Compliance with TGA prescribing information - Weekly or second weekly cetuximab for the treatment of metastatic colorectal cancer.

Loft M[1,2], Shapiro J[3], Lee M[1,2,4,5], Wong R[1,5,6], Tie J[1,2,4,7], Kosmider S[4], Wong V[1], Jalali A[1,4], Lee B[1,7], Ananda S[1,4,7], Gibbs P[1,2,4]

1. Division of Personalised Oncology, Walter and Eliza Hall Institute of Medical Research, Melbourne VIC Australia

2. Department of Medical Biology, University of Melbourne, Melbourne VIC Australia

3. Department of Medical Oncology, Cabrini Hospital, Melbourne VIC Australia

4. Department of Medical Oncology, Western Health, Melbourne VIC Australia

5. Department of Medical Oncology, Eastern Health, Melbourne VIC Australia

6. Eastern Health Clinical School, Monash University, Melbourne VIC Australia

7. Department of Oncology, Peter MacCallum Cancer Centre, Melbourne VIC Australia

Corresponding author:

Matthew Loft

Address: Walter and Eliza Hall Institute, 1G Royal Pde Parkville 3052 Victoria

Email: matthewjloft@gmail.com

Phone: +61403971016

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Abstract

Background:

Treatment with cetuximab provides a survival benefit for patients with RAS wild-type metastatic colorectal cancer (mCRC). Practice-defining cetuximab studies utilised weekly (q1w) administration. More convenient second weekly (q2w) administration is supported by pharmacokinetic data and a recent meta-analysis, but large head-to-head studies have not been conducted. TGA prescribing information states cetuximab be administered q1w for all indications.

Methods:

We analysed data from a prospective mCRC database at 7 Melbourne hospitals from January 2010 to August 2019. Characteristics and outcomes for cetuximab treated patients were examined, comparing q1w versus q2w schedules. Progression free survival (PFS) and overall survival (OS) were the primary endpoints.

Results:

Of 214 eligible patients, 103 (48%) received q1w and 111 (52%) received q2w cetuximab. Q2w cetuximab has been used in >70% of patients from 2015. Q2w was more commonly used in public patients (70% versus 13% in private, $p < 0.001$), in left-sided primary tumours (83% vs 68%, $p = 0.025$) and in combination with chemotherapy (73% q2w vs 40% q1w, $p < 0.001$). Q2w treatment was less common in BRAFV600E mutated tumours (4% vs 13%, $p = 0.001$). PFS was similar across all

lines of therapy, including when analyses were limited to a left-sided primary and there was no difference in OS in multivariate analysis.

Conclusion:

This real-world analysis shows q2w cetuximab has become the dominant method of administration, despite TGA guidance. Our outcome data adds to other data supporting the use of q2w cetuximab as the standard option. Consideration could be given to modifying current TGA advice.

Keywords

Cetuximab, every second week, metastatic colorectal cancer, EGFR, RAS wild type

Introduction

Colorectal cancer is the third most common cancer worldwide and the second most common cause of cancer-related death [1]. Survival outcomes for metastatic colorectal cancer (mCRC) continue to improve [2], in part due to increasing use of cetuximab and panitumumab in selected patients. Both of these agents target the epidermal growth factor receptor (EGFR), with a head to head study in the chemorefractory disease setting demonstrating equivalent efficacy and safety [3]. The initial studies demonstrating a survival advantage for EGFRi were conducted in chemorefractory patients, with later studies demonstrating a survival benefit in early lines of therapy, where the EGFRi was given in combination with chemotherapy [4,5].

All the pivotal studies of cetuximab utilised a weekly schedule (q1w), whereas standard combination chemotherapy is administered second weekly (q2w). Supporting the use of the more convenient q2w schedule of cetuximab was an initial pharmacokinetic study that revealed drug levels consistent

with q1w administration [6]. Further support for the q2w schedule comes from single arm first line combination chemotherapy studies, where outcomes were consistent with earlier studies using weekly cetuximab with the same chemotherapy backbone [7-9]. In a small randomised head to head phase II study that enrolled 152 patients, q1w versus q2w treatment was associated with similar response rates, survival outcomes and safety profile [10]. In a recent meta-analysis of existing data, no difference was found in PFS, OS or response rate for q1w versus q2w treatment [11].

The United States Food and Drug Administration (FDA) approved the q2w regimen in addition to the q1w regimen in April 2021. Recent guidelines from the European Society of Medical Oncology, adapted in the COVID-19 environment, recommend considering the use of q2w treatment. In Australia, treatment administration is governed by the Therapeutic Goods Association (TGA) and a q1w schedule is still recommended for all indications. Here we use data from a comprehensive clinical registry to examine changes in cetuximab schedule over time, any differences between patients treated with a q1w versus q2w treatment, and undertake a multivariate analysis to better understand the outcomes achieved.

Methods

Eligibility

Patients from Melbourne Health, Peter MacCallum Cancer Centre, Eastern Health, Western Health, Melbourne Private, Western Private and Cabrini Hospital who received cetuximab from January 2010 to August 2019 were identified from the Treatment of Recurrent and Advanced Colorectal Cancer (TRACC) registry. TRACC [12], established in 2009, is a point of care database collecting prospective data on consecutive patients diagnosed with metastatic colorectal cancer at multiple contributing sites. All data analysed was retrieved from the TRACC registry, excepting the frequency of cetuximab treatment administration which was obtained by chart review as it is not a routine TRACC data point. The treatment schedule at commencement of cetuximab administration was used in all analyses. Patients were divided into two time groups (2010-14 and 2015-19) in line with the

Pharmaceutical Benefits Scheme (PBS) approval of cetuximab in the first-line setting in 2015. Patients receiving panitumumab were excluded from this analysis.

Data extracted included patient demographics, performance status, treatment location, line of therapy where cetuximab was received, primary tumour site, sites of metastatic disease, reasons for treatment discontinuation and progression free survival. Progression free survival was defined as the time from commencement of therapy until the date of disease progression or death, censored at the date of last review in the absence of an event. This study was approved by Melbourne Health ethics committee (HREC/18/MH/28, reference number 201910/3).

Statistical Analysis

Demographics, disease and treatment characteristics were described using descriptive statistics and compared for patients who received q1w versus q2w cetuximab. Chi-square analysis and Fisher's exact tests were used for comparison of categorical variables, and the Mann-Whitney test for comparison of continuous variables. Univariate and multivariate analysis for survival was performed using cox regression. The Kaplan-Meier method was used to calculate survival data, with log-rank tests being used to assess differences in survival rate. Analyses were performed with Stata 12.

Results

Cetuximab use

As shown in Figure 1a, from an initial cohort of 2214 patients diagnosed with metastatic colorectal cancer from 2009 – 2019 at the 7 participating hospitals, we identified a cohort of 214 patients who had received cetuximab where frequency of administration could be reliably determined. Figure 1b shows the increasing use of q2w cetuximab since 2015, with 71% of patients commencing q2w treatment in 2019. Patients were more likely to receive q2w cetuximab when given in combination

with chemotherapy than when cetuximab was administered as monotherapy (73% vs 40%, p < 0.001).

Demographics, disease characteristics

Demographics and disease characteristics are presented in Table 1. Patients receiving q1w versus q2w cetuximab treatment were a similar age (median 62.5 vs 59.3 years, p = 0.274) and there was an equal proportion of good performance status (ECOG 0-1) patients (92.2% vs 91.9%, *p* = 1.000). In the first line setting q2w cetuximab was more common (94%). BRAF mt data was available for 139 cetuximab treated patients (65%), with 17 patients (12%) of these RAS wt patients identified as BRAF mt. Patients treated in public versus private were more likely to receive q2w cetuximab (70% vs 13%, p < 0.001) and more likely to receive first line cetuximab (Table 2, 20.6% vs 5.9%, p = 0.005).

Patient treatment and outcomes

As also shown in Table 1, for the 188 patients where treatment had been completed, there was no difference in the proportion of patients that had stopped treatment due to adverse events for q1w versus q2w (6.1% vs 12.2%, p = 0.061). The bulk of patients discontinued therapy due to progressive disease (74.5% vs 58.9%).

Progression free survival data by line of therapy is shown in Figure 2. There is a trend for superior PFS outcomes with q2w treatment in the second line setting, but no significant differences are observed. When PFS analyses are limited to left side only patients (Figure 3A and 3B) for patients receiving an EGFR inhibitor in second line (HR 0.63, p = 0.13, 95% CI 0.34-1.15) or later lines of therapy (HR 1.12, p = 0.63, 95% CI 0.71-1.77), there is also no difference in outcome for q1w versus q2w cetuximab use.

Also shown in Figure 2 is overall survival data for patients with a left side primary only. In univariate analysis (Table 3) factors associated with improved overall survival were cetuximab treatment schedule, primary tumour side, performance status, year treated and BRAF mutation status. In a

multivariate analysis (MVA) as shown in Table 4 there was no difference in OS between q2w and q1w cetuximab. Factors that maintained significance in MVA included primary tumour side, performance status and year treated. BRAF status was excluded from the MVA due to the significant number of patients with unknown status.

Discussion

Within the Australian context, the PBS provides instruction to clinicians as to the patients that are eligible for treatment with a specific drug therapy [13]. The TGA provides instruction as to how an approved drug should be administered [14]. This advice may or may not be updated over time as new data emerges. To our knowledge the adherence of medical oncologists to TGA instruction has not previously been explored. A widely used local resource, eviQ, constructed and updated by healthcare professionals, superseded the q1w schedule in favour of the q2w schedule in December 2020[15]. Here, using an agent, cetuximab, where the evidence base has evolved over time to support a change in administration from q1w to q2w, we explore the evolution in clinical practice, including the impact of patient and site characteristics.

Our study has shown a substantial increase in the use of q2w cetuximab since 2015, this schedule now being used in the majority of patients. There are multiple patient and disease characteristics that varied for q1w vs q2w administration, some of which are known prognostic and predictive factors. Across all lines of therapy, the PFS outcomes appear similar for both treatment schedules. In a multivariate analysis and where analyses are restricted to left side primary patients, we also found no difference in OS.

We have previously reported the evolution of EGFRi use in Australia over time, including the increased use in first line and reducing use in patients with a right side primary [16]. Here we show that cetuximab treatment schedule has also evolved, with the first use of q2w cetuximab in 2011, with this becoming dominant from 2015. The increase in q2w schedule use follows the publication of data from a randomized phase II study, which reported similar outcomes for q1w versus q2w schedules

[10]. The use of q2w is also supported by prospective single arm studies achieving expected outcomes, such as the large phase II APEC study, and an earlier study examining cetuximab pharmacokinetics for q1w versus q2w administration [6,8].

Challenging any analysis of the impact of cetuximab schedule on outcomes is that the increasing use of q2w cetuximab has coincided with several substantial changes in clinical practice. Of most significance is the understanding of the impact of primary tumour side on prognosis and on EGFRi benefit, with left side tumours having a better prognosis and greater treatment benefit [17]. Many other factors also impact PFS, including patient age, performance status and tumour BRAF mt status [18]. Clearly each of these factors must be considered to give the most informative insight into the outcomes when comparing cetuximab schedules. When excluding right side patients where no PFS benefit is seen, the PFS survival curves for q1w and q2w look similar. Notably, along with removing the impact of any imbalance in primary tumour side for the two cetuximab schedules, this also excludes the majority of patients with a BRAF V600E mutation, the majority of which are seen in patients with a right-side primary [18].

Cetuximab and encorafenib were recently PBS-listed (1st January 2022) for BRAF mt metastatic CRC patients in line with recent publication of the BEACON trial [19], which used q1w cetuximab. It will be of interest to track the frequency of administration of cetuximab in this setting going forward. Of note, the ongoing BREAKWATER trial (NCT04607421), where these drugs are being given in combination with chemotherapy in the first line setting, is using q2w cetuximab, as are other ongoing clinical trials.

To our knowledge there is only one previous analysis of cetuximab treatment schedule in real world patients with metastatic CRC, which has only been reported in abstract form. This analysis of a large US insurance claims database reported crude (HR 1.05) and adjusted (HR 1.04) hazard ratios for overall survival that were similar for q1w and q2w cetuximab administration [20]. Factors included in the adjusted analysis weren't specified, but confounding was adjusted for. In our analysis, where we

were able to examine more granular data for patient and disease characteristics, we were also able to demonstrate similar outcomes for each schedule, this time measuring the impact on PFS. We consider PFS a more meaningful measure of true impact given overall survival outcomes are determined in part by the success of failure of any prior or subsequent therapy that a patient receives.

Clearly the q2w schedule is more convenient for patients, requiring less hospital visits and cost saving for the health system as each hospital visit adds additional cost. There would also be significant travel cost savings to the patient and for those still in the workforce less leave would need to be taken. Additionally, in the era of the global COVID-19 pandemic, less frequent administration is recommended to mitigate risk, particularly for an at-risk patient population [21]. Interesting differences we found were both the decreased uptake of q2w cetuximab and less use of cetuximab in first line in the private setting. Regarding the former there may be several explanations, including the relative availability of day centre chairs, with spots harder to find in the public setting. This could also possibly be influenced by the reimbursement structure in the private setting, where the treating clinician is remunerated per visit for intravenous therapy. Another possibility, which would be in keeping with the lower use of first line cetuximab, is that practice in the private setting may be slower to evolve.

There are limitations to our analysis. The predominant use of weekly cetuximab in the early years of our registry and the predominant use of fortnightly in the latter years means that factors not captured in the TRACC registry may have differed between the two schedules. Furthermore, the use of q2w cetuximab therapy is more common in combination with chemotherapy given the ease of aligning with most commonly used q2w chemotherapy schedule. Given there is no formal attempt to capture safety data in the TRACC database we did not seek to compare adverse events for q1w versus q2w. Unknown factors that impact outcomes may also have confounded the selection of

weekly versus two weekly treatment, however beyond convenience we would suggest there is no other clinical rationale for one versus the other.

Conclusion

There is increasing use of q2w cetuximab in routine care despite the TGA recommendation remaining based on the data supporting the original approval. This is in contrast to United States and European guidelines which have been updated, with q2w administration now actively promoted. In the absence of large randomised studies addressing the optimal schedule for cetuximab, our data provides reassurance to clinicians that the q2w cetuximab schedule is not inferior in the routine care setting. Our data is in line with previous data supporting this schedule, including a small randomised trial and multiple single arm studies. This evidence combined, along with the notable absence of any studies suggesting that q2w cetuximab could be inferior to q1w cetuximab and the lack of data to suggest worse toxicity, supports not only the continued use of the more convenient schedule, but more backing to use it as the preferred treatment schedule and justification to expand current regulations on its use in Australia.

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Figure Legends

Figure 1a. CONSORT diagram describing frequency of initial cetuximab administration across any line of therapy for TRACC patients enrolled between 2009 and 2019.

Figure 1b Cetuximab administration schedule over time.

Figure 2. Forest plot of progression free survival by line of therapy for all patients and OS for patients with a left side primary**.**

Figure 3A and 3B. PFS by primary tumour side

Table 1. Demographics and disease details

	Total cohort	**1-weekly**	**2-weekly**	**P value**
Total n (%)	214	103 (48.1%)	111 (51.9%)	
Age years median	61.7	62.5	59.3	0.274
Gender				
Male	123 (57.5%)	56 (54.4%)	67 (60.4%)	0.408
Female	91 (42.5%)	47 (45.6%)	44 (39.6%)	
Treatment Location				
Public	146 (68.2%)	44 (42.7%)	102 (91.9%)	**<0.001**
Private	68 (31.8%)	59 (57.3%)	9 (8.1%)	
ECOG				
0-1	197 (92.1%)	95 (92.2%)	102 (91.9%)	1.000
≥2	17 (7.9%)	8 (7.8%)	9 (8.1%)	
Line of cetuximab treatment				
1	34 (15.9%)	2 (1.9%)	32 (28.8%)	**<0.001**
2	81 (37.9%)	42 (40.8%)	39 (35.14%)	
3	80 (37.4%)	47 (45.6%)	33 (29.7%)	
≥4	19 (8.9%)	12 (11.7%)	7 (6.3%)	
Cetuximab administration				
Combination with chemotherapy	122 (57.0%)	41 (39.8%)	81 (73.0%)	**<0.001**
Cetuximab monotherapy	92 (43.0%)	62 (60.2%)	30 (27.0%)	
Median weeks on cetuximab	14.3	11.4	17.1	0.055
BRAF status				
Mutated	17 (7.9%)	13 (12.6%)	4 (3.6%)	**0.001**
WT	122 (57.0%)	46 (44.7%)	76 (68.5%)	
Unknown	77 (36.0%)	44 (42.7%)	31 (27.9%)	
Reason cease cetuximab (any line)				
Progressive disease (PD)	126 (58.9%)	73 (70.9%)	53 (47.7%)	
Toxicity	17 (7.9%)	6 (5.8%)	11 (23.4%)	**0.001**
Ongoing	26 (12.1%)	5 (4.9%)	21 (18.9%)	
Other	45 (21.0%)	19 (18.5%)	26 (23.4%)	
Primary site				
Left/Rectum	162 (75.7%)	70 (68.0%)	92 (82.9%)	
Right	44 (20.6%)	29 (28.2%)	15 (13.5%)	**0.025**
Other	8 (3.7%)	4 (3.9%)	4 (3.6%)	
Site of metastases				
Liver	156 (72.9%)	75 (72.8%)	81 (73.0%)	1.000
Lung	63 (29.4%)	27 (26.2%)	36 (32.4%)	0.369
Lymph nodes	68 (31.8%)	32 (31.1%)	36 (32.4%)	0.884
Peritoneum	49 (22.9%)	26 (25.2%)	23 (20.7%)	0.515
Bone	6 (2.8%)	2 (1.9%)	4 (3.6%)	0.684

Table 2. Breakdown of cetuximab line of therapy by treatment location

Cetuximab line of therapy	Total	Private	Public	p
1st	34 (15.9%)	4 (5.9%)	30 (20.6%)	**0.005**
2nd	81 (37.9%)	26 (38.2%)	55 (37.7%)	
3rd	80 (37.4%)	27 (39.7%)	53 (36.3%)	
≥4th	19 (8.9%)	11 (16.2%)	8 (5.5%)	

Table 3. Univariate analysis for improved OS

Variable	mOS	P value	HR (95% CI)
Cetuximab Schedule n = 214			
1 weekly	29	**0.011**	0.64 (0.45-0.90)
2 weekly	40		
Stage IV at diagnosis n = 214			
Yes	30	0.865	1.03 (0.72-1.48)
No	31		
Primary Site n = 206			
Left + Rectum	34	**0.001**	1.95 (1.30-2.92)
Right	22		
ECOG n = 214			
0-1	32	**0.003**	2.49 (1.37-4.54)
≥2	17		
Treatment location n = 214			
Public	29	0.519	0.89 (0.62-1.27)
Private	34		
Year treated n = 214			
2010-2014	28	**0.001**	0.56 (0.40-0.80)
2015-2019	37		
BRAF n = 139			
Mutated	18	**0.003**	0.43 (0.24-0.75)
Wild type	37		
Line of cetuximab treatment n = 214			
1	52	0.258	0.89 (0.73-1.09)
2	26		
3	32		
≥4	50		

Table 4. Multivariate analysis for improved overall survival n = 206

Variable	Hazard ratio	P value	95% CI
Cetuximab Schedule			
1 weekly	0.87	0.509	0.58-1.31
2 weekly	1		
ECOG			
0-1	2.94	**0.001**	1.59-5.41
≥2	1		
Primary Site			
Left + Rectum	1.87	**0.003**	1.23-2.83
Right	1		
Year Treated			
2010-2014	0.59	**0.011**	0.40-0.89
2015-2019	1		

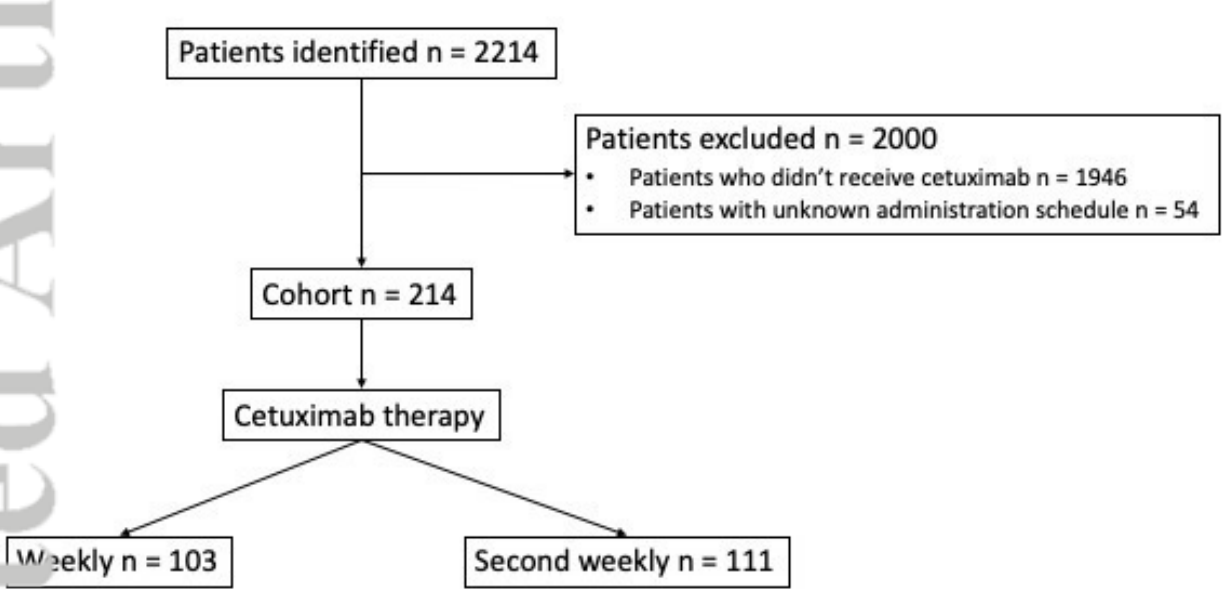

Figure 1a.jpg

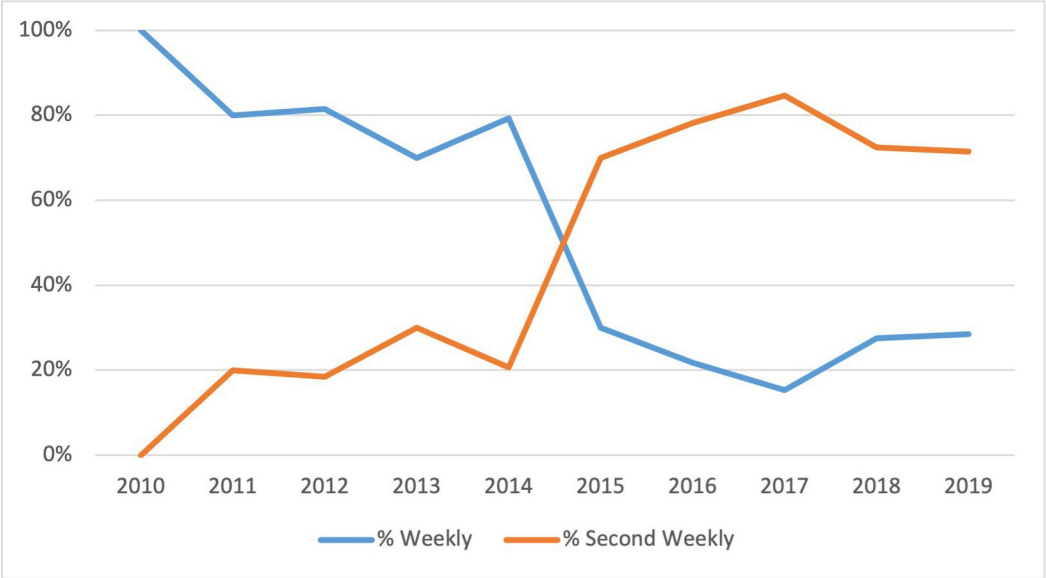

Figure 1b.jpg

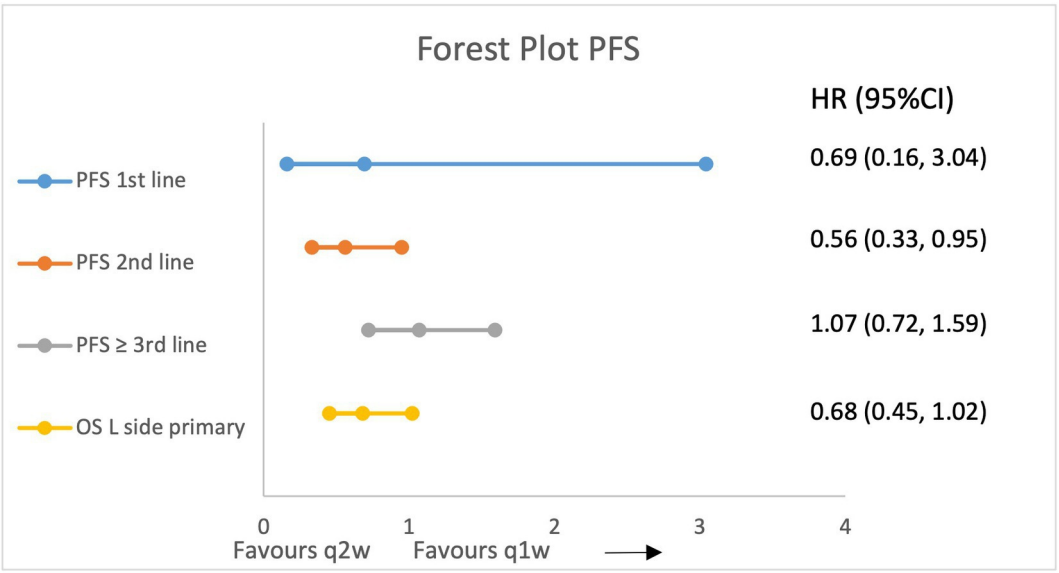

Figure 2.jpg

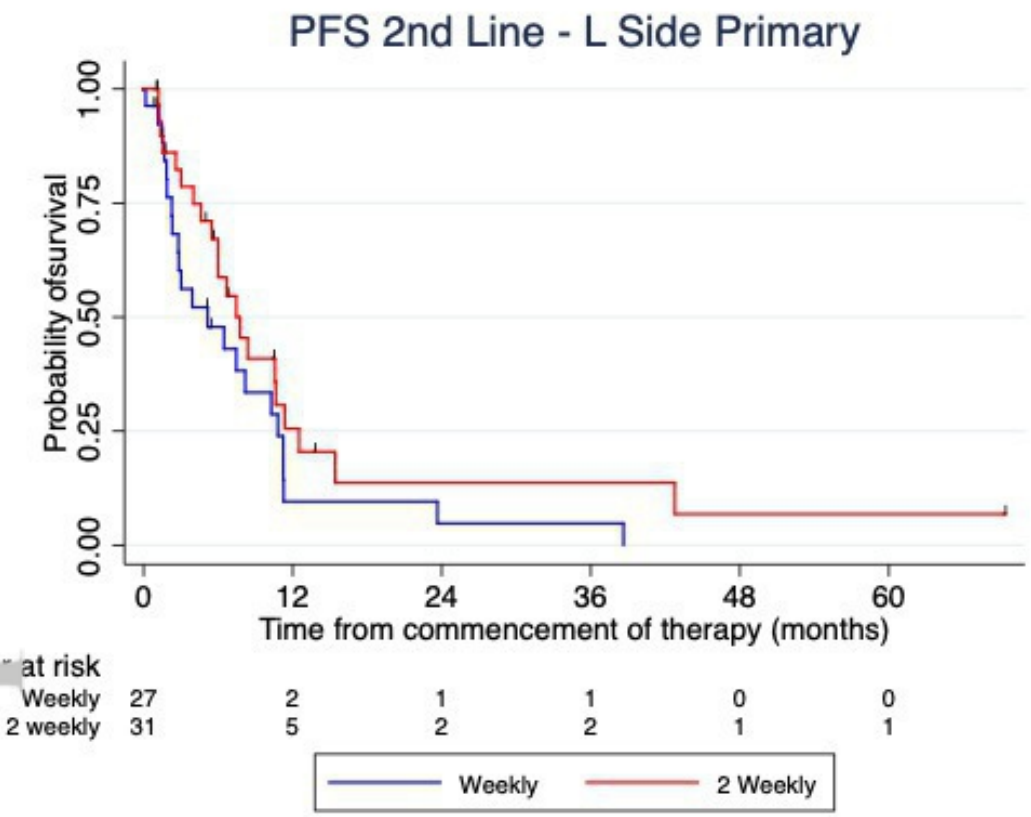

Figure 3a.jpg

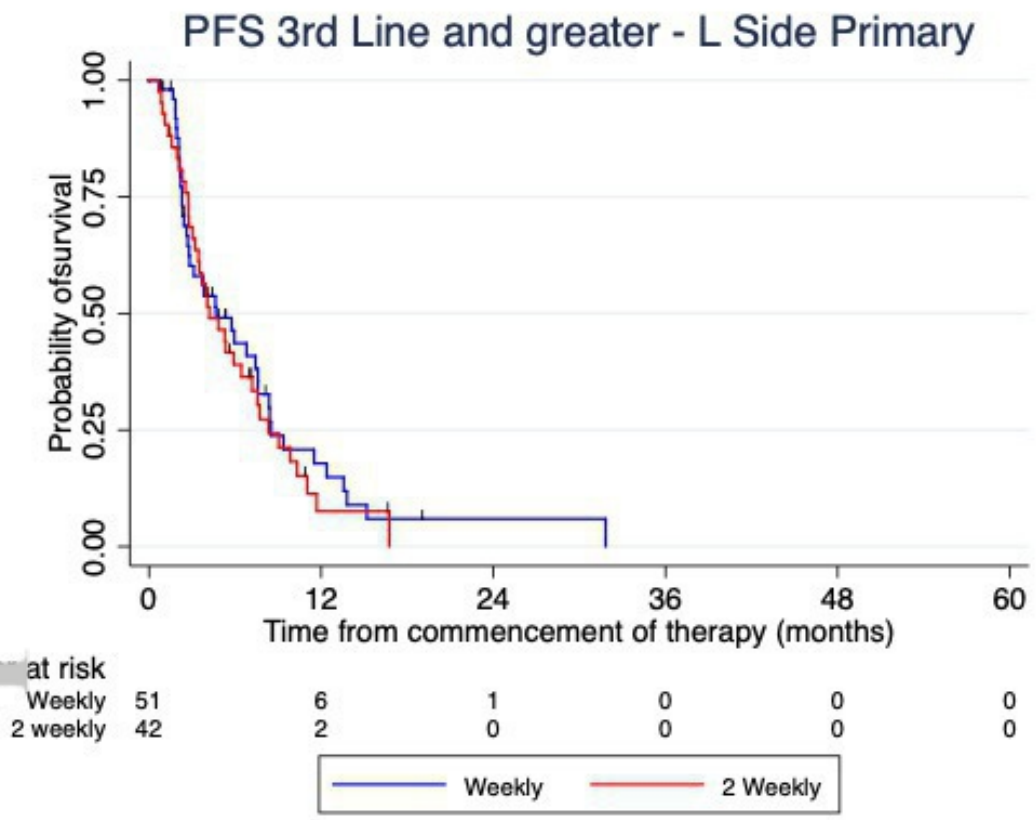

Figure 3b.jpg