S4 Table. Most frequent grade ≥ 3 treatment-emergent adverse events for phase II and III studies of anti-angiogenic agents

Author	Trial design/ Setting	No. of patients[a)]	Treatment	Most frequent grade ≥ 3 treatment-emergent adverse events (most to least frequent, left to right)			
VEGF ligand- and VEGFR-2-targeted therapy							
Shah et al. [1]	Phase II, single-arm/ 1st-line	44	Bevacizumab+docetaxel/cisplatin/5-FU	Leukopenia (64%)	Neutropenia (50%)	Fatigue (25%)	Thrombocytopenia (25%)
Shah et al. [2]	Phase II, single-arm/ 1st-line	47	Bevacizumab+cisplatin/irinotecan	Hypertension (28%)	Neutropenia (28%)	Thromboembolism (25%)	Lymphopenia (23%)
Enzinger et al. [3]	Phase II, single-arm/ 1st- and 2nd-line	35	Bevacizumab+docetaxel/cisplatin/irinotecan	Peripheral neuropathy (10%)	Bleeding (10%)	Thromboembolic event (7%)	Hypertriglyceridemia, absolute neutrophil count (7%)
El-Rayes et al. [4]	Phase II, single-arm/ 1st-line	38	Bevacizumab+docetaxel/oxaliplatin	Neutropenia (34%)	Dehydration (11%)	Nausea (11%)	GI perforation, chronic neuropathy, diarrhea (8%)
Uronis et al. [5]	Phase II, single-arm/ 1st-line	37	Bevacizumab+capecitabine/oxaliplatin	Venous thrombosis (11%)	Hypertension (5%)	Hemorrhage (3%)	Dural-cutaneous fistula, perforation/fistula (3%)
Ohtsu et al. (AVAGAST) [6]	Phase III, randomized, double-blind, placebo-controlled/ 1st-line	774	Bevacizumab+fluoropyrimidine/cisplatin vs. placebo+fluoropyrimidine/cisplatin	Neutropenia (35% vs. 37%)	Anemia (10% vs. 14%)	Decreased appetite (8% vs. 11%)	Diarrhea (8% vs. 4%)

Shen et al. (AVATAR) [7]	Phase III, randomized, double-blind, placebo-controlled/ 1st-line	202	Bevacizumab+capecitabine/cisplatin vs. placebo+capecitabine/cisplatin	Neutropenia (18% vs. 14%)	Hemorrhage (12% vs. 4%)	Vomiting (10% vs. 22%)	Leukopenia (9% vs. 4%)
Okines et al. (ST03) [8]	Phase II/III, randomized, double-blind, placebo-controlled/ 1st-line	1,063	Bevacizumab+epirubicin/capecitabine/cisplatin vs. placebo+epirubicin/capecitabine/cisplatin	Neutropenia (30% vs. 24%)	Lethargy (12% vs. 10%)	Hand-foot syndrome (9% vs. 7%)	Diarrhea (7% vs. 6%), nausea (7% vs. 6%)
Yoon et al. [9]	Phase II, randomized, double-blind, placebo-controlled/ 1st-line	168	Ramucirumab+FOLFOX vs. placebo+FOLFOX	Neutropenia (27% vs. 36%)	Fatigue (18% vs. 15%)	Neuropathy (9% vs. 11%)	NR
Fuchs et al. (REGARD) [10]	Phase III, randomized, double-blind, placebo-controlled/ 2nd-line	355	Ramucirumab vs. placebo	Hypertension (8% vs. 3%)	Abdominal pain (6% vs. 3%)	Anemia (6% vs. 8%)	Fatigue (6% vs. 10%)
Wilke et al. (RAINBOW) [11]	Phase III, randomized, double-	665	Ramucirumab+paclitaxel vs. placebo+paclitaxel	Neutropenia (41% vs. 19%)	Leukopenia (17% vs. 7%)	Hypertension (14% vs. 2%)	Fatigue (12% vs. 5%)

	blind, placebo-controlled/ 2nd-line						
Tyrosine kinase inhibitor therapy							
Li et al. [12]	Phase II, randomized, double-blind, placebo-controlled/ 3rd-line	144	Apatinib QD vs. apatinib BID vs. placebo	Hand-foot syndrome (4% vs. 13% vs. 2%)	Hypertension (9% vs. 11% vs. 0)	Thrombocytopenia (4% vs. 9% vs. 4%)	Anemia (2% vs. 7% vs. 6%)
Qin [13]	Phase III, randomized, double-blind, placebo-controlled/ 3rd-line	267	Apatinib vs. placebo	Hand-foot syndrome (8.5% vs. 0%)	Elevated transaminase (8.0% vs. 4.4%)	Bleeding (3.4% vs. 7.7%)	Hyperbilirubinemia (7.4% vs. 6.6%)
Koizumi et al. [14]	Phase II, randomized, double-blind, placebo-controlled/ 1st-line	93	Orantinib+S-1/cisplatin vs. placebo+S-1/cisplatin	Hemoglobin (49% vs. 26%)	Neutropenia (31% vs. 35%)	Platelets (24% vs. 7%)	Anorexia (18% vs. 9%), lymphocytes (18% vs. 13%)
Lee et al. [15]	Phase II, single-arm/ 1st-line	66	Pazopanib+capecitabine/oxaliplatin	Neutropenia (15%)	Anemia (11%)	Thrombocytopenia (11%)	Anorexia (8%)
Thuss-Patience et	Phase II, randomized	87	Pazopanib+5-FU/ leucovorin/oxaliplatin vs. placebo+5-	NR	NR	NR	NR

al. [16]	, double-blind, placebo-controlled/ 1st-line		FU/leucovorin/oxaliplatin				
Janjigian et al. [17]	Phase II, single-arm/ 1st-line	36	Regorafenib+FOLFOX	Neutropenia (36%)	NR	NR	NR
Pavlakis et al. (INTEGRATE) [18]	Phase II, randomized, double-blind, placebo-controlled/ 2nd- or 3rd-line	152	Regorafenib vs. placebo	Hypertension (10% vs. 2%)	AST level increased (9% vs. 0%)	ɣ-glutamyltransferase level increased (6% vs. 8%)	ALT level increased (8% vs. 6%)
Sun et al. (ECOG 5203) [19]	Phase II, single-arm/ 1st-line	44	Sorafenib+docetaxel/cisplatin	Neutropenia (64%)	Leukopenia (41%)	Dehydration (20%)	Hand-foot syndrome, fatigue, nausea (16%)
Martin-Richard et al. (GEMCAD) [20]	Phase II, single-arm/ 2nd-line	40	Sorafenib+oxaliplatin	Asthenia (18%)	Neutropenia (10%)	Thrombocytopenia (8%)	Abdominal pain, diarrhea, neurotoxicity, toxic syndrome (5%)
Kang et al. (STARGATE) [21]	Phase II, randomized, open-label/ 1st-line	195	Sorafenib+capecitabine/cisplatin vs. placebo+capecitabine/cisplatin	Neutropenia (21% vs. 37%)	Palmar-plantar erythrodysesthesia syndrome (7% vs. 1%)	Febrile neutropenia (2% vs. 6%)	NR
Janjigian et al. [22]	Phase II, single-arm/2nd-	34	Sorafenib	Hand-foot rash (24%)	Fatigue (6%)	GI-espohpagus fistula (3%) Hypertension	Dehdration (3%), acne rash (3%),

	line					(3%)	vomiting (3%)
Bang et al. [23]	Phase II, single-arm/ 2nd-line	78	Sunitinib	Thrombocytopenia (35%)	Neutropenia (29%)	Anemia (17%)	Leukopenia (12%)
Moehler et al. [24]	Phase II, single-arm/ 2nd-line	52	Sunitinib	Neutropenia (13%)	Leukopenia (10%)	Fatigue (6%)	Anemia, thrombocytopenia, vomiting (4%)
Yi et al. [25]	Phase II, randomized, open-label/ 2nd-line	107	Sunitinib+docetaxel vs. placebo+docetaxel	Neutropenia (32% vs. 20%)	Febrile neutropenia (27% vs. 16%)	Leukopenia (21% vs. 14%)	Anemia (11% vs. 10%), diarrhea (11% vs. 2%)
Wu et al. [26]	Phase II, single-arm/ 2nd-line	25	Sunitinib	Fatigue (24%)	Anaemia (20%)	Leukopenia (16%)	Thrombocytopenia (16%)
Alsina et al. [27]	Phase II, single-arm/ 1st-line	48	Telatinib+capecitabine/cisplatin	NR	NR	NR	NR

5-FU, 5-fluorouracil; BID, twice daily; FOLFOX, folinic acid, 5-fluorouracil, and oxaliplatin; NR, not reported; QD, once daily. [a)]N value reported represents the total number of patients enrolled in the study.

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