

## Supplementary Materials

### Supplementary Table 1 Trials included

First Author	Study Name (Clinical Trial Identifier)	Total N	N of Countries	Included Region	Years of Accrual	Treatment
Fuchs et al. <sup>27</sup>	BICC-C (NCT00101686)	547	4	United States ANZC	2003-2004	FOLFIRI ± bevacizumab versus mIFL ± bevacizumab versus CapeIRI*†
Hurwitz et al. <sup>28</sup>	AVF2107g (NCT00109070)	923	2	United States ANZC	2000-2002	IFL ± bevacizumab*
Saltz et al. <sup>29</sup>	N016966 (NCT00069095)	1653	18	United States ANZC United Kingdom Eastern Europe Central Europe Southern Europe	2003-2005	XELOX ± bevacizumab versus FOLFOX-4 ± bevacizumab*
Kabbinavar et al. <sup>30</sup>	AVF2192g (NCT00109226)	209	3	United States ANZC	2000-2002	FU/LV ± bevacizumab*†
Goldberg et al. <sup>31</sup>	N9741 (NCT00003594)	1408	3	United States ANZC Eastern Europe	1998-2002	FOLFOX versus IFL versus IROX versus other combinations of fluorouracil, irinotecan and oxaliplatin†
Tournigand et al. <sup>32</sup>	OPTIMOX1 (NCT00006468)	600	5	Central Europe Southern Europe	2000-2002	FOLFOX ± LV5FU2 maintenance
Chibaudel et al. <sup>33</sup>	OPTIMOX2 (NCT00274872)	202	1	Central Europe	2004-2006	FOLFOX with LV5FU2 maintenance versus treatment discontinuation%

First Author	Study Name (Clinical Trial Identifier)	Total N	N of Countries	Included Region	Years of Accrual	Treatment
Tournigand et al. <sup>34</sup>	C97-3 (NCT00003260)	220	1	Central Europe	1997-1999	FOLFOX followed by FOLFIRI or FOLFIRI followed by FOLFOX‡
Hecht et al. <sup>35</sup>	PACCE (C249) (NCT00115765)	969	1	United States	2005-2006	Oxaliplatin-based or irinotecan-based chemotherapy ± panitumumab*
Douillard et al. <sup>36</sup>	PRIME (C203) (NCT00364013)	943	12	ANZC United Kingdom Eastern Europe Central Europe Southern Europe	2006-2008	FOLFOX ± panitumumab*
Koopman et al. <sup>37</sup>	CAIRO1 (NCT00312000)	780	1	Central Europe	2003-2004	Capecitabine followed by irinotecan then CAPOX versus CAPIRI followed by CAPOX‡
Tol et al. <sup>38</sup>	CAIRO2 (NCT00208546)	627	1	Central Europe	2005-2006	CAPOX and bevacizumab ± cetuximab*
Van Cutsem et al. <sup>39</sup>	CRYSTAL (NCT00154102)	942	21	ANZC United Kingdom Eastern Europe Central Europe Southern Europe	2004-2005	FOLFIRI ± cetuximab*
Adams et al. <sup>15</sup>	COIN (NCT00182715)	2289	2	United Kingdom	2005-2008	Intermittent FOLFOX/CAPOX versus continuous FOLFOX/CAPOX ± cetuximab*%‡
Seymour et al. <sup>17</sup>	FOCUS (NCT00008060)	2118	4	United Kingdom Southern Europe	2000-2003	Fluorouracil followed by irinotecan versus fluorouracil followed by combination chemotherapy versus combination therapy†‡
Seymour et al. <sup>40</sup>	FOCUS2 (NCT00070213)	459	1	United Kingdom	2004-2006	Fluorouracil or capecitabine ± oxaliplatin‡
Diaz-Rubio et al. <sup>41</sup>	03-TTD-01 (NCT00202774)	342	1	Southern Europe	2002-2004	XELOX versus oxaliplatin and fluorouracil in continuous infusion

First Author	Study Name (Clinical Trial Identifier)	Total N	N of Countries	Included Region	Years of Accrual	Treatment
Diaz-Rubio et al. <sup>42</sup>	Macro (NCT00335595)	480	1	Southern Europe	2006-2008	XELOX plus bevacizumab followed by XELOX plus bevacizumab or single-agent bevacizumab as maintenance therapy*
Tebbutt et al. <sup>43</sup>	AGITG (MAX) (NCT00294359)	471	3	ANZC United Kingdom	2005-2007	capecitabine versus capecitabine + bevacizumab versus capecitabine + bevacizumab + mitomycin C*†
Souglakos et al. <sup>44</sup>	HORG 99.30	283	1	Southern Europe	1999-2004	FOLFOXIRI versus FOLFIRI <sup>#</sup>
Falcone et al. <sup>45</sup>	GONO (NCT01219920)	244	1	Southern Europe	2001-2005	FOLFOXIRI versus FOLFIRI <sup>#</sup>
Porschen et al. <sup>46</sup>	AIO 22	474	1	Central Europe	2002-2004	CAPOX versus FUFOX
Moosmann et al. <sup>47</sup>	FIRE II (CIOX) (NCT00254137)	146	1	Central Europe	2004-2006	cetuximab plus CAPIRI versus cetuximab plus CAPOX*
Bokemeyer et al. <sup>48</sup>	OPUS (NCT00125034)	333	12	Eastern Europe Central Europe Southern Europe	2005-2006	FOLFOX ± bevacizumab*
Stintzing et al. <sup>49</sup>	FIRE III (NCT00433927)	592	2	Central Europe	2007-2012	FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab*
Loupakis et al. <sup>50</sup>	TRIBE (NCT00719797)	508	1	Southern Europe	2008-2011	FOLFIRI plus bevacizumab versus FOLFOXIRI plus bevacizumab*#
Venook et al. <sup>51</sup>	CALGB-80405	1945	2	United States ANZC	2005-2012	Chemotherapy plus Bevacizumab versus Chemotherapy plus Cetuximab versus Chemotherapy plus Bevacizumab plus Cetuximab

\*: contains targeted therapy; †: contains a single-agent chemotherapy arm; #: contains a triple-agent chemotherapy arm ; %: contains an intermittent chemotherapy arm

**Supplementary Table 2 Number of patients and studies covered by region.**

Region	No. of Patients (%)	No. of Studies
United States	5728 (26.6%)	7
United Kingdom+Ireland	5230 (24.3%)	7
Central Europe	4305 (20.0%)	12
Southern Europe	2759 (12.8%)	11
Australia/New Zealand/Canada	1681 (7.8%)	9
Eastern Europe	1004 (4.7%)	5
South America	254 (1.2%)	3
Asia 1	227 (1.1%)	2
Northern Europe	129 (0.6%)	3
Africa	119 (0.6%)	4
Asia 2	73 (0.3%)	1

**Supplementary Table 3 Summaries of European Regions**

Region	Country of Origin	No. of Studies	No. of Patients
Central Europe	Austria	5	153
	Belgium	3	178
	France	7	932
	Germany	7	1269
	Israel	3	158
	Switzerland	2	25
	The Netherlands	3	832

<b>Region</b>	<b>Country of Origin</b>	<b>No. of Studies</b>	<b>No. of Patients</b>
Eastern Europe	Bulgaria	1	17
	Czech Republic	3	87
	Hungary	3	159
	Latvia	1	13
	Lithuania	1	3
	Poland	3	353
	Romania	2	57
	Russia	3	178
	Slovakia	1	15
	Ukraine	3	122
Southern Europe	Cyprus	1	30
	Greece	2	293
	Italy	6	1012
	Portugal	3	12
	Spain	7	840
	Turkey	2	15
Northern Europe	Denmark	1	9
	Finland	2	19
	Norway	1	28
	Sweden	3	73
United Kingdom and Ireland	Ireland	2	59
	United Kingdom	6	3029
	United Kingdom-England	1	1854
	United Kingdom-Scotland	1	37
	United Kingdom-Wales	1	197

**Supplementary Table 4 Proportion of the population entered into studies covered by region.**

Region	No. of Patients (%)	2010 population *	**Trial entry /100,000 Popn.	2010 Popn.* Age 65+	**Trial entry/100,000 Popn. 65+
United States	5728 (26.6%)	310	1.85	40.3	14.21
United Kingdom+Ireland	5230 (24.3%)	66.7	7.84	10.45	50.05
Central Europe	4305 (20.0%)	195.8	2.20	35.05	12.28
Southern Europe	2759 (12.8%)	204.3	1.35	29.44	9.37
Australia/New Zealand/Canada	1681 (7.8%)	60.9	2.76	8.26	20.35
Eastern Europe	1004 (4.7%)	286.4	0.35	35.05	2.86
South America	254 (1.2%)	384	0.07	32.49	0.78
Asia 1	227 (1.1%)	211.6	0.11	35.05	0.65
Northern Europe	129 (0.6%)	25.5	0.51	4.32	2.99
Africa	119 (0.6%)	89.9	0.13	3.2	3.72
Asia 2	73 (0.3%)	1406.2	0.01	111.82	0.07

\*Population data extracted from: [https://www.prb.org/wp-content/uploads/2010/11/10wpds\\_eng.pdf](https://www.prb.org/wp-content/uploads/2010/11/10wpds_eng.pdf)

\*\* Figures significantly over estimate trial entry as trial recruitment may have happened over anything up to a 15 year period (1997-2012)

**Supplementary Table 5a Baseline patient and disease characteristics by region for trials included in the primary analysis**

	Central Europe (N=4305)	Southern Europe (N=2759)	United States (N=5728)	Eastern Europe (N=1004)	ANZC (N=1681)	United Kingdom +Ireland (N=5230)	United Kingdom Total (N=20707)
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**Age at Enrollment (C)**

N	4302	2759	5727	1004	1681	5228	20701
Mean (SD)	62.5 (9.7)	61.8 (9.9)	59.9 (11.8)	59.3 (10.1)	61.8 (10.8)	63.4 (9.9)	61.7 (10.6)
Median	64.0	63.0	60.0	60.0	63.0	64.0	63.0
Q1, Q3	56.0, 70.0	56.0, 70.0	52.0, 69.0	53.0, 67.0	55.0, 70.0	57.0, 71.0	55.0, 70.0
Range	(19.0- 86.0)	(21.0- 84.0)	(18.0- 90.0)	(19.0- 82.0)	(20.0- 86.0)	(18.0- 87.0)	(18.0- 90.0)
P-value (vs. UK+Ireland)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	REF	

**Age at Enrollment (G)**

Missing	3	0	1	0	0	2	6
<=70	3363	2179	4551	872	1290	3916	16171
	(78.2%)	(79.0%)	(79.5%)	(86.9%)	(76.7%)	(74.9%)	(78.1%)
>70	939	580	1176	132	391	1312	4530
	(21.8%)	(21.0%)	(20.5%)	(13.1%)	(23.3%)	(25.1%)	(21.9%)
P-value (vs. UK+Ireland)	0.0002	<0.0001	<0.0001	<0.0001	0.1287	REF	

**Enrollment Era**

Missing	0	4	0	0	0	0	4
<2005	2376	1215	2868	98 (9.8%)	862	2436	9855
	(55.2%)	(44.1%)	(50.1%)		(51.3%)	(46.6%)	(47.6%)
>=2005	1929	1540	2860	906	819	2794	10848
	(44.8%)	(55.9%)	(49.9%)	(90.2%)	(48.7%)	(53.4%)	(52.4%)
P-value (vs. UK+Ireland)	<0.0001	0.0348	0.0003	<0.0001	0.0008	REF	

**Gender**

**Supplementary Table 5a Baseline patient and disease characteristics by region for trials included in the primary analysis**

	Central Europe (N=4305)	Southern Europe (N=2759)	United States (N=5728)	Eastern Europe (N=1004)	ANZC (N=1681)	United Kingdom +Ireland (N=5230)	United Kingdom Total (N=20707)
Missing	15	0	0	0	0	0	15
Female	1610 (37.5%)	1045 (37.9%)	2383 (41.6%)	443 (44.1%)	617 (36.7%)	1786 (34.1%)	7884 (38.1%)
Male	2680 (62.5%)	1714 (62.1%)	3345 (58.4%)	561 (55.9%)	1064 (63.3%)	3444 (65.9%)	12808 (61.9%)
P-value (vs. UK+Ireland)	0.0006	0.0009	<0.0001	<0.0001	0.0557	REF	
<b>Performance Score</b>							
Missing	34	7	195	0	0	2	238
0-1	4093 (95.8%)	2679 (97.3%)	5458 (98.6%)	948 (94.4%)	1623 (96.5%)	4731 (90.5%)	19532 (95.4%)
2	178 (4.2%)	73 (2.7%)	75 (1.4%)	56 (5.6%)	58 (3.5%)	497 (9.5%)	937 (4.6%)
P-value (vs. UK+Ireland)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	REF	
<b>Primary Site</b>							
Missing	815	29	3479	1	426	9	4759
Both	57 (1.6%)	86 (3.2%)	16 (0.7%)	16 (1.6%)	38 (3.0%)	34 (0.7%)	247 (1.5%)
Colon Only	2299 (65.9%)	1911 (70.0%)	1769 (78.7%)	623 (62.1%)	902 (71.9%)	3560 (68.2%)	11064 (69.4%)
Rectum Only	1134 (32.5%)	733 (26.8%)	464 (20.6%)	364 (36.3%)	315 (25.1%)	1627 (31.2%)	4637 (29.1%)
P-value (vs. UK+Ireland)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	REF	
<b>Liver Involved</b>							
Missing	1139	960	2588	880	599	168	6334

**Supplementary Table 5a Baseline patient and disease characteristics by region for trials included in the primary analysis**

	Central Europe (N=4305)	Southern Europe (N=2759)	United States (N=5728)	Eastern Europe (N=1004)	ANZC (N=1681)	United Kingdom +Ireland (N=5230)	United Kingdom Total (N=20707)
Involved	2514 (79.4%)	1375 (76.4%)	2410 (76.8%)	94 (75.8%)	831 (76.8%)	3841 (75.9%)	11065 (77.0%)
Not Involved	652 (20.6%)	424 (23.6%)	730 (23.2%)	30 (24.2%)	251 (23.2%)	1221 (24.1%)	3308 (23.0%)
P-value (vs. UK+Ireland)	0.0002	0.6375	0.3670	0.9851	0.5185	REF	
<b>Lung Involved</b>							
Missing	1220	960	2591	880	600	169	6420
Involved	1103 (35.8%)	603 (33.5%)	1237 (39.4%)	51 (41.1%)	428 (39.6%)	1956 (38.6%)	5378 (37.6%)
Not Involved	1982 (64.2%)	1196 (66.5%)	1900 (60.6%)	73 (58.9%)	653 (60.4%)	3105 (61.4%)	8909 (62.4%)
P-value (vs. UK+Ireland)	0.0089	0.0001	0.4792	0.5753	0.5630	REF	
<b>N of Metastatic Sites (G)</b>							
Missing	1160	909	991	691	243	167	4161
0	12 (0.4%)	7 (0.4%)	58 (1.2%)	0 (0.0%)	4 (0.3%)	19 (0.4%)	100 (0.6%)
1	1653 (52.6%)	890 (48.1%)	2235 (47.2%)	131 (41.9%)	478 (33.2%)	1976 (39.0%)	7363 (44.5%)
2+	1480 (47.1%)	953 (51.5%)	2444 (51.6%)	182 (58.1%)	956 (66.5%)	3068 (60.6%)	9083 (54.9%)
P-value (vs.UK+Ireland)	<0.0001	<0.0001	<0.0001	0.3557	0.0003	REF	
<b>Type of Treatment</b>							

**Supplementary Table 5a Baseline patient and disease characteristics by region for trials included in the primary analysis**

	Central Europe (N=4305)	Southern Europe (N=2759)	United States (N=5728)	Eastern Europe (N=1004)	ANZC (N=1681)	United Kingdom +Ireland (N=5230)	Total (N=20707)
Anti-ANG Only	769 (17.9%)	1110 (40.2%)	2165 (37.8%)	62 (6.2%)	522 (31.1%)	82 (1.6%)	4710 (22.7%)
Anti-EGFR Only	669 (15.5%)	238 (8.6%)	663 (11.6%)	425 (42.3%)	151 (9.0%)	715 (13.7%)	2861 (13.8%)
Both	257 (6.0%)	0 (0.0%)	797 (13.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1054 (5.1%)
No Biologics	2610 (60.6%)	1411 (51.1%)	2103 (36.7%)	517 (51.5%)	1008 (60.0%)	4433 (84.8%)	12082 (58.3%)
P-value (vs. UK+Ireland)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	REF	

REF=reference group for comparison

**Supplementary Table 5b Baseline patient and disease characteristics by region for all trials**

	ANZC (N=1681)	Africa (N=119)	Asia 1 (N=227)	Asia 2 (N=73)	Central Europe (N=4305)	Eastern Europe (N=1004)	Northern Europe (N=129)	South America (N=254)	Southern Europe + Ireland (N=2759)	United Kingdom (N=5230)	United States (N=5728)	Total (N=21509)
<b>Age at Enrollment (C)</b>												
N	1681	119	226	73	4302	1004	129	254	2759	5228	5727	21502
Mean (SD)	61.8 (10.8)	55.8 (11.5)	55.5 (10.8)	56.0 (11.6)	62.5 (9.7)	59.3 (10.1)	61.6 (9.3)	57.2 (13.3)	61.8 (9.9)	63.4 (9.9)	59.9 (11.8)	61.5 (10.7)
Median	63.0	57.0	57.0	56.0	64.0	60.0	63.0	58.0	63.0	64.0	60.0	63.0
Q1, Q3	55.0, 70.0	48.0, 65.0	48.0, 63.0	49.0, 63.0	56.0, 70.0	53.0, 67.0	57.0, 67.0	50.0, 68.0	56.0, 70.0	57.0, 71.0	52.0, 69.0	55.0, 70.0
Range	(20.0- 86.0)	(27.0- 77.0)	(24.0- 82.0)	(24.0- 77.0)	(19.0- 86.0)	(19.0- 82.0)	(18.0- 79.0)	(22.0- 83.0)	(21.0- 84.0)	(18.0- 87.0)	(18.0- 90.0)	(18.0- 90.0)

**Supplementary Table 5b Baseline patient and disease characteristics by region for all trials**

	ANZC (N=1681)	Africa (N=119)	Asia 1 (N=227)	Asia 2 (N=73)	Central Europe (N=4305)	Eastern Europe (N=1004)	Northern Europe (N=129)	South America (N=254)	Southern Europe + Ireland (N=2759)	United Kingdom (N=5230)	United States (N=5728)	Total (N=21509)
P-value (vs. UK+Ireland)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0334	<0.0001	<0.0001	REF	<0.0001	
<b>Age at Enrollment (G)</b>												
Missing	0	0	1	0	3	0	0	0	0	2	1	7
<=70	1290	108	211	64	3363	872	110	208	2179	3916	4551	16872
	(76.7%)	(90.8%)	(93.4%)	(87.7%)	(78.2%)	(86.9%)	(85.3%)	(81.9%)	(79.0%)	(74.9%)	(79.5%)	(78.5%)
>70	391	11 (9.2%)	15 (6.6%)	9 (12.3%)	939	132	19	46	580	1312	1176	4630
	(23.3%)				(21.8%)	(13.1%)	(14.7%)	(18.1%)	(21.0%)	(25.1%)	(20.5%)	(21.5%)
P-value (vs. UK+Ireland)	0.1287	<0.0001	<0.0001	0.0123	0.0002	<0.0001	0.0071	0.0118	<0.0001	REF	<0.0001	
<b>Enrollment Era</b>												
Missing	0	0	0	0	0	0	0	0	4	0	0	4
<2005	862	54	86	70	2376	98 (9.8%)	108	44	1215	2436	2868	10217
	(51.3%)	(45.4%)	(37.9%)	(95.9%)	(55.2%)		(83.7%)	(17.3%)	(44.1%)	(46.6%)	(50.1%)	(47.5%)
>=2005	819	65	141	3 (4.1%)	1929	906	21	210	1540	2794	2860	11288
	(48.7%)	(54.6%)	(62.1%)		(44.8%)	(90.2%)	(16.3%)	(82.7%)	(55.9%)	(53.4%)	(49.9%)	(52.5%)
P-value (vs. UK+Ireland)	0.0008	0.7954	0.0101	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0348	REF	0.0003	
<b>Gender</b>												
Missing	0	0	0	0	15	0	0	0	0	0	0	15
Female	617	50	92	38	1610	443	62	112	1045	1786	2383	8238
	(36.7%)	(42.0%)	(40.5%)	(52.1%)	(37.5%)	(44.1%)	(48.1%)	(44.1%)	(37.9%)	(34.1%)	(41.6%)	(38.3%)
Male	1064	69	135	35	2680	561	67	142	1714	3444	3345	13256
	(63.3%)	(58.0%)	(59.5%)	(47.9%)	(62.5%)	(55.9%)	(51.9%)	(55.9%)	(62.1%)	(65.9%)	(58.4%)	(61.7%)
P-value (vs. UK+Ireland)	0.0557	0.0739	0.0476	0.0014	0.0006	<0.0001	0.0010	0.0011	0.0009	REF	<0.0001	

**Supplementary Table 5b Baseline patient and disease characteristics by region for all trials**

	ANZC (N=1681)	Africa (N=119)	Asia 1 (N=227)	Asia 2 (N=73)	Central Europe (N=4305)	Eastern Europe (N=1004)	Northern Europe (N=129)	South America (N=254)	Southern Europe + Ireland (N=2759)	United Kingdom (N=5230)	United States (N=5728)	Total (N=21509)
<b>Performance Score</b>												
Missing	0	0	0	0	34	0	1	1	7	2	195	240
0-1	1623	115	226	73	4093	948	125	245	2679	4731	5458	20316
	(96.5%)	(96.6%)	(99.6%)	(100.0%)	(95.8%)	(94.4%)	(97.7%)	(96.8%)	(97.3%)	(90.5%)	(98.6%)	(95.5%)
2	58 (3.5%)	4 (3.4%)	1 (0.4%)	0 (0.0%)	178	56 (5.6%)	3 (2.3%)	8 (3.2%)	73 (2.7%)	497	75 (1.4%)	953
					(4.2%)					(9.5%)		(4.5%)
P-value (vs. UK+Ireland)	<0.0001	0.0229	<0.0001	0.0057	<0.0001	<0.0001	0.0059	0.0007	<0.0001	REF	<0.0001	
<b>Primary Site</b>												
Missing	426	9	0	0	815	1	3	0	29	9	3479	4771
Both	38 (3.0%)	9 (8.2%)	9 (4.0%)	3 (4.1%)	57 (1.6%)	16 (1.6%)	2 (1.6%)	10 (3.9%)	86 (3.2%)	34 (0.7%)	16 (0.7%)	280 (1.7%)
Colon Only	902	75	153	41	2299	623	69	163	1911	3560	1769	11565
	(71.9%)	(68.2%)	(67.4%)	(56.2%)	(65.9%)	(62.1%)	(54.8%)	(64.2%)	(70.0%)	(68.2%)	(78.7%)	(69.1%)
Rectum Only	315	26	65	29	1134	364	55	81	733	1627	464	4893
	(25.1%)	(23.6%)	(28.6%)	(39.7%)	(32.5%)	(36.3%)	(43.7%)	(31.9%)	(26.8%)	(31.2%)	(20.6%)	(29.2%)
P-value (vs. UK+Ireland)	<0.0001	<0.0001	<0.0001	0.0004	<0.0001	<0.0001	0.0042	<0.0001	<0.0001	REF	<0.0001	
<b>Liver Involved</b>												
Missing	599	70	137	0	1139	880	5	189	960	168	2588	6735
Involved	831	30	73	43	2514	94	93	48	1375	3841	2410	11352
	(76.8%)	(61.2%)	(81.1%)	(58.9%)	(79.4%)	(75.8%)	(75.0%)	(73.8%)	(76.4%)	(75.9%)	(76.8%)	(76.8%)
Not Involved	251	19	17	30	652	30	31	17	424	1221	730	3422
	(23.2%)	(38.8%)	(18.9%)	(41.1%)	(20.6%)	(24.2%)	(25.0%)	(26.2%)	(23.6%)	(24.1%)	(23.2%)	(23.2%)
P-value (vs. UK+Ireland)	0.5185	0.0172	0.2495	0.0008	0.0002	0.9851	0.8212	0.7035	0.6375	REF	0.3670	
<b>Lung Involved</b>												
Missing	600	70	137	0	1220	880	5	189	960	169	2591	6821

**Supplementary Table 5b Baseline patient and disease characteristics by region for all trials**

	ANZC (N=1681)	Africa (N=119)	Asia 1 (N=227)	Asia 2 (N=73)	Central Europe (N=4305)	Eastern Europe (N=1004)	Northern Europe (N=129)	South America (N=254)	Southern Europe + Ireland (N=2759) (N=5230)	United Kingdom	United States (N=5728)	Total (N=21509)
Involved	428 (39.6%)	17 (34.7%)	34 (37.8%)	31 (42.5%)	1103 (35.8%)	51 (41.1%)	47 (37.9%)	21 (32.3%)	603 (33.5%)	1956 (38.6%)	1237 (39.4%)	5528 (37.6%)
Not Involved	653 (60.4%)	32 (65.3%)	56 (62.2%)	42 (57.5%)	1982 (64.2%)	73 (58.9%)	77 (62.1%)	44 (67.7%)	1196 (66.5%)	3105 (61.4%)	1900 (60.6%)	9160 (62.4%)
P-value (vs. UK+Ireland)	0.5630	0.5715	0.8665	0.5062	0.0089	0.5753	0.8663	0.2967	0.0001	REF	0.4792	
<b>N of Metastatic Sites (G)</b>												
Missing	243	62	137	0	1160	691	5	189	909	167	991	4554
0	4 (0.3%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	12 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (0.4%)	19 (0.4%)	58 (1.2%)	101 (0.6%)
1	478 (33.2%)	22 (38.6%)	35 (38.9%)	34 (46.6%)	1653 (52.6%)	131 (41.9%)	58 (46.8%)	35 (53.8%)	890 (48.1%)	1976 (39.0%)	2235 (47.2%)	7547 (44.5%)
2+	956 (66.5%)	34 (59.6%)	55 (61.1%)	39 (53.4%)	1480 (47.1%)	182 (58.1%)	66 (53.2%)	30 (46.2%)	953 (51.5%)	3068 (60.6%)	2444 (51.6%)	9307 (54.9%)
P-value (vs. UK+Ireland)	0.0003	0.2521	0.8428	0.3804	<.0001	0.3557	0.1822	0.0485	<0.0001	REF	<0.0001	
<b>Type of Treatment</b>												
Anti-ANG Only	522 (31.1%)	17 (14.3%)	23 (10.1%)	6 (8.2%)	769 (17.9%)	62 (6.2%)	46 (35.7%)	20 (7.9%)	1110 (40.2%)	82 (1.6%)	2165 (37.8%)	4822 (22.4%)
Anti-EGFR Only	151 (9.0%)	16 (13.4%)	60 (26.4%)	0 (0.0%)	669 (15.5%)	425 (42.3%)	3 (2.3%)	96 (37.8%)	238 (8.6%)	715 (13.7%)	663 (11.6%)	3036 (14.1%)
Both	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	257 (6.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	797 (13.9%)	1054 (4.9%)
No Biologics	1008 (60.0%)	86 (72.3%)	144 (63.4%)	67 (91.8%)	2610 (60.6%)	517 (51.5%)	80 (62.0%)	138 (54.3%)	1411 (51.1%)	4433 (84.8%)	2103 (36.7%)	12597 (58.6%)

**Supplementary Table 5b Baseline patient and disease characteristics by region for all trials**

	ANZC (N=1681)	Africa (N=119)	Asia 1 (N=227)	Asia 2 (N=73)	Central Europe (N=4305)	Eastern Europe (N=1004)	Northern Europe (N=129)	South America (N=254)	Southern Europe + Ireland (N=2759)	United Kingdom (N=5230)	United States (N=5728)	Total (N=21509)
P-value (vs. UK+Ireland)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	REF	<0.0001

REF=reference group for comparison

**Supplementary Table 6a Median OS estimates by region for all trials**

Region	N	Median OS (95% CI)	Difference vs. UK (95% CI)	P-value (vs. UK)
Central Europe	4305	20.8 (19.4, 22.2)	5.86 (3.81, 7.91)	<.0001
Southern Europe	2698	20.5 (19.0, 22.0)	5.51 (3.39, 7.63)	<.0001
United States	5670	20.2 (18.9, 21.6)	5.26 (3.24, 7.29)	<.0001
Asia 1	215	18.1 (14.7, 21.4)	3.09 (-0.56, 6.73)	0.0968
Australia/New Zealand/Canada	1674	17.9 (16.3, 19.5)	2.92 (0.73, 5.1)	0.0088
Eastern Europe	940	17.5 (15.2, 19.8)	2.52 (-0.23, 5.28)	0.0725
Africa	100	16.6 (13.4, 19.7)	1.58 (-1.89, 5.06)	0.3725
South America	244	16.4 (13.6, 19.3)	1.47 (-1.76, 4.7)	0.3730
Northern Europe	80	15.7 (12.1, 19.4)	0.77 (-3.2, 4.74)	0.7050
United Kingdom+Ireland	5187	15.0 (13.5, 16.5)	REF	REF
Asia 2	67	13.3 (7.9, 18.7)	-1.68 (-7.25, 3.9)	0.5559

REF=reference group for comparison

**Supplementary Table 6b Median PFS estimates by region for all trials**

Region	N	Median PFS (95% CI)	Difference vs. UK (95% CI)	P-value (vs. UK)
Africa	114	9.1 (7.6, 10.5)	1.75 (0.15, 3.36)	0.0320
Central Europe	4305	8.7 (8.0, 9.4)	1.36 (0.38, 2.33)	0.0066
United States	5728	8.7 (8.0, 9.3)	1.34 (0.38, 2.3)	0.0062
Southern Europe	2759	8.5 (7.8, 9.2)	1.16 (0.18, 2.15)	0.0205
Northern Europe	124	8.4 (6.8, 10.0)	1.04 (-0.71, 2.79)	0.2445
Asia 1	227	8.2 (6.7, 9.7)	0.87 (-0.77, 2.52)	0.2972
Eastern Europe	1003	8.0 (7.0, 9.1)	0.7 (-0.54, 1.95)	0.2687
Australia/New Zealand/Canada	1677	7.7 (6.9, 8.4)	0.33 (-0.7, 1.36)	0.5260
South America	242	7.5 (6.2, 8.8)	0.19 (-1.29, 1.67)	0.8009
United Kingdom+Ireland	5230	7.3 (6.7, 8.0)	REF	REF
Asia 2	73	7.1 (5.0, 9.2)	-0.21 (-2.45, 2.02)	0.8513

REF=reference group for comparison

**Supplement Table 7 Subgroup OS and PFS estimates by region**

	Central Europe (N=4305)	Southern Europe (N=2759)	United States (N=5728)	Eastern Europe (N=1004)	ANZC (N=1681)	United Kingdom +Ireland (N=5230)
<b>Overall Survival</b>						
<b>Females</b>						
Median OS in month (95% CI)	19.0 (17.6, 20.5)	19.4 (17.6, 21.2)	20.2 (18.8, 21.6)	16.9 (13.6, 20.3)	18.1 (16.4, 19.8)	16.4 (14.9, 17.8)
Difference vs. UK+Ireland	2.69	3.04	3.88	0.56	1.72	REF
P-value (vs. UK+Ireland)	0.0113	0.0107	0.0002	0.7655	0.1323	REF
<b>Males</b>						
Median OS in month (95% CI)	19.0 (17.6, 20.5)	19.0 (17.3, 20.8)	20.2 (18.8, 21.6)	16.9 (13.5, 20.3)	18.1 (16.4, 19.8)	16.4 (14.9, 17.8)
Difference vs. UK+Ireland	2.69	2.67	3.88	0.55	1.72	REF
P-value (vs. UK+Ireland)	0.0120	0.0237	0.0002	0.7687	0.1357	REF
<b>Age&lt;=70</b>						
Median OS in month (95% CI)	19.0 (17.6, 20.5)	18.7 (17.1, 20.3)	20.2 (18.8, 21.6)	17.7 (14.0, 21.3)	17.9 (16.2, 19.6)	15.8 (14.3, 17.2)
Difference vs. UK+Ireland	3.25	2.92	4.45	1.89	2.11	REF
P-value (vs. UK+Ireland)	0.0019	0.0090	<.0001	0.3479	0.0619	REF
<b>Age&gt;70</b>						
Median OS in month (95% CI)	19.0 (17.6, 20.4)	19.1 (17.4, 20.8)	20.2 (18.9, 21.6)	17.7 (14.1, 21.3)	18.5 (16.7, 20.2)	15.8 (14.4, 17.2)
Difference vs. UK+Ireland	3.24	3.36	4.44	1.89	2.69	REF
P-value (vs. UK+Ireland)	0.0016	0.0030	<.0001	0.3396	0.0189	REF
<b>PS 0-1</b>						
Median OS in month (95% CI)	19.8 (18.1, 21.4)	20.2 (18.3, 22.1)	20.5 (19.0, 22.1)	16.0 (12.4, 19.6)	18.0 (16.1, 19.8)	15.2 (13.6, 16.8)
Difference vs. UK+Ireland	4.51	4.95	5.3	0.78	2.72	REF
P-value (vs. UK+Ireland)	0.0001	0.0001	<.0001	0.6949	0.0303	REF
<b>No Biologics</b>						
Median OS in month (95% CI)	19.0 (17.4, 20.6)	17.6 (15.9, 19.4)	18.0 (16.3, 19.7)	17.6 (13.4, 21.8)	16.7 (14.9, 18.6)	16.0 (14.5, 17.4)
Difference vs. UK+Ireland	3.06	1.68	2.04	1.62	0.79	REF
P-value (vs. UK+Ireland)	0.0057	0.1489	0.0746	0.4745	0.5161	REF
<b>Any Biologic</b>						

**Supplement Table 7 Subgroup OS and PFS estimates by region**

	Central Europe (N=4305)	Southern Europe (N=2759)	United States (N=5728)	Eastern Europe (N=1004)	ANZC (N=1681)	United Kingdom +Ireland (N=5230)
Median OS in month (95% CI)	19.3 (16.8, 21.8)	22.6 (18.9, 26.2)	22.6 (20.5, 24.8)	16.1 (11.4, 20.9)	20.6 (17.7, 23.6)	16.3 (13.4, 19.1)
Difference vs. UK+Ireland	3.05	6.28	6.36	-0.12	4.34	REF
P-value (vs. UK+Ireland)	0.1151	0.0076	0.0005	0.9647	0.0377	REF
<b>Progression-Free Survival</b>						
<b>Females</b>						
Median PFS in month (95% CI)	8.1 (7.4, 8.9)	8.0 (7.2, 8.9)	8.1 (7.3, 8.9)	7.2 (5.8, 8.5)	7.6 (6.8, 8.5)	7.3 (6.5, 8.0)
Difference vs. UK+Ireland	0.9	0.79	0.84	-0.08	0.4	REF
P-value (vs. UK+Ireland)	0.0999	0.1584	0.1276	0.9210	0.4974	REF
<b>Males</b>						
Median PFS in month (95% CI)	8.1 (7.4, 8.9)	8.1 (7.3, 8.9)	8.1 (7.3, 8.9)	7.2 (5.8, 8.5)	7.7 (6.9, 8.6)	7.3 (6.5, 8.0)
Difference vs. UK+Ireland	0.9	0.85	0.84	-0.08	0.48	REF
P-value (vs. UK+Ireland)	0.0998	0.1279	0.1274	0.9210	0.4142	REF
<b>Age&lt;=70</b>						
Median PFS in month (95% CI)	8.2 (7.4, 9.0)	8.0 (7.2, 8.8)	8.0 (7.3, 8.8)	7.2 (5.8, 8.5)	7.8 (6.9, 8.6)	7.2 (6.5, 7.9)
Difference vs. UK+Ireland	1	0.85	0.85	-0.02	0.58	REF
P-value (vs. UK+Ireland)	0.0635	0.1226	0.1148	0.9798	0.3133	REF
<b>Age&gt;70</b>						
Median PFS in month (95% CI)	8.2 (7.4, 8.9)	8.1 (7.3, 8.9)	8.0 (7.3, 8.8)	7.4 (6.0, 8.8)	8.0 (7.2, 8.9)	7.2 (6.5, 7.9)
Difference vs. UK+Ireland	1	0.9	0.85	0.21	0.86	REF
P-value (vs. UK+Ireland)	0.0573	0.1017	0.1073	0.7924	0.1350	REF
<b>PS 0-1</b>						
Median PFS in month (95% CI)	8.2 (7.4, 9.0)	8.4 (7.6, 9.3)	8.2 (7.4, 9.0)	7.0 (5.6, 8.4)	7.5 (6.6, 8.4)	7.1 (6.3, 7.9)
Difference vs. UK+Ireland	1.11	1.34	1.11	-0.11	0.43	REF
P-value (vs. UK+Ireland)	0.0529	0.0215	0.0525	0.8958	0.4840	REF
<b>No Biologics</b>						
Median PFS in month (95% CI)	7.4 (6.6, 8.2)	7.5 (6.7, 8.3)	6.7 (5.7, 7.6)	8.3 (6.5, 10.1)	6.7 (5.8, 7.7)	7.0 (6.2, 7.7)

**Supplement Table 7 Subgroup OS and PFS estimates by region**

	Central Europe (N=4305)	Southern Europe (N=2759)	United States (N=5728)	Eastern Europe (N=1004)	ANZC (N=1681)	United Kingdom +Ireland (N=5230)
Difference vs. UK+Ireland	0.41	0.54	-0.31	1.34	-0.24	REF
P-value (vs. UK+Ireland)	0.4701	0.3440	0.6123	0.1729	0.7009	REF
<b>Any Biologic</b>						
Median PFS in month (95% CI)	9.7 (8.7, 10.6)	9.4 (8.3, 10.5)	9.8 (8.9, 10.6)	6.0 (4.6, 7.3)	9.2 (8.1, 10.3)	7.8 (6.9, 8.7)
Difference vs. UK+Ireland	1.91	1.63	2.01	-1.82	1.43	REF
P-value (vs. UK+Ireland)	0.0044	0.0233	0.0015	0.0276	0.0449	REF

REF=reference group for comparison

**Supplementary Table 8a Adjusted and unadjusted OS by region and by time era**

	Unadjusted Survival			Adjusted Survival		
	Event/Total	Median (95% CI) <sup>KM</sup>	Survival Estimates (95% CI) <sup>KM</sup>	Event/Total	Median (95% CI) <sup>KM</sup>	Survival Estimates (95% CI) <sup>KM</sup>
<b>1997-2005</b>						
<b>Region</b>						
Australia/New Zealand/Canada	574/851	17.6 (17.0-18.6)	12 months: 69.8 (66.8-73.0%) 24 months: 30.6 (27.0-34.7%)	574/851	17.8 (17.1-18.9)	12 months: 69.8 (66.7-73.0%) 24 months: 31.1 (27.4-35.3%)
Central Europe	1702/2171	18.8 (18.1-19.7)	12 months: 70.6 (68.7-72.6%) 24 months: 37.4 (35.3-39.6%)	1680/2146	18.1 (17.3-18.8)	12 months: 68.9 (66.9-70.9%) 24 months: 35.3 (33.2-37.5%)
Southern Europe	812/1207	18.9 (17.9-20.2)	12 months: 70.3 (67.8-73.0%) 24 months: 38.3 (35.4-41.5%)	812/1205	18.2 (17.1-19.3)	12 months: 68.4 (65.7-71.2%) 24 months: 36.5 (33.6-39.7%)

**Supplementary Table 8a Adjusted and unadjusted OS by region and by time era**

	Unadjusted Survival			Adjusted Survival		
	Event/Total	Median (95% CI) <sup>KM</sup>	Survival Estimates (95% CI) <sup>KM</sup>	Event/Total	Median (95% CI) <sup>KM</sup>	Survival Estimates (95% CI) <sup>KM</sup>
United Kingdom	2000/2383	14.8 (14.3-15.4)	12 months: 60.7 (58.7-62.7%) 24 months: 24.6 (22.9-26.5%)	2000/2382	15.3 (14.8-16.1)	12 months: 62.4 (60.4-64.5%) 24 months: 26.1 (24.2-28.1%)
United States	2114/2853	18.1 (17.5-18.8)	12 months: 67.5 (65.8-69.2%) 24 months: 35.7 (33.8-37.7%)	1928/2660	18.1 (17.4-19.0)	12 months: 67.5 (65.7-69.3%) 24 months: 35.9 (33.9-38.1%)
<b>2005-2012</b>						
<b>Region</b>						
Australia/New Zealand/Canada	408/583	19.8 (18.0-21.5)	12 months: 71.2 (67.6-75.0%) 24 months: 38.7 (34.6-43.2%)	408/583	20.4 (18.7-22.1)	12 months: 72.0 (68.3-76.0%) 24 months: 40.5 (36.2-45.2%)
Central Europe	688/944	20.7 (19.3-22.2)	12 months: 72.7 (69.9-75.6%) 24 months: 42.7 (39.6-46.1%)	685/940	19.2 (17.5-20.9)	12 months: 70.0 (67.0-73.1%) 24 months: 40.0 (36.8-43.4%)
Eastern Europe	152/215	17.1 (14.2-18.8)	12 months: 65.7 (59.5-72.7%) 24 months: 29.1 (22.8-37.0%)	152/215	17.7 (15.5-21.6)	12 months: 66.9 (58.5-76.4%) 24 months: 33.9 (25.6-44.8%)
Southern Europe	360/636	26.3 (24.7-29.9)	12 months: 82.7 (79.8-85.7%) 24 months: 54.6 (50.7-58.9%)	360/636	21.6 (20.0-25.2)	12 months: 76.8 (72.8-81.1%) 24 months: 46.4 (41.7-51.6%)
United Kingdom	2271/2656	14.8 (14.2-15.4)	12 months: 60.0 (58.1-61.9%) 24 months: 27.9 (26.2-29.6%)	2271/2656	15.3 (14.7-16.0)	12 months: 61.5 (59.6-63.5%) 24 months: 29.4 (27.6-31.3%)

<sup>KM</sup>Kaplan-Meier method

**Supplementary Table 8b Adjusted and unadjusted PFS by region and by time era**

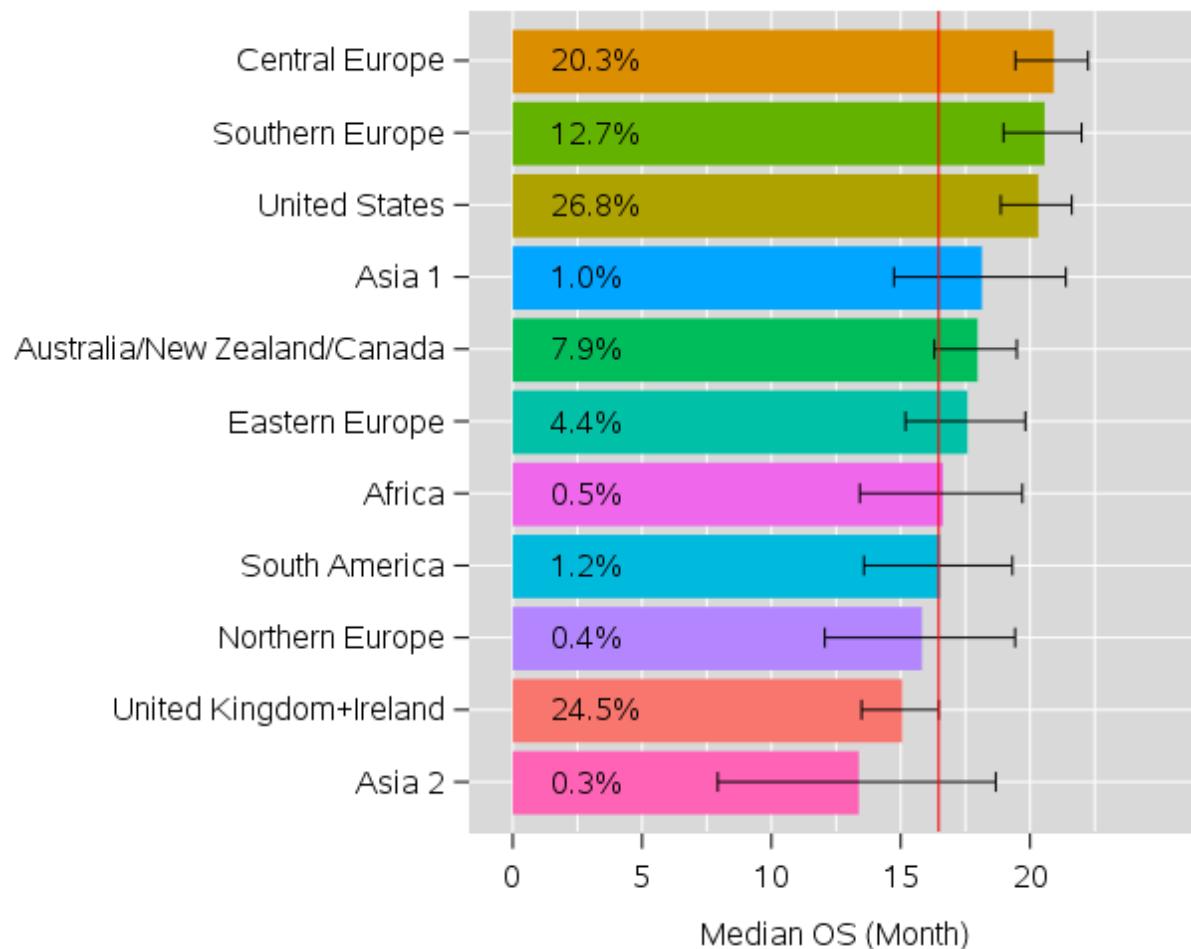
	Unadjusted Survival			Adjusted Survival		
	Event/Total	Median (95% CI) <sup>KM</sup>	Survival Estimates (95% CI) <sup>KM</sup>	Event/Total	Median (95% CI) <sup>KM</sup>	Survival Estimates (95% CI) <sup>KM</sup>
<b>1997-2005</b>						
<b>Region</b>						
Australia/New Zealand/Canada	765/850	7.6 (7.2-7.9)	6 months: 63.3 (60.2-66.7%) 12 months: 23.7 (21.0-26.8%)	765/850	7.6 (7.2-7.9)	6 months: 63.0 (59.7-66.4%) 12 months: 23.9 (21.1-27.0%)
Central Europe	2027/2170	7.9 (7.6-8.1)	6 months: 64.4 (62.4-66.5%) 12 months: 25.4 (23.6-27.3%)	2005/2146	7.6 (7.2-7.9)	6 months: 62.7 (60.6-64.8%) 12 months: 23.9 (22.2-25.8%)
Southern Europe	1084/1207	8.4 (8.0-8.9)	6 months: 67.6 (65.0-70.3%) 12 months: 28.5 (26.0-31.2%)	1083/1205	8.2 (7.8-8.6)	6 months: 66.3 (63.6-69.1%) 12 months: 26.7 (24.3-29.4%)
United Kingdom	2273/2361	7.4 (6.9-7.7)	6 months: 59.7 (57.8-61.8%) 12 months: 16.1 (14.6-17.6%)	2273/2360	7.5 (7.1-7.9)	6 months: 60.7 (58.7-62.7%) 12 months: 16.8 (15.3-18.5%)
United States	2527/2839	7.6 (7.4-8.0)	6 months: 60.6 (58.8-62.5%) 12 months: 27.5 (25.8-29.2%)	2337/2646	7.6 (7.4-8.0)	6 months: 60.8 (59.0-62.8%) 12 months: 27.5 (25.8-29.4%)
<b>2005-2012</b>						
<b>Region</b>						
Australia/New Zealand/Canada	538/583	8.2 (7.5-8.6)	6 months: 64.4 (60.6-68.4%) 12 months: 27.3 (23.8-31.2%)	538/583	8.3 (7.5-8.7)	6 months: 65.3 (61.4-69.4%) 12 months: 27.9 (24.3-32.0%)
Central Europe	828/943	8.9 (8.3-9.6)	6 months: 71.3 (68.4-74.3%) 12 months: 36.3 (33.2-39.6%)	825/939	8.7 (8.1-9.3)	6 months: 70.0 (67.0-73.1%) 12 months: 34.6 (31.5-38.0%)

**Supplementary Table 8b Adjusted and unadjusted PFS by region and by time era**

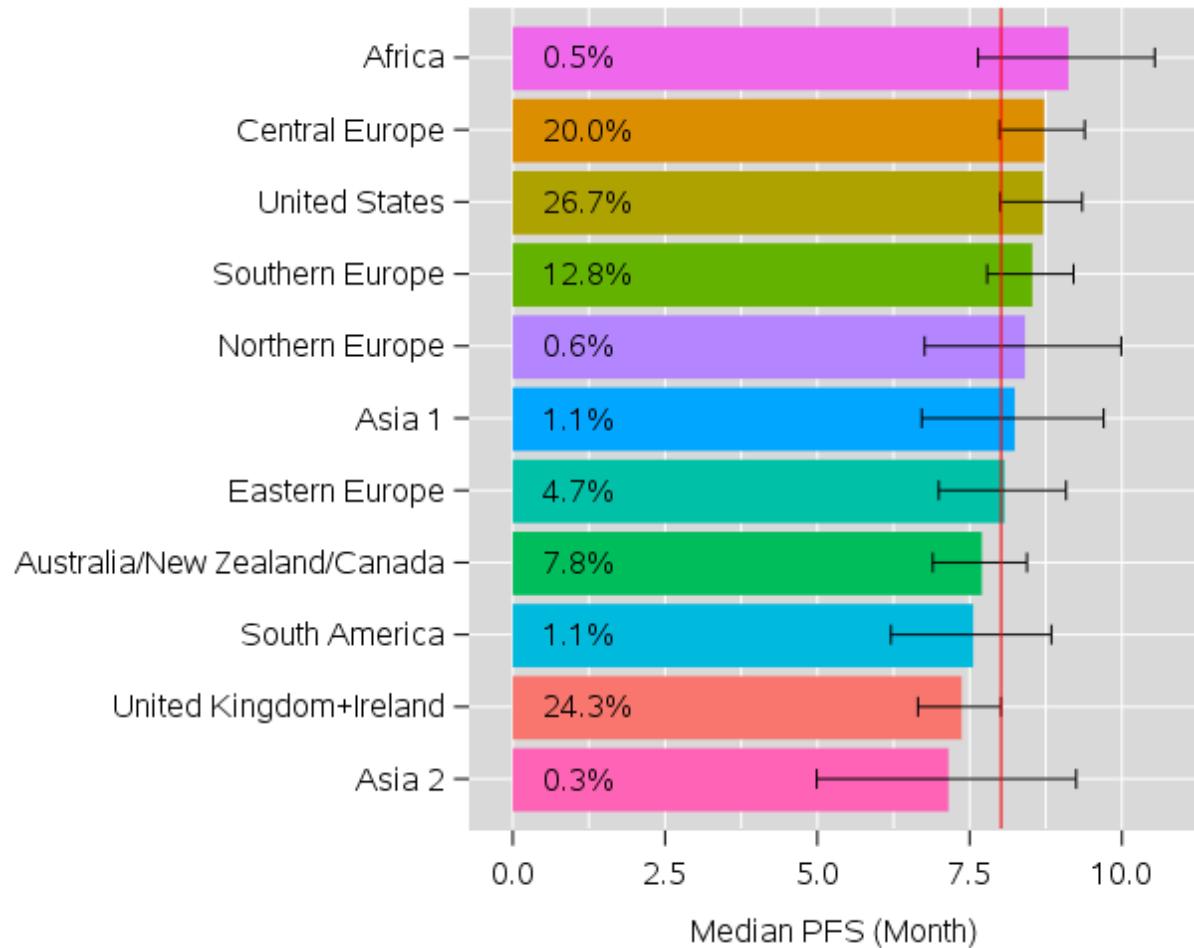
	Unadjusted Survival			Adjusted Survival		
	Event/Total	Median (95% CI) <sup>KM</sup>	Survival Estimates (95% CI) <sup>KM</sup>	Event/Total	Median (95% CI) <sup>KM</sup>	Survival Estimates (95% CI) <sup>KM</sup>
Eastern Europe	130/215	7.1 (5.7-7.4)	6 months: 51.6 (44.8-59.4%) 12 months: 22.3 (16.0-31.1%)	130/215	7.2 (5.6-7.7)	6 months: 51.7 (42.2-63.2%) 12 months: 22.3 (14.9-33.4%)
Southern Europe	527/634	10.1 (9.6-10.8)	6 months: 78.2 (75.0-81.5%) 12 months: 40.0 (36.2-44.1%)	527/634	9.3 (8.6-9.7)	6 months: 70.2 (65.9-74.8%) 12 months: 33.6 (29.5-38.2%)
United Kingdom	2518/2600	6.3 (6.2-6.5)	6 months: 55.1 (53.2-57.0%) 12 months: 15.0 (13.6-16.4%)	2518/2600	6.3 (6.2-6.6)	6 months: 55.9 (54.0-58.0%) 12 months: 15.4 (14.0-16.9%)

<sup>KM</sup>Kaplan-Meier method;

## Supplementary Materials



Suppl. Figure 1 Median OS estimates by region for all trials



**Suppl. Figure 2 Median PFS estimates by region for all trials**