NCL Joint Formulary Committee (JFC) Meeting

Minutes from the meeting held on Thursday 25th July 2013

In UCL Room 347, SSEES, 16 Taviton Street, WC1H 0BW

1. Present:	Prof R MacAllister	NCL JFC Chair
	Dr A Jones	Consultant Oncologist, RFH/UCLH
	Dr E Boleti	Oncology RFH
	Mr A Dutt	NHS Islington, Head of Medicines Management
	Mr P Gouldstone	NHS Enfield, Head of Medicines Management
	Mr TF Chan	BCFH Chief Pharmacist
	Ms N Shah	NHS Camden, Head of Medicines Management
	Mr G Irvine	Lay Member
	Ms S Drayan	NMUH Chief Pharmacist
	Mr T James	MEH Chief Pharmacist
	Dr M Kelsey	WH DTC Chair
	Ms W Spicer	RFH Chief Pharmacist
In Attendance:	Dr A Grosso	UCLP Pharmacist
	Dr M Leandro	UCLH Rheumatology (Applicant)
	Dr M Ehrenstein	UCLH Rheumatology (Applicant)
	Ms S Moore	UCLH Specialist nurse – Rheumatology
	Ms A Fox	UCLH Specialist nurse – Rheumatology
	Ms K Chapman	MEH Formulary Pharmacist/JFC Support Pharmacist
	Ms S Sanghvi	UCLH Formulary Pharmacist
	Ms R Holland	UCLH Formulary Pharmacist
	Dr G Arand	NMUH Applicant
	Prof M Johnson	RFH Applicant
	Ms E Mortty	Haringey Medicines Management
	Mr P Bodalia	RNOH Deputy Chief Pharmacist
	Mr K Thakrar	UCLH Pharmacist
	Dr M Hamilton-Farrell	Co-Chair Joint Prescribing Group, Barts Health
	Mr M Wyke-Joseph	NMUH Formulary Pharmacist
	Mr N Marshall	RFH Consultant HIV Pharmacist
	Dr R Sofat	Consultant Pharmacologist
	Ms I Samuels	RFH Formulary Pharmacist
Apologies:	Dr S Shaw	RFH DTC Chair
	Dr H Taylor	WH Chief Pharmacist
	Prof L Smeeth	NCL JFC Vice Chair
	Dr R Fox	RNOH DTC Chair
	Dr T Sadhu	NHS Enfield
	Dr L Wagman	NHS Barnet CCG
	Dr R Urquhart	UCLH Chief Pharmacist
	Ms L Reeves	C&I Mental Health Trust
	Dr A Tufail	MEH DTC Chair
	Prof A Hingorani	Clinical Pharmacologist
	Mr A Shah	RNOH Chief Pharmacist
	Dr W Zermansky	Haringey CCG
	Dr M Broadbent	BCF DTC Chair
	Mr A Karr	NCL Procurement Chair

2. Minutes of the last meeting

The previous meetings minutes were accepted as accurate.

3. Matters arising

There were no matters arising.

4. Members & applicants declarations of relevant conflicts of interest

RA Biologic Applicants: Dr M Ehrenstein: Consultancy for Roche and Chugai. Dr M Leandro: Honoraria for consultancy and oral presentations and congress attendance from Roche and Chugai. Ms S Moore: received support from Roche for course attendance.

Dolutegravir Applicant: Dr. M Johnson: recruited patients for the SAILING study

5. Medicine applications & reviews

5.1 RA biologic monotherapy: tocilizumab/rituximab/abatacept (Applicants: Dr Leandro/Dr Ehrenstein& Presentation: K Thakrar, K Chapman, S Sanghvi)

The Committee considered applications for the use of three different biologic therapies (tocilizumab; rituximab; abatacept) for rheumatoid arthritis to be used as monotherapy when methotrexate is contraindicated or not tolerated. This indication is not covered by current NICE guidance.

Tocilizumab: The Committee considered recent studies that suggest tocilizumab monotherapy achieves similar rates of remission to the combination of tocilizumab and methotrexate. The Committee first reviewed the results from the ADACTA study - a phase IV, randomised, double-blind, multi-centre study of 24 weeks' duration to compare the efficacy and safety of tocilizumab monotherapy with adalimumab monotherapy in patients with RA who were intolerant to methotrexate (MTX). Eligible patients were aged ≥ 18 years old with RA for 6 months or more, and unable to tolerate MTX. Patients previously treated with a biologic DMARD were excluded. Participants were randomised (1:1 ratio) to receive tocilizumab (8mg/kg) every four weeks plus placebo subcutaneously every two weeks or adalimumab (40mg) subcutaneously every two weeks plus placebo intravenously every four weeks. The primary efficacy end point was change in DAS28-ESR from baseline to week 24; the mean change in DAS28-ESR was significantly greater in the tocilizumab group than in the adalimumab group (-3.3 versus -1.8, respectively; 95% CI -1.8 to -1.5; p<0.0001), confirming superiority of tocilizumab over adalimumab. The secondary end points also showed statistical significance in favour of tocilizumab for DAS28 remission; ACR20, ACR50, ACR70 rates, and EULAR good response.

The Committee also reviewed the ACT-RAY study, a randomised, double-blind, phase III trial designed to evaluate the safety and efficacy of adding tocilizumab (8mg/kg every four weeks) to MTX (n=279) versus switching to tocilizumab monotherapy (n=277). Inclusion criteria were patients with confirmed RA (according to ACR criteria) with active disease despite MTX therapy. The primary end point was the DAS28 remission rate (DAS28 <2.6) at week 24. A higher proportion of patients in the combination group (tocilizumab plus MTX) achieved DAS28 remission compared with the tocilizumab monotherapy group (40.4% vs 34.8%; p =0.189). However, the absolute difference between the two groups of 5.65% (95% CI -2.4% to 13.6%) was much smaller than what had been considered as a clinically relevant change in the expected DAS28 remission rate (12.5%). With regards to the secondary end points, the difference between the two groups at week 24 was similar, with a small numerical trend (of unknown clinical significance) favouring the combination arm. There was no difference in the ACR scores between the two groups. In addition, the radiographic outcomes show that the percentage of patients who had no disease progression (defined as the total Genant-modified Sharp Score of <0) was 65.7% in the combination group and 59.1% in the monotherapy group (p =0.0871). The Committee noted that the study has limitations in that there are no EULAR results for good response alone; the data provided is a composite of good and moderate responses, and although the additional analysis has some good radiological data, the clinical relevance of each score and its correlation with disease states is unknown.

With regard to safety, the Committee noted that the incidence of adverse events between the tocilizumab monotherapy (82.1%) and adalimumab monotherapy (82.7%) arms in the ADACTA study was similar. The most commonly reported adverse events were: upper respiratory tract infections, nasopharyngitis, and worsening of rheumatoid arthritis symptoms. A published ACT-STAR study was a 24-week, open-label study assessing the safety and tolerability of tocilizumab monotherapy (8mg/kg every four weeks) versus tocilizumab in combination with a DMARD. Similar rates of adverse effects were seen between the two treatment groups. The Committee agreed that results published in ADACTA study confirm the superiority of tocilizumab monotherapy over adalimumab monotherapy,

whereas the results from the ACT-RAY study show that tocilizumab monotherapy was of similar efficacy to that of tocilizumab in combination with MTX.

Rituximab: The Committee considered a randomized, double-blind, controlled study by Edwards *et al.* of 161 patients who had active rheumatoid arthritis despite treatment with MTX to receive one of four treatments: oral MTX (≥10 mg per week) (control); rituximab alone (1000 mg on days 1 and 15); rituximab plus cyclophosphamide (750 mg on days 3 and 17); or rituximab plus MTX. On the basis of the primary end point of an ACR 50 response at week 24, the regimens of rituximab in combination with either MTX or cyclophosphamide resulted in levels of response that were significantly higher (P=0.005) than the levels in the control group. The ACR 50 response in the rituximab-monotherapy group was numerically higher than the response in the control group (which received only MTX) but the difference did not reach statistical significance (P=0.059).

The Committee reviewed a retrospective observational study by Solau *et al*. evaluating the response to rituximab treatment in daily practice in the following three specific situations: rheumatoid factor (RF)-negative RA patients, rituximab monotherapy patients and TNF inhibitor-naive patients. One thousand milligrams (1000 mg) of rituximab was administered twice at an interval of 15 days. Therapeutic response was determined at mean 20 weeks after the infusion on the basis of DAS28 scores and EULAR response criteria. Twenty-nine received rituximab as a monotherapy, and five received the drug together with another disease-modifying treatment (leflunomide in three cases and sulfasalazine in the other two cases). No statistically significant baseline differences were observed between patients treated with rituximab and MTX and those treated with rituximab alone. However, the patients in the monotherapy group were older (P = 0.02). A EULAR response was observed in 79.3% of the monotherapy patients and in 73.8% of the patients who had received rituximab with methotrexate.

The Committee considered the safety of rituximab from a study by Edwards *et al* which found that all treatment groups had a similar overall incidence of adverse events, with 73 to 85 percent of patients reporting at least one event; 30 to 45 percent of patients in each group had events associated with the first infusion. The majority of adverse events associated with rituximab infusions were characterized as mild or moderate. The Committee concluded that there does not appear to be any evidence of an increased incidence of adverse effects when rituximab is used in monotherapy compared with combined MTX/rituximab therapy.

The Committee agreed that while it is preferable to use rituximab in conjunction with methotrexate [licensed usage], rituximab monotherapy appears an efficacious and a reasonable option for the treatment of RA for patients who cannot tolerate, or have contraindications to, methotrexate.

Abatacept: The Committee considered evidence supporting the efficacy of abatacept monotherapy, for patients with methotrexate intolerance or contraindications. It was noted that two preparations of abatacept are licensed in the UK; one delivered by subcutaneous (SC) injection and the other by intravenous (IV) infusion. The Committee noted that at the time the abatacept NICE TA was published the SC injection was not available, and was therefore not considered in the NICE pathway.

The Committee reviewed a 6-month open label study of abatacept in patients with active RA who had failed anti-TNF therapy for 3 months or longer and had a disease activity score in 28 joints (DAS28) of 5.1 or more by Schiff *et al*. There were two arms; washout patients (n=449) who discontinued anti-TNF therapy at least 2 months before screening, and direct switch patients (n=597) who were initiated on abatacept 10mg/kg IV infusion at their next scheduled anti-TNF therapy dose. After 6 months, the improvement in efficacy and quality of life with abatacept was similar in both arms, with mean reduction in DAS-28 of 2.0 and a clinically meaningful improvement in DAS-28 in 56.1% of patients. There were no significant differences in secondary outcomes including improvement in quality of life and safety. A subset of 43 patients (20 washout, 23 direct-switch) received abatacept as monotherapy. The efficacy in these patients was comparable to that seen in patients with a background DMARD. The mean reduction in DAS-28 was 1.8 with clinically meaningful improvement in DAS-28 in 48.8% of patients in the abatacept monotherapy group.

The Committee reviewed the results of a 4-month multi-centre, parallel-arm, open-label study, with an on-going long-term extension period, evaluating the immunogenicity to SC abatacept, with or without methotrexate and in the absence of an IV loading dose by Nash *et al*. Patients were stratified to receive either abatacept SC 125mg weekly as monotherapy or in combination with methotrexate.

Both arms showed similar, low immunogenicity rates at 4 months and in the long-term extension period. In terms of clinical efficacy, the mean reduction in DAS-28 at 4 months was 1.7 (95% CI 1.3-2.1) in the combination group and 1.9 (95% CI 1.4-2.5) in the monotherapy group. The percentage of patients with clinically meaningful DAS28 improvement at month 4 was 62.5% in the combination group and 66.7% in the monotherapy group. These improvements were maintained in patients in both arms who entered the extension period up to 18 months, with reduction in DAS-28 scores of 1.8 and 2.9 in the combination and monotherapy groups respectively. SC abatacept in the absence of an IV loading dose was well tolerated, regardless of whether patients received monotherapy or combination therapy, with a similar safety and efficacy profile to previous studies of both SC and IV abatacept. The Committee noted that the study was limited as it was small,pharma-company funded, and had an open label, non-randomised design.

With regard to safety, the Committee noted that Schiff *et al* study found 83.7% of patients who received abatacept monotherapy reported adverse events, with 9.3% of these considered serious adverse events. This was similar to patients receiving a background DMARD. In general, the most commonly reported adverse events are upper respiratory tract infections, headache, nausea, sinusitis, diarrhoea, bronchitis and fatigue.

The Committee heard that the applicants have contacted rheumatologists across the NCL group who were in agreement with the proposed use of the above biologics, and an NCL wide pathway would be possible, specifying which would be first, second and third-line. Ms Shah advised the Committee that a business case would be required to support the pathway, and agreed that one business case will suffice for NCL so long as the applicants provide each CCG with an estimated number of patients to be treated at each hospital site. The Committee also requested written confirmation from the pharmaceutical company on the patient access scheme details with respect to their equivalent offerings for use as monotherapy.

In summary, the Committee concluded thatall three treatments as monotherapy provide a reasonable clinical option for patients who are intolerant to, or unable to receive methotrexate, and all three drugs were recommended pending the above confirmations and CCG business case approval.

5.2 Dolutegravir (unlicensed; ViiV Healthcare) for integrase resistant HIV (Applicant: Prof M Johnson; Presentation: I Samuels)

The Committee reviewed the evidence to support an application for dolutegravir, a novel treatment for integrase resistant HIV. Dolutegravir is not currently licensed in any country, and is currently provided free of charge on a patient access scheme until licensing (expected mid-2014).

The Committee heard that there are currently no alternative treatment options for patients with this form of resistance. There are two licensed integrase inhibitors available, raltegravir and elvitegravir, however unlike dolutegravir; neither have activity against HIV with INI mutations. Although now considered a chronic disease, a small proportion of patient harbour extensive HIV resistance, including resistance to the available first generation integrase inhibitors. *In vitro* studies demonstrate limited cross-resistance between dolutegravir and raltegravir or elvitegravir.

The Committee reviewed results from the Viking I and II studies, a multi-centre, phase IIb, open-label, single arm pilot with two sequential cohorts of HIV-1 infected individuals who have failed on the integrase inhibitor raltegravir and have evidence of raltegravir resistance at screening. Two cohorts were enrolled within this protocol, the first was given dolutegravir (DTG) 50mg once daily (cohort I)for 24 weeks, however, the [viral load] response of some subjects prompted protocol amendment and subsequent evaluation leading to an increase to dolutegravir 50 mg twice-daily in the second cohort (cohort II). In both cohorts, subjects continued their failing regimen (with the exception of raltegravir which was stopped) and added dolutegravir for 10 days. Background therapy could be optimised from day 11 onwards. Subjects were grouped according to their integrase mutations to ensure a broad range of mutations were included, but results were not analysed according to mutation. Subjects were antiretroviral therapy (ART) experienced, HIV-1 infected adults (≥ 18 years of age) with plasma HIV-1 RNA levels of ≥ 1000 copies/mL, genotypic integrase (INI) resistance, and documented genotypic and/or phenotypic resistance to ≥ 1 compounds in each of 2 other approved classes of ART (nucleoside reverse transcriptase inhibitors [NRTIs], non-nucleoside reverse transcriptase inhibitors [NNRTIs], protease inhibitors [PIs], and fusion/entry inhibitors).

The primary endpoint of efficacy at day 11 as measured by a viral load [VL] of < 400copies/ml or ≥0.7 log10 copies/mL was achieved in 78% of patients in cohort I and 96% in cohort II. 41% and 54% of patients achieved a VL of < 400c/ml in cohort I and II respectively. 17% patients achieved a VL of < 50c/ml in cohort II compared to 11% in cohort I. The Committee heard that 5 patients demonstrated evolution of additional integrase resistant mutations, a reduction in DTG susceptibility, or both (2/18 with viral failure I cohort I, 3/15 with viral failure in cohort II) by day 11 of the study.

The Committee considered the initial results of the VIKING-3extension of the previous VIKING cohorts; data was presented as an oral abstract and has not yet been published in a peer-reviewed journal. VIKING-3 recruited a further 183 patients with documented resistance to the integrase inhibitors raltegravir or elvitegravir and resistance to at least 2 other ART classes. Patients received 8 days of DTG 50mg BD in addition to their current failing ARV regimen (but stopped raltegravir) and then were allowed to optimise their ART regimen from day 9 onwards. A third of patients had no primary INI resistance at screening, but had previous documented resistance from prior INI failure. A week 24 snapshot analysis showed 72/114 (63%) had achieved VL<50c/mL, with 37/144 (32%) classed as virologic non-responders. Response was lower in those with the Q148 mutations (although this only accounted for 5% of patients). Week 48 results are not yet available.

The Committee noted that with regards to safety there are limited data due to the short follow-up time in studies. However, more extensive follow up, with a larger group of patients has been performed in the treatment-naïve setting (50mg daily) which showed an increase in serum creatinine of 10mmol/ml. This typically occurs within the initial 4-8 weeks and persists whilst on therapy. The Committee noted that adverse effects are similar to those of other integrase inhibitors and generally include diarrhoea insomnia, headache, bronchitis or cough. Dolutegravir is taken as one tablet, twice a day.

The applicant informed the Committee that a patient access scheme is currently in place, and when dolutegravir achieves marketing authorisation in the UK it is likely to be priced similarly to other integrase inhibitors currently available. The applicant expects to see between 3-6 patients per year.

In summary, the Committee agreed that dolutegravir is effective in patients with documented resistance to INI and has a similar safety profile to other INIs. The Committee recommended dolutegravir for inclusion in the formulary for use in patients with noted resistance to other INIs. However, it was noted that each Trust would have to sign-off the financial risk of using this treatment under the [free-of-charge] patient access scheme as this scheme will cease upon successful UK licensing

5.3 Ibandronic acid for the prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases(Applicant: Dr G Anand; Presentation: K Chapman)

The Committee considered an application for ibandronic acid for the prevention of skeletal events in breast cancer patients with bone metastases.

The committee reviewed results from a randomised, double-blind placebo-controlled phase III trial from Body *et al* evaluating the safety and efficacy of intravenous ibandronic acid for the treatment of skeletal complications in breast cancer patients with bone metastases. 466 patients were randomised to receive ibandronic acid at either 2mg by bolus injection or 6mg by infusion over 1-2 hours, or placebo. The study was not blinded with regard to dose of ibandronic acid. Only 40% of patients completed the full 96 weeks of treatment. The primary reasons for study withdrawal included adverse events, death, treatment refusal, loss to follow-up and protocol violation. Results indicate that 6mg IV ibandronic acid is effective and safe in the treatment of bone metastases from breast cancer compared to placebo. Patients receiving the 6mg infusion had a 20% relative reduction in the skeletal morbidity period rate (SMPR) compared with the placebo group (1.19 versus 1.48 periods with events per patient year; p=0.004). An 11% reduction was observed for ibandronic acid 2mg, but this was not statistically significant.

The Committee also reviewed results from a randomised, placebo-controlled trial by Heras*et al* evaluating the efficacy and safety of intravenous ibandronic acid in patients with metastatic bone

disease following breast cancer. The primary efficacy end point of the study was the proportion of patients (n=150) who developed skeletal-related events (SREs) over 24 months. Ibandronic acid significantly reduced the proportion of patients who experienced an SRE compared with placebo (36% vs. 48%; P = 0.027). Multiple event analysis showed that ibandronic acid reduced the risk of developing an SRE by 32% (hazard ratio = 0.69; 95% confidence interval 0.42–0.79; P = 0.003).

The Committee heard that the license for oral ibandronic acid is based on pooled data from two multi-centre, placebo-controlled, randomised, double-blind phase III trials involving a total of 563 women over 96 weeks. The primary efficacy measure was again the SMPR. The results show that ibandronic acid significantly reduced the mean SMPR compared to placebo (0.99 versus 1.15 periods with events per year, p=0.004); the clinical significance of this reduction was not clear.

The Committee considered the efficacy of oral ibandronic acid compared to intravenous zoledronic acid from a short-term open-label Phase III study by Body *et al*. 275 women who were randomised to treatment with oral ibandronic acid 50mg/day or intravenous zoledronic acid (4mg every four weeks) for up to 12 weeks. The primary endpoint was the mean percentage change in serum levels of the bone resorption marker cross-linked C-terminal telopeptide of type I collagen (S-CTX).Oral ibandronic acid was shown to be statistically non-inferior to zoledronic acid for this primary end-point, and there were no statistically significant differences between the two treatments in terms of bone pain. The majority (95%) of patients were receiving concurrent therapy of breast cancer and both groups were well balanced at baseline. The Committee noted that the evidence for equivalence is limited in this study by its short duration, and that a biochemical rather than clinical endpoint was used.

The Committee considered a Cochrane review by Wong *et al* that found that use of ibandronic acid in women with advanced breast cancer and clinically evident metastases significantly reduced the risk of developing a skeletal event by 14% (RR 0.86; 95% CI 0.73-1.02) for 50mg oral ibandronic acid (p=0.08) and 18% (RR 0.82; 95% CI 0.67-1.00) for 6mg IV ibandronic acid (p=0.04). This compares to a 16% reduction in risk for 1600mg oral clodronate [(RR 0.84; 95% CI 0.72-0.98) p=0.03]. However, zoledronic acid 4mg IV showed the greatest risk reduction of 41% [(RR 0.59, 95% CI 0.42-0.82) p=0.001].Wong *et al*concluded that oral ibandronic acid (50mg taken daily), in addition to chemotherapy or hormone therapy, is effective in reducing bone pain, the rate of SREs and improving global quality of life. It may also delay the time to SREs and may diminish the likelihood of developing a new SRE.

The Committee noted that in regard to safety,the most common adverse effects are gastrointestinal (GI) disturbance and hypocalcaemia (as with other bisphosphonates). When compared with zoledronic acid in the Body *et al* (2007) study, GI symptoms occurred slightly more frequently in the ibandronic acid group (11% versus 8%); whereas musculoskeletal disorders, general disorders and nervous system disorders were more commonly seen in association with zoledronic acid. There may be a lower risk of renal toxicity with ibandronic acid than other bisphosphonates.

The Committee raised the potential use of IV zoledronic acid in preference to other agents for this indication; it was noted that a switch from sodium clodronate to ibandronic acid for this indication would be a significant cost saving, however, the use of generic zoledronic acid is potentially a more cost-effective option when drug costs alone are taken into account.

The Committee concluded that oral ibandronic acid appears to be a cost-effective and safe option for prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases. This would replace the current option of sodium clodronate as the first-line oral bisphosphonate for this indication. However it was noted that IV zoledronic acid maybe the most effective bisphosphonate for this indication.

Dr Boleti reported that she is currently in the consultation stage of a treatment pathway to clarify the place in therapy of all treatment options for patients with breast cancer and bone metastases (with particular reference to IV bisphosphonates and denosumab). This is intended to be agreed and used across all NCL Trusts and CCGs. Ms Chapman agreed to circulate this draft document for comments prior to the next meeting.

In summary, the Committee agreed that oral ibandronic acid should be made available but that further clarification on its exact place in therapy is still required.

5.4 Oral vinorelbine (Navelbine®; Fabre) for advanced breast cancer and advanced non-small cell lung cancer (Applicant: Dr G Anand; Presentation: M Wyke-Joseph)

The Committee considered an application for oral vinorelbine to replace IV vinorelbine for patients receiving chemotherapy for advanced breast cancer (ABC) and advanced non-small cell lung cancer (NSCLC). Vinorelbine is an anti-neoplastic drug of the vinca alkaloid family which has traditionally been used as an intravenous (IV) formulation. NICE guidance 121 (Lung Cancer) and 81 (Advanced Breast Cancer) both recommend vinorelbine for treatment of these conditions. The Committee heard the oral vinorelbine is recommended for use within NHS Wales as a single agent for the treatment of advanced breast cancer stage III and IV relapsing after or refractory to an anthracycline-containing regimen(in line with current NICE recommendations for IV vinorelbine). It has also been accepted for restricted use within NHS Scotland for the first line treatment of stage lll or IV non-small-cell lung cancer (NSCLC).

The Committee reviewed results from the Bourgeois *et al* study assessing the equivalence of oral and IV products. Vinorelbine was administered as 30 mg/m^2(IV) and 80 mg/m^2 oral with a standard meal and 5-HT3 antagonists at 2 week intervals to patients with advance solid tumours. Pharmacokinetics was assessed in forty-eight patients; mean AUC was 1,230ng/ml ± 290 (IV) and 1,216ng/ml ± 521 (PO). The confidence interval of the AUC ratio (0.83–1.03) was within the required regulatory range (0.8–1.25) and proved the bioequivalence between the two doses. The absolute bioavailability was 37.8 ± 16.0%. Patient tolerability was comparable between both forms with no significant difference in haematological or non-haematological toxicities (grade 3–4).

The Committee reviewed results from the Jassem *et al* study which was a randomized phase II trial of oral vs. IV vinorelbine that was designed to determine the efficacy and safety of oral vinorelbine with an intra-patient dose escalation in previously untreated patients with advanced NSCLC. 115 patients with stage IIIB or IV NSCLC were randomized in a 2 to 1 ratio to receive either oral vinorelbine at a dose of 60 mg/m^2/week for the first three administrations and then increased to 80 mg/m^2/week in the absence of severe neutropenia, or IV vinorelbine at 30 mg/m^2/week. The median progression-free survival with oral and IV vinorelbine was 3.2 months and 2.1 months respectively and the median survival - 9.3 and 7.9 months respectively. The most common haematological toxicity was neutropenia, which was severe (grade 3-4) in 46% of patients in the oral arm, and in 62% of patients in the IV arm. Non-haematological toxicities including nausea, vomiting, anorexia, weight loss, diarrhoea and constipation were generally mild to moderate.

These studies confirm that the dose equivalence for vinorelbine [30 mg/m^2IV:80 mg/m^2 oral].

The Committee heard that IV vinorelbine is a vesicant, requiring special precaution if extravasation occurs. A 2008 NPSA alert recommends administration via slow IV infusion rather than IV bolus, as administration commonly results in burning pain and phlebitis (grade 3-4). The most commonly reported adverse effects for the oral formulation are bone marrow depression with neutropenia, anaemia and thrombocytopenia, gastrointestinal toxicity with nausea, vomiting, diarrhoea, stomatitis and constipation. Fatigue and fever were also reported very commonly. The dose-limiting adverse effect of neutropenia is prominent with both formulations. Vinorelbine has been shown to be associated with a lower neurotoxicity compared with other vinca alkaloids. Cardiac events are rarely reported (approximately 1%). There are no relevant differences in toxicity profile between oral and intravenous formulations, although oral vinorelbine seems to produce less haematological toxicity.

The Committee agreed that vinorelbine has been shown to be equivalent when administered as both oral and IV formulations; and noted that the oral form is recognised by both NHS Wales and NHS Scotland as an effective means of delivering anticancer treatment to restricted cases of lung and breast cancer patients. The Committee noted that there might be a patient preference for oral therapy.

The Committee considered the possibility of a workload reduction for both nursing and pharmacy staff with oral vinorelbine, and that reduced infusion time might increase capacity in already busy chemotherapy and pharmacy departments. The Committee discussed at length whether this would offset the considerable cost impact. The Committee heard that currently IV vinorelbine is a last line

option for both breast and lung cancer treatment at UCLH and that oral vinorelbine is limited to patients with no venous access.

In summary the Committee agreed that oral and IV vinorelbine are equivalent, however, were not convinced that oral vinorelbine offers a significant advantage over the intravenous preparation, and is unlikely to result in a significant reduction in workload to nursing staff to justify such a large cost impact. The Committee agreed that oral vinorelbine would be recommenced only for patients who are not able to receive any IV treatments, because they had no intravenous access. The Committee asked that audit data also be presented in one year to analyse the number of patients receiving oral vinorelbine.

6.Local DTC recommendations

6.1 RFH: Everolimus (Votubia®; Novartis) for renal angiomyoplipomas
Everolimus was recommended for patients with renal angiomyoplipomas who are at risk of complications but who do not require immediate surgery, and is reserved for patients with multiple AMLs in one or both kidneys and one or more lesions of >3cm in diameter. The Committee agreed with this recommendation but use is restricted to renal consultants in renal genetics specialist clinic only. Protocols and funding for use are yet to be finalised.

6.2 RFH: Liposomal lidocaine cream 4% (LMX®; Ferndale) as a topical anaesthetic (Approved in place of EMLA)
Liposomal lidocaine cream 4% (LMX®) was recommended as a topical anaesthetic of first-choice prior to venous cannulation or venepuncture for paediatrics. The Committee agreed with this recommendation.

6.3UCLH: Octreotide (Sandostatin®; Novartis) for hyperinsulinaemic hypoglycaemia post bariatric surgery.
Octreotide for hyperinsulinaemic hypoglycaemia post bariatric surgery was recommended as a second-line option to acarbose (also formally recommended for first-line use). The Committee agreed to limit these recommendations to bariatric centres only.

6.4 UCLH: Chlorin E6 (Fotolon®; ApocarePharma) for photodynamic therapy
Chlorin E6 PDT in radiologically occult or inoperable late stage lung cancer that is unsuitable for other treatments was recommended for specialist use at UCLH only. The Committee agreed with this recommendation.

7. Moorfields Eye Hospital Glaucoma Pathway

The Committee were presented with a proposed glaucoma treatment pathway produced by Moorfields Eye Hospital. This one page algorithm clarifies the place in therapy of currently available glaucoma medications. Ms Shah questioned the use of brinzolamide as the first line carbonic anhydrase inhibitor, as it is three times more expensive than dorzolamide. Ms Chapman agreed to look into the rationale behind this decision and report back to the Committee.

8. NCL-MMC minutes

The NCL-MMC minutes were not available for this meeting.

9. Date of next meeting: 22nd August 2013 (location TBC).

10. Any other Business

10.1 Updating Terms of Reference

The Committee discussed whether the Terms of Reference should be updated following comments from the CCGs surrounding evaluating drugs that are commissioned by NHS England and therefore CCGs will not be able to influence funding outcomes. Prof MacAllister suggested that no change should be made to the Terms of Reference until more is known about the impact of the NHS changes.

10.2 Membership

Prof MacAllister again called upon the membership to suggest potential clinicians members The Committee were asked to approach clinicians from a variety of disciplines to join the JFC. Prof MacAllister nominated Dr R Sofat to become an additional clinical pharmacologist member. The Committee agreed with this nomination and welcomed Dr Sofat as a new member.