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NCRI Haematological Oncology Clinical Studies Group

Annual Report 2016-17

Partners in cancer research

NCRI Haematological Oncology
CSG Annual Report 2016-17

1. Executive Summary (including top 3 achievements in the year)

The Haematological Oncology CSG is one of the largest and most complex CSGs, with seven disease-specific Subgroups, two Working Parties (WPs) and an overall trial portfolio of >100 studies. In addition to contributing to the design of individual study proposals, the CSG plays a crucial cross-cutting role in setting expectations, sharing best practice and addressing common challenges. The CSG also provides a framework for coordinating and driving forward research in areas that transcend individual disease areas, such as Supportive Care, Transfusion and Late Effects (SCTLE), Stem-Cell Transplantation, Cellular Therapy and TYA.

The CSG has maintained its performance in terms of trial development over the last reporting period. Key achievements include full restoration of recruitment into the main AML portfolio (AML18/AML19/Li-1), amendment/extension of the frontline CLL portfolio (FLAIR/RIAltO) and securing of funding for frontline trials in Myeloma (Myeloma XV) and MPN (MITHRIDATE). Remaining challenges include developing frontline trials in CML, MDS and less fit patients with Myeloma, replacing UKALL14 (ALL), Li-1 (AML) and RIAltO (CLL), implementing at least one of the five trial proposals developed by the SCTLE WP and developing new trial proposals through the Aplastic Anaemia WP. It is anticipated that recruitment into interventional studies, which is 20% down from 2014/2015, will recover to previous levels once the frontline Myeloma portfolio is restored, although this is likely to take another one/two years.

The CSG is fortunate to have access to research infrastructure provided by the Bloodwise Trials Acceleration Programme (TAP), IMPACT, Myeloma UK and CRUK/NIHR ECMC Networks, and it is crucial that opportunities to develop and deliver early-phase studies via these networks is fully exploited. It is also important to establish seamless connectivity between early and late phase programmes in all areas and strengthen engagement with the wider scientific community to optimise trial design and align with current funding strategy at CR-UK.

2. Structure of the Group

The CSG brings together seven different Subgroups, each focussing on specific disease areas (AML, ALL, CML, CLL, Myeloma, MPN, MDS), plus time-limited working parties in Supportive Care, Transfusion and Late Effects (2015-2017) and Aplastic Anaemia (2017-2019). CSG members include 18 clinicians, two statisticians, a senior trial co-ordinator, two consumers, two NCRI trainees and observers from CRUK and Bloodwise, the latter providing linkage with Bloodwise

TAP. The CSG currently has representation from most regions in the UK including two of the three devolved nations.

3. CSG & Subgroup strategies

Main CSG

The Group's scientific strategy is to improve the objective and patient-reported outcome of haematological cancers through the development and evaluation of stratified and/or response-adapted approaches to therapy based on predictive biomarkers and sensitive assessment of residual tumour burden, coupled with the optimisation of supportive care and recognition and management of late effects.

At the core of this strategy is a recognition of the importance of innovative trial design and high-quality biobanking as a platform for cutting-edge biomarker discovery/development projects, linking in with Industry and the broader scientific community and exploiting transformational/ capacity-building programmes such as Bloodwise TAP, the Myeloma UK Clinical Trial Network, the IMPACT Trials Network for stem-cell transplantation, the Genomics England Ltd 100,000 Genomes Project and relevant NIHR/MRC Initiatives. The CSG also has excellent links with key stakeholders; these have been further strengthened by the recent appointment of the Clinical Lead for the Haematological Oncology GeCIP, Dr Anna Schuh, onto the Group.

Operationally, the CSG aims to maintain a balanced and continuously replenishing portfolio of academic and Industry studies in all major disease areas. Wherever possible, data generated from linked preclinical programmes is used to inform on the design of early-phase trials which in turn are used to inform on the development and/or adaptation of phase III studies in a seamless way. Samples from phase III trials then feed back into preclinical research to complete the translational loop. Aspects of this model have worked well in most disease areas but there is scope for enhanced transition between its various components.

Although trial delivery is generally good, the CSG is not complacent and aims to enhance recruitment by strengthening links with the Clinical Research Networks. International collaboration is important to accelerate the delivery of research in niche populations and is firmly embedded in several areas.

MDS Subgroup (Chair, Dr Dominic Culligan)

The MDS Subgroup has continued the phase II ELASTIC study of azacitidine and eltrombopag in high risk MDS, which is now entering the final extended cohort pending a safety review after the completion of cohort four. The joint study with the National Blood Authority (REDDS) has recruited well, including cooperation with centres in New Zealand and Australia, and only requires three more patients. The Subgroup opened a phase II study in CMML (MONOCLE) with the novel drug Terfinostat in February 2017 and five patients have been recruited with centres steadily opening across the UK. We have continued to work on a potential three way randomised phase II study of the novel regimen VBaP with ESA versus Danazol with ESA versus ESA alone, for anaemic low risk MDS patients. We have also started planning a follow-up study to the successful REDDS study with requests from France to join. MDSBIO continues to provide high quality scientific data in MDS.

The commercial portfolio has continued to expand considerably across phases and contains eight open studies (compared to five last year). We have added trials of interesting novel agents to the portfolio, including Luspatercept, which is recruiting way ahead of target in the UK, Durvalumab and Venatoclax.

CML Subgroup (Chair, Professor Mhairi Copland)

The CML Subgroup aims to deliver world class clinical research across all phases of CML, contribute to the development of best practice in the management of CML and provide education for healthcare professionals and patients to improve outcomes for all CML patients. SPIRIT2, the largest study comparing first-line imatinib versus dasatinib, continues in follow-up and "last patient last visit" is March 2018; data analyses are underway. The SPIRIT2 Biobank is a rich source of translational research articles and presentations. SPIRIT3 was abandoned due to withdrawal of funding by Ariad. With the introduction of generic imatinib, no front-line study in chronic-phase CML is proposed at present but this will be revisited in the next 12-18 months. The first 12 month discontinuation phase of DESTINY will be reported at EHA this year. MATCHPOINT and OPTIC are open and continuing to recruit. National education events for both CML healthcare professionals and patients/carers were held in Manchester in September 2016 with internet/social media streaming. A further event for patients and carers is proposed for Birmingham in November 2016. Moving forward, our key strategic aim is to open studies in two areas (1) resistance – TASTER trial has been submitted to CRUK EMP and (2) de-escalation/discontinuation follow-up study to DESTINY.

AML Subgroup (Chair, Professor Nigel Russell)

AML is a rare disease and the UK has been at the forefront internationally in improving outcome using innovative trial design that asks several randomised questions. One of the reasons of the success of these trials is their logical development with the key findings from the previous trial being incorporated into the design of the following one. Thus, AML19 incorporates findings from AML15 and 17 and design of AML18 is influenced by findings from AML16.

Our objectives have evolved over the last few years to improve outcomes by the introduction of selective, molecularly targeted therapies into the existing backbone of chemotherapy, to develop an increasingly personalised approach to therapy and to utilise MRD assessments and predictive molecular signatures of treatment response that will allow appropriate stratification of therapy. This has most recently been validated in NPM1 +ve AML where MRD assessment can stratify patients into good and poor risk. APL is the obvious success story of targeted therapy on AML. This increasing complexity of diagnostic sub-stratification in AML with greater recognition that a "one size fits all" approach to study design may be becoming outmoded and that a targeted treatment for subgroups is more desirable means that collaborations with other European AML Study groups will become increasingly important.

MPN Subgroup (Chair, Dr Adam Mead)

The MPN Subgroup aims to deliver world-class clinical and translational research, implement positive findings and enhance patient knowledge. The Subgroup's portfolio is very broad, recruiting well and comprises a good balance of academic and commercial trials, with several members taking lead roles in these trials as global CIs. In terms of delivery of interventional academic studies, the MAJIC study has completed recruitment for both ET and PV. The MAJIC ET cohort, the first investigator led study of ruxolitinib internationally, has completed primary endpoint analysis; results have been presented and a manuscript will be submitted soon.

MPD RC112 recruited well in the UK and results were presented at ASH (oral presentation). MPD RC114 is now closed to recruitment and results were presented at ASH (oral presentation). The Phazar study (TAP) is open and recruiting well. The TAMARIN study (TAP) is now open and recruiting. The Subgroup also oversees a number of observational and biobanking studies (MOSAICC, MEASURES, Clonal Disorders, Molecular Pathogenesis of MPN, INForMeD) which are recruiting well and have contributed to multiple publications. For commercial studies, the UK has

top recruiting sites for the pacritinib studies (PERSIST-1 and PERSIST-2) where the global CIs are Subgroup members.

MITHRIDATE: a Multicenter International sTudy comparing ruxolitinib with either HydRoxycarbamIDe or interferon Alpha as first line ThErapy for high risk polycythemia vera (CI: Professor Claire Harrison) - this academic study is now fully funded and will open to recruitment in late 2017. This is the first study of ruxolitinib as a first line treatment for PV and will recruit approximately 600 patients over five years.

CLL Subgroup (Chair, Professor Peter Hillmen)

The CLL Subgroup runs phase III trials for previously untreated patients with CLL, supported by a series of phase II trials run through Bloodwise TAP, studying novel agents and combinations to inform the design of the future phase III trials incorporating adaptive trial design. Trial associated translational research is of central importance and depends on samples stored in our UK CLL Trials Biobank. The strategy for the Subgroup is to streamline the Phase II trials, translational research and phase III trials to move rapidly towards logical combinations of agents, to test them quickly, to progress to prolongation of remissions and as quickly as possible to cure. We aim to move to treatment for a defined period, unlike the currently with targeted treatments, with comprehensive pharmaco-economics to ensure cost effectiveness and the translation of advances into the NHS.

Our phase III trials test the replacement of chemo-immunotherapy with targeted treatment (ibrutinib plus rituximab in FLAIR), which is the best chemo-immunotherapy in unfit patients (RIAltO) and consolidation therapy for MRD positive patients following conventional therapy (GALACTIC). We are currently adapting FLAIR to add an arm combining ibrutinib plus venetoclax on the basis of data from our Bloodwise TAP CLARITY Trial in relapsed CLL. This will increase the size of the trial to over 1,500 patients, making it the largest phase III trial ever performed in CLL and has recently been approved by the CRUK. The amendment will open in June 2017.

ALL Subgroup (Chair, Professor Adele Fielding)

The overall goal of the ALL Subgroup is to improve the outcome for adults with ALL.

Exploiting funding opportunities

An educational grant of £55K was awarded by Jazz Pharma to support coordination of UKALL60+. Funding will be sought from CRUK to extend UKALL14 and for UKALL15. Funding will be sought from Bloodwise to investigate the post-allograft immune signature and from Shire for MAAT kits to measure asparaginase activity in samples collected from UKALL14.

Collaboration with industry

The two large commercial RCTs of novel agents in relapsed ALL (Inovate and TOWER), of which the UK was a key contributor, have been recently published in NEJM.

High quality correlative science

Prestigious awards in 2016 include a CRUK programme grant “Personalizing therapy for adults with ALL” in collaboration with the Sanger Institute (Co-PIs: Fielding and Moorman) and a Bloodwise Gordon Piller studentship to work on IKZF1 in ALL (PI: Fielding). In addition, a collaboration has been established with Dr Marc Mansour at UCL to investigate T-ALL biology.

Wider collaboration

Trials are being developed in collaboration with the NCRI CCL CSG. The Dutch-Belgian group HOVON contribute to UKALL60+ while New Zealand will contribute to UKALL15. There is strong

representation on the European Working Group on ALL.

Myeloma Subgroup (Chair, Professor Gordon Cook)

As part of our collaborative and inclusive ethos, our strategic plan for the Myeloma Subgroup is as to devise a strategic "run-through" design to our portfolio so that early phase trials genuinely inform the late phase trial developments; to use innovative designs aiming to be leaders in the field (as well as providing key UK-specific healthcare data to assist in regulatory approval) and to foster engagement between practicing haematologists in the UK, supporting their endeavours to participate in clinical research and to involve them in the public advertisement of our results.

To ensure the long-term strategy and continuity of clinical research activity, we aim to establish a robust plan centred on the development of succession planning through engagement of new personnel to work alongside established researchers. We aim to have correlative science at the centre of our studies, and thus there is a need to establish cellar and open bio-sampling governance. Taken together, we aim to publish our clinically impactful studies in high-ranking journals to change clinical practice.

4. Task groups/Working parties

Supportive Care, Transfusion & Late Effects Working Party (Chair, Professor John Snowden)

The SCTLE WP commenced in October 2015 to assess the feasibility of studies of blood transfusion, late effects and survivorship, palliative care and psychosocial supportive care over a two year period. Membership includes representatives from relevant Haem Onc CSG Subgroups, NHSBT, Supportive & Palliative Care CSG, Psychosocial Oncology & Survivorship CSG, TYA & GCT CSG and patient representatives.

The portfolio includes a number of established studies covering late effects (TRYMS: Testosterone Replacement in Young Male cancer Survivors), palliative medicine (factors associated with place of care and place of death); transfusion (TOPPS, INCITE, TREATT, HLA Epitope, RING, REDDS and REDEEM).

The WP has also developed five further projects:

1. Intravenous immunoglobulin as infection prophylaxis in haemato-oncology and HSCT.
2. Cardio-metabolic risk factors and late effects in survivors of haematological cancer and HSCT.
3. Fertility and pregnancy following intensive (non-transplant) treatment for acute leukaemia.
4. Psycho-social impact of watchful-waiting strategies in chronic haematological malignancies.
5. Rehabilitation strategies post-intensive chemotherapy for acute leukaemia and autologous HSCT for myeloma/lymphoma.

Aplastic Anaemia Working Party (Chair, Professor Judith Marsh)

A proposal for a new Aplastic Anaemia (AA) Working Party was approved in February 2017. The WP has four main objectives:

1. Raising the profile of AA as an important pre-malignant condition.
2. Establishing a more coordinated and efficient approach to the development and delivery future clinical trials
3. Facilitating translational research as a prerequisite for future clinical trials.

4. Enhancing consumer involvement in AA research by providing a focus for engaging with the national patient support group.

Two prospective randomised trials are already in progress. The national HLA epitope matched platelet transfusion trial for allo-immunised patients with aplastic anaemia, MDS and AML (PI: Marsh, funded by NHSBT) has successfully recruited and data analysis is in progress. In addition, the prospective randomised EBMT 'RACE' trial of ATG, cyclosporine with or without eltrombopag, is recruiting throughout Europe (UK PI: Professor Marsh). Kings College London is designated research centre for CR-UK-funded research project linked to RACE to identify molecular signature that predicts malignant transformation to MDS/AML. New phase I/II AA clinical trials are currently in set-up at King's College. The WP meets regularly via teleconferences to progress these projects with a view to completing systematic reviews and grant applications by autumn 2017.

5. Patient recruitment summary for last 5 years

There are currently more than 130 studies in the Haematological Oncology CSG portfolio. 25 trials closed to recruitment and 45 opened during the reporting period. This continuing expansion of the portfolio is almost entirely due to a proliferation of small Industry studies targeting molecularly defined niche populations. Many of these studies are beyond the control, and even knowledge, of the CSG and its Subgroups. Balancing this trend, the Group has maintained its portfolio of larger basket-type trials in most of the major disease populations.

Table 1 Summary of patient recruitment by Interventional/Non-interventional

Year	All participants		Cancer patients only		% of cancer patients relative to incidence	
	Non-interventional	Interventional	Non-interventional	Interventional	Non-interventional	Interventional
2012/2013	2708	3109	2572	3099	19.5	23.5
2013/2014	2925	3027	2818	3027	21.4	23.0
2014/2015	3132	3320	2972	3320	22.5	25.2
2015/2016	2370	2747	2370	2743	17.97	20.80
2016/2017	5534	2578	5522	2571	41.87	19.49

Overall recruitment figures into interventional and non-interventional studies is almost entirely attributable to recruitment of patients with blood cancers. Recruitment of such patients into interventional trials peaked in 2014-15, fell sharply in 2015-16 and has fallen slightly more during 2016-17. Despite this, recruitment relative to incidence remains generally good at about 19.5%. This represents a 20% reduction since 2014-15. In contrast, recruitment of patients with blood cancer into non-interventional studies has more than doubled since last year, increasing to an all-time high of 41.9% of incident cases.

The fall in recruitment into interventional studies was largely due to a gap between major frontline trials in high-recruiting disease areas such as AML and myeloma and seems to have largely bottomed out following the opening of AML 19 in October 2015. However, an important gap still remains in myeloma following the closure of Myeloma XI in February 2016. The expectation is that recruitment will return to previous levels once the two replacement studies for Myeloma XI (Myeloma XIV and XV) are open.

The dramatic increase in recruitment into non-interventional studies comes as a complete surprise and is hard to explain as there has not been any significant change in the availability of

such studies across the CSG.

6. Links to other CSGs, international groups and network subspecialty leads

The CSG has a number of links to other groups. These are outlined below:

- Sites in Australasia have recruited into the REDDS study in MDS, while a complementary study has been run in Canada.
- CML Subgroup members contribute to the European LeukemiaNet (ELN) and European Investigators on Chronic Myeloid Leukemia (EICML) expert groups.
- AML Subgroup members organised the inaugural European AML Workshop in Cardiff in September 2016. Subjects included trial design, Industry perspective, regulatory issues and proposals, plans and challenges in mounting international collaborative studies.
- Other AML intergroup collaborations include analysis of ATO treatment of t-APL and intensive treatment outcomes in adult AML patients with t(6;9).
- The ALL Subgroup collaborates with the NCRI CCL CSG and HOVON.
- Professor Fielding is Cancer Lead for the North Thames CRN.
- The Myeloma Subgroup has representation on SPED.
- The AA WP has strong links with the EBMT SAA Working Party and AA&MDS International Foundation.
- The CLL Subgroup and German CLL Study Group have reciprocal membership on DMCs.
- Links to ERIC (the European Research Initiative in CLL) to standardize key laboratory tests including the measurement of minimal residual disease and prognostic markers.
- Oliver Ottmann and Steve Knapper organised the 1st European AML Workshop in Cardiff in September 2016. Subjects included trial design, industry perspective and interests within the context of the European regulatory framework and proposals, plans and challenges in mounting international intergroup studies. A follow-up meeting is planned for September 2017. Other intergroup collaborations have included analysis of the treatment of t-APL with ATO and the outcome of intensively treated adult AML patients with t(6;9).

7. Funding applications in last year

The CSG's success at the CRUK CRC has continued with 6/8 applications funded, approved or invited to full. Other events of note include renewal of the Bloodwise Trials Acceleration Programme (TAP) in May 2016. Funding was awarded to the coordinating hub in Birmingham plus one FTE research nurse at each of the 13 recruiting centres for a three year period. The TAP portfolio consists of 19 trials (1 in set-up, 11 open and 7 closed or in follow-up), with 946 patients recruited into TAP studies since its launch in 2012. Another major initiative was launched in October 2016 to accelerate and facilitate the delivery of early-phase trials in stem-cell transplantation. The project (IMPACT) is funded by NIHR, Anthony Nolan, Leuka and NHSBT. It is anticipated that 9-12 trials will be delivered over the 4-year pilot, with approximately 400-500 patients participating. The co-ordinating hub is in Birmingham and 10 recruiting centres were recently selected, each of which will receive funding for 1.0 FTE research nurse. Finally, Myeloma UK have funded 2 new studies, MUKeleven (VIReL) and MUKfourteen (KeyCR) which will be delivered through their Clinical Trial Network with its co-ordinating hub in Leeds.

Table 2 Funding submissions in the reporting year

Cancer Research UK Clinical Research Committee (CRUK CRC)			
Study	**Application type**	**CI**	**Outcome**
May 2016			
Front-Line therapy in CLL: Assessment of Ibrutinib + Rituximab (previously known as CLL10)	No-cost Amendments Application	Professor Peter Hillmen	Supported
Identification of the pathogenetic genomic signature that predicts for dysplastic and leukaemic transformation in severe aplastic anaemia following treatment with eltrombopag	Full application	Professor Ghulam Mufti	Funded
CRUK/10/052: RIAltO: A Randomised Investigation of Alternative Ofatumumab-based regimens for less fit patients with CLL	No-cost Amendments Application	Professor Andrew Pettitt	Supported
CRUK/12/043: AML 18 - A trial for older patients with acute myeloid leukaemia and high risk myelodysplastic syndrome	No-cost Amendments Application	Dr Robert Hills	Supported
A phase 3 trial to assess a novel triplet IRDa versus CRDa in patients with newly diagnosed Multiple myeloma not suitable for a stem cell transplant with randomisation according to frailty between standard therapy and dose adjusted therapy	Full application	Professor Graham Jackson & Professor Gordon Cook	Funded
November 2016			
Myeloma XV: RADAR: Risk Adapted therapy Directed According to Response comparing treatment escalation and de-escalation strategies in newly diagnosed patients with multiple myeloma (NDMM) suitable for stem cell translation (TE)	Outline application	Professor Kwee Yong	Invited to full
MITHRIDATE: A Multicenter International sTudy comparing ruxolitinib with either HydRoxycarbamIDe or interferon Alpha as first line ThErapy for high risk polycythemia vera	Outline application	Professor Claire Harrison	Not invited to full
Identification of predictive genomic and transcriptomic biomarkers for TKI response in CML-CP	Full (Biomarker Project Award)	Professor Jane Apperley	Not Supported
Other committees			
Study	**Committee & application type**	**CI**	**Outcome**
Establishing the safety and efficacy of low dose interleukin-2 in refractory aplastic anaemia	NIHR	Professor Ghulam Mufti	Submitted, outcome awaited
An assessment of the mechanism of action and identification of response predictors of eltrombopag in thrombocytopenic patients with aplastic anaemia and low to intermediate-1 risk MDS ('TAME' study)	Novartis UK	Professor Ghulam Mufti	Submitted, outcome awaited
High dimensional immune-phenotyping with mass spectrometry using CyTOF panels to delineate immune signatures for response and relapse for severe aplastic anaemia patients treated in the EBMT 'RACE' study	Novartis Global	Professor Judith Marsh	Submitted, outcome awaited
Tranexamic acid in thrombocytopenic MDS patients	NIHR	Dr Dominic Culligan	Not supported
Next-generation biobanking: a lymphoma	MRC Capital	Professor Andrew	Invited to

tissue/data bank for all occasions (includes CLL trials)	Tissue Banking Call	Pettitt	full
AVAIL-T: Anti-PDL1 (Avelumab) for relapsed and refractory peripheral T-cell lymphoma	TAP – July 2016	Professor Simon Wagner	Awarded
Phase II randomised trial of CC-486 (oral azacitidine) versus intensive chemotherapy as salvage therapy in patients with acute myeloid leukaemia (AML)	TAP – December 2016	Professor Charles Craddock	Withdrawn
STELLAR: A phase II randomised study of CHOP-R in combination with acalabrutinib compared to CHOP-R followed by acalabrutinib at disease progression for patients with newly diagnosed Richter's syndrome	TAP – December 2016	Professor Anna Schuh	Pending

8. Collaborative partnership studies with industry

The CSG continues to enjoy strong links with industry in terms of the large number of industry-led studies on the portfolio, plus industry support in the form of free drug and/or central running costs for academic studies. Commercial studies now account for more than 50% of trials on the CSG portfolio. Companies with which the CSG collaborates include: Abbvie, Acerta, Amgen, Ariad/Incyte, AstraZeneca, Bristol-Myers Squibb, Celgene, Epizyme, Genentech, Gilead, Janssen, Jazz, Novartis/GSK, Onconova, Pfizer, Pharmacyclics, ProStrakan, Roche, Shire, Sigma Tau, Sunesis and Takeda.

New commercial trials are sometimes (but not always) discussed with the CSG prior to implementation. Such an arrangement is mutually beneficial as it allows a structured approach to portfolio management and minimises competition for small patient groups. On the negative side, the recent takeover of Ariad by Incyte resulted in loss of Industry support for the SPIRIT3 trial in CML leaving a major gap in the portfolio.

A collaboration has been established with Sunesis and Janssen to introduce the combination of Vosaroxin and Decitabine into the AML18 trial for patients with known adverse risk cytogenetics at diagnosis. There are ongoing collaborations concerning CPX-351 with Jazz pharma.

9. Impact of CSG activities

Within the reporting period, data from the AML17 trial was used to support a successful licence extension application to the EMA for Arsenic Trioxide as first line therapy for standard risk Acute Promyelocytic Leukaemia. The trial has also resulted in MRD monitoring becoming standard of care for NPM1 +ve AML in the UK and indeed internationally (NEJM 2016;374(5):422-33). In ALL, the NICE approval of Pegylated asparaginse was supported by data from the UKALL14 trial, while the UK also made a major contribution to Industry studies that resulted in the FDA/EMA approval of blinatumomab and the filing of inotuzumab for regulatory approval in relapsed/refractory ALL.

In myeloma, the recently closed phase III studies (Myeloma X and Myeloma XI/XI+) have established the role of salvage ASCT and sequential biological agent-based induction and maintenance strategies respectively, that are influencing clinical care delivery both in the UK and internationally. In CLL, the UK made a major contribution to commercial studies that resulted in the FDA/EMA approval of venetoclax. CSG and Subgroup members contributed to 22 NICE appraisals involving bosutinib, dasatinib, ibrutinib, pomalidomide, ixazomib, idelalisib, azacytidine, carfilzomib, vosaroxin, blinatumumab, clofarabine, daratumumab, venetoclax,

lenalidomide, erythrocyte-encapsulated asparaginase, ponatinib, midostaurin, inotuzumab, elotuzumab and pembrolizumab. The CSG also contributed comments as part of the review of eight CRUK applications.

The CSG has also contributed to the development of guidelines including BSH guidelines for the diagnosis and management of eosinophilia, updated guidelines on polycythaemia and new best practice guidelines for the management of mastocytosis.

10. Consumer involvement

Throughout the reporting year, the two CSG consumer members (Lesley Roberts and Gillian Murphy) have again played an active and supportive role in CSG activities as well as those of the Myeloma Subgroup (Lesley) and the Supportive Care, Transfusion and Late-Effects Working Party (Gillian). As well as participation in CSG meetings and the Annual Trials Day, consumer input and comments were made to several CRC applications and Patient Information Sheets.

During her final year as a CSG consumer member, Lesley has completed a NICE Quality Assurance committee task, evaluating blood cancer guidelines recently published. This resulted in the publication of four revision statements. Lesley is also on two Trial Management Committees (PROMS and ACCORD). She serves on the main board of INVOLVE and is involved in local PPI representation. Gillian is a member of the Royal Marsden/ICR BRC Patient and Carer Research Review Panel, and actively engages with the blood cancer charities Bloodwise and Anthony Nolan in several capacities. She has recently become involved as a patient representative and co-applicant in developing a psychosocial/radiography proposal. Both Lesley and Gillian are NIHR PRAIs.

In addition to consumer representation on the CSG, the seven Subgroups each have trained, motivated and effective consumer representatives, who are actively involved in all aspects of trial development, with co-applicant status on some Subgroup proposals. As well as direct links to the Myeloma Subgroup and Supportive Care Working Party provided by Lesley and Gillian, a strong relationship with the consumer representative on the ALL Subgroup (John Reeve), has been maintained. Links with the representative with the AML Subgroup (Rich Castle) have recently been developed, and increasing communication between all of the Subgroup consumer members remains a key aim to further enhance the effective consumer involvement within haematological oncology.

Both Lesley and Gillian feel respected and valued by the CSG members, and appreciate the supportive environment in which their views are always welcomed.

11. Open meetings/annual trials days/strategy days

The CSG holds an Annual Trials Review Meeting every summer which is organised by the Birmingham CTU and funded via pharma sponsorship. The 2016 meeting was held at RIBA in Central London. There were over 100 attendees including clinicians (41%), nurses (27%), trial co-ordinators (13%) and data managers (5%). 97% of attendees considered the overall content to be a good mix, and 89% of delegates considered the number of presentations just right. 13%, 41%, 38% and 8% of attendees considered the meeting extremely useful, very useful, useful and quite useful, respectively. A concerted effort has been made to increase sponsorship and sufficient funds are now available for the 2017 meeting to be held at the preferred venue of the Royal College of Physicians.

To further facilitate collaborative working and publicise research, a number of Subgroups have established umbrella organisations involving not only clinicians but also scientists and patients. Examples include the UK CLL Forum, the UK MDS Forum and the recently established UK Myeloma Research Alliance (UKMRA). These organisations meet one or two times a year. In addition, the MPN Subgroup runs a biennial two day national update event for clinical staff and patients plus seven regional patient fora in partnership with the patient advocacy group MPN voice. In CML, national education events for both Healthcare Professionals and Patients/Carers were held in Manchester in September 2016 with internet/social media streaming. In AML, successful AML Roadshows have been held for investigators and research nurses in Glasgow and Bristol to publicise the AML Trials portfolio.

12. Priorities and challenges for the forthcoming year

Priorities

1. Succession planning: The Chairs of the AML, ALL and MDS Subgroups are all due to rotate off the main CSG during the next year. Each of these individuals have fulfilled their respective roles with distinction, and it is crucial that successors are appointed who are equally capable and committed. It is also important that the outgoing Subgroup Chairs continue to contribute to CSG activities by engaging with and, where appropriate, leading in their respective areas of research. The Chair of the Supportive Care, Transfusion & Late Effects Working Party is also due to rotate off the Group and it is important to ensure that focus is maintained on this important area of CSG activity. Finally, the Chair of the main CSG will complete his six year term in 2018 and it is crucial that a successor is appointed who can take the Group forward.
2. Maintaining a comprehensive CSG portfolio: The CSG aims to have large frontline trials in place for all major disease areas. However, gaps have emerged between successful trials in AML and myeloma, resulting in a 20% reduction in recruitment. The situation has been resolved for AML (although developing a replacement for Li-1 is a priority) but there is still a gap in Myeloma. It is therefore crucial that Myeloma XIV and XV are implemented at the earliest opportunity.

   It is also important to transition as seamlessly as possible between UKALL14 and UKALL15. The recent success in obtaining funding for MITHRIDATE fills a gap in frontline MPN trials but such studies are still lacking in MDS and CML. An MDS trial (RAPRIMA) was developed but not funded, while prospects for developing a major frontline study in CML look bleak following withdrawal of Industry support for SPIRIT-4 and the advent of generic imatimib.
3. Optimising engagement with other stakeholders: The CSG is fortunate to have access to additional clinical research capacity via the TAP, IMPACT and Myeloma UK Clinical Trials Networks. To fully exploit the opportunities provided by these initiatives, it is crucial that there is full strategic alignment between all parties through cross-membership of the respective groups. The CSG also needs to link in with the CRUK/NIHR ECMC Network, especially given the proposal to form a Haemato-Oncology Group.

   Engagement with the NIHR Clinical Research Networks is also important in order to optimise trial delivery. Some CSG members have local leadership roles in these networks but more formal engagement will be sought through a joint meeting, hopefully also involving the Lymphoma CSG. The CSG also needs to consolidate its relationship with other CSGs including Psychosocial Oncology & Survivorship and Supportive & Palliative Care to deliver the new studies developed through the SCTLE Working Party.

Challenges

1. Research funding: It is crucial that the CSG's approach to trial design is fully aligned with current thinking at CRUK. It is clear that there is a growing emphasis on ambitious basket trials that bring together an important clinical question and high-quality science. Whilst the Group's portfolio includes stand-alone sample collections and trials with bolt-on scientific questions, there are relatively few trials where high-quality science is integral to study design. Developing credible studies of this type across the board requires stronger engagement with the wider non-clinical scientific community to ensure that all available expertise is fully exploited. Achieving this connectivity should facilitate translation of pre-clinical observations into trial questions, as well as reverse translation to investigate disease heterogeneity and develop new predictive biomarkers for stratifying patients in the next generation of clinical trials. Obtaining funding for supportive care studies (not within the remit of CRUK) remains a formidable challenge.
2. Applying innovative trial design across the CSG: The CSG has led the way in applying factorial trial design in AML, ALL and Myeloma. It has also pioneered basket studies in which patients are stratified for different treatments based on molecular characterisation and/or sensitive quantification of treatment response (AML, ALL, CML, CLL). In AML, exploratory questions have been integrated into multifactorial phase III studies, while in CLL, an early-phase programme feeds seamlessly into phase III trials. Applying these approaches in other areas is clearly the way forward but presents significant challenges, sometimes due to lack of actionable mutations and/or biomarkers for disease stratification, and sometimes due to misalignment with the strategic plans of some pharma companies. Addressing these shortfalls requires stronger engagement with the scientific community and further strengthening of relationships with pharma companies in order to influence decision making at the highest level.
3. Integration of genomics into clinical trials: The genomics revolution presents many opportunities and challenges for cancer. Haemato-oncology is at the vanguard of these developments owing to the relative ease in obtaining fresh tumour material. For example, collaborations with the Sanger Institute have been established to investigate genomic alterations in ALL and AML trials, while CLL trials were selected as one of three pilots for the GEL 100,000 Genomes Project. Haemato-oncology is an important part of the main GEL programme, eligibility being linked to several trials in AML, CLL and Myeloma. Following closure of the programme in December 2018, there could be a decision to switch national commissioning of routine molecular diagnostics to centrally performed whole-genome sequencing (WGS), starting with AML/MDS. To keep one step ahead of these developments, the Clinical Lead for the Haemato-Oncology GEL Clinical Interpretation Partnership (GeCIP) has been co-opted onto to the CSG.

13. Appendices

Appendix 1 - Membership of main CSG and subgroups

Appendix 2 – CSG and Subgroup strategies

- A – Main CSG Strategy
- B – MDS Subgroup Strategy
- C – CML Subgroup Strategy
- D – AML Subgroup Strategy
- E – MPN Subgroup Strategy
- F – CLL Subgroup Strategy
- G – ALL Subgroup Strategy

H – Myeloma Subgroup Strategy
I – Supportive Care, Transfusion & Late Effects Working Party Strategy

Appendix 3 - Portfolio Maps

Appendix 4 - Publications in previous year

Appendix 5 - Major international presentations in previous year

Professor Andrew Pettitt (Haematological Oncology CSG Chair)

Appendix 1

Membership of the Haematological Oncology CSG

Name	Specialism	Location
Dr Satyen Gohil*	Clinical Research Fellow	London
Dr Charlotte Pawlyn*	Clinical Research Fellow	Surrey
Dr Gillian Murphy	Consumer	Surrey
Mrs Lesley Roberts	Consumer	Leek
Professor Gordon Cook	Haematologist	Leeds
Professor Mhairi Copland	Haematologist	Glasgow
Dr Dominic Culligan	Haematologist	Aberdeen
Dr Adele Fielding	Haematologist	London
Dr Francesco Forconi	Haematologist	Southampton
Professor Peter Hillmen	Haematologist	Leeds
Dr Richard Kaczmarski	Haematologist	London
Professor Judith Marsh	Haematologist	London
Dr Adam Mead	Haematologist	Oxford
Professor Stephen O'Brien	Haematologist	Newcastle
Dr Andrew Peniket	Haematologist	Oxford
Professor Andrew Pettitt (Chair)	Haematologist	Liverpool
Dr Christopher Pocock	Haematologist	Kent
Professor Ciro Rinaldi	Haematologist	Lincolnshire
Professor Nigel Russell	Haematologist	Nottingham
Dr Clare Rowntree	Haematologist	Cardiff
Professor John Snowden	Haematologist	Sheffield
Professor Kwee Yong	Haematologist	London
Dr Alasdair Rankin	Research Director, Bloodwise	London
Ms Shamyla Siddique	Senior Trials Coordinator	Birmingham
Professor Walter Gregory	Statistician	Leeds
Dr Robert Hills	Statistician	Cardiff

* denotes trainee member

Membership of the Subgroups

ALL Subgroup		
Name	**Specialism**	**Location**
Professor Oliver Ottmann	Clinical Professor	Cardiff
Dr Anna Castleton	Consultant Haematologist	London
Mr John Reeve	Consumer	Witham
Professor Anthony Moorman	Epidemiologist	Newcastle
Dr Adele Fielding (Chair)	Haematologist	London
Dr Rachael Hough**	Haematologist	London
Professor David Marks	Haematologist	Bristol
Dr Andrew McMillan	Haematologist	Nottingham
Dr Tobias Menne	Haematologist	Newcastle
Dr Nick Morley	Haematologist	Sheffield
Dr Clare Rowntree	Haematologist	Cardiff
Ms Amy Kirkwood**	Statistician	London
Dr Bella Patel**		London

CLL Subgroup		
Name	**Specialism**	**Location**
Mr Nick York	Consumer	
Dr David Allsup	Haematologist	Hull
Dr Adrian Bloor	Haematologist	Manchester
Dr Chris Fegan	Haematologist	Cardiff
Dr George Follows	Haematologist	Cambridge
Dr Chris Fox	Haematologist	Nottingam
Professor Peter Hillmen (Chair)	Haematologist	Leeds
Dr Chris Pepper	Haematologist	Cardiff
Dr Anna Schuh	Haematologist	Oxford
Ms Dena Cohen	Statistician	Leeds

CML Subgroup		
Name	**Specialism**	**Location**
Ms Sandy Craine	Consumer	
Dr Naumann Butt	Haematologist	Liverpool
Dr Jenny Byrne	Haematologist	Nottingham
Professor Richard Clark	Haematologist	Liverpool
Professor Mhairi Copland (Chair)	Haematologist	Glasgow
Dr Paolo Gallipoli*	Haematologist	Cambridge
Dr Andrew Goringe	Haematologist	Cardiff
Professor Tessa Holyoake	Haematologist	Glasgow
Dr Brian Huntly	Haematologist	Cambridge
Dr Adam Mead	Haematologist	Oxford
Professor Steve O'Brien	Haematologist	Newcastle
Dr Graeme Smith	Pathologist	Leeds

AML Subgroup		
Name	**Specialism**	**Location**
Mr Richard Castle	Consumer	
Professor David Bowen	Haematologist	Leeds
Professor Charles Craddock	Haematologist	Birmingham
Dr Dominic Culligan	Haematologist	Aberdeen
Dr Mike Dennis	Haematologist	Manchester
Dr Sylvie Freeman	Haematologist	Birmingham
Dr Gail Jones	Haematologist	Newcastle
Dr Steven Knapper	Haematologist	Cardiff
Professor Mary Frances McMullin	Haematologist	Belfast
Professor Nigel Russell (Chair)	Haematologist	Nottingham
Dr Robert Lown*	Haemato-Oncologist	Southampton
Professor Keith Wheatley	Statistician	Birmingham

MDS Subgroup		
Name	**Specialism**	**Location**
Ms Sophie Wintrich	Consumer	
Professor David Bowen	Haematologist	Leeds
Dr Jamie Cavenagh	Haematologist	London
Dr Dominic Culligan (Chair)	Haematologist	Aberdeen
Dr Mike Dennis	Haematologist	Manchester
Dr Mark Drummond	Haematologist	Glasgow
Emma Das Gupta	Haematologist	Nottingham
Dr Sally Killick	Haematologist	Bournemouth
Dr Juliet Mills	Haematologist	Worcester
Professor Ghulam Mufti	Haematologist	London
Dr Manoj Raghavan	Haematologist	Birmingham
Dr Paresh Vyas	Haematologist	Oxford

MPD/N Subgroup		
Name	**Specialism**	**Location**
Ms Alisia O'Sullivan	Consumer	
Dr Sahra Ali	Haematologist	Hull
Dr Nauman Butt	Haematologist	Wirral
Dr Mark Drummond	Haematologist	Glasgow
Dr Andrew Duncombe	Haematologist	Southampton
Dr Joanne Ewing	Haematologist	Birmingham
Professor Tony Green	Haematologist	Cambridge
Dr Claire Harrison	Haematologist	London
Dr Steven Knapper	Haematologist	Cardiff
Dr Adam Mead (Chair)	Haematologist	Oxford
Professor Mary Frances McMullin	Haematologist	Belfast
Dr Frances Wadelin	Haematologist	Nottingham

Myeloma Subgroup		
Name	**Specialism**	**Location**
Mrs Lesley Roberts	Consumer	Leek
Dr Jenny Bird	Haematologist	Bristol
Dr Andy Chantry	Haematologist	Sheffield
Professor Gordon Cook (Chair)	Haematologist	Leeds
Dr Mark Cook	Haematologist	Bristol
Dr Matthew Jenner	Haematologist	Southampton
Dr Guy Pratt	Haematologist	Birmingham
Dr Karthik Ramasamy	Haematologist	Oxford
Professor Mark Drayson	Immunologist	Birmingham
Professor Walter Gregory	Statistician	Leeds

*denotes trainee member

**denotes non-core member

Supportive Care, Transfusion & Late Effects Working Party		
Name	**Specialism**	**Location**
Dr Eila Watson	Chair in Supportive Cancer Care	Oxford
Dr Stella Bowcock	Consultant Haematologist	London
Dr Harpreet Kaur	Consultant Haematologist	Sheffield
Dr Panos Kottaridis	Consultant Haematologist	London
Dr Donal McLornan	Consultant Haematologist	London
Dr Andy Peniket	Consultant Haematologist	Oxford
Dr Mallika Sekhar	Consultant Haematologist	London
Dr Simon Stanworth	Consultant Haematologist	Oxford
Dr Gillian Murphy	Consumer	Surrey
Professor John Snowden	Haematologist	Sheffield
Dr Sara Ali	Haematologist	Hull
Professor Jenny Byrne	Haematologist	Nottingham
Dr Nick Morely	Haematologist	Sheffield
Professor Andy Pettitt	Haematologist	Liverpool
Dr Clare Rowntree	Haematologist	Cardiff
Ms Laura Meehan	Haemato-oncology Lead Nurse	Glasgow
Professor Sam Ahmedzai	Palliative Medicine	Sheffield
Dr Feng Li	NCRI Survivorship Lead	London
Professor Annie Young	Nurse	Warwick
Dr Jo Armes	Research Fellow	London
Ms Jane Nunnick	Senior Haematology Research Nurse	Birmingham
Dr Rachel Taylor	Senior Research Manager	London

These Working Parties only communicate via teleconference.

Aplastic Anaemia Working Party		
Name	**Specialism**	**Location**
Austin Kulasekararaj	Consultant Haematologist	London
Dr Simon Stanworth	Consultant Haematologist	Oxford
Dr Anita Hill	Haematologist	Leeds
Dr Sally Killick	Haematologist	Bournemouth
Professor Judith Marsh	Haematologist	London
Professor Ghulam Mufti	Haematologist	London
Professor John Snowden	Haematologist	Sheffield
Dr Sujith Samarasinghe	Paediatric Haematologist	London
Ms Nana Benson-Quarm	Research Nurse	London
Consumer		Pending

Appendix 2

CSG & Subgroup Strategies

A – Main CSG Strategy

The Haem Onc CSG was originally established through the merging of several independent MRC Working Groups which became Subgroups under the new NCRI structure. Although the WGs were individually successful, the establishment of a parent CSG created an opportunity to consider research priorities in a more holistic way, identify common objectives and share best practice. This resulted in the development and delivery of a new generation of cutting-edge studies. Owing to the accessibility of fresh tumour material, haematological oncology has always led the way in molecular stratification, and the advent of new technologies, coupled with the development of highly targeted therapies, now presents an opportunity for haematological oncology be at the vanguard of the development of precision medicine in cancer.

Scientific strategy

The CSG's overall scientific strategy is to improve the objective and patient-reported outcome of haematological cancers through the development and evaluation of stratified and/or response-adapted approaches to therapy based on predictive biomarkers and sensitive quantification of residual tumour burden, coupled with the optimisation of supportive care and of recognition and management of late effects. At the core of this strategy is the need for innovative trial design, coupled with high-quality biobanking as a platform for biomarker discovery/development and the identification of new drug targets. It is crucial to ensure optimal connectivity between clinical research and basic/ translational science in order to produce the strongest possible funding applications. It is also important to ensure seamless connectivity between the Group's early-phase clinical research and late-phase trials to ensure that the early-phase trials have an explicit purpose within the portfolio and that preliminary observations of interest are subjected to definitive testing in the most efficient way possible.

Priority areas for clinical research

The CSG aims to maintain a balanced and continuously replenishing portfolio of academic and industry studies in all major disease areas, using data from the CSG's early-phase trial programmes to inform on the next generation of phase III studies. In addition, the CSG aims to expand research in supportive care, transfusion and late effects as important cross-cutting themes. This has been achieved through the establishment of a Working Party in collaboration with the Supportive & Palliative Care CSG. A WP has also been established to develop research proposals in Aplastic Anaemia. The Group aims to apply a more co-ordinated approach to transplant studies by working more closely with the BSBMT and establish closer collaborative links with the CCL and TYA CSGs to ensure an optimally co-ordinated approach for all TYA patients with leukaemia.

Biobanking and translational research

Precision medicine requires the identification of molecularly defined patient subgroups who are likely to benefit from specific, targeted therapies. This, in turn, requires the identification of new drug targets and the development of predictive biomarkers. Samples obtained from patients recruited into clinical trials provide an ideal – and in many cases unique - resource for such translational research, and one of the CSG's priorities is to ensure that all of its major studies are supported by high-quality biobanking coupled with a comprehensive and co-ordinated programme of correlative science employing cutting-edge technologies. It is equally important

that information generated from laboratory research programmes is used to inform on the design of new clinical trials.

Engagement with industry

Industry engagement is of fundamental importance to the CSG owing to the need to investigate new drugs that are not available through the NHS. Pharma companies may also provide a potential source of funding for trial coordination, biobanking and correlative science. The Group's relationship with industry has evolved in an organic fashion through the endeavours of individuals to develop clinical trials and is, for the most part, excellent. It is, however, crucial that all proposals for new industry-sponsored studies are discussed with the CSG in order to plan the portfolio and minimise competition for niche study populations.

Engagement with charity-funded research infrastructure initiatives

The CSG is fortunate to have access to additional clinical research capacity via the TAP, IMPACT and Myeloma UK Clinical Trials Networks. To fully exploit the opportunities provided by these initiatives, it is crucial that there is full strategic alignment between all parties through cross-membership of the respective groups. The CSG also needs to links in with the CRUK/NIHR ECMC Network, especially given the proposal to form a Haemato-Oncology Group within the ECMC Network.

Engagement with Genomic England Ltd (GEL)

Haemato-oncology has been at the vanguard of the GEL 100,000 Genomes Project owing to the relative ease in obtaining fresh tumour material. Following closure of the programme in December 2018, there could be a decision to switch national commissioning of routine molecular diagnostics to centrally performed whole-genome sequencing (WGS), starting with AML/MDS. To keep one step ahead of these developments, the Clinical Lead for the Haemato-Oncology GEL Clinical Interpretation Partnership (GeCIP) has been co-opted onto to the CSG.

Trial delivery

Delivering trials to time and target remains one of the key priorities of the CSG. It is therefore important that the CSG engages effectively with the delivery networks. This will be achieved by involving Subspecialty Leads (SSLs) in CSG meetings and by continuing to showcase the CSG portfolio at the annual trials review meeting. Consideration is being given to holding a national joint meeting with SSLs.

Consumer engagement

Consumer representation on the CSG is crucial, not only for writing and commenting on patient information sheets, but also for formulating new research questions, gauging patient acceptance of new studies, optimising trial design and publicising new studies within the patient community. It is also important that the CSG has broad geographical representation.

CSG membership

In order for the CSG to fulfil its function, it is crucial that CSG members cover a broad range of expertise including not only the seven main disease areas (AML, ALL, CML, CLL, MPN, MDS, myeloma) but also supportive care, transfusion, late effects, stem-cell transplantation, TYA and translational science. Given the importance of optimising trial design, the CSG also places much emphasis on statistician representation. The appointment of a senior trial coordinator to the Group provides expertise in trial delivery. The CSG feels that the balance in membership is about right but that it could benefit from the inclusion of a senior research nurse at the next rotation.

Membership rotation
The CSG recognises the importance of membership rotation as a way of maintaining dynamism and preventing stagnation. However, it is also important that the breadth and depth of expertise within the CSG is not compromised as a result of enforced membership rotation if new applicants do not offer the same level of expertise as that provided by existing members who are due to rotate. To avoid this scenario, it is important that opportunities to join the CSG are widely advertised within the relevant specialist communities, and that Subgroup Chairs give due consideration to succession planning.

Training opportunities
The long-term sustainability of clinical research depends on there being a pipeline of future clinical researchers, and it is crucial that the clinical research community provides training opportunities for such individuals. The CSG is committed to contributing to this process by taking part in the CSG Trainee Scheme.

B – MDS Subgroup Strategy

The strategy of the MDS Subgroup is to develop a portfolio of Phase I, II and III studies which cover, as much as possible, low risk and high risk MDS and supportive care questions across all groups.

There are a number of challenges in developing trials for MDS patients, which are more acute than for other malignant blood diseases. Firstly, patients are very elderly with a median age of about 73 years. The majority of these patients are managed in District General Hospitals and two thirds are managed with supportive care only, with no active MDS therapy being delivered. Secondly and linked to this, there are very few drugs that currently work in MDS. Presently, only two disease modifying drugs have a license in MDS: azacitidine for high-risk patients and lenalidomide for a small group of low risk patients with del5q. Furthermore, a very small number of drug companies have a relative monopoly of drugs for MDS and consequently trial development in this environment is frequently strategic. This is perceived so as not to develop internal competition between drugs and as such puts some restrictions on trial design and innovation by the Subgroup. Finally, most drugs in development in haematological cancer are anti-proliferative in their activity. Whilst such therapies have a role in high risk MDS, they have little or no role in low risk MDS.

Low risk MDS represents two thirds of the patients and treatments to improve bone marrow failure, particularly anaemia, improve supportive care strategies and delay progression of bone marrow failure are needed. Recently, Luspatercept, (ACE-536), has been developed to stimulate erythropoiesis independently of EPO. The Subgroup has participated in an exciting randomised phase III commercial study in sideroblastic anaemia. This completed recruitment considerably ahead of schedule in May 2017 and this is exactly the type of approach needed in low risk MDS.

The MDS Subgroup strategy includes collaboration with the AML Subgroup and UK transplant groups in high risk MDS where there is large overlap in treatment approaches, whilst developing standalone strategies at phase II and III in supportive care, low risk MDS and novel combination therapies in high risk disease. As part of this collaboration we have put forward a major amendment to NCRI AML 19 trial to enable a wider range of high risk MDS patients to take part. This will be considered over the summer of 2017.

During the last 12 months, the MDS Subgroup has continued to recruit to the phase II ELASTIC study of azacitidine and eltrombopag in high risk MDS completed recruitment to the first four cohorts of patients. Despite recent closure of a global trial of the combination (SUPPORT)

because of futility and a concern about possible progression on the combination, the IDMC has found no such concerns with ELASTIC so far and agreed to open the final fifth cohort. A joint study with the National Blood authority (REDDS), led by Dr Simon Stanworth, has completed recruitment on time in May 2017 from a difficult group of patients. This is a pilot to see if a strategy of randomising MDS patients on supportive care between a permissive and a restrictive blood transfusion regimen is possible. Quality of life is the primary endpoint. The trial also opened and recruited in New Zealand and an identical pilot in Canada is running in parallel. An outline grant proposal for a follow-up REDDS-2 study has been submitted in May 2017 to Bloodwise for consideration of funding. This will compare the best approach from REDDS with a novel approach of weekly single transfusion support without the need for cross matching if the antibody screen is negative. If successful, the plan is to extend this into an international, multicentre, phase III trial.

Funding from Bloodwise has led to the opening in early 2017 of a phase II study in CMML to follow on from the successful CMML201 trial that was published in Leukaemia in 2014. This study, Led by Dr Steve Knapper, will look at the safety and clinical effectiveness of the monocyte targeted HDAC inhibitor, Terfinostat. If there is acceptable toxicity profile and evidence of efficacy then the group strategy would be to take this forward in a randomisation against hydroxycarbamide or azacitidine. A number of patients have already been recruited and sites continue to open.

The phase III strategy of the Subgroup is to continue to support the large and successful AML trials delivered through the AML Working Group by including appropriate high-risk MDS patients and this currently includes AML 18, LI-1 and AML 19. However, the Subgroup continues to work towards a stand-alone Phase III trial. In terms of therapy the aim is to identify potential combinations with azacitidine that can then be randomised against azacitidine alone. However, this strategy worldwide has yet to identify a successful combination and RAvVA, which fully recruited and closed in late 2015, has added to this knowledge base and ELASTIC may identify an appropriate combination to test further.

Our lead approach for the last two or more years has been to develop a randomised, phase III, placebo controlled trial of supportive care. This would randomise a wide range of high-risk MDS patients receiving azacitidine or low intensity therapy within the LI-1 trial to prophylaxis with an oral antibiotic or oral anti-fungal drug, both or neither. The primary endpoint would be time to first infection. However, a range of secondary endpoints would look at key health economic issues in these elderly patients, including time in hospital, use of IV antibiotics, antibiotic resistance, and hospital acquired infections and survival. The trial, RAPRIMA, was declined for funding by HTA as it did not fit into their current portfolio. However, a submission for funding was made to Bloodwise in July 2015 and following an invited re-submission in February 2016, with appropriate modifications and clarifications, the Bloodwise Clinical Trials Committee recommended that the trial be funded. However, the Trustees of Bloodwise declined this recommendation because of financial difficulties at the Charity. This has been more than two years of work for the sub group and is incredibly disappointing. We have recently started work on a potential randomised phase II study for low risk MDS patients who have failed therapy with erythropoiesis stimulating agents (ESAs). This will randomise patients to the addition of Danazol or addition of the novel regimen VBaP, for anaemic low risk MDS patients, and this will be a focus of the group going forward over the next year.

The Subgroup has developed a sizeable company run portfolio of phase II and III studies in high and low risk MDS. This is running throughout the UK the pivotal, worldwide, randomised trial of

oral azacitidine versus placebo for low risk MDS patients (Celgene 003). However, the entry criteria are so precise, perhaps for company strategic reasons, that recruitment has proved incredibly difficult. This year we have added interesting drug trials including a large randomised phase III trial of Rigosertib versus clinician choice for patients who have failed azacitidine (open) and the completed randomised phase III trial of the drug Luspatercept (ACE-536) that promotes erythropoiesis for sideroblastic anaemia. The Subgroup has added randomised commercial trials to the portfolio of the Checkpoint inhibitor, Durvalumab and the BCL-2 inhibitor Venetoclax, for high risk patients.

The Subgroup has engaged with a number of companies with the aim of developing a portfolio of phase I studies. This is important given how few therapies are currently available for MDS patients. In particular, high-risk patients who fail the only licensed treatment (azacitidine) have a dismal prognosis and this is a major area of unmet need. To this end, we have continued to run a phase I study of antI-IL3 antibody therapy at six sites in the UK which recruits very well and with the UK Government organisation, CATAPULT, opened a phase I trial of anti-WT1 cytotoxic T-cell therapy in patients who have failed azacitidine.

Finally, the MDS-Bio tissue bank is one of the most successful ventures of this type. With over 7,000 samples and improving linked clinical data, this biomedical resource has already contributed to major breakthroughs in understanding the molecular basis of MDS and the basis of response to some treatments, such as lenalidomide. A significant number of publications in the very top impact factor journals have resulted and the Subgroup is linking all future trial development with this platform. The first successful application of this linked approach is ELASTIC.

C – CML Subgroup Strategy

The aim of the CML Subgroup is to improve treatment outcomes and patient experience for all CML patients. In order to achieve this, our strategy is to develop a clinical trials portfolio, including both academic and commercial studies, which will enable us to offer a clinical trial to the majority of CML patients at all stages of their treatment journey. A second aim is to deliver high quality, internationally recognised translational research in CML through the continued support and management of the SPIRIT2, DESTINY and MATCHPOINT clinical trial CML Biobanks.

Moving forward, our strategy over the next 12 months is to develop in the following areas:

1. Clinical trials: our key strategic aim is to open studies in two areas (1) resistance – TASTER trial submitted to CRUK EMP and (2) de-escalation/discontinuation follow-up study to DESTINY. We also have a clinical study 'CALLS' in development, a commercial study in collaboration with Incyte to assess Next Generation Sequencing for the diagnosis of BCR-ABL mutations. In terms of a front-line study for patients with newly diagnosed chronic phase CML, following the withdrawal of funding for SPIRIT3 and the introduction of generic imatinib, we acknowledge that this is a challenging area for clinical trial development at present, but we plan to re-visit in the future.
2. Presentations/Publications: DESTINY, CHOICES and SPIRIT2 will be presented at ASH in December. DESTINY already has an oral presentation of the first 12-month discontinuation phase at EHA in June. The de-escalation phase of the DESTINY clinical trial has been accepted for publication in Lancet Haematology. CHOICES and SPIRIT2 are currently undergoing data cleaning and statistical analyses, with a view to manuscripts in the next 12 months. In addition, the Subgroup is preparing a BCSH guideline to advise on practical management of CML.

3. Correlative science: The clinical trial biobanks continue to be a rich source for research projects and publications. Over the next 12 months, the Subgroup aims to secure finding to further evaluate samples from the DESTINY clinical trial. Discussions surrounding GeCIP and sample collection for CML continue, but it is acknowledged that this is challenging as only extreme responders will be evaluated; the mechanism for doing this has yet to be defined.
4. Patient partnership: We have a consumer representative on our Subgroup who is a very active contributor to meetings and study design. We are also planning a patient and carer education day later in the year – likely Birmingham in November 2017.

D – AML Subgroup Strategy

The aim of the AML Subgroup is to run large multicentre clinical trials across the UK and with international collaborators. Our objectives to improve outcome by introducing selective, novel and molecularly targeted therapies into the existing backbone of chemotherapy combinations developed in previous trials. Furthermore, we aim to identify molecular signatures of treatment response that will allow appropriate stratification of therapy.

Priority

To analyse treatment response in relationship to mutational profile in a collaboration with the Sanger Institute based upon an analysis of samples from over 2,400 patients entered into our trials. This will help inform the design of the next generation of NCRI AML trials.

Challenge

To design a follow-up trial for patients not fit for intensive therapy to replace the LI1 trials.

E – MPN Subgroup Strategy

The overarching strategy of the MPN Subgroup is to build a strong diverse network of clinicians, nurses, scientists in partnership with patients. Our aims are to:

- Ensure that basic science research in the UK remains cutting edge.
- Develop new scientists and clinician scientists to carry forward today's legacy.
- Ensure that MPN patients (encompassing a broad range of different disease entities) have the opportunity to participate in as diverse a portfolio of clinical trials as possible.
- Support sample banks in MPN and deliver results from them.
- Participate in and provide educational activities for clinicians and patients this includes guidelines as well as face to face educational meetings.
- Ensure there are up to date comprehensive national guidelines for MPN via the BSH process.
- Support NICE appraisal of novel therapeutics in MPN.

Biobanking and translational research

The Subgroup supports cutting-edge translational research through large sample banks of MPN samples and promoting strong links between clinical and scientific research programmes. Over the last few years, members of the Subgroup, utilizing MPN sample banks, have made a number of major international contributions to the understanding of the genetics and biology of MPNs including the description of somatic mutations of JAK2, CALR and EZH2. Going forward, the Subgroup will continue to support patient biobanks, including sample collections linked to clinical trials. There are extensive biobanking protocols built into academic studies run through the Subgroup, including PT1, MAJIC, PHAZAR, TAMARIN, and the forthcoming MITHRIDATE study and translational research studies utilizing these samples are underway. Through strong links with industry, members are also working with sample banks collected in industry studies, e.g.

RESUME study of myelofibrosis (over 200 samples available). We have established a new study focused on familial MPNs (INForMeD study) that is recruiting well in Oxford and will be rolled out to a number of other sites over the next 12 months.

Priority areas for clinical research

The Subgroup oversees clinical trials (phase I, II and II) across a broad range of different disease entities. Our overarching strategy is to ensure that clinical trial options are available for patients with each disease type and at first line and following failure of standard therapy. The key disease areas are:

- MPN epidemiology; we plan to open a large and innovative epidemiological study over the next 12 months (MOSAICC) aiming to better understand factors which predispose to MPN development.
- Polycythaemia vera; here we will be opening a large randomised trial of ruxolitinib versus best available therapy later this year (MITHRIDATE; CI: Claire Harrison).
- Essential thrombocythaemia; here a first line trial is currently lacking and is a priority for the Subgroup.
- Second line trial options are available for PV and ET patients including TAMARIN (actively recruiting) and MOMBAT (in set up; planned to open over the next 12 months) studies. These innovative studies have both resulted from translational research in the UK and are focused on repurposing of established treatments (tamoxifen in TAMARIN and methotrexate in MOMBAT) for therapy of MPN patients.
- Myelofibrosis; these patients with more advanced MPN have a major unmet need and we have a number of commercial trials in the portfolio as first and subsequent lines of therapy. New studies over the next 12 months will include PAC203 (pacritinib second line), a trial assessing the efficacy of luspatercept to treat MF associated anaemia and an early phase study of venetoclax in myelofibrosis.
- Accelerated phase and blast crisis MPN – we anticipate that the PHAZAR study (combining azacitidine with ruxolitinib) will complete recruitment over the next 12 months.

Engagement with Industry

The Subgroup works in close partnership with industry as exemplified by a number of studies with Subgroup members as global CI and a large number of industry studies, complementing academic studies, in the portfolio. Collaborations with industry have also been instrumental in supporting translational research in MPNs through funding of sample collections (MAJIC study). Collaboration with industry has also been essential to help underpin funding of major academic trial initiatives, e.g. MITHRIDATE is funded in part through Novartis.

Engagement with charity-funded research infrastructure initiatives

The Subgroup is closely linked with charity funded clinical research through the Bloodwise TAP network which has been instrumental in the delivery of a number of studies including MAJIC (first TAP study), PHAZAR, TAMARIN and MOMBAT.

Engagement with Genomic England Ltd (GEL)

MPNs are an excellent and tractable disease model to apply next generation sequencing technology and MPN subgroup members are fully engaged with the GEL initiative. Up to now, recruitment has been hampered by GEL requirements for germline control DNA which is not practical in most GMCs. In order to address this, we are working closely with GEL to establish new sample collection pipelines that will allow patients with unclassifiable MPNs to be recruited.

Trial delivery
The Subgroup has an excellent track record of successful delivery of trials and high recruitment into industry studies internationally.

Consumer engagement
The Subgroup has longstanding and ongoing consumer representation. The subgroup works closely with a national MPN charity (MPN voice) and oversees a number of patient/carer meeting nationally each year.

F – CLL Subgroup Strategy

The aim of the CLL Subgroup is to improve the outcome of treatment for patients with CLL including those who are fit for intensive fludarabine-based therapy, the elderly, unfit and those with poor risk CLL such as those with Richter's transformation. The strategy is to develop a streamlined approach with a series of rapidly recruiting phase II trials under the auspices of the Bloodwise Trials Acceleration Programme recruiting patients with relapsed refractory CLL. The results of these phase II trials feed directly into the phase III programme in which previously untreated patients are treated with the novel combinations from the TAP programme.
In addition, the Biobanking of samples from the CLL trials over the last 10 years is supporting a comprehensive portfolio of translation research in numerous centres across the UK which add further value to the portfolio. We are the only collaborative group internationally that is using the assessment of minimal residual disease to define duration of therapy with the novel targeted treatments, such as ibrutinib and venetoclax, with the ultimate aim of curing CLL. There is a comprehensive pharmaco-economics programme associated with the trial portfolio in ensure that the advances made can be translated rapidly into the NHS and other healthcare systems worldwide.

Key aims

1. Complete recruitment in the RIAltO trial (CI: Professor Andrew Pettitt) for patients unfit for fludarabine-based therapy. This trial will recruit over 600 patients and is the only study worldwide to test the front-line application of bendamustine plus a CD20 antibody (ofatumumab) compared to chlorambucil plus ofatumumab approach, which is the standard of care. In addition a cohort of patients in this trial is addressing the question of the addition of a B-cell receptor inhibitor (idelalisib) to chemoimmunotherapy. This question is also unique internationally and should provide a further follow-up in the next 12 months.
2. Complete recruitment into the original FLAIR Trial (CI: Professor Peter Hillmen) that compares a non-chemotherapy approach (ibrutinib plus rituximab) against the standard of care for patients considered fit for fludarabine-based therapy (FCR). The original FLAIR will recruit a total of 754 patients, should complete recruitment early in 2018 and will be the largest trial addressing this question.
3. Roll out the amendment of the FLAIR Trial that adds two additional arms to the trial (ibrutinib monotherapy and ibrutinib plus venetoclax) and increases the total number of patients in FLAIR to approximately 1,576 patients. When the original FLAIR completes recruitment (expected in the first half of 2018) one of the ibrutinib containing arms (ibrutinib plus rituximab or ibrutinib monotherapy) will be dropped and three arms will continue to recruit. This trial is the only phase III trial internationally testing I+V, an oral only regime, in the treatment of CLL.
4. To continue the rapid development of the Bloodwise TAP Trials including reporting the initial responses in the CLARITY trial (CI: Professor Peter Hillmen) of ibrutinib plus venetoclax. We aim to expand cohorts of patients in CLARITY further testing novel

combinations. The CALiBRe trial of idelalisib has re-opened now modified for patients who fail or are intolerant of ibrutinib.

5. We will continue the development of trials for rare variants of CLL which have poor outcomes with standard therapies, such as Richter's transformation. The STELLAR TAP Trial (CI: Professor Anna Schuh) for Richter's transformation testing a novel combination of chemoimmunotherapy plus acalabrutinib, a second generation Btk inhibitor, should open in 2018.
6. The analysis of the whole genome sequencing for over 400 paired germ-line and tumour samples from the ADMIRE, ARCTIC and RIAltO Trials recruited from the UKCLL Biobank via the Genomics England (CI: Professor Anna Schuh) will be performed in the next 12 months. This is a unique opportunity that is expected to revolutionize our understanding of CLL and, as the samples are from our trials, will maximize their impact.
7. Application for funding of the UKCLL Bionank (CI: Professor Andrew Pettitt) to ensure the continued support of this essential component of the Subgroup's activity. An outline application to the MRC has been submitted and we hope to have the opportunity to submit a full proposal.

G – ALL Subgroup Strategy

The ALL Subgroup aims to maintain a comprehensive programme of clinical research and correlative science accessible to all patients with ALL and in doing so provide research training opportunities to generate a pipeline of future Chief Investigators. Delivery of the Subgroup's strategy is based on proactive engagement with local PIs, industry and international collaborative groups. Achievements include excellent accrual into the main frontline trial (UKALL14), which is recruiting ahead of schedule, and excellent collaboration with industry. For example, a UK centre (Royal Free) was the highest recruiter to a recent Amgen study of blinatumomab (BITE). In addition, the Subgroup has maintained its succession of high-profile publications and international presentations.

Challenges include delivering to time and target the frontline trial for older patients (UKALL60+). This has been addressed through the provision of an additional trial coordinator by the UCL CTU. Other challenges include the establishment of referral pathways and logistical/administrative support required for the successful delivery of trials for important but niche populations. In addition, it has proved very difficult to work with international partners. Thus, the interpretation of EU regulations differs widely between countries, and generating a protocol which is acceptable to two different competent authorities with an academic sponsor is at the limit of what can be achieved with the limited funding we have available compared to commercial organisations.

H – Myeloma Subgroup Strategy

Objective

We aim to be an internationally recognized cooperative with truly impacting clinical research that facilitates change in clinical practice within the UK and beyond whilst strategically providing the evidence-base for commissioning and regulatory authority decision-making.

Strategic outline

As part of our collaborative and inclusive ethos, our strategic plan for the Myeloma Subgroup is as follows:

1. The creation of a new brand for the clinical research cooperative that can signify the collaborative and unified approach within the UK and be easily identified internationally.
    - The UK Myeloma Research Alliance
    - Governance under the NCRI CSG (as the Myeloma Subgroup)

2. To “dove-tail” the work of the therapy accelerated trial network (Myeloma UK CTN) with the development of the phase IIb/III/IIIb programme so that innovative clinical interventions can be “road tested” then used as the experimental arms in multicenter RCT designs.
    - MUKnine (high risk protocol) and UK MRA Myeloma XV frontline line phase III high risk arm
3. To develop trials using innovative designs aiming to be leaders in the filed as well as providing key UK-specific healthcare data to assist in regulatory approval.
    - MUKeight and NICE submission for Ixazomib
4. To foster engagement between practicing Haematologists in the UK, supporting their endeavors to participate in clinical research, and to involve them in the public advertisement of our results.
    - UKMRA Clinical trials day
5. To ensure the long-term strategy and continuity of clinical research activity, a robust plan is in place to develop succession planning by involving new personnel to work alongside established researchers.
    - New members have been enlisted to the TMG for both UK MRA Myeloma XIV and Myeloma XV phase III studies
6. As custodians of the biosampling relating clinical interventions studies, it is our ai to maintain a register of how such samples are used, detailing collaborators and funders of such work, ensuring those who contribute samples, have a full understanding of their use and with due credit where appropriate.
    - UKMRA Translational Studies registry
7. We aim to publish in high-ranking journals of clinical impact, representative of the importance of our work. As part of our inclusivity and engagement policies, it is important that those who contribute to the successful completion of studies are awarded due credit in either co-authorship or in acknowledgment.
    - Publication policy under development

I – Supportive Care, Transfusion & Late Effects Working Party Strategy

The Working Party has developed six new trials ideas which is in early development stages:

- IVIG trial: psycho-social impact of watchful waiting strategies in chronic haematological Malignancies by Eila Watson. This is being developed with the POS and Supportive & Palliative Care CSGs. This is for MPN, MDS, CLL and some myeloma patients - MacMillan will be approached for funding in the first instance.
- Rehabilitation strategies post-intensive chemotherapy for acute leukaemia and autologous Hematopoietic stem cell transplantation (HSCT) for myeloma by Annie Young - application to be submitted to RfPB.
- Intravenous immunoglobulin as infection prophylaxis in haemato-oncology and HSCT, led by Simon Stanworth and Harpreet Kaur - BSBMT-CTC to be approached for funding.
- Cardiometabolic risk factors and late effects in survivors of haematological cancer and HSCT following intensive (non-transplant) treatment for acute leukaemia led by Harpreet Kaur – the WP is looking at adding this onto an existing trial in the first instance and MacMillan could also be approached for funding.

- PREeMPT study: Is it feasible to conduct a randomised controlled trial of pre-transplant exercise (prehabilitation) for multiple myeloma patients awaiting autologous stem cell transplantation led by Harpreet Kaur.
- Fertility and pregnancy following intensive (non-transplant) treatment for acute leukaemia by Sara Ali - discussions on trial design have started.

The NCRI have launched the Living With and Beyond Cancer (LWBC) initiative which the WP will be involved with when it comes to an end in summer 2017.

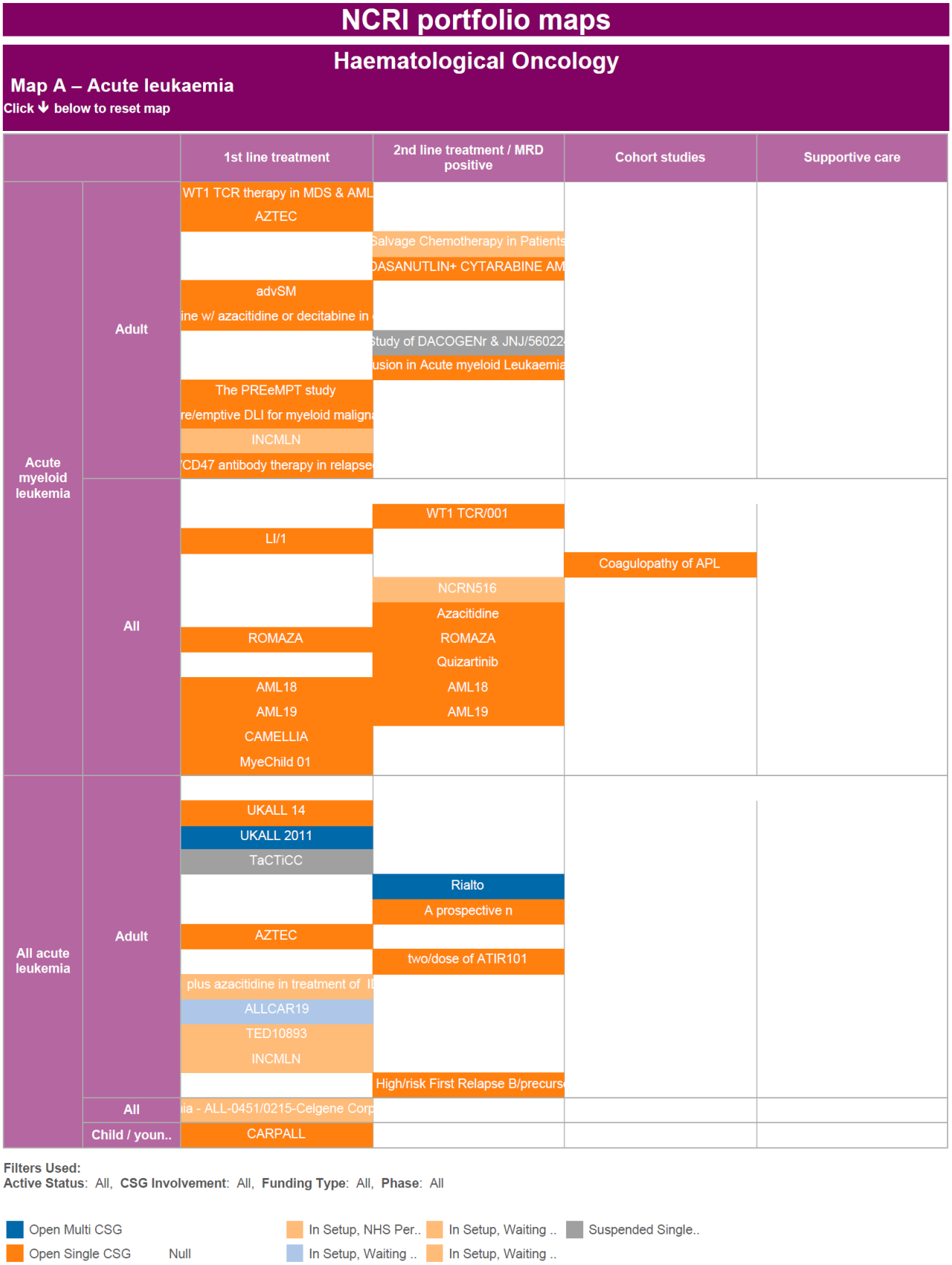
J - Aplastic Anaemia Working Party Strategy

For the next two years, the strategy for the AAWP is:

1. To raise profile of aplastic anaemia (AA) nationally and highlight the risk of transformation of AA to MDS/AML, for not only acquired but also constitutional AA.
2. To promote a continued and more coordinated and efficient approach to the development of and enrolment into future clinical trials nationally and internationally.
3. To ensure that translational research is a prerequisite for all future clinical trials in aplastic anaemia.
4. Engagement of the national aplastic anaemia patient support group with NCRI to promote patient education and patient involvement in all future clinical trials and research.

Appendix 3

Portfolio maps



NCRI portfolio maps

Haematological Oncology

Map B – Chronic leukaemia

Click ↓ below to reset map

		1st line treatment	2nd line treatment / MRD positive	Cohort studies	Supportive care
Chronic lymphocytic leukaemia	All	RIAltO FLAIR AZTEC MONOCLE advSM CLARITY TED10893	PCI/32765 (Ibrutinib) ib in Previously Treated Subjects IOR00208 Combined with Idelalisi DURVALUMAB UTX-TGR-304 apsed or Refractory Chronic Lymp	FCLL Genetic Epidemiology of CLL Investigating D IciCLLe Mathematical mo white cells from patients with CLL Calibre ENABLE/ NGS Cell shape recognition technology TIDaL	
Chronic myeloid leukaemia	All	tinib in Resistant Chronic Phase AZTEC TED10893 Atsral-3	WT1 TCR/001 Matchpoint Ponatinib Vs Nilotini two/dose of ATIR101 toclax in Relapsed/Refractory sub	UK TARGET/CML study	

Filters Used:
Active Status: All, **CSG Involvement**: All, **Funding Type**: All, **Phase**: All

Open Multi CSG
Open Single CSG
In Setup, HRA Ap..
In Setup, Waiting ..
In Setup, Waiting ..
Suspended Single..

NCRI portfolio maps

Haematological Oncology

Map C – Myelodysplastic syndrome, myeloproliferative neoplasms, transplant trials

Click ↓ below to reset map

		1st line treatment	2nd line treatment / mrd positive	Cohort studies	Supportive care
Myelodysplastic syndrome	All	LI/1 AZACITIDINE + BSC ELASTIC	Intermediate-1 Risk	MDSBio	REDDS
		advSM AZACITIDINE			Anemia Due to Risk
		TAMARIN AZACITIDIN +// DURVALUMAB			
		Atsral-3 Venetoclax in MDS			
Myeloproliferative neoplasms	All	RETHINK Givinostat in JAK2V617F positive CMNs	POSTAGE	Clonal BC Disorders Molecular patho	
Transplant trials	All	ProT4 (Prophyla	ProT4 (Prophyla	CMV TCR Gene Therapy (CMV TCR001)	
		UK Haplo v1.0			
		FIGARO ICAT	FIGARO ICAT		GS/5806 in HCT RSVinfection in URT
		WT1 TCR therapy in MDS & AML			
		REVERSE			

Filters Used:
Active Status: All, **CSG Involvement**: All, **Funding Type**: All, **Phase**: All

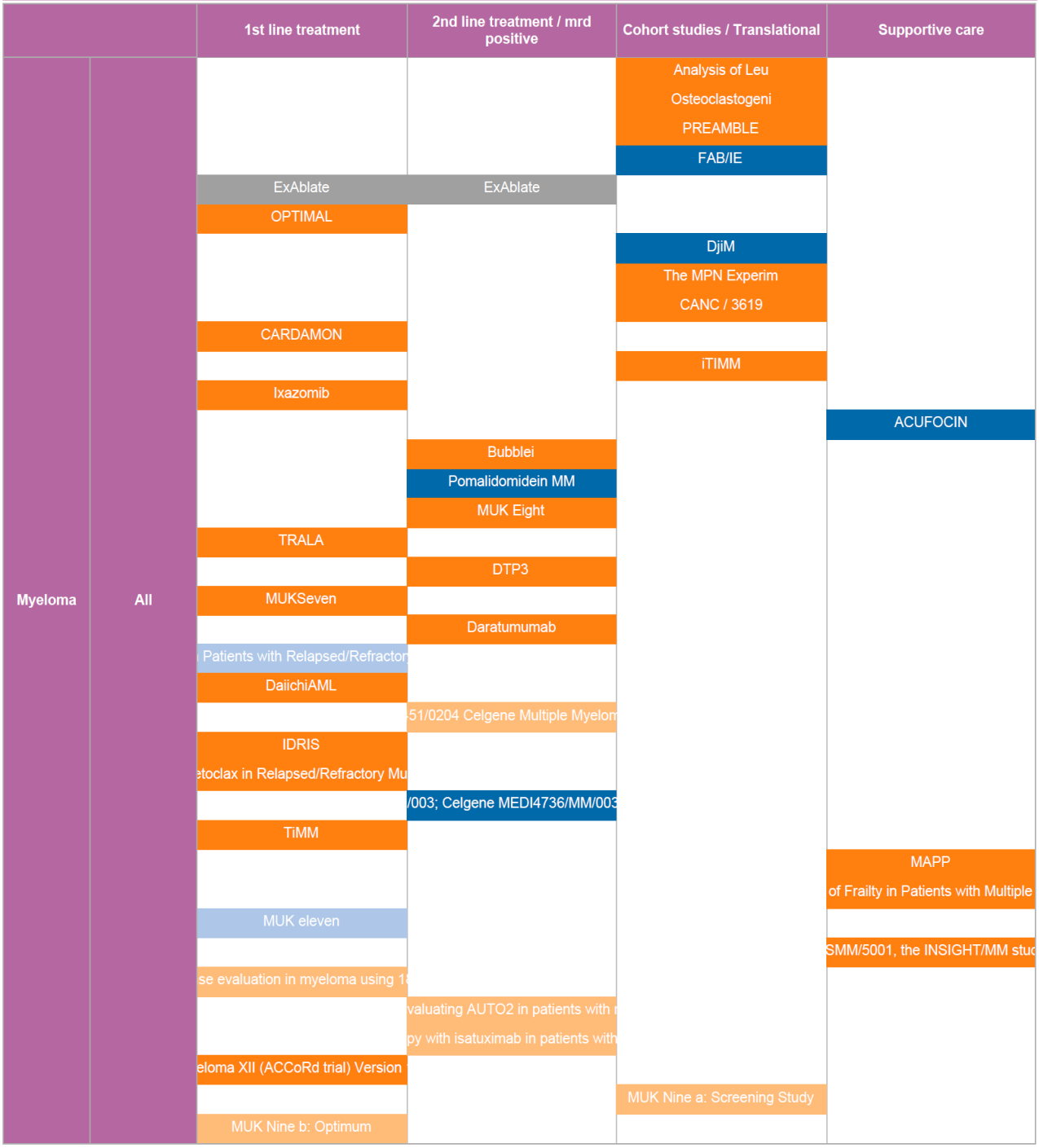
Open Multi CSG Null In Setup, Waiting .. Suspended Single..
Open Single CSG In Setup, NHS Per.. In Setup, Waiting ..

NCRI portfolio maps

Haematological Oncology

Map D – Myeloma

Click ↓ below to reset map



Filters Used:
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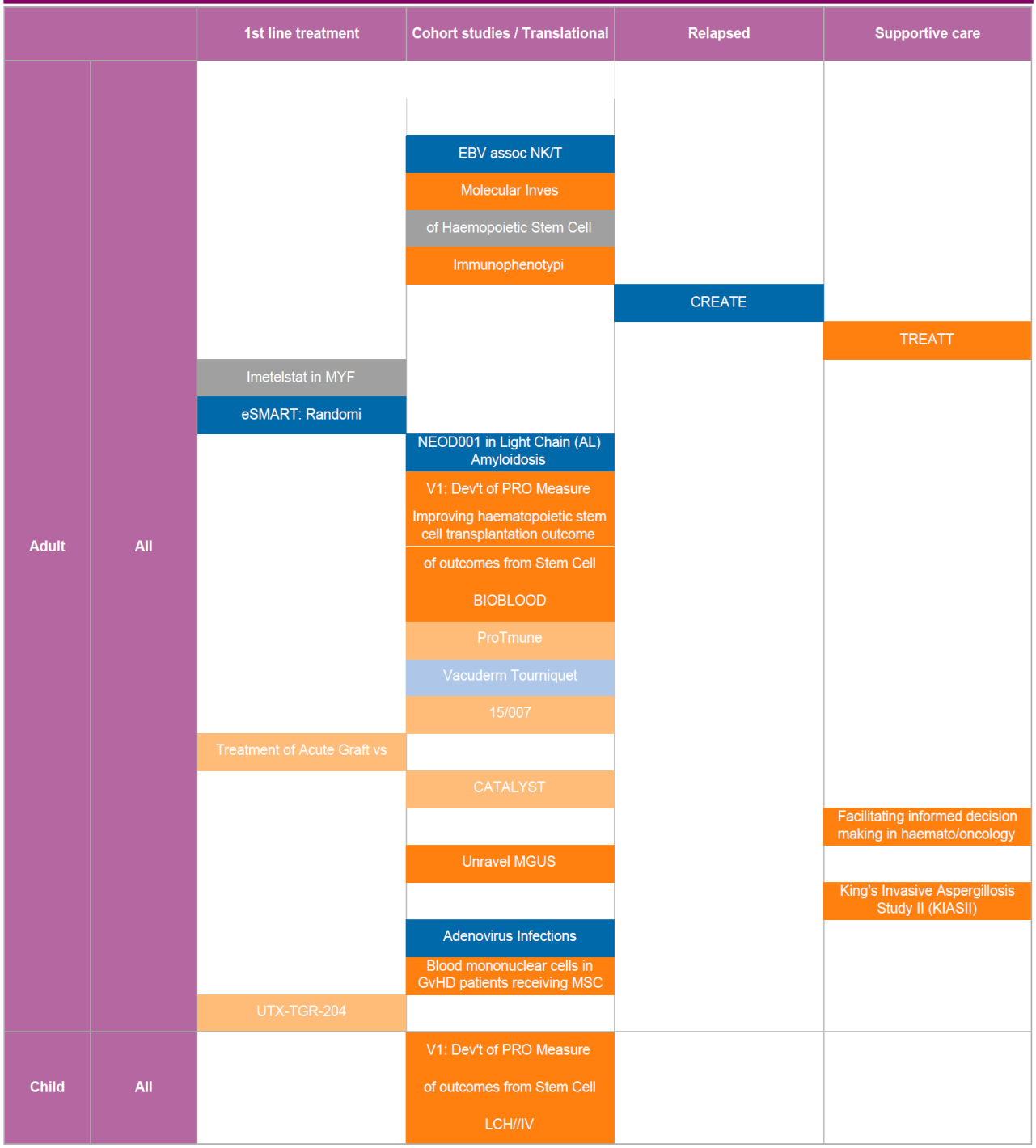
Open Single CSG | In Setup, Waiting .. | In Setup, Waiting .. | Suspended Multi ..

NCRI portfolio maps

Haematological Oncology

Map E – Other studies

Click ↓ below to reset map



Filters Used:
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Open Multi CSG
Open Single CSG
Null
In Setup, Waiting ..
In Setup, Waiting ..
In Setup, Waiting ..
Suspended Single..

Appendix 4

Publications in the reporting year

Study	Reference
AML17	Burnett AK, Russell NH, Hills RK. Higher daunorubicin exposure benefits FLT3 mutated acute myeloid leukemia. Blood. 2016 Jul 21;128(3):449-52.
	Knapper S, Russell N, Gilkes A, Hills RK, Gale RE, Cavenagh JD, Jones G, Kjeldsen L, Grunwald MR, Thomas I, Konig H, Levis MJ, Burnett AK. A randomized assessment of adding the kinase inhibitor lestaurtinib to first-line chemotherapy for FLT3-mutated AML. Blood. 2017 Mar 2;129(9):1143-1154.
	Hills RK, Ivey A, Grimwade D. UK National Cancer Research Institute (NCRI) AML Working Group. Assessment of Minimal Residual Disease in Standard-Risk AML. N Engl J Med. 2016 Aug 11;375(6)
	Khan N, Hills RK, Virgo P, Couzens S, Clark N, Gilkes A, Richardson P, Knapper S, Grimwade D, Russell NH, Burnett AK, Freeman SD.Expression of CD33 is a predictive factor for effect of gemtuzumab ozogamicin at different doses in adult acute myeloid leukaemia. Leukemia. 2016 Nov 15. doi: 10.1038
AML16	Burnett AK, Russell NH, Hills RK, Kell J, Nielsen OJ, Dennis M, Cahalin P, Pocock C, Ali S, Burns S, Freeman S, Milligan D, Clark RE. A comparison of clofarabine with ara-C, each in combination with daunorubicin as induction treatment in older patients with acute myeloid leukaemia. Leukemia. 2017 Feb;31(2):310-317
AML AML 10, 11, 12, 14, 15 and 16	Ferguson P, Hills RK, Grech A, Betteridge S, Kjeldsen L, Dennis M, Vyas P, Goldstone AH, Milligan D, Clark RE, Russell NH, Craddock C; UK NCRI AML Working Group. An operational definition of primary refractory acute myeloid leukemia allowing early identification of patients who may benefit from allogeneic stem cell transplantation. Haematologica. 2016 Nov;101(11):1351-1358
Myeloma XI	J Jones, DA Cairns, W Gregory, C Collett, C Pawlyn, R Sigsworth, A Striha, M Jenner, G Cook, M Kaiser, M Drayson, FE Davies, K Boyd, R Owen, GH Jackson & GJ Morgan. (2016) A low incidence of second primary malignancies is observed in the Myeloma XI trial for newly diagnosed multiple myeloma patients. Blood Cancer Journal (in press).
SPIRIT2 Biobank	Abraham SA, Hopcroft LE, Carrick E, Drotar ME, Dunn K, Williamson AJ, Korfi K, Baquero P, Park LE, Scott MT, Pellicano F, Pierce A, Copland M, Nourse C, Grimmond SM, Vetrie D, Whetton AD, Holyoake TL. 2016. Dual targeting of p53 and c-MYC selectively eliminates leukaemic stem cells. Nature, 534:341-6.

MUK six	R Popat, S Brown, L Flanagan, A Hall, W Gregory, B Kishore, M Streetly, H Oakervee, S Hallam, M Smith K Yong, G Cook & JD Cavenagh, on behalf of the Myeloma UK Early Phase Clinical Trial Network. (2016) Bortezomib, Thalidomide, Dexamethasone plus Panobinostat (VTD-P) for patients with Relapsed Multiple Myeloma: results of the MUK six phase I/II Clinical Trial. Lancet Haematology, Vol. 3, No. 12, e572–e580.
	C Pawlyn, MF Kaiser, C Heuck, CP Wardell, A Murison, S Chavan, DC Johnson, L Melchor, DA Cairns, EM Boyle, JR Jones, D Begum, P Proszek, G Cook, MT Drayson, RG Owen, WM Gregory, GH Jackson, B Barlogie, FE Davies, BA Walker & GJ Morgan. (2016) The spectrum and clinical impact of epigenetic modifier mutations in myeloma. Submitted to Clinical Cancer Research, pii: clincanres.1790.2015.
Myeloma X	G Cook, AJ Ashcroft, DA Cairns, C Williams, A Hockaday, JD Cavenagh, JA Snowden, C Parrish, K Yong, J Cavet, H Hunter, JM Bird, G Pratt, S Chown, E Heartin, S O'Connor, MT Drayson, JM Brown & TCM Morris on behalf of the National Cancer Research Institute Haemato-oncology Clinical Studies Group. (2016) The impact of salvage autologous stem cell transplantation on overall survival in patients with relapsed multiple myeloma: Final results from the BSBMT/UKMF Myeloma X Relapse (Intensive) randomised open-label phase 3 trial. The Lancet Haematology, 3, 7; e340–e351
	Li N, Johnson DC, Weinhold N, Studd JB, Orlando G, Mirabella F, Mitchell JS, Meissner T, Kaiser M, Goldschmidt H, Hemminki K, Morgan GJ, Houlston RS. Multiple myeloma risk variant at 7p15.3 creates an IRF4-binding site and interferes with CDCA7L expression. Nat Commun. 2016 Nov 24;7:13656. Doi 10.1038/ncomms13656.
	Law PJ, Sud A, Mitchell JS, Henrion M, Orlando G, Lenive O, Broderick P, Speedy HE, Johnson DC, Kaiser M, Weinhold N, Cooke R, Sunter NJ, Jackson GH, Summerfield G, Harris RJ, Pettitt AR, Allsup DJ, Carmichael J, Bailey JR, Pratt G, Rahman T, Pepper C, Fegan C, von Strandmann EP, Engert A, Försti A, Chen B, Filho MI, Thomsen H, Hoffmann P, Noethen MM, Eisele L, Jöckel KH, Allan JM, Swerdlow AJ, Goldschmidt H, Catovsky D, Morgan GJ, Hemminki K, Houlston RS. Genome-wide association analysis of chronic lymphocytic leukaemia, Hodgkin lymphoma and multiple myeloma identifies pleiotropic risk loci. Sci Rep. 2017 Jan 23;7:41071. doi: 10.1038/srep41071.
	Mitchell JS, Li N, Weinhold N, Försti A, Ali M, van Duin M, Thorleifsson G, Johnson DC, Chen B, Halvarsson BM, Gudbjartsson DF, Kuiper R, Stephens OW, Bertsch U, Broderick P, Campo C, Einsele H, Gregory WA, Gullberg U, Henrion M, Hillengass J, Hoffmann P, Jackson GH, Johnsson

	E, Jöud M, Kristinsson SY, Lenhoff S, Lenive O, Mellqvist UH, Migliorini G, Nahi H, Nelander S, Nickel J, Nöthen MM, Rafnar T, Ross FM, da Silva Filho MI, Swaminathan B, Thomsen H, Turesson I, Vangsted A, Vogel U, Waage A, Walker BA, Wihlborg AK, Broyl A, Davies FE, Thorsteinsdottir U, Langer C, Hansson M, Kaiser M, Sonneveld P, Stefansson K, Morgan GJ, Goldschmidt H, Hemminki K, Nilsson B, Houlston RS. Genome-wide association study identifies multiple susceptibility loci for multiple myeloma. Nat Commun. 2016 Jul 1;7:12050. doi: 10.1038/ncomms12050.
	Pawlyn C, Bright MD, Buros AF, Stein CK, Walters Z, Aronson LI, Mirabella F, Jones JR, Kaiser MF, Walker BA, Jackson GH, Clarke PA, Bergsagel PL, Workman P, Chesi M, Morgan GJ, Davies FE. Overexpression of EZH2 in multiple myeloma is associated with poor prognosis and dysregulation of cell cycle control. Blood Cancer J. 2017 Mar 31;7(3):e549. doi: 10.1038/bcj.2017.27
	Johnson DC, Weinhold N, Mitchell JS, Chen B, Kaiser M, Begum DB, Hillengass J, Bertsch U, Gregory WA, Cairns D, Jackson GH, Försti A, Nickel J, Hoffmann P, Nöethen MM, Stephens OW, Barlogie B, Davis FE, Hemminki K, Goldschmidt H, Houlston RS, Morgan GJ. Genome-wide association study identifies variation at 6q25.1 associated with survival in multiple myeloma. Nat Commun. 2016 Jan 8;7:10290. doi: 10.1038/ncomms10290.

Appendix 5

Major international presentations in the reporting year

Study	Conference details
AML17	Russell NH, Burnett AK, Hills RK, Betteridge S, Dennis M, Dillon R, Grimwade D on behalf of the NCRI AMLWorking Group. Long Term Follow Up From The NCRI AML17 Trial Of Attenuated Arsenic Trioxide And ATRA Therapy For Newly Diagnosed And Relapsed Acute Promyelocytic Leukaemia - American Society of Haematology (ASH) Annual General Meeting. San Diego, Dec 2016.
	Knapper S, A Grech, P Cahalin, H Kaur, P Mehta, D Richardson, D Taussig, R Hills, A Burnett, N Russell AN EVALUATION OF THE TYROSINE KINASE INHIBITOR PACRITINIB IN PATIENTS WITH RELAPSED FLT3-MUTATED ACUTE MYELOID LEUKAEMIA (THE UK NCRI AML17 STUDY) - European Haematology Association (EHA), Copenhagen, June 2016
	N Russell, R Hills, J Kell, J Cavenagh, L Kjeldsen, MF McMullin, P Cahalin, M Dennis, L Friis, A Grech, D Milligan, R Clark1, A Burnett HIGHER DOSE DAUNORUBICIN APPEARS BENEFICIAL IN PATIENTS HARBOURING A FLT3-ITD MUTATION: UPDATED RESULTS OF THE UK NCRI AML17 TRIAL - European Haematology Association (EHA), Copenhagen, June 2016
UKALL14	Okasha D, et al. Reduced intensity conditioning (RIC) allogeneic hematopoietic stem cell transplantation for adult de novo acute lymphoblastic leukemia: a prospective study from the UKALL14 trial (ISRCTN 66541317) - European Hematology Association Annual Scientific Meeting 2016