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**Additional File 2. Frequency categories of adverse reactions reported in the pooled analysis considered for the safety pooling.**

Adverse reactions are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

<b>Infections and infestations</b>	
Very common	Infections a,
<b>Blood and lymphatic system disorders</b>	
Very common	Anaemia
Common	Thrombocytopenia, neutropenia, leukopenia, lymphopenia

Uncommon	Pancytopenia
Rare	Pure red cell aplasia
<b>Immune system disorders</b>	
Uncommon	Hypersensitivity
<b>Metabolism and nutrition disorders</b>	
Very common	Decreased appetite, hyperglycaemia, hypercholesterolaemia
Common	Hypertriglyceridaemia, hypophosphataemia, diabetes mellitus, hyperlipidaemia, hypokalaemia, dehydration, hypocalcaemia
<b>Psychiatric disorders</b>	
Common	Insomnia
<b>Nervous system disorders</b>	
Very common	Dysgeusia, headache
Uncommon	Ageusia
<b>Eye disorders</b>	
Common	Eyelid oedema

Uncommon	Conjunctivitis
<b>Cardiac disorders</b>	
Uncommon	Congestive cardiac failure
<b>Vascular disorders</b>	
Common	Haemorrhage b, hypertension
Uncommon	Flushing, deep vein thrombosis
<b>Respiratory, thoracic and mediastinal disorders</b>	
Very common	Pneumonitis c, epistaxis
Common	Cough, dyspnoea
Uncommon	Haemoptysis, pulmonary embolism
Rare	Acute respiratory distress syndrome
<b>Gastrointestinal disorders</b>	
Very common	Stomatitis d, diarrhoea, nausea
Common	Vomiting, dry mouth, abdominal pain, mucosal inflammation, oral pain, dyspepsia, dysphagia

<b>Hepatobiliary disorders</b>	
Common	Aspartate aminotransferase increased, alanine aminotransferase increased
<b>Skin and subcutaneous tissue disorders</b>	
Very common	Rash, pruritus
Common	Dry skin, nail disorders, mild alopecia, acne, erythema, onychoclasia, palmar-plantar erythrodysesthesia syndrome, skin exfoliation, skin lesion
Rare	Angioedema
<b>Musculoskeletal and connective tissue disorders</b>	
Common	Arthralgia
<b>Renal and urinary disorders</b>	
Common	Proteinuria, blood creatinine increased, renal failure
Uncommon	Increased daytime urination, acute renal failure
<b>Reproductive system and breast disorders</b>	

Common	Menstruation irregular e
Uncommon	Amenorrhoea e
<b>General disorders and administration site conditions</b>	
Very common	Fatigue, asthenia, peripheral oedema
Common	Pyrexia
Uncommon	Non-cardiac chest pain
Rare	Impaired wound healing
<b>Investigations</b>	
Very common	Weight decreased

a Includes all reactions within the 'infections and infestations' system organ class including (common) pneumonia and (uncommon) herpes zoster, sepsis, and isolated cases of opportunistic infections [e.g. aspergillosis, candidiasis, pneumocystis jirovecii (carinii) pneumonia (PJP, PCP) and hepatitis B (see also section 4.4)]

b Includes different bleeding events not listed individually

c Includes (common) pneumonitis, interstitial lung disease, lung infiltration and (rare) pulmonary alveolar haemorrhage, pulmonary toxicity, and alveolitis

d Includes (very common) stomatitis, (common) aphthous stomatitis, mouth and tongue ulceration and (uncommon) glossodynia, glossitis

e Frequency based upon number of women from 10 to 55 years of age in pooled data

