Population-based cohort study of the efficacy of Brentuximab-Vedotin in relapsed systemic Anaplastic Large Cell Lymphoma using Public Health England data

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Author contribution:

MJB, NMC and CPF conceived and designed the study. MJB and SJH designed the database. SJH collected the data. MJB supervised data collection. SJH and MJG performed statistical analysis. SJH wrote the manuscript. MJB, NMC, MJG and CPF reviewed the manuscript.

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SJH and MJG have nothing to declare.

Abstract:

Systemic anaplastic large cell lymphoma (sALCL) is a rare T-cell lymphoma associated with poor prognosis after relapse. The immuno-conjugate Brentuximab Vedotin (BV) first became available for relapsed sALCL in England in 2013, following the results of a pivotal phase II study.

We present a population-based study describing outcomes of relapsed sALCL in England after BV, using Public Health England (PHE) data.

We obtained information on all relapsed/refractory (r/r) sALCL patients ≥18 years treated with BV monotherapy in England between 1st Jan 2014-31st Dec 2019. The final cohort comprised 127 patients with a median age of 60 years (range 19-89). 18 (14.2%) had received stem cell transplant in first remission. Median 2-year overall survival (OS) was 46.6%. The vast majority of deaths (59) occurred within 18 months, with very few events after this. Receipt of BV as second line compared to third or fourth line was associated with significantly improved survival (2-year OS 50.3% vs 29.7%, p = 0.03). There was no difference in OS for different subgroups, including ALK status, age, gender, or receipt of SCT in first response.

We report excellent survival following treatment with BV in a real-world setting, comparable with previous clinical trial data.

Introduction

Systemic anaplastic large cell lymphoma (sALCL) is a subtype of T cell lymphoma, characterised by strong and uniform expression of the cell surface receptor CD30 (1,2). It is sub-classified further based on the expression of the anaplastic lymphoma kinase (ALK) protein, which is

associated with more favourable survival outcomes (3). Until recently, standard front-line therapy comprised CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) based regimens, and despite modest improvement in outcomes over time (4,5), disease relapse remained common, especially in the ALK negative group. The International Peripheral T-Cell Lymphoma Project reported 5-year progression-free survival (PFS) of 60% and 36% for ALK+ve and ALK-ve sALCL, and 5-year overall survival (OS) of 70% and 49% respectively (6). A recent large real world study of 214 patients treated with conventional chemotherapy reported 4-year time to treatment failure (TTF) of 28.2% and OS 43.9% in ALK-ve sALCL compared to 57.6% and 78.6% in ALK+ve disease (7).

At relapse, chemo-resistance to salvage chemotherapy limits the number of patients receiving consolidation with potentially curative autologous or allogeneic stem cell transplantation (SCT) (8,9). One large population-based cohort reported a median overall survival of just three months for both sALCL subtypes at relapse (10), and therefore many centres employ autologous transplantation in first remission in an attempt to improve outcomes despite a lack of robust evidence supporting this approach (11,12).

Brentuximab vedotin (BV) is an antibody-drug conjugate which targets the CD30 protein on the surface of the tumour cells, and has demonstrated excellent outcomes in relapsed sALCL (13). The pivotal phase II trial of BV monotherapy for 58 patients with relapsed sALCL, reported overall response rates (ORR) of 86% and a complete response (CR) rate of 57%, independent of ALK status. This translated into an estimated 60% OS and 39% PFS at five years (14).

More recently, the international double-blind randomised ECHELON2 trial confirmed that initial treatment with A+CHP (BV, cyclophosphamide, doxorubicin, and prednisolone) improved PFS and OS when compared to CHOP for patients with CD30+ve lymphoma. Over 70% of these patients had sALCL, and it was this sub-group who derived the most benefit (5). Based on evidence from these two studies, BV was funded in NHS England for the treatment

of relapsed or refractory sALCL from April 2013, and, subsequently, A+CHP was routinely commissioned for adults with untreated sALCL in August 2020.

To date, there have been no true population-based studies describing outcomes of BV for r/r ALCL in routine clinical practice, with the largest retrospective series in Italy describing outcomes for 40 patients. Given the high drug acquisition costs, it is essential to establish the benefits of drugs such as BV in routine clinical practice with mature follow-up data, and to explore which subgroups may benefit most.

Public Health England (PHE) collects information on all cancer diagnoses in England via the National Cancer Registration and Analysis Service (NCRAS). Over the last decade, incremental improvements have been made in the quality of data held. This includes the mandatory collection of the Cancer Outcomes and Services Dataset (COSD), Systemic Anti-Cancer Therapy (SACT), Hospital Episodes Statistics (HES) and Classification of Interventions and Procedures (OPCS-4) data for all NHS trusts from April 2012, with a phased implementation up until April 2014. As BV has been available since April 2013, we used routinely collected PHE data to evaluate outcomes for patients with relapsed sALCL with BV monotherapy in England.

Methods

Anonymised patient data were requested from Public Health England (PHE) via the Office of Data Release (ODR) for patients diagnosed with sALCL who had received treatment with brentuximab vedotin (BV) using the NCRAS registry and SACT dataset. Inclusion criteria consisted of relapsed systemic ALCL, age 18 and over at diagnosis and to have received

brentuximab between 1st January 2014 and 31st December 2019. Exclusion criteria included a diagnosis of primary cutaneous ALCL or breast-implant associated ALCL, and patients who received BV as first-line therapy, or in combination with other agents. Data for patients enrolled in the ECHELON 2 study were not collected due to the double-blind nature of the study.

Baseline demographics requested included gender, birth month and year, up to date vital status, ALK status, previous and any subsequent SACT and the number of cycles of BV received by each patient. The receipt of autologous/allogeneic SCT either prior to or following BV was assessed using SACT data, for example the use of BEAM/LEAM for autologous SCT and CAMPATH 1H/fludarabine for allogeneic SCT. These data were sorted and compiled into a single data collection table in Excel. Those patients without sufficient data for BV treatment or previous lines of therapy were excluded. Patients who were otherwise eligible but whose prior SACT was clearly consistent with an alternative haematological malignancy were also excluded.

The primary outcome was OS for all patients following BV and was calculated from the start of BV treatment to the date of death from any cause and was censored at the last date when the patient was known to be alive. Secondary outcomes included the description and analysis of baseline demographics, SACT received prior to BV, and the median number of BV cycles received. Subgroups were defined on the basis of age (<40 years, ≥40 years), sex, number of treatment lines (2nd line, 3rd/4th line) and ALK status. Kaplan-Meier plots were used to display overall survival for each subgroup, with the log rank test used to compare all-cause mortality between groups in univariate analysis. Cox regression was used for multivariate analysis, with hazard ratios used to quantify the relative risk of all-cause mortality between subgroups. Data were analysed using the statistical package R version 4.0.3.

Results

A total of 173 eligible patients were identified, of whom 46 were excluded: 21 because of absent data regarding first-line chemotherapy (all received prior to 2013), 12 due to insufficient data regarding BV dates and cycles, three who had received BV in combination with other therapies, nine whose prior therapies were consistent with diagnoses of Hodgkin's lymphoma (had received ABVD first line) or cutaneous T cell lymphoma (had received single

agent methotrexate first line), in addition to one participant in the ECHELON-2 trial, who were excluded as previously described (figure 1). The final cohort therefore comprised 127 patients with relapsed or refractory sALCL, with a median age of 60 years (range 19-89) at commencement of BV. Baseline characteristics are summarised in Table I.

Median follow up time was 10 months (range 1-66 months). 49 (38.6%) patients had ALK+ve disease and 78 (61.4%) were ALK-ve with median ages of 57 and 60.5 years respectively. The median time from first sALCL diagnosis to BV was nine months (range 1-143). 106 (83.5%) patients received BV second line, and 13 (10.2%) third or fourth line. 95 (74.8%) had received CHOP first line and 11 (%) CHOEP. Eight patients had unclear prior lines of therapy due to insufficient data on the dates and cycles of prior treatments and therefore were not included in analyses for treatment lines. 18 (14.2%) patients had received SCT in first remission (16 autologous, two allogeneic). The median number of BV cycles received was five (range 1-17) with 101 patients (79.5%) receiving <12 cycles, 14 (11.0%) $\geq$12 cycles, and further 12 patients did not have complete information on the number of cycles received. While no response data was available in this study, 20 (15.7%) deaths occurred prior to cycle 5, the time point at which the commissioning agreement mandated a response assessment to allow ongoing therapy for responders. In general, within the study timeframe, there was a trend to increased numbers of patients treated with BV per year.

At the time of data collection, a total of 63 of the 127 patients had died. The median two-year OS was 46.6%, with the vast majority of deaths (59) occurring before 18 months, followed by an apparent near plateau in survival with only four subsequent deaths (figure 2). There were no statistical differences in OS between ALK+ve and ALK-ve patients (2-year OS 47.6% vs 46.1% respectively, figure 3), patients age <40 vs ≥40 years (2-year OS 43.0% vs 47.7%, figure 4), age <60 vs ≥60 (2-year OS 44.7% vs 48.9%), genders (2-year OS 50.3% males vs 40.3% females), or for receiving SCT in first remission (2-year OS 46.7% for no transplant vs 47.6% for transplant).

Receiving BV as second line therapy was however associated with a significant improvement in survival, with 2-year OS 50.3% versus 29.7% for those treated third or fourth-line (p = 0.03, figure 5). Multivariate analysis showed receiving BV as third or fourth line versus second line was independently associated with increased mortality compared with second line therapy (hazard ratio 2.59 [95% CI 1.17-5.76]) (table II). When the other variables were each included in a model containing only line of therapy, none were predictive of outcome.

Only two patients received SCT following BV (one autologous, one allogeneic), and both remain alive 18+ months post-transplant. Two patients had re-treatment with BV at nine and ten months after first treatment with BV, one of whom received the allogeneic SCT, and the other remains alive 12+ months post re-treatment without transplantation.

Discussion

Our study provides encouraging real-world data for BV as an effective therapy for sALCL relapsing after standard chemotherapy induction, and recapitulates the results of the pivotal phase II trial Pro et al (14). The main findings are that the overall survival (OS) for patients at two years post-BV is 46.6%, which is significantly improved from historical survival data for relapsed sALCL (10). The majority of deaths occurred within the first 18 months, with only four subsequent deaths reported. Notably, there were very few consolidation SCT undertaken,

demonstrating BV therapy is potentially curative in this context. There were no demographic or clinical differences between excluded patients with ALCL and the eligible patients.

In general our findings are in line with the results from Pro et al, where the majority of deaths occurred in the first 12 months, although they reported a higher OS with an estimated 60% 5-year-survival (14). This may relate to differences in the demographics as well as comparing a prospective clinical trial dataset with a population-based dataset. In Pro et al, participants were ≥12 years whereas we only considered those patients ≥18 years, meaning the median age of our cohort was 60 years compared to 52 years. Although age was not found to be a predictor for survival, it may be a factor in receiving SCT post-BV: In Pro et al, 16/58 (27.6%) patients went on to have a SCT, compared to only 2/127 (1.6%) in our study.

There were no observed differences in OS for the standard prognostic factors, such as ALK status and age, consistent with the data from Pro et al, where they found similar 5-year-survival results between age groups: patients <40 had a 5-year survival rate of 63%, versus 59% in ≥40 years. For ALK status, they also reported similar results, with an estimated probability of survival at five years of 61% for ALK-ve, and 56% for ALK+ve participants (14). Data are also similar to an Italian retrospective study which reported results for 40 patients with relapsed/refractory ALCL treated with BV. Best response was observed after a median of four cycles with an overall response rate of 62.5%. The 2-year OS and PFS were 56.9% and 39.1% respectively. Of the 18 patients who achieved CR, 15 remained in complete remission, although all long-term responders at the time of the report were aged <30 years (15).

The more favourable outcomes seen with ALK+ve sALCL for first-line therapy appear to be largely age-dependent (3,16). Sibon et al reported that ALK +ve patients tend to be younger with a better performance status, and less likely to have elevated β2-microglobulin levels. In their multivariate analysis, age, rather than ALK status, was an independent factor for survival (3). Similarly, another study found that if the comparison between ALK+ve and ALK-ve patients

was limited to those 40 years and older, there was no difference in failure-free survival (FFS) or OS (6). Our data suggested receiving BV as second line therapy was associated with a significant improvement in OS, compared to those receiving it third or fourth line. However, due to wide confidence intervals in our analysis, this does not completely rule out other potential effects. This contrasts with Pro et al where the number of prior lines of therapy did not impact outcome, although only eight patients received BV second line.

Two patients in our cohort were re-treated with BV, and had an ongoing response with both patients alive ≥12 months post-treatment. Although data is lacking, there could be a rationale for re-treating with BV at relapse in combination with other cross-resistant regimes, provided that they had a good response to BV previously, as is the case with rituximab in B-cell lymphoma. There is currently very limited data on re-treatment with BV in ALCL although two small studies have showed encouraging response rates, and may provide a bridge to allogenic SCT (17,18).

Utilising routinely collected population-based data from PHE provides confidence that this cohort represents the vast majority of relapsed/refractory sALCL treated with BV in NHS England thereby minimising selection bias. The timeline of this study was aligned with mandatory data collection for COSD, the use of ICD-03 coding, and SACT, ensuring completeness of data. This method of data collection allows a relatively large cohort of patients even for a rare disease such as sALCL, and therefore could be extrapolated to other rare haematological malignancies. Information on SACT has been collected since April 2012, the need for registration of patients prior to BV use translated in capture of with the vast majority of patients treated with BV within the study.

There were some limitations of our study. SACT data coverage may not have been complete in the early years of the study, and the majority of patients excluded due to inadequate data on BV were treated in this time period. Furthermore, our data are observational so no direct

causal effect can be inferred from any associations reported, and the relatively small sample size resulted in wide confidence intervals for the comparison in mortality risks between different subgroups. We did not request any information on response imaging, patient dose reductions/delays or the clinical reasons why. Progression-free survival could not be measured within our study, although both this and time to next treatment could be explored in future studies. Collection of centralised PHE/SACT data for sALCL in addition to future collection of genomic data should pave the way for improved unbiased large-scale epidemiological studies of cancer treatments.

In conclusion, our results report encouraging real-world survival following treatment with BV for relapsed/refractory sALCL and introduces a novel strategy of undertaking high quality, nationwide population-based studies. We have demonstrated how accurate population-based data can be utilised to inform the pharmaco-economical evaluations of high-cost drugs in routine clinical practice.

Table I: Description of baseline characteristics:

Characteristic	**N = 127**
Age in years - median (range)	60 (19-89)
<40 years (n, %)	23 (18.1%)
≥40 years (n, %)	104 (81.9%)

Sex (n, %)	
Male	83 (65.4%)
Female	44 (34.6%)
Stage of sALCL at diagnosis: (n, %)	
Stage 1	13 (10.2%)
Stage 2	20 (15.7%)
Stage 3	27 (21.3%)
Stage 4	53 (41.7%)
Unknown staging	14 (11.0%)
Alk +ve (n, %)	49 (38.6%)
Alk -ve (n, %)	78 (61.4%)
BV therapy as: (n, %)	
2nd line	106 (83.5%)
3rd - 4th line	13 (10.2%)
Unclear treatment lines	8 (6.3%)
No. of cycles of BV (median, range)	5 (1-17)
No. of months from diagnosis to BV (median, range)	9 (1-143)
Stem cell transplant in first remission: (n, %)	18 (14.2%)
Allograft	2 (1.6%)
Autograft	16 (12.6%)

Table II: Univariate and multivariate analysis

	UNIVARIATE		MULTIVARIATE	
VARIABLE	**HR (CI 95%)**	**p**	**HR (CI 95%)**	**p**
ALK status:				
ALK negative	1		1	
ALK positive	0.94 (0.56-1.56)	0.81	1.04 (0.59-1.83)	0.90

Age in years:				
Age <40	1		1	
Age ≥40	1.05 (0.56-1.97)	0.88	1.18 (0.56-2.49)	0.67
Sex:				
Male	1		1	
Female	1.34 (0.81-2.22)	0.26	1.48 (0.82-2.66)	0.19
Line of therapy:				
2nd line	1		1	
3rd or 4th line:	2.28 (1.08-4.84)	**0.03**	2.59 (1.17-5.76)	**0.0195**

Footnote: HR = hazard ratio. CI = confidence interval

Figure 1:

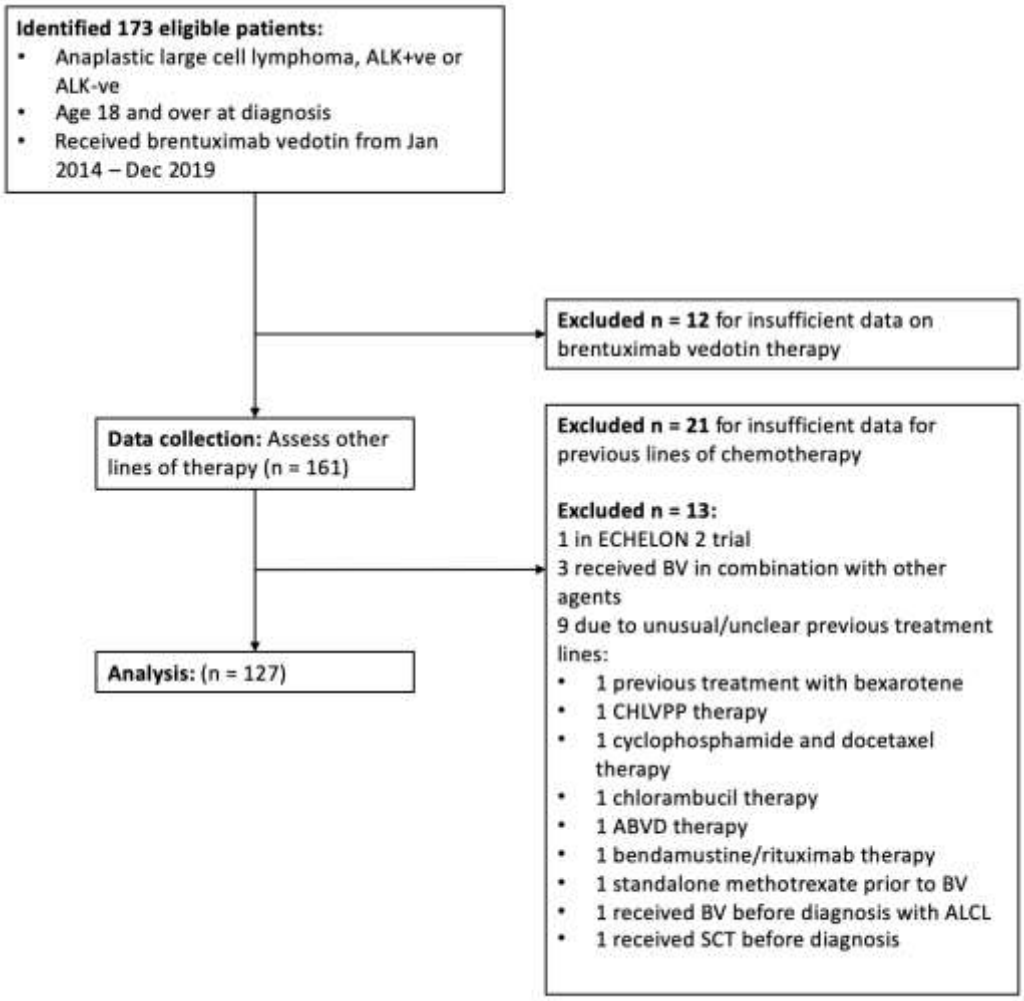

Identified 173 eligible patients:
• Anaplastic large cell lymphoma, ALK+ve or ALK-ve
• Age 18 and over at diagnosis
• Received brentuximab vedotin from Jan 2014 – Dec 2019
Excluded n = 12 for insufficient data on brentuximab vedotin therapy
Data collection: Assess other lines of therapy (n = 161)
Excluded n = 21 for insufficient data for previous lines of chemotherapy
Excluded n = 13:
1 in ECHELON 2 trial
3 received BV in combination with other agents
9 due to unusual/unclear previous treatment lines:
• 1 previous treatment with bexarotene
• 1 CHLVPP therapy
• 1 cyclophosphamide and docetaxel therapy
• 1 chlorambucil therapy
• 1 ABVD therapy
• 1 bendamustine/rituximab therapy
• 1 standalone methotrexate prior to BV
• 1 received BV before diagnosis with ALCL
• 1 received SCT before diagnosis
Analysis: (n = 127)

Figure 2:

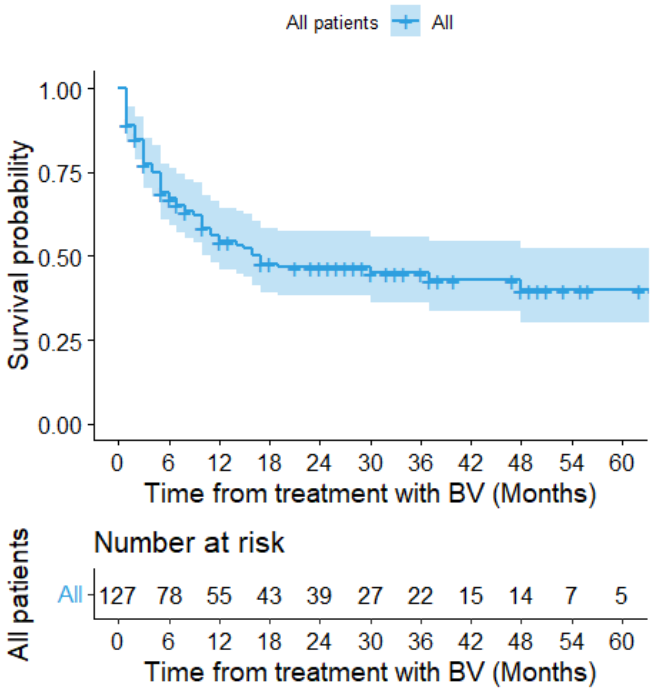


Figure 3:

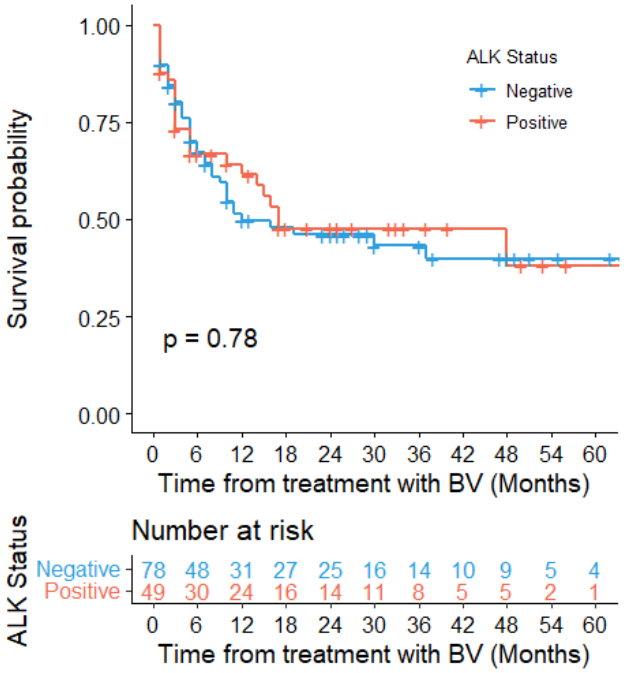


Figure 4:

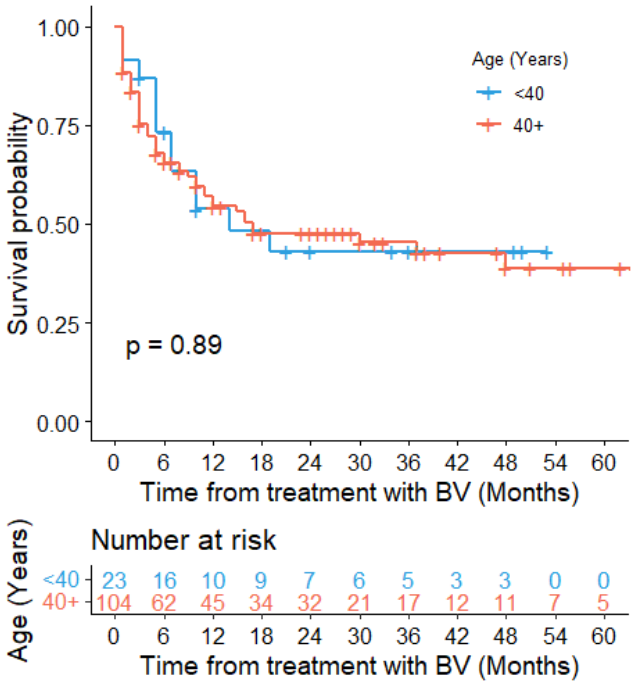
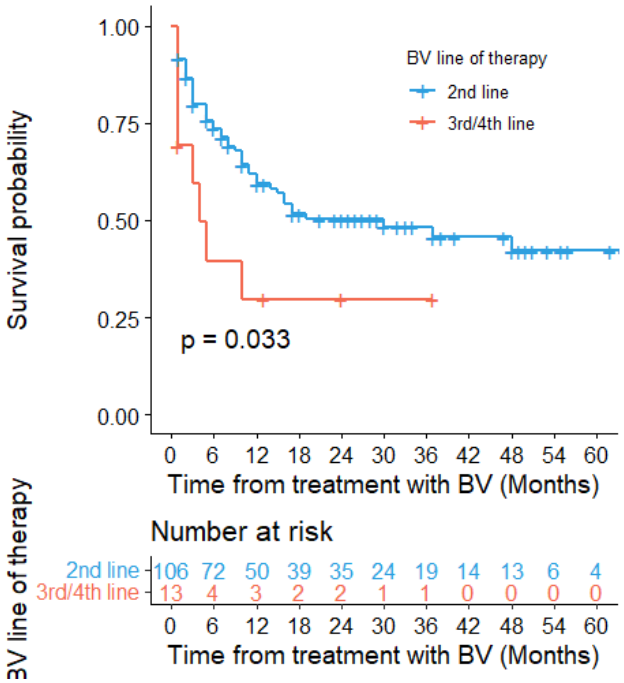


Figure 5:



L**egends to the figures:**

Figure 1: Flow-chart outlining participant selection

Figure 2: Kaplan-Meier graph: Overall survival for all patients post-BV. Number of events: 63

Figure 3: Kaplan-Meier graph: Overall survival for ALK positive participants versus ALK negative. Number of events ALK positive: 24. Number of events ALK negative: 39

Figure 4: Kaplan-Meier graph: Overall survival for those <40 years versus those ≥40 years. Number of events age <40 years: 12. Number of events age ≥40 years: 51

Figure 5: Kaplan-Meier graph: Overall survival for those who received BV second line versus those 3rd or 4th line. Number of events 2nd line: 49. Number of events 3rd/4th line: 8.