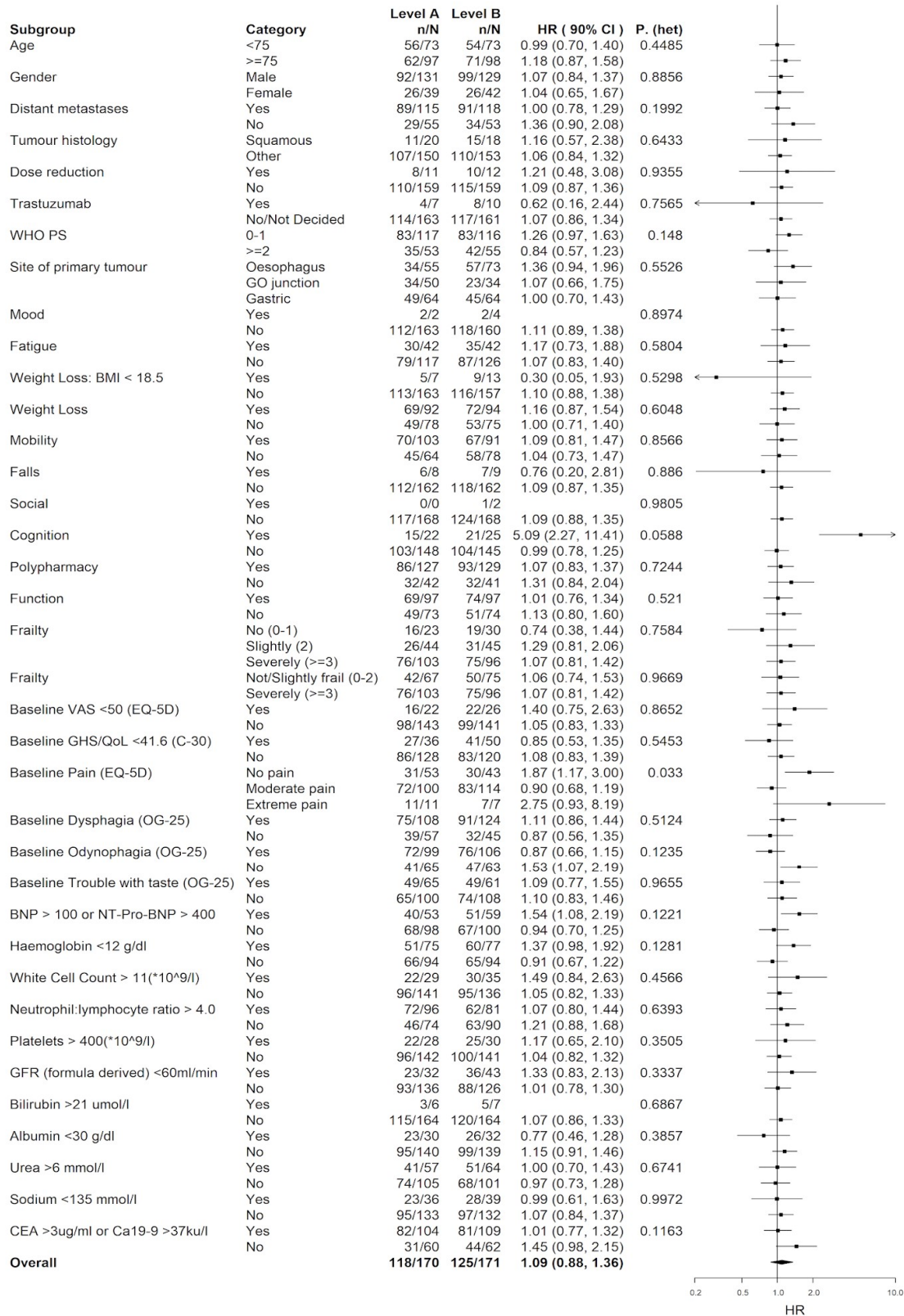
eFigure 4: Forest plot for CHEMO-INTENSITY PFS (Level A vs. Level B)



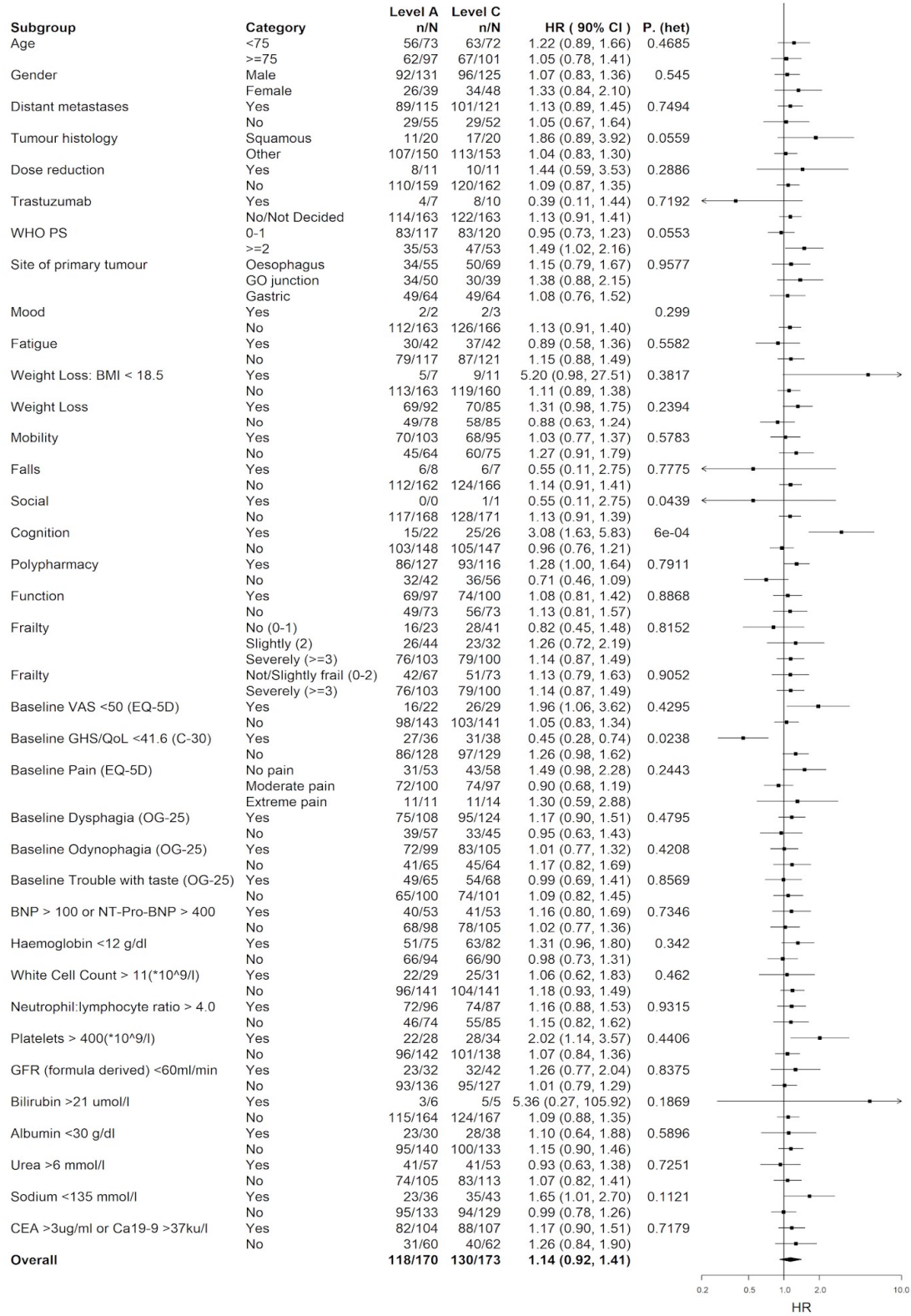
eFigure 5: Forest plot for CHEMO-INTENSITY PFS (Level A vs. Level C)



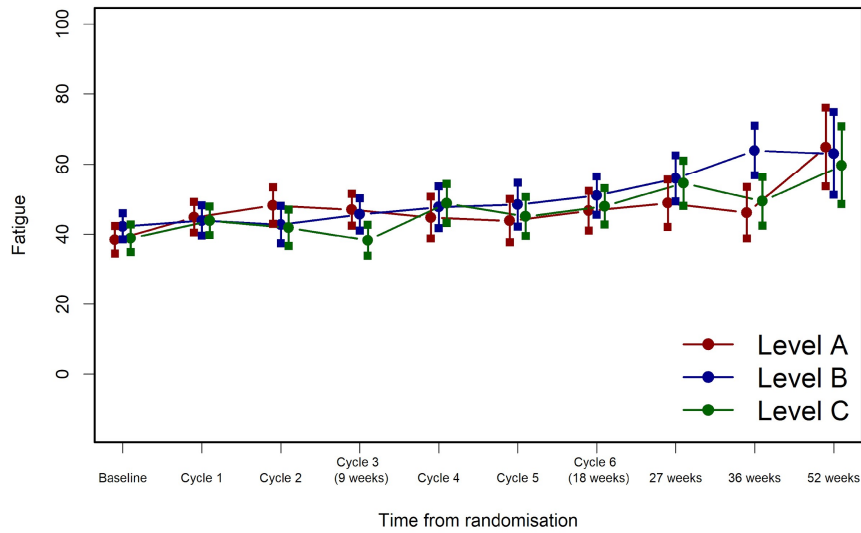
eFigure 6: Forest plot for CHEMO-INTENSITY OS (Level A vs. Level B)



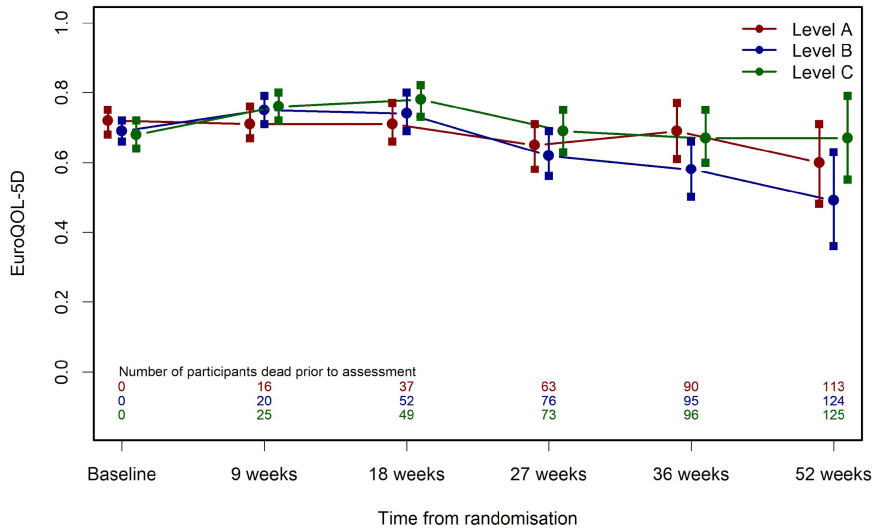
eFigure 7: Forest plot for CHEMO-INTENSITY OS (Level A vs. Level C)



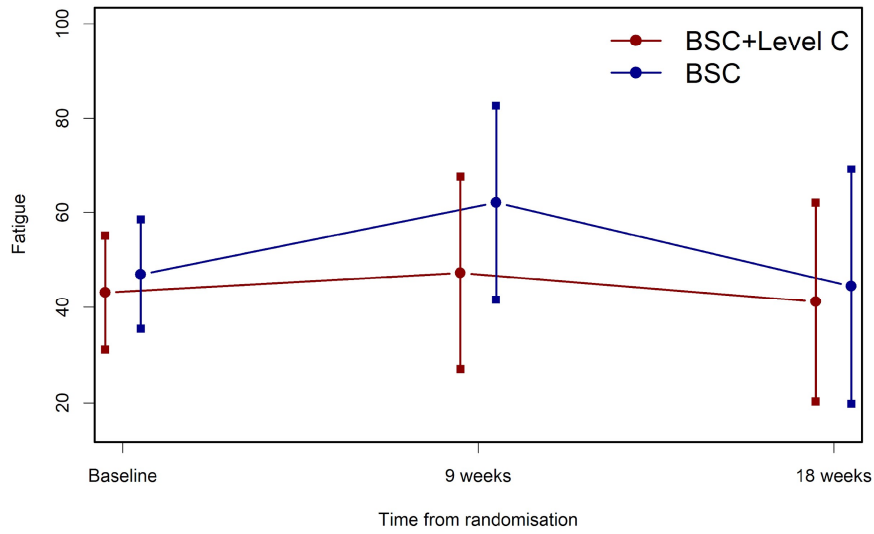
eFigure 8: EORTC-QLQ-C30 Fatigue scale in the CHEMO-INTENSITY pathway
 (Mean and 95% Confidence Intervals for baseline, adjusted mean and 95% Confidence Intervals for subsequent assessments)



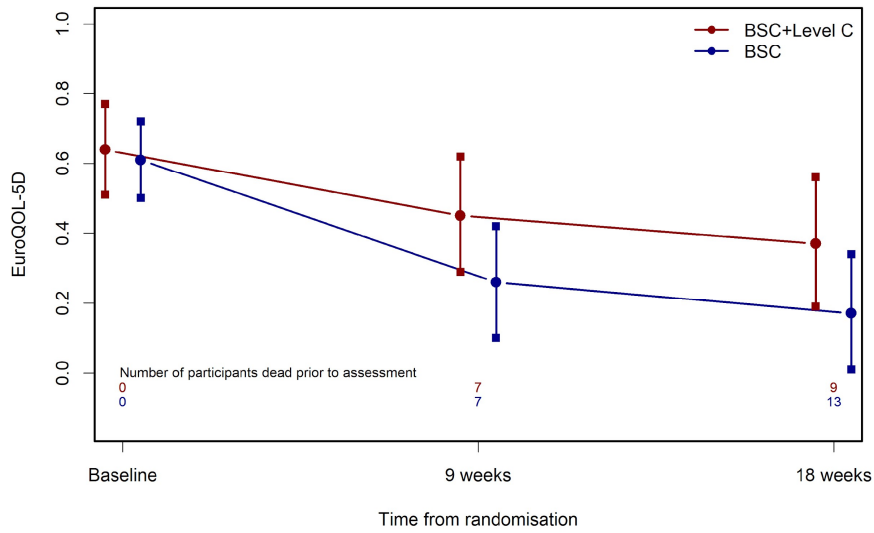
eFigure 9: EuroqoL EQ-5D-3L Score in the CHEMO-INTENSITY pathway
 (mean and 95% Confidence Intervals for baseline, adjusted mean and 95% Confidence Intervals for subsequent assessments)



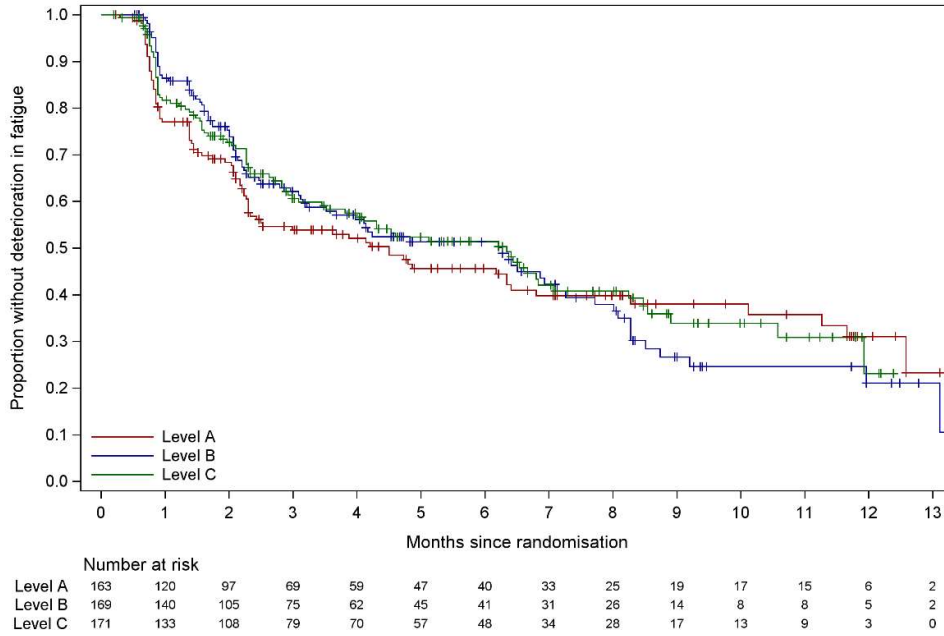
eFigure 10: EORTC-QLQ-C30 Fatigue scale in the CHEMO-BSC pathway
 (mean and 95% Confidence Intervals for baseline, adjusted mean and 95% Confidence Intervals for subsequent assessments)



eFigure 11: EuroqoL EQ-5D-3L Score in the CHEMO-BSC pathway
 (mean and 95% Confidence Intervals for baseline, adjusted mean and 95% Confidence Intervals for subsequent assessments)



eFigure 12: Time to Deterioration of Fatigue in the CHEMO-INTENSITY Pathway



eFigure 13: Per Protocol Population: PFS curves by randomised treatment arm

