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Patient preferences and predicted relative uptake for targeted therapies in metastatic colorectal cancer: a discrete choice experiment

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Transparency

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Author contributions

XYW: study conception and design, data analysis and interpretation, manuscript drafting and revision; AQJL: data collection, analysis and interpretation; QYS: data, collection, analysis and interpretation; JWKC: study conception and design, manuscript revision; MHC: study conception and design, manuscript revision; WST: study conception and design, manuscript revision; HLW: study conception and design, data interpretation and manuscript revision. All authors gave the final approval of the version to be published and agreed to be accountable for all aspects of the work.

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Abstract

Objective

Ras wild-type metastatic colorectal cancers (mCRC) may be treated with anti-vascular endothelial growth factor (VEGF) or anti-epidermal growth factor receptor (EGFR) agents. We aim to estimate patients' preferences for mCRC treatment and relative importance of cost, efficacy improvement, avoidance of side effects and therapy convenience, and relative uptake between profiles that resemble Bevacizumab (anti-VEGF) and Cetuximab (anti-EGFR), two commonly prescribed mCRC targeted therapies.

Methods

Discrete choice experiment (DCE) was administered to English- or Chinese-speaking Stage 2 or 3 colon cancer patients at the National Cancer Centre Singapore. DCE attributes comprise progression-free survival (PFS), severity of acne-like skin rashes, severity of bleeding, out-of-pocket cost per month and frequency of drug administration. Mixed logit model was used to calculate preference weights for all attribute levels. Subgroup analyses were conducted by interacting attribute levels with selected respondent characteristics. Relative uptake rates for various medication scenarios were studied.

Results

169 respondents aged 61.5 ± 10.5 years completed the survey. They placed the greatest weight on cost, followed by bleeding and skin rashes, then PFS and finally frequency of drug administration. This was similarly observed in the subgroup analyses. A scenario with shorter PFS but less severe side effects has a slightly higher relative uptake at 55%. One quarter of respondents reported that they would not take the treatment they preferred in the choice task.

Conclusion

Patients were willing to trade off some degree of efficacy to avoid certain severity of side effects. It is therefore crucial for patients and physicians to discuss patients' preferences and circumstances to understand which attributes are more important, as well as patients' views on the trade-offs between treatment benefits and risks.

Keywords: targeted therapy; metastatic colorectal cancer; discrete choice experiment; patient preferences; relative uptake

Short title: Patient preferences and predicted relative uptake for targeted therapies in colorectal cancer

1 Introduction

Colorectal cancer (CRC) is a leading cause of morbidity and mortality worldwide. Over 1.8 million new CRC cases and 881,000 deaths are estimated to occur in 2018, accounting for about 1 in 10 cancer cases and deaths [1]. Singapore is one of the countries with the highest incidence, at age-standardized rates of 38.6 per 100,000 person-years in men and 27.0 per 100,000 person-years in women from 2011 to 2015. CRC tends to be diagnosed at later stages, with about one-third of cases diagnosed at Stage 3 and one-quarter at Stage 4 [2]. Metastatic CRC (mCRC) patients have dramatically lower survival rates as compared to earlier stage patients, but there is an overall increase in survival of CRC patients across all stages over the years [2].

The overall increased in survival of CRC patients can be attributed to advancements in the treatment landscape of mCRC, where biologic agents demonstrate significant survival benefits when added to standard chemotherapy regimens [3]. These therapies inhibit either the vascular endothelial growth factor (VEGF; e.g. Bevacizumab, Aflibercept and Regorafenib) or the epidermal growth factor receptor (EGFR; e.g. Cetuximab and Panitumumab) [4]. For patients with KRAS, NRAS and BRAF mutated mCRC tumors, they are limited to anti-VEGF agents as they do not respond well to EGFR antibodies [5,6]. While these targeted therapies greatly improve survival outcomes, they are also associated with adverse events like bleeding, hypertension, thromboembolic events (Bevacizumab) and acne-like skin rashes, diarrhea and stomatitis (Cetuximab) [7]. Physicians and patients must weigh between the benefits and risks when making treatment decisions, particularly in Ras wild-type cancers where either anti-VEGF or EGFR agents may be used.

Several studies have elicited preferences for CRC therapy [8 – 11], but only two used discrete choice experiment (DCE) [12,13], a quantitative method increasingly used in healthcare to value health and non-health outcomes, investigate trade-offs between these outcomes as well as predict uptake [14,15]. One study found that among mCRC patients, increasing progression-free survival (PFS) from 8 months to 12 months was approximately 3.5 times as important as reducing the treatment-related risk of heart attack from 2% to 0% [12]. They also found that older patients (> 48 years old) placed greater weight on improving PFS and avoiding gastrointestinal perforation and skin rash than younger patients, while the relative importance of avoiding a heart attack and serious bleeding was the same in both subgroups.

In another study, a strong increase in life expectancy was given the greatest weight amongst all attributes [13]. Out-of-pocket cost is a major concern influencing treatment choice [16], but neither of the studies investigated its influence relative to other characteristics. Hence, we aim to estimate patients' preferences for mCRC treatment and the relative importance of cost, efficacy improvement, avoidance of side effects and therapy convenience in making treatment decisions. Subgroup analyses were conducted to test for differences in preferences by respondent characteristics such as age, gender and education level. We also compared the relative uptake between profiles that resemble two commonly prescribed targeted therapies Bevacizumab and Cetuximab, in a multi-ethnic Singapore population using DCE.

2 Methods

2.1 Recruitment and sample size

The study was conducted among colon cancer patients at the National Cancer Centre Singapore from July 2016 to December 2016. We screened for potential participants by reviewing the medical records of patients attending the colorectal cancer clinic. Patients who fit the eligibility criteria were approached by the interviewers during their clinic appointments to participate in the study. Those who gave consent after the study has been explained to them were recruited. Inclusion criteria include age 21 years and above, English- or Chinese-speaking, physician-confirmed diagnosis of Stage 2 or 3 primary colon cancer between three weeks to five years ago at point of recruitment and

Singapore citizen or permanent resident assessed to be cognitively able by interviewers. Cognitive ability refers to having the capability to read and understand the consent form and the survey questions, in particular the first question (fixed task).

Patients with Stage 1 colon cancer, any stage of rectal cancer (below peritoneal reflection), or recurrent cancer were excluded, as they differ from study population in terms of treatment strategies and prognosis. Stage 4 colon cancer patients were also excluded to avoid potential psychological distress or false sense of hope based on the hypothetical medication profiles. Interviewers provided the respondents with the survey questions via the Sawtooth Software Offline Surveys application on an Android tablet and their responses were captured in it. All interviewers were trained by the first author to ensure that they answer respondents' queries in the same way. All respondents provided written informed consent prior to participation. The study was approved by the SingHealth Centralized Institutional Review Board (Reference number: 2014/895/A).

Based on the Orme's Rule of Thumb [17], the minimum sample size required is 84, but we aimed for twice that number at 168 to ensure enough statistical power. This was planned for before the publication of a practical guide on sample size requirements by de Bekker-Grob et al. [18], which was specified for multinomial logit model.

2.2 Study measures

Respondents were taken through a three-page explanation (Appendix 1) on CRC Stage 4 medications before attempting the DCE. They were asked to imagine that they had progressed to Stage 4 cancer and had to choose between two therapy options. Sociodemographic characteristics, sources of healthcare financing, clinical characteristics and history were solicited. Respondents received S$20 (approximately US$14) in cash as compensation for their time and effort.

2.3 DCE construction

Our DCE was developed based on good research practices [19], using a three-phase approach [20]. In Phase 1, we performed literature review and patient interviews (n = 6) to identify the relevant attributes, namely progression-free survival, side effects, out-of-pocket cost and frequency of drug administration (Table 1). Subsequently, we selected acne-like skin rashes and bleeding to represent and compare the toxicity of Cetuximab and Bevacizumab respectively, due to their frequency, severity and ease of visualization. Levels were based on the Common Terminology Criteria Adverse Events version 3.0 and 4.0 [21,22]. In Phase 1, we explored the topic of healthcare financing, where we asked how much they were willing to pay per month, if there is a drug that can extend their lives up to 6 months. The amount ranged from S$2,000-S$3,000 to S$40,000-S$50,000. Some would consider using their life savings, while others also considered borrowing money or even selling their houses to pay for treatment. However, there were a handful who would not go to such extremes as they were quite advanced in age and did not see the need for intensive treatment. Based on these insights, as well as institutional formulary pricing and health insurance payouts (Medishield Life), we arrived at a realistic out-of-pocket cost estimates, ranging from S$1,000 to S$9,000 per month. Convenience (frequency of drug administration) attribute was based on the drugs' dosing schedule.

Based on Phase 1 results, a draft DCE questionnaire containing background information and five choice tasks was designed and pilot-tested in 17 patients in Phase 2. Feedback on pictorial representation and description of attributes were solicited. In Phase 3 which is the current DCE, PFS levels were changed to 8, 16 and 24 weeks to better reflect the additional efficacy offered by targeted therapies when added to standard chemotherapy. Side effects levels remained unchanged. Cost remained as monthly to avoid dependency on treatment duration, and the values were reduced to reflect realistic amounts after subsidies and deductions, as well as patients' reported willingness to pay as revealed during the Phase 1 interviews.

Respondents were presented with a series of choice tasks and asked to choose one out of two alternatives labelled 1 and 2 in each task. They were then asked if they would really take the treatment in real life if their doctor offered it to them. This is known as a dual-response none question (closed-ended question in Part B of Figure 1, sample scenario resembling Cetuximab [Medication 1] and Bevacizumab [Medication 2]). It prevents overestimation of treatment uptake as preference for one option over another does not mean that the preferred option will be endorsed.

Sawtooth Lighthouse Studio 9.0.1. (Sawtooth Software, Orem, Utah, United States) was used to generate 24 unique questionnaire versions, each containing two fixed tasks and 12 choice tasks randomly generated using balanced overlap method. It allowed for moderate attribute level overlap across alternative scenarios and better discrimination when respondents use non-compensatory rules in making decisions between choice alternatives [23]. Although this reduced statistical efficiency as the number of levels that were directly compared was reduced, it lightened the cognitive burden on the respondents. A subset of the full-choice design (i.e. fractional factorial design) was sampled for each respondent, while ensuring level balance and near-orthogonality within each respondent's profile [24]. It was logically assumed that Medication 1 (24 weeks of PFS, no acne-like skin rashes, mild bleeding, S$1,000 and administered every two weeks) would be preferred to Medication 2 (8 weeks of PFS, moderate acne-like skin rashes, severe bleeding, S$9,000 and administered every week) in the first fixed task. Hence, respondents who chose Medication 2 were excluded out of concerns that their data may be invalid. The second fixed task reflected the profiles resembling Cetuximab (Medication 1) and Bevacizumab (Medication 2) (shown in Figure 1).

3 Statistical analysis

3.1 Patients' preferences and relative importance

Respondent characteristics were described using counts and percentages for categorical variables and mean (standard deviation, SD) for continuous variables. DCE data was estimated using mixed logit model in the preference space to calculate the preference weights for all attribute levels using Stata 14.2 (StataCorp LLC, College Station, Texas, United States). Mixed logit was chosen over other models e.g. multinomial logit, as it accounts for preference heterogeneity around parameter estimates among respondents, which was observed in our data as indicated by a likelihood ratio test for the joint significance of the standard deviations [25].

A main effects model was estimated, with all attribute levels being effects-coded. With effects coding, the estimate for the omitted (reference) level is the negative sum of the included levels' estimates, and zero represents the mean effect of all levels of the attribute [26]. Hence, each P value is a measure of the statistical significance of the difference between the estimated preference weight and the mean effect of the attribute [27]. All levels were estimated as random parameters with a normal distribution. The scale of the preference weights is arbitrary, but differences between them can be interpreted as a measure of the importance of the change relative to other changes in attribute levels. Alternative-specific constants (ASC) for choosing the left-sided alternative and choosing not to undergo the treatment were also included in the main effects model.

In addition, we conducted subgroup analyses to test for differences in preferences by language spoken (English or Chinese), gender, age (> 65 years), marital status (married or not), cancer stage (stage 2 or 3), education level (high school senior and above), household income (S$3,000 per month and above) and chemotherapy status (taken before or not). Each subgroup analysis was conducted by interacting every attribute level in the model (except PFS and cost) with an effects-coded variable identifying respondents belonging to the subgroup and adding all interaction terms to the main effects model. PFS and cost were coded as continuous variables as they have fairly linear relationships with preference weight when coded as categorical, and because the mixlogit command

permits a limited number of random variables (n = 20). A Wald test was used to test for joint significance of interaction terms. P values were not adjusted for multiple comparisons as subgroup analyses were exploratory; $p < 0.05$ were considered significant.

3.2 Predicted relative uptake

In budget impact analysis and program planning, one will be interested in predicted uptake for various scenarios. Details on the calculation of predicted relative uptake i.e. probability of selecting one profile over another using preference weights are in Appendix 2. Scenarios include base case profiles resembling Cetuximab and Bevacizumab and other profiles with different combinations of PFS and side effects. A profile resembling Cetuximab would provide 8 weeks of PFS, with moderate skin rashes, no bleeding, costing S$9,000 a month and administered every week. A profile resembling Bevacizumab would provide 16 weeks of PFS, with no skin rashes but moderate bleeding, costing S$5,000 a month and administered every two weeks.

3.3 Dual-response none

Respondent choice in the closed-ended question of Part B (Yes or No) was included as the ASC for choosing not to undergo treatment, which adjusts the attribute coefficients to account for people opting out. Proportion of patients who chose not to take up treatment in real life at least once or all the time were described using counts and percentages.

4 Results

4.1 Respondent characteristics

One hundred and sixty-nine respondents completed the survey (169 out of 389 eligible patients; 43.4% response rate). On average, respondents took 23.7 minutes (SD: 9.9 minutes) to complete the survey. Reasons for non-participation included refusal without providing reason, inability to understand English or Chinese language and missed or re-scheduled appointments. The average age of respondents was 61.5 years old (SD 10.5 years). Characteristics such as age, ethnicity, highest education completed, housing type, household income, healthcare financing and cancer stage were significantly different between those who attempted the English and Chinese questionnaire (Table 2).

4.2 Respondent preferences for mCRC targeted therapies (n = 169)

4.2.1 Attribute estimates and relative importance

The estimated relative preference weights for each attribute level with 95% confidence intervals are presented in Figure 2. Large positive values signify more preference while smaller negative values signify less preference. The vertical distance between levels indicate the relative importance for each attribute. Table 3 provides the detailed parameter estimates of the mixed logit (main effects) model.

Among the five attributes that describe mCRC targeted therapies, respondents placed the most weight on out-of-pocket cost, with a strong preference for a treatment that costs S$1,000 per month over one that costs S$9,000 per month ($p < 0.001$). A change in cost from S$1,000 to S$5,000 per month was more important than any other changes in attribute level, in particular the worsening of bleeding from moderate to severe. However, a change from S$5,000 to S$9,000 per month was less important than that. Bleeding was considered the next most important attribute judging by the distance between no and severe bleeding, followed by acne-like skin rashes, judging by the distance between no and severe skin rashes. Respondents had significantly distinct preferences for various levels of bleeding severity. On the other hand, respondents were indifferent towards avoiding mild skin rashes. PFS was ranked fourth most important based on vertical distance between levels, after side effects. Respondents were willing to forgo some improvement in PFS (8 weeks to 16 weeks) to avoid moderate skin rashes and moderate bleeding. However, they were not willing to forgo more improvement (8 weeks to 24 weeks) to avoid moderate skin rashes. There was slightly more

preference for a treatment that offers 24 weeks of PFS compared to 16 weeks, although this difference was not statistically significant. Finally, respondents placed the least weight on frequency of drug administration, where there was no meaningful difference between treatments administered every two weeks compared to every week.

There seems to be a preference in choosing the left-sided alternative (p-value <0.001), reflecting a left-sided bias (i.e. participants tend to choose the option that is shown on the left rather than the right). To determine if the bias affects relative importance and preference ranking within each attribute, we compared models that included and excluded ASC "Choose left" (Appendix 3). We found that the relative importance and preference ranking within each attribute remained unchanged. Since the model that included ASC 'Choose left' has a lower Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) (AIC/BIC = 2452.333/2626.882 versus 2551.89/2713.01), we used it to fit our data. Also, the likelihood ratio test for the joint significance of all standard deviations has a p-value of <0.001, implying that the null hypothesis that all standard deviations are equal to zero is rejected, meaning there is significant preference heterogeneity.

4.2.2 Interactions between respondent characteristics and attribute levels

We also assessed if preferences differed by language spoken, gender, age group, marital status, cancer stage, education level, household income and chemotherapy status. There were no significant differences in preferences by age group (p = 0.495) and marital status (p = 0.075). As for the remaining subgroups (language spoken, gender, cancer stage, education, income and chemotherapy status), the relative importance of avoiding bleeding is greater than avoiding skin rashes and therapy convenience (Appendix 4). If we focus on the distance between levels for bleeding and rashes, those who have never used chemotherapy place more importance on avoiding bleeding (as compared to skin rashes), than all other subgroups. As PFS and cost were coded as continuous instead of categorical, it is not meaningful to compare their coefficients against other categorical attributes. Nonetheless, we observed that cost was unanimously significant in determining treatment choice, while PFS influenced choice only in the gender and income subgroups.

4.3 Predicted relative uptake rates in various scenarios

Predicted relative uptake rates for various scenarios are shown in Table 4. Both actual (patient's choice in fixed task #2) and predicted (based on sum of estimated preference weights) found similar levels of relative uptake, at about 17 to 24% for Cetuximab (Scenario 1), and 76 to 83% for Bevacizumab (Scenario 2). This implies that the estimated model predicted preferences fairly accurately. If we consider a scenario where patient develops severe rashes but also experienced improvement in PFS (Scenario 3; severity of skin rashes has been positively associated with efficacy [28]) and compare it against Scenario 4 where there is equal efficacy and cost but accompanied by severe bleeding, the predicted relative uptake swings in Scenario 3's favor at 68%. Comparing between a scenario with shorter PFS but less severe side effects (Scenario 5) and a scenario with longer PFS but more severe side effects (Scenario 6), the former has a slightly higher uptake at 55% versus 45%.

4.4 Dual-response none

Ninety-eight in 169 respondents (58.0%) answered 'No' to 'Will you select this option in real life?' at least once in 12 choice tasks. 43 in 169 (25.4%) respondents would always opt out of the hypothetical mCRC targeted therapy in real life. Out of 2028 choice tasks, 858 (42.0%) are answered as 'No'.

5 Discussion

Based on the vertical distance between the extreme attribute levels, CRC patients placed the greatest weight on out-of-pocket cost, followed by side effects such as bleeding and skin rashes, then PFS and finally frequency of drug administration. A recent DCE by González et al. that investigated preferences for mCRC treatment [12] also concluded that PFS (three levels: 6 months, 8 months and 12 months) was relatively less important than toxicity attributes such as cardiopulmonary arrest, gastrointestinal perforation and serious hemorrhage. It found that physicians were willing to tolerate greater probability of adverse events than patients, although the differences were mostly non-significant. Post-hoc analyses revealed that some patients and physicians were willing to forgo efficacy in terms of PFS to avoid treatment-related toxicities [12], which is similar to our findings. This similarity is striking because the two study populations were rather different in terms of age, education level and cancer stage.

In another study by Schmidt et al. that investigated therapy preferences of patients with lung and colon cancer [13], it was found that life expectancy (overall survival: not increased, slightly increased and strongly increased) was the most important among colon cancer patients, followed by physical capacity, outward appearance, food intake and digestion and clinic waiting time. Differences in these findings could be because preferences are conditional on the attributes included in the survey and the range presented. In our study and the DCE by González et al. [12], specific side effects were presented as attributes, whereas the study by Schmidt et al. grouped side effects by systems affected e.g. physical capacity, appearance and digestion. This might have influenced the way respondents perceive the importance of side effects when choosing therapy. Also, Schmidt et al. used qualitative measure of overall survival rather than quantitative measure of PFS to represent efficacy.

As for cost, majority of aging cancer patients in Singapore found the existing financial schemes helpful in reducing out-of-pocket expenses but also expressed the need for further assistance to offset these costs, especially for users of targeted therapies and those with poorer health status [29]. Thus, it is not surprising that out-of-pocket cost turns out to be the most important and significant determinant of treatment choice. Interestingly, we noticed that a change from S$1,000 to S$5,000 is considered slightly more important than a change from S$5,000 to S$9,000, even though the difference is the same at S$4,000. Still, the costs presented in this survey may not be similar to the actual out-of-pocket costs that respondents will pay if they need targeted therapies in the future. We also considered the possibility that respondents dominated on cost or PFS, meaning that these attributes had such a large impact on their choice that they did not consider other attributes [30]. We observed that they only dominate on cost when the difference is huge i.e. S$1,000 vs S$9,000 and the differences between side effects and PFS are minimal e.g. mild vs moderate and 16 weeks vs 24 weeks. There are some who were willing to pay the S$8,000 difference to avoid severe side effects and/or much improved PFS. Respondents did not appear to dominate on PFS. We tallied the counts and found that 2% of respondents always picked the option with the highest PFS (3 out of 169), 7% always picked the option with no bleeding (12 out of 169) and 15% always picked the option with the lowest cost (25 out of 169). None of the respondents always picked the option with no skin rashes or less frequent drug administration.

We observed a bias towards the left-sided alternative and considered the possibility that left-sided profiles are consistently superior throughout the questionnaire. This is not found to be true when we checked through the design. Respondents could have been influenced by the first (fixed) task where Option 1 was superior. Alternatively, they might have applied simplifying heuristics when undertaking this survey. However, we tried to minimize the application of heuristics by getting interviewers to emphasize to the respondents that either option may appeal more to them, at the start of the DCE. Respondents chose the left-side option in about 6.1 (± 1.9) out of 12 choice tasks.

We also did not observe any serial non-traders who always chose the left-sided option in every choice task. Through the interaction analyses, we found that respondent preferences did not differ by age group and marital status. A few studies also found that sociodemographic characteristics like gender or age did not influence preferences for cancer therapy [31-33]. Also, those who have never used chemotherapy placed more importance on avoiding bleeding, likely because they do not know what to expect in terms of side effects.

In general, we found significant preference heterogeneity for most attribute levels, highlighting the importance of tailoring mCRC targeted therapy according to patient's current health status, treatment goals and financial considerations. This can be done through shared decision making, in which patients are fully informed of the trade-offs between treatment risks and benefits, and their values and preferences are incorporated into treatment decisions [34].

When considering the various profiles, respondents appear to prefer the profile resembling Bevacizumab (Scenario 2) over the profile resembling Cetuximab (Scenario 1), as shown by the higher relative uptake rate. This is likely because Scenario 2 costs only slightly more than half of Scenario 1. However, when the two profiles have similar efficacy, toxicity severity and cost, profile resembling Cetuximab (Scenario 3) is preferred over profile resembling Bevacizumab (Scenario 4). This is due to the larger disutility associated with severe bleeding, as compared to severe acne-like skin rashes. On average, conditional on the attributes included and the levels presented, the study provides results on preferences for skin rashes over bleeding, although not all patients share these preferences. Also, the uptake rate for a profile with shorter PFS but less severe side effects was higher, demonstrating the preference for quality of life over efficacy.

About 25% of respondents always opted out, similar to 29.0% of older adults with anxiety diagnosis who opted out of medically supervised benzodiazepine discontinuation programs [35] and 21.4% of Type 2 diabetes mellitus patients who opted out of diabetes lifestyle management programs [36]. We did not observe any significant difference in respondent characteristics between those who always opted out and those who did not (not shown). This contrasts with a population-based study in Taiwan which found that age and cancer staging are associated with treatment delay or refusal in clinical setting [37]. Given that our respondents are in earlier cancer stages and making hypothetical decisions on future therapy options, we caution against extrapolation of these findings.

This study is not without its limitations. First, we assumed no interactions between the attribute levels. However, it has been reported that severity of acne-like skin rashes is positively associated with the efficacy of Cetuximab [38]. Second, we acknowledge that in the first fixed task, there may be respondents who did not consider the full profile and really prefer more frequent drug administration, or insensitive to price, but we think that most patients are sensitive to side effects and would choose the profile with less side effects. However, we acknowledge that respondents are learning how to answer DCE questions in the first few tasks and the responses may be noisier but may get more consistent afterwards. Third, we did not solicit the reasons for not choosing the treatment option in real life, and this could allow us to better understand the barriers towards uptake of targeted therapy. We also did not include more toxicity attributes (only one per targeted therapy) and might not have given a comprehensive view of the risk-benefit profile, but it was a conscious effort to reduce cognitive burden. Out-of-pocket costs in this survey were based on Phase 1 interviews, formulary prices and expected insurance payouts, and are higher than the average household income for much of the sample. Fourth, as we had relied on a rule-of-thumb for estimating sample size, our study may have been underpowered despite an effort to use twice the estimated sample size. A literature review has reported that the mean sample size for DCE studies in healthcare published between 2005 and 2008 was 259 [39], with nearly 40% of the sample sizes in the range of 100 to 300 respondents. Hence, we may have missed out some associations due to lack

of statistical power. Other limitations include the uncertainty surrounding the use of heuristics or simplifying tactics to make decisions. Due to the nature of our sampling and recruitment, our study population tend to consist of patients who were adherent to clinic appointments and receptive to taking part in research. They might be more proactive in seeking treatment and more likely to choose 'Yes' in the dual-response none option, than non-responders. In addition, we could not reach out to patients who were not literate in English or Chinese. Thus, our study findings may not be generalizable to them.

In this sample of stage 2 and 3 CRC patients, we identified preferences for mCRC targeted therapies and quantified the influence of cost relative to other treatment characteristics. Patients were willing to trade off some degree of efficacy to avoid certain severity of side effects. It is therefore crucial for patients and physicians to discuss patients' preferences and circumstances to understand which attributes are more important, as well as patients' views on the tradeoffs between treatment benefits and risks. Future research should focus on optimizing shared decision making as a model of care in oncology.

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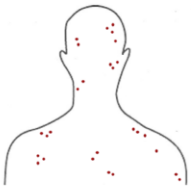
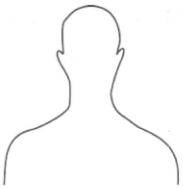
Appendices – See supplemental file

Tables with caption(s) – See table file

Figures captions

Sample Scenario
(Part A) If these are your only options for a Stage IV colorectal cancer therapy, and this is the cost you would actually pay, which would you prefer to buy?

	Medication 1	Medication 2
Progression-free survival	8 weeks	16 weeks
Severity of acne-like skin rashes	 Moderate	 None
Severity of bleeding	 None	 Moderate
Out-of-pocket cost per month	S$9,000	S$5,000
Frequency of administration	Every week	Every two weeks
	☐	☐

(Part B) From the above medication (1 or 2) that you have chosen, will you really select this medication in real life?
☐ Yes
☐ No

Figure 1. Sample choice scenario that represents Cetuximab (Medication 1) and Bevacizumab (Medication 2).

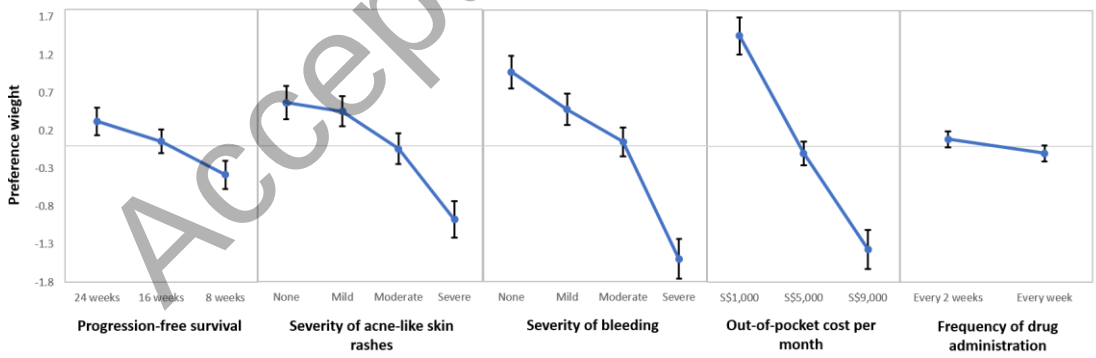


Figure 2. Patient preference weights (n = 169)

Table 1. Attributes and levels of mCRC targeted therapies

	Attribute	**Description**		**Levels**
1	Progression-free survival	The period of time in which the cancer remains at the same stage when you start the treatment and there is no increase in symptoms.	1	8 weeks
			2	16 weeks
			3	24 weeks
2	Severity of acne-like skin rashes	Acne-like skin rashes is a side-effect of the medications. These rashes typically appear on the face, scalp, upper chest and back.	1	None
			2	Mild
			3	Moderate
			4	Severe
3	Severity of bleeding	Seriousness of bleeding that occurs after administration of the medication. Bleeding is not restricted to any specific location, but common sites include brain, nose, gastrointestinal tract and lungs.	1	None
			2	Mild
			3	Moderate
			4	Severe
4	Out-of-pocket cost per month (after subsidies and deductions)*	Cost of the cancer medication per month that you need to pay out of your own pocket until the disease progresses or until you pass away.	1	S$1,000 (US$700)
			2	S$5,000 (US$3,500)
			3	S$9,000 (US$6,300)
5	Frequency of drug administration	How often you need to come to the cancer center for the infusion of the cancer medication, on top of your usual doctor visits.	1	Every week
			2	Every two weeks
	*S$1 is approximately US$0.70			

Table 2. Self-reported respondent characteristics (n = 169)

	Total number N (%)	**English-speaking N (%)**	**Chinese-speaking N (%)**	**p-value**
Sociodemographic characteristics				
Total number of respondents	169 (100)	98 (58)	71 (42)	
Age in years (SD)	62 (11)	59 (12)	65 (7)	<0.001
Gender				0.711
Male	98 (58)	58 (59)	40 (56)	
Female	71 (42)	40 (41)	31 (44)	
Ethnicity				<0.001
Chinese	143 (85)	72 (74)	71 (100)	
Malay	12 (7)	12 (12)	0 (0)	
Indian	6 (4)	6 (6)	0 (0)	
Others	8 (5)	8 (8)	0 (0)	
Marital status				0.622
Married	137 (81)	77 (79)	60 (85)	
Single	23 (14)	15 (15)	8 (11)	
Others (divorced, widowed)	9 (5)	6 (6)	3 (4)	
Highest education completed				<0.001
Elementary school and below	35 (21)	7 (7)	28 (39)	
High school sophomore or technical school	81 (48)	45 (46)	36 (51)	
High school senior	32 (19)	27 (28)	5 (7)	
College and above	21 (12)	19 (19)	2 (3)	
Housing type				0.001
Small public housing	8 (5)	5 (3)	3 (2)	
Medium public housing	82 (49)	35 (21)	47 (66)	
Large public housing	56 (33)	43 (25)	13 (18)	
Private apartment or landed property	23 (14)	15 (9)	8 (13)	
Monthly household income				0.002
Below S$3000	84 (50)	43 (44)	41 (58)	
S$3000 to S$7999	48 (29)	31 (32)	17 (24)	
S$8000 and above	29 (17)	23 (23)	6 (8)	
Unsure	8 (5)	1 (1)	7 (10)	
Healthcare financing (more than one can be applicable)				0.012
Medifund[a]	23 (14)	16 (16)	7(10)	
Medisave[b]	150 (89)	87 (89)	63 (89)	
Private medical insurance	75 (44)	46 (47)	29 (41)	
Eldershield[c]	23 (14)	21 (21)	2 (3)	
More than one insurance product but unsure of details	6 (4)	3 (6)	3 (4)	
Others (e.g. pension, Medishield[d] etc.)	16 (10)	12 (12)	4 (6)	
Nil reported	2 (1)	0 (0)	2 (3)	
Clinical characteristics and history				
Years since colorectal cancer	1.8 (1.5)	1.9 (1.5)	1.8 (1.5)	0.556

diagnosis (SD)				
AJCC 7th staging				0.023
Stage 2	40 (24)	17 (17)	23 (32)	
Stage 3	129 (76)	81 (83)	48 (68)	
Chemotherapy treatment status				0.793
Currently on chemotherapy	44 (26)	25 (26)	16 (23)	
Taken chemotherapy in the past	104 (62)	62 (63)	42 (59)	
Have not taken chemotherapy before	21 (12)	11 (11)	10 (14)	
ECOG status				0.658
0	118 (70)	69 (70)	49 (69)	
1	36 (21)	22 (22)	14 (20)	
2	1 (0.6)	0 (0)	1 (1)	
Not known	14 (8)	7 (7)	7 (10)	

[a]Medical endowment fund for the needy
[b]National medical savings scheme
[c]Severe disability insurance scheme
[d]Basic health insurance plan
AJCC = American Joint Committee on Cancer; ECOG = Eastern Cooperative Oncology Group; SD = Standard Deviation.

Table 3. Mean and SD of respondent preference weights for attribute levels of mCRC targeted therapies and interactions between respondent characteristics and attribute levels

Attribute level[a]	**Mean preference weight (95% CI)**	**P-value**	**SD of mean preference weight (95% CI)**[b]	**P-value**
Progression-free survival				
24 weeks	0.323 (0.140 to 0.505)	0.001	0.710 (0.477 to 0.944)	<0.001
16 weeks	0.059 (-0.094 to 0.213)	0.446	-0.036 (-0.240 to 0.167)	0.727
8 weeks[c]	-0.382 (-0.570 to -0.194)	<0.001	-	
Severity of acne-like skin rashes				
None	0.567 (0.346 to 0.789)	<0.001	-0.283 (-0.611 to 0.044)	0.090
Mild	0.452 (0.254 to 0.650)	<0.001	0.094 (-0.202 to 0.391)	0.533
Moderate	-0.043 (-0.247 to 0.160)	0.676	-0.378 (-0.613 to -0.142)	0.002
Severe[c]	-0.976 (-1.216 to -0.736)	<0.001	-	
Severity of bleeding				
None	0.974 (0.759 to 1.190)	<0.001	0.472 (0.162 to 0.783)	0.003
Mild	0.479 (0.271 to 0.687)	<0.001	-0.575 (-0.949 to -0.201)	0.003
Moderate	0.051 (-0.141 to 0.243)	0.603	0.001 (-0.211 to 0.213)	0.993
Severe[c]	-1.504 (-1.766 to -1.241)	<0.001	-	
Out-of-pocket cost per month				
S$1,000[c]	1.463 (1.219 to 1.707)	<0.001	-	
S$5,000	-0.094 (-0.252 to 0.064)	0.243	0.233 (-0.003 to 0.468)	0.053
S$9,000	-1.369 (-1.626 to -1.113)	<0.001	1.318 (1.051 to 1.584)	<0.001
Frequency of drug administration				
Every two weeks	0.093 (-0.016 to 0.201)	0.095	-0.019 (-0.173 to 0.134)	0.804
Every week[c]	-0.093 (-0.201 to 0.016)	0.095	-	
Alternative-specific constants				
Choose left	0.547 (0.394 to 0.699)	<0.001	0.646 (0.462 to 0.831)	<0.001
Choose none	0.962 (0.698 to 1.227)	<0.001	3.034 (2.661 to 3.408)	<0.001

Negative preference weight represents disutility. Grand mean has an expected utility of zero.
[a]All parameter estimates were derived from the mixed logit model with main effects

estimated in the preference space.
[b]The sign of the estimated standard deviations is irrelevant and should be interpreted as being positive. The likelihood ratio test for the joint significance of all standard deviations has a P-value of <0.001, implying that the null hypothesis that all standard deviations are equal to zero is rejected, that is, there is significant preference heterogeneity.
[c]Signifies the reference level of each attribute. Parameter estimates of reference levels were obtained using the lincom command in Stata.
CI =Confidence Interval; SD = Standard Deviation.

Table 4. Predicted relative test uptake rates in various scenarios

	Scenario 1	**Scenario 2**	**Scenario 3**	**Scenario 4**	**Scenario 5**	**Scenario 6**
Attribute levels in each scenario	**Profile resembling Cetuximab**	**Profile resembling Bevacizumab**	**Profile resembling Cetuximab**	**Profile resembling Bevacizumab**	**Shorter PFS but less severe side effects**	**Longer PFS but more severe side effects**
Progression-free survival	8 weeks	16 weeks	16 weeks	16 weeks	8 weeks	26 weeks
Severity of acne-like skin rashes	Moderate	None	Severe	None	Mild	Moderate
Severity of bleeding	None	Moderate	None	Severe	Mild	Moderate
Out-of-pocket cost per month	S$9,000	S$5,000	S$5,000	S$5,000	S$5,000	S$5,000
Frequency of administration	Every week	Every two weeks	Every week	Every two weeks	Every two weeks	Every two weeks
Relative uptake rate, actual (Holdout task #2)	23.7%	76.3%	-	-	-	-
Relative uptake rate, predicted (preference weight)	17.0%	83.0%	67.9%	32.1%	55.4%	44.6%