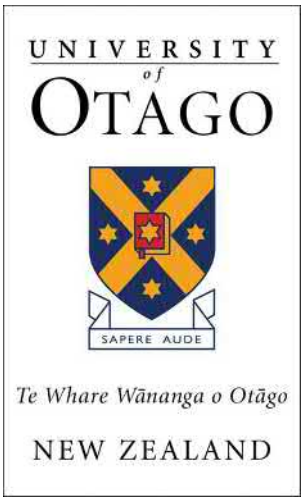

Real World Outcomes of Funded Cancer Medicines

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SPONSOR PHARMAC (Pharmaceutical Management Agency)

LOCATION PHARMAC (Pharmaceutical Management Agency)

ABSTRACT

Background

Cancer-related death is a leading cause of mortality worldwide. New treatments are being released with promising results in clinical trials; however, analysis of real-world health outcomes achieved with these drugs has been lacking. This project looked at four new cancer drugs, azacitidine, abiraterone, gefitinib and lenalidomide, across six clinical indications, to assess their performance in New Zealand clinical practice compared with efficacy data from clinical trials.

Materials and methods

We used Ministry of Health databases to identify all patients who had been funded on these four medicines between January 2012 and December 2016 and obtain details for time on treatment and overall survival (OS) measures. This was compared with key clinical trials in each medication.

Results

Two drugs had shorter OS than the clinical trials. Azacitidine had a median OS of 41 weeks in myelodysplastic syndrome, 24 weeks in acute myeloid leukaemia, and 28 weeks in chronic myelomonocytic leukaemia, much shorter than the 105 weeks in key trial. Gefitinib had OS 47 weeks, compared with 96.2 – 118.7 weeks in the three comparator trials. Lenalidomide and abiraterone did not reach median OS at the time of analysis, but both trended shorter than the clinical trials. Comparative results using PFS varied.

Discussion

Our results support previous analysis indicating that medication efficacy in clinical trials may not translate and generalise to good effects in New Zealand clinical practice. The magnitude of these disparities for azacitidine and gefitinib is particularly concerning.

INTRODUCTION

Since 1989, cancer-related death has surpassed ischaemic heart disease as the leading cause of mortality in NZ, accounting for 29.4% of deaths in 2012 (E16). Advanced and metastatic cancers have a large share in the burden of disease. Many new cancer treatments are currently being evaluated and released, and patients, clinicians and policy makers face hard decisions about which are worth investing in.

PHARMAC is the NZ pharmaceutical management agency, which makes decisions about which medicines should be funded in this country. PHARMAC's statutory goal is to achieve the best health outcomes that are reasonably achievable from pharmaceutical treatment and from within the funding available. Unfortunately, efficacy as demonstrated in clinical trials does not always translate to effectiveness in practice (1-4), so it is difficult to assess real health outcomes achieved. This project was conceived to investigate the health benefits that have been brought about by new cancer medications funded in NZ, comparing efficacy from clinical trials with observed effectiveness in the NZ population.

Four drugs recently funded in NZ for advanced cancer indications were chosen to evaluate this: azacitidine, abiraterone, gefitinib and lenalidomide. Respectively, they are funded for myelodysplastic syndromes, acute myeloid leukaemia and chronic myelomonocytic leukaemia; metastatic castration-resistant prostate cancer; non-small-cell lung cancer; and relapsed or refractory multiple myeloma. PHARMAC funding for these drugs on the Pharmaceutical Schedule was implemented between August 2012 and May 2015. We used data extracted from routine collections to describe health outcomes that are being achieved from recent funding decisions.

MATERIALS AND METHODS

Medicines to evaluate were selected as cancer drugs that had duration of funding in NZ on the Pharmaceutical Schedule at least as long as projected overall survival from clinical trials. They were excluded if there had been significant changes in managing the conditions since the key trials. This derived azacitidine, abiraterone, gefitinib and lenalidomide.

All patients receiving these four medicines from the date of listing on the Pharmaceutical Schedule to December 2016 were included in this analysis. Each of the four medicines were listed on the Pharmaceutical Schedule under Special Authority (SA); a set of eligibility criteria to initially receive or continue funding. Appendix 1 outlines the SA criteria for these medicines (5).

We used the date of the initial Special Authority being granted as the start date of treatment. These authorities must be renewed after a period of time (varying from 4 to 12 months in the study medications), and in all study medicines include criteria that the disease has not progressed. Therefore, time on treatment (TT) may be an estimate of progression-free survival. We calculated time on treatment using dispensing data, adjusting for early mortality before the end of dispensing period. Patients were censored at the date of the data catch.

Data collection

Data was sourced from the Special Authority, Pharmhouse, and Cancer Registry databases, maintained by the Ministry of Health, with the intent of acquiring data to determine progression free survival and overall survival of relevant patients. Data was available at the individual patient level and was unidentifiable.

The Special Authority database enabled the identification, selection, and acquiring of most qualitative criteria. Application approval was matched to the Pharmhouse database, which provides patient dispensing details (such as the quantity (units) of pharmaceutical treatment provided and approximate dispensing dates), and demographic details (persons age, location that treatment were dispensed, ethnicity, date of birth and death). Dispensing data was collected for the time period 1 January 2012 to 30 November 2016. The resulting dataset was cross referenced and verified to the Cancer Registry database (confirming criteria such as diagnosis, date of birth/death and age). The final dataset was stored on a SQL Server.

Clinical trial selection

We reviewed papers that were considered by the Pharmacology and Therapeutics Advisory Committee (PTAC) prior to approval of the medicines for funding (6-11) and conducted a Medline search for additional literature published after PTAC evaluation. This included new trials and updated survival data for trials that had previously been reviewed. The papers were reviewed and the trials with inclusion criteria most similar to the funded indications in New

Zealand were used in this analysis. If a trial was reported in more than one paper, the most recent reported OS and PFS were used. Specific trial inclusion criteria and comparison to Special Authorities are in Appendix 2.

Statistical analysis

R version 3.3.1 was used to analyse the data. Due to the low number of patients for acute myeloid leukaemia, chronic myelomonocytic leukaemia, and high risk myelodysplastic syndrome, stepwise Poisson regression modelling was not performed in these groups. Cox and Kaplan Meier modelling was performed for all indications.

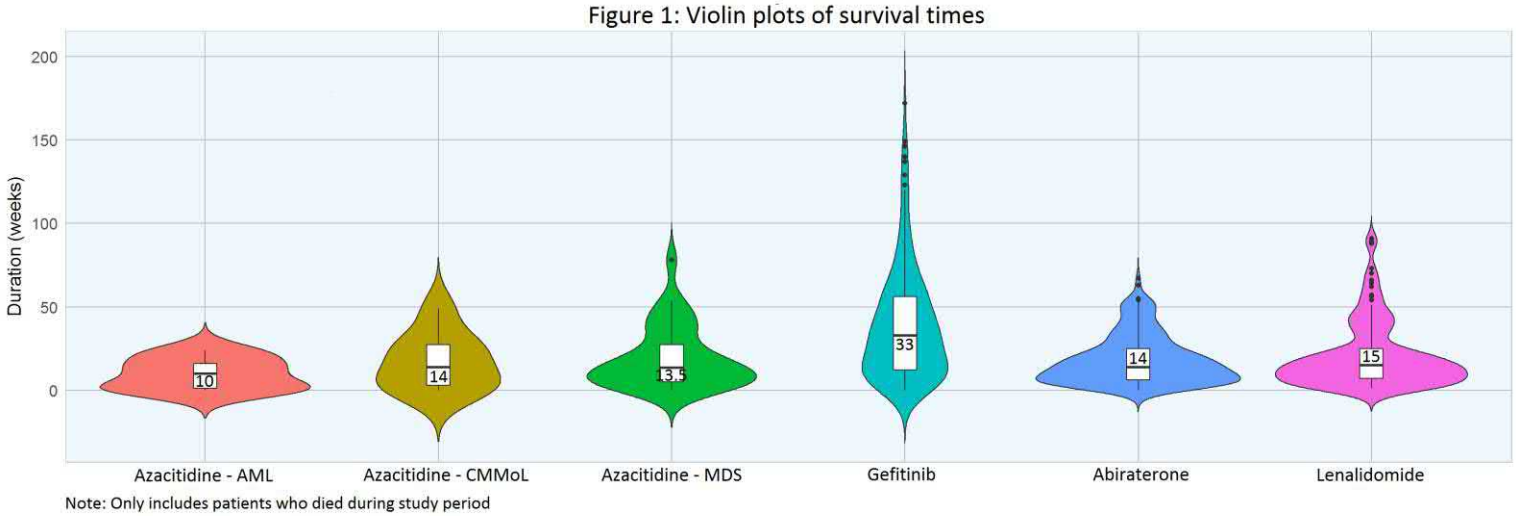
Results were reported as median survivals with either interquartile ranges (IQR) or 95% confidence intervals (95%CI) depending on available reported results in the corresponding RCT.

RESULTS

For the four medicines with six indications, we identified eight trials; one trial for azacitidine, two each for abiraterone and lenalidomide, and three for gefitinib. For the 2012 – 2016 period we calculated time on treatment and overall survival times for 1565 patients across the six indications. Summary survival statistics are in Table 1 below and patient demographics are in tables 2 to 5.

All indications had right-skewed distributions. Figure 1 shows distribution of patient survival times.

Figure 1: Violin plots of survival times



Azacitidine

Background

Azacitidine is a DNA methyltransferase inhibitor. It is funded in New Zealand for three indications; myelodysplastic syndromes classified as intermediate-2 (INT-2) or high risk by the IPSS scoring system, chronic myelomonocytic leukaemia, and low marrow blast count acute myeloid leukaemia.

Table 1: Survival Data for New Zealand 2012-2016 and corresponding RCTs			
Medicine	***Time on Treatment*** Wks (IQR) *(95%*	***PFS*** Wks (IQR) *(95%*	***Overall Survival*** Wks (IQR) *(95%*

Table 1: Survival Data for New Zealand 2012-2016 and corresponding RCTs					
			CI)	*CI)*	*CI)*
Azacitidine					
	RCT	**AZA-CSR-005** (16, 17)		60.4 (18.0 – 118.3) *(40.7 – 118.3)*	105.0 (45.0 – NR) *(76.7 – NR)*
	NZ	**MDS**	41 (13 – NR) *(25 – NR)*		41 (6 – 78) *(25 – NR)*
		CMMoL	28 (4 – NR) *(9 – NR)*		28 (4 – NR) *(9 – NR)*
		AML	24 (10 – NR) *(13 – NR)*		24 (10 – NR) *(13 – NR)*
Abiraterone					
	RCT	**Taxane-pretreated COU-AA-301** (19, 20)		12.6 (11.9 – 28.1) *(12.3 – 12.9)*	*67.7 (63.4 – 72.9)*
		COU-AA-302 (21-23)	59.1 (35.6 – 117.4)	70.7 (34– 142)[a]	148.7 *(140.1 – 157.7)*
	NZ	**Overall**	67+ (23 – NR) *(NR)*		67+ (23 – NR) *(NR)*
		Taxane-pretreated			50+ (19 – NR) *(43 – NR)*
		Taxane-naïve			67+ (27 – NR) *(NR)*
Gefitinib					
	RCT	**WJTOG3405** (26)		39.4 (28 –75)[a] *(34.3 – 59.6)*	Not reached
		NEJ002 (24-25)		46.3 (27 – 70)[a]	118.7 (83 – 234)[a]
		IPASS (27-29)		40.7[b]	92.6 (59 – 264)[a]
	NZ	**Overall**	48 (19 – 92) *(38 – 56)*		47 (18 – 92) *(37 – 56)*
Lenalidomide					
	RCT	**MM-009/MM-010** (32-37)	43.2	47.6 (20 – NR)[a]	126.9 (78 – NR)[a]
	NZ	**Overall**	51+ (12 – NR) *(42 – NR)*		91+ (21 – NR) *(88 – NR)*

[a] Estimated IQR from Kaplan-Meier curve where the accurate figure was not presented in the relevant papers

[b]Neither IQR nor confidence interval were accessible for this figure

The myelodysplastic syndromes (MDS) are a group of diseases characterised by bone marrow dysfunction with low peripheral blood cell counts. In NZ, azacitidine is only funded for primary myelodysplastic syndromes, not dysplasia arising secondary to radiation or chemotherapy. Prior to 2002, chronic myelomonocytic leukaemia (CMMoL) and acute myeloid

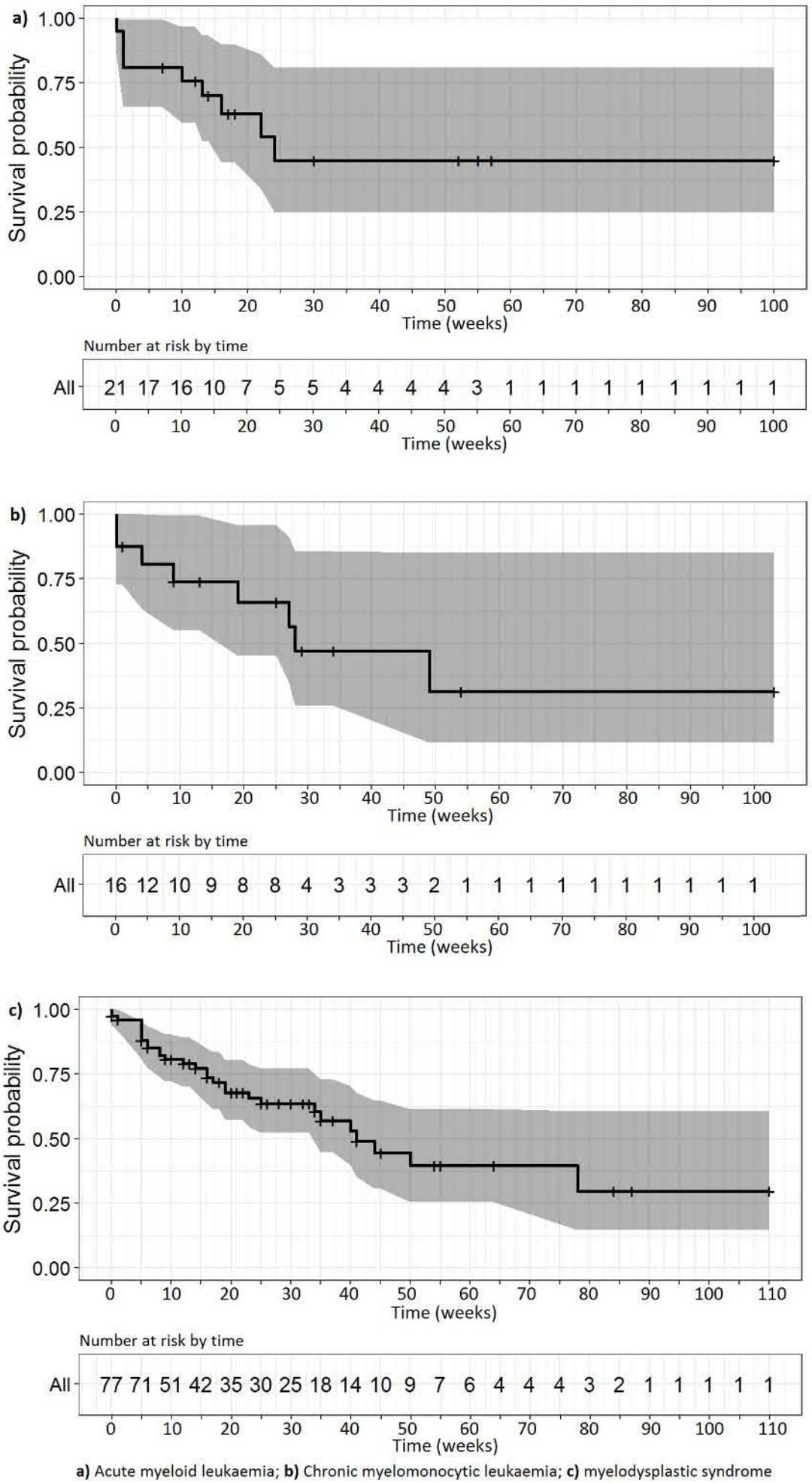
leukaemia (AML) were both considered to be variants of MDS. In the 2002 WHO classification they were reclassified as separate entities. The key study in azacitidine was begun before the definition change; therefore, some of the analysis considers these three conditions together as a group. (12-15)

RCT results

The AZA-CSR-005 (16, 17) trial reported an OS of 105 weeks (95% CI 76.7 – not reached), and a later analysis including only those patients who have AML under the new criteria also gave OS as 105 weeks (62.7 – not reached) (18). PFS was reported as time to disease progression, relapse after response, or death from any cause; this was 60.4 weeks (40.7 – 118.3).

Table 2: Azacitidine	**NZ population**	**RCT population**
Patient demographics	n = 116	n = 179
Gender (M)	82 (70.7%)	132 (73.7%)
Ethnicity		
European	92 (79.3)	177 (98.9)
Asian	9 (7.8)	2 (1.1)
Māori	9 (7.8)	0
Pacific	2 (1.7)	0
MELAA	1 (0.9)	0
Other	1 (0.9)	0
Unknown	2 (1.7)	0
Age		
Median age (range)	68 (46-83)	69 (42-83)
≤54	4 (3.4)	6 (3.4)
55-64	17 (14.7)	51 (28.5)
65-74	53 (45.7)	84 (46.9)
≥75	42 (36.2)	38 (21.2)
Indication		
Acute myeloid leukaemia	21 (18.1)	54 (30.2)
Chronic myelomonocytic leukaemia	16 (13.8)	10 (5.6)
Myelodysplastic syndrome	79 (68.1)	115 (64.2)
Median follow-up (weeks)		90.4

Figure 2: Azacitidine Overall Survival



a) Acute myeloid leukaemia; **b)** Chronic myelomonocytic leukaemia; **c)** myelodysplastic syndrome

NZ results

In collected data there were 21 patients prescribed azacitidine for AML, 16 for CMMoL, and 79 for high-risk MDS (table 2). Median survival time was 24 weeks in AML (95% CI: 13 – not reached), 28 weeks in CMMoL (9 – NR), and 41 (25 – NR) in high-risk MDS (see figure 2). Time on treatment was 24 weeks in AML, 28 in CMMoL, and 44 in MDS (see figure 7 below).

All indications within azacitidine had too small patient groups to give robust subgroup analyses.

Abiraterone

Background

Abiraterone is funded for metastatic castration-resistant prostate cancer. Patients on conventional anti-androgen therapy often still have some level of circulating androgen, and abiraterone decreases androgen production to undetectable levels. It has demonstrated activity even in anti-androgen-resistant cancer. There are two groups of patients funded in New Zealand; those who have had at least two anti-androgen treatments but no taxane chemotherapy regime, and those who have received taxane-containing chemotherapy and have had progressive disease since then.

RCT results

The major trial of abiraterone in taxane-pretreated patients was COU-AA-301 (19-20). This defined PFS as the first of PSA progression, radiographic progression, skeletal event, pain progression or increase in required cancer treatment. It reported a modified PFS of 12.6 weeks (12.3 – 12.9) and OS 67.7 (63.4 – 72.9)

COU-AA-302 is the key trial in taxane naïve patients (21-23). This reported a radiographic PFS of 70.7 (IQR 34.2 – 141.9), and duration on treatment 59.1 weeks (35.6 – 117.4); OS was 148.7 weeks (95% CI 140.1 – 157.7).

Table 3: Abiraterone Patient demographics	**NZ population**	**RCT population**
	n = 754	n = 1343
Ethnicity		n = 797[a]
European	626 (83.0)	743 (93.2)
Māori	53 (7.0)	0
Pacific	21 (2.8)	0
Asian	16 (2.1)	11 (1.4)
MELAA	2 (0.3)	31 (3.4)
Other	2 (0.3)	11 (1.4)
Unknown	34 (4.5)	0

Table 3: Abiraterone Patient demographics	NZ population n = 754	RCT population n = 1343
Age		
Median age (range)	67 (37-93)	70[b] (42-95)
≤64	105 (13.9)	367 (28.1)
65-69	117 (15.5)	285 (21.2)
70-74	141 (18.7)	286 (21.3)
≥75	391 (51.9)	405 (30.2)
Taxane pretreated	123 (16.3)	797 (59.3)
Median follow-up (weeks)		160.3[b]

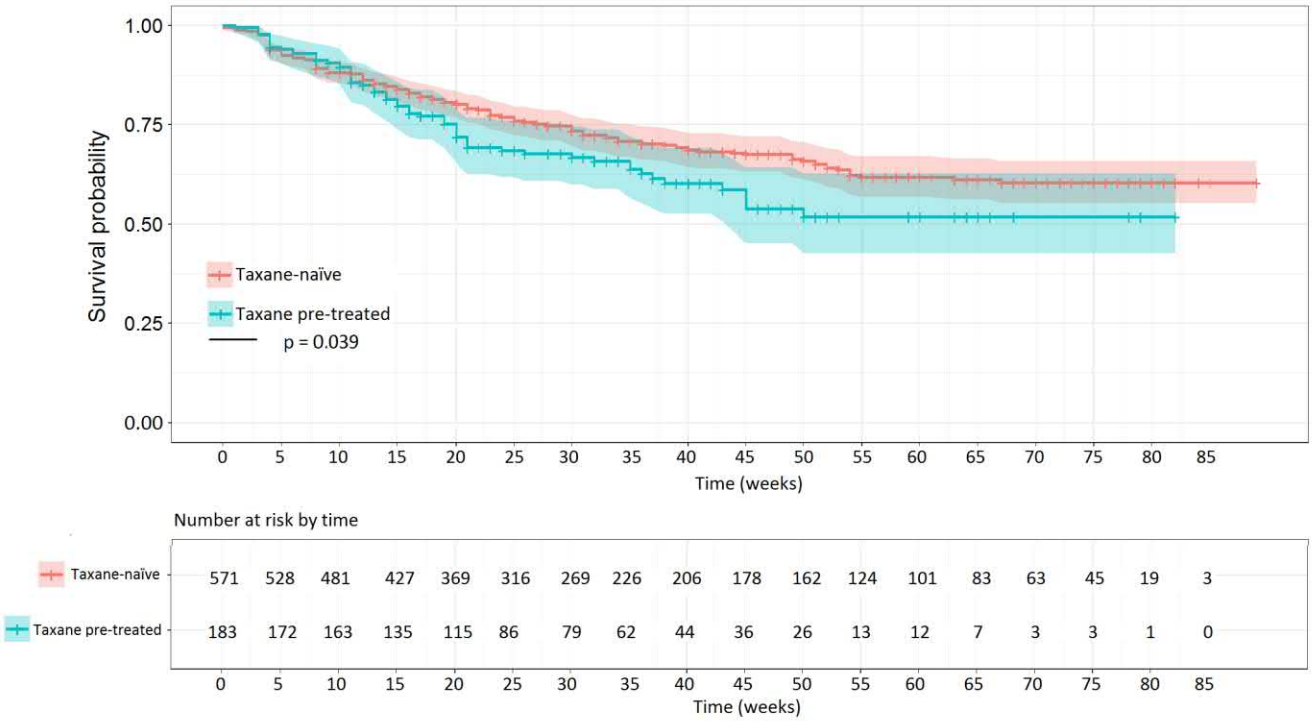
[a] COU-AA-301 only

[b]Patient-number weighted median across multiple studies

NZ results

754 patients in NZ initiated abiraterone between May 2015 and September 2016 (Table 3). Of these, 183 were taxane pre-treated, and 571 taxane-naïve. Overall survival was not reached at 67 weeks across both of these groups; separately, it was above 51 weeks (43 – NR) in taxane-pretreated, and not reached at 67 weeks in taxane-naïve (see figure 3). This difference was significant, p = 0.039. Median time on treatment was not reached at 67 weeks (see figure 7).

Figure 3: Abiraterone Overall Survival



In our results, age was significantly linked with survival, but the effect size was small; each additional year of age was associated with an increase in weekly hazard of death of 2% (p = 0.01). On investigation, there was a difference between taxane-pretreated and taxane-naïve patients with regards to age; almost 60% of taxane-naïve patients were 75 or older, and less than 20% of taxane-pretreated patients were 75 or older, so it is possible that this had an effect on survival.

Gefitinib

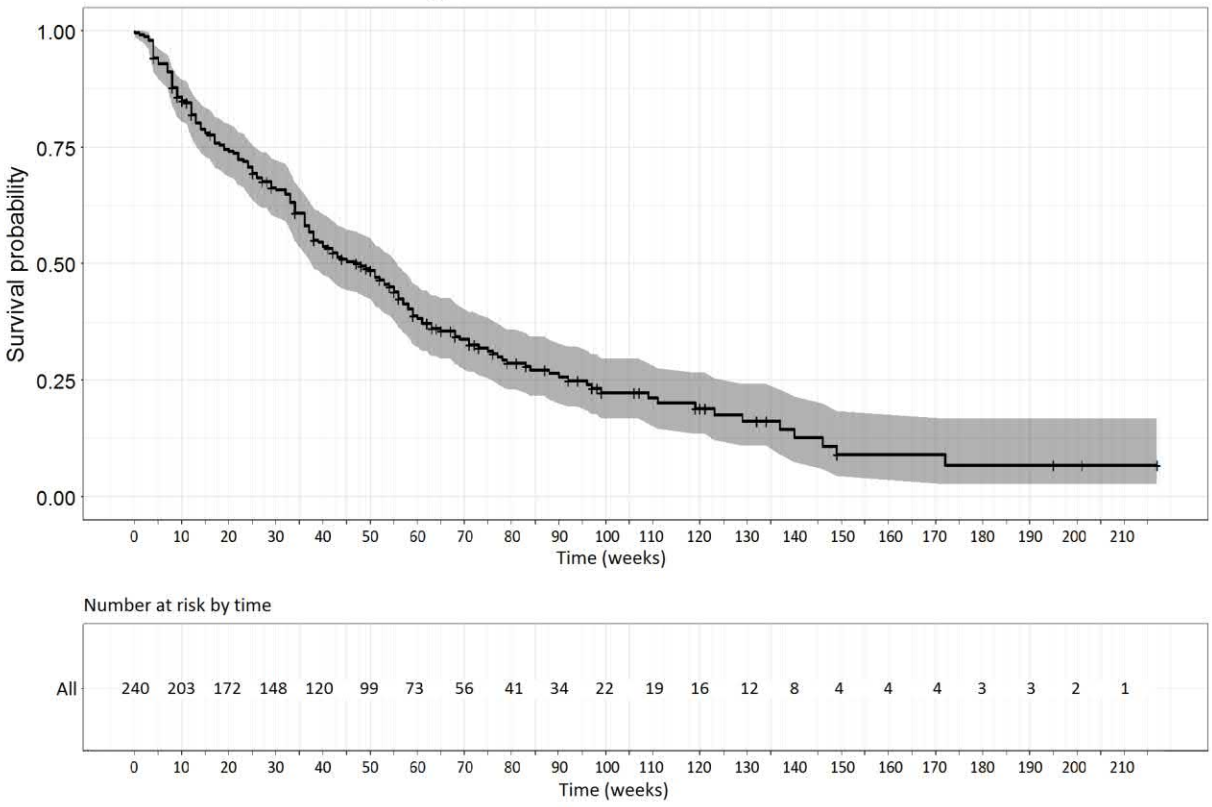
Background

Gefitinib is used in NZ as a first-line treatment for patients with non-squamous non-small-cell lung cancer (NSCLC) who have been shown to have a sensitising mutation in the epithelial growth factor receptor (EGFR) gene. The initial studies of gefitinib were conducted before the presence of the EGFR mutation was known.

RCT results

We identified three major trials including EGFR positive patients. NEJ002 (24-25) and WJTOG3405 (26) were both exclusively EGFR positive, and from IPASS (27-29) we looked only at the EGFR positive subgroup. PFS ranged from 39.4 to 46.3 weeks, and OS from 92.6 to 118.7. These studies were all done in Asian populations.

Figure 4: Gefitinib Overall Survival



NZ results

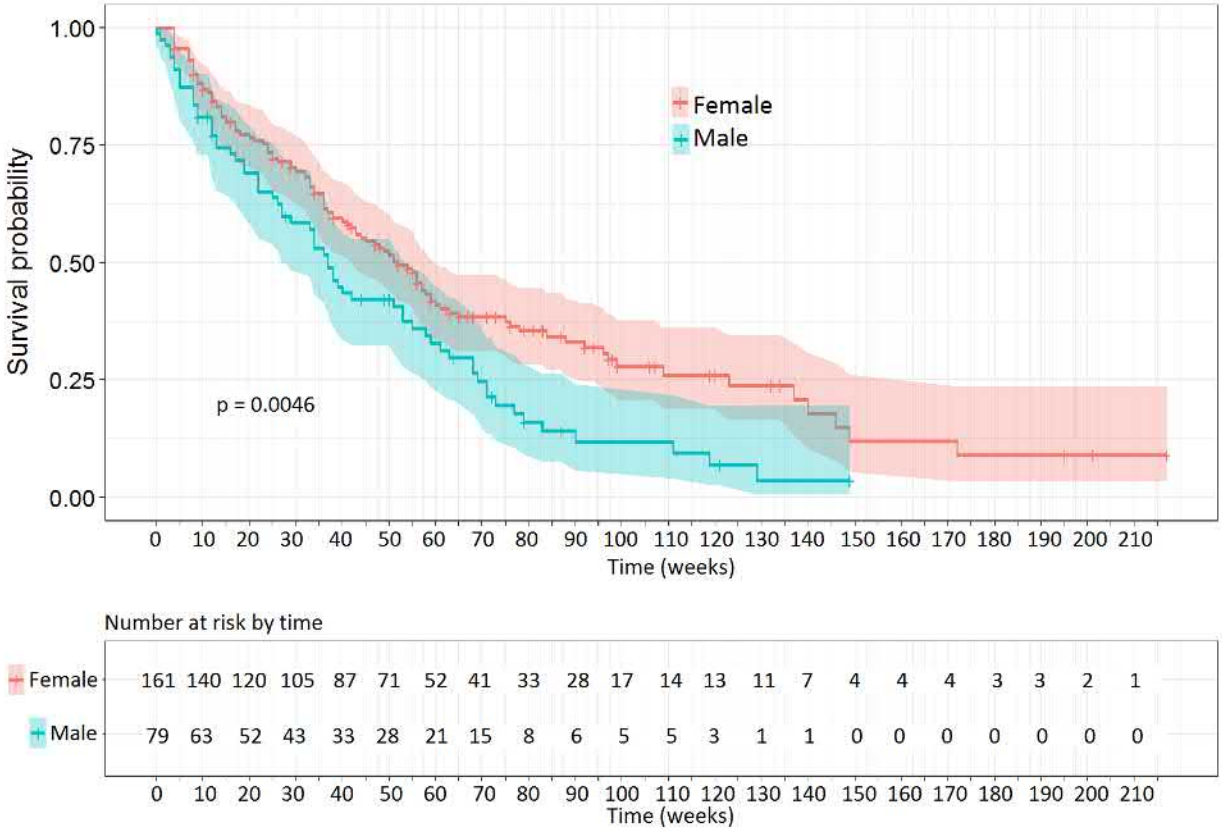
Our study included 270 patients who initiated gefitinib between August 2012 and September 2016 (table 4). All of these patients were EGFR positive. Median overall survival was 47 weeks (95%CI 37 – 56) (figure 4). Our patients had a time on treatment of 48 weeks.

Gender caused a significant difference in survival (figure 5). Male patients had an overall survival of 36-37 weeks, and female patients 51 weeks (p = 0.0046). We found small differences by ethnicity, where patients of Pacific Island ethnicity had shorter OS than other ethnicities.

Table 4: Gefitinib	**NZ population**	**RCT population**
Patient demographics	n = 270	n = 809
Gender (M)	85 (31%)	194 (24%)
Ethnicity		
European	153 (56.7)	
Asian	64 (23.7)	(100%)[a]
Pacific	25 (9.2)	
Māori	23 (8.5)	
MELAA	1 (0.4)	
Unknown	4 (1.5)	
Age		
Median age (range)	64 (38-92)	64[b,c] (34 – 75)
≤54	46 (17.0)	Age ranges not given
55-64	76 (28.1)	
65-74	71 (26.3)	
≥75	77 (28.5)	
Median follow-up (weeks)		61.9[b,c]

[a]estimated
[b]Patient-number weighted median across multiple studies
[c]NEJ002 and WJTOG3405

Figure 5: Gefitinib OS by gender



Lenalidomide

Background

Lenalidomide is a thalidomide analogue used in patients with relapsed or refractory multiple myeloma. Multiple myeloma (MM) is a haematological malignancy characterised by clonal proliferation of a small number of plasma cell lines. Myeloma treatment is normally initiated when the first signs of end-organ damage – bone or renal disease – are seen, as there is insufficient evidence for the efficacy of early treatment. (30-31) In New Zealand lenalidomide is approved as a third-line treatment for MM, or second-line if the patient has suffered severe side effects on bortezomib or thalidomide.

RCT results

The key trials of lenalidomide are MM-009 and MM-010 (32-37). Analysed together, they reported PFS 47.6 (IQR 20.2 – not reached) and OS 126.9 weeks (78.0 – not reached).

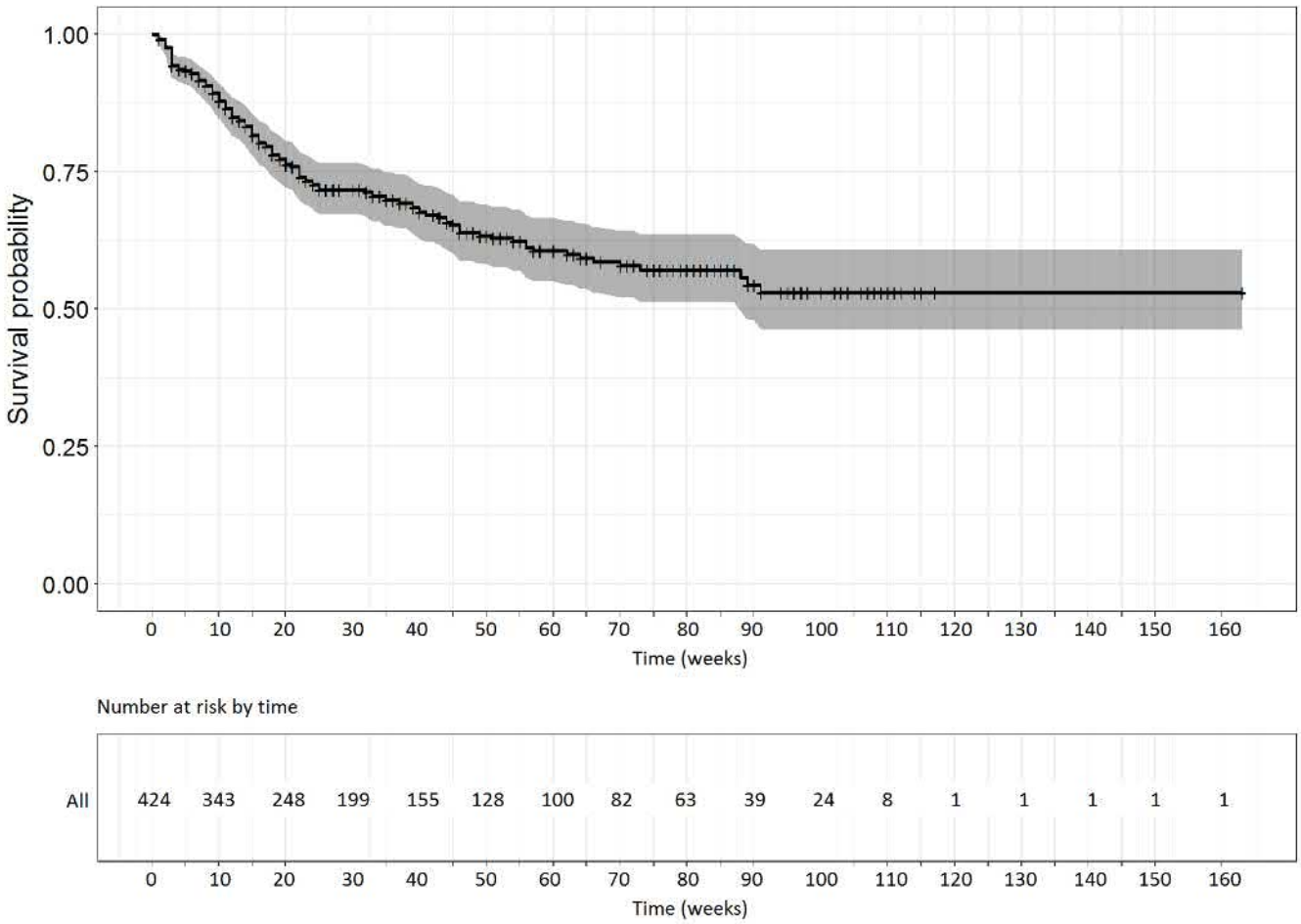
NZ results

Our analysis included 424 patients who initiated lenalidomide between September 2014 and October 2016 (table 5). Median OS was not reached at 91 weeks, but it is noted that very few patients remain in the survival curve (figure 6). Median treatment time was not reached at 51 weeks (figure 7). Increased age was associated with an increase in risk ($p < 0.01$), and patients who had lenalidomide as a third- line treatment had a 2.4 times higher chance of death within a given week over those who used it as second-line treatment ($p < 0.01$).

Table 5: Lenalidomide Patient demographics	**NZ population**	**RCT population**
	n = 424	n = 346
Gender (M)	253 (59.7)	206 (59.5)
Ethnicity		
European	357 (84.2)	306 (88.4)
Māori	28 (6.6)	
Pacific	20 (4.7)	6 (1.7)[a]
Asian	13 (3.1)	
MELAA	1 (0.2)	30 (8.7)
Other	1 (0.2)	4 (1.2)
Unknown	4 (0.9)	0
Age		
Median age (range)	65 (32-93)	63 (33-86)
≤54	42 (9.9)	70 (20.2)
55-64	80 (18.9)	118 (34.1)
65-74	151 (35.6)	122 (35.3)
≥75	151 (35.6)	43 (12.4)
Line of treatment		n = 353
Second	68 (16.0)	133 (37.7)
Third or later	356 (84.0)	220 (62.3)
Median follow-up (weeks)		205.7

[a]Asian, Pacific Island and Māori populations were reported as one group

Figure 6: Lenalidomide Overall Survival



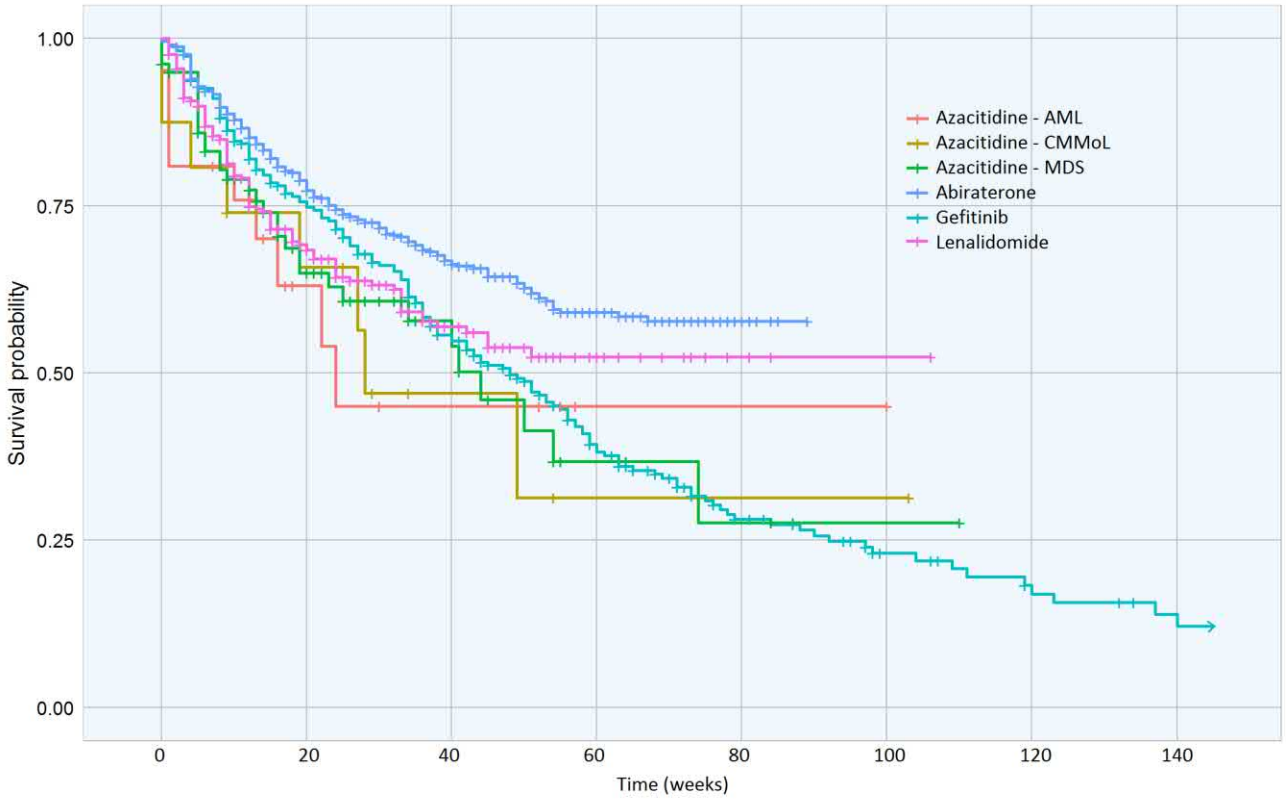
DISCUSSION

Previous papers have reported a difference between efficacy in clinical trials and effectiveness in clinical practise in a number of disease settings (1-4). In oncology, a number of papers have published data comparing either extended access programmes or routine clinical use of oncology medications to key clinical trials (38-46). While some of these reported PFS or OS values lower than key clinical trials (38, 42, 44), the most extreme result was a PFS of 83% of the clinical trial value; some (40, 41, 43, 45) reported PFS or TTP values longer than the key clinical trials in the relevant medications.

We encountered a much greater magnitude of difference in the study drugs; the median overall survival is only **39%** of the clinical trial median in azacitidine**,** and at best **40-51**% in gefitinib depending on trial used as comparator. Abiraterone and lenalidomide approached the median but did not cross it in the study, so they would benefit from further investigation after they have been funded for a greater period of time, However, the trend in both drugs appears to be to a shorter overall survival than trials indicated. We did report that our time on treatment was longer than clinical trial PFS in some cases; however, this is likely to have resulted from a failure of TT in modelling PFS, rather than a true result.

There are a number of factors that might account for this difference. In all disease groups, our patients had a similar median age and age range, but the patients may have been more unwell. We were not able to describe the disease state of the patients at the time of treatment initiation;

Figure 7: Time on treatment



the New Zealand Cancer Registry collects details of the cancer (including morphology and staging) at the time of initial diagnosis, but does not track it later in the course of the disease. Additionally, most of the trials specified WHO performance scores for patients to be included, whereas in New Zealand only azacitidine and abiraterone have criteria on this. We know that our patients tended to have a broader range of ethnicity than the clinical trials, and in particular had more Māori and Pacific Island patients. We did not power this analysis to detect survival difference between ethnicities, but this may have impacted the overall results if there was a real difference in survival. . With the lenalidomide group, a higher proportion of our patients had received two or more prior treatments, and our results confirm a prior study (36) in showing that patients who have had more than one prior line of treatment have a lower overall survival.

We assumed that clinicians were making accurate Special Authority requests; it is possible that they may tick incorrect boxes in order to achieve access to the treatment for a patient they believe may benefit. We also could not assess if patients took a drug as prescribed, as our data extended only to the dates and quantities dispensed.

While our results were lower than expected from trial data, this paper does not address whether patients in New Zealand are living longer and with less disease burden than they would if they did not receive the treatments investigated, as we do not have a comparable cohort of patients who have a similar severity of disease but were not treated.

There are inherent limitations in comparing continuation rates in New Zealand with earlier clinical trials, with potential for bias and confounding that cannot be eliminated by the data. This is essentially a cohort study of New Zealand patients, with the comparators being previous patients overseas. We aimed to choose conditions that had not had large changes in management since the trials were conducted, but this does not remove all possibility of standard of care changing.

We wanted to look at progression-free survival directly, but were unable to measure this from our collected data. The NZ Cancer Registry is an incidence register, so it reports only the initial cancer and not any measures of progression. There are national event databases that we could perhaps use (the National Minimum Dataset and National Non-Admitted Patient Collection), but these do not collect exhaustive data on patient events, so would miss many progression events.

The use of time on treatment as a proxy for progression free survival is somewhat debateable. It could be skewed in either of two directions. We assumed that under the Special Authority renewals, a patient cannot have their approval renewed if they have progression, and therefore patients who progress should discontinue the treatment. However, patients may also discontinue for a number of other reasons, which cannot be accounted for in this analysis. This

tends to decrease TT below PFS. Alternately, some patients may be on the medication past the true time of progression, as measures of progression are typically investigated less frequently in routine clinical use than in study protocols, and ending criteria may be less strongly enforced. This tends to lengthen TT over PFS. We note that in our study time on treatment often appeared to be longer than overall survival; this is likely to be because of patients not completing a dispensed course of medications at the time of death, and indicates a substantial number of patients were on the study medication until death. This suggests TT is unlikely to be modelling PFS closely in this New Zealand patient group.

CONCLUSION

Our findings indicate that recent cancer drugs may not be performing as well in the New Zealand setting as would be expected based on clinical trial data. Two of the four drugs analysed performed considerably worse than expected in overall survival, and the other two trended similarly poorly. These indicate that caution should be used when translating the results of clinical trials to predicting outcomes generalised to the real world setting.

More research would be valuable. Abiraterone and lenalidomide should be assessed again at a later date to confirm overall survival medians. This report only addresses four of the over one hundred cancer medications funded in New Zealand. It would also be valuable to have better access to progression data in national registries for this kind of analysis.

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Conflicts of Interest

Nil

REFERENCES

1. Flather, M., Delahunty, N., & Collinson, J. (2006). Generalizing results of randomized trials to clinical practice: reliability and cautions. Clinical Trials, 3(6), 508-512. http://dx.doi.org/10.1177/1740774506073464
2. Treweek, S. & Zwarenstein, M. (2009). Making trials matter: pragmatic and explanatory trials and the problem of applicability. Trials, 10(1). http://dx.doi.org/10.1186/1745-6215-10-37
3. Tunis, S., Stryer, D., & Clancy, C. (2003). Practical Clinical Trials: Increasing the value of clinical research for decision making in clinical and health policy. JAMA, 290(12). http://dx.doi.org/10.1001/jama.290.12.1624
4. Sekine, I., Takada, M., Nokihara, H., Yamamoto, S., & Tamura, T. (2006). Knowledge of Efficacy of Treatments in Lung Cancer Is Not Enough, Their Clinical Effectiveness Should Also Be Known. Journal Of Thoracic Oncology, 1(5), 398-402.
5. Pharmaceutical Management Agency. (2016). New Zealand Pharmaceutical Schedule: August 2016. Wellington: Pharmaceutical Management Agency.
6. Pharmaceutical Management Agency. (2009). PTAC minutes - 2009-08. Retrieved from https://www.pharmac.govt.nz/about/committees/ptac/ptac-minutes/
7. Pharmaceutical Management Agency. (2010). PTAC minutes - 2010-08. Retrieved from https://www.pharmac.govt.nz/about/committees/ptac/ptac-minutes/
8. Pharmaceutical Management Agency. (2010). PTAC minutes - 2010-11. Retrieved from https://www.pharmac.govt.nz/about/committees/ptac/ptac-minutes/
9. Pharmaceutical Management Agency. (2011). PTAC minutes - 2011-11. Retrieved from https://www.pharmac.govt.nz/about/committees/ptac/ptac-minutes/
10. Pharmaceutical Management Agency. (2013). PTAC minutes - 2013-05. Retrieved from https://www.pharmac.govt.nz/about/committees/ptac/ptac-minutes/
11. Pharmaceutical Management Agency. (2013). PTAC minutes - 2013-08. Retrieved from https://www.pharmac.govt.nz/about/committees/ptac/ptac-minutes/
12. Hasserjian, R. (2015). Advances in the diagnosis and classification of myelodysplastic syndromes. Diagnostic Histopathology, 21(5), 203-211. http://dx.doi.org/10.1016/j.mpdhp.2015.06.005
13. Vardiman, J., Harris, N., & Brunning, R. (2002). The World Health Organization (WHO) classification of the myeloid neoplasms. Blood, 100(7), 2292-2302. http://dx.doi.org/10.1182/blood-2002-04-1199
14. Arber, D., Orazi, A., Hasserjian, R., Thiele, J., Borowitz, M., & Le Beau, M. et al. (2016). The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood, 127(20), 2391-2405. http://dx.doi.org/10.1182/blood-2016-03-643544
15. Raj, K. & Mufti, G. (2006). Azacytidine (Vidaza®) in the treatment of myelodysplastic syndromes. Therapeutics And Clinical Risk Management, 2(4), 377-388. http://dx.doi.org/10.2147/tcrm.2006.2.4.377
16. Pharmion Corporation. (2007). A Multicenter, Randomized, Open-Label, Parallel-Group, Phase 3 Trial of Subcutaneous Azacitidine Plus Best Supportive Care Versus Conventional

Care Regimens Plus Best Supportive Care for the Treatment of Myelodysplastic Syndromes (MDS). Unpublished.
17. Fenaux, P., Mufti, G., Hellstrom-Lindberg, E., Santini, V., Finelli, C., & Giagounidis, A. et al. (2009). Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. The Lancet Oncology, 10(3), 223-232. http://dx.doi.org/10.1016/s1470-2045(09)70003-8
18. Fenaux, P., Mufti, G., Hellstrom-Lindberg, E., Santini, V., Gattermann, N., & Germing, U. et al. (2009). Azacitidine Prolongs Overall Survival Compared With Conventional Care Regimens in Elderly Patients With Low Bone Marrow Blast Count Acute Myeloid Leukemia. Journal Of Clinical Oncology, 28(4), 562-569. http://dx.doi.org/10.1200/jco.2009.23.8329
19. Cougar Biotechnology, Inc. (2010). A phase 3, randomized, double-blind, placebo-controlled study of abiraterone acetate plus prednisone in patients with metastatic castration-resistant prostate cancer who have failed doxetaxel-based chemotherapy. Unpublished.
20. Fizazi, K., Scher, H., Molina, A., Logothetis, C., Chi, K., & Jones, R. et al. (2012). Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. The Lancet Oncology, 13(10), 983-992. http://dx.doi.org/10.1016/s1470-2045(12)70379-0
21. Ryan, C., Smith, M., de Bono, J., Molina, A., Logothetis, C., & de Souza, P. et al. (2013). Abiraterone in Metastatic Prostate Cancer without Previous Chemotherapy. New England Journal Of Medicine, 368(2), 138-48. http://dx.doi.org/10.1056/NEJMoa1209096
22. Rathkopf, D., Smith, M., de Bono, J., Logothetis, C., Shore, N., & de Souza, P. et al. (2014). Updated interim efficacy analysis and long-term safety of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy (COU-AA-302). European Urology, 66, 815-825. http://dx.doi.org/10.1016/j.eururo.2014.02.056
23. Ryan, C., Smith, M., Fizazi, K., Saad, F., Mulders, P., & Sternberg, C. et al. (2015). Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. The Lancet Oncology, 16(2), 152-160. http://dx.doi.org/10.1016/s1470-2045(14)71205-7
24. Maemondo, M., Inoue, A., Kobayashi, K., Sugawara, S., Oizumi, S., & Isobe, H. et al. (2010). Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. The New England Journal Of Medicine, 362(25), 2380-8. http://dx.doi.org/10.1056/NEJMoa0909530
25. Inoue, A., Kobayashi, K., Maemondo, M., Sugawara, S., Oizumi, S., & Isobe, H. et al. (2012). Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naive non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). Annals Of Oncology, 24(1), 54-59. http://dx.doi.org/10.1093/annonc/mds214

26. Mitsudomi, T., Morita, S., Yatabe, Y., Negoro, S., Okamoto, I., & Tsurutani, J. et al. (2010). Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. The Lancet Oncology, 11(2), 121-128. http://dx.doi.org/10.1016/s1470-2045(09)70364-x
27. Mok, T., Wu, Y., Thongprasert, S., Yang, C., Chu, D., & Saijo, N. et al. (2009). Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma. New England Journal Of Medicine, 361(10), 947-957. http://dx.doi.org/10.1056/nejmoa0810699
28. Fukuoka, M., Wu, Y., Thongprasert, S., Sunpaweravong, P., Leong, S., & Sriuranpong, V. et al. (2011). Biomarker Analyses and Final Overall Survival Results From a Phase III, Randomized, Open-Label, First-Line Study of Gefitinib Versus Carboplatin/Paclitaxel in Clinically Selected Patients With Advanced Non-Small-Cell Lung Cancer in Asia (IPASS). Journal Of Clinical Oncology, 29(21), 2866-2874. http://dx.doi.org/10.1200/jco.2010.33.4235
29. Mok, T., Saijo, N., Thongprasert, S., Yang, J., Wu, Y., & Young, H. et al. (2015). 426PDEfficacy by blind independent central review (BICR): Post hoc analyses of the phase III, multicentre, randomised IPASS study of 1st-line gefitinib (G) vs carboplatin/paclitaxel (C/P) in Asian patients (pts) with EGFR mutation-positive advanced NSCLC:. Annals Of Oncology, 26(suppl 9), ix129.1-ix129. http://dx.doi.org/10.1093/annonc/mdv532.10
30. Röllig, C., Knop, S., & Bornhäuser, M. (2015). Multiple myeloma. The Lancet, 385(9983), 2197-2208. http://dx.doi.org/10.1016/s0140-6736(14)60493-1
31. Brioli, A., Melchor, L., Walker, B., Davies, F., & Morgan, G. (2014). Biology and Treatment of Myeloma. Clinical Lymphoma Myeloma And Leukemia, 14, S65-S70. http://dx.doi.org/10.1016/j.clml.2014.06.011
32. Celgene Corporation. (2005). Lenalidomide: A multicentre, randomised, parallel-group, double-blind, placebo-controlled study of CC-5013 plus dexamethasone versus dexamethasone alone in previously treated subjects with multiple myeloma. Unpublished.
33. Celgene Corporation. (2005). A multicenter, randomized, parallel-group, double-blind, placebo-controlled study of CC-5013 plus dexamethasone versus dexamethasone alone in previously treated subjects with multiple myeloma. Unpublished.
34. Dimopoulos, M., Spencer, A., Prince, H., Harousseau, J., Dmoszynska, A., & San Miguel, J. et al. (2007). Lenalidomide plus Dexamethasone for Relapsed or Refractory Multiple Myeloma. New England Journal Of Medicine, 357(21), 2123-32. http://dx.doi.org/10.1056/NEJMoa070594
35. Weber, D., Chen, C., Niesvizky, R., Wang, M., Belch, A., & Stadtmauer, E. et al. (2007). Lenalidomide plus Dexamethasone for Relapsed Multiple Myeloma in North America. The New England Journal Of Medicine, 357(21), 2133-42. http://dx.doi.org/10.1056/NEJMoa070596
36. Stadtmauer, E., Weber, D., Niesvizky, R., Belch, A., Prince, M., & San Miguel, J. et al. (2009). Lenalidomide in combination with dexamethasone at first relapse in comparison with its use as later salvage therapy in relapsed or refractory multiple myeloma. European Journal Of Haematology, 82(6), 426-432. http://dx.doi.org/10.1111/j.1600-0609.2009.01257.x
37. Dimopoulos, M., Chen, C., Spencer, A., Niesvizky, R., Attal, M., & Stadtmauer, E. et al. (2009). Long-term follow-up on overall survival from the MM-009 and MM-010 phase III

trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. Leukemia, 23(11), 2147-2152. http://dx.doi.org/10.1038/leu.2009.147

38. Thientosapol, E., Tran, T., Della-Fiorentina, S., Adams, D., Chantrill, L., Stockler, M., & Kiely, B. (2013). Survival times of women with metastatic breast cancer starting first-line chemotherapy in routine clinical practice versus contemporary randomised trials. Internal Medicine Journal, 43(8), 883-888. http://dx.doi.org/10.1111/imj.12178
39. Iavarone, M., Cabibbo, G., Piscaglia, F., Zavaglia, C., Grieco, A., & Villa, E. et al. (2011). Field-practice study of sorafenib therapy for hepatocellular carcinoma: A prospective multicenter study in Italy. Hepatology, 54(6), 2055-2063. http://dx.doi.org/10.1002/hep.24644
40. Stadler, W., Figlin, R., McDermott, D., Dutcher, J., Knox, J., & Miller, W. et al. (2010). Safety and efficacy results of the advanced renal cell carcinoma sorafenib expanded access program in North America. Cancer, 116(5), 1272-1280. http://dx.doi.org/10.1002/cncr.24864
41. Beck, J., Procopio, G., Bajetta, E., Keilholz, U., Negrier, S., & Szczylik, C. et al. (2011). Final results of the European Advanced Renal Cell Carcinoma Sorafenib (EU-ARCCS) expanded-access study: a large open-label study in diverse community settings. Annals Of Oncology, 22(8), 1812-1823. http://dx.doi.org/10.1093/annonc/mdq651
42. Sternberg, C., Calabrò, F., Bracarda, S., Cartenì, G., Lo Re, G., & Ruggeri, E. et al. (2015). Safety and Efficacy of Sunitinib in Patients from Italy with Metastatic Renal Cell Carcinoma: Final Results from an Expanded-Access Trial. Oncology, 88(5), 273-280. http://dx.doi.org/10.1159/000369256
43. Castellano, D., Puente, J., de Velasco, G., Chirivella, I., López-Criado, P., & Mohedano, N. et al. (2014). Safety and effectiveness of vinflunine in patients with metastatic transitional cell carcinoma of the urothelial tract after failure of one platinum-based systemic therapy in clinical practice. BMC Cancer, 14(1). http://dx.doi.org/10.1186/1471-2407-14-779
44. Howard, D., Chambers, C., & Cusano, F. (2008). Efficacy vs. effectiveness — docetaxel and prednisone in hormone refractory prostate cancer. Journal Of Oncology Pharmacy Practice, 14(1), 45-49. http://dx.doi.org/10.1177/1078155207085387
45. Di Costanzo, G., Tortora, R., Iodice, L., Lanza, A., Lampasi, F., & Tartaglione, M. et al. (2012). Safety and effectiveness of sorafenib in patients with hepatocellular carcinoma in clinical practice. Digestive And Liver Disease, 44(9), 788-792. http://dx.doi.org/10.1016/j.dld.2012.04.001
46. Cioffi, P., Marotta, V., Fanizza, C., Giglioni, A., Natoli, C., Petrelli, F., & Grappasonni, I. (2013). Effectiveness and response predictive factors of erlotinib in a non-small cell lung cancer unselected European population previously treated: A retrospective, observational, multicentric study. Journal Of Oncology Pharmacy Practice, 19(3), 246-253. http://dx.doi.org/10.1177/1078155212465994

APPENDICES

Appendix 1: Special Authority Criteria

Azacitidine

Initial application only from a haematologist or medical practitioner on the recommendation of a haematologist. Approvals valid for 12 months for applications meeting the following criteria:

All of the following:

1 Any of the following:

1.1 The patient has International Prognostic Scoring System (IPSS) intermediate-2 or high risk myelodysplastic syndrome; or

1.2 The patient has chronic myelomonocytic leukaemia (10%-29% marrow blasts without myeloproliferative disorder); or

1.3 The patient has acute myeloid leukaemia with 20-30% blasts and multi-lineage dysplasia, according to World Health Organisation Classification (WHO); and

2 The patient has performance status (WHO/ECOG) grade 0-2; and

3 The patient does not have secondary myelodysplastic syndrome resulting from chemical injury or prior treatment with chemotherapy and/or radiation for other diseases; and

4 The patient has an estimated life expectancy of at least 3 months.

Renewal only from a haematologist or medical practitioner on the recommendation of a haematologist. Approvals valid for 12 months for applications meeting the following criteria:

Both:

1 No evidence of disease progression; and

2 The treatment remains appropriate and patient is benefitting from treatment.

Abiraterone

Initial application only from a medical oncologist, radiation oncologist, urologist or medical practitioner on the recommendation of a medical oncologist, radiation oncologist or urologist. Approvals valid for 5 months for applications meeting the following criteria:

All of the following:

1 Patient has prostate cancer; and

2 Patient has metastases; and

3 Patient's disease is castration resistant; and

4 Either:

4.1 All of the following:

4.1.1 Patient is symptomatic; and

4.1.2 Patient has disease progression (rising serum PSA) after second line anti-androgen therapy; and

4.1.3 Patient has ECOG performance score of 0-1; and

4.1.4 Patient has not had prior treatment with taxane chemotherapy; or

4.2 All of the following:

4.2.1 Patient's disease has progressed following prior chemotherapy containing a taxane; and

4.2.2 Patient has ECOG performance score of 0-2; and

4.2.3 Patient has not had prior treatment with abiraterone.

Renewal — (abiraterone acetate) only from a medical oncologist, radiation oncologist, urologist or medical practitioner on the recommendation of a medical oncologist, radiation oncologist or urologist. Approvals valid for 5 months for applications meeting the following criteria:

All of the following:

1 Significant decrease in serum PSA from baseline; and

2 No evidence of clinical disease progression; and

3 No initiation of taxane chemotherapy with abiraterone; and

4 The treatment remains appropriate and the patient is benefiting from treatment.

Gefitinib

Initial application only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months for applications meeting the following criteria:

All of the following:

1 Patient has locally advanced, or metastatic, unresectable, non-squamous Non Small Cell Lung Cancer (NSCLC); and

2 Either:

2.1 Patient is treatment naive; or

2.2 Both:

2.2.1 The patient has discontinued erlotinib within 12 weeks of starting treatment due to intolerance; and

2.2.2 The cancer did not progress whilst on erlotinib; and

3 There is documentation confirming that disease expresses activating mutations of EGFR tyrosine kinase; and

4 Gefitinib is to be given for a maximum of 3 months.

Renewal only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months where radiological assessment (preferably including CT scan) indicates NSCLC has not progressed.

Lenalidomide

Initial application — (Relapsed/refractory disease) only from a haematologist or medical practitioner on the recommendation of a haematologist. Approvals valid for 6 months for applications meeting the following criteria:

All of the following:

1 Patient has relapsed or refractory multiple myeloma with progressive disease; and

2 Either:

2.1 Lenalidomide to be used as third line* treatment for multiple myeloma; or

2.2 Both:

2.2.1 Lenalidomide to be used as second line treatment for multiple myeloma; and

2.2.2 The patient has experienced severe (grade >= 3), dose limiting, peripheral neuropathy with either bortezomib or thalidomide that precludes further treatment with either of these treatments; and

3 Lenalidomide to be administered at a maximum dose of 25 mg/day in combination with dexamethasone.

Renewal only from a haematologist or medical practitioner on the recommendation of a haematologist. Approvals valid for 6 months for applications meeting the following criteria:

Both:

1 No evidence of disease progression; and

2 The treatment remains appropriate and patient is benefitting from treatment.

Note: Indication marked with * is an Unapproved Indication (refer to Interpretations and Definitions). A line of treatment is considered to comprise either: a) a known therapeutic chemotherapy regimen and supportive treatments or b) a transplant induction chemotherapy regimen, stem cell transplantation and supportive treatments. Prescriptions must be written by a registered prescriber in the lenalidomide risk management programme operated by the supplier.

Appendix 2: Comparison of Inclusion Criteria

Drug	*Special authority criteria*	*Trial inclusion criteria*
Azacitidine	**Myelodysplastic syndrome**	**AZA-CSR-005**
	IPSS INT-2 or high risk	87% IPSS INT-2 or high risk, 2.8% INT-1, 8.9% indeterminate or NA
	ECOG performance score 0-2	ECOG performance score 0-2
	Life expectancy 3+ months	No non-cancer disease likely to limit life expectancy below 12 months
	Prior therapy unspecified	No prior transplant or cytotoxic therapy
	MDS not secondary	MDS not secondary
	Chronic myelomonocytic leukaemia	**AZA-CSR-005**
	10-29% marrow blasts	10-29% marrow blasts
	No myeloproliferative disorder	"myelodysplastic CMMoL"
	Prior therapy unspecified	No prior transplant or cytotoxic therapy
	ECOG performance score 0-2	ECOG performance score 0-2
	Life expectancy 3+ months	No non-cancer disease likely to limit life expectancy below 12 months
		Survival analysed with MDS patients
	Acute myeloid leukaemia	**Fenaux et al 2010**
	20-30% blasts, multi-lineage dysplasia	20-30% marrow blasts in 97% of patients
	ECOG performance score 0-2	ECOG performance score 0-2
	Life expectancy 3+ months	Life expectancy 3+ months
Abiraterone	**Prostate cancer – not taxane pretreated**	**COU-AA-302**
	Symptomatic	Asymptomatic to mildly symptomatic
	Rising PSA after second-line anti-androgen	PSA or radiographic progression
	ECOG performance score 0-1	ECOG performance score 0-1
	Ongoing therapy unspecified	Ongoing androgen deprivation
	Prostate cancer – taxane pretreated	**COU-AA-301**
	Disease progression post taxane chemotherapy	Disease progression post taxane chemotherapy

		ECOG performance score 0-2		ECOG performance status 0-2
		No prior abiraterone treatment		1-2 lines cytotoxic chemotherapy
		Ongoing therapy unspecified		Ongoing androgen deprivation
Gefitinib	**Non-small cell lung cancer**		**WJTOG3405/IPASS/NEJ002**	
		Treatment naïve OR		Treatment naïve
		Erlotinib intolerance and no progression while on erlotinib		No prior biologic or immunologic therapy (IPASS) No prior EGFR-targeted therapy (WJTOG3405)
		Confirmed EGFR positive		EGFR positive (WJTOG3405/NEJ002) EGFR positive subgroup used in analysis (IPASS)
		ECOG performance score unpecified		ECOG performance score 0-1 (WJTOG3405) ECOG performance score unpecified (IPASS/NEJ002)
		Non-squamous NSCLC		NSCLC not otherwise specified
Lenalidomide	**Multiple myeloma**		**CC-5013-MM-009, CC-5013-MM-010**	
		Third line treatment OR second line after bortezomib or thalidomide toxicity		Second line or later treatment
		Relapsed or refractory multiple myeloma with progressive disease		Disease progression on treatment or relapse after treatment
		ECOG performance score unpecified		ECOG performance score 0-2
		Given with dexamethasone (dose unspecified)		Given with high-dose dexamethasone

Appendix 3: Analytical tools used

```
## R version 3.3.1 (2016-06-21)
## Platform: x86_64-w64-mingw32/x64 (64-bit)
## Running under: Windows 10 x64 (build 14393)
##
## locale:
## [1] LC_COLLATE=English_United States.1252
## [2] LC_CTYPE=English_United States.1252
## [3] LC_MONETARY=English_United States.1252
## [4] LC_NUMERIC=C
## [5] LC_TIME=English_United States.1252
##
## attached base packages:
## [1] stats     graphics  grDevices utils     datasets  methods   base
##
## other attached packages:
##  [1] sandwich_2.3-4  glm2_1.1.2      survival_2.40-1 survminer_0.2.2
##  [5] dplyr_0.5.0     purrr_0.2.2     readr_1.0.0     tidyr_0.6.0
##  [9] tibble_1.2      ggplot2_2.2.0   tidyverse_1.0.0 lubridate_1.6.0
## [13] RODBC_1.3-14
##
## loaded via a namespace (and not attached):
##  [1] Rcpp_0.12.7      knitr_1.15       magrittr_1.5     splines_3.3.1
##  [5] munsell_0.4.3    lattice_0.20-34  colorspace_1.3-0 R6_2.2.0
##  [9] stringr_1.1.0    plyr_1.8.4       tools_3.3.1      grid_3.3.1
## [13] gtable_0.2.0     DBI_0.5-1        htmltools_0.3.5  yaml_2.1.14
## [17] lazyeval_0.2.0   assertthat_0.1   digest_0.6.10    Matrix_1.2-7.1
## [21] evaluate_0.10    rmarkdown_1.1    stringi_1.1.2    scales_0.4.1
## [25] zoo_1.7-13
```

The above packages were used in the following order:

- RODBC: utlised for the extraction of data directly from ORACLE and SQL Server based databases
    - RODBC description
- Lubridate/dplyr: used to prepare data for analysis (transform, correct date formats, time measurement).
    - Dplyr description
    - Lubridate description
- Survival/survival miner: Provided standard survival analysis functions (Cox/Hazard proportional analysis, Kaplan-meier, and cox models)
    - Survival description
    - Survival miner description
    - Ggplot: system used to declaratively create graphics and charts. GGplot description