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NCRI Haematological Oncology Clinical Studies Group

Annual Report 2014/2015

Partners in cancer research

NCRI Haematological Oncology CSG Annual Report 2014/15

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

The Haematological Oncology CSG is one of the largest and most complex CSGs, with 7 disease-specific subgroups and an overall trial portfolio approaching 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 co-ordinating and driving forward research in areas that transcend individual disease areas such as supportive care/late effects, stem-cell transplantation and TYA.

It is evident from the metrics provided by the NCRI Secretariat that the CSG has built on its performance in previous years in terms of trial development and delivery, with a high level of success in obtaining funding for new studies, coupled with strong recruitment into existing ones. Links with other relevant parties including other CSGs, industry partners, international collaborative groups and LCRN Subspecialty Leads have been further strengthened, and the CSG has continued to engage with local clinical research teams and national patient groups via the Annual Haem Onc Trials Review Meeting and disease-specific educational events. The CSG has also had a major impact on clinical practice through the delivery of several pivotal studies and through the contribution of CSG/Subgroup members to numerous NICE appraisals.

The following achievements are illustrative of the CSG's success during the reporting period:

- Recruitment has continued to increase year on year, with record figures for 2014/2015. This is true of all participants (n=6452) and cancer patients (n=6292), and of interventional (n=3320) and non-interventional (n=3132) studies. This achievement reflects the CSG's focus on the development of large phase 3 trials for all major patient groups and the successful delivery of these trials, e.g. AML17 which recruited ~3,500 patients.
- 12/13 funding applications for clinical or translational studies were approved at outline or final stage, including 3/3 CTAAC submissions. Of particular note is the designation of CLL as one of only 3 pilots for the Genomics England Ltd 100,000 Genomes Project with the allocation of £3.5M to perform whole genome sequencing on samples stored in the UK CLL Trials Biobank.
- The CSG's portfolio of clinical and translational studies has continued to generate a steady stream of high-profile conference presentations and high-impact research outputs including publications in NEJM, Lancet, Lancet Oncology, Blood and Leukemia.

The CSG's most significant challenge remains the delivery of industry and academic studies to time and target, especially in niche areas where there are competing studies that were developed without CSG consultation.

2. Structure of the Group

The CSG comprises 7 Subgroups focussing on specific disease areas (AML, ALL, CML, CLL, myeloma, MPN, MDS) with very little overlap in core membership (see Appendix 1). In addition, 3 cross-cutting focus areas have been identified (supportive care/late effects, stem-cell transplantation and TYA), with designated leads in place for first 2 of these areas; it is hoped that CSG membership rotation will allow the appointment of a lead for TYA.

In terms of membership, the CSG comprises 14 clinicians, 2 statisticians, a senior trial co-ordinator, 2 consumer members, 2 NCRI Training Fellows and a representative from LLR – the latter providing a crucial link through to the LLR Trials Acceleration Programme (TAP). The CSG has representation from most parts of the UK including 2 of the 3 devolved nations. The most significant change in CSG composition has been the replacement of the Myeloma Subgroup Chair in July 2014.

3. CSG & Subgroup strategies

Main CSG

The CSG'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 the need for innovative trial design, coupled with high-quality biobanking as a platform for biomarker discovery/development.

Operationally, 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 (including those funded by LLR and Myeloma UK) to inform on the next generation of phase 3 studies. In addition, the CSG aims to expand research in supportive care and late effects as important cross-cutting themes. This will be achieved through the establishment of a Working Party. The CSG also aims to apply a more co-ordinated approach to transplant studies by working more closely with the BSBMT. Finally, the CSG aims to establish closer collaborative links with the CCL and TYA CSGs to ensure an optimally co-ordinated approach for all TYA patients with leukaemia.

Acute Lymphoblastic Leukaemia (ALL) Subgroup (Chair, Dr Adele Fielding)

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. For example, two members of the Subgroup (Dr Fielding and Professor Marks) are educational speakers at ASCO 2015, Professor Moorman is an educational speaker at EHA 2015, and Dr Fielding is a speaker in EHA Haematology in Focus 2015.

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.

Acute Myeloid Leukaemia (AML) Subgroup (Chair, Professor Nigel Russell)

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. The AML17 trial closed in Dec 2014 after recruiting over 3500 patients in over 100 centres and will be replaced by AML19, which opens in Q2 2015. AML18 for older fit patients opened in November 2014 and is recruiting well. This is the first study to use MRD assessment to direct therapy in older patients with AML. The Subgroup continues to publish results in high-impact journals, with outcomes from the daunorubicin dose question being published in Blood. Furthermore, our experience of arsenic trioxide in APL is being used by TEVA for license extension for frontline therapy. We are at the forefront of the application of sensitive standardised PCR assays to predict outcome and guide molecularly targeted therapy as part of the molecular monitoring in AML17, and this will continue into AML19.

Chronic Lymphocytic Leukaemia (CLL) Subgroup (Chair, Professor Peter Hillmen)

The CLL Subgroup has reported on the two randomized Phase II trials for fit patients requiring therapy (ADMIRE and ARCTIC) and has had accepted the HTA monograph reporting the results of the ARCTIC Trial. We are now in the process of preparing several manuscripts from these studies. The next phase III trial for this group of patients, the FLAIR Study, opened in September and is ahead of its recruitment target with more than 100 patients randomized and over 50 Centres open to recruitment. The most recent phase III trial for elderly patients, Complement 1, has been successful published in the Lancet in 2015. The follow-on trial, the RIAltO trial, has been modified to include one of the novel small targeted therapies, idelalisib, and continues to recruit. In addition we have opened a third phase III trial, the GALACTIC Study, which looks at the consolidation of remissions in order to deepen remissions and improve time to progression. The CLL group has also successfully supported a series of early phase trials within the LLR Trials Acceleration Programme, namely IcICLLe, CALiBRe and CyCLLe, which are being used to understand the mechanisms of action of novel agents, to study combination of agents biologically and to inform the design of future phase III trials. In addition, the UK CLL Biobank

continues to successfully recruit patients and the stored material is being used for a large number of translational research studies including the whole genome sequencing of 1000 CLL genomes from our trials. The strategy for the Subgroup is to streamline the phase II trials, translational research of the group and our 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.

Chronic Myeloid Leukaemia (CML) Subgroup (Chair, Professor Mhairi Copland)

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 (and SPIRIT3) CML Biobanks.

Our key achievements in the last year have been the completion of recruitment to DESTINY, offering optimally patients the opportunity to reduce and stop therapy and the opening of MATCHPOINT for patients with blast phase CML. The CHOICES trial has also completed recruitment and is in follow-up. In addition, there have been high profile presentations of the one year and two year SPIRIT2 data at ASH and BSH, respectively. The SPIRIT2 Biobank has been very successful in enabling translational research, resulting in a number of publications in high impact journals. Our subgroup is committed to physician training and patient education; we have recently welcomed a trainee member and we continue to organise an annual Patient Meeting which is increasingly utilising social media and internet streaming to widen our audience and increase participation.

Our main challenges are opening SPIRIT3, planned for late 2015, and developing an effective CML GeCIP sub-domain within the Haemato-oncology domain.

Myelodysplastic Syndrome (MDS) Subgroup (Chair, Dr Dominic Culligan)

The strategy of the MDS Subgroup is to develop a portfolio of phase 1, 2 and 3 studies that cover low and high-risk MDS and supportive care questions across all groups. There are a number of challenges in developing trials for MDS patients that are more acute than for other malignant blood diseases. First, patients are very elderly with a median age of about 73yrs. Second, there are very few drugs that currently work in MDS. Furthermore, a very small number of pharma companies have a relative monopoly of drugs for MDS, and trial development in this environment is frequently driven by commercial strategy. Finally, most drugs in development in haematological cancer are anti-proliferative. Such drugs have little role in low-risk MDS, and treatments to improve bone marrow failure, particularly anaemia, are needed.

During the last 12 months the MDS Subgroup has opened the phase 2 ELASTIC study of azacitidine and eltrombopag in high risk MDS and a joint study (REDDS) with the National Blood Authority. The Subgroup has received funding from LLR for a phase 2 study in CMML with the drug Terfinostat. Our lead phase 3 approach is to develop a randomised, phase 3, placebo controlled trial of antibiotic prophylaxis. The trial (RAPRIMA) was declined for funding by HTA as it did not fit into their current portfolio. However, a submission for funding will be made to LLR in July 2015.

The Subgroup has engaged with a number of companies with the aim of developing a portfolio of phase 1 studies. To this end we have opened a phase 1 study of antI-IL3 antibody therapy and are working with the UK Government organisation (CATAPULT) to open a phase 1 trial of anti-WT1 cytotoxic T-cell therapy.

Myeloproliferative Neoplasms (MPN) Subgroup (Chair, Prof Claire Harrison)

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 and recruiting well. This, in turn, has attracted multiple pharma companies to include the UK in their studies of novel agents and, in some cases, to provide novel agents for investigator-led studies. The Subgroup's portfolio 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 academic studies, the MOSAICC pilot has finished recruiting, MAJIC completed recruitment for ET and is recruiting strongly for PV, MPD RC112 is starting to recruit well, and MPD RC114 and Phazar should be opening shortly. 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.

The Subgroup continues to generate translational research of the highest calibre. In particular, the flagship "Causes of Clonal Haemopoiesis" project has led to the discovery of a prevalent mutation in the calreticulin gene (NEJM 2013) and more recently the clinical importance of the sequence in which multiple mutations are acquired in MPNs (NEJM 2015) and the identification of factors that predispose to MPNs.

The Subgroup's partnership with patient representation and charities is strong. For the second year running, two national education events for clinicians and patients, respectively, were held in November; these back-to-back meetings are now firmly established as an important annual event in the haemato-oncology calendar. In addition, the Subgroup has supported 5 regional patient advocacy meetings throughout the UK during the reporting period.

We are developing a phase 1b study with tamoxifen to submit to TAP and a transfusion pilot for next year. In addition we have developed a strategy for strong translational science from the MAJIC study which will hopefully run into the Phazar trial. We are seeking funding to pursue the MOSAICC study following completion of the pilot.

Challenges include completing negotiations with Novartis regarding a frontline PV study. These negotiations have been ongoing for 3 years; the most recent development has been a request for another proposal revision. Other challenges include completing BCSH guidelines on eosinophilia and mastocytosis.

Myeloma Subgroup (Chair, Professor Gordon Cook)

The Myeloma Subgroup continues to oversee a large and complex trial portfolio, ranging from phase II-III clinical intervention studies and incorporating governance of an accelerated therapy Clinical Trials Network (Myeloma UK CTN) focusing on phase I-IIb trials. This comprehensive portfolio incorporates both academic and commercial studies, contributing significantly to the overall accrual and output of the Haemato-Oncology CSG. To date, the completion and publication of our outputs have significantly contributed to the clinical practice both in the UK and internationally. Following from the publication of the first manuscript from the successful

phase III Myeloma X trial, the results have now been incorporated into the International Myeloma Working Group Guidelines on relapsed disease management. The current front-line phase III study, Myeloma XI/XI+ is nearing recruitment target, so planning is underway for a replacement frontline phase III strategy: Myeloma XIV (CI: Professors Jackson & Cook) and XV (CI Prof K Yong). Our frontline supportive care study, TEAMM, continues to recruit ahead of schedule and our phase II allogeneic stem cell transplantation, the LenaRIC trial, has now successfully completed recruitment. The Myeloma UK CTN continues to expand its trial portfolio, with 3 studies completed, 2 studies actively recruiting and 4 in the planning stage. The portfolio continues to be attractive to commercial collaborators. The Subgroup's priorities over the next year will be to strategize our future plans for trial development in all stages of disease whilst maintaining the current balance between commercial and academic studies, delivering studies to time and target and continue to develop translational aspects of the portfolio. We will endeavour to be utterly inclusive in our working as we aim to be internationally competitive in a very high standard academic space.

4. Task groups/Working parties

Supportive care and late effects

A formal proposal for an NCRI Working Party (WP) to develop a portfolio of supportive care and late effects studies primarily related to haemato-oncology was submitted to the NCRI Secretariat in March 2015 by the CSG's designated lead in this area (Professor Snowden). It is envisaged that the WP will be a collaboration with the Supportive & Palliative Care CSG. Over a 2-year period, the WP will aim to assess the feasibility of a Subgroup to cover studies of blood transfusion, late effects and survivorship, bone oncology, palliative care and psychosocial aspects. The Working Party will facilitate the development of a structured trials portfolio, joint "ownership" of cross-cutting themes by the relevant subgroups, allocation of primary responsibility for shared studies within the CSGs, and the exploitation of synergies with other groups.

The WP Chair will have dual membership of the Haem Onc CSG and the Supportive and Palliative Care CSG, and the WP would include nominated representatives from the all disease-specific Subgroup within the Haem Onc CSG, as well as from the Lymphoma CSG. Psychosocial Oncology and Survivorship CSG, TYA CSG and consumer representatives will also be invited. Given the importance of Transfusion Medicine in the supportive care of haematological cancers, 2 representatives from the NIHR Haematology CSG (transfusion interest – 1 NHSBT, 1 non-NHSBT) will be invited. Over the two year period, two in-person meetings and 6 teleconferences are expected.

The current portfolio includes a number of fully recruited and open studies covering late effects (TRYMS: Testosterone Replacement in Young Male cancer Survivors), palliative medicine (factors associated with place of care and place of death); bone oncology (FAB-IE: Functional Assessment of Bone Metastases-Integrin Expression), transfusion studies (TOPPS: Trial of prophylactic vs. no-prophylactic transfusions; INCITE: Intracranial haemorrhage in Thrombocytopenic haematology patients; TREATT: TRial to EvaluAte Tranexamic acid therapy in Thrombocytopenia; HLA Epitope trial to compare the effect of HLA epitope-matched with standard HLA matched platelet transfusions in alloimmunised thrombocytopenic patients with aplastic anaemia, MDS or AML;

RING: Resolving Infection in Neutropenia with Granulocytes; and red blood cell transfusion thresholds and QoL in MDS and MPN: REDDS and REDEEM).

Haemopoietic stem-cell transplantation

This is an important and organisationally extremely complex component of the CSG portfolio. A Clinical Lead (Dr Peggs) has been appointed to achieve a better understanding of challenges and opportunities for existing and future studies.

In fact, a number of transplant trials have been successfully completed during the reporting period and preliminary results reported at major international meetings. These include:

- CMV-IMPACT - A phase III randomised study to investigate the use of adoptive cellular therapy for CMV in sibling donor transplant - preliminary results presented at ASH 2014 and Tandem BMT 2015.
- CMV-ASPECT - A phase II randomised study to investigate the use of adoptive cellular therapy for CMV in unrelated donor transplants - preliminary results presented at Tandem BMT 2014; final analyses complete; manuscript in preparation.

LenaRIC (post-allograft lenalidomide maintenance in AML) has also reached target recruitment and, along with RIC UCBT (umbilical cord blood transplant), remains in the early follow-up phase.

A new industry study (MK8228: A phase III randomized blinded placebo-controlled study to evaluate the safety and efficacy of letermovir for the prevention of clinically significant human CMV in adult CMV-seropositive allogeneic HSCT recipients) is recruiting well, and the UK has recruited ahead of schedule to another industry study investigating vaccination to varicella (NCRN261: Herpes Zoster in haematopoietic stem cell transplant (HCT) recipients).

Significant challenges remain in terms of successful delivery to time and target, including the level of engagement of the transplant community, and a failure of other disease-specific subgroups to recognise the impact of new studies on recruitment to cross-cutting transplant trials. Half of the British Society of Blood and Marrow Transplantation (BSBMT) annual Scientific Day this year was devoted to clinical trials, highlighting those that are struggling to recruit, discussing new studies under development, and raising awareness of the overall portfolio. This session was well received, with the plan to make it a permanent fixture of the programme. It was agreed that all new trials would be brought to both the BSBMT CTC and NCRI CSG, and that the Chair of the BSBMT CTC would apply for membership of the CSG in order to increase awareness across both groups and develop better integration. It was also agreed that any trials with elements relating to transplant that were being developed within the disease-specific subgroups would be discussed with the transplant lead.

5. Patient recruitment summary for last 5 years

In the Haem Onc CSG portfolio, 30 trials closed to recruitment and 32 opened.

Several conclusions can be drawn from the figures in tables 1 and 2. First, recruitment relative to incidence in 2014/2015 was extremely high. This applies to both interventional (25.2%) and non-interventional (22.5%) studies. Second, despite our perception in last year's annual Report that annual accrual had probably reached a plateau, recruitment in absolute terms has actually continued to increase year on year. This increase applies to all participants and cancer patients,

and is seen in both interventional and non-interventional studies. The Table below has been calculated from the figures provided and shows the overall number of participants and cancer patients recruited into Haem-Onc trials over the last 5 years:

Year	All participants	Cancer patients
2010/2011	4525	4363
2011/2012	5667	5564
2012/2013	5817	5671
2013/2014	5952	5845
2014/2015	6452	6292

The increase in recruitment over this 5-year period is 42.6% for all participants and 44.2% for cancer patients. This notable achievement is a reflection of the CSG's strategy of ensuring that large phase 3 trials are in place for all major patient groups, minimising delays between successive trials and being proactive in identifying and removing any barriers to recruitment.

Table 1 Summary of patient recruitment by RCT/Non-RCT

Year	All subjects		Cancer patients only		% of cancer patients relative to incidence	
	Non-RCT	RCT	Non-RCT	RCT	Non-RCT	RCT
2010/2011	2024	2501	1862	2501	17.5	23.5
2011/2012	2910	2757	2807	2757	26.4	25.9

Table 2 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

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

Network Subspecialty Leads

A joint workshop was held on 9 March 2015 involving CSGs and Subspecialty Leads in selected areas including Haem Onc. The following proposals were made:

- CSG meeting papers and minutes should be circulated to the 15 Subspecialty Leads
- 2-3 LCRN representatives should be invited to CSG meetings on a rotational basis
- A joint meeting should be held every year to discuss delivery of the CSG portfolio

Several CSG members have major LCRN leadership roles.

NCRI Lymphoma CSG

CLL and ALL can present as either leukaemia or lymphoma, and it has been agreed with the Lymphoma CSG that there should be a single approach to these diseases. In addition, the two CSGs share ownership of Waldenstrom's macroglobulinaemia and lymphoma transplant trials. Links between the two CSGs are currently maintained by a jointly appointed member. The BSBMT Clinical Trials Committee secretary is also on the Lymphoma CSG, further helping to foster further links around transplant studies.

NCRI Children's Cancer and Leukaemia CSG

Since TYA patients with ALL fare better with paediatric regimens, it has been agreed that patients up to 24 years of age should enter the paediatric trial (UKALL2011) rather than the adult one (UKALL14).

NCRI Palliative and Supportive Care CSG

Red-cell transfusion studies have been developed jointly with the MDS (REDDS) and MPN (REDEEM) Subgroup.

NCRI CTRad

A trial for high-risk solitary plasmacytoma (IDRIS) has been developed in collaboration with CTRad.

British Society for Bone Marrow Transplantation

Several CSG and Subgroup members are also members of the BSBMT Exec Committee. This link is crucial for the planning and successful delivery of transplant studies in all disease areas.

National patient groups

The ALL, CLL, CML, MPN, MDS and myeloma Subgroups all have strong links with their respective national patient groups. These links have produced a major positive impact on trial development and delivery.

International collaborative groups

The ALL Subgroup has links with the Danish, Irish and Dutch/Belgian HOVON groups, all of which are recruiting into UKALL60+, while Australia and New Zealand have expressed an interest in joining UKALL14. The CLL Subgroup has links with the German CLL Study Group through reciprocal membership of DMCs. The MPN Subgroup has strong collaborative links with Australia, New Zealand, France and the Mayo Clinic via the PT1 trial and is currently developing a new study for PV with the French and Nordic groups.

European LeukemiaNET

CSG and Subgroup members are active contributors to the European Working Group on ALL (EWALL), the European Research Initiative in CLL (ERIC) and the working group for CML.

7. Funding applications in last year

Table 3 Funding submissions in the reporting year

Clinical Trials Advisory and Awards Committee (CTAAC)			
Study	**Application type**	**CI**	**Outcome**
July 2014			
None			
November 2014			
IDRIS: Phase III randomised trial of immunomodulatory therapy in high risk solitary bone plasmacytoma	Full Application	Dr Shirley D'Sa	Funded
A phase III study to determine the role of augmented conditioning therapy in second autologous stem cell transplant (ASCT) as consolidation therapy in patients with relapsed multiple myeloma following prior ASCT	Outline Application	Professor Gordon Cook	Full application invited
March 2015			
A phase III study to determine the role of augmented conditioning therapy in second autologous stem cell transplant (ASCT) as consolidation therapy in patients with relapsed multiple myeloma following prior ASCT	Full Application	Professor Gordon Cook	Funded
Other committees			
Study	**Committee & application type**	**CI**	**Outcome**
IcICLLe amendment (CLL)	LLR CTC, Full Application	Professor Peter Hillmen	Funded
CLARITY (CLL)	LLR CTC, Full Application	Professor Peter Hillmen	Funded
BUBBLE (myeloma)	LLR CTC, Full Application	K Yong	Funded
VIRel/MUKeleven (myeloma)	Celgene	Professor Gordon Cook	Funded
MASCOT (myeloma)	Celgene	K Yong	Funded
GEL CLL Pilot - £3.5M for WGS of trial samples	Genomics England Ltd	A Schuh P Hillmen A Pettitt	Funded
RAPRIMA (MDS)	NIHR HTA, Full Application	Dr Dominic Culligan	Not funded
MONOCLE: A phase 2 study of the MONOcyte-targeted histone deacetylase inhibitor tefinostat (CHR-2845) in Chronic myelomonocytic Leukaemia	LLR, Full Application	S Knapper	Funded
Personalising therapy for adults with acute lymphoblastic leukaemia (ALL)	CR-UK Science Committee (outline)	Dr Adele Fielding A Moorman	Full application invited
Phase 1 study of oncolytic measles virus in relapsed ALL	MRC developmental pathway	Dr Adele Fielding	Scored above funding threshold

8. Collaborative partnership studies with industry

The CSG enjoys strong links with industry in terms of the large number of industry-led studies on the portfolio and industry support for academic studies, examples of which are given below.

ALL - Roche, GSK and Sigma Tau are providing drugs for UKALL14. Sigma Tau also provides some funding for correlative science and collaborative support for assays. In addition, trials involving blinatumomab are underpinned by a strong collaborative partnership with Amgen.

AML - The LI1 trial is currently evaluating 4 new targeted therapies in a Pick-A-Winner study, with 2 new agents in the pipeline, all of which are provided by industry collaborators. In addition, the AML18 and AML19 trials involve collaborations with multiple Pharma companies.

CLL - The CLL Subgroup has a strong relationship with numerous industry partners including Pharmacyclics, Janssen, Roche, Genetech, Gilead, Abbvie, Acerta Pharma and GlaxoSmithKline, with recruitment into global industry-sponsored trials that was second only to the USA. The group also benefits from industry support for a number of academic Phase II and III studies.

CML - Collaboration with Ariad was pivotal to the development of SPIRIT3 and MATCHPOINT. In addition, Ariad is providing free ponatinib for both trials together with significant funding for SPIRT3. Bristol-Myers Squibb continues to provide free dasatinib for SPIRIT2.

MDS - The MDS Subgroup has strong collaborative links with Celgene, Novartis and GSK which underpin trials of azacitidine-based combinations and iron chelation studies. The group has also contributed in a major way to the Celgene AZA003 and AZA005 and Novartis TELESTO studies and is involved in a phase 1 study of a novel anti-IL3R alpha antibody developed by ProStrakan.

MPN - Novartis are supporting MAJIC - the first academic study to investigate ruxolitinib and the only ongoing study of ruxolitinib in ET. This support extends to biobanking and investigation of the biological basis for resistance to hydroxycarbamide and responses to ruxolitinib.

Myeloma - Collaboration with industry partners is crucial for a number of studies overseen by the Myeloma Subgroup. These include a phase I study investigating a novel HDAC inhibitor with an aminopeptidase inhibitor (MUKthree), a phase IIb study comparing two proteasome inhibitors (MUKfive: Carfil/Cyclo/Dex vs Bort/Cyco/Dex) and a proof-of-principle study of a proteaosome inhibitor, IMiD and HDAC inhibitor (MUKsix: VTD-Panobinostat).

9. Impact of CSG activities

ALL - UKALL12 was the biggest ever trial in adult ALL and resulted in a change in practice in many areas of ALL therapy, most notably routine monitoring of MRD, deployment of stem-cell transplantation, international cytogenetic risk classification and the use of imatinib in Ph+ ALL. In addition, the international BITE trial in which the UK group played a leading role resulted in the recent FDA approval of blinatumomab for relapsed ALL.

AML - National trials have effectively become the standard of care for AML in the UK, with approximately 70% of all patients receiving their treatment as part of a trial. As a consequence of the results achieved with Mylotarg in AML15 and AML16, this drug is now commissioned as part of AML18 and AML19 despite as yet being unlicensed. Likewise, the results of AML17 has

established DA (60mg/m2) as the standard dose schedule for this regimen. The results of frontline APL treatment with arsenic trioxide are in the process of transforming initial therapy for APL.

CLL - The frontline COMPLEMENT-1 trial has led to CDF approval and NICE appraisal of chlorambucil plus ofatumumab in older, less fit patients. In addition, NIHR-adopted industry trials (Resonate and Gilead 0116) have led to the EMA approval of ibrutinib and idelalisib for relapsed refractory CLL; both drugs are available via the CDF and under consideration by NICE.

CML - The SPIRIT trial of CML demonstrated that using interferon in newly diagnosed patients in the UK wasn't feasible due to lack of tolerability, whereas SPIRIT2 has enabled patients to obtain access to dasatinib as first line treatment.

MDS - The MDS Subgroup has completed and published two trials, LEN-5 and CMML201. The results both cast doubt on the perceived benefit, from previous smaller trials and retrospective studies, of expensive therapies: Azacitidine in CMML and Lenalidomide in high risk MDS with del(5q) as a single agent or in combination with chemotherapy. As such both studies have informed NHS practice accordingly.

MPN - The PT1 trial has saved the NHS ~£20M pa in drug acquisition costs by showing that anagrelide does not offer any advantages over hydroxycarbamide in the frontline setting.

Myeloma - Myeloma VII had worldwide impact, and clearly established high dose melphalan supported by autologous stem cell transplant (ASCT) following chemotherapy as superior to previous treatment, in younger patients. This determined the treatment policies. Subsequently, Myeloma IX, the largest RCT ever in myeloma, demonstrated that zoledronic acid, in addition to reducing skeletal damage, showed an overall survival benefit and changed practice worldwide. The recently published results from Myeloma X have now been incorporated into the International Myeloma Working Group Guidelines on relapsed transplantation.

Horizon scanning. Although not formally consulted by the Technology Strategy Board (TSB), the CSG has provided valuable perspective to the LLR regarding the TSB's Cell Therapy Catapult initiative.

NICE appraisals

CSG/Subgroup members have contributed to over 20 NICE appraisals in the last year and provided comment on 6 CRUK funding applications.

10. Consumer involvement

The two consumer members of the Haematological Oncology CSG continued to play an active and valuable role in the CSG including membership of three subgroups – Myeloma, ALL and CLL – and three Trial Management/Steering Groups. Consumer input and comments were made to 6 CTAAC applications during the year + 3 Patient Information Leaflets.

Good progress has been made in identifying, recruiting, training and inducting two new consumer representatives for the AML subgroup. As a result, all 7 subgroups now have trained, motivated and active consumer representatives, better able to provide more consistent involvement in all aspects of clinical trials.

One consumer continues to be a member of the NICE Myeloma Guideline Development Group, the main board of INVOLVE and is involved in local PPI representation: and the other has been appointed as a member of the new NICE Blood Cancer Service Guidance Guidelines Committee.

Working with Blood Cancer charities and Patient Support Groups and harnessing social media is proving to be an effective way of engaging more patients in clinical trials and supporting the development of new trials and treatments. It is encouraging that, as one of the consumer members, rotates off the CSG there is a strong field of applicants for the position.

11. Open meetings/annual trials days/strategy days

The Annual NCRI Haematological Oncology Trials Review Meeting took place on 1 July 2014 in Central London (Imperial College). As in previous years, the meeting was arranged jointly with the Leukaemia Subgroup of the CCL CSG, with parallel sessions in 2 lecture theatres. There were 261 attendees comprising 146 delegates for the Adult part of the meeting, 84 for the Paediatric part, 11 on-day sign-ins and 20 Pharma delegates. Feedback forms were received from 62 attendees at the Adult part of the meeting. The table below shows the results to the question: "How useful did you find this event?"

Extremely Useful (n)	Useful (n)	Fairly Useful (n)	Not Useful (n)	Total (n)		Extremely Useful (%)	Useful (%)	Fairly Useful (%)	Not Useful (%)	Total (%)
30	27	5	0	62		48.4	43.5	8.1	0.0	100.0

Compared to previous meetings which have historically been held at the Royal College of Physicians, there were more negative comments regarding the programme, organisation and catering. Most comments related to the acoustics within the lecture theatres, rushed presentations and the location/facilities of the venue. Since very few delegates attend both Adult and Paediatric meetings, and since the requirement for 2 lecture theatres severely limits the choice of venue, it was agreed that the adult and paediatric meetings will be held separately in subsequent years, with the paediatric section of the meeting being included in the 2015 CCL CSG Trials Meeting programme.

12. Progress towards achieving the CSG's 3 year strategy

Listed below are the key issues raised at the last triennial review in 2012, together with a summary of how the CSG has been addressing these issues:

- **The portfolio would benefit from a more focussed and strategic approach in view of funding constraints.** The CSG has enjoyed a period of sustained success in obtaining funding for its studies over the last 3 years. Nevertheless, it is recognised that to maximise the impact of the CSG's endeavours at international level, portfolio development should, wherever possible, be shaped around strengths and opportunities that are unique to the UK.
- **Academic studies should not be compromised by industry studies.** The CSG has worked hard with industry partners to ensure the success of both industry and academic studies. However, this process requires pharmaceutical companies to engage with the CSG.
- **More can be done in MPN and MDS.** Both subgroups have greatly expanded their respective portfolios through industry collaboration and the development of important academic studies such as MAJIC (MPN) and RAPRIMA (MDS).

- **More emphasis on studies relating to living with haematological malignancies**. A designated lead has been appointed from within the CSG with a view to establishing a Working Party to drive forward research in this area.
- **Optimise involvement with TAP**. TAP is now a standing agenda item at CSG meetings, and the LLR Director of Research is a CSG member and regular attender.

13. Priorities and challenges for the forthcoming year

Priorities for the Haem Onc CSG in the next year are outlined below:

- One of the CSG's top priorities for 2015/2016 is to ensure that major phase 3 trials are in place across all disease areas, especially high-recruiting diseases such as AML and myeloma, and there are some important gaps in the portfolio that need to be plugged as a matter of urgency. Specifically, there is currently no trial for younger patients with AML following the closure of AML17. The successor to AML17 (AML19) has been funded, and launching this new study is clearly a major priority. Similarly, Myeloma XI/XI+ is due to close shortly, and it is crucial that a funding application for its successor is prepared and submitted at the earliest opportunity. For a variety of reasons, MDS and MPN are challenging disease areas in which to develop major phase 3 trials clinical trials. Despite this, much progress has been made in both areas, and it is crucial that the remaining hurdles (funding and industry support) are overcome.
- The restructuring of the UK CRN and creation of 15 LCRNs with Haem Onc Subspecialty Leads presents a major opportunity for the CSG to improve trial delivery by providing an organisational framework for identifying and, where possible, removing barriers to trial set-up and recruitment. However, to fully exploit this opportunity, it is crucial that the CSG engages in a meaningful way with the Subspecialty Leads. Some suggestions as to how this might occur were made at the Subspecialty Leads workshop in March 2015, and these will be discussed at the July CSG meeting.
- Supportive care and late effects are of central importance in haematological cancers owing the intensity of treatments used coupled in many cases with the prolonged nature of the remissions achieved. There are many important questions to address and consequently this is likely to be a very fertile area for impactful research. To drive forward research in this area, the clinical lead (Professor Snowden) has submitted a formal request to establish a cross-cutting WP, linking in with other relevant groups such as the Supportive & Palliative Care CSG, the Psychosocial Oncology & Survivorship CSG and the TYA CSG. If approved, the WP should have a transforming effect on the CSG's trial portfolio.

Challenges for the CSG are given below:

- Allogeneic haematopoietic stem-cell transplantation (or allografting) is the haemato-oncologist's "nuclear weapon", i.e. it can be curative in diseases that are incurable with conventional treatment but is also associated with significant morbidity and mortality due to graft-versus-host disease and opportunistic infection. Improving the efficacy and reducing the toxicity of allografting is a major research priority for the CSG. However, transplant studies have mostly been developed in an ad-hoc manner by single centres, with little or no consideration given to strategic planning, the size of the study population or overlap with disease-specific studies. Consequently, although there have been notable exceptions, transplant studies have become notorious for failing to recruit to time and target. One of the CSG's main challenges is to turn this situation around. To this end, the clinical lead (Dr Peggs)

has been working closely with the BSBMT and wider the transplant community to establish a more co-ordinated and realistic approach to these studies.

- A significant proportion of haematological cancers affect the TYA age group, most notably ALL where there is compelling evidence that such patients fare much better with more intensive paediatric protocols. Based on this evidence, it has been agreed that TYA patients with Philadelphia negative ALL should be offered entry into the paediatric UKALL2011 trial rather than the adult UKALL14 study. Whether or not paediatric protocols offer an advantage in TYA patients with other types of leukaemia is less clear. It is hoped that the next round of membership rotations will allow the appointment of a Clinical Lead with an interest in TYA who can link in with the CCL CSG to ensure a co-ordinated approach and crystallise research questions in this area.
- The CSG has excellent links with industry which have underpinned a succession of innovative and successful investigator-led and industry-led studies. Many companies now recognise the benefit of working with the CSG and its Subgroups to ensure that new studies are compatible with the existing portfolio and to proactively manage situations where studies compete for the same patient groups. It is therefore disappointing and frustrating in equal measure when industry studies that directly compete with existing NIHR studies are added to the CSG portfolio without prior CSG consultation or approval. This is especially true of niche areas that require full national participation for successful trial delivery. Similar considerations apply to the implementation of the TSB Cell Therapy Catapult.

14. Concluding remarks

It is a very stimulating and rewarding experience to chair such a vibrant and successful CSG. However, in order to maintain the current level of activity, it is essential that the group continually replenishes its portfolio of large phase 3 trials, especially in the more common disorders such as AML and myeloma. Engagement with the delivery network via the Subspecialty Leads will be pivotal to the success of these trials. In addition to maintaining current activity, major opportunities exist to expand the portfolio in cross-cutting areas. To this end, significant progress has been made in establishing a more structured approach to developing research in supportive care/late effects, culminating in a formal proposal to establish a Working Party in this area. Progress has also been made in understanding the many and complex challenges associated with the successful delivery of transplant studies; it is hoped that this understanding will provide a platform for enhanced collaboration and, ultimately, the development of a new generation of transplant trials delivered to time and target. Developing TYA as a focus area within the CSG has proved more challenging, but this can hopefully be addressed through the appointment of new CSG member(s) who specialise in TYA.

15. Appendices

Appendix 1 - Membership of main CSG and subgroups

Appendix 2 – CSG and Subgroup strategies

A – Main CSG Strategy

B – Acute Lymphoblastic Leukaemia (ALL) Subgroup Strategy

C – Acute Myeloid Leukaemia (AML) Subgroup Strategy

D – Chronic Lymphoblastic Leukaemia (CLL) Subgroup Strategy

E – Chronic Myeloid Leukaemia (CML) Subgroup Strategy
F – Myelodysplastic Syndrome (MDS) Subgroup Strategy
G – Myeloproliferative Neoplasms (MPN) Subgroup Strategy
H – Myeloma Subgroup Strategy

Appendix 3 - Portfolio Maps

Appendix 4 - Publications in previous year

Appendix 5 - Major international presentations in previous year

Professor Andrew Pettitt (Haem Onc CSG Chair)

Appendix 1

Membership of the Haem Onc CSG

Name	Specialism	Location
Mr John Reeve (CLG)	Consumer	Witham
Mrs Lesley Roberts (CLG)	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 Claire Harrison	Haematologist	London
Professor Peter Hillmen	Haematologist	Leeds
Dr Richard Kaczmarski	Haematologist	London
Professor Paul Moss	Haematologist	Birmingham
Professor Stephen O'Brien	Haematologist	Newcastle
Dr Karl Peggs	Haematologist	London
Professor Andrew Pettitt (Chair)	Haematologist	Liverpool
Professor Nigel Russell	Haematologist	Nottingham
Professor John Snowden	Haematologist	Sheffield
Ms Shamyla Siddique	Senior Trials Coordinator	Birmingham
Professor Walter Gregory	Statistician	Leeds
Dr Robert Hills	Statistician	Cardiff
Dr Paolo Gallipoli*		Cambridge
Dr Robert Lown*		Southampton

* denotes trainee

Membership of the Subgroups

ALL Subgroup		
Name	**Specialism**	**Location**
Mr John Reeve	Consumer	Witham
Professor Anthony Moorman	Epidemiologist	Newcastle
Dr Sridhar Chaganti	Haematologist	Birmingham
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
Dr Matthew Smith	Haematologist	London
Ms Amy Kirkwood	Statistician	London

AML Subgroup		
Name	**Specialism**	**Location**
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
Professor Keith Wheatley	Statistician	Birmingham

CLL Subgroup		
Name	**Specialism**	**Location**
Dr David Allsup	Haematologist	Hull
Dr Adrian Bloor	Haematologist	Manchester
Dr Andrew Duncombe	Haematologist	Southampton
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
Professor Andrew Pettitt	Haematologist	Liverpool
Ms Dena Cohen	Statistician	Leeds

CML Subgroup		
Name	**Specialism**	**Location**
Dr Naumann Butt	Haematologist	Liverpool
Dr Jenny Byrne	Haematologist	Nottingham
Professor Richard Clark	Haematologist	Liverpool
Professor Mhairi Copland (Chair)	Haematologist	Glasgow
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

MDS Subgroup		
Name	**Specialism**	**Location**
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
Professor Ghulam Mufti	Haematologist	London
Dr Manoj Raghavan	Haematologist	Birmingham
Dr Paresh Vyas	Haematologist	Oxford

Myeloma Subgroup		
Name	**Specialism**	**Location**
Mrs Lesley Roberts	Consumer	Leek
Dr Jenny Bird	Haematologist	Bristol
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

MPN Subgroup		
Name	**Specialism**	**Location**
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 (Chair)	Haematologist	London
Dr Steven Knapper	Haematologist	Cardiff
Dr Adam Mead	Haematologist	Oxford
Professor Mary Frances McMullin	Haematologist	Belfast
Dr Frances Wadelin	Haematologist	Nottingham

Appendix 2

CSG & Subgroup Strategies

A – Main CSG Strategy

Background. 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 Working Groups 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 led to 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 offers an unprecedented opportunity to go a step further by applying a more tailored approach to treatment.

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 assessment 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.

Research priorities. 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 (including those funded by LLR and Myeloma UK) to inform on the next generation of phase 3 studies. In addition, the CSG aims to expand research in supportive care and late effects as important cross-cutting themes. This will be achieved through the establishment of a Working Party in collaboration with the Supportive and Palliative Care CSG. The CSG also aims to apply a more co-ordinated approach to transplant studies by working more closely with the BSBMT. Finally, the CSG aims to 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.

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 also provide a potential source of funding for trial co-ordination, biobanking and translational research. The CSG'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 crucial that this relationship is maintained and 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 LLR and Myeloma UK. Leukaemia and Lymphoma Research (LLR) is an NCRI partner that funds basic, translational and clinical research in haematological oncology including a significant part of the CSG portfolio. The LLR Trials Acceleration Programme (TAP) provides a unique infrastructure for the development and delivery of early-phase studies through a hub-and-spoke network, and it is crucial that this programme is developed in close collaboration with the CSG and its Subgroups. To this end, the LLR Director of Research is an ex-officio member of the CSG, and TAP is a standing agenda item at CSG meetings. In addition, Myeloma UK funds early-phase studies in myeloma. It is crucial that the CSG fully exploits the opportunities afforded by its association with these two charities.

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 in CSG meetings and by continuing to showcase the CSG portfolio at the annual trials review meeting.

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.

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 7 main disease areas (AML, ALL, CML, CLL, MPN, MDS, myeloma) but also supportive care/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 CSG also aim to have broad geographical representation.

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 Fellowship Scheme.

B – Acute Lymphoblastic Leukaemia (ALL) Subgroup Strategy

The overall strategy of the ALL Subgroup is to improve the outcome for adults with ALL. This involves:

- a trial for every patient at every stage of their disease
- all possible novel approaches to be available in the UK - no patient should ever need to leave the country for a new approach
- carry out the best possible correlative science with every trial
- close working and collaboration nationally and internationally with commercial and academic organisations to learn, work together and create new approaches
- training of the next generation of physicians and scientists around clinical trial work in ALL

C – Acute Myeloid Leukaemia (AML) Subgroup Strategy

The strategy of the AML Subgroup is to:

- maintain a continuous programme of Clinical trials for patients with AML overall age ranges and fitness
- maintain the reputation of the NCRI group as a leading international clinical trials collaborative group in AML
- deliver improved survival for patients plus maintain the AML trials as a standard of care for the treatment of AML in the UK
- investigate novel therapies that can improve survival in AML by targeting minimal residual disease
- maintain international collaborations with other clinical trial groups
- develop novel prognostic and predictive genetic markers to improve patient stratification.

D – Chronic Lymphoblastic Leukaemia (CLL) Subgroup Strategy

The strategy of the CLL Subgroup is currently under review.

E – Chronic Myeloid Leukaemia (CML) Subgroup Strategy

In order to achieve our aims of (i) improving treatment outcomes and patient experience, and (ii) delivering high quality translational research in CML, our strategy has four core elements:

- Development of 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;
- Co-operative working to manage the SPIRIT Biobanks and develop and deliver basic and translational research that will lead to improvements in CML treatment;
- Dissemination of clinical trial and translational research results;
- Health professional and consumer education.

Clinical Trials Portfolio

SPIRIT2: This trial closed to recruitment in March 2013. The 12 and 24 month data have been presented at ASH and EHA and a manuscript is planned for late 2015. The primary endpoint will be reached in March 2018 and a final manuscript and presentations are planned for late 2018.

DESTINY: Recruitment was complete in April 2015. Twelve month de-escalation data for all patients will be evaluable April 2016 and 24 month discontinuation data (end of study) in April 2018. The findings from this study will form the basis of the de-escalation and stopping phase of SPIRIT3. Additional de-escalation/stopping studies will be designed pending the early results from DESTINY (de-escalation and 12 month discontinuation data).

MATCHPOINT: This LLR Trials Acceleration Programme funded Phase 1 study is currently recruiting blast phase CML patients using the novel "EffTox" design. A total of 24 patients will be recruited over 24-30 months.

SPIRIT3: This will be our flagship Phase 3 study and is scheduled to open in late 2015. It will take chronic phase CML patients from diagnosis to treatment discontinuation (where appropriate) and also incorporates the third generation tyrosine kinase inhibitor (TKI) ponatinib for treatment resistance. Importantly, SPIRIT3 will embrace generic imatinib, which comes off patent in 2016.

Commercial studies: Where possible, the CML Working Party incorporates commercial clinical trials into their portfolio. We currently have the BFOUR study open in newly diagnosed chronic phase CML patients and will shortly have the OPTIC study open in patients with TKI resistance in selected centres.

Future studies: An important element of our strategy is design and delivery of new trials. We are currently in the early stages of determining the feasibility and design of an early phase clinical trial, incorporating novel small molecule inhibitors for TKI refractory patients.

Translational Research

Biobanking: The CML Working Party acts as gatekeeper to the SPIRIT Biobank which has stored cells and RNA from all patients in the SPIRIT2 trial. These samples are made available to researchers, with ethically approved projects, following an approvals process.

GeCIP: The CML Working Party (led by Jane Apperley) has been successful in obtaining a sub-domain within the haemato-oncology GeCIP. This will assess the genomic profile of 240 "extreme

responders" with CML and provide data to inform future studies across different scientific disciplines, including bio-informatics and multiple "omics" approaches.

SPIRIT3: To compliment the SPIRIT3 clinical trial, a rigorous programme of translational studies is planned, including epigenetic, genetic, proteomic and functional studies. A task force from within the CML Working Party is meeting regularly to develop this work further and identify additional future funding opportunities.

Education

Health Professionals: We hold an annual education meeting for Health Professionals; the next meeting will be Q1-2016. In addition, we are in the early stages of preparation of a BCSH guideline addressing "Management of CML in the UK".

Consumers: We hold an annual patient conference, which this year will be held at the Hammersmith Hospital, London, on Saturday 14th November. The venue moves around the country to improve accessibility and the conference will be webcast live to increase participation. Two consumer representatives will be invited to join the CML Working Party in the next 6 months.

F – Myelodysplastic Syndrome (MDS) Subgroup Strategy

The strategy of the MDS Subgroup is to develop a portfolio of Phase 1,2 and 3 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 73yrs. 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 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 roll in high risk MDS, they have little or no roll 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.

The MDS subgroup strategies include one of collaboration with the AML Working Group and UK transplant groups in high risk MDS where there is large overlap in treatment approaches, whilst developing stand alone strategies at Phase 2 and 3 in supportive care, low risk MDS and novel combination therapies in high risk disease.

During the last 12 months the MDS Subgroup has opened the Phase 2 ELASTIC study of azacitidine and eltrombopag in high risk MDS and completed recruitment to the first cohort of patients. A joint study with the National Blood authority has also opened; REDDS. 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 and if this and an identical pilot in Canada are successful then the plan is to extend this into an International, multicentre, phase 3 trial. The Subgroup has received funding from LLR for a phase 2 study in CMML to follow on from the successful CMML201 trial which was published in Leukemia in 2014. This study 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.

Throughout the last year the group has continued to run and recruit to a number of investigator led and Company run trials that remain open. Recruitment to MDS trials remains a challenge internationally. The question of the role of iron chelation in elderly, low risk, MDS patients remains one of the most important. However all three trials run and supported by the subgroup have struggled. Our own De-Iron study looking at the role of early iron chelation has now opened in some 20 UK sites with regular requests from new sites. However, despite several major amendments to ease entry criteria, recruitment remains slow. The recent DMEC meeting supported the trial continuing given improved recruitment and screening during the last six months and the belief that this remains an important clinical question. Similarly, the Novartis run international phase 3 trial; TELESTO had to reduce the recruitment target from over 600 to just

over 200 and change the endpoint from survival to safety. This study completed recruitment in late 2014 to the new target and the UK was the second largest recruiter worldwide through the subgroup. However, a number of phase 2 trials have recruited well including the randomised HLA epitope study and the randomised RAvVA trial run in conjunction with the AML Working group. Both of these studies are nearly completed. The group is running in the UK the pivotal, worldwide, randomised trial of oral azacitidine vs. 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.

The phase 3 strategy of the group is to continue to support the large and successful AML trials run through the AML Working Group by including appropriate high risk MDS patients and this currently includes AML 18, LI-1 and the soon to open AML 19. However, the Subgroup continues to work towards a stand-alone Phase 3 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 will add to this knowledge base and ELASTIC may identify an appropriate combination to test further. Our lead approach, therefore, is to develop a randomised, Phase 3, placebo controlled trial of supportive care. This will randomise a wide range of high-risk MDS patients receiving azacitidine or low intensity therapy within the LI-1 trial to joint prophylaxis with an oral antibiotic and oral anti-fungal drug or joint placebos. The primary endpoint will be time to first infection. However, a range of secondary endpoints will look at key health economic issues in these elderly patients, including time in hospital, use of IV antibiotics, antibiotic resistance, 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 will be made to LLR in July 2015.

The subgroup has engaged with a number of Companies during the last 12 months with the aim of developing a portfolio of Phase 1 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 opened a Phase 1 study of antI-IL3 antibody therapy in 6 sites in the UK and are working with the UK Government organisation; CATAPULT, to open a Phase 1 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 5000 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 technology. The first successful application of this linked approach is ELASTIC.

G – Myeloproliferative Neoplasms (MPN) Subgroup Strategy

The strategy of the MPN Subgroup is to build a strong diverse network of clinicians, nurses, scientists in partnership with patients. The aims of this network 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 have the opportunity to participate in as diverse a portfolio of clinical trials as possible
- support sample banks in MPN
- 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 BCSH process.
- support NICE appraisal of novel therapeutics in MPN

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.

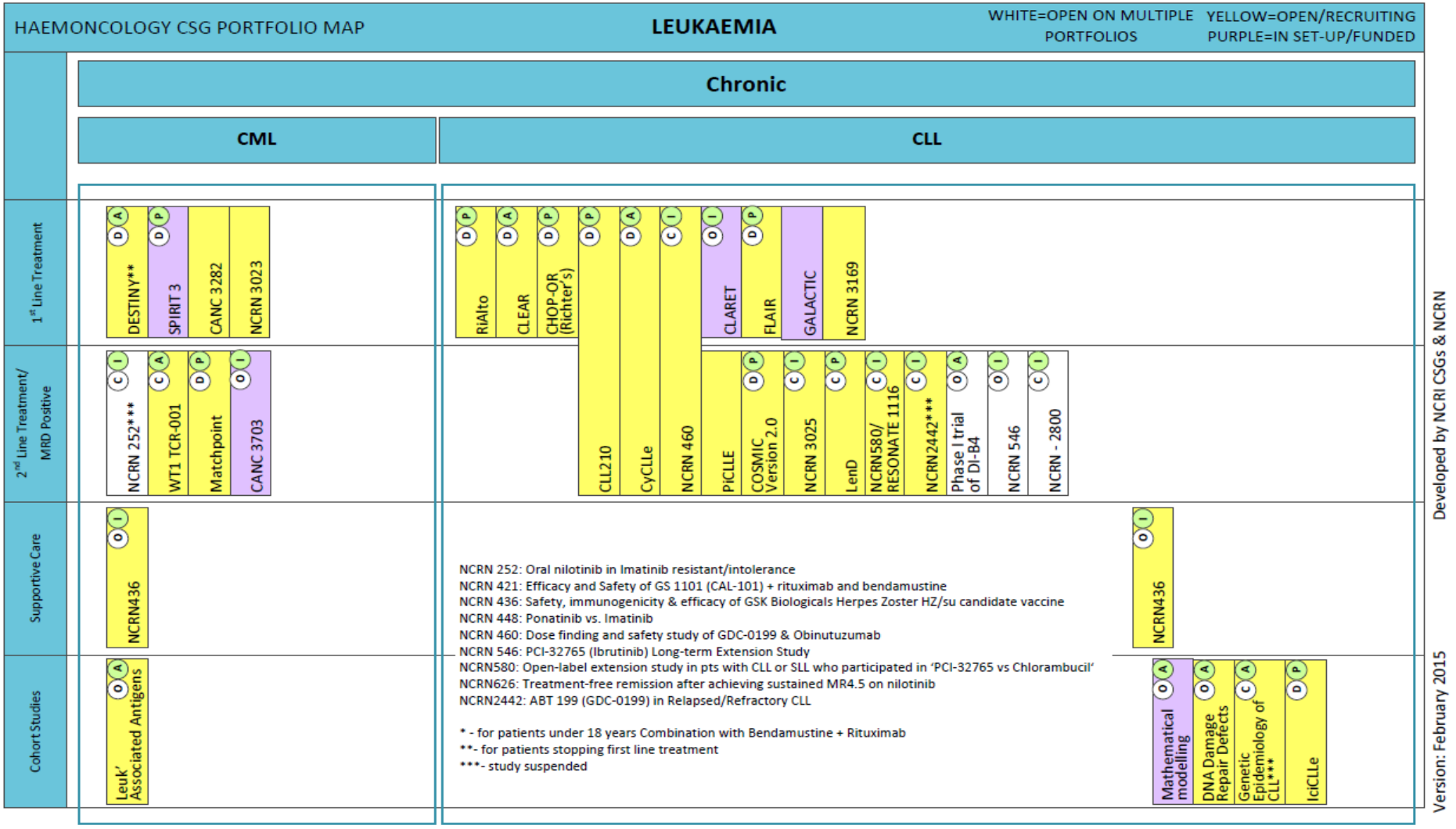
Strategic outline

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

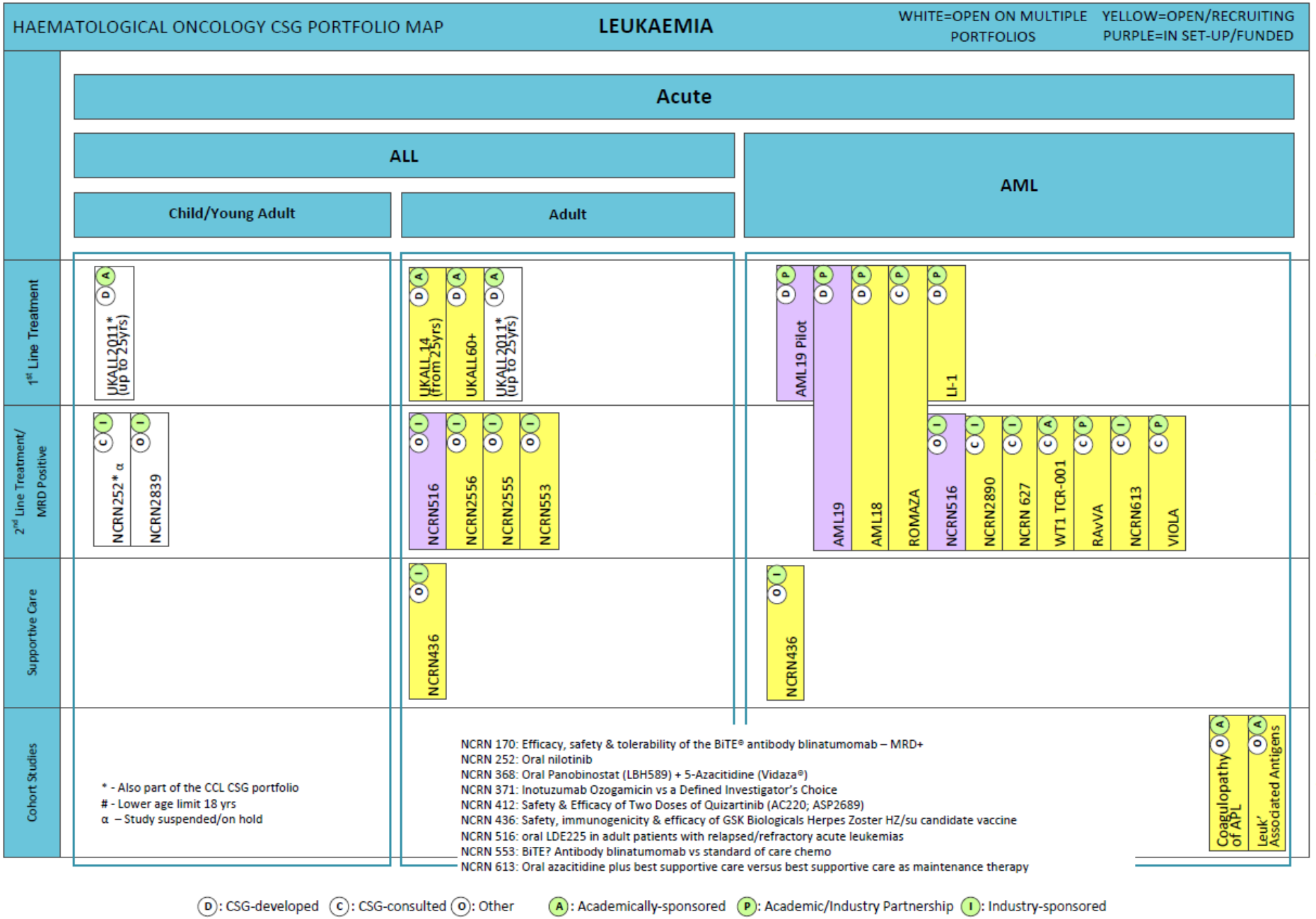
- The creation of a new brand for the clinical research cooperative, that can signify the collaborative and unified approach within the UK and be easily identified internationally
    - The UK Myeloma Research Alliance
    - Governance under the NCRI CSG (as the myeloma subgroup)
- To "dove-tail" the 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
- To develop trials using innovative designs aiming to be leaders in the field as well as providing key UK-specific healthcare data to assist in regulatory approval
    - MUKeight and NICE submission for Ixazomib
- 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
- 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
- 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
- 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

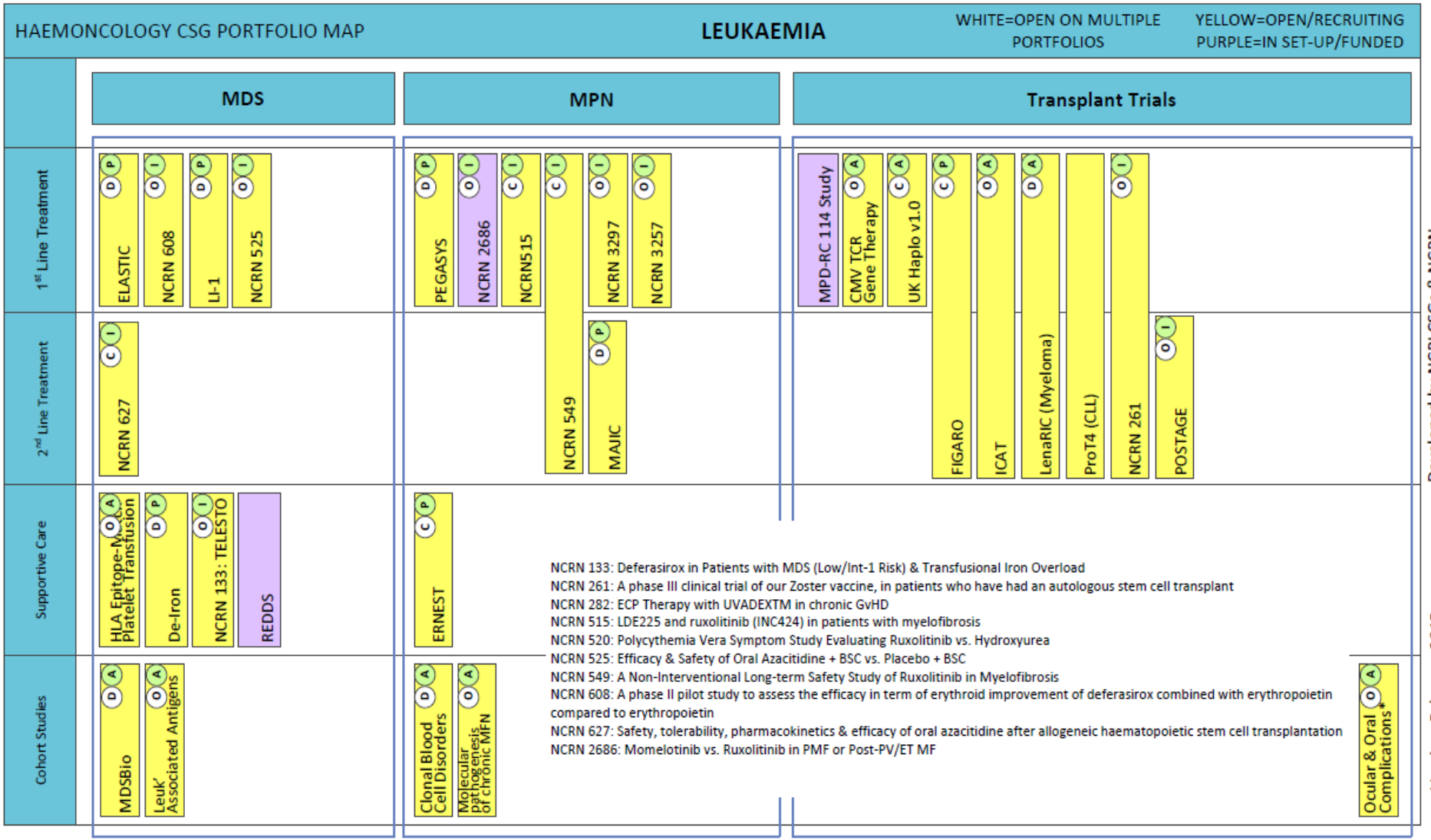
Appendix 3

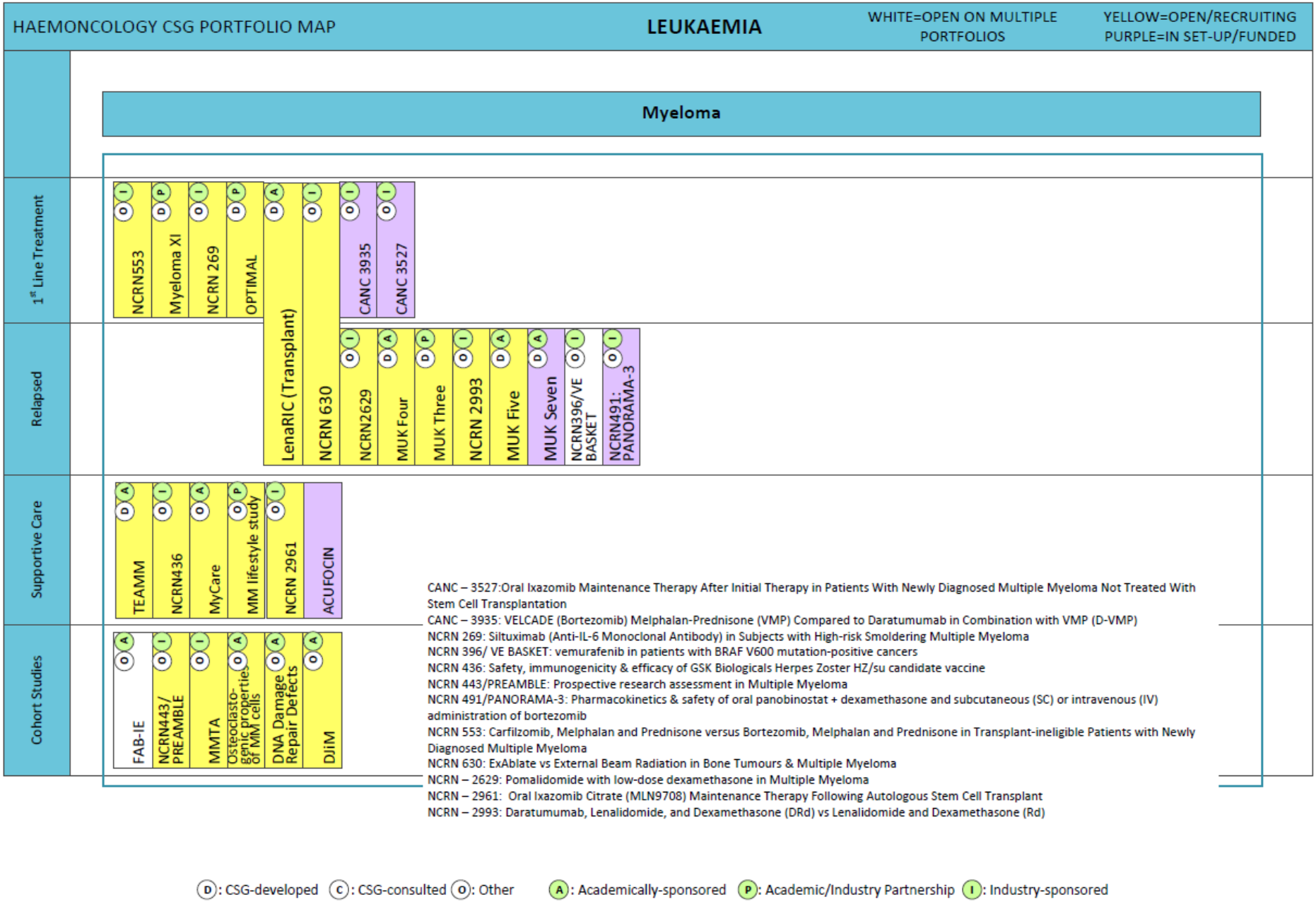
Portfolio maps



(D): CSG-developed (C): CSG-consulted (O): Other (A): Academically-sponsored (P): Academic/Industry Partnership (I): Industry-sponsored


HAEMATOLOGICAL ONCOLOGY CSG PORTFOLIO MAP
LEUKAEMIA
WHITE=OPEN ON MULTIPLE PORTFOLIOS
YELLOW=OPEN/RECRUITING
PURPLE=IN SET-UP/FUNDED
Acute
ALL
AML
Child/Young Adult
Adult
1st Line Treatment
2nd Line Treatment/ MRD Positive
Supportive Care
Cohort Studies
UKALL2011* (up to 25yrs)
UKALL 14 (from 25yrs)
UKALL60+
UKALL2011* (up to 25yrs)
AML19 Pilot
LI-1
NCRN252* α
NCRN2839
NCRN516
NCRN2556
NCRN2555
NCRN553
AML19
AML18
ROMAZA
NCRN516
NCRN2890
NCRN 627
WT1 TCR-001
RAvVA
NCRN613
VIOLA
NCRN436
NCRN436
Coagulopathy of APL
Leuk' Associated Antigens
* - Also part of the CCL CSG portfolio
# - Lower age limit 18 yrs
α – Study suspended/on hold
NCRN 170: Efficacy, safety & tolerability of the BiTE® antibody blinatumomab – MRD+
NCRN 252: Oral nilotinib
NCRN 368: Oral Panobinostat (LBH589) + 5-Azacitidine (Vidaza®)
NCRN 371: Inotuzumab Ozogamicin vs a Defined Investigator's Choice
NCRN 412: Safety & Efficacy of Two Doses of Quizartinib (AC220; ASP2689)
NCRN 436: Safety, immunogenicity & efficacy of GSK Biologicals Herpes Zoster HZ/su candidate vaccine
NCRN 516: oral LDE225 in adult patients with relapsed/refractory acute leukemias
NCRN 553: BiTE? Antibody blinatumomab vs standard of care chemo
NCRN 613: Oral azacitidine plus best supportive care versus best supportive care as maintenance therapy
Developed by NCRI CSGs & NCRN
Version: February 2015
(D): CSG-developed (C): CSG-consulted (O): Other (A): Academically-sponsored (P): Academic/Industry Partnership (I): Industry-sponsored


HAEMONCOLOGY CSG PORTFOLIO MAP
LEUKAEMIA
WHITE=OPEN ON MULTIPLE PORTFOLIOS
YELLOW=OPEN/RECRUITING
PURPLE=IN SET-UP/FUNDED
MDS
MPN
Transplant Trials
1st Line Treatment
2nd Line Treatment
Supportive Care
Cohort Studies
ELASTIC
NCRN 608
LI-1
NCRN 525
PEGASYS
NCRN 2686
NCRN515
NCRN 549
NCRN 3297
NCRN 3257
MPD-RC 114 Study
CMV TCR Gene Therapy
UK Haplo v1.0
FIGARO
ICAT
LenaRIC (Myeloma)
ProT4 (CLL)
NCRN 261
POSTAGE
NCRN 627
MAJIC
HLA Epitope-Matched Platelet Transfusion
De-Iron
NCRN 133: TELESTO
REDDS
ERNEST
MDSBio
Leuk' Associated Antigens
Clonal Blood Cell Disorders
Molecular pathogenesis of chronic MFN
Ocular & Oral Complications*
NCRN 133: Deferasirox in Patients with MDS (Low/Int-1 Risk) & Transfusional Iron Overload
NCRN 261: A phase III clinical trial of our Zoster vaccine, in patients who have had an autologous stem cell transplant
NCRN 282: ECP Therapy with UVADEXTM in chronic GvHD
NCRN 515: LDE225 and ruxolitinib (INC424) in patients with myelofibrosis
NCRN 520: Polycythemia Vera Symptom Study Evaluating Ruxolitinib vs. Hydroxyurea
NCRN 525: Efficacy & Safety of Oral Azacitidine + BSC vs. Placebo + BSC
NCRN 549: A Non-Interventional Long-term Safety Study of Ruxolitinib in Myelofibrosis
NCRN 608: A phase II pilot study to assess the efficacy in term of erythroid improvement of deferasirox combined with erythropoietin compared to erythropoietin
NCRN 627: Safety, tolerability, pharmacokinetics & efficacy of oral azacitidine after allogeneic haematopoietic stem cell transplantation
NCRN 2686: Momelotinib vs. Ruxolitinib in PMF or Post-PV/ET MF
Developed by NCRI CSGs & NCRN
Version: February 2015
* study suspended
(D): CSG-developed (C): CSG-consulted (O): Other
(A): Academically-sponsored (P): Academic/Industry Partnership (I): Industry-sponsored


HAEMONCOLOGY CSG PORTFOLIO MAP
LEUKAEMIA
WHITE=OPEN ON MULTIPLE PORTFOLIOS
YELLOW=OPEN/RECRUITING
PURPLE=IN SET-UP/FUNDED
Myeloma
1st Line Treatment
Relapsed
Supportive Care
Cohort Studies
NCRN553
Myeloma XI
NCRN 269
OPTIMAL
LenaRIC (Transplant)
NCRN 630
CANC 3935
CANC 3527
NCRN2629
MUK Four
MUK Three
NCRN 2993
MUK Five
MUK Seven
NCRN396/VE BASKET
NCRN491: PANORAMA-3
TEAMM
NCRN436
MyCare
MM lifestyle study
NCRN 2961
ACUFOCIN
FAB-IE
NCRN443/ PREAMBLE
MMTA
Osteoclasto-genic properties of MM cells
DNA Damage Repair Defects
DJiM
CANC – 3527:Oral Ixazomib Maintenance Therapy After Initial Therapy in Patients With Newly Diagnosed Multiple Myeloma Not Treated With Stem Cell Transplantation
CANC – 3935: VELCADE (Bortezomib) Melphalan-Prednisone (VMP) Compared to Daratumumab in Combination with VMP (D-VMP)
NCRN 269: Siltuximab (Anti-IL-6 Monoclonal Antibody) in Subjects with High-risk Smoldering Multiple Myeloma
NCRN 396/ VE BASKET: vemurafenib in patients with BRAF V600 mutation-positive cancers
NCRN 436: Safety, immunogenicity & efficacy of GSK Biologicals Herpes Zoster HZ/su candidate vaccine
NCRN 443/PREAMBLE: Prospective research assessment in Multiple Myeloma
NCRN 491/PANORAMA-3: Pharmacokinetics & safety of oral panobinostat + dexamethasone and subcutaneous (SC) or intravenous (IV) administration of bortezomib
NCRN 553: Carfilzomib, Melphalan and Prednisone versus Bortezomib, Melphalan and Prednisone in Transplant-ineligible Patients with Newly Diagnosed Multiple Myeloma
NCRN 630: ExAblate vs External Beam Radiation in Bone Tumours & Multiple Myeloma
NCRN – 2629: Pomalidomide with low-dose dexamethasone in Multiple Myeloma
NCRN – 2961: Oral Ixazomib Citrate (MLN9708) Maintenance Therapy Following Autologous Stem Cell Transplant
NCRN – 2993: Daratumumab, Lenalidomide, and Dexamethasone (DRd) vs Lenalidomide and Dexamethasone (Rd)
Developed by NCRI CSGs & NCRN
Version: February 2015
(D): CSG-developed (C): CSG-consulted (O): Other
(A): Academically-sponsored (P): Academic/Industry Partnership (I): Industry-sponsored

HAEMONCOLOGY CSG PORTFOLIO MAP
LEUKAEMIA
WHITE=OPEN ON MULTIPLE PORTFOLIOS
YELLOW=OPEN/RECRUITING
PURPLE=IN SET-UP/FUNDED
Other
Child
Adult
1st Line Treatment
2nd Line Treatment/ MRD Positive
Supportive Care
Cohort Studies
Physical activity rehab for survivors
Physical activity rehab for survivors
TRYMS
Adverse drug reactions in a children's regional oncology unit*
Study of haematology in newborns with DS
BRIGHTLIGHT
Decision making with teenagers, parents and clinicians
Characterising differences between normal and defective HSPCs
Leukaemic Stem Cells support by human Vascular Stem Cells
Molecular Investigation of Haematopoietic Malignancy
InCiTE
EBV associated NK/T cell malignancies
BRIGHTLIGHT
Version: February 2015
Developed by NCRI CSGs & NCRN
* - Study suspended
(D): CSG-developed (C): CSG-consulted (O): Other
(A): Academically-sponsored (P): Academic/Industry Partnership (I): Industry-sponsored

Appendix 4

Publications in the reporting year

MUK One Trial

S Schey, S Brown, AL Tillotson, K Yong, C Williams, F Davies, G Morgan, J Cavenagh, G Cook, M Cook, G Orti, C Morris, D Sherratt, L Flanagan, W Gregory & J Cavet. (2015), On behalf of the Myeloma UK Early Phase Clinical Trial Network. Identifying a tolerable but optimally active dose of bendamustine in combination with thalidomide and dexamethasone in patients with relapsed or refractory multiple myeloma: Results of the MUK*one* trial. *British journal of Haematology*, (in press)

Myeloma X Trial

Cook, C Williams, JM Brown, DA Cairns, J Cavenagh, JA Snowden, AJ Ashcroft, M Fletcher, C Parrish, K Yong, J Cavet, H Hunter, JM Bird, A Chalmers, S O'Connor, MT Drayson & TCM Morris On behalf of the National Cancer Research Institute Haemato-oncology Clinical Studies Group. A Second Autologous Stem Cell Transplant Induces Superior Durability of Response following Bortezomib-containing Re-induction Therapy for Relapsed Multiple Myeloma (MM): Final Results from the BSBMT/UKMF Myeloma X (Intensive) Trial. *(2014) The Lancet Oncology,* doi:10.1016/S1470-2045(14) 70245-1.

Myeloma IX Trial

GH Jackson, GJ Morgan, FE Davies, P Wu, WM Gregory, SE Bell, AJ Szubert, N Navarro-Coy, MT Drayson, RG Owen, S Feyler, AJ Ashcroft, FM Ross, J Byrne, H Roddie, C Rudin, KD Boyd, W Osborne, G Cook & JA Child. (2014) Osteonecrosis of the jaw and renal safety in patients with newly diagnosed multiple myeloma: MRC Myeloma IX study results, (2014), *British Journal Haematology,* 166, 109-117. doi: 10.1111/bjh.12861.

NCRN336 - Phase II study to evaluate efficacy and safety of blinatumomab in relapsed/refractory ALL (BITE)

Topp MS, Gökbuget N, Stein AS, Zugmaier G, O'Brien S, Bargou RC, Dombret H, Fielding AK, Heffner L, Larson RA, Neumann S, Foà R, Litzow M, Ribera JM, Rambaldi A, Schiller G, Brüggemann M, Horst HA, Holland C, Jia C, Maniar T, Huber B, Nagorsen D, Forman SJ, Kantarjian HM. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study (2015) *Lancet Oncol.* Jan;16(1):57-66. doi: 10.1016/S1470-2045(14)71170-2. Epub 2014 Dec 16.PMID:25524800

UKALL14

Patel B, Dey A, Castleton AZ, Schwab C, Samuel E, Sivakumaran J, Beaton B, Zareian N, Zhang CY, Rai L, Enver T, Moorman AV, Fielding AK. Mouse xenograft modeling of human adult acute lymphoblastic leukemia provides mechanistic insights into adult LIC biology (2014) *Blood.* Jul 3;124(1):96-105. doi: 10.1182/blood-2014-01-549352. Epub 2014 May 13.PMID:24825861

UKALL12

Russell LJ, Enshaei A, Jones L, Erhorn A, Masic D, Bentley H, Laczko KS, Fielding AK, Goldstone AH, Goulden N, Mitchell CD, Wade R, Vora A, Moorman AV, Harrison CJ. IGH@ translocations are prevalent in teenagers and young adults with acute lymphoblastic leukemia and are associated with a poor outcome (2014) *J Clin Oncol.* May 10;32(14):1453-62. doi: 10.1200/JCO.2013.51.3242. Epub 2014 Apr 7. Erratum in: J Clin Oncol. 2014 Nov 10;32(32):3687. *J Clin Oncol*. 2015 Feb 20;33(6):672.PMID:24711557

Chilton L, Buck G, Harrison CJ, Ketterling RP, Rowe JM, Tallman MS, Goldstone AH, Fielding AK, Moorman AV. High hyperdiploidy among adolescents and adults with acute lymphoblastic leukaemia (ALL): cytogenetic features, clinical characteristics and outcome (2014) *Leukemia.* Jul;28(7):1511-8. doi: 10.1038/leu.2013.379. Epub 2013 Dec 19.PMID:24352198

SPIRIT 2

SG. O'Brien, C Hedgley, S Adams, L Feroni, JF. Apperley, TL. Holyoake, C Pocock, JL. Byrne, LM. Seeley, W L. Osborne, JM. Goldman, M Copland, RE. Clark (2014) Spirit 2: An NCRI Randomised Study Comparing Dasatinib with Imatinib in Patients with Newly Diagnosed CML. *Blood* Volume: 124 Issue: 21 Published 6 December 2014

SPIRIT 2 (Biobank)

Alonso-Dominguez JM, Grinfeld J, Alikian M, et al. PTCH1 expression at diagnosis predicts imatinib failure in chronic myeloid leukaemia patients in chronic phase *(2015) Am J Hematol* ;90(1):20-6. doi: 10.1002/ajh.23857. Epub 2014 Oct 18. PMID:25250944

CMML 201

Drummond MW, Pockock C, Boissinot M, Mills J, Brown J, Cauchy P, Cross, NC, Hartley S, Kell J, Szubert A, Cockerill PN, Bowen DT. A multi-centre phase 2 study of azacitidine in chronic myelomonocytic leukaemia (2014) *Leukemia;*28: 1570-1572

MDS Bio

Khan N, Freeman SD, Virgo P, Couzens S, Richardson P, Thomas I, Grech A, Vyas P, Grimwade D, Russell NH, Burnett AK, Hills RK. An immunophenotypic pre-treatment predictor for poor response to induction chemotherapy in older acute myeloid leukaemia patients: blood frequency of CD34+CD3low blasts (2015) *Br J Haematol* April4 [E-pub].

Gerstung M, Pellagatti A, Malcovati L, Giagounidis A, Porta MG, Jädersten M, Dolatshad H, Verma A, Cross NC, Vyas P, Killick S, Hellström-Lindberg E, Cazzola M, Papaemmanuil E, Campbell PJ, Boultwood J. Combining gene mutations with gene expression data imrpoves outcome prediction in myelodysplastic syndromes. (2015), *Nat Commun.* 6: Article number: 5901.

Bradbury C, Houlton AE, Akiki S, Gregg R, Rindl M, Khan J, Ward J, Khan N, Griffiths M, Nagra S, Hills R, Burnett A, Russell N, Vyas P, Grimwade D, Craddock C, Freeman SD. Prognostic value of monitoring a candidate immunophenotypic leukemic stem/progenitor cell population in patients allografted for acute myeloid leukemia (2014) *Leukemia,* Nov 26. doi: 10.1038/leu.2014.327. PMID:25425198.

Ju YS, Alexandrov LB, Gerstung M, Martincorena I, Nik-Zainal S, Ramakrishna M, Davies HR, Papaemmanuil E, Gundem G, Shlien A, Bolli N, Behjati S, Tarpey PS, Nangalia J, Massie CE, Butler AP, Teague JW, Vassiliou GS, Green AR, Du MQ, Unnikrishnan A, Pimanda JE, Teh BT, Munshi N, Greaves M, Vyas P, El-Naggar AK, Santarius T, Collins VP, Grundy R, Taylor JA, Hayes DN, Malkin D; ICGC Breast Cancer Group; ICGC Chronic Myeloid Disorders Group; ICGC Prostate Cancer Group, Foster CS, Warren AY, Whitaker HC, Brewer D, Eeles R, Cooper C, Neal D, Visakorpi T, Isaacs WB, Bova GS, Flanagan AM, Futreal PA, Lynch AG, Chinnery PF, McDermott U, Stratton MR, Campbell PJ. Origins and functional consequences of somatic mitochondrial DNA mutations in human cancer. (2014) *Elife.* Oct 1;3. doi:10.7554/eLife.02935 PMID:25271376.

Woll PS, Kjällquist U, Chowdhury O, Doolittle H, Wedge DC, Thongjuea S, Erlandsson R, Ngara M, Anderson K, Deng Q, Mead AJ, Stenson L, Giustacchini A, Duarte S, Giannoulatou E, Taylor S, Karimi M, Scharenberg C, Mortera-Blanco T, Macaulay IC, Clark SA, Dybedal I, Josefsen D, Fenaux P, Hokland P, Holm MS, Cazzola M, Malcovati L, Tauro S, Bowen D, Boultwood J, Pellagatti A, Pimanda JE, Unnikrishnan A, Vyas P, Göhring G, Schlegelberger B, Tobiasson M, Kvalheim G, Constantinescu SN, Nerlov C, Nilsson L, Campbell PJ, Sandberg R, Papaemmanuil E, Hellström-Lindberg E, Linnarsson S, Jacobsen SE. Myelodysplastic syndromes are propagated by rare and distinct human cancer stem cells in vivo (2014) <http://www.ncbi.nlm.nih.gov/pubmed/24835589> *Cancer Cell*. 25 p794-808

NCRN 549 (ROBUST)

Mead AJ, Milojkovic D, Knapper S, Garg M, Chacko J, Farquharson M, Yin J, Ali S, Clark RE, Andrews C, Ktiouet Dawson M, Harrison C. Response to ruxolitinib in patients with intermediate-1-, intermediate-2-, and high-risk myelofibrosis: results of the UK ROBUST Trial.*Br J Haematol*. 2015 Mar 30.

NCRN188 - RESPONSE

AM, Kiladjian JJ, Griesshammer M, Masszi T, Durrant S, Passamonti F, Harrison CN, Pane F, Zachee P, Mesa R, He S, Jones MM, Garrett W, Li J, Pirron U, Habr D, Verstovsek S. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. Vannucchi *N Engl J Med*. 2015 Jan 29;372(5):426-35.

MOSAICC

Anderson LA, McMullin MF. Epidemiology of MPN: what do we know? *Curr Hematol Malig Rep*. 2014 Dec;9(4):340-9.

Titmarsh GJ, McMullin MF, McShane CM, Clarke M, Engels EA, Anderson LA. Community-acquired infections and their association with myeloid malignancies. *Cancer Epidemiol*. 2014 Feb;38(1):56-61.

Titmarsh GJ, Duncombe AS, McMullin MF, O'Rorke M, Mesa R, De Vocht F, Horan S, Fritschi L, Clarke M, Anderson LA. How common are myeloproliferative neoplasms? A systematic review and meta-analysis. *Am J Hematol*. 2014 Jun;89(6):581-7.

The Causes of Clonal Blood Cell Disorders & NCRN 549 (ROBUST)

Reilly JT, McMullin MF, Beer PA, Butt N, Conneally E, Duncombe AS, Green AR, Mikhaeel G, Gilleece MH, Knapper S, Mead AJ, Mesa RA, Sekhar M, Harrison CN. Use of JAK inhibitors in the

management of myelofibrosis: a revision of the British Committee for Standards in Haematology Guidelines for Investigation and Management of Myelofibrosis 2012. *Br J Haematol*. 2014 Nov;167(3):418-20.

The Causes of Clonal Blood Cell Disorders

Harrison CN, Butt N, Campbell P, Conneally E, Drummond M, Green AR, Murrin R, Radia DH, Mead A, Reilly JT, Cross NC, McMullin M *(2014)* Modification of British Committee for Standards in Haematology diagnostic criteria for essential thrombocythaemia.. *Br J Haematol*. 2014 Nov;167(3):421-3.

AML16

Khan N, Freeman SD, Virgo P, Couzens S, Richardson P, Thomas I, Grech A, Vyas P, Grimwade D, Russell NH, Burnett AK, Hills RK. An immunophenotypic pre-treatment predictor for poor response to induction chemotherapy in older acute myeloid leukaemia patients: blood frequency of $CD34_+$ $CD38_{low}$ blasts. *2015* [Epub ahead of print] *Br J Haematol*, Apr 14. doi: 10.1111/bjh.13398,

Russell NH, Kjeldsen L, Craddock C, Pagliuca A, Yin JA, Clark RE, Howman A, Hills RK, BurnettAK, A comparative assessment of the curative potential of reduced intensity allografts in acute myeloid leukaemia, (2014) . *Leukemia.* 2014 Nov 7. doi: 10.1038/leu.2014.319. [Epub ahead of print]

Lazenby M, Gilkes AF, Marrin C, Evans A, Hills RK, Burnett AK. The prognostic relevance of flt3 and npm1 mutations on older patients treated intensively or non-intensively: a study of 1312 patients in the UK NCRI AML16 trial. L*eukemia.* 2014 Oct;28(10):1953-9.

AML17

Burnett AK, Russell NH, Hills RK, Kell J, Cavenagh J, Kjeldsen L, McMullin MF, Cahalin P, Dennis M, Friis L, Thomas IF, Milligan D, Clark RE. A randomised comparison of daunorubicin 90mg/m2 vs 60mg/m2 in AML induction: results from the UK NCRI AML17 trial in 1206 patients. *Blood*. 2015 Apr 1. pii: blood-2015-01-623447.

AML12,14,15,16

Walter RB, Othus M, Burnett AK, Löwenberg B, Kantarjian HM, Ossenkoppele GJ, Hills RK, Ravandi F, Pabst T, Evans A, Pierce SR, Vekemans MC, Appelbaum FR, Estey EH, Resistance prediction in AML: analysis of 4601 patients from MRC/NCRI, HOVON/SAKK, SWOG and MD Anderson Cancer Center. *Leukemia*. 2015 Feb;29(2):312-20

AML12, 15

Linch DC, Hills RK, Burnett AK, Khwaja A, Gale RE., Impact of FLT3(ITD) mutant allele level on relapse risk in intermediate-risk acute myeloid leukemia. *Blood*. 2014 Jul 10;124(2):273-6

AML15,16

Mohamed I, Hills RK, Burnett AK. Who is an "older" patient with acute myeloid leukaemia (AML)? An investigation of two NCRI/AML trials. *Br J Haematol*. 2014 Apr;165(1):147-51

Appendix 5

Major international presentations in the reporting year

UKALL14 and UKALL60+

Zakout G, Rai-Shetty L, Moorman AV, Fielding AK, Telomere DNA content and TP53 state provide an insight into genomic instability in older adult patients with ALL, *Haematologica*, 2014, 99 p6, European Haematology Association

NCRN336 - Phase II study to evaluate efficacy and safety of blinatumomab in relapsed/refractory ALL (BITE)

Stein, A., Topp, M. S., Goekbuget, N., Bargou, R. C., Dombret, H., Fielding, A. K, Forman, S. J. (2014). Allogeneic Hematopoietic Stem Cell Transplantation Following Anti-CD19 BiTE (R) Blinatumomab in Adult Patients with Relapsed/Refractory B-Precursor Acute Lymphoblastic Leukemia (ALL). *Blood*, 124 (21)., European Haematology Association

SPIRIT 2

S.G. O'Brien, R.E. Clark, C. Hedgley, J. Apperley, L. Foroni, C. Pocock, T. Holyoake, J. Byrne, C. Hodgson, W .Osborne, M. Copland, J.M. Goldman SPIRIT 2: an NCRI randomised study comparing dasatinib with imatinib in patients with newly diagnosed CML (2014) British Society for Haematology, 54th Annual Scientific Meeting, ICC Birmingham, 28th -30th April 2014.

Stephen O'Brien, Corinne Hedgley, Sarah Adams, Letizia Foroni, Jane Apperley, Tessa Holyoake, Chris Pocock, Jenny Byrne, Lynn Seeley, Wendy Osborne, John McCullough, Mhairi Copland, John Goldman, Richard Clark. SPIRIT 2: An NCRI Randomised Study Comparing Dasatinib with Imatinib in Patients with Newly Diagnosed CML (2014) European School of Haematology (ESH) 16th Annual John Goldman Conference on Chronic Myeloid Leukemia: Biology and Therapy. Philadelphia USA, 4-7th September 2014

O'Brien SG, Hedgley C, Adams S, et al. SPIRIT2: An NCRI randomised study comparing dasatinib with imatinib in patients with newly diagnosed CML. The American Society of Hematology (ASH) 56th ASH Annual Meeting, San Francisco, USA, 6-9th Dec 2014; *Blood* 2014;124:517.

SPIRIT 2 (Biobank)

Gerrard G, Hagkarim NC, Szydlo R, et al. Transcript levels of the hedgehog pathway member PTCH1 and SMO are predictive of imatinib failure in pre-treatment chronic myeloid leukaemia. The European Hematology Association (EHA) 19th Annual Meeting, Milan, Italy, 12-15th Jun 2014; *Hematologica* 2014;99(s1):S1316.

PACE

Le Coutre PD, Kim DW, Pinilla-Ibarz J, et al. Ponatinib in patients (pts) with Philadelphia chromosome-positive (Ph+) leukemias resistant or intolerant to dasatinib or nilotinib or with the T315I mutation: longer-term follow up of the PACE trial. The European Hematology Association (EHA) 19th Annual Meeting, Milan, Italy, 12-15th Jun 2014; *Hematologica* 2014;99(s1):S893.

Milojkovic D, Baker A, Whitehead L, et al. A national experience of the use of ponatinib in patients failing multiple tyrosine kinase inhibitors confirms efficacy in a heavily pre-treated cohort of patients with Ph+ leukaemias. The European Hematology Association (EHA) 19th Annual Meeting, Milan, Italy, 12-15th Jun 2014; *Hematologica* 2014;99(s1):S896.

Cortes J, Kim D-W, Pinilla-Ibarz J, et al. Long-term follow up of ponatinib efficacy and safety in the Phase 2 PACE trial. The American Society of Hematology (ASH) 56th ASH Annual Meeting San Francisco USA, 6-9th Dec 2014; *Blood* 2014;124:3135.

EPIC

Chuah C, Guerci-Bresler A, Rosti G, et al. EPIC: A Phase 3 trial of ponatinib versus imatinib in patients (pts) with newly diagnosed chronic myeloid leukemia in chronic phase. The European Hematology Association (EHA) 19th Annual Meeting, Milan, Italy, 12-15th Jun 2014; *Hematologica* 2014;99(s1):S679.

Lipton J, Chuah C, Guerci-Bresler A, et al. EPIC: A phase 3 trial of ponatinib compared with imatinib in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CP-CML). The American Society of Hematology (ASH) 56th ASH Annual Meeting San Francisco USA, 6-9th Dec 2014; *Blood* 2014;124:519.