ASH 2012 CLL Summary

What an exciting time for CLL! As our understanding of the disease has developed over the last 20 years, this has led directly to the development of novel therapeutic agents that appear to promise truly 'game-changing' outcomes for our patients.

ASH quote for 2012

Bruce Cheson at the microphone after the ABT199 phase 1 data was presented:

'[these are] exceptionally exciting data – the world is changing for lymphoma patients'

As always with my meeting summaries, these are a mix of personal interpretation and summaries from various talks and poster presentations. PLEASE remember there will be inaccuracies, as I will have missed some details, and apologies if you are an author and I have misinterpreted your presentation (this has happened before!).

There's a lot of data discussed here – including some lymphoma - I will also try and get the lymphoma summaries finished, but looking at the jobs list, that might not happen for ASH 2012….

George Follows

CLL / Lymphoma Lead, Cambridge, UK

Chair, UK CLL Forum

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Nicholas Chiorazzi

This was a fantastic overview lecture of the biology of CLL from a cellular perspective. Broad perspectives think of:

1. Mutational IgvH status as a fixed imprint of cell of origin that likely has lasting impact on biology
2. Surface marker e.g. CD38 CD49 etc reflect activity etc as real-time indicators
3. Genomic mutations – a mix of historical and evolving dynamics

Correlating the relationship between IgH mutational and biology of the cells

i. ***Direct relationship*** – mutated – see fewer Ag therefore less direct +
   Evidence: v biased IgvH / Stereotypy of CDR3 (30% of M and 50% of U-CLL) / polyreactiveity of Ig with multiple Ag – clear lab difference between unmutated(3/4) and

mutated (1/10). If bind 1 Ag oft bind more.Ag mostly autoAg – biproduct of apoptotic cells. Lack of binding good correlation with better survival. Signalling – lab asssaysunmutated stronger signals.

ii. ***Indirect relationship –*** interaction with other cells eg T cells may be fundamentally different between different cells of origin. BCR structure is fixed within the clone. Nature paper this year (Minden 2012) – manipulation of cell to express BCR and show signal immediately without need for Ag – Igbind each other and set off signal.

Cell Surface phenotype

i. Unique activities of individual surface proteins eg CD38 – not discussed
ii. Shared activities – signalling – map downstream phosphorylation status ad show clear diffs between CD38+ / ZAP70+ etc. Trafficing – certain molecules eg CD38 and 49d etc colocalise and clearly effect migration of cells. Within a clone there are clear variations of expression of cell surface markers - ?realtime reflection of activity of parts of the clone? – e.g. CD38 fraction – isolate and show higher Ki67

Genomic differences – clearly some fixed from early and affect the ability of the clone to signal etc and will / can evolve etc.

i. Old data on karyotypes etc – reflect different disease biology and subclones
ii. Mutations – growing associations between certain mutations and 'evolutionary' stage of the clones. Correlation of some mutations with some cytog. Generally the mutational genomic complexity is more in the AML type level than DLBL or solid organ cancer. Most identified mutations assoc with altered protein structure, so strong suggestion that biologically active.

<u>Adrian Wiestner</u>

Note the CML contrast – CLL is not driven by a mutation, but rather an addiction to signalling and we know through extensive biology research this means addiction to the host (microenvironment). Could CLL represent an opportunistic tumour that thrives on any activating signal it finds, or is it a misregulated autoreactive B cell that is dependent on autoregulation?

Efforts to link the CLL cell to the environment show there are clear differences. 24 patients – LN, BM, Pblood. Clear GEP signature of BCR activation in LN>BM>>PB.Similar – much higher P-SYK in this order.

Many interacting pathways and proteins downstream of BCR – most attractive targets are SYK, PI3K, BTK – all show target potential in TCL1 xenograft model. Can cross this mouse with BTK deficient mouse and show much slower generation of CLL.

Look at 3 compartments of patients on therapy. Most dramatic early change is in LN. Biopsy after 1 or 3 doses of ibrutinib, see very rapid reduction in Ki67 – with GEP see rapid fall n expression of BCR activation signature genes. Blood – much slower effect on cells - ? reflect different state of these cells. ?release phenomenon from LN. Note serum CCL4 which has been linked to BCR target gene

expression, falls rapidly with ibrutinib therapy. Early BM data suggest response is slower, but can show marked clearance of BM with persisting prominent PB lymphocytosis.

Fostamatinib trial (SYK inhibitor) – 3 non-responders had high levels of CD38 contrast with the 11 responders. Note, BCR GEP signal did not fall with fostamatinib.

Ibrutinib – was fear that would compromise Ig levels by switching off B cell signalling. However, in patients find they maintain IgG and M and increase IgA. Also see beneficial shift in T cell profile to Th2 immunity - ? acting via inhibition of IL-2 dependent pathways. Remember these kinase pathwyas can have very broad effects within the immune system – not always easy to predict what the final read-out will be! Note one patient on GS1101 has developed resistance through upregulaton of Pi3K alpha.

Paulo Ghia

Talk on MRD. I found this less interesting. There is quite a lot of comparative data comparing flow with PCR. There is a good chance that NGS will push the sensitivity a log or two further in terms of sensitivity. There is much debate as to whether MRD can appropriately be used as an early endpoint for assessment of therapy.

HOWEVER – peripheral blood MRD is thrown up in the air with the newer therapies. If on the new drugs a patient remains well for years with no LN and no B symptoms, I guess they would happily accept a persisting lymphocytosis i.e the old criteria of objective response may no longer correlate with patient benefit. Therefore working out how best to measure surrogate endpoints of success for the new drugs will be challenging.

With our current therapies, there was no discussion as to whether any evidence supports the early termination of potentially toxic drugs (eg FCR) if patients achieve early / interim MRD. This is a real question posed by clinicians and patients every week and I thought it warranted debate.

Freda Stevenson

Freda gave a presentation in the BCR signalling session. She discussed aspects of anergy and how there is potentially more anergy in mutated CLL. She presented a range of data – there is better Ag-IgM signalling when Ag is bound to beads – suggests signalling in the context of membranes is better. I guess much of this data is derived from PB CLL cells, and it is clear from other data that where the CLL comes from is critical in terms of biology.

Lou Staudt

This was a fantastic talk. There are different types of signalling from BCR. He reviewed signalling data from a range of different cell types and compare tonic signalling which is probably Ag independent with chronic active signalling.

He has widely used shRNA inhibition as an experimental model to knock out parts of the BCR signalling pathway and find which cell types are dependent on which parts. E.g. Burkitts – 2/3 die if knock down CD79a or SYK, however, they are OK if K/D Card11.

NGS of Burkittsi.d. mutations in TCF3 and ID3. TCF3 is a activating mutation, but ID3 is inhibitory, i.e. they are oncogenic and TSG respectively. Both are bHLH TFs bind IgH and L enhancers. TCF3 is the activator that binds and drives expression. ID3 heterodimerizes with TCF3 and acts as a negative regulator.K/O TCF3 → no B cells, i.e. critical gene. It appears that TCF3 is a critical TF that regulates a large range of gene expression in B cells with high overlap in Burkitts.

TCF3 also interacts directly to switch off active BCR signalling →inhibit SHP phos and see increase in PI3K activity. i.e. activating mutation in TCF3 (1/3 of BL) acts both on DNA, but also feeds into the signalling pathways higher up, augmenting AKT phosphorylatioin and increases PI3 kinase activity, i.e. this mutation also drives activity from the tonic pathway (I need to check all of this). Pan kinase inhibitors (BKM 120) profound killing effect on BL cells.

Then he compared with DLBL.

Basically an ABC cell comes from stacking up of plasmablasts that can't differentiate There is NFKB activatin that leads to IRF4 that should → plasma cells. But, genetic or epigenetic bock of BIMP1, so the cells cant differentiate and pile up at this stage.

Hallmark of AbC is chronic active signalling from BCR. Various different pathways from CD79a / Card11 complex / MYD88 etc. Suggestion that mutations can interact to amplify signals, but depending on there positional relationship to BTK, can predict whether ibrutinib will work.

Note – majority of MYD 88 mutations are L265P – strong independent mutation, but co-operate with IRAK1 and IRAK4 (inhibition of these can be very effective – later presentation).

Of ABC – 29% MYD mutations, 23% CD79a (10% overlap – suggests cooperation) and 10% card11. When looked at phase 2 trial saw exact fir with IBT responses – 5/7 CD79a, 4/5 both CD79a and MYD88, 0/5 MYD88 only (i.e. confirms BCR independent and MYD88 dependent) and 0/4 card11 only. **FANTASTIC example for the direction of travel for molecular diagnostics and targeted therapies in the future. This was patient data predicted then linked to molecular profiles.**

John Byrd

John gave a ranging presentation mainly concentrating on the inhibitors of SYK / PI3K. There was little too new in this summary – he pointed out that perhaps fostamatinib had been abandoned in haematological malignancy too early. In one early trial, there were 6/11 CLL responders. He is only aware of one on-going open study in relapsed DLBL. He showed GS1101 data which is particularly impressive in CLL. Mice had an IBD reaction with this drug – patients commonly get mild diarrhoea with only a few cases of more inflammatory diarrhoea. A transaminitis is noted more in NHL – this tends to work through with on-going treatment.

Clonal evolution in CLL – Landau Plenary

Using next generation sequencing with 160 cases (paired CLL and normal) identified 25 recurrent driver mutations (16 previously identified). We already know that CLL can be very variable in terms of clonal structure (our paper with the Sanger in PNAS 2008). Anna Schuh has already demonstrated heterogenous patterns of clonal evolution (Blood 2012). I enjoyed the presentation, but for me the strength was simply in the patient numbers analysed. They concluded that clonal expansion very

much correlated with chemotherapy treatment, implication being that treatment caused the expansion of subclones. This might be the case, but I strongly suspect there will be significant selection bias as they will have overselected patients who had relapsed post treatment i.e. already a much worse cohort. They correlated clonal diversity with prognosis (with independent multivariate analysis), but again for me, there must significant bias in this dataset.

Jan Berger–ibrutinib in plus rituximab–MD Anderson

Dr Berger presented data on 40 patients treated with combination oral ibrutinib plus rituximab. Patients were either relapsed CLL for first line 17 P. They saw the initial lymphocyte rise but by 12 weeks many patient's counts were normal with an average 50% reduction compared with pretreatment counts. Haemoglobin showed continuous improvement. Side effects generally well tolerated but 25% with mild diarrhoea–predominantly in the first few weeks. 38/40 patients continue on study. 2 patient's.–Aspergillus infection plus oral ulceration. Overall response rate 83% at 6 months but 3 patients had persisting lymphocytosis and partial remission.

Kyle Beckwith

Dr Beckwith presented data using a novel Immunogen compound. This combines anti-CD37 with a TM1 toxin. Both components of this immuno conjugate have been shown in separate use one to be effective at killing CLL cells. CD37 is expressed at high levels on CLL. They constructed an elegant mouse model with human CD37 transgenic mice crossed with the TCL mouse model of CLL. The immuno conjugate was remarkably effective at clearing CLL. I am unsure how far this is from clinical development.

John Byrd

Dr Byrd presented data on 116 patients treated with ibrutinib. 31 with treatment naive with the remainder relapsed refractory. Adverse events were reported in 20% of patients most having resolved by 3 months. There was no change in immunoglobulin levels. Grade 3 infection were much higher in relapse refractory patient at 40% compared with 10% in treatment naive. The treatment naive patients 4/31 had stable disease. I think one patient died of cryptococcal pneumonia (? this).

None of the traditional risk factors appear to have relevance to disease response or disease progression. In the relapsed cohort many progression events were missed his transformation. With median followup 26 months, progression free survival in treatment naive patients was 96% (80% for relapsed patients). Note that 6 patients previously treated with GS 1101–4 responded.

A BT263

This BH3 mimetic has shown early promise in CLL but there have been problems with thrombocytopenia. The re arm trial which had recruited 118 patient's as now being suspended in favour of development of ABT 199–this compound is much more specific for BC L–2 and therefore has much less cough target effect on BCL–XL.

Stephen Coutre – Stanford

Phase I trial looking at combinations of GS1101 with either rituximab, then to mass seen or tenderness in plus rituximab. Relapsed refractory patients–51 patient's fairly evenly treated between the arms. Similar overall response rates between 80–90 percent. 4/19 PD on GS1101 + rituximab (i.e. no bendamustine) compared with 1/32 PD in arms with bendamustine. However, all 6 deaths occurred in bendamustine arms. From whole cohort, PFS plateau seems around 60% from 12 months which is impressive data for this very difficult group of patients. Range of reasons for discontinuation – only 2 patients stopped beyond 48 weeks. They have one patient who progressed who responded to ibrutinib.

Veltuzumab

Subcut anti-CD20 antibody from Immunomedics. Fairly frequent dosing and responses in CLL not too good – as would expect.

Davids – phase I trial with ABT-199

NHL / CLL – R/R post at least one line of therapy.

CLL – single patient with 200mg tablet – marked decrease in lymphocytes after 8 hours, rapid decrease in LN and increase in LDH – laboratory TLS – not clinical.

Followed by dose reduction in CLL 50mg then 100mg →200mg

NHL increasing doses up to 900mg → 1 x TLS from 30 cases.

Fatty foods→increases AUC. Looking very interesting for mantle cell. 7/7 PR. Some remarkable rapid early responses (one patient with 22cm x 16cm LN – completely resolved within 8 days!). FL – 7/8 = SD but lower doses in phase I - ? need higher doses for FL.

CLL waterfall plot was staggering! ORR = 81%, PR=70%. Phase 1b with bendamustine ongoing.

Quotes from Bruce Cheson at the microphone

'exceptionally exciting data'. 'The world is changing for lymphoma patients'

CLL POSTERS / ORALS that were interesting, but I didn't review in person

FCR and prolonged cytopenias

Czech study – 252 patients treated with FC / FCR. Noted 30% prolonged cytopenias and clear correclation with 5 year OS. 75% vs 57%. Also ¼ of prolonged cytopenias developed MDS during follow-up with median OS 6 months.

Irish – FCR with rituximab at 375mg/m2 for all cycles

52 patients (mean age only 52!). Overall unfavourable cohort by SHM. 40% MRD negative by course 4, 70% MRD negative by end of therapy. Median follow-up of 20 months, 6 MRD neg→MRD pos. Only one patient with primary refractory disease had had further chemotherapy.

TRU-016 combined with bendamustine

Very interesting small molecule (SMIP) that binds CD37 – shown efficacy in CLL models and R/R trial of 57 patients. Previous max dose 20mg / kg. In this trial 6 patients at 15mg, then 6 at 20mg along with bendamustine at 70mg/m2 on day 1 and2. Neutropenia reported. Rapid early responses 9/12 in first cycle. 4 / 12 CRs, and early read out from investigator responses of 100% ORR. Looks very interesting.

French survey of relapsed CLL and treatment strategies

Highly variable! R-B, R-CHOP, R-FC, R-steroids etc Overall PFS was 12 months and median OS from first relapse was 36 months. Note those that were allografted had higher 4 year OS (70% vs 40%) but obvious selection bias. R-B had better OS than R-CHOP and campath.

Phase I trial of engineered anti-CD19 antibody in CLL (Xencor)

Modest toxicity. Some responses, but no future as monotherapy. ? a role in combination?

Lenalidomide + dexamethasone as first line CLL

Canadian study. Start with low dose 5mg, building to maximum 25mg OD. Neutropenia remains an issue. Rash and fatigue in over ½ patients – around 2/3 patients achieved PR / Cr with no progressions to date. Note response can be slow.

MD Anderson 2nd cancer data in assoicatioin with FCR

Patients treated from 2004 to 2010. 235 patients with median f-up 3.2 years. (this seems a small fraction of the patients they have presented previously). However, 90 patients had prior cancer and 39 developed cancer on follow-up. 11 MDS, 10 skin, others a mix. 24 Richters. Overall, Richters survival was the worst, but any previous or subsequent cancer history grouped patients in worse OS group.

Mayo clinic data looking at OS of younger patients

They found higher unmutated and short TTT in <55 years old, and most marked divergence from age matched controls as regards OS.

Mayo clinic data – risk of Richters from 1641 patients

Cumulative risk is 2.1% by 5 years. All worse prognostic markers appear to correlate with Richters, as does fludarabine and alkylator therapy. I guess the two must be linked.

Weill-Cornell BTK cell biology

Key component of inhibition of BTK signalling is a block on proliferation with fall off of proliferating cells.

FCR and aspirin! MD Anderson data

231 patients not taking aspirin vs 49 taking aspirin. Cohorts split by PFS and OS – apparently significant.

German review of bendamustine / BR for first line CLL in community practice

Not a trial, and clinician assessments of response, but ORR of 83 to 100% depending on the patient cohort. 12 to 17% patients hospitalised at some stage during treatment.

PWT143 – a novel PI3Kdelta inhibitor (Pathway therapeutics)

Highly effective at very low concentrations in vitro – orders of magnitude lower than GS1101 and ibrutinib. ? development plan?

Italian results with F+R followed by lenalidomide maintenance

Overall disappointing results from first 22 patients. Trial not progressed to next stage.

German lenalidomde for R/R CLL

3 different starting doses. Overall the trial continues with adequate responses for dose progression.

Cytokine analysis of stromal co-cultures with CLL

Very interesting data looking at interaction of CLL cells and stroma. GS1101 and ibrutinib clearly reduce the ability of stroma to rescue CLL cells after bendamustine treatment. Also reduce cytokine secretion. Fits nicely with our understanding of how these novel agents are thought to work.

Longterm analysis of MDACC FCR survivors

Of original FCR cohort 222 were treated over 10 years ago, 127 (58%) alive at 10 years and 78 (35%) alive a disease free at 10 years. 33 deaths in CR / PR fro minfection (5), seond malignancy (8), Richters (8), MDS (9) -> i.e. around 15% of patients die in first remission from non-CLL causes. They correlate 10 year PFS with initial response (interestingly they co-associate nPR and PR in this analysis), and completion of 6 cycles FCR, B2M and unmutated.

Spanish data on MRD post FCM-R and R-maintenance

Interesting. BM appears more sensitive than PB in their hands. Maximal benefit of R-maint may be in MRD + patients → 3 cases became MRD negative and overall prolonged PFS. No data on infections.

MDACC – looking at statins and relapsed CLL

284 relapsed patients treated with FCR. 35 on statins. 14/35 – no disease progression vs 36/249 no disease progression in non-statins. Also double median OS. ? how to explain this. ? direct relationship or ? unknown bias. From previous animal modelling, statins had been shown to impair the effect of rituximab. However, CLL patients have hig presence of dyslipidaemia. / relevant?

MDACC – PET in CLL

750 patients with at least 1 PET in CLL!!! SUV max greater than 10 marked difference in OS. If SUV <5, then low chance of Richters, and chance increases with SUV (not an absolute correlation). Fall of SUV post treatment also shows strong correlation with survival.

CD49d – expression correlates with t(12)

Key adhesion molecule. CD49d + cells show profiles of phosphor-activation – constitutive antigen R binding.

Italian data on Notch1, SF3B and BIRC3 mutations and 1st line treatment

Notch1 (20%) coassociates with t(12) and poor prognostic features. Lower Cr rates. SF3B - 13% - no correlation with poor prognosis in this study. BIRC3 rarer. Other Italian data looking at a larger patient group concluded Notch1 mutations in 10% of patients. In all subgroups (mutated, unmut, t(12) or not) etc. associates with shorter TTT and lower RR and lower OS. Munich data from 538 patients – found 13%. Clear association with unmutated, 17p del and t(12)

In vitro data with antibody anti-CXCR4

Fully humanised antibody (BMS) to CXCR4 – co-culture stromal assays. Effective inhibitor of CXCR12-4 interaction.

Gilead lab data looking at combination of GS1101 with novel syk inhibitor

Logic is that signalling downstream of BCR branches in multi-faceted way, so targeting 2 separate points in the p-way may give additional efficacy. GS-9973 – highly selective syk inhibitor. With a range of invitro activity assays, found synergistic effects with both agents together.

MDACC – analysis of characteristics of 172 pt with 11q deletion

57 – 11q alone, 105/172 – 11q + 13q, 10/172 – large mix of coassociated variables. Surprising claim was low level of bulky disease by CT and PET. 16/108 patients who were scanned. They did find shorter TTT, but comparing with a separate 13q deleted cohort, no diff in ORR and OS. Note mix of protocols. Note – other datasets have looked at characterstics of 11q patients at time of treatment. Could this account for the differences?

John Byrd's group looking at Zap-70 promoter methylation

This has floated around for a while. Now validated on an independent patient cohort. If the promoter is methylated, this correlates with better outcome. Surely there are complex co-associations behind this finding.

Pim kinase and its role in CXCR4 expression and phosphorylation

Freiburg group – increasing interest in how this kinase is mutated and overactive in a range of haem malignancy. They how direct correlation with CXCR4 –P state, expression and CLL homing. Inhibitors reduce homing and induce apoptosis.

CLonal evolution in CLL – Universtiy of Michingan

Longitudinal study of 143 patients studying aCNA, aUPD and mutations in 3 specific genes. i.e. large study, but limited analysis tools compared with Plenary session and Anna Schuh's sequencing. Comparisons made 24 months apart for no therapy patients and at relapse for chemotherapy patients. 27/143 acquired changes – 19% over the study, i.e. 81% genetically stable. 19/27 added lesions and lost none, i.e. clear clonal evolution. 4/27 acquired TP53 mutaion and 2/27 acquired NOTCh. Only 1 relapsing case had a clone that had no relation to the presenting clone by aCNA, aUPD. 50% of the clonal evolution cohort had received chemotherapy, i.e. suggestion that chemotherapy drives this process. (I cant accept this is so definite at this stage – CLL patients that need to be treated have selected themselves as more aggressive. This reanalysis was done on those cases relapsing after chemotherapy, so again, further selected to be the most difficult. Is it safe to say at this stage that chemotherapy is driving the evolution of the clone, or is chemotherapy and relapse a marker for the most unstable CLL cases??).

Claudia Hafferlach – impact of homozygosity and size of 13q deletion

Large numbers of patients from very large reference lab in Germany. Basically hard to show any difference in TTT or OS – additional 11q did show shorter TTT.

Other cancers in CLL patients – MDACC data

We know this is elevated. From 1364 MDACC patients with median f-up 8 years, found around ¼ CLL patients had another cancer. Simplifying the figures, about ½ pre-diagnosis (older cohort) and ½ post diagnosis. Skin>>prostate>breast/lung/GI etc etc. If develop 2nd cancer after diagnosis, this is a often a major contributing factor to death. If no 2nd cancer, major causes of death remain CLL or CLL-related complications.

Note Mayo clinic data in another presentation suggests CLL skin cancer patients do worse than expected – particularly skin cancer presenting post CLL-therapy.

PET-CT in CLL – Mayo clinic

All patient records of 4030 CLL patients seen at the Mayo clinic over 5 year period. 526 PET / CT scans, 472/526 = abnormal. 78 scans - useful for directing biopsy → 21 Richters and 9 other cancers. Overall concluded that 37 scans revealed novel complications of CLL – i.e. 8% of PET / CT scans provided new information. Presumably the cohort was already pre-selected on clinical grounds, so I can't place this figure. Is this a good 'hit-rate'??

T(12) datasets from British Columbia and MDACC

BC data – 19% of CLL patients. Low level co-association with 17p-, 11q- and slightly higher with 13q-. These 13q patients appeared to have longer TTT.??better OS. Otherwise BC data did not identify this cohort as poorer risk. If 13q-, then don't have notch.

MDACC data (312 t(12) patients) suggest higher incidence of progressive disease, Richters and second cancers.

Ingo Ringshausen – Munich – looking at the role of stromal cells in CLL

Mouse modeling of PKC pathways in stromal cells. Fascinating data – when they cross TCL1 leukaemic cells into mice with PKC pathway knocked out in stromal cells (not able to activate NFkB), CLL can't engraft (also compromised in other LPDs).

Nick Chiorazzi's group (Piers Pattern) looking at B-T interactions

They have a NOD scid transplant model of CLL – they have shown the importance of autologous T-cells in maintaining B-cell activation and engraftment. They have shown a tendency to plasma cell differentiation of CLL cells is an 'escape' in this model. Is this due to loss of T-cell signalling? I didn't get this bit…

They have also looked at GEP of cells from CD5high, CXCR4 low (i.e.proliferative) and the opposite fractions from the same clone. From GEP showed correlation with high expression of genes associated with cell division in the former, and genes associated with death associated pathways in the latter.

Inhibition of the CXCR4-CXCL12 axis with spiegelmers

Novel compounds – spiegelmers are L-isomer oligonucleotides that are designed to specifically bind proteins. Nox-A12 has been designed to bind CXCL12 (SDF-1). This chemokine is central to cell migration and interaction with stromal cells. Intriguingly Nx-A12 deregulates this axis by increasing exracellular release of CXCL12, but inhibits its function → alters migration of CLL cells in in vitro assays. As survival signals are disrupted, they hypothesised this will remove the protective stromal effect that can overcome chemotherapy cytotoxicity. They show in assays that CLL cells post chemotherapy exposure are much more likely to die after NoxA12 treatment.

German CLL8 data and distribution of mutations

P53 mutations evenly distributed between notch and SF3B1 and consistently do worse.. With their data, Notch mutated patients had worse PFS. NO benefit seen for notch1 mutated patients with rituximab. SF3B1 mutation patients did worse in both arms of the trial. From previous data, we know that the no FISh abnormality group had no benefit from rituximab. Now we have this notch data. The addition of R brings additional cost and possibly additional complications. Is this retrospective analysis strong enough to effect prescribing practices?? Could the REACH cohort be analysed as an alternative validation cohort??

French FCR data – 4 cycles with alternative dosing strategies

Overall similar total R dose, but FC for 4 cycles. Less chemotherapy overall. ORR 96%, so efficacy seems clear. Median age 71 (65-85) and early treatment related mortality was 3.1%.

Long term CLL8 follow-up

Just about 6 years f-up – 38% of FCR patients still in 1st remission and 70% FCR alive. 2nd malignancies around 10%. 4% Richters and 1.5% MDS/AML.

John Gribben – tracking 'pseudoexhaustion' in CLL T cells

CD160 and CD224 are upregulated on exhausted T cells. Chronic viral infection etc. Lose IFNg response. Similar pattern seen in CLL – some reversal with lenalidomide.

MLL lab – large data set on SF3B1 mutations in CLL

Quite complex as around 10% of CLL. Higher association with other poorer markers such as unmutated and 11q etc. With 13q, marked effect on TTT – 1 year vs 7 without!

Sarah Canon – FR +lenalidomide

Very low dose lenalidomide. ORR 65% which seems low. Acceptable toxicity.

German data on Notch / SF3B1 / TP53 mutations in fludarabine refractory patients

Most enrichment in TP53 – 37% in this study. Others – SF3B1 = 17%, notch – 13%.

German refractory / 17p deleted trial – treated with campath

12% deaths from infection. 1st line 17p- clearly do better. Suggestion of better OS with allograft than campath consolidation, but very different ages etc.

German data looking at biology of SF3B1 mutation

Show mutated CLL cells don't upregulate p53 target mRNA following irradiation etc. Looked most similar to 11q- deleted cells, i.e. defective but not absent p53 response. In vitro – less apoptosis post irradiation / chemotherapy. ? what is the cause of this link?

CAR technology in CLL and ALL

This is the most striking development in leukaemia therapeutics. A number of presentations at ASH outlined the technology and excitement! A key feature has been development of the construct technology. Autologus T cell harvest and transfection. Reinfusion. 3/9 CLL no response. 2/9 transient PR and 3/9 CR. All CR patients had a cytokine release syndrome and no CR patient has relapsed. CART19 lymphocytes can be detected in blood in responding patients (and in the CSF in the single ALL patient). Note use of IL-6 antagonist tocilizumab from day 3-10 resolved the fevers etc.

Davide Rossi MUCY risk profiling

637 time fixed new dx CLL and 257 CLL with sequential samples. Analysed mutations in TP53 / Notch / SF3B1 / MYD88 and BIRC3 and FISH for standard and BIRC3. Split into 4 prognostic groups. 13q alone – not statistically diff from OS of general population. Low risk = t(12) or normal with no mutations. Intermed risk – Notch / SF3B1 and /or 11q BUT normal p53 or BIRC3. Highest risk had either deletion or mutation of TP53.

NOTE – this model does not weight for MUT / UNMUT or Rai stage etc.

Lenalidomide monotherapy as first line for CLL

25 patient phase 2. Follow-up now out to 47 months. Note relatively low ORR of 56%. Tumour flare and cytopenias (neutropenia++) remain an issue. Of original 25 patients, 12 remian on study. 13 stopped – 8 toxicity / 4 lck of response and 1 remote second cancer. 1/25 = lung. 1/25 = richters.

A cohort may achieve long term remissions on low doses. Myelosuppression remains an issue.

SAMHD1 – Oxford

Protein controls the use of dNTPs. Mutation → accumulation of dNTPs. Is this a novel tumour suppressor. 100 local patients – found mutated in 8 /100 – 6/8 were chemo refractory. From larger pool of pt, 15/200. Early data but interesting.

John Byrd – monotherapy ofatumumab for CLL

For me, there was little surprising in this data. Fairly good toxicity profile. RR similar to rituximab.

MDACC – ofatumumab + lenalidomide

Relapsed CLL – 36 patients. Less tumour flare than expected. Neutropenia as would probably expect. Approx 70% response rates including 3 MRD negative CRs. Median response was 22 months, so fairly respectable in this population.