OFF-LABEL DRUG USE IN ONCOLOGY: PERSPECTIVES FROM SINGAPORE PRACTICE SETTING

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Declaration

I hereby declare that this thesis is my original work and it has been written by me entirely. I have duly acknowledged all the sources of information which have been used in the thesis. This thesis has also not been submitted for any degree in any university previously

Saiyed Mohammad Masnoon Abdul Kadar

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List of abbreviations

AE	Adverse Events or Effects
ASCO	American Society of Clinical Oncology
CR	Complete Response
CI	Confidence Interval
DCR	Disease Control Rate
ESMO	European Society of Medical Oncology
EMEA	European Medicine Agency
EGFR	Epidermal Growth Factor Receptor
FDA	Food and Drug Administration
FAERS	FDA Adverse Event Reporting System
HSA	Health Sciences Authority
MCRC	Metastatic Colorectal Cancer
NCCS	National Cancer Centre Singapore
NCCN	National Comprehensive Cancer Network
OS	Overall Survival
ORR	Objective Response Rate
PFS	Progression Free Survival
PBRER	Periodic Benefit Risk Evaluation Report
PIGF	Placental Growth Factor
PMS	Post Marketing Surveillance
RCT	Randomized Control Trials
RECIST	Response Evaluation Criteria In Solid Tumors
SD	Stabilised Disease
SAP	Special Access Program
SPSS	Statistical Package For Social Sciences
TTP	Time To Progression
VEGF	Vascular Endothelial Growth Factor

Table of Contents

List of tables

List of figures

Summary

While off-label drug use in oncology is an international issue and had significant implications for the health care system, the information on the off-label use of the targeted agents is currently poorly documented. This may be particularly important as more than 30 targeted agents are approved by FDA since 1997. Most of these drugs have narrow approved indications with respect to cancer types and stage of the disease and they could be used in off-label manner due to their wide anti-cancer activity. Hence, investigations are needed to provide a better understanding of off-label use associated with targeted therapies considering the reimbursement constraints, high cost, and uncertain scientific evidence. Aflibercept which is a potent angiogenesis inhibitor is selected as targeted drug candidate for the investigation in this thesis.

While special access programs (SAP) provide a pathway for accessing unregistered and investigational drugs for those patients who have limited options available with the approved treatments. There is a possibility that drugs obtained under SAP might be used differently from approved regulatory recommendations. Off-label drug use under SAP program may compromise clinical outcomes and patient safety due to limited evidence of efficacy outside trial setting and incomplete information on toxicities risk. It is thus important to evaluate whether the targeted therapies are used in off-label manner for Asian patients under SAP.

Furthermore, off-label drug use practice is likely indispensable in cancer therapy, particularly for patients with limited treatment options. It is thus desirable to establish a practice framework for guiding off-label prescribing that have a favourable benefit-risk ratio. This will in turn safeguard both practitioners and patients. As oncology practitioners play an important role in any clinical practice framework and current

information on their perceptions regarding off-label drug use in oncology in Asia has not been studied, it is thus pertinent to hear their views.

Study Objectives

1. To conduct systematic literature review of off-label use of aflibercept for oncology indications
2. To study the off-label use of aflibercept under SAP in Singapore.
3. To study the perceptions of oncology practitioners on off-label use in cancer therapy.

Summary of important findings

The thesis found that none of the off-label use of aflibercept for any indication could be recommended for routine practice based on the current scientific evidence. The thesis also gave preliminary indication that off-label does exist in SAP and this finding should be confirmed in a larger study with adequate sample size. The off-label use of drugs under SAP would have its own unique clinical, safety and ethical implications for prescribers and patients. Lastly, the thesis provided the data which highlighted the concerns expressed by oncology practitioners on off-label prescribing in oncology. This certainly demands the formulation of practice framework monitoring off-label use of anti-cancer drugs at the institutional level. A research study evaluating the impact of practice framework on reducing irrational off-label prescribing and adverse events due to it could be designed. This could be of great value in improving practice standards and patient safety.

1 Introduction

1.1 Definition of off-label drug use

The role of the drug regulatory bodies worldwide is to approve a medicine for clinical practice based on randomized control trials and strict licensing standards. They also publish prescribing information based on the data of the pivotal trials submitted in support of the marketing authorisation applications. Prescribing information (PI) serves as a clinical guidance document for practitioners in routine practice population. However, this product information is not intended to prevent the practitioners from using his or her best medical judgment in the best interest of patients. Indeed, the practice of medicine will necessitate the practitioners to use the medicines by drawing a conclusion from medical literature and tailor it to individual patient encountered in clinical practice. Thus, use of a drug in routine clinical practice might not comply with the prescribing information.

Off-label drug use defined as all use of an approved medicine not mentioned in the prescribing information regarding therapeutic indication, dosage, route of administration or patients population (1, 2). The evidence guiding off-label drug use might vary both in quality and consistency. Off-label drug use based on little or no scientific evidence is termed as off-evidence drug use (3). For example, prescribing a drug for indication outside clinical trial without knowing the results of the clinical trial. Off-label drug use is dissimilar from compassionate drug use. Compassionate drug use also known as expanded access facilitate the use of investigational therapies to either individual or group of patients suffering from chronic, severely debilitating, or deadly illness, without a suitable approved treatment accessible and who cannot participate in clinical trials or get unlicensed medicines (4). Off-label drug use is further demarcated from unlicensed

drug use which means the use of therapeutic entity which has never received any regulatory approval for any clinical use in either pediatrics or adult population (5). Physicians are generally allowed to prescribe the drug in an off-label manner in most regions except country like India where it is illegal (6). Off-label status of a drug could vary among different countries due to different timings of marketing authorisation or lack of drug approvals for newer indications.

Table 1 Summary of definitions

Off-label drug use	Clinical practice of prescribing medicines outside the terms mentioned in the Prescribing Information (PI).
Unlicensed drug use	Drugs which are not subjected to review for their efficacy and safety by drug regulatory agencies.
Investigational therapies	Drugs are being scientifically studied but are yet to be approved by the licensing authorities for clinical practice.
Compassionate use	Prescribing newly unapproved agents through individual patient use request or expanded access programs (EAPs) to treat life-threatening diseases for which there are no available treatment options.
Extemporaneous preparations	It is the procedure of compounding various ingredients to formulate an unlicensed medication for a single patient in agreement with the prescription.

1.2 Prevalence of off-label pharmacotherapy in medical practice

The off-label use of drugs in routine practice is done principally to address the unmet medical need. It is challenging to estimate the exact prevalence of off-label drug use. This is due to lack of reliable healthcare databases and difficulty in detecting off-label indications in medical records. In addition, the prescriptions which are inconsistent with the terms of the FDA label are not recorded separately by health insurances or other national databases (7). On the other hand, pharmaceutical organizations are not required to give precise information on their drug sales for off-label uses. In fact, sales associated with off-label drug uses may generate additional revenue for them without them investing in expensive clinical trials (8).

Off-label use is widespread across almost all different diseases and healthcare settings (9). Among all, children are frequently prescribed medication in an off-label manner as pharmaceutical companies had not carried out and submitted pediatric clinical trials data to regulatory bodies at the time of drug approval. As a result, the pediatrician had no option left but to prescribe medicine off-label. One of the largest research study carried out in the United States concluded that most pediatric patients were prescribed minimum one off-label medicine which also accounted for 40% of total medication expenditures (10). Studies have also been published reporting off-label use in several pediatric subspecialty services including gastroenterology, cardiology and pain management (11-13). Recently, there is evidence linking increased risk of adverse drug events with off-label prescribing in children (14). In the neonates, almost all drugs are administered in off-label manner (15). In the adult population, off-label use has been reported across various healthcare settings and diseases. Off-label drug prescribing is exceedingly widespread across clinical areas like psychotic disorders, dermatology, adult critical

care, cardiology, neurology, nephrology and obstetrics (1, 16-18). Based on the published literature, it appears that off-label use of drugs is widespread across several diseases internationally and is likely to grow in coming years (15, 19).

1.3 Benefit and risk of off-label drug use

In era of contemporary medicine, off-label drug use has become standard practice in some diseases grounded on the scientific evidence and practitioners' clinical expertise (20). These drugs are provided either to meet a public health requirement not covered by an approved licensure or to warrant medicine access to particular patient groups (21). From these aspects, off-label drug prescribing is beneficial as it not only improves access to valuable medicines to patients but also allows innovation in routine practice especially, when approved therapeutic regimens have failed or emerging evidence suggest changes in treatment protocols (9).

Instances of off-label prescribing that benefited patients comprise use of aspirin for prophylaxis against cardiovascular disease in diabetes, use of tacrolimus as last-hope therapy for autoimmune disorders, use of gabapentin as first line treatment for painful diabetic neuropathy and use of cisplatin for the off-label indication in cancer of head and neck, esophagus, gastric, lung, lymphoma and anal canal (22, 23). In some cases, such as use of bevacizumab for curing age-related macular degeneration, off-label drug therapy is considered to have the same therapeutic efficacy and is more cost-effective than the currently approved drug ranibizumab (24, 25). However, due to a lack of proper regulation, off-label drug prescribing has the potential of exposing patients to uncertain risks (26). This is mainly due to the fact that off-label drug uses are not systematically appraised by regulators, guidelines formulators or even healthcare policymakers. Non-

evidence based off-label drug use may pose unknown toxicity risk (27, 28). Several widely practiced off-label drug uses have also been found to be either harmful or ineffective when properly scrutinized (29). For example in a study by Radley et al, where 150 million off-label prescriptions were evaluated, they found that 73% of off-label drug use lacks strong scientific evidence that compromises patient safety or represents wasteful medication use (30).

Additionally, other studies have reported off-label drug use as an independent factor contributing to the occurrence of adverse drug reactions (31, 32). This is because a drug used in off-label setting may exhibit different pharmacodynamic and pharmacokinetic profile in the body, thus predicting frequency and severity of side-effects could be very challenging. Another example is the treatment of men who are at a high risk of prostate cancer using 5α-reductase inhibitors in an off-label manner to decrease cancer risk as suggested by the ASCO guidelines published in 2009 (33). This off-label use was however concluded to be dangerous as data from the REDUCE trial indicated an augmented risk of a more aggressive form of cancer with dutasteride therapy. This in turn prompted a drug safety alert published by FDA in 2011 for this toxicity concern (34). Other data that highlighted the risk linked with off-label drug use includes the systematic assessments within the post-marketing surveillance programs by the RADAR (Research on Adverse Drug events And Reports) working group where that serious and unknown ADRs are often found to be occurring due to off-label drug use for which scientific evidence does not exist (35).

1.4 Pharmacovigilance of off-label drug use

Unfortunately, the present pharmacovigilance and post-market surveillance methods do not monitor off-label drug use. Standard monitoring approaches using the FDA's Adverse Event Reporting System (FAERS) do not specifically look for off-label indications. Some methods have been proposed using the data mining approach in clinical notes or capturing indications during electronic prescribing to enhance surveillance of off-label indications (36, 37). Pharmaceutical companies could greatly assist in shaping the safety data of off-label drug use. They should as part of the signal detection process, evaluate off-label indication by searching for patterns of use and safety concerns. As there could be little or no other data in the database or medical literature to support off-label drug safety analysis, individual cases become more critical in the analysis. These cases should be maintained in the signal list and reported to the drug regulatory authorities and other stakeholders if the cases meet expedited reporting provisions. Also, it is essential to comprehend that off-label drug safety information must be incorporated in Periodic Benefit Risk Evaluation Report (PBRER) and, if essential, in risk evaluation and mitigation plan as well as risk management plan.

The off-label drug use without strong evidence base could greatly alter the benefit-risk ratio and could be catastrophic for the patients rather than providing any meaningful clinical effects. This is especially relevant for off-label use of newly marketed drugs and novel off-label use of old drug with limited background information regarding efficacy and particularly toxicity data, even if the drug itself has been available in market for more than 3-5 years.

1.5 Regulatory reforms for off-label drug use

The regulation pertaining to practice of off-label drug use are not harmonised across the world. In the United States, off-label drug use can be legally prescribed but it restricts manufacturers from promoting the unapproved use of licensed drugs (38). In 2006, the ASCO emphasized the necessity to update and completely apply the 'standard medical compendia' used by Medicare in the US to cover designated, evidence-based, off-label use of oncology drug (39). Off-label prescribing is even legal in Europe but each member state has own regulations (40). European Society of Medical Oncology (ESMO) has suggested the drug regulatory bodies to take some responsibility for off-label drug use. ESMO proposed listing standard off-label indications for anticancer drugs that could be approved by the European Medicines Agency (EMEA). This mechanism would not resolve the whole problem at once, but it would, at least, streamline the condition and improve the physician's position particularly concerning the question of medical liability when challenged with the described contradictions of off-label drug use (41). This might facilitate the creation of compendia of oncology drugs, enlisting those off-label uses adjudged to be evidence based and legitimate to practice. It could partly ensure physician's freedom to prescribe quality of care and thus prevent legal liabilities.

Off-label drug use is very common in pediatric oncology. Hence, Europe launched Paediatric Medicine Regulation in 2007 with an aim to improve pediatric clinical trials and medicines but it fails to facilitate an increase of early drug trials and many children with advanced malignancies are still denied access to innovative drugs (42). Many European countries like Austria, France, Germany, Spain, the UK, and Switzerland considered off-label drugs as a problem in the drug supply to patients and took different ways to handle the problem so as to moderate its negative effects (43). Many reforms

have been suggested in different countries. In Japan, a drug can be licensed for off-label indication based on the evaluation of published literatures whereas China had recommended a grading mechanism for off-label indications (44, 45).

1.6 Ethical standards for off-label prescribing

The ethical reasoning for off-label drug use is to offer best possible treatment to patient grounded on the sound evidence base. However, the evidence guiding off-label drug prescription could differ greatly on the case to case basis (46). Scientists frequently test off-label drug use using informal research but in routine practice off-label drug prescribing should be based on the proper therapeutic goal and individual patient need (20). Professional bodies like American Medical Association and American Cancer Society supports off-label drug use and has issued useful guidelines on off-label drug prescribing (47, 48). These advisory statements implicitly advocate three main ethical considerations pertinent to off-label drug use: (1) Appraisal of most up-to-date evidence supporting off-label drug use; (2) gathering data and doing research when there is insufficient evidence regarding an off-label use; and (3) Addressing disclosure requirement to patients about what prescriber should inform them about off-label status of therapy, obtaining verbal or written consent and explaining probable benefit, risk and economic consequences.

1.7 Off-label drug use: reimbursement issues for cancer treatments

Off-label drug use has been found to increase the economic burden on cancer patients. The total expenditure associated with off-label chemotherapies was reported as US$4.5 billion and US$2 million in two studies (49, 50). When there is inadequate evidence

from trials, it becomes more difficult to determine if there is sufficient value for off-label drug use to warrant successful reimbursement (51). Considering cancer treatments are expensive, the situation worsens when off-label drugs are not reimbursed and would ultimately increase out-of-pocket costs to patients. Many oncologists reported changing their therapeutic regimens due to reimbursement constraints resulting in poor medicines access to cancer patients (52). In the US, Medicaid would reimburse off-label drug use that is listed in compendia such as the American Hospital Formulary Service's Drug Information and Thomson Healthcare's Drug Points System (39). Interestingly, few managed care establishments and private health insurance plans in the US have refused to pay the cost of drugs used in an off-label manner to treat cancer disease stating that these clinical uses are "experimental" or "investigational."

Few countries, such as the United Kingdom limit or reject access to unapproved drugs use on the grounds of lack of proven cost-effectiveness. In Sweden, bortezomib and trastuzumab were reimbursed by the National Reimbursement System for routine use at the choice of concerned medical oncologists, exemplifying their willingness to prescribe for off-labelled indications. Sweden along with Finland, permitted reimbursement of intravenous cancer drugs provided that they are included in the hospital-based practice guidelines formulated by medical oncologists. But these guidelines could vary according to the treating cancer centre. For example, the off-label use of bevacizumab for the treatment of glioblastoma had different reimbursement coverage across the hospitals in Finland and Sweden (53). France recently opted for new French law with an objective to warrant safety of drugs and other health care products. This new regulatory mechanism called as "Temporary Recommendations for Use" enabled France for provisionally overseeing the prescribing of drugs for unapproved indications and subsequent

successful reimbursement in clinical practice (54). Japan rejected reimbursement for off-label drug use while Italy changed its rule to facilitate use and reimbursement of cheaper off-label alternative such as bevacizumab in age-related macular degeneration (55, 56).

1.8 Reasons for off-label prescribing in cancer pharmacotherapy

Once a drug is approved by the regulatory authorities, a particular pattern of off-label prescribing is observed in routine practice. Initially, there are individual patients treated with off-label drug use by oncologists and later on their clinical outcomes are reported in scientific literature in the form of case reports, case series, symposia reports, and small cohorts. These publications are deliberated to be "evident" by other prescribers and served as guidance for legitimate and more manifested off-label drug use. Eventually, this approach might even result in a situation where off-label drug use is accepted as standard care such as for several childhood cancers (57).

There are myriad of reasons why off-label drug use is indispensable practice in cancer therapy. These reasons are highly diverse and complicated. First, the data included in the prescribing information cannot guide clinical care of a diverse range of tumor types and patients' characteristic in routine practice. In routine practice, cancer patients have several co-morbidities, contraindications, older age, medical history and drug allergies which limit the applicability of the approved regimen. As a result, many anti-cancer drugs are prescribed in altered doses, drug combinations, schedule of treatment, route of administration and duration of therapy different from FDA approved recommendation. Second, the difficulty in conducting Phase III randomized clinical trials for orphan or uncommon tumors with sufficient statistical power to measure the significant impact on overall survival. For such cases, inadequate evidence from phase II trials may show the

benefit of drugs and thus, those drugs may be implemented in clinical practice in an off-label manner. Third, there is a lag time between encouraging clinical trials findings, either published in peer-reviewed journals or reported at scientific symposia, the sponsor's new drug application for FDA review and the subsequent FDA authorization. Fourth, pharmaceutical companies are unwilling to apply for supplementary indications of previously approved drug in the market due to the expiration of the patent or lack of enough financial incentives. Going by the definition, if this medicine is being adopted by oncologists after the release of clinical trial results preceding FDA approval, this medicine can be considered as off-label drug use based on sound scientific evidence.

Fifth, it is even possible that a drug approved for a cancer with specific gene expression is also active in patients having different type of genetic mutation. For example, crizotinib approved for anaplastic lymphoma kinase (ALK)-rearranged non-small cell lung cancer was found to be efficacious in patients with c-ros oncogene 1 (ROS1) oncogene rearrangement (58). Sixth, medical oncologists managing patients suffering with advanced or metastatic stage of disease are willing to try drugs with uncertain evidence outside trial as a hope that these off-label drugs may offer prolonged survival frequently at the request of their patients (3, 26, 59). Lastly, insufficient prescriber's knowledge of the existing FDA-approved drug labels also contributed to off-label use (60).

1.9 Extent of off-label anti-cancer drug use in routine practice

The use of the chemotherapy outside their recommendations of the prescribing information can be defined as off-label drug use for a different tumour or reasons as shown in Table 2. In general, they can be broadly classified into four main different

types namely [1] Unapproved drug for specific tumour group, [2] Unapproved drug for specific stage of disease (neoadjuvant, adjuvant, palliative, curative), [3] Unapproved line of treatment, and [4] Modified application of drug (e.g. dose, frequency, combination, route of administration). Off-label use of anti-cancer agents is widespread in oncology (5, 19, 61). As per the estimate made by NCCN in 2005, 50 to 75% of chemotherapies are prescribed for off-label indications in the United States (62). The general characteristics of various studies reporting on the extent of off-label chemotherapies are described in Tables 3.

Table 2 Off-label drug use reasons and corresponding examples in oncology.

No.	**Off-label reasons**	**Example***
1	**Type or subtype of cancer**	• Oxaliplatin is indicated for colorectal cancer but prescribed in breast cancer. • Trastuzumab used in ERBB2-negative instead of ERBB2-positive breast cancer. • Liposomal doxorubicin is approved for metastatic breast cancer in patients with an increased cardiovascular risk but is used in patients without this risk.
2	**Dose**	• High dosing of carboplatin in intensive chemotherapies instead of the approved dose.
3	**Expression of dosing**	• Fixed dose of trastuzumab prescribed instead of that adjusted for bodyweight.
4	**Drug approved as monotherapy but given as**	• Raltitrexed combined with irinotecan in metastatic colorectal cancer.

	combination therapy	• Trastuzumab with chemotherapy in pretreated metastatic breast cancer.
5	**Drug approved in combination but given as single agent**	• Single agent bevacizumab administered for metastatic colorectal cancer.
6	**Unapproved combination**	• Trastuzumab is given with vinorelbine instead of paclitaxel or docetaxel in untreated metastatic breast cancer.
7	**Schedule of administration**	• Every week instead of every 3 weeks for paclitaxel and docetaxel.
8	**Duration of treatment**	• Trastuzumab is given beyond progression in metastatic breast cancer.
9	**Route of administration**	• Intraperitoneal injection of cisplatin rather than intravenous. • Subcutaneous administration of alemtuzumab instead of intravenous.
10	**Age**	• Use of adult-approved drugs in children.
11	**Line of treatment**	• Panitumumab for 1st line of treatment instead of pretreated advanced colorectal cancer.
12	**Course of disease**	• Use of irinotecan for adjuvant therapy rather than treatment of advanced colorectal cancer.

*There might be changes in current off-label status due to subsequent regulatory approval in a specific country.

Table 3 Characteristics of the studies assessing prevalence of off-label drug use in different settings and cancers

No	Author (Year)	Drugs Studied	Type of cancer studied	Data Source	Study design	Study Duration	Sample size	OL category	OL use (%)	Patients receiving OL drugs (%)
1	Anne et al (2015)[63]	All approved for breast cancer	Breast cancer	SEER-Medicare	RS	9 years	13,347	2,3	75	--
2	Sophie et al (2015)[64]	107 approved anticancer drugs	Breast cancer	Electronic database	RS	8.5 years	2,663	2,3,4	55	13
3	Kalis et al (2015)[65]	Oral chemotherapies	--	Community cancer centre	RS	35 months	990	1,2,3	29	--
4	Joerger et al (2014)[66]	--	--	Hospital	PS	3 months	985	1,2,3,4	27	32
5	Wang et al (2014)[67]	--	--	Hospital	PS	6 months	1,122	1,2,3,4	41	71
6	Conti et al (2013)[49]	Ten patented drugs	--	Electronic prescribing	RS	1 year	--	1,2,3	30	--
7	Dawn et al (2013)[68]	All	Metastatic cancers	SEER-Medicare	RS	10 years	37,351	1	--	33%
8	Carlos et al (2013)[69]	Intravenous drugs	Breast, Colorectal, Ovarian, Lung.	SEER-Medicare	RS	15 years	1,35,608	1	--	53
9	Mellor et al (2012)[70]	--	--	Hospital	PS	6 months	--	1,2	--	--
10	de Souza et al (2012)[50]	Bevacizumab, Cetuximab, Capecitabine & Panitumumab	Metastatic colon cancer	Insurance claims	RS	34 months	1,041	3,4	--	13
11	Cioffi et al (2012)[71]	--	--	Hospital	PS	3 years	843	1,2,3,4	--	15
12	Tilleul et al (2012)[72]	Temozolomide	--	Hospital	PS	6 months	831	1,4	48	--
13	Bonifazi et al (2012)[73]	Bevacizumab	Metastatic colorectal cancer	Registry	RS	2 years	637	1,3,4	--	62
14	Gota et al (2011)[23]	10 drugs	--	Survey	PS	--	--	1	6 out of 10 drug	--
15	Van den Berg et al (2011)[57]	--	--	Hospital	PS	2 weeks	39	1,4	43	87
16	Neugut et al (2010)[74]	Bevacizumab	Metastatic colon cancer	SEER-Medicare	RS	16 months	371	2	--	7
17	Roila et al (2009)[75]	--	--	Hospital	PS	2 days	644	1,3,4	19	43
18	Powers et al	--	--	Hospital	RS	1 year	186	1,2,4	50	--

	(2009)[76]									
19	Dean-colomb (2009)[77]	--	Breast cancer	SEER-Medicare	RS	12 years	2,082	1	78	35
20	Sallie-Anne (2007)[78]	Trastuzumab	Metastatic breast cancer	Australian Medicare	RS	40 months	1,469	4	--	22
21	Leveque et al (2005)[79]	--	--	Hospital	PS	1 year	1,206	1	7	--
22	Poole et al (2004)[80]	--	--	Hospital	PS	1 day	130	1,4	18	85
23	Conroy et al (2003)[81]	--	--	Hospital	PS	4 weeks	51	1,4	26	100
24	Laetz et al (1991)[52]	--	--	Survey	PS	--	--	1,3	33	56

*****OL: Off-label, RS: Retrospective study, PS: Prospective Study, OL categories: 1) Unapproved drug for specific tumour group, 2) Unapproved drug for specific stage of disease (neoadjuvant, adjuvant, palliative, curative), 3) Unapproved line of treatment 4) Modified application of drug (e.g. dose, frequency, combination, route of administration), SEER: Surveillance, Epidemiology, and End Results.

1.9.1 Studies published in North America

The first ever exploration on the extent of off-label use in cancer therapy was carried out by the General Accounting Office in the United States (52). They found the off-label use of anti-cancer drugs to be extensively prevalent and 33% of prescriptions were off-label with more than half (56%) of all the cancer patients were prescribed minimum one off-labelled drug. They also found that off-label drug use depends on patients' characteristics, the therapeutic intent, the stage of cancer and reimbursement policies. As the study was designed in the form of the survey with small sample size, the accuracy of the true prevalence of off-label use could be different from actual practice.

Subsequently, in a larger study carried out at MD Anderson Cancer Centre using SEER database revealed that approximately 35% of distant stage breast cancer patients received off-label drugs (77). They also assessed the appropriateness of the off-label prescriptions using DRUGDEX classifications and found that 71% of off-label uses were without supporting evidence. In another study which assessed chemotherapy prescribing

pattern in a military treatment facility in the US, 50% of regimens in outpatients were off-label and commonly observed in the adjuvant (49%) and palliative setting (34%) (76).

Apart from these, Jonas de Souza et al studied unsupported off-label chemotherapy regimens of bevacizumab, cetuximab, capecitabine & panitumumab for the treatment of metastatic colon cancer in the United States (50). They evaluated three regimens which NCCN guidelines recommended against the use for routine practice. These include - 1) bevacizumab use beyond disease progression; 2) capecitabine monotherapy as a salvage treatment after failure on a fluoropyrimidine-containing treatment; 3) cetuximab or panitumumab after disease progression who has previously received EGFR monoclonal antibodies. They found that 13% of patients (out of 1041 mCRC patients) received any one of these off-label treatments without any scientific evidence. These off-label regimens were estimated to be costing about US$2 million. Carlos et al using the SEER-Medicare database found that 53% of 1,35,608 total patients aged above 65 years old received at least one off-label prescription (69). Off-label use was common among all types of cancers studied and 24% of breast cancer, 86% of non-small lung cancer, 98% of small cell lung cancer and 47% of ovarian cancer patients' received one claim containing off-label use.

In another study using same SEER-Medicare databases, Dawn et al retrospectively evaluated off-label use in metastatic cancers patients and found that such practice was present in 33% of cases among 37,351 patients reviewed (68). Of those who received off-label drugs, 69% of off-label drug use was based on compendia listing. The mean number of off-label claims was 10% and highest among patients with prostate cancer

and lowest in colorectal cancer patients. Conti et al studied the off-label use of 10 patent protected drugs using infused outpatients chemotherapy orders of 122 medical oncology practices across 35 US states (49). Overall, 30% of chemotherapy orders were off-label and 14% of off-label drug use fulfilled the NCCN-supported recommended cancer site. But 10% off-label use was not consistent with NCCN recommendations for line of treatment and/or cancer stage. The spending on off-label chemotherapeutic regimens accounted for US$2 billion for off-label supported by NCCN and US$2.5 billion for off-label drug use but unsupported by NCCN guidelines.

A study by Kalis et al at a community oncology centre in US assessing oral chemotherapy found that off-label drug use amounted to 29% among 990 patients receiving 44 different medications (65). Three percent of off-label prescriptions were unsupported by NCCN treatment guidelines. Sophie et al studied off-label drug use among female breast cancer patients and quality of supporting evidence (64). A total of 2,663 breast cancer patients received 1,636 (13%) off-label prescriptions representing unique 36 off-label cancer therapies. Most off-label use was evidence-based but more likely to be related with private health insurance, young age, ethnicity and drugs with narrow indication with longer market existence. Off-label use was higher for alkylating agents and topoisomerase inhibitors than other class of chemotherapies. Off-label use with limited evidence was found with bevacizumab, carboplatin and leuprolide.

Anne et al evaluated prevalence and safety of off-label drug use in older breast cancer patients aged above 65 years using SEER-Medicare database in United States (63). A total of 13,347 breast cancer patients were treated with 16,127 different treatment regimens. Sixty-four percent (10,391) of treatment regimens were off-label/NCCN-

supported and 11% (1,749) regimens were off-label/NCCN-unsupported with higher percent of such drug use in stage III/IV patients and these practices were mainly in the form of neoadjuvant and altered adjuvant regimens. The main reason for off-label/NCCN-unsupported use (76%) was use of drug outside approved stage of cancer and/or line of treatment, while drugs not indicated for breast cancer amounted for 19% of off-label/NCCN-unsupported use and 1% of total drug use. Hospitalization and emergency room visits were substantially higher with patients receiving off-label/NCCN-unsupported treatment regimens.

1.9.2 Studies published in Europe

Conroy et al prospectively studied the incidence and nature of off-label and unlicensed prescribing in pediatric patients with acute lymphoblastic leukaemia and other cancer types (81). They found that 26% and 19% of prescriptions were off-label and unlicensed respectively. Among the small sample population, all the pediatric cancer patients received at least one off-label drug administration during their course of illness. Van den Berg et al using the medication order data from the pediatric oncology ward at a children hospital in Netherland found that 43% of prescriptions were off-label and 87% patients received at least one off-label/unlicensed use during their hospital stay (57).

A prospective French study which assessed adult ambulatory prescriptions found very low proportion of off-label drug use (7%) which might be due to the narrow definition of off-label use that was only based on unapproved indication (79). An Italian study done over two randomized non-consecutive days over two weeks at 15 oncology centres, found that 19% of prescriptions were off-label and most of them were based on the published randomized control trials (75). The authors acknowledged their study for small

sample size limiting their generalizability of the results and arbitrary classification of different off-label uses. Bonifazi et al conducted an assessment of prescribing pattern, the incidence of adverse events and survival rate of bevacizumab for the treatment of advanced colorectal cancer using Lombardy health care database in Italy (73). They found that bevacizumab was prescribed to 62% of patients for an unapproved line of treatment, stage of cancer and drug combinations. Approximately 10% of entire sample patients suffered fatal toxicities and median overall survival was 21 months with no significant difference between gender and age groups. However, they did not report adverse events and survival outcomes separately for patients receiving off-label prescriptions.

Tilleul et al prospectively evaluated the off-label use of temozolomide among 831 adult patients across 21 French hospitals (72). A total of 5,982 temozolomide treatment cycles were evaluated and 48% of them were off-label. Global regulatory conformity of approved recommendation in terms of treatment duration, drug combination or dose, was 62% for newly diagnosed glioblastoma patients treated with temozolomide plus radiotherapy, 72% for temozolomide maintenance therapy, and 66% for glioblastoma and anaplastic astrocytoma in progression/relapse patients. Off-label use based on insufficient evidence was found in 5.4% patients. Cioffi et al studied the influence of the pharmacist on facilitating evidence-based off-label prescribing in the oncology ward of an Italian hospital (71). From an assessment of prescriptions of 843 cancer patients spanning over three years of duration, they found that 15% of patients received drugs for unapproved indications. Pharmacists were able to reduce off-label uses from 28% to 10% and also prevented inappropriate drug use cases by suggesting alternative treatment regimens to physicians.

Joerger et al prospectively studied the off-label use of systemic chemotherapies administered to cancer patients at Swiss hospitals network (66). A total of 1,737 chemotherapy administrations for 985 patients were evaluated over a period of three months. Overall, 32% of patients were prescribed at least one off-label drug, which corresponds to a total of 27% of off-label prescriptions. Main reason for off-label use was unapproved indication (16%) and modified drug application (10%). Off-label drug use was highest in palliative setting (76%). ESMO unsupported off-label drug use was rare (6%) but higher for bevacizumab in the treatment of advanced breast and ovarian cancer and for lenalidomide in the treatment of non-Hodgkin lymphoma.

1.9.3 Studies published in Australia

Poole et al conducted a one-day prospective study at Peter MacCallum Cancer Centre in Australia which indicated that 18% of prescriptions were off-label for hospitalized patients mainly due to unapproved dosing (10%) and unapproved indication (9%) (80). The main limitation of the research findings was cross-sectional nature of study, small sample size and lack of information regarding patients' characteristics. In another study, Mellor et al aimed to analyse 448 treatment protocols containing 82 different anti-cancer drugs that involved off-label and unlicensed prescribing at a specialist oncology centre in Australia (70). Overall, 189 treatment protocols (42%) were off-label and 3 (0.7%) were unlicensed. All these unapproved treatment protocols were not reimbursed by the national health insurance. Out of 189 off-label treatment protocols, 132 (70%) were based on treatment guidelines and 21% were based on phase 2 or 3 clinical trials. In addition to this, another Australian study that focused on the off-label use of trastuzumab in the treatment of metastatic breast cancer found that 22% of patients received the drug

in an off-label manner (78). The median duration of the trastuzumab monotherapy as well combination therapy was longer than trial conditions.

1.9.4 Studies published in Asia

A cross-sectional questionnaire-based study by Gota et al in India revealed that 6 out of 10 important oncology drugs were prescribed in an off-label manner for different indications fully supported by NCCN guidelines with the exception of unapproved use of gemcitabine in sarcomas and liver cancer which was based on Phase 2 trials (23). The data from China also revealed that 71% of drugs were used in an off-label manner in 41% of patients in a sample population of 1122 cancer patients (67). A total of 317 (28%) of patients received 445 (17%) medical orders which were both off-label and unsupported by NCCN guidelines. Off-label use not complying NCCN guidelines was higher for unapproved indications (90%) than unapproved drug concentration (8%) and unapproved route of administration (2%). Heavily pre-treated and pancreatic cancer patients mostly received off-label and off-NCCN chemotherapies.

Based on the published literature, off-label drug use appears to be indispensable practice in oncology with high prevalence use across different countries. It is practised across almost all types of cancers, stage of cancer and cancer care settings. Off-label drug use in hospitalized, as well as ambulatory care patients, was in the same range of 18 to 50% prescriptions. The main reasons for off-label drug use were a lack of approved indication for specific tumour type, unapproved line of treatment and modified drug application. Off-label drug use without support of standard treatment guidelines or drug compendia was substantially higher in some of the published studies. Off-label drug use with curative intent was in the range of 10 to 41% while that in the adjuvant therapy for early

stage cancer and palliative care in the advanced stage of cancer was in the range of 8.5 to 49% and 34 to 76% respectively. Drugs like bevacizumab, trastuzumab, docetaxel, oxaliplatin, capecitabine, gemcitabine, rituximab and cetuximab were frequently mentioned in the literature for off-label drug use in different cancer types or lines of treatment. There was lack of consensus regarding common definition off-label drug use because of the different categories of off-label drug use. In addition to this, off-label drug use reported in the literature years back might not be considered off-label in today's scenario due to changes in prescribing information. Hence, the exact prevalence and comparison of off-label drug use are difficult to determine and it changes over time.

2 A systematic literature review of off-label use of aflibercept for oncology indications

2.1 Introduction

One of the key mechanism which regulates the formation of the new blood vessel is called as 'Angiogenesis' and is considered as a driving factor leading to the growth of cancerous tissues and metastasis of primary solid tumours (82). This pathway is governed by intricate signalling network that includes several interacting proangiogenic and anti-angiogenic signals, mainly vascular endothelial growth factor (VEGF), integrins and angiopoietins (83, 84). The vascular endothelial growth factor pathway has been recognised as one of the cardinal regulators of tumour angiogenesis. VEGF-receptor system activation stimulates a complex signalling pathway involving endothelial cell development, movement, and survival from the previously existing blood vessels. VEGF also facilitates vessel permeability and has been linked with malignant effusions. VEGF mobilizes progenitor cells to distant neovascularization sites from bone marrow. Because of its continued expression and projected genetic stability, makes targeting VEGF an important strategy to arrest solid tumours growth (85, 86). Currently, numerous drug antagonists of VEGF pathway, including the VEGF Trap (aflibercept), monoclonal antibodies (ramucirumab and bevacizumab) and tyrosine kinase inhibitors (sunitinib, sorafenib, cabozantinib, regorafenib, pazopanib, axitinib and vandetanib) have been proved clinically efficacious in the treatment of various solid tumours and are approved for routine practice across the world (87).

Aflibercept (Zaltrap®) also called as VEGF-Trap, is a recombinant, decoy receptor fusion protein, which directly acts on VEGF-A, VEGF-B, and placental growth factor (PIGF) to stop angiogenesis. It is a conjugated protein comprising of second and third immunoglobulin (Ig) domain of VEGFR receptors 1 and 2 respectively, attached to the

stable region (Fc) of humanized IgG1 (88, 89). Aflibercept binds various isoforms of VEGF-A, VEGF-B, and PIGF. On the other hand, bevacizumab only binds to VEGF-A. The activity of Aflibercept is more inclined towards VEGF-A and their intrinsic receptors (89, 90). Aflibercept is of special attention in comparison to other anti-VEGF drugs because when exposed they have resulted to escalate PIGF levels which may increase VEGF-A expression and signalling and thus activates angiogenesis and contribute resistance to angiogenesis therapies. Hence, a drug like aflibercept which is capable of targeting both VEGF and PIGF has the capacity to decrease the likelihood of resistance from developing. Moreover, it could be combined with other drugs with several targets which could possibly enhance efficacy without causing additional toxicities (91).

Aflibercept is currently approved by regulatory bodies for clinical use as combination regimen with fluorouracil, irinotecan, and leucovorin (the FOLFIRI regimen) for the palliative treatment of metastatic colorectal cancer patients who have progressive disease following first-line oxaliplatin-based chemotherapy. The FDA approval decision was grounded on the Phase III trial (VELOUR study) in which aflibercept in combination with FOLFIRI significantly increased overall survival and progression-free survival by 1.4 months and 2.1 months respectively in comparison to placebo. Aflibercept received USFDA-mandated black-box warning on treatment-related haemorrhage, gastrointestinal perforation, and compromised wound healing. The advised dosage of aflibercept is 4 mg/kg body weight as an intravenous infusion administered every two weeks prior to FOLFIRI combination chemotherapy. Treatment with aflibercept is provided until progression in disease or intolerable toxicity (92, 93). Although FDA approved for the treatment of metastatic colorectal cancer, aflibercept has the capacity to apply direct or

continuous VEGF blockade in combination with other treatment modalities. Aflibercept provides additional benefit through regression of capillaries, endothelial cell apoptosis, decrease in tumour vessel mass and perfusion, blockage of ascites formation and decrease in tumour vessel genes. Several physiologic models and tumour xenografts have demonstrated promising preclinical results which increased clinical investigations for newer off-label therapeutic options in many cancer types (89, 94-101). Multiple clinical studies have been performed to investigate the off-label use of aflibercept for different oncology conditions, but there is no systematic review literature to date. This review attempts to summarize various off-label uses of aflibercept in oncology.

2.2 Method

Two independent investigators searched for research papers using the scientific MEDLINE-PubMed database from inception to July 2016. The search plan comprised of the following search terminologies and equivalents: (aflibercept AND cancer). To be considered suitable for the systematic review, any study who main objective was to evaluate the extent or clinical outcome of the off-label use of aflibercept for oncology indications. Pre-clinical research, phase 1 trial, pharmacokinetic or dose ranging studies, biomarkers research and meta-analysis were excluded from the review. Full-text articles and abstracts with sufficient information were assessed for inclusion. Furthermore, hand-searching of the bibliographies of potentially eligible articles was also performed to identify additional studies. We also searched and included conference abstracts presented at American Society Clinical Oncology (ASCO), the Gastrointestinal Cancers Symposium and the European Society of Medical Oncology (ESMO) from the year 2010 to 2016. The quality of randomised controlled studies was appraised by the Jadad 7-item scale that comprised of randomization of patients, double-blinding of treatments

administered, and withdrawals and/or drop out of recruited patients; the final score was described in a range from 0 to 5 (102). Non-randomised control trials were appraised using the Methodological Index for Nonrandomized Trials (MINORS) (103). Conference abstracts were not scored.

2.3 Results

The search found a total of 201 publications suitable for the inclusion in the review. For the initial screening, 196 papers were evaluated. After examination of the titles, abstracts, and full-text publications, 22 studies were included in the review. The general characteristics of various studies on the extent and outcomes of off-label use of aflibercept are described in Table 4. There were total 22 studies on the off-label use of aflibercept mainly done with an aim to assess efficacy and safety for unapproved cancer indication. None of the study estimated the prevalence of off-label use of aflibercept in routine oncology practice. There were five studies in colorectal cancer (104-108), three studies in lung cancer (109-111), six studies in gynaecological cancer (112-117), three studies in urological cancers (118-120) and one study for cancer of pancreas, thyroid, breast, glioma and melanoma (121-125). The majority of the studies included were phase II trials (n=19) (104-108, 110-117, 119, 120, 122-125) and three studies were phase III trials (109, 118, 121). All the six randomized studies had Jadad score more than or equal to 3 (104, 109, 114, 116, 118, 121). The eleven non-randomized studies have a mean quality score of 11.8 (105, 110-113, 115, 117, 119, 123-125).

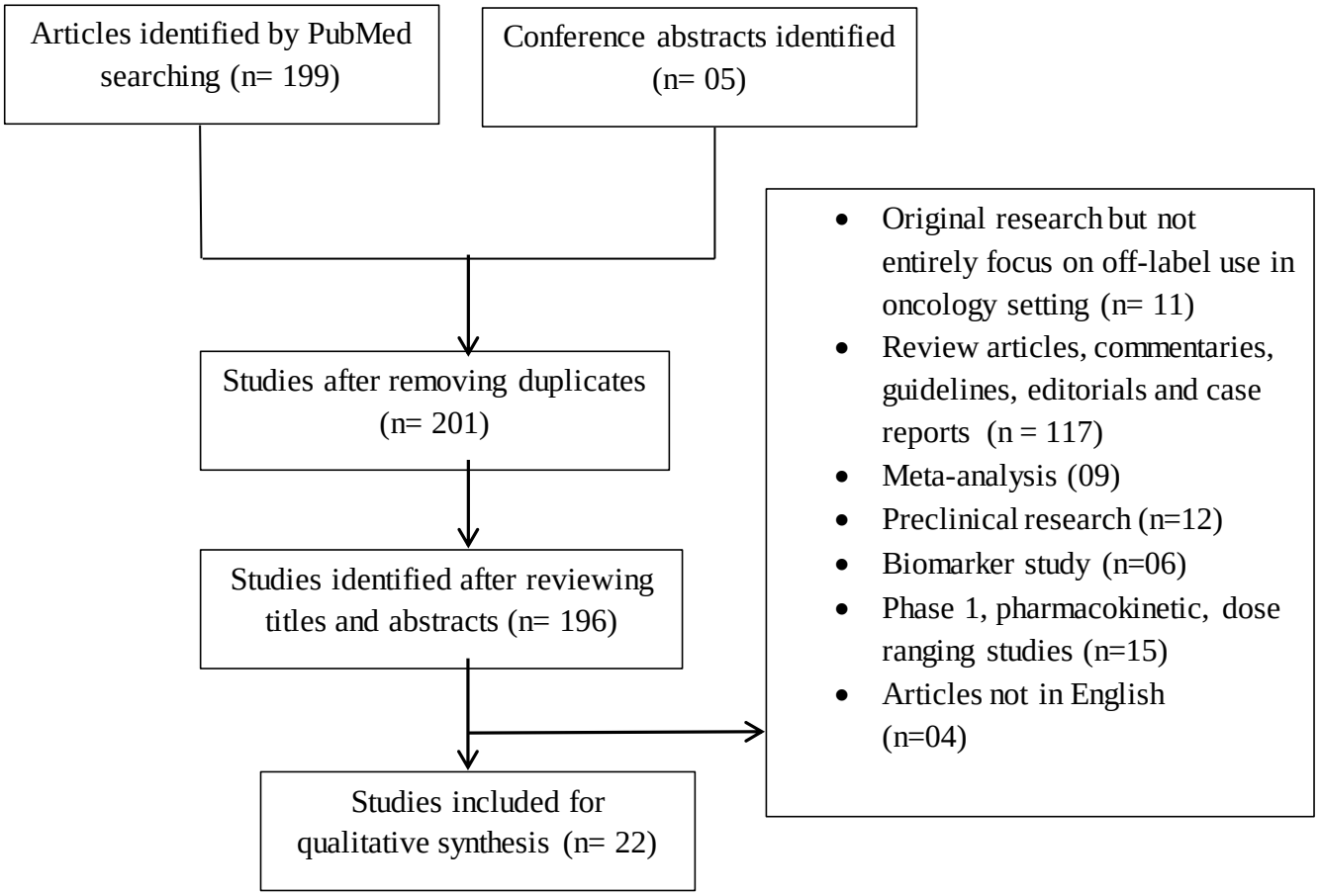

Figure 1 Flow diagram showing study extraction and selection

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Table 4 Characteristics of the included studies focusing on the off-label use of aflibercept

Sr. No	Reference	OL category	Study design	Treatment arm(s)	Study population	Clinical activity	Main conclusion	Quality score
1	Folprecht et al [104]	4	Randomized, open-label phase II study	Aflibercept (4mg/kg) plus mFOLFOX6 vs. mFOLFOX6	Metastatic colorectal cancer (n=236)	PFS: 8.77 vs. 8.48 months Response rate: 49.1 vs. 45.9%	Increased toxicity	3
2	Tang et al [105]	3	Non-randomized open-label, phase II study	Aflibercept (4mg/kg)	Metastatic colorectal cancer (n=75)	PFS: 2 months (bevacizumab-naïve) and 2.4 months (bevacizumab pretreated) OS: 10.4 months (bevacizumab-naïve) and 8.5 months (bevacizumab pretreated)	Limited activity with moderate toxicity	13
3	Benoist et al [106]	4	Single-arm phase II study	Aflibercept (4mg/kg) plus OPTIMOX	Metastatic colorectal cancer (n=49)	PFS: 9.3 months ORR: 65.9% (29/44 evaluable patients)	Clinically active	--
4	John et al [107]	4	Single-arm phase I/II study	Aflibercept (6mg/kg) plus capecitabine	Metastatic colorectal cancer (n=55)	PFS: 4.1 months OS: 9.3 months ORR: 6% (2/35 evaluable patients)	Acceptable safety profile with encouraging clinical activity	--
5	Peter et al [108]	1	Phase II, non-randomized, single arm study	Aflibercept (4mg/kg) plus 5-Fluorouracil and radiation	Stage II/III rectal cancer (n=39)	pCR: 25% (4/32 resected patients)	Well tolerated	--
6	Ramlau et al [109]	1	Phase III randomized control study	Aflibercept (6mg/kg) plus docetaxel vs. placebo plus docetaxel	Metastatic non-small-cell lung cancer (n=913)	PFS: 5.2 vs. 4.1 months OS: 10.1 vs. 10.4 months ORR: 23.3% (94/404 evaluable patients) vs. 8.9% (36/406 evaluable patients)	Increased toxicity	5
7	Leighl et al [110]	1	Phase II, non-randomized, single arm study	Aflibercept (4mg/kg)	Lung adenocarcinoma (n=98)	PFS: 2.7 months OS: 6.2 months ORR: 2%	Well tolerated	14
8	Chen et al	1	Phase II, non-	Aflibercept (6mg/kg)	Metastatic	PFS: 5 months	Trial terminated	12

	[111]		randomized, single arm study	plus pemetrexed and cisplatin	non-small-cell lung cancer (n=42)	ORR: 26% (10/34 evaluable patients)	due to serious toxicity	
9	Coleman et al [113]	1	Single-arm phase I/II study	Aflibercept (6mg/kg) plus docetaxel	Recurrent ovarian, primary peritoneal, or fallopian tube cancer (n=46)	PFS: 6.4 months OS: 26.6 months ORR: 54% (24/46 evaluable patients)	Substantial anti-tumour activity	12
10	Mackay et al [112]	1	Phase II, non-randomized, single arm study	Aflibercept (4mg/kg)	Uterine leiomyosarcoma (n=41) Carcinosarcoma (n=22)	For uterine leiomyosarcoma TTP: 1.8 months For Carcinosarcoma TTP : 1.6 months	Modest activity in uterine leiomyosarcoma Minimal activity in Carcinosarcoma	13
11	Tew et al [114]	1	Randomized, double-blind, phase II, parallel-arm study	Aflibercept (2mg/kg) vs. Aflibercept (4mg/kg)	Advanced ovarian cancer (n=218)	For aflibercept (2mg/kg) cohort PFS 13 weeks, OS: 59 weeks ORR: 11.5% For aflibercept (4mg/kg) cohort PFS: 13.1 weeks , OS: 49.3 weeks ORR:11.6%	Well tolerated	3
12	Coleman et al [115]	1	Phase II, non-randomized, single arm study	Aflibercept (4mg/kg)	Recurrent or persistent endometrial cancer (n=49)	PFS: 2.9 months OS: 14.5 months ORR: 7% (3/44 evaluable patients)	Clinically active but significant toxicity	15
13	Gotlieb et al [116]	1	Randomized, double-blind, phase II, parallel-arm study	Aflibercept (4mg/kg) vs. placebo	Malignant ovarian ascites (n=55)	Time to repeat paracentesis: 55.1 vs. 31.8 days	Effective but use with caution due to fatal toxicity	5
14	Colombo et al [117]	1	Phase II, non-randomized, single arm study	Aflibercept (4mg/kg)	Malignant ovarian ascites (n=16)	Repeat paracentesis response rate: 62.5% PFS: 59.5 days	Effective but safety concerns	13
15	Tannock et	1	Phase III	Docetaxel plus	Metastatic	PFS: 6.9 vs. 6.2 months	No survival	5

	al [118]		randomized control study	prednisolone with vs without Aflibercept (6mg/kg)	castrate-resistant prostate cancer (n=1224)	OS: 22.1 vs. 22.2 months	benefit but added toxicity	
16	Twardowski et al [119]	1	Phase II, non-randomized, single arm study	Aflibercept (4mg/kg)	Metastatic Urothelial Cancer (n=22)	PFS: 2.7 months ORR: 4%	Limited activity and well tolerated	12
17	Roberto et al [120]	1	Phase II, randomized, parallel arm study	Aflibercept (1mg/kg) vs. Aflibercept (4mg/kg)	Renal cell carcinoma (n=94)	PFS: 8.3 vs. 10.9 weeks ORR: 3.1 vs. 1.7%	Clinically active	--
18	Rougier et al [121]	1	Phase III randomized control study	Aflibercept plus gemcitabine vs. gemcitabine plus placebo	Metastatic pancreatic cancer (n=546)	PFS: 3.7 vs. 3.7 months OS: 6.5 vs. 7.8 months	Well tolerated	5
19	Sherman et al [122]	1	Phase II, non-randomized, single arm study	Aflibercept (4mg/kg)	Radioactive iodine-refractory thyroid cancer (n=21)	Stabilised disease: 86% (18 /21) No response reported	Stabilised disease common and manageable toxicity	--
20	Sideras et al [123]	1	Phase II, non-randomized, single arm study	Aflibercept (4mg/kg)	Metastatic breast cancer (n=21)	PFS: 2.7 months OS: 12.7 months	Efficacy not achieved	13
21	de Groot et al [124]	1	Phase II, non-randomized, single arm study	Aflibercept (4mg/kg)	Recurrent malignant glioma (n=58)	For anaplastic cohort PFS: 24 weeks, ORR: 18% (7/39) For glioblastoma cohort PFS: 12 weeks, ORR: 44% (7/16)	Minimal activity and moderate toxicity	11
22	Tarhini et al [125]	1	Phase II, non-randomized, single arm study	Aflibercept (4mg/kg)	Stage III/IV melanoma (n=41)	PFS: 3.7 months OS: 16.3 months ORR: 7.5% (3/41 evaluable patients)	Promising activity	14

*PFS: Progression-free survival, OS: Overall Survival, PCR: Pathological complete response, ORR: overall response rate, TTP: Time to progression, OL categories: 1) Unapproved drug for specific tumour group, 2) Unapproved drug for specific stage of disease (neoadjuvant, adjuvant, palliative, curative), 3) Unapproved line of treatment 4) Modified application of drug (e.g. dose,frequency, combination, route of administration).

2.3.1 Colorectal cancer

Aflibercept blocked the angiogenesis pathway in various preclinical xenograft models of human colon cancer. Phase 2-3 trials suggested significant anti-tumour activity of aflibercept in mCRC patients progressed after oxaliplatin-based regimen (93, 105, 126-128). The current NCCN guideline for colon cancer states that aflibercept is only active when prescribed in combination with FOLFIRI in FOLFIRI naïve patients. Aflibercept is only recommended in the second-line treatment setting in combination with FOLFIRI or irinotecan after disease progression on regimen not comprising of irinotecan (129). There is a paucity of evidence to recommend off-label use of aflibercept with FOLFIRI in patients who progressed on bevacizumab plus FOLFIRI.

The off-label use of aflibercept as first-line for the treatment of mCRC has been studied in two phase II trials (104, 106). The AFFIRM study randomised 236 chemo-naïve mCRC patients to receive either mFOLFOX6 plus aflibercept or mFOLFOX6 alone (104). The median progression-free survival (PFS) was 8.5 months (95% CI; 7.89-9.92) for the aflibercept plus mFOLFOX6 group and 8.8 months (95% CI; 7.62-9.27) for the mFOLFOX6 group. The clinical response was observed in 49% (95% CI; 39.7-58.6) and 46% (95% CI; 36.4-55.7) for the patients treated with and without aflibercept respectively. The trial did not have sufficient statistical power to draw a meaningful comparison between the two treatment groups. The authors concluded that aflibercept does not provide any benefit in terms of PFS but increased serious toxicities risk including hypertension, proteinuria, neuropathy, and clotting disorders.

The VELVET trial assessed the safety and efficacy of the OPTIMOX-aflibercept as first-line treatment of mCRC patients (106). The cohort comprised of 49 patients who

fortnightly received six cycles of mFOLFOX7 plus aflibercept as induction therapy. Subsequently, patients received fluoropyrimidine (5FU or capecitabine) plus aflibercept maintenance therapy till disease progression or toxicity. The median PFS was 9.3 months (95% CI; 8.7-12.6) and the objective response rate was 59.2% (N = 29/49). The common grade 3-4 adverse events were hypertension (23%), fatigue (12%), neuropathy (10%) and neutropenia (10%). The investigators concluded that OPTIMOX-aflibercept could be a potential treatment regimen for chemo-naïve mCRC patients and recommended additional study to confirm the findings in a larger population.

Tang et al carried out a phase 2 trial evaluating the clinical activity of aflibercept as single agent in refractory metastatic colorectal cancer patients (105). There were two groups in the entire cohort of seventy-five patients; bevacizumab-naive (n = 24) and previous bevacizumab (n = 51). The median PFS was 2 months (95% CI; 1.7-8.6) in bevacizumab-naïve and 2.4 months (95% CI; 1.9-3.7) in the previous bevacizumab group. Median overall survival (OS) was 10.4 months (95% CI; 7.6-15.5) and 8.5 months (95% CI; 6.2-10.6) respectively. The study concluded that single-agent aflibercept cannot be recommended due to limited clinical activity and previous bevacizumab has no role on efficacy. In another study, a novel combination regimen of aflibercept plus capecitabine was evaluated by a phase 1-2 trial in a cohort of 47 patients with mCRC with chemotherapy refractory disease (107). The median PFS was 4.1 months (95% CI; 2.3-4.8), median OS was 9.3 months (95% CI; 6.2–N/A) and the response rate was 6% in 35 evaluable patients. The authors determined that the clinical activity of this novel combination regimen was encouraging for further investigations.

Aflibercept could be considered to be given in combination with anti-VEGF monoclonal antibodies. But at present, there is not data supporting the use of aflibercept as combination therapy with bevacizumab, cetuximab or panitumumab in an off-label manner (129). The role of aflibercept in combination with 5-fluorouracil and radiation as potential neo-adjuvant therapy for stage II/III rectal cancer patients was studied in a phase 2 trial (108). A total of thirty-nine patients participated in the study which has pathological complete response rate (pCR) as the primary endpoint and disease-free survival (DFS), sphincter preservation (SP) rate and overall survival (OS) as secondary efficacy endpoints. A total of 32 patients were resected, 8 (25%) patients attained pCR, and the pathologic partial response was detected in 24 (75%) patients: 9 macroscopic, 15 microscopic). The sphincter preservation rate was 72%; 31 (97%) patients had R0 resection. Median OS and DFS were not achieved at the time point of data collection.

2.3.2 Lung cancer

VEGF pathway is important in the growth and progression of lung cancer as demonstrated in several pre-clinical tumour xenograft models. There are drugs including bevacizumab, sunitinib, and sorafenib which have shown significant angiogenesis inhibition either as a single agent or combination chemotherapy regimens (130, 131). A phase 2 trial was designed to study efficacy and safety of single-agent aflibercept in patients with platinum and erlotinib-resistant lung adenocarcinoma (110). A total of 98 patients were recruited, the median PFS was 2.7 months (95% CI; 2.2-3.4), median OS was 6.2 months (95% CI; 4.8-11.4) and the overall response rate by intent-to-treat approach was 2% (95% CI; 0.2-7.2). The common grades 3-4 adverse events were proteinuria, hypertension, and dyspnoea. The authors concluded that aflibercept as single

agent has limited clinical activity in heavily pretreated lung adenocarcinoma patients but well-tolerated with no unpredicted toxicities.

The international VITAL trial evaluated the efficacy of aflibercept plus docetaxel versus docetaxel monotherapy in 913 patients with metastatic non-squamous NSCLC progressed to platinum-based regimen (109). Aflibercept did not have any important impact on the overall survival. The median OS was 10.1 months (95% CI; 9.2 - 11.6) for aflibercept plus docetaxel and 10.4 months (95% CI; 9.2 - 11.9) for docetaxel alone. But the PFS appeared to be longer with aflibercept arm. The median PFS was 5.2 months (95% CI; 4.4 - 5.6) for aflibercept plus docetaxel and 4.1 months (95% CI; 3.5 - 4.3) for docetaxel monotherapy. However, aflibercept increased the risk of grade 3-4 adverse events including fatigue, neutropenia, stomatitis, and hypertension.

A phase 2 trial evaluated the efficacy and safety of topotecan plus aflibercept versus topotecan plus placebo in extensive stage small-cell lung cancer patients previously treated with platinum-based regimen. Aflibercept combination regimen showed better 3-month PFS (27% v 10%; P=0.02) but the toxicity was increased. OS was not considerably enhanced in both groups. A phase 2 trial was designed to evaluate safety and efficacy of aflibercept plus cisplatin and pemetrexed in patients with previously untreated metastatic non-squamous NSCLC (111). The study was reported median PFS of 5 months and ORR was 26% in 38 evaluable patients. But the study was later terminated because of three confirmed and two suspected cases of reversible posterior leukoencephalopathy syndrome (RPLS).

2.3.3 Gynaecological cancers

Increased expression of the VEGF levels has been linked with disease progression and poor prognosis in several gynaecological malignancies and endometrial sarcomas including carcinosarcoma and leiomyosarcoma (95, 127, 132-135). The efficacy and safety of aflibercept plus docetaxel was assessed by a Phase 1-2 trial in patients with recurrent ovarian, primary peritoneal, or fallopian tube cancer (113). The ORR was confirmed in 25 (54%) of 46 patients (95% CI; 39-69). The median PFS and OS was 6·4 months (95% CI; 5·1-10·3) and 26·6 months (95% CI; 13·1-N/A) respectively. The investigators concluded that aflibercept plus docetaxel appeared to be safe and clinically active in patients with recurrent ovarian cancer and strongly suggested that this combination could be clinically developed further into a worthwhile option for this type of patients.

A multi-centre phase 2 trial was undertaken to assess safety and efficacy of aflibercept monotherapy in patients with gynaecological soft tissue sarcoma (112). A total of 41 women with uterine leiomyosarcoma and 22 women with carcinosarcoma (19 uterine, 3 ovarian) participated in the study. In the leiomyosarcoma group, 11 (27%) women had stabilised disease with no apparent objective response seen. The 6 month PFS was 17%, with a median time to progression (TTP) of 1.8 months (95% CI; 1.6-2.1). In the carcinosarcoma group, 2 (9%) patients had SD and median TTP was 1.6 months (95%CI; 1.1-1.7) with no objective responses observed in the group. Aflibercept showed modest clinical activity in women with uterine leiomyosarcoma and negligible activity in women with carcinosarcoma. Tew et al evaluated the efficacy and safety of aflibercept at 2 different doses (2 mg/kg and 4 mg/kg) in patients with recurrent, platinum-resistant ovarian, peritoneal, or fallopian tube cancer who disease progressed after receiving

topotecan and/or pegylated liposomal doxorubicin (114). The median PFS was 13 weeks (95% CI; 11.7-16.7) and 13.3 weeks (95% CI; 12-18.9] in 2mg/kg (n=106) and 4mg/kg (n=109) cohort respectively. The median OS was 59 weeks (95% CI; 41.6-84.1) and 49.3 weeks (95% CI; 37.4-62.7) respectively. The response rate was similar in both cohorts. The authors concluded that aflibercept at both doses did not reach the primary endpoints.

A Phase 2 trial assessed safety and efficacy of single-agent aflibercept for the treatment of recurrent or persistent endometrial cancer (115). Among 44 patients recruited, the median PFS was 2.9 months (90% CI; 2.1-6.21) and median OS was 14.5 months (90% CI; 9.86-20.44 months). Although study met the pre-trial efficacy parameters, significant toxicities concerning cardiovascular, constitutional, metabolic haemorrhage were observed. A phase 2 trial showed that single-agent aflibercept reduced the need to repeat paracentesis in 55 patients suffering from malignant ascites in advanced ovarian cancer (116). The median paracentesis-free survival was 42 days (95% CI: 27 – 60) with aflibercept and 18 days (11 - 25) with placebo. In another phase 2 trial, 10 out of 16 enrolled patients with advanced epithelial ovarian cancer and symptomatic malignant ascites attained a response; the repeat paracentesis response rate of 62.5% (95% CI; 35.4-84.8) (117). The median PFS was 59.5 days (95% CI; 41-83). Aflibercept was found to be active against malignant ascites.

2.3.4 Urologic cancers

Aflibercept has been evaluated and is active either alone or with chemotherapy in preclinical models of prostate, renal cell and urothelial carcinoma (136-138). A phase 3 trial called ‘VENICE study’ compared aflibercept plus docetaxel and prednisolone versus placebo plus docetaxel and prednisolone in chemotherapy-naïve men with

metastatic castrate-resistant prostate cancer (118). Among a total of 1224 patients participated, the median PFS was 6·9 months (95% CI; 6·2–7·4) with aflibercept and 6·2 months (95% CI; 5·6-6·9) with the standard therapy. The median OS was 22·1 months (95% CI; 20·3-24·1) in the aflibercept group and 21·2 months (95% CI; 19·6–23·8) with standard therapy. There was a higher incidence of grade 3-4 gastrointestinal disorders, fatigue, hypertension, and infections. In conclusion, aflibercept did not result in longer overall survival but increased the incidence of fatal toxicities.

A single-agent aflibercept phase 2 trial in patients with metastatic urothelial cancer previously treated with platinum-based regimen found that aflibercept was well-tolerated but had limited clinical activity in this group of patients (119). Among 22 patients enrolled, only patients reported partial response and the median PFS was 2.79 months (95% CI; 1.74-3.88). A phase 2 trial assessed clinical activity of aflibercept at two different doses (1mg/kg and 4 mg/kg) in patients with clear cell metastatic renal carcinoma (120). A total of 59 and 35 patients were enrolled in 4 mg and 1 mg dose cohorts respectively. The median PFS was 10.9 weeks (90%CI; 8.7-15.4) and 8.3 weeks (90%CI; 7.9-9.6) in 4 mg and 1 mg dose cohort respectively. The authors concluded that aflibercept was active in clear cell renal carcinoma and worthy of further investigations.

2.3.5 Endocrine cancers

Pre-clinical research had suggested that targeting VEGF reduced tumour development and progression in thyroid and pancreatic cell lines (96, 139). A phase 3 trial assessed whether adding aflibercept to gemcitabine therapy improved overall survival in metastatic pancreatic cancer patients (121). The study was stopped prematurely as there was not significant improvement in overall survival with the addition of aflibercept. Based on the data of 546 patients at study cessation, the median OS and median PFS was

7.8 months (95% CI; 6.8-8.6) and 3.7 months (95% CI; 3.5-4.6) respectively which was non-superior than the placebo group.

A phase 2 trial studied safety and efficacy of aflibercept in patients with progressive, RAI-refractory/fluorodeoxyglucose (18-F)-avid, recurrent/metastatic, non-medullary, nonanaplastic thyroid cancer (122). Among 21 patients recruited, eighteen patients achieved stabilised disease and none of the patients has a partial or complete response. 10 out of 18 patients with stable disease continued for more than 6 months, 3 patients for more than 12 months and the median duration of stabilised disease on aflibercept was 178 days. The investigators concluded that aflibercept was not active in advanced thyroid cancer but durable disease stabilisation was common and adverse events were manageable.

2.3.6 Breast cancer

Aflibercept decreased the levels of VEGF secreted from both murine and human breast cancer cells and efficiently blocked VEGF-induced tyrosine phosphorylation of VEGFR2. Aflibercept as a single agent significantly reduced tumour microvessel density, tumour vasculature, cell proliferation and tumour growth of BT474 human breast cancer xenografts. Aflibercept reduced levels of both human VEGF and PlGF protein in-vivo (140). However, a phase 2 trial assessing the efficacy and safety of single-agent aflibercept failed to meet the expected efficacy goals in previously treated 21 metastatic breast cancer patients (123). At the time of study termination, median PFS and median OS was reported as 2.7 months (95% CI; 1.8-5) and 12.7 months (95% CI; 6.7-31.1) respectively. The common grade 3-4 toxicities were hypertension, fatigue, and dyspnoea.

2.3.7 Glioblastoma

Based on the promising results of aflibercept in preclinical glioma models, a phase 2 trial assessed its efficacy and safety in patients with recurrent malignant glioblastoma and anaplastic glioma (124, 141). The median PFS for patients with anaplastic glioma was 24 weeks (95% CI; 5-31) and 12 weeks (95% CI; 8-16) for glioblastoma patients. Aflibercept showed negligible evidence of activity in glioma and the trial was unsuccessful to meet the primary endpoints.

2.3.8 Melanoma

Aflibercept demonstrated to be potent to block angiogenesis and tumour shrinkage in pre-clinical melanoma model (142). Based on this, a multicentre phase 2 trial evaluated efficacy and safety of single-agent aflibercept in 41 patients with stage 3-4 melanoma of cutaneous and uveal origin (125). The median OS and PFS were 16.3 months (95% CI; 9.2-N/A) and 3.7 months (95% CI; 2.8-6.8) respectively. The partial response rate in 40 evaluable patients was 7.5% (95% CI; 2-20) and 50% patients have a 4 month or longer PFS. Aflibercept showed a promising response in metastatic melanoma of cutaneous or uveal origin that warranted further investigations either as single-agent aflibercept or in combination with other chemotherapy.

2.4 Discussion

The systematic literature review gave a summary of emerging evidence regarding the various off-label use of VEGF-targeting recombinant fusion protein aflibercept in cancer treatment. This study was conducted to generate data regarding the off-label use of newer targeted anti-cancer agents with aflibercept chosen as a prototype study drug. The major finding of this review revealed that aflibercept has been clinically assessed for

different off-label use but currently none of the off-label use can be recommended for routine practice either as a single agent or in combination chemotherapy. This is due to lack of efficacy, increased risk of toxicity or insufficient scientific evidence. The role of aflibercept for clinical use in advanced carcinoid and esophagogastric cancer is presently under investigation (143, 144).

The promising result of inhibiting angiogenesis in cancer animal models was clinically proven only for second-line treatment of colorectal cancer which has obtained FDA approval. However, this was not observed for other solid tumours causing contrasting findings in the pre-clinical research and human clinical trials. There are few possible explanations as to why angiogenesis inhibition using aflibercept failed to deliver in clinical trials, particularly the high rate of toxicity observed in patients which frequently led to treatment discontinuation and poor patient compliance (104, 105, 109, 111, 115-117, 119, 124, 125). One reason could be the impact of narrow patient selection criteria which could not provide sufficient population heterogeneity (109, 110, 114, 121, 123). Another reason is that for some malignancies investigated including breast and prostate which are less aggressive, no impact of treatment arm on cancer progression or survival was observed given the short duration of follow-up (118, 123). Patient cross-over and impact of previous treatment exposure could also act as a potential confounder. All these factors can influence the clinical response and statistically significant survival benefits for the off-label use of aflibercept in these tumours.

Some scientists have argued that a problem exists with angiogenesis inhibition as an approach for anticancer treatment since in several clinical trials angiogenesis inhibitors failed despite encouraging pre-clinical results (145). One possible explanation is that

while anti-angiogenesis compounds display tumour regression property, they also have an intrinsic property to induce tumour resistance. Tumours exposed to anti-angiogenic drugs acquire phenotypic resistance due to VEGF-independent vascular regrowth utilising pro-angiogenic ligands of fibroblast growth factor-2 (FGF2) (146). Another fact observed with anti-VEGF therapies is the aggressive metastatic tumour growth and invasiveness following short exposure to treatment (147, 148). In addition to this, preclinical animal models for studies in angiogenesis inhibition use fast growing transplantable mouse tumours or human tumour xenografts which are generally grown as solid, localized tumours in subcutaneous tissues. This undoubtedly exaggerates the anti-tumour effects using anti-angiogenic agents. In such preclinical models, distant metastatic are not the focus of treatment and anti-angiogenic effect of study drug could be different at such sites because of the unique vasculature of tumour mass (149, 150). Moreover, the transplantable tumour models comprise of a high proportion of immature new vessels which are more susceptible to escalated anti-angiogenic effects. Thus, the significant antitumour effects observed in pre-clinical models might not be observed during the clinical research.

The major limitation of the review is the variability in quality as well as the quantity of evidence assessing safety and efficacy of the off-label use of aflibercept. This makes recommending any off-label use for routine practice extremely difficult or impossible. In the present review, a wide array of data presented in randomized double-blind controlled trials, non-randomised controlled trials, single arm studies and conference abstracts were considered for evidence appraisal to study the off-label use of aflibercept. Many of the controlled trials included in the review were of low quality due to lack of randomization, blinding, inadequate control arm and sample size in the study design. This may raise the

question on the quality of evidence and its reliability for informing clinical decisions and other relevant stakeholders. But for certain cancers, limited evidence could be reasonable for off-label prescribing. For treating rare tumours, this could be standard oncology practice. In France, a registry of 249 soft tissue sarcoma patients treated them with targeted therapies including several tyrosine kinase inhibitors based on the evidence published as conference abstracts and biological hypothesis (151). In cancer setting, what constitutes 'good evidence' would be considerably lenient as providers often rely on data derived from low-quality studies or gray literature. A study estimated that almost 50% of the conference abstracts on studies regarding new oncology drugs remained unpublished (152).

2.5 Conclusion

Aflibercept has the ability to bind with all isomers of VEGF-A as well as to VEGF-B and PIGF that are critical in angiogenesis pathway. Pre-clinical and clinical research has delivered evidence that support angiogenesis inhibition effects resulting in meaningful tumour shrinkage and statistically significant survival benefits with manageable toxicities. However, this is only true for metastatic colorectal cancer when aflibercept is used in accordance with FDA approved indication. Currently, the off-label use of aflibercept in indications including prostate, breast, renal, urothelial, pancreatic, melanoma, glioblastoma, ovarian and lung cancer is not recommended for clinical practice. All these off-label uses are considered as 'investigational' unless good evidence supporting such use is further accrued. Also, the role of aflibercept in other solid tumours is not yet successful might be due to activation of resistance pathway or other mechanisms not applicable to anti-angiogenesis therapy. The identification of predictive biomarkers which can help identify patients who are most suited for aflibercept based therapy is also required.

3 Off-label prescribing of aflibercept under special access program in Singapore

3.1 Introduction

The use of medicines approved by a country's regulatory authority constitutes an important part of the quality of care and patient safety agenda. However in routine clinical practice, the physician may select a drug that have yet received formal marketing authorisation for the patient's particular disease but has relevant scientific evidence guiding its use by the patient. Hence, regulatory bodies in many countries have created special access program (SAP) to provide medicines with a good balance of benefit and risk and are yet to complete formal licensing procedures (153, 154).

SAPs permit patients to get drugs that lack formal regulatory approval for commercial use. SAPs have several forms in different countries mainly called as special access, compassionate use, expanded access or named patients assistance programs (155). These programs are created to facilitate drug access on the basis of compassion and not meant to undermine clinical trial enrollment and drug development process (156). In Singapore, this program is availed on named patient basis by the Health Sciences Authority (HSA) (157). The approval for unregistered drug product must be obtained from the Therapeutic Product Branch of HSA. The physician must apply to HSA on a named patient basis through a separate application form and must contain information of the medicinal product to be imported for use and details of the importer, as well as the prescriber responsible. The medicinal product must be available within 6 months of application otherwise stated and prescribing physician must keep a proper record of its supply and use. The advantages of this program are that it may be used to provide investigational drugs as "last hope" for patients with exhausted lines of treatments and

for orphan indications (158). This program also enables access to drugs when there is no incentive for the pharmaceutical company to seek local registration. Many countries mandate adverse event reporting for drugs used under the SAPs but currently there is no regulatory requirement for reporting efficacy and safety data for such drugs in Singapore (157).

The drugs provided by pharmaceutical companies under SAP are generally free of any cost involved. However, there are concerns expressed that the drugs used as expanded access may lead to inappropriate drug use. This could be mainly in the form of off-label drug use which is sometimes also termed as 'off-protocol therapies' in this particular setting (159). In view of the accelerated drug approval process and the significant lag time between USFDA/EMA and HSA approvals, it is foreseeable that the use of SAPs may increase in the future. Therefore, it is timely to examine the use of drugs under the SAPs so that greater clarification can be provided on the appropriateness of their use in the local population. This may in turn provide important information that may guide such practices locally. Also, it is argued that such drug use outside trial condition and that too with incomplete information when the trial is still being conducted might jeopardize the patient's safety (160). Hence, we conducted an exploratory descriptive study reporting off-label use and clinical outcomes of aflibercept under SAP at a major public cancer center in Singapore. Aflibercept was approved by USFDA in 2012, and HSA in 2014. Pending local registration in Singapore, Aflibercept was available under named patient assistance program for treatment of metastatic colorectal cancer which was terminated after it was registered with the HSA.

3.2 Methods

3.2.1 Study design

We retrospectively reviewed unregistered drug application forms from January 2012 to December 2014 submitted to HSA requesting aflibercept on the basis of expanded access program at NCCS. We consecutively included all the cancer patients who received aflibercept without any specific exclusion criteria. The study was approved by the Singhealth ethical review board. The requirement of informed consent was waived for this study. The primary aim of the study was to report any off-label use associated with aflibercept use in cancer patients. The secondary objective was to report efficacy and safety of aflibercept under SAP for the indicated use. Off-label use was assessed for indication, line of treatment and dose. For prescribing information, both USFDA and HSA labels were reviewed.

3.2.2 Data collection

Based on the information gathered from the HSA application forms, two oncology pharmacists retrieved medical records of adult cancer patients who received aflibercept under expanded access use with palliative intent from the NCCS electronic database. The information on patient baseline characteristics such as age, gender and ethnicity were extracted. Clinical information including the primary site of cancer, stage of cancer, Eastern Cooperative Oncology Group (ECOG) performance, lines of treatment received, indication, corresponding drug response and toxicities were also extracted from the patients' medical records into the study data collection form (Appendix II).

3.2.3 Statistical analysis

Baseline characteristics and toxicity data were evaluated by descriptive statistics. Objective clinical responders were patients who achieved complete response (CR) or

partial response (PR). Disease control was achieved in patients with CR, PR, or stable disease (SD). All the outcomes were documented as reported by the physicians in the medical records based on the Response Evaluation Criteria In Solid Tumors (RECIST) criteria (161). Progression-free survival (PFS) was measured from the start of aflibercept therapy to the date of an event, defined as the first documented progression under treatment or death because of any reason under treatment. Patients who did not have any event were censored during the course of treatment and in cases of premature treatment cessation, before the end of follow-up or at the date of the last contact still under treatment. Overall survival (OS) was defined as the period between the start of aflibercept therapy till documented event of death or censored at the date of the last contact for patients who are alive. PFS and OS were measured using the Kaplan-Meier method and reported as medians with corresponding two-sided 95% confidence intervals (CIs). Safety assessment was based on the incidence and severity of toxicities, graded according to the Common Terminology Criteria for Adverse Events (CTCEA) criteria. All the analysis was carried out in 22.0 version of Statistical Package for Social Sciences (SPSS) software.

3.3 Results

3.3.1 Patient characteristics

From January 2012 to December 2014, 22 patients at NCCS were screened and got approval from HSA to receive aflibercept under SAP. Two patients never received the drug leaving a total of 20 patients receiving courses of aflibercept therapy. Majority of patients (40%) received 1 to 4 cycles of chemotherapy, followed by patients (35%) receiving more than 10 chemotherapy cycles and rest of patients (25%) received 5 to 10 chemotherapy cycles before starting aflibercept. The patients' characteristics are

presented in Table 5. The population consisted predominantly of Chinese patients (90%) and the mean age was 58 years old. Most of the patients (90%) had ECOG status of 0 or 1. All the patients received aflibercept with palliative intent. Most patients (75%) were metastatic at diagnosis and had 3 or more distant metastatic sites at the start of aflibercept chemotherapy. The common sites for distant metastasis were peritoneum (60%), liver (55%) and lung (55%).

Table 5 Patients Characteristics (N=20).

Patients Characteristics	**N = 20 (%)**
Gender	
• Male	11 (55)
Ethnicity	
• Chinese	18 (90)
• Malays	01 (05)
• Others	01 (05)
Age at diagnosis (years)	
• Mean $\pm$ SD	58 $\pm$12
Primary tumour localization	
• Sigmoid colon	17 (85)
• Cecum	02 (10)
• Rectum	01 (05)
Molecular status	
• KRAS-wild type	06 (30)
• KRAS-mutated	03 (15)
• KRAS-unknown	07 (35)
• BRAF-wild type	05 (25)
• BRAF-mutated	02 (10)
Metastatic at diagnosis	
• Yes	15 (75)
Metastatic sites involved at baseline excluding primary organ	
• 1	03 (15)
• 2	08 (40)
• 3 or more	09 (45)
Metastatic Sites	
• Peritoneum	12 (60)
• Liver	11 (55)
• Lung	10 (55)
• Lymph nodes	10 (55)
• Ovary	03 (15)
• Bone	03 (15)

ECOG status at the start of aflibercept use • 0 • 1 • 2	 08 (40) 10 (50) 02 (10)
Previous Radiotherapy	09 (45)
Previous Surgery	11 (55)
Previous Chemotherapy* • Adjuvant XELODA • Adjuvant XELOX • XELOX • XELOX plus Bevacizumab • XELOX plus Cetuximab • FOLFOX • FOLFOX plus Bevacizumab • FOLFIRI • XELIRI • XELODA	 05 (25) 04 (20) 10 (50) 02 (10) 01 (05) 01 (05) 02 (10) 01 (05) 01 (05) 01 (05)
Median follow-up time from diagnosis	25 months

*For the treatment of metastatic colorectal cancer unless stated.

3.3.2 Off-label use of aflibercept

All the patients received aflibercept for the palliative treatment of metastatic colorectal cancer which is an FDA approved indication. Aflibercept was given in combination with folfiri (irinotecan plus folinic acid and 5-fluorouracil). It was administered at a dose of 4 mg per kg body weight as intravenous infusion for 1 hour every 2 weeks. All the patients on average received six cycles of aflibercept. Most of the patients (85%) received oxaliplatin containing regimen. Off-label use of aflibercept was found in 5 patients (25%) among the entire cohort. Off-label use was due to prescription of aflibercept plus folfiri for unapproved line of treatment (25%). One patient received XELIRI (irinotecan and capecitabine combination) and other patient received XELODA (capecitabine) as second-line treatment before receiving aflibercept in the third-line treatment setting.

Table 6 Information on Aflibercept usage under SAP (N=20).

Indication • Treatment of metastatic colorectal cancer	 20 (100)
Intent of aflibercept therapy • Palliative	 20 (100)
Start dose • 4 mg per kg	 20 (100)
Previous oxaliplatin containing regimen	17 (85)
Modification in FOLFIRI due to toxicity	09 (45)
Average number of aflibercept treatment cycles • Median (Range)	 06 (1-26)
Off-label use for unapproved line of treatment • Third-line treatment setting • First-line treatment setting	 02 (10) 03 (15)

3.3.3 Efficacy of aflibercept therapy

For the entire sample population, two patients (10%) achieved partial response, ten patients (50%) achieved stabilised disease (SD) and disease control rate was (DCR) was 60% (n=12). None of the patient achieved complete response. Carcinoembryonic antigen was normalised (≤ 3ng/ml) in three patients following treatment with aflibercept. The median follow-up from diagnosis was 25 months. As shown in Figure 4, the median PFS for the whole group was 5.9 months (95% CI; 5.7- 6.4) and median OS was 15 months (95% CI; 10.9 - 19). The main reason for treatment discontinuation was progression in disease status (75%).

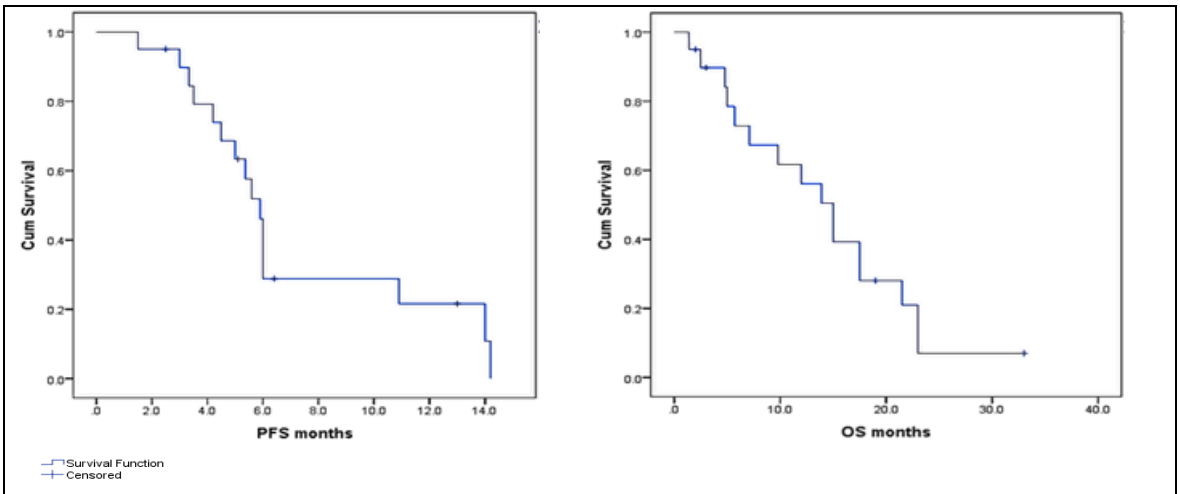


Figure 2 Progression-free survival (PFS) and Overall survival (OS) data for the whole group (N=20).

3.3.4 Toxicities related to aflibercept therapy

The toxicity due to aflibercept and folfiri combination regimen is shown in Table 7. Grade 1-2 toxicities were experienced by 50% of the patients and grade 3-4 adverse events were encountered in 5% of total patients. The common toxicity of any grade was nausea, fatigue and neutropenia. During the treatment, febrile neutropenia and proteinuria were the only serious toxicity reported among the two patients. There was no case of treatment-related death.

Table 7 Toxicities and laboratory abnormalities due to aflibercept plus folfiri combination therapy.

Type of toxicity	Toxicities	Total N (%)	Grade 1 N (%)	Grade 2 N (%)	Grade 3/4 N (%)
Blood/Bone Marrow	Neutropenia	08 (40)	05 (25)	03 (15)	00 (00)
	Febrile neutropenia	04 (20)	02 (10)	01 (05)	01 (05)
	Lymphopenia	05 (25)	05 (25)	00 (00)	00 (00)
	Thrombocytopenia	02 (10)	02 (10)	00 (00)	00 (00)
Gastrointestinal	Mucositis	04 (20)	04 (20)	00 (00)	00 (00)
	Anal Fistula	01 (05)	01 (05)	00 (00)	00 (00)
	Stomatitis	02 (10)	02 (10)	00 (00)	00 (00)
	Nausea	10 (50)	10 (50)	00 (00)	00 (00)
	Constipation	03 (15)	03 (15)	00 (00)	00 (00)
Cardiovascular	Hypertension	02 (03)	01 (05)	01 (05)	00 (00)
	Thromboembolic event	01 (05)	00 (00)	01(05)	00 (00)
Respiratory system	Hoarseness	03 (15)	03 (15)	00 (00)	00 (00)
Connective tissues	Arthralgia	01 (05)	01 (05)	00 (00)	00 (00)
Nervous system	Peripheral Neuropathy	04 (20)	04 (20)	00 (00)	00 (00)
	Paresthesia	05 (25)	05 (25)	00 (00)	00 (00)
Metabolism and nutrition disorders	ALT increased	03 (15)	03 (15)	00 (00)	00 (00)
	AST increased	04 (20)	04 (20)	00 (00)	00 (00)
	Weight loss	04 (20)	04 (20)	00 (00)	00 (00)
	Loss of appetite	05 (25)	05 (25)	00 (00)	00 (00)
	Proteinuria	01 (05)	00 (00)	00 (00)	01 (05)
Lymphatic	Peripheral edema	01 (05)	01 (05)	00 (00)	00 (00)
Dermatology	Alopecia	01 (05)	01 (05)	00 (00)	00 (00)
	Skin reactions	04 (20)	04 (20)	00 (00)	00 (00)
General symptoms	Fever	03 (15)	03 (15)	00 (00)	00 (00)
	Fatigue	07 (35)	05 (25)	02 (10)	00 (00)

*below are described the numbers and percentages of patients with at least one toxicity of each grade. (Patient could have experienced several grades for the same type of toxicity). ALT: alanine aminotransferase, AST: Aspartate transaminase.

3.4 Discussion

The present study for the first time provided evidence regarding the existence of off-label prescribing in cohort of patients receiving therapy under SAP in an Asian oncology centre. Aflibercept which is a potent angiogenesis inhibitor was found to be prescribed in off-label manner among 25% of all patients. The use of drugs in an off-label manner under SAP implies that cost and accessibility issues impact the drug use practices. The drug was generally well-tolerated with acceptable toxicity profile. The aflibercept treatment showed reasonable efficacy in terms of PFS and OS among the Singaporean patients.

The main reason for off-label use of aflibercept was unapproved line of treatment as first-line and third-line treatment settings. The use of aflibercept in first-line setting is not recommended as the AFFIRM trial found that aflibercept did not improve the survival but led to increased toxicities (104). There is no data supporting the use of aflibercept in the third-line treatment setting and beyond. One patient in this study cohort was prescribed aflibercept plus folfiri as third-line treatment after irinotecan containing regimen (XELIRI) which was not recommend for use by NCCN treatment guidelines for metastatic colorectal cancer (129). The study did not found any form of off-label use of aflibercept either as single agent or in combination with drugs other than FOLFIRI for the treatment of metastatic colorectal cancer. The efficacy of the aflibercept in this study based on the median PFS (5.9 *vs* 6.9 months) and median OS (15 *vs* 13.5 months) was comparable with VELOUR study (93). A retrospective analysis for aflibercept under SAP in Malaysia found that aflibercept was well-tolerated and efficacy in terms of PFS was 6.12 months and OS was 12 months (162). They also found that 12% patients received aflibercept plus folfiri in off-label manner in first-line

treatment setting. The main serious toxicity observed was proteinuria and febrile neutropenia. A meta-analysis found that aflibercept carries an increased risk of high grade proteinuria in cancer patients with a cumulative incidence rate of 7.9 % (95% CI; 6.1–10.2) (163). The exact mechanism regarding aflibercept mediated proteinuria is yet to be established. Higher grade febrile neutropenia was more frequent with aflibercept plus folfiri (4%) than folfiri alone (2%) in the VELOUR study (93). Although the incidence for serious toxicity is low in the study population, the treating oncologist should be aware of potential serious side-effects and provide appropriate interventions to patients.

There are myriad of studies which have estimated off-label of anti-cancer drugs in routine practice (49, 63-67). Off-label prescribing of anticancer medicines under SAP is rarely reported. A Canadian study surveyed oncologists at a major academic hospital on use of enzalutamide in metastatic castrant-resistant prostate cancer under the SAP (164). The survey was completed for patients treated with enzalutamide by the oncologists. Enzalutamide which was approved for the post-docetaxel setting was given in off-label manner before the exposure to docetaxel in 65% of total patients. Out of 65% patients treated in off-label manner, 46% patients were given enzalutamide as first-line before the trial data on efficacy and safety was even released. The one of the reasons cited by treating oncologists to use enzalutamide in off-label manner was availability of drug under the SAP and free availability. The drugs used under SAP are provided by pharmaceutical companies without charging the patients. Hence, there is almost no reimbursement constraint for off-label prescribing of oncology products as experienced in routine practice (39). A recent study in Spain assessed the off-label use of bevacizumab which is also a potent angiogenesis inhibitor (165). In this retrospective observational study among 226 cancer patients, 43% of treatment episodes for

bevacizumab were off-label mainly due to unapproved indication (35 episodes) and unapproved line of treatment (31 episodes).

The investigational drug use under SAP are becoming increasingly controversial (166). Every year thousands of cancer patients are getting treated under expanded or compassionate access programs across the world (167-174). The main concern is that the drug is only approved for specific indication or line of treatment and off-label use for clinical situations where reliable statistics didn't exist could jeopardize patient safety. Because the newer agents or even combinations could have unexpected toxicity risk in the treatment setting outside the approved recommendations. For example, combination of ipilimumab and vemurafenib, both being potent BRAF inhibitor resulted in increased hepatotoxicity. This signifies that even though both agents are regulatory approved for the treatment of advanced melanoma, the requirement of clinical trial data is highly necessary for novel off-label use (175). The same concern over efficacy for the off-label drug use in SAP exists. If there is not enough evidence, either quality of life or survival should improve. For example, no practice setting should allow use of sorafenib as adjuvant therapy in hepatocellular carcinoma as it doesn't improve survival or quality of life irrespective of patients' wish or willingness to pay (176, 177).

There are factors related to patients and treating oncologists that could lead to off-label prescribing in SAP. As patients sometimes might misunderstand that chemotherapy could cure their cancer and be convinced to try a new drug as 'last hope' outside the trial conditions (178). Recently, a survey found that terminally ill patients in hopes of gaining access to experimental therapeutics are increasingly using social media and online petitions and majority of them are cancer patients (179). On the other hand, oncologists

have limited guidance on when to stop systematic chemotherapy in advanced cancers, especially in those who have exhausted approved drugs and lines of treatment (180). Also, oncologists are ethically obliged to offer the option of investigational drugs, but it might come at the cost of reduced trial participation (181). But we should bear in mind that in the context of life threatening disease like cancer, effective palliation may be undermined if patients are led to believe that the new experimental drug is their "last hope". This lost opportunity is a real harm that must be considered in any risk-benefit calculation (182).

The main limitation of the study was that the study has small sample size and focused on one drug only. Also this was a single centre study and hence, it is difficult to extrapolate the results. There should be more research on the appropriateness of drug use under SAP for knowledge generation and for improvement of patient safety and professional standards.

3.5 Conclusion

The study found the use of aflibercept outside the approved treatment regimen in metastatic colorectal cancer patients. The clinical place of aflibercept in the treatment of metastatic colorectal cancer would continue to be informed by future practice trends and new clinical trial data. This finding of providing the evidence of off-label prescribing in SAP is preliminary and requires further investigations as the impact of treatment on clinical outcomes and quality of life is uncertain.

4 Perception of oncology practitioners towards off-label use of anticancer medicines

4.1 Introduction

Off-label drug use applies when drugs are used for indication, dosage, route of administration or patients population that are different from those mentioned in their prescribing information (1). Such off-label drug use is particularly common in the field of cancer therapy, where there is a substantial unmet medical requirement, the variety of patient populations and a constellation of rare tumour types which together make standard therapy protocols more difficult to apply. Hence, off-label prescribing is an indispensable practice to provide patients what is necessary for their medical care based on the premise of available scientific evidence (49, 63-66, 183).

However, several concerns make off-label use of anti-cancer medicines controversial. Scientific evidence guiding the off-label prescribing is frequently inadequate. Coupled with uncertain clinical, humanistic and economic outcomes, a clinical judgement to prescribe off-label drugs may be sub-optimal in many clinical scenarios (184). All these concerns heightened the reason to understand practice concerning off-label drug use from the oncology practitioners' perspective. The previous study in the US reported significant variation in practice and attitudes among oncologists regarding such practice. The lack of consensus among oncologists could be a potential reason for variable drug access to patients with similar medical conditions (41, 185). Moreover, the non-medical oncology practitioners including nurses and pharmacists also play very significant role in cancer care. Oncology nurses provide patient services through different roles and clinical setting, such as nurse-run treatment centres, chemotherapy pre-screening, chemotherapy administration, manage symptoms and providing psychosocial support. They play vital

supportive roles in the treatment decisions and in improving communication between the clinicians and other members of the patient's healthcare team (186, 187). On the other hand, oncology pharmacists have to fulfil the roles of patient advocates and drug information specialists. Pharmacists could query and intervene off-label prescriptions containing anti-cancer drugs with insufficient evidence for efficacy and safety (188). As such, the views of nurses and pharmacists on off-label drug use are also critical.

Increasingly, oncologist practitioners are positioned under the professional and ethical code of conduct and responsibilities ensuring rationale drug use practice. Hence, the knowledge of their perceptions pertaining to off-label prescribing in cancer therapy is necessary. Currently, the oncology practitioners' perceptions on practice of off-label chemotherapy use and issues pertaining to lack of efficacy, unfavourable benefit-risk ratio, economic burden and informed consent for patients are not well documented. This study, therefore, attempted to document the perceptions of oncology practitioners regarding off-label drug use practice at the largest ambulatory cancer centre situated in Singapore. The study also compared perceptions regarding off-label drug use between medical oncologists and non-medical practitioners (pharmacists and nurses combined).

4.2 Methods

4.2.1 Settings

The National Cancer Centre (NCC) is one of the three public institutional centres for the diagnosis, treatment and research of cancer in Singapore. The NCC works across three main domains of cancer care, research, and education. NCC provides clinical services through its five clinical divisions (medical oncology, surgical oncology, radiation oncology, oncologic imaging and palliative care). There are three separate research

departments; clinical trials and epidemiological sciences, medical sciences and cellular and molecular research. The NCC delivers education to the general population, students from the three medical institutes in Singapore, local and overseas resident fellows, as well as, post-graduate research scholars. It currently treats 70% of government subsidized cancer patients and 50% of all patients in the island nation (189).

4.2.2 Study design

This was a cross-sectional survey-based research study conducted between November 2015 and January 2016. We attempted to gather maximum responses within the sample oncology practitioners working at the NCC. All medical oncologists (n=37), oncology trained nurses (n=36), and pharmacists (n=22) working at NCC were invited to participate in the study. Based on the information regarding oncology practitioners working at NCC, a total of 95 questionnaires were prepared for distribution**.** All the participants completed the survey questionnaire by pen and paper mode. The completed surveys were received after a one-month period. The survey did not contain any personal information that could potentially specify the identity of a particular participant. The questionnaire was written in English and required about 20 minutes for self-administration. The study was reviewed and approved by the Singhealth Institutional Review Board.

4.2.3 Survey design

The questionnaire (Appendix I) was developed after extensive literature review. A panel consisted of medical oncologists, oncology pharmacists, advanced practice nurses and academic pharmacists, examined the research instrument for face and content validity.

Criterion validity was not determined due to the absence of existing validated surveys. Pilot work was performed by three medical oncologists, three nurses and three pharmacists. Subsequently, questions were adjusted as appropriate for clarity and understanding before conducting the actual study. The questionnaire principally concentrated on off-label drug use in cancer therapy and consisted of three main segments. The first segment focused on explaining the objective of the study and information concerning the definition of off-label drug use. Several examples were provided to explain the terms for participants who might not be aware of the terminology. The second part described demographic details and information about each oncology practitioner's clinical experience including age, gender, profession, years of practice in oncology, patient load, and time spent on direct patient care. The third section was designed to capture perceptions regarding the practice of off-label drug use with an emphasis on the use of scientific evidence, expected efficacy, safety concerns, informed consent and out-of-pocket cost issues.

4.2.4 Data analysis

The information regarding participants' demographic and clinical practice is shown as frequencies and percentages. The responses on Likert scale (survey questions numbered 1, 9 and 12) were dichotomized into two categories. "Strongly agree" and "Agree" were categorized as "agree", while "Strongly disagree", "Disagree" and "Neutral" were categorized as "disagree" (190). To facilitate the analysis for group comparison, the non-medical practitioners included the nurses and pharmacists. Statistics such as Chi-square or Fischer exact test were employed to measure significant variances between two groups. The variables for multivariate regression analysis were selected based on the value of variance inflation factor (VIF < 3) as measure of multicollinearity and adequate

number of participants for each sub-category. Multivariate logistic regression was performed to adjust for potential confounding effects (such as age, gender, years of practice in oncology, patient load, time spent on patient care and profession). The effect size of the bivariate associations was represented as crude and adjusted odds ratio (OR). A two-tailed p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using Statistical Package for Social Sciences version 22 (SPSS Inc. Chicago, IL).

4.3 Results

4.3.1 Demographics

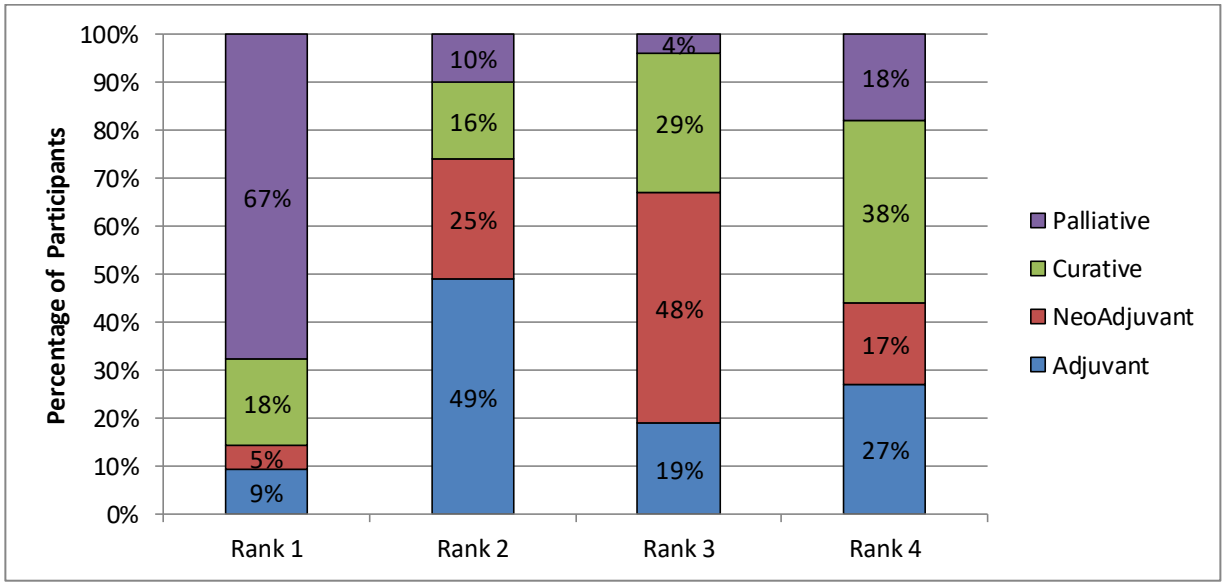
A total of 81 survey questionnaires were returned, providing a response rate of 85% (81 responses out of 95 practitioners). Among the surveyed oncology practitioners, the majority of them were nurses (38%) and medical oncologists (37%). The majority of the participants were females (n= 59; 73%) and aged between 31 and 40 years old (n= 33; 41%). Majority of medical oncologists (n= 23; 76%) and nurses (n=21; 67%) have practice experience in oncology of more than 6 years. Overall, 64% participants on average had a patient load of at least 100 cancer patients per month. Majority of medical oncologists (n=21; 69%), pharmacists (n=17; 85%) and nurses (n=28; 89%) reported spending minimum 40 hours of their time on direct patient care per week. The detailed demographics of the participants are summarized in Table 8.

Table 8 Demographic and practice information of the oncology practitioners.

Demographic details	Oncology practitioners N=81 (%)	Medical Oncologists N=30 (%)	Pharmacists N=20 (%)	Nurses N=31 (%)
Age (years)				
20 - 30	22 (27)	02 (07)	10 (50)	10 (32)
31 - 40	33 (41)	11 (36)	07 (35)	15 (48)
>40	26 (32)	17 (57)	03 (15)	06 (18)
Gender				
Male	22 (27)	19 (64)	03 (15)	00 (00)
Female	59 (73)	11 (36)	17 (85)	31 (100)
Years of practice in oncology				
<02	12 (15)	04 (14)	03 (15)	05 (16)
02 – 05	19 (24)	03 (10)	11 (55)	05 (16)
06 – 10	28 (34)	12 (40)	05 (25)	11 (35)
>10	22 (27)	11 (36)	01 (05)	10 (32)
Patients load per month				
21 - 50	09 (11)	05 (16)	01 (05)	03 (09)
51 – 100	20 (25)	06 (19)	04 (20)	10 (32)
101 – 150	19 (23)	06 (19)	03 (15)	10 (32)
>150	33 (41)	13 (45)	12 (60)	08 (26)
Time spent on patients care per week (hours)				
<40	21 (26)	09 (30)	03 (15)	03 (09)
41 - 60	39 (48)	14 (46)	14 (70)	16 (51)
>60	21 (26)	07 (23)	03 (15)	12 (38)
Off-label prescriptions prescribed/administered/dispensed in last one month				
<05	38 (47)	20 (64)	04 (20)	14 (45)
06 – 10	24 (30)	04 (14)	08 (40)	12 (38)
11 - 20	11 (13)	02 (07)	07 (35)	02 (06)
>20	08 (10)	04 (07)	01 (05)	03 (09)

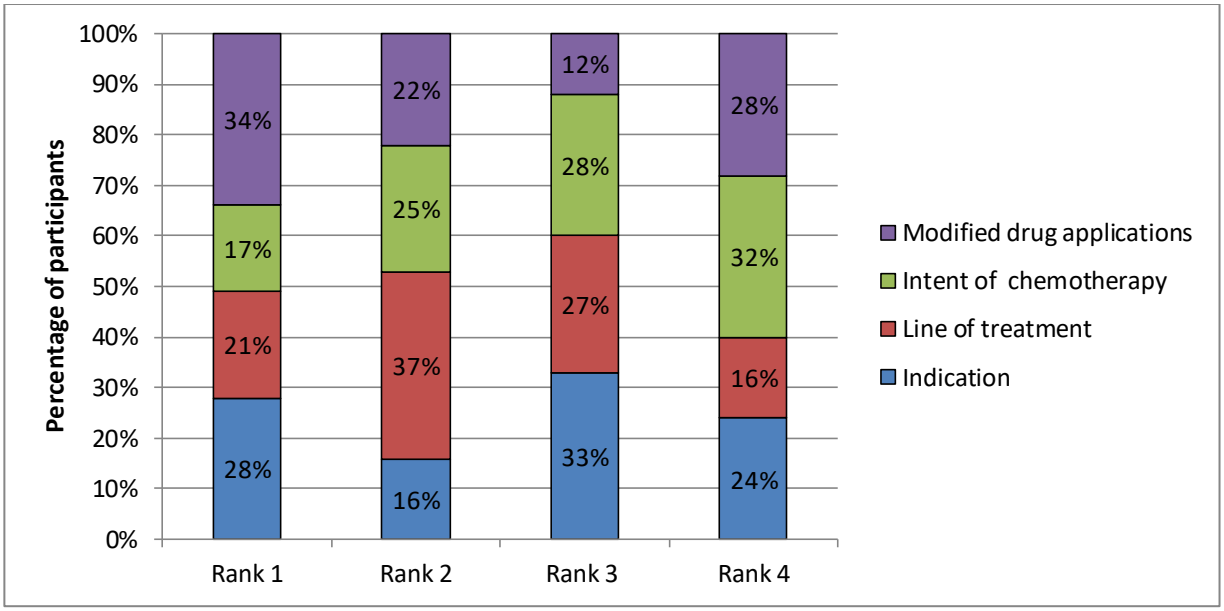
4.3.2 The practice of off-label drug use in oncology.

Majority of the surveyed oncology practitioners (77%) encountered maximum ten prescriptions containing off-label use during last one month of clinical practice. Off-label drug use was considered to be integral practice in cancer therapy by 57% of the participants. Off-label drug use was reported to be most common in palliative (67%) and adjuvant care (49%), followed by neoadjuvant (48%) and curative setting (38%) as shown in Figure 3.



≠Rank 1: Most common, Rank 4: Least common.

Figure 3 Reported therapeutic intent of off-label drug use.



≠Rank 1: Most common, Rank 4: Least common.

Figure 4 Reported categories of off-label drug use.

Table 9 Reported reasons for off-label prescribing (n=81).

Reasons	All Participants (%)	Medical Oncologists (%)	Non-medical practitioners			p-value
			Pharmacists (%)	Nurses (%)	Both (%)	
Advanced stage of disease where other lines of treatments are exhausted.	47 (58)	19 (63)	14 (70)	14 (45)	28 (55)	0.46
Rare oncologic conditions.	38 (47)	16 (53)	13 (65)	09 (29)	22 (43)	0.38
No approved agents for disease.	35 (43)	15 (50)	14 (70)	06 (19)	20 (39)	0.34
Sound evidence of efficacy and safety for off-label prescription.	33 (41)	16 (53)	13 (65)	04 (13)	17 (33)	0.08
Off-label therapy show better efficacy than standard therapy.	25 (31)	04 (13)	13 (65)	08 (26)	21 (41)	0.012
Lack of trial availability at the institution.	18 (22)	12 (40)	04 (20)	02 (06)	06 (12)	0.003
Patients refuse to enter clinical trial or are ineligible for them.	17 (21)	07 (23)	06 (30)	04 (13)	10 (20)	0.69

*The numbers may not add up to the total number of participants due to missing data. The p-value was calculated using the chi-square test or Fischer exact test as appropriate. The p-value is indicative of significance between medical oncologists and non-medical practitioners (pharmacists and nurses combined).

Among different categories of off-label drug use percieved to be practised, modified drug applications (34%), unapproved line of treatment (37%) were the most common forms of off-label drug use, followed by unapproved indication (33%) and unapproved

therapeutic intent (32%) as shown in Figure 4. The reasons and evidence base for off-label drug use are summarised in Tables 9 and 10. Major reasons cited by the participants were failure of standard lines of treatment in advanced stage of cancers (58%), rare tumours (47%), lack of approved drugs for particular cancer indication (43%) and sound evidence of supporting efficacy and safety of off-label drug use (41%).

However, off-label drug therapy having better efficacy than standard therapy was perceived as the more compelling reason for off-label prescribing by non-medical practitioners than medical oncologist (41% *vs.*13%, p=0.012). On the contrary, medical oncologists considered the lack of clinical trial availability at the institution as one of the reasons for off-label prescribing compared to non-medical practitioners (40% *vs.* 12%, p=0.003). Patient refusal or ineligibility for trial (21%) was the least convincing reason for off-label use in cancer therapy.

Table 10 Reported use of different evidence base for off-label prescribing (n=81).

Source of Evidence	All Participants (%)	Medical Oncologists (%)	Non-medical practitioners			p-value
			Pharmacists (%)	Nurses (%)	Both (%)	
Data from Phase 3 randomised control trial.	56 (69)	26 (86)	17 (85)	13 (42)	30 (59)	0.12
Off-label use included in treatment guidelines, such as NCCN	54 (66)	23 (76)	16 (80)	15 (48)	31 (61)	0.14
Meta-analysis of randomised control trials.	48 (59)	20 (66)	13 (65)	15 (48)	28 (55)	0.30
Data from Phase 2 clinical trial.	38 (47)	22 (73)	09 (45)	07 (22)	16 (31)	0.001
Conference abstracts of meetings, such as ASCO or ESMO.	29 (36)	17 (56)	08 (40)	04 (13)	12 (23)	0.003
Meta-analysis of observational studies.	25 (31)	09 (30)	06 (30)	10 (32)	16 (31)	0.89
Well conducted observational studies.	14 (28)	05 (16)	02 (10)	07 (22)	09 (17)	0.91
Case report or Case series.	19 (23)	07 (23)	03 (15)	09 (29)	12 (23)	0.98
Drug compendia information.	13 (16)	03 (10)	07 (35)	03 (09)	10 (19)	0.35

*The numbers may not add up to the total number of participants due to missing data. The p-value was calculated using the chi-square test or Fischer exact test as appropriate. The p-value is indicative of significance between medical oncologists and non-medical practitioners (pharmacists and nurses combined).

The majority of oncology practitioners supported off-label use based on Phase 3 randomized control trial (69%), treatment guidelines, such as NCCN (66%) and meta-analysis of randomised control trial (59%). It was found that medical oncologists would consider phase 2 trial data (73% *vs.* 31%, p=0.001) and conference abstracts (56% *vs.* 23%, p=0.003) as reasonable evidence for off-label drug prescribing than non-medical practitioners. Evidence from observational studies (28%), case reports or series (23%) and drug compendia (16%) were the least preferred reasons by oncology practitioners.

Table 11 Reported concerns with off-label prescribing (n=81).

Concerns	**All Participants (%)**	**Medical Oncologists (%)**	**Non-medical practitioners**			**p-value**
			Pharmacists (%)	**Nurses** (%)	**Both** (%)	
Lack of efficacy	47 (58)	19 (63)	14 (70)	14 (45)	28 (55)	0.90
Patients understanding	38 (47)	16 (53)	13 (65)	09 (29)	22 (43)	0.08
Questionable Safety	35 (43)	15 (50)	14 (70)	06 (19)	20 (39)	0.47
Out-of-pocket cost	33 (41)	16 (53)	13 (65)	04 (13)	17 (33)	0.004
Insufficient scientific evidence	25 (31)	04 (13)	13 (65)	08 (26)	21 (41)	0.02
No Informed consent	18 (22)	12 (40)	04 (20)	02 (06)	06 (12)	0.33
Legal liabilities	17 (21)	07 (23)	06 (30)	04 (13)	10 (20)	0.06

*The numbers may not add up to the total number of participants due to missing data. The p-value was calculated using the chi-square test or Fischer exact test as appropriate. The p-value is indicative of significance between medical oncologists and non-medical practitioners (pharmacists and nurses combined).

4.3.3 Concerns with off-label drug use

The main concerns with off-label use in cancer therapy are described in Table 11. Among the oncology practitioners, lack of efficacy (58%), patients understanding (47%) and drug safety (43%) were the top concerns with the practice of off-label drug usage. Medical oncologists were more concerned about out-of-pocket cost (53% *vs.* 33%, p=0.004) than non-medical practitioners. On the other hand, non-medical practitioners stated to be more apprehensive with insufficient scientific evidence supporting off-label

use (41% *vs.* 13%, p =0.02) than medical oncologists. Lack of informed consent (22%) and legal liabilities (21%) were the additional concerns expressed. Overall, more than half of the oncology practitioners (58%) stated to have experienced adverse events with off-label drug use.

4.3.4 Recommendation with off-label drug use in routine clinical practice

The expected outcomes and recommendations for off-label drug use practice are represented in Table 12. There was no consensus regarding survival benefit among oncology practitioners. Higher survival benefit of six months was more endorsed by non-medical practitioners (37% *vs.* 13%, p=0.02) than medical oncologists. Of all the oncology practitioners, 59% of the participants agreed upon moderate improvement in the quality of life of cancer patients with off-label drug use. Among all, discussion about off-label use with patients (71%), obtaining informed consent (86%) and institutional level guidance (75%) were highly recommended. On multivariate analysis as shown in Table 13, none of the variable was found to be significantly associated with perceived importance of off-label drug use in cancer therapy among different oncology practitioners.

Table 12 Recommendation with the practice of off-label prescribing (n=81).

Recommendations	All Participants (%)	Medical Oncologists (%)	Non-medical practitioners			p-value
			Pharmacists (%)	Nurses (%)	Both (%)	
1-3 months survival benefit	23 (28)	11 (39)	05 (20)	07 (22)	12 (23)	0.22
4- 6 months survival benefit	23 (28)	11 (39)	05 (20)	07 (22)	12 (23)	0.22
More than 6 months survival benefit	23 (28)	04 (13)	09 (45)	10 (32)	19 (37)	0.02
Slight improvement in overall quality of life	16 (19)	04 (13)	04 (20)	08 (26)	12 (23)	0.38
Moderate improvement in overall quality of life	41 (59)	17 (56)	10 (50)	14 (44)	24 (46)	0.40
Significant improvement in overall quality of life	22 (27)	09 (30)	06 (30)	07 (22)	13 (25)	0.66
Discussion with patients about off-label use	58 (71)	19 (63)	15 (75)	24 (77)	39 (76)	0.20
Obtaining informed consent from patients	70 (86)	28 (93)	12 (60)	30 (97)	42 (82)	0.16
Need for Institutional level guidance	61 (75)	20 (66)	17 (85)	24 (77)	41 (80)	0.25

*The numbers may not add up to the total number of participants due to missing data. The p-value was calculated using the chi-square test or Fischer. The p-value is indicative of significance between medical oncologists and non-medical practitioners (pharmacists and nurses combined).

Table 13 Correlations between perceived importance of off-label drug use and respondents characteristics.

Variable	Crude odds ratio (95 % CI)	p-value	Adjusted odd ratio (95 % CI)#	p-value
Professions				
Medical Oncologists	0.65 (0.26-1.64)	0.36	1.61 (0.37-6.98)	0.52
Non-Medical Practitioners	1 (reference)	--	1 (reference)	--
Age				
20-30	0.62 (0.20-1.98)	0.42	0.43 (0.10-1.73)	0.24
31-40	0.85 (0.30-2.42)	0.76	1.61 (0.53-4.80)	0.39
>40	1 (reference)	--	1 (reference)	--
Gender				
Male	0.68 (0.25-1.85)	0.45	0.82 (0.18-3.82)	0.83
Female	1 (reference)	--	1 (reference)	--
Years of practice in oncology				
>10	1.20 (0.29-4.90)	0.80	0.78 (0.19-3.21)	0.73
06 - 10	1.37 (0.26-3.86)	0.58	3.06 (0.46-20.56)	0.25
02 – 05	2.80 (0.61-12.85)	0.19	1.27 (0.16-9.85)	0.81
<02	1 (reference)	--	1 (reference)	--
Patients load per month				
>150	0.35 (0.77-1.57)	0.17	0.35 (0.06-1.91)	0.22
101-150	0.89 (0.18-4.37)	0.88	0.49 (0.12-1.90)	0.31
51-100	0.80 (0.16-3.88)	0.78	0.53 (0.14-1.89)	0.39
21- 50	1 (reference)	--	1 (reference)	--
Time spent on patients care per week (hours)				
>60	1.39 (0.47-4.11)	0.55	0.75 (0.16-3.34)	0.70
41 -60	1.22 (0.36-4.18)	0.75	0.84 (0.25-2.81)	0.77
<40	1 (reference)	--	1 (reference)	--

*Non-medical practitioners include pharmacists and nurses. #adjusted for remaining variables.

4.4 Discussion

As far as our knowledge is concerned, this is the first original survey research done within Asia to gather oncology practitioners' perceptions on the practice of off-label use in cancer therapy. The benefit of this important evidence would ensure the design of suitable clinical guidance and education strategies for the oncology community. The majority of the oncology practitioners recognised the fact that off-label drug use is integral and common practice in cancer pharmacotherapy. Off-label drug use was perceived to be practised across almost all types of chemotherapeutic regimens and therapeutic intents. However, the majority of participants acknowledged their concerns over the lack of efficacy, uncertain safety, increased out-of-pocket costs and ethical issues pertaining to patients' understanding and informed consent.

The prevalence of off-label prescribing in this study is self-reported by the participants which might not relate to the findings based on the assessment of drug prescriptions. This discordance between self-perceived prevalence and prescriptions could be explained due to the fact that healthcare professionals sometimes do not correctly identify a drug's FDA approval status for a particular indication at the time of prescribing, administering or dispensing (60). The main reported therapeutic intent for off-label drug use was palliative care. This finding is consistent with previous studies which reported off-label drug use being prominent in advanced cancers (52, 66, 68). The second common goal for off-label drug use was adjuvant setting where the objective of the therapy is to prevent reoccurrence of tumour once it is surgically removed. Drugs which are found to be active in metastatic disease are often used in an adjuvant setting in

an off-label manner. A drug may exhibit altered benefit-risk profiles in differing settings for the same cancer type. For example, in colorectal cancer, many drugs (including bevacizumab) with proven efficacy in the metastatic setting but have failed to improve outcomes in the adjuvant treatment (191). Despite this lack of clinical benefit, bevacizumab is still being prescribed in the adjuvant setting in colorectal cancer (73, 74).

Similarly, drugs approved in adjuvant setting are used in neo-adjuvant setting as in the case of breast cancer surgery where pertuzumab is the only regulatory approved drug (63, 64, 66, 67, 73, 192, 193). Modified drug application was the most common category of off-label use which could be explained mainly due to lack of available dosage forms or combination agent, drug allergies, co-morbidities, organ functions etc. (66, 75, 80). While the unapproved line of treatment was perceived to be second common category pertaining to off-label drug use due to use of approved drugs beyond specified number of lines of treatment and also due to continuing use of treatment beyond disease progression in advanced cancers. For example, use of trastuzumab in off-label manner beyond disease progression in patients with metastatic breast cancer (78). Off-label drug use was also reported for unapproved indication which could be explained due to lack of FDA approved drugs for rare tumours or diagnosis of cancer with specific genetic mutations (58, 151).

Many participants reported that off-label drug use could be considered when it is better than standard therapy or had strong evidence to support the practice. This attitude could be explained by the fact that clinical trials could not guide every prescription in routine practice and off-label use based on evidence-based approach is necessary (61). One such example has been observed in local setting where attenuated dosing of sunitinib yielded

comparable efficacy and reduced toxicity than the regulatory approved regimen (194). But in many cases, off-label drug use has become standard care. For example, a combination of ifosfamide and etoposide for Ewing's sarcoma for primitive neuroectodermal tumour of the bone and paediatric cancers (195). The participants perceived that lack of clinical trial availability and patients' refusal or ineligibility to recruit as less convincing reasons for off-label drug use. The previous study found that oncologists were reluctant to offer off-label therapies to those patients who refused to participate in the trial and agreed that patients should be discouraged from experimental drug use outside trials (185). It is also reported that access to experimental therapies outside trial in the form of off-label drug use could also potentially limit trial recruitment and impact the accumulation of gold standard evidence (181). Non-medical practitioners were less likely to recommend off-label use based on phase 2 trial data and conference abstracts. But medical oncologists might consider it appropriate for cancers with specific genetic alterations or treatment of rare tumours where large scale trials are difficult to conduct (75, 151). Drug compendia were least convincing evidence and studies found them as not reliable because lack of transparency in their review process for the off-label indication in oncology (196).

Lack of efficacy and questionable safety with off-label drug use were the key concerns with off-label drug use. Off-label chemotherapies without sound scientific evidence would not provide any meaningful clinical benefit but potentially expose patients to the risk of toxicities and increase treatment costs (50, 63, 197). A 20% rate of hepatic sinusoidal obstructive syndrome was noticed when gemtuzumab, a drug approved as single agent for acute myelogenous leukaemia, was prescribed as an off-label chemotherapy treatment in combination with thioguanine (35). Recently, the first ever

randomised control trial designed to study clinical outcomes with off-label drug use versus standard regimen found that off-label drug use provided no clinical advantage (198). The perceived toxicity concern might be attributed to inadequate information about off-label drug use regarding dosing guidelines, contraindications, drug interactions and side-effects profile. Hence, non-medical practitioners would certainly face difficulties in drug compounding, administration, and patient counselling activities. Moreover, the information on off-label drug use is poorly disseminated among healthcare professionals (196, 199).

Medical oncologists were more concerned regarding out-of-pocket cost as they usually participate in the decision-making process for off-label use and discuss cost issues with patients. This might be explained by the fact that the national insurance policy (MediShield Life) in Singapore has a maximum claimable limit of S$3000 per calendar month for selected chemotherapy (200). Likewise developed countries such as USA and Australia, many insurance companies denied reimbursements for off-label indications to treat cancer on the ground that these uses are "experimental" or "investigational" thus increasing patients out-of-pocket costs (39, 201).

The participants reported their concerns regarding patients understanding and informed consent with off-label drug use. This might be attributed to the misconceptions among patients regarding treatment intent of chemotherapies in advanced cancers which often lead to the demand of drugs access beyond approved usage (178, 180, 202). As a recommendation, patients should be properly educated about every off-label drug use, supporting evidence, the risk of toxicities and financial impact on treatment costs (43, 203). Obtaining informed consent was highly recommended by participants to safeguard

patient autonomy leading to better healthcare decision with off-label use and to prevent any future legal liabilities (204). The oncology practitioners had a general consensus on moderate enhancement in the overall quality of life than specific survival gains with off-label drug use and these findings are consistent with previous studies with similar objective (205). The need for robust practice framework and clinical guidance was highlighted by participants as a necessity to facilitate judicious off-label prescribing and it could be similar to those suggested by Australian guidelines (29) A collaborative practice model among oncology practitioners could assist with evidence-based off-label prescribing and support best practice standards (71, 206-208).

This research study has some limitations. "Self-reported" surveys have drawbacks with respect to accurately evaluating prescribing, dispensing and drug use practice. The survey questionnaire depends on participants' self-administration, which may provide responses that are appealing to the researcher rather than indicating what the participant actually considers. To reduce self-reporting bias, the confidentiality of the participants was confirmed and clarified to the participants. There is also the probability of recall bias. An effort to reduce this factor was carried out, i.e. by restricting the period of recall to 1 month. Our sample consisted of heterogeneous oncology practitioners (medical oncologist, nurses and pharmacist). Future studies with one group of oncology practitioners or qualitative studies on patients and caregivers are recommended to gather their insights. Our survey was also Singapore specific, but given that such issues are international, our results should be of interest to healthcare professionals in other countries particularly in Southeast Asia. Moreover, we did not consider paediatric oncology which is also an important area and has its own implications for off-label drug use that need to be addressed by similar studies in future (209). As such, the present

study should be regarded as an effort to gather general views on this important issue and should not be interpreted as sole evidence on any aspect of this issue.

4.5 Conclusion

Off-label drug use in cancer care is considered to be important by oncology practitioners. However, they expressed several concerns such as lack of efficacy, safety, and costs that need to be adequately addressed. Findings from the study also suggested the need for patient involvement in the decision-making process, the consideration for clinical guidance and educational strategies at institution level to facilitate judicious practice to facilitate off-label drug use in the oncology setting.

5 Future Directions

Off-label drug use in oncology is here to stay as it is not possible to do clinical trials for each and every prescription and getting regulatory approvals for it. However, the whole system could be structured to maximize the likelihood of a favourable benefit – risk ratio for patients under robust clinical governance guidelines which can work across all the care settings, prescribing, supply, administration, and reimbursement.

The data on the prevalence of off-label use of anti-cancer drugs in Singapore is unknown. A population-based cohort study determining the prevalence of off-label use of anti-cancer drugs is needed. It would be also prudent to assess cost component associated with off-label drug use. For those off-label uses where the evidence is limited, it is highly necessary to study their efficacy and safety to guide future prescribing. As off-label drug use is often demanded by patients, qualitative surveys to know their insights regarding off-label use would help to understand and strengthen the ethical basis for off-label prescribing.

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7 Appendices

7.1 Appendix I

Questionnaire

"Perception of Oncology practitioners towards off-label use of anticancer medicines"

Health Science Authority (HSA) is the drug regulatory body of Singapore. HSA Drug regulatory body approves a drug for use in clinical practice based on controlled studies and strict licensing criteria. HSA also publishes the label for each drug providing guidance to clinical practitioners for its clinical use. Off-label use is defined as the use of drug which is not consistent with the regulatory label. In oncology, off-label use is common and could be classified into different categories. They include unapproved indication, unapproved line of treatment, unapproved intent of treatment or unapproved modification of dose. Specific examples are given below.

Off-label category	Example
Unapproved indication	*Oxaliplatin* is a drug approved for colorectal cancer but used in breast cancer
Unapproved line of treatment	*Panitumumab* is used as first line therapy instead of treatment of pre-treated metastatic colorectal cancer
Unapproved intent of treatment	Use of *irinotecan* in the adjuvant setting instead of metastatic colorectal cancer
Unapproved modification of dose	High dosing of *carboplatin* in intensive chemotherapies instead of approved dose

Ref: Leveque, Dominique. "Off-label use of anticancer drugs." The lancet oncology 9.11 (2008): 1102-1107*

Demographics of respondent

1. **Age (years)**
   - □ 20 – 30 □ 31 – 40 □ 41 – 50 □ 51 – 60 □ > 60
2. **Gender**
   - □ Male □ Female
3. **Profession**
   - □ Medical Oncology
   - □ Surgical Oncology
   - □ Radiation Oncology
   - □ Pharmacist
   - □ Nurse
4. **Years of practice in Oncology**
   - □ < 2 □ 2 – 5 □ 6 – 10 □ > 10

5. Patient load <u>per month</u>

□ < 20 □ 21 – 50 □ 51 – 100 □ 101 – 150 □ > 150

6. Time spent on direct patient care <u>per week</u> (hours)

□ < 40 □ 40 – 60 □ > 60

1. Off-label use of cancer therapies are integral part of oncology practice.

□ Strongly Agree □ Agree □ Neutral □ Disagree □ Strongly Disagree

If agree, please give reason(s). (*Tick **ALL** that apply*)

□ Advanced stage of disease where other lines of treatments are exhausted.
□ No approved agents for disease.
□ Rare oncologic conditions.
□ Sound evidence of efficacy and safety for off-label prescription.
□ Off-label therapy show better efficacy than standard therapy.
□ Lack of trial availability at the institution.
□ Patients refuse to enter clinical trial or are ineligible for them.
□ Others:

2. What type of evidence constitutes appropriate off-label anticancer drug use? (*Tick **ALL** that apply*)

□ Case report or case series
□ Well conducted observational studies
□ Meta-analysis of observational studies
□ Data from Phase 2 clinical trials
□ Data from Phase 3 randomised control trials
□ Meta-analysis of randomised control trials
□ Drug compendia information
□ Off-label use included in treatment guidelines, such as NCCN
□ Conference abstracts of reputed meetings, such as ASCO or ESMO

3. In your opinion, which is the **most common category of off-label use**? *Please **rank** on a scale of 1 to 4 where 1 is the most common and 4 is the least common.*

	Indication
	Line of treatment
	Intent of cancer therapy (neoadjuvant, curative, adjuvant and palliative)
	Modified application of drug (e.g. dose, frequency, combination, route of administration)

4. In your opinion, which is the **most common therapeutic intents** for off –label drugs use in cancer patients? Please ***rank*** on a scale of 1 to 4 where 1 is the most common and 4 is the least common.

	Neo-adjuvant
	Adjuvant
	Curative
	Palliative

5. How often did you **prescribe/dispense/administer** off-label drugs in the **last 1 month**?
   - ☐ Less than 5 prescriptions
   - ☐ 5-10 prescriptions
   - ☐ 10-20 prescriptions
   - ☐ More than 20 prescriptions
   - ☐

6. What are your **main concerns** when you prescribe/dispense/administer off-label medicines? (*Select the **top 3** concerns*)
   - ☐ Lack of efficacy
   - ☐ Questionable Safety
   - ☐ Insufficient scientific evidence
   - ☐ No Informed consent
   - ☐ Patients' understanding
   - ☐ Legal liabilities
   - ☐ Cost to patients
   - ☐ Others:_____

7. In your opinion, what should be a **clinically meaningful outcome** from use of off-label anticancer medicine?

   A. Survival benefit (*Tick **one option** only*)
   - ☐ 1-3 months
   - ☐ 4-6 months
   - ☐ More than 6 months
   - ☐ Survival benefit is not a consideration at all

   B. Quality of life (*Tick **one option** only*)
   - ☐ Slight improvement
   - ☐ Moderate improvement
   - ☐ Significant improvement
   - ☐ Quality of life is not a consideration at all

8. Have you ever encountered **any adverse drug events (ADR)** when you prescribe/ dispense/administer off-label anticancer medicines?
   - ☐ Yes
   - ☐ No

   If yes, which type of ADR?
   - ☐ Mild
   - ☐ Moderate
   - ☐ Severe or life threatening

9. It is a **good practice to discuss** off-label use with patients/caregivers while making medical decisions.
   - ☐ Strongly Agree
   - ☐ Agree
   - ☐ Neutral
   - ☐ Disagree
   - ☐ Strongly Disagree

10. Should **informed consent** be obtained from patients when prescribing off-label anticancer medicines?
    - ☐ Yes
    - ☐ No

    If yes, please specify the mode.
    - ☐ Verbal consent
    - ☐ Written consent
    - ☐ Both

11. In your opinion, do you think that off-label use of anticancer medicine would **increase out-of-pocket cost** to patients?

    □ Yes □ No

    If yes, please provide reasons ……..

12. There should be more institutional guidance to facilitate safe use of off-label drug use for the patients who need it.

□ Strongly Agree	□ Agree	□ Neutral	□ Disagree	□ Strongly Disagree

Thank you for your participation in study!

7.2 Appendix II

Data Collection Form

Baseline characteristics:

Gender: M/F **Patient's age (yrs.) at diagnosis:** **Patient's age (yrs.) at start of treatment:**

Ethnicity: ☐ Chinese/Malay/Indian/Others

Date of Diagnosis: **Date of last follow-up:** **Date of Death:**

Disease characteristic:

Primary site of cancer: ☐

If patient has multiple primaries, indicate additional sites:

Stage of Cancer: ☐ I/II/I/IV

Metastatic phase at diagnosis: ☐ Yes /No

Metastatic site (s):

ECOG Performance Status: ☐ **at start of previous chemotherapy** ☐ **at start of unregistered use**

Prior Treatment for Cancer

Received radiation therapy: ☐ Yes /No.

Received surgical treatment: ☐ Yes/No

Total number of prior chemotherapy regimens: ☐ 1st line, ☐ 2nd line, ☐ ≥ 3rd

Details of previous chemotherapy:

Stage of Disease at start of unregistered drug use: ☐ 1: No evidence of progression, 2: Disease progression, 3: stable disease, 4: unknown

Localisation of Relapse: localized/metastatic/both

Current treatment for cancer

Unregistered Drug name:

Intent of unregistered drug use: Curative/Adjuvant/Neoadjuvant/Palliative

Current Treatment line: ☐ 1st/2nd /3rd or more

Concomitant chemotherapy with unregistered drug: Chemotherapy Only/targeted therapy/ Chemotherapy + targeted therapy

Unregistered chemotherapy start date:

Date of first event of disease progression after start unregistered chemotherapy:

Date of last unregistered drug use:

Last date of supply for oral unregistered drug use:

No. of cycles of unregistered drug administered:

Best clinical response: ☐ **CR/PR/SD/PD [**CR (Complete Disappearance of Lesions), PR (Partial Response), SD (Stable), PD (Progressive disease)]

Visit and response reported:

Reason for unregistered drug use discontinuation:

Toxicities : Classified based on NCI Common Terminology Criteria for Adverse Events

Type of toxicity	Grade 1 (n)	Grade 2 (n)	Grade 3 (n)	Grade 4 (n)