

# “Focus on...” session: monoclonal antibodies

## 141 LYMPHOMA PATIENTS TREATED WITH RITUXIMAB-CONTAINING REGIMENS DO NOT ACHIEVE PROTECTIVE SEROLOGICAL RESPONSES TO H1N1 INFLUENZA VIRUS AFTER VACCINATION

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**Background:** Rapid and prolonged depletion of normal B cells is observed in lymphoma patients treated with rituximab-containing regimens. This may preclude normal immune responses to vaccines. We have previously shown that patients receiving chemotherapy without rituximab can get serological responses to influenza vaccination. In light of the H1N1-epidemic in 2009, we aimed to investigate the immune response to the H1N1 influenza A-vaccine in lymphoma patients treated with chemotherapy in combination with rituximab (R-chemo) or rituximab alone (R-single).

**Material and Methods:** Lymphoma patients receiving R-chemo or R-single therapy within the last 6 months before vaccination with the H1N1-vaccine were included. Healthy volunteers taking the vaccination served as control group. In blood samples taken immediately before (pre-sample) and at least 3 weeks after vaccination (post-sample), antibody titers were determined using the hemagglutination-inhibition test, with turkey red blood cells as indicator cells and influenza A/California/07/2009 (H1N1v) virus as test antigen. An antibody titer  $\geq 40$  was considered protective. The post-sample values in patients and controls were compared.

**Results:** Post-samples in 72 patients (68 non-Hodgkins lymphoma) and 89 controls were analyzed for serological response. We excluded 4 patients and 36 controls with a pre-sample antibody titer  $\geq 40$ , indicating possible infection before vaccination. Thus, 68 patients and 53 controls were included in the final analysis. No patients compared to 43 controls achieved a protective titer  $\geq 40$  against H1N1 after vaccination. Three patients showed a minimal response (titer 20), the remaining none at all.

**Conclusions:** Unlike healthy individuals, lymphoma patients treated with rituximab in combination with chemotherapy or rituximab alone, do not respond adequately to a single dose of H1N1 influenza vaccine. Although the 2009 H1N1-pandemic cannot be directly compared with the common seasonal influenza, we suggest that patients treated with rituximab-containing regimens should receive repeated vaccinations against influenza with a low threshold for treatment with antivirals in influenza-like illness.

## 142 FC $\gamma$ R POLYMORPHISMS DO NOT INFLUENCE RESPONSE TO RITUXIMAB IN ASYMPTOMATIC, NON-BULKY FOLLICULAR LYMPHOMA; RESULTS FROM INTERGROUP TRIAL OF RITUXIMAB VS “WATCH AND WAIT”

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**Introduction:** It has been suggested that polymorphism of Fc $\gamma$  receptors (Fc $\gamma$ R), particularly Fc $\gamma$ RIIIa, influence response to rituximab (R) although this has not been found in all series. The discrepancies may result in part from small series sizes, different types of lymphoma studied and dilution of R's influence when combined with cytotoxics. The “Watch and Wait” trial comparing R alone vs watchful waiting (W&W) in patients with asymptomatic non-bulky follicular lymphoma (fNHL) provides an opportunity to assess the impact of Fc $\gamma$ R polymorphisms on a larger patient cohort.

**Materials and Methods:** Patients were treated with W&W, 4 infusions of R 375mg/m<sup>2</sup> at weekly intervals (R4) or R4 followed by R maintenance 375mg/m<sup>2</sup> 2 monthly for 2 years (R4+M). Response to treatment was assessed at 7 and 13 months. Three polymorphisms were ascertained Fc $\gamma$ RIIIA V158F, Fc $\gamma$ RIIA H131R and Fc $\gamma$ RIIb I232T.

**Results:** In total 276 patients received R and DNA is available on 257 of them. When considering all patients who received R, the proportion achieving CR or CRu at either time point was not significantly influenced by any of the Fc $\gamma$ R polymorphisms, nor were there significant differences in time to next treatment or progression free survival.

Further analyses explored the impact of R maintenance. R4+M patients (n=175) had significantly higher CR/CRu rate and significantly fewer events than R4 (n=75). There was no significant interaction for the Fc $\gamma$ RIIIa or Fc $\gamma$ RIIb polymorphisms, although it did appear that patients with the Fc $\gamma$ RIIIa HH genotype have a better PFS response to maintenance R. This, however, was largely based on a high event rate in the 10 HH patients who only received R4, rather than a low event rate in those receiving R4+M.

**Conclusions:** The finding that Fc $\gamma$ RIIIa polymorphisms do not influence the response to R4+M in fNHL may have relevance to the design of next generation CD20 antibodies. No impact of Fc $\gamma$ RIIIa polymorphisms was seen in those just receiving R4 but the relatively small number of patients in this arm (n=79) limits firm conclusions.

## 143 FC GAMMA RECEPTOR IIB ON HUMAN B CELLS PROMOTES RITUXIMAB INTERNALIZATION AND REDUCES CLINICAL EFFICACY

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**Introduction:** The anti-CD20 monoclonal antibody (mAb) rituximab is invaluable in the treatment of B-cell neoplasms, but resistance remains a significant problem. Anti-CD20 mAb can be classified as type I (rituximab, ofatumumab) or type II (tositumomab, GA101) according to their activities in various in vitro effector assays. We recently reported that type I mAb, unlike type II, are internalised from the surface of normal and malignant B cells. Such internalisation is important because it consumes mAb and reduces therapeutic efficacy. Here, we report that the inhibitory Fc gamma receptor (Fc $\gamma$ RIIb) on target B-cells is a key regulator of this process.

**Material and Methods:** Internalisation of anti-CD20 mAb in primary tumour material is analysed using an in vitro flow cytometry-based fluorescence quenching assay. Western blotting and confocal microscopy are used to elucidate the events post-internalisation.

**Results:** Rapid internalisation was particularly evident in most cases of chronic lymphocytic leukaemia and mantle cell lymphoma (MCL), but not from the majority of follicular or diffuse large B-cell lymphomas, possibly explaining their differing clinical responses to rituximab. Within each disease, the speed and extent of internalisation was heterogeneous. Internalisation of rituximab correlated strongly with Fc $\gamma$ RIIb expression on tumour cells regardless of lymphoma subtype. Transfection of Fc $\gamma$ RIIb converted Fc $\gamma$ RIIb<sup>-</sup> Ramos cells into rapid internalisers in a dose-dependent manner. Internalisation also resulted in reduced macrophage phagocytosis of mAb-coated targets and could be inhibited by blocking Fc $\gamma$ RIIb. Internalisation was largely cell-intrinsic, independent of contact with other Fc $\gamma$ RIIb-expressing cells, in a process wherein Fc $\gamma$ RIIb was phosphorylated and internalised along with CD20 and mAb prior to lysosomal degradation. This data is supported by clinical results showing that high Fc $\gamma$ RIIb expression predicted less durable responses following rituximab-containing regimens in a small cohort of MCL patients.

**Conclusions:** High Fc $\gamma$ RIIb expression provides a potential biomarker of response to rituximab-containing therapy and may identify patients for which treatment with type II anti-CD20 mAb may be preferable.

## 144 RESULTS FROM A PHASE II STUDY (BO20999) OF R05072759 (GA101) MONOTHERAPY IN RELAPSED/REFRACTORY AGGRESSIVE NON-HODGKIN'S LYMPHOMA

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**Background:** GA101 is a type II, glycoengineered, humanized monoclonal anti-CD20 antibody currently in clinical trials.

**Methods:** Forty patients with CD20+ aggressive lymphoma (aNHL) were randomized to receive GA101 in a low-dose (LD, n=21 [10 DLBCL/11 MCL]) or a high dose (HD, n=19 [15 DLBCL/4 MCL]) cohort. GA101 monotherapy was given on d1, d8, d22 and q21 days for total of 9 infusions. In the LD cohort, GA101 was given 400mg all infusions; in the HD cohort, d1 and d8 at 1600mg and 800mg thereafter. Primary

endpoint was end of treatment response (EOR), assessed 4 weeks after last infusion. Secondary objectives included safety and pharmacokinetics.

**Results:** End of treatment response (EOR) was 24% (5/21) in the LD cohort and 32% (6/19) in the HD cohort. For DLBCL patients EOR was 28% and for MCL patients EOR was 27%. Of 13 refractory patients in LD, 1 patient achieved PR (8%) and of 12 refractory patients in HD, 3 patients achieved PR (25%). The most common AEs were G1-2 infusion related reactions (LD 81%, HD 68% of patients). Fourteen patients experienced at least one SAE during treatment period (LD=9, HD=5), with 7 related to GA101 (LD n=5, HD n=2), and 5 of these events associated with the first infusion (IRR=3; TLS=2), one after day 8 infusion (pyrexia), and one after cycle 6 infusion (bradycardia). During treatment, related G3-4 hematological AEs were transient neutropenia (n = 1 in HD), anemia (n = 2 in LD) and thrombocytopenia (n = 3 in LD). Ten patients had at least one G1-2 infection (5 in each cohort) with no G3-4 infections reported. GA101 plasma profiles were explored reflecting that mantle cell lymphoma patients in the HD (n=4) and LD (n=10) appeared to show lower plasma concentrations compared to DLBCL patients. There were 17 patient deaths reported (LD=11, HD=6), with 14 due to PD and 3 due to AE (1 during treatment period; cardio-respiratory arrest; not GA101-related).

**Conclusions:** GA101 monotherapy is well tolerated showing promising efficacy in heavily pre-treated aggressive NHL patients. Trials are currently ongoing exploring GA101 in combination with chemotherapy.

#### 145 A PHASE 2B TRIAL COMPARING DACETUZUMAB + R-ICE VS PLACEBO + R-ICE IN PATIENTS WITH RELAPSED DIFFUSE LARGE B-CELL LYMPHOMA

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**Background:** Dacetuzumab (SGN-40), a humanized anti-CD40 monoclonal antibody that mediates antitumor activity via multiple mechanisms of action, has demonstrated modest single-agent activity in DLBCL in prior phase 1 and 2 trials.

**Methods:** A phase 2b, double-blind, placebo-controlled trial compared efficacy and safety of 3 cycles of R-ICE + dacetuzumab (8 mg/kg) vs R-ICE + placebo in DLBCL patients (pts) who failed prior R-CHOP. Primary endpoint was CR; response was assessed by CT/PET. Additional endpoints include failure-free survival (FFS) and overall survival (OS).

**Results:** A total of 151 pts (median age 59, range 22–74) were randomized in 10 countries. There were no notable differences in demographics, completion of planned therapy, stem cell collection or subsequent autologous stem cell transplant (ASCT) between arms. AEs seen more often in dacetuzumab pts included cytopenias, cough, and infection; however these did not affect administration or completion of therapy. A planned futility analysis, conducted after 50% of planned pts (n=112) were treated, revealed a similar CR rate (36% dacetuzumab vs 42% placebo) and ORR rate (64% vs 68%). Because CR rate was not improved with dacetuzumab, further enrollment and treatment were stopped per study design. After following pts ≥ 1 year, there is a trend toward improved FFS (hazard ratio [HR]=0.789) and OS (HR=0.714) for dacetuzumab pts. Among pts who underwent subsequent ASCT (47% dacetuzumab vs 53% placebo), the survival (OS) advantage with dacetuzumab is statistically significant (HR=0.167, p=0.008). Fewer deaths have occurred in pts who received dacetuzumab vs placebo (40% vs 50% respectively) with a 14% reduction in death due to disease progression (25% vs 39% respectively).

**Conclusions:** Dacetuzumab can be safely combined with R-ICE without compromising stem cell collection in pts with DLBCL who previously failed R-CHOP. Data suggest that this combination may improve FFS and OS. The improved OS, despite no improvement in the CR rate, may be explained by the potential immunomodulatory effect of a partially agonistic CD40 antibody. Additional survival data are being collected to guide future development decisions.