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ORIGINAL RESEARCH

Aneurysm and Artery Dissection Following the Use of Vascular Endothelial Growth Factor Inhibitor: A Real-World Analysis Using a Spontaneous Reporting System

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BACKGROUND: Pharmacological inhibition of angiogenesis via the vascular endothelial growth factor pathway is an important therapeutic target that prevents tumor growth and the formation of metastases. Although vascular endothelial growth factor inhibitor (VPI) is well understood as a well-defined safety profile, few real-world studies are comparing the incidence, clinical features, and prognosis of the aneurysm and artery dissection.

METHODS AND RESULTS: To evaluate and compare the links between different VPIs and aneurysm and artery dissection, we identified 634 reports with VPIs in the US Food and Drug Administration Adverse Event Reporting System database ranging between January 2004 to March 2020. We used the reporting odds ratio for the association between the use of VPIs and aneurysm and artery dissection. The reporting odds ratio (3.68, 95%, 2.18−6.23) shows that ramucirumab has a stronger correlation than other VPIs. The results show a significant difference in onset time (P<0.001). The median time to aneurysm and artery dissection was 79.5 (interquartile interval, 19.0–273.5) days after VPI administration. The results also show that VPI-associated aneurysm and artery dissection was reported more often in men (n=336, 59.68% versus n=227, 40.32%), and there were more cases in patients aged between 45 to 74 years than those <45 years (n=312, 68.12% versus n=18, 3.93%); patients aged ≥75 years accounted for 27.95% (n=128). Finally, the suspected drugs generally led to 19.98% deaths and 29.81% hospitalizations.

CONCLUSIONS: We identified signals for aneurysm and artery dissection following various VPIs in real-world practice via the Food and Drug Administration Adverse Event Reporting System, which represents the first step for continued pharmacovigilance investigation.

Key Words: cancer ■ disproportionality analysis ■ patient safety ■ pharmacovigilance ■ voluntary incident reporting

Vascular endothelial growth factor (VEGF) plays a significant role in physiological and pathological angiogenesis. The interaction between VEGF and VEGF receptors expressed on endothelial cells leads to the increase of normal blood vessel proliferation, migration, degeneration, and permeability. Pharmacological inhibition of angiogenesis via the VEGF pathway is a vital therapeutic target that prevents tumor growth and the formation of metastases.[1,2] Anti-VEGF therapies that are approved for use in various types of cancer include small molecule tyrosine kinase inhibitors targeting multiple molecular pathways, monoclonal

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CLINICAL PERSPECTIVE

What Is New?

- Although vascular endothelial growth factor inhibitor has been widely understood as a clear safety profile, few real-world studies compare the incidence, clinical features, and prognosis of aneurysm and artery dissection.

What Are the Clinical Implications?

- Population characteristics show that VPI-associated aneurysm and artery dissection was reported more often in men than women and in patients aged between 45 to 74 years than those <45 years; patients aged ≥75 years accounted for 27.95%.
- The results in vascular endothelial growth factor inhibitor use indicate that the median time to onset of aneurysm or artery dissection was 79.5 days, the suspected drugs generally led to 19.98% deaths and 29.81% hospitalizations, and ramucirumab had a stronger correlation than other vascular endothelial growth factor inhibitors.

Nonstandard Abbreviations and Acronyms

AAD	aneurysm and artery dissection
FAERS	Food and Drug Administration Adverse Event Reporting System
FDA	Food and Drug Administration
ROR	reporting odds ratio
VPI(s)	vascular endothelial growth factor inhibitor(s)

antibodies, fusion proteins, and VEGF itself. Currently, 24 vascular endothelial growth factor pathway inhibitors (VPIs) are commercially available (Table S1). Hypertension and proteinuria are the most common adverse events of drugs that target the VEGF pathway.[3] However, more serious adverse events, such as aneurysms and aortic dysfunction have been reported in the use of anti-VEGF drugs.[4–7] Since 2008, there have been reports of aneurysm and artery dissection (AAD) associated with VPI treatments.[8] However, most evidence comes from the Pharmaceutical and Medical Devices Agency rather than clinical cohorts or case-control studies,[8–10] which is insufficient to understand relatively rare adverse events. At present, there is no pharmacovigilance study to explore the relationship between VPI-mediated AAD, and the knowledge of vascular safety profile following various VPIs remains poorly represented in clinical practice. Therefore, the purpose of this study is to evaluate and compare the associations between various VPIs and AAD by investigating the Food and Drug Administration Adverse Event Reporting System (FAERS), a publicly accessible database of patient safety events. Meanwhile, we investigated death and hospitalization proportions of AAD and the time to onset of AAD for VPI regimens.

METHODS

Data Source

This study was approved by an institutional review committee, and patient's informed consent was not necessary. The data that support the findings of this study are available from the corresponding author upon reasonable request. This retrospective pharmacovigilance study was conducted using data obtained from the FAERS database from January 2004 to March 2020. The FAERS database, a voluntary reporting system that is publicly accessible contains information on adverse drug events and medication error reports submitted by healthcare professionals, consumers, and manufacturers in the United States and other regions. FAERS data included 8 data sets that cover the information necessary for pharmacovigilance research.[11,12] Following the Food and Drug Administration (FDA) recommendations, we identified 634 reports by choosing the latest date FDA received case (FDA_DT) if the CASEIDs were the same and the higher PRIMARYID if the CASEIDs and FDA_DTs were the same.

Adverse Events and Drug Identification

We used MedDRA (Version 23.0) Preferred Term "aneurysms and artery dissections" (code: 10002363) to investigate adverse events in the REAC files (See Table S2 for the list of preferred terms of PTs). In the data mining process, IBM Micromedex (IBM Corp., Armonk, NY, USA) was used as a dictionary to select the generic and brand names of VPIs.

Data Mining

The disproportionality analysis compares the proportion of selected specific adverse drug reactions reported by a single or combination of VPI, with the proportion of the same adverse drug reactions reported in the complete database. Based on the disproportionality analysis, the reporting odds ratio (ROR) was used to identify the association between a drug and an adverse event. The equation for the algorithm is:

$$ROR = (a/b)/(c/d)$$

a: Number of reports containing both the suspect drug and the suspect adverse drug reaction; b: Number of

reports containing the suspect adverse drug reaction with other medications (except the drug of interest); c: Number of reports containing the suspect drug with other adverse drug reactions (except the event of interest); d: Number of reports containing other medications and other adverse drug reactions.

The corresponding 95% CIs were applied for the association between the use of VPIs and AAD. A value of ROR-1.96SE>1, N>2 (N: the number of co-occurrences, that "co-occurrences" refers to reports containing both the suspect drug and the suspect adverse drug reaction.) was considered as signal strength.[13–15] This rule for signal detection measures associations between drugs and adverse events. We evaluated the time to onset of AADs by defining the interval between the onset date of adverse events and the start date of VPI therapy. We also analyzed reports of death and hospitalization attributable to adverse events and calculated the proportions of death and hospitalization with the total number of AADs induced by VPI as the denominator.

Statistical Analysis

Descriptive analysis was used to summarize the clinical features of patients with AAD. The onset time of VPI-associated AAD between different VPIs was compared using the Kruskal–Wallis test and Dunn multiple comparison test. Death and hospitalization proportions of AAD were compared between different VPIs using Pearson Chi-square test or Fisher exact test. Statistical significance was set to $P<0.05$ with a 95% CI. All statistical analyses were performed using GraphPad Prism 8 (GraphPad Software Inc., San Diego, CA, USA).

RESULTS

General Characteristics

Among the 634 reports of VPI-associated AAD, 497 (78.39%) were submitted by healthcare professionals, 115 (18.14%) were submitted by consumers, leaving 22 (3.47%) cases with unspecified reporters.

The clinical features of these patients are shown in Table 1, Table 2, and Table S3. From 2004 to 2020, the number of reported cases of VPI-associated AAD gradually increased, reaching a peak of 92 cases (14.51%) in 2018. The data were collected from 6 regions and 43 countries. where 225 (35.50%) cases were from Asia, 223 (35.17%), and 146 (23.04%) from North America and Europe, respectively. Per country, 203 (32.02%) cases were reported from Japan (Asia), followed by 201 (31.7%) from the United States (North America) and 28 (4.42%) from France (Europe). Per type of VPI, the highest number of AAD reports were from bevacizumab 223 (35.57%), followed by ranibizumab 104 (16.59%) and sunitinib 96 (15.31%). VPIs were suitable for various tumor types, and the most common cases in this study were patients with renal cancer (n=115, 18.86%). Excluding the cases of unspecified age, the mean age of patients was 67.43 years. There exhibited more cases aged 45 to 74 than <45 years (n=312, 68.12% versus n=18, 3.93%). Patients aged ≥75 years accounted for 27.95% (n=128) of reported cases. Excluding the

Table 1. Characteristics of Cases with VPI-Associated Aneurysm and Artery Dissection

Characteristics	Reports, n (%)
Reporter	
Consumer	115 (18.14)
Health-professional	497 (78.39)
Unspecified	22 (3.47)
Age groups (y)	
<18	1 (0.16)
18–44	17 (2.68)
45–64	145 (22.87)
65–74	167 (26.34)
75–84	103 (16.25)
>85	25 (3.94)
Unknown or missing	176 (27.76)
Sex	
Women	227 (35.8)
Men	336 (53)
Unknown or missing	71 (11.2)

VPI indicates vascular endothelial growth factor inhibitor(s).

Table 2. Number of VPI-Associated Events and VPI-Associated Other Events

VEGFI as suspected drugs	VPI-associated with adverse events	VPI-associated with other adverse events
Sorafenib	38	16 724
Ponatinib	8	2443
Aflibercept	33	16 899
Pegaptanib	1	414
Nintedanib	25	7308
Axitinib	14	6945
Bevacizumab	223	45 645
Ramucirumab	14	2353
Ranibizumab	104	19 048
Brolucizumab	2	499
Sunitinib	99	31 748
Regorafenib	8	6294
Vandetanib	2	788
Pazopanib	20	20 199
Lenvatinib	31	6392
Cabozantinib	12	12 226

ADR indicates aneurysm and artery dissection events; VEGFI, vascular endothelial growth factor inhibitor(s); and VPI, vascular endothelial growth factor inhibitor(s).

unspecified data, men were reported more than women (n=336, 59.68% versus n=227, 40.32%).

Disproportionality Analysis

The signal strength of 16 VPI drugs with AAD was calculated by the RORs algorithm (Table 3). Only sorafenib, sunitinib, lenvatinib, ponatinib, nintedanib, bevacizumab, ramucirumab, and ranibizumab showed signals, and the correlation between adverse reactions and reported drugs was generally low.

Time to Onset of VPI-Associated Aneurysm and Artery Dissection

The median time to onset of VPI-associated AAD was 79.5 days (interquartile interval, 19.0–273.5). We classified the onsets within 120 days as a quick onset. It was noteworthy that AAD could quickly onset within 120 days after the first dose. The quick onset of all VPI-associated AAD cases have occurred in sorafenib (13.59%), ponatinib (1.09%), aflibercept (3.80%), nintedanib (3.80%), axitinib (1.09%), bevacizumab (36.41%), ramucirumab (1.63%), ranibizumab (7.61%), brolucizumab (0.54%), sunitinib (11.41%), regorafenib (3.26%), vandetanib (0.54%), pazopanib (2.72%), lenvatinib (10.87%), and cabozantinib (1.63%). We found a significant difference between the various VPI treatments (Kruskal–Wallis test, $P<0.001$), with a minimum median time of 13.5 days (interquartile interval, 3.0–59.0) for regorafenib and a maximum of 494.5 days (interquartile interval, 60.3–1000.0) for ponatinib.

Table 3. Aneurysm and Artery Dissection Signals Based on the Reporting Odds Ratio Algorithms

Drugs	No.	ROR (95% 2-sided CI)
Sorafenib	38	1.41 (1.02–1.93)*
Axitinib	14	1.25 (0.74–2.11)
Apatinib	0	…
Sunitinib	99	1.93 (1.59–2.36)*
Regorafenib	8	0.79 (0.39–1.57)
Vandetanib	2	1.57 (0.39–6.29)
Pazopanib	20	0.61 (0.39–0.95)
Lenvatinib	31	3 (2.11–4.28)*
Cabozantinib	12	0.61 (0.34–1.07)
Ponatinib	8	2.03 (1.01–4.06)*
Aflibercept	33	1.21 (0.86–1.70)
Fruquintinib	0	…
Pegaptanib	1	1.49 (0.21–10.64)
Tivozanib	0	…
Brivanib	0	…
Conbercept	0	…
Linifanib	0	…
Nintedanib	25	2.12 (1.43–3.14)*
Motesanib	0	…
Cediranib	0	…
Bevacizumab	223	3.05 (2.67–3.48)*
Ramucirumab	14	3.68 (2.18–6.23)*
Ranibizumab	104	3.39 (2.80–4.11)*
Brolucizumab	2	2.48 (0.62–9.94)

ROR indicates reporting odds ratio.
*The results were considered signal strength.

Death and Hospitalization Proportions Because of VPI-Associated AAD

The prognoses of VPI-associated AAD were evaluated by death and hospitalization proportions from adverse vascular events after various VPI treatments (Figure). VPI-associated AAD generally led to outcomes with 19.98% (n=185) deaths and 29.81% (n=276) hospitalizations. No significant difference in death and hospitalization proportions across different VPI regimens was observed (Pearson Chi-squared test for overall comparison, $P>0.05$).

DISCUSSION

To the best of our knowledge, this study is the first and largest collection of links, timing, and prognosis for AAD after using various VPIs. Moreover, data based on the FAERS reflect real-world practice. Not all VPI-associated drugs can produce signals. The highest signal reported for AAD was ramucirumab (ROR, 3.68; 95% CI, 2.18–6.23), followed by ranibizumab (ROR, 3.39; 95% CI, 2.8–4.11) and bevacizumab (ROR, 3.05; 95% CI, 2.67–3.48). Bevacizumab was the first VPI approved by the FDA in 2004. Unfortunately, 4 years later, Aragon-Ching (2008) argued that it be a drug potentially related to aortic dissection.[8] The case reports of AAD caused by the use of VPIs[5,6,8–10,16–22] has limited sample size, relatively low incidence, and many confounding factors, as a result, there is not adequate certainty to draw a clear conclusion on the safety of the drug. Besides, it is also a challenge to evaluate and characterize it through persuasive randomized controlled trials.

Based on the FAERS system, reports of VPI-associated AAD events were increasing annually. Among the results, 18.14% of the reports were provided by consumers. This phenomenon indicated that VPI-associated AAD is being gradually recognized. Our results also indicate that VPI-associated AAD based on the FAERS were closely associated with middle-aged and elderly patients as well as male patients. Although there have been reports that VPI therapy can cause severe vascular damage, its exact role in the initiation of AAD remains unclear.[6]

In this pharmacovigilance study, not all VPIs were associated with AAD. However, ramucirumab presented

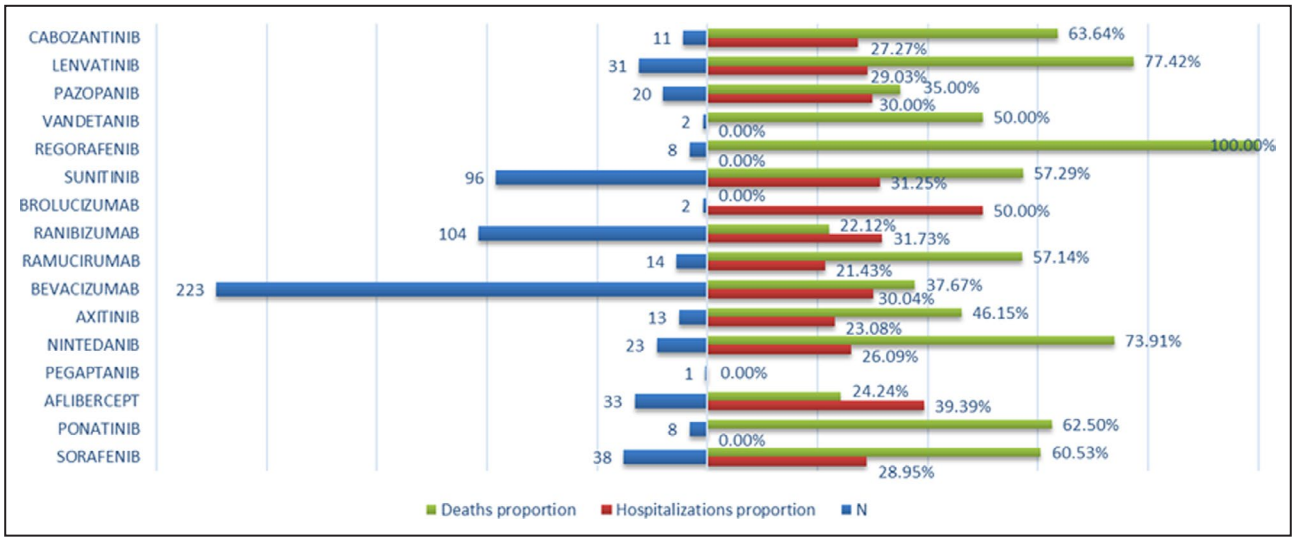

Figure 1. Two-way butterfly diagram of the death and hospitalization proportions of the aneurysm and artery dissection.

the strongest association among all VPIs. In contrast, bevacizumab showed a relatively weak association. In contrast, the AAD caused by bevacizumab has received widespread attention in clinical practice.[5,7,8,10,23] Of course, the confounding of hypertension occupied a large part. Regrettably, clinical studies still lack a direct comparison of the effects on the vasculature between different VPIs. Another major finding was that the median time for vascular effects after VPI regimens is 79.5 days (interquartile interval, 19.0–273.5), and the AAD could quickly onset within 120 days after the first dose. Therefore, once VPI is initiated, it is required to monitor vascular function at least for those sensitive patients. Diversity in the onset time between VPI regimens suggests that individualized intensive monitoring can be performed after VPI administration. In particular, it is recommended that observing vascular function immediately after applying regorafenib and regularly assessing the need for long-term VPI use to avoid possible harm.

The proportion of deaths and hospitalizations was investigated to further clarify the severity of VPI-associated AAD. The results show that AAD generally led to 29.81% (n=276) hospitalizations and 19.98% (n=185) deaths. Regorafenib exhibited the highest hospitalizations at 53.33% (n=8), but the number of deaths related to AAD was close to zero. Notably, the number of reports of regorafenib related to AAD was not as high as other VPIs in this study. Ranibizumab showed an obvious signal, the hospitalizations were 17.69% (n=23), and the deaths were 25.38% (n=33). These data may indicate that the users of ranibizumab required more intensive care after the onset of AAD. These findings can be applied to the clinical decision on the best VPI treatment plan. Considering the patient's age, sex, and vascular function to identify high-risk patients with AAD. Although this study has the advantages of investigating real-world research and data mining technology, it must be addressed and understood that drug signal analysis based on spontaneous adverse event reports also has disadvantages. This study has certain limitations. First, there are some restrictions on using the FAERS database. The voluntary nature of reporting may not always guarantee the accuracy and completeness of raw data, which could cause reporting bias and noise. In addition, there is no systematic collection of data on possible confounding factors, including patient background information and concomitant medications publicly available. These are particularly important for patients with vascular abnormalities after VPI treatment. Second, the results of the death and hospitalization proportions only rely on the original records provided by the FAERS. The real cause of the deaths and hospitalizations is not clearly explained, so there might be a certain result deviation based on the FAERS database itself. Third, adverse events are rarely reported to the health authorities (probably only 2%–18%).[24] Given those limitations, it may be too early to draw any definite conclusion based on this initial effort of investigation.

Although FAERS has some inherited limitations, it revealed aspects of VPI-associated AAD, providing clues for more related research. Reporting systems are invaluable resources to enhance our understanding of root causes and contributing factors to adverse events.[25] Using publicly accessible FDA databases of patient safety to investigate, understand, and learn from adverse events has been widely recognized in the community, which holds the potential to be generalizable to other patent safety concerns.[26,27]

CONCLUSIONS

In this study, we identify factors associated with AAD following treatment with various VPIs in actual practice based on the FAERS database. One finding indicates that not all VPIs are associated with AAD. Based on the ROR algorithm, only sorafenib, sunitinib, lenvatinib, ponatinib, nintedanib, bevacizumab, and ramucirumab exhibited a stronger association with AAD. There was also a significant difference in the time to onset of AAD after different VPIs, which should be immediately noted after the first dose of the VPI regimens. Our findings represent the first step in the ongoing pharmacovigilance study that will encourage further research to test, validate, or reproduce the results of this study.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Tables S1–S3

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SUPPLEMENTAL MATERIAL

Table S1. Generic names and brand names of vascular endothelial growth factor inhibitors in MICROMEDEX®.

Generic name	Brand name
Sorafenib	Nexavar®
Axitinib	Inlyta®
Apatinib	-
Sunitinib	Sutent®
Regorafenib	Stivarga®
Vandetanib	Caprelsa®
Pazopanib	Votrient®
Lenvatinib	Lenvima®
Cabozantinib	Cabometyx®, Cometriq®
Ponatinib	Iclusing®
Aflibercept	Eylea®, Zaltrap®
Fruquintinib	-
Pegaptanib	Macugen®
Tivozanib	Fotivda®
Brivanib	-
Conbercept	-
Linfanib	-
Nintedanib	Ofev®
Motesanib	-
Cediranib	-
Bevacizumab/Rhumab	Avastin®, Mvasi®, Zirabev®
Ramucirumab	Cyramza®
Ranibizumab	Rhufab V2®, Lucentis®
Brolucizumab	Beovu®

Table S2. The list of preferred terms of PTs.

PT	code
Arterial intramural haematoma	10074971
Aneurysm recanalisation	10075396
Aneurysm perforation	10075395
Aneurysm arteriovenous	10002331
Aneurysm	10002329
Aneurysm ruptured	10048380
Splenic vein aneurysm	10078322
Splenic artery aneurysm	10041645
Retinal aneurysm rupture	10079121
Retinal aneurysm	10064145
Renal artery dissection	10049942
Renal aneurysm	10038366
Pulmonary artery aneurysm	10037336
Mesenteric artery aneurysm	10079556
Hepatic artery aneurysm	10019634
Arterioenteric fistula	10070296
Bronchial artery aneurysm	10079552
Coeliac artery aneurysm	10079553
Cardiac aneurysm	10007513
Coronary artery dissection	10048631
Coronary artery aneurysm	10011071
Artery dissection	10061660
Intratumoural aneurysm	10072808
Infective aneurysm	10058017
Loeys-Dietz syndrome	10081284
Vascular access site dissection	10077763
Shunt aneurysm	10064552
Vascular dissection	10070693
Vascular anastomosis aneurysm	10063079
Vein dissection	10077109
Venous aneurysm	10062174
Acute aortic syndrome	10074337
Aortic aneurysm rupture	10002886
Aortic aneurysm	10002882
Aortic aneurysm syphilitic	10002887
Aortic intramural haematoma	10067975
Aortic dissection rupture	10068119
False lumen dilatation of aortic dissection	10072788
Penetrating aortic ulcer	10077118
Carotid artery dissection	10050403
Carotid aneurysm rupture	10051328
Basilar artery aneurysm	10077607
Carotid artery aneurysm	10007686
Aortic dissection	10002895
Cerebral aneurysm ruptured syphilitic	10008076
Cerebral aneurysm perforation	10075394
Wyburn Mason's syndrome	10048661
Vertebral artery dissection	10071716
Vertebral artery aneurysm	10077498
Ruptured cerebral aneurysm	10039330
Intracranial artery dissection	10073565
Intracranial aneurysm	10022758
Charcot-Bouchard microaneurysms	10054749
Arteriovenous fistula aneurysm	10066916
Femoral artery aneurysm	10016427
Arteriovenous graft aneurysm	10064775
Femoral artery dissection	10052326
Peripheral artery aneurysm	10057521
Peripheral artery aneurysm rupture	10079908
Peripheral artery dissection	10057520
Subclavian artery aneurysm	10042331

Table S3. Characteristics of cases with VPI-associated aneurysm and artery dissection.

Characteristics	Reports, no. (%)
Year	
2004	2(0.32)
2005	3(0.47)
2006	15(2.37)
2007	10(1.58)
2008	22(3.47)
2009	27(4.26)
2010	30(4.73)
2011	42(6.62)
2012	30(4.73)
2013	36(5.68)
2014	49(7.73)
2015	70(11.04)
2016	47(7.41)
2017	50(7.89)
2018	92(14.51)
2019	70(11.04)
2020	39(6.15)
Area	
Africa	2(0.32)
Asian	225(35.50)
Europe	146(23.04)
North America	223(35.17)
Oceania	10(1.58)
South America	21(3.32)
Country not specified	7(1.11)
Indication	
Adenocarcinoma	5(0.81)
Anaplastic astrocytoma	1(0.16)
Breast cancer	18(2.96)
Bronchial carcinoma	2(0.32)
Cell carcinoma	46(7.54)
Cervix carcinoma	5(0.82)
Colon cancer	36(5.90)
Colorectal cancer	33(5.40)
Diabetic eye disease	38(6.24)
Gastric cancer	27(4.42)
Glioma	3(0.49)
Hepatic cancer	12(1.97)
Idiopathic pulmonary fibrosis	20(3.28)
Large intesting carcinoma	3(0.49)
Leiomyosarcoma metastatic	1(0.16)
Lip and/or oral cavity cancer	1(0.16)
Lung adenocarcinoma	15(2.46)
Macular degeneration	50(8.20)
Macular oedema	2(0.32)
Metastatic gastric cancer	1(0.16)
Myeloid leukaemia	8(1.30)
Neoplasm malignant	8(1.30)
Neovascularisation	2(0.32)
Neuroendocrine tumour	3(0.49)
Neurofibromatosis	1(0.16)
Oesophageal adenocarcinoma stage IV	1(0.16)
Osteosarcoma	1(0.16)
Ovarian cancer	19(3.10)
Pancreatic carcinoma	9(1.48)
Pathologic myopia	1(0.16)
Peritoneal carcinoma metastatic	1(0.16)
Polypoidal choroidal vasculopathy	1(0.16)
Prostate cancer	7(1.15)
Pulmonary fibrosis	1(0.16)
Rectal cancer	23(3.77)
Renal cancer	115(18.86)
Retinal oedema	4(0.66)
Retinal vein occlusion	19(3.11)
Retinopathy of prematurity	1(0.16)
Skin cancer	1(0.16)
Thyroid cancer	16(2.62)
Venous occlusion	1(0.16)
Visual impairment	2(0.32)
Drug use for unknown indication	46(7.55)