Haematological malignancies and myeloma

Oral presentations (Mon, 21 Sep, 11:00–13:00)
Haematological malignancies and myeloma

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Phase II study of IPH1101 (with low dose of IL-2) in combination with rituximab re-treatment in patients with follicular lymphoma

O. Casasnovas[1], C. Thieblemont[2], J.F. Rossi[3], H. Sicard[4], S. Ingoure[4], F. Audibert[5], S. Lafaye de Micheaux[6], G. Laurent[7]. *[1]CHU le Bocage, Clinical Hematology, Dijon, France; [2]CHU Saint Louis, Clinical Hematology, Paris, France; [3]CHU Lapeyronie, Clinical Hematology, Montpellier, France; [4]Innate Pharma, gd T Cell Platform, Marseille, France; [5]Innate Pharma, Clinical Operation, Marseille, France; [6]Innate Pharma, Clinical Program Development, Marseille, France; [7]CHU Purpan, Clinical Hematology, Toulouse, France*

Background: Non-conventional γδ T lymphocytes have potent anti-tumoral activity, particularly against malignant B cells. IPH1101 is an agonist of γδ T cells, which in the presence of low doses of IL-2 potentiates their direct cytotoxic activity.
ADCC is a major molecular mechanism underlying rituximab's efficacy. Increasing the number and the activation state of killer lymphocytes mediating ADCC is therefore believed to be beneficial for therapeutic potency. Since γδ T cells have been found to be capable of mediating ADCC, modulating γδ T cells in the context of rituximab is worth being tested in a clinical trial. The main purpose is to assess the clinical efficacy of IPH1101 with low doses of IL-2, combined with a standard rituximab treatment, in patients (pts) with follicular lymphoma.
Material and Methods: This is an open label, multinational study consisting of a Phase (ph) I-like part followed by a ph II part. The ph I part has shown a good safety and immuno-biological efficacy profile for the highest dose of IL-2; consequently, the following pts were treated with the combination of rituximab (375 mg/m^2) administered 4 times weekly, IPH1101 (750 mg/m^2) administered i.v. 3 times (every 3 weeks) and IL-2 (8 MIU) administered daily s.c. for 5 days starting on the day of each IPH1101 adm. All pts presented FL which had relapsed after 1 to 4 lines of previous therapy including at least one rituximab-containing line. Inclusion criteria set forth that pts should have no lesion >7 cm.
Results: We report here recent data from the first 15 pts: 3 pts from the ph I part (4 MIU IL-2) and 12 pts at 8 MIU IL-2. Among the 15 pts, 12 were evaluable for efficacy. The safety was good, and most of the drug-related adverse events were, as expected, flu like symptoms of grade 1 or 2. The 4 SAEs reported were hypotension, allergic reaction (back pain), ALAT elevation, and asthenia.The immuno-biological follow up showed specific and sustained γδ T cell amplifications, induction of FcRgIIIa on the targeted γδ T cell population and treatment-induced anti-tumor activity of patients' PBMC ex vivo. After at least 3 months post treatment, investigators reported, among the 12 evaluable pts, 9 responses (75%) of which 6 were CR (50%).
Conclusion: These observations confirm the good safety profile and the biological rationale of this approach. Furthermore, the efficacy in this first set of pts is very promising. The number of CRs is notable and deserves to be confirmed in a larger sample of pts. Updated results will be presented at the meeting.

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Tolerability profile of carfilzomib enables full-dose anti-tumor treatment for up to 12 months

J. Kaufman[1], M. Wang[2], D. Siegel[3], A.K. Stewart[4], A. Jakubowiak[5], V. Kukreti[6], K. McDonagh[7], S. Jagannath[8], M. Alsina[9], R. Vij[10]. *[1]Emory University, Winship Cancer Institute, Atlanta, USA; [2]University of Texas, MD Anderson Cancer Center, Houston, USA; [3]Hackensack University, John Theurer Cancer Center, Hackensack, USA; [4]Mayo Clinic, Department of Hematology/Oncology, Scottsdale, USA; [5]University of Michigan, Department of Internal Medicine, Ann Arbor, USA; [6]Princess Margaret Hospital, Department of Hematology, Toronto, Canada; [7]University of Kentucky, Markey Cancer Center, Lexington, USA; [8]St. Vincent's Comprehensive Cancer Center, Medical Oncology and Hematology, New York, USA; [9]University of South Florida, H. Lee Moffitt Cancer Center, Tampa, USA; [10]Washington University School of Medicine, Division of Hematology and Oncology, Saint Louis, USA*

Background: Carfilzomib (CFZ) is a proteasome inhibitor with single-agent activity against hematologic malignancies, including bortezomib (BTZ)-refractory myeloma (MM) (Jagannath, ASH 2008). CFZ is highly selective and lacks the off-target activities of BTZ (Kapur, ASH 2008). PX-171−004 is an ongoing Phase II study of the safety and efficacy of CFZ in MM patients (pts) with relapsed disease after 1−3 prior therapies. An Overall Response Rate (ORR) of 35.5% for all pts was previously reported (Vij, ASH 2008). Here we present updated safety data on the first 31 pts.
Methods: CFZ 20 mg/m^2 was administered Days 1, 2, 8, 9, 15 and 16 in a 28-day cycle, for up to 12 cycles. Dexamethasone 4 mg was administered prior to each dose in Cycle 1. The primary endpoint was ORR [Partial Response + Very Good Partial Response + Complete Response]. Secondary endpoints included safety.
Results: 31 pts were enrolled; 14 (45%) BTZ-naïve and 17 (55%) BTZ-exposed. Of the BTZ-exposed cohort, 15 (88%) relapsed after stem cell transplantation and 16 (94%) had received at least one IMID-containing regimen. To date, pts have received an average of 6.6 treatment cycles and eleven pts (35%) reached 12 cycles without evidence of disease progression or development of treatment-limiting adverse events (AEs). CFZ achieved an ORR of 57% and 18% in BTZ-naïve and BTZ-exposed pts, respectively. The most common non-hematologic AEs were fatigue (61%), nausea (58%) and vomiting (36%); all were Grades 1/2. Grades 3/4 AEs included neutropenia (10%), anemia (6.5%), upper respiratory infection (6.5%), tumor lysis syndrome (6.5%), dyspnea (6.5%), and thrombocytopenia (6.5%). One report of Grade 3 peripheral neuropathy (PN) occurred in a pt with Grade 1 PN at baseline, attributed to prior thalidomide. The Grade 3 PN resolved to baseline status prior to the pt's final carfilzomib dose. The overall incidence of emergent PN was low (2 pts, 6.5%) despite 73% of pts entering study with a history of PN.
Conclusions: These preliminary results demonstrate that CFZ monotherapy is highly active and well tolerated, with >30% of pts reaching 12 cycles of therapy without evidence of tumor progression or treatment limiting AEs. Importantly, both the rate and severity of PN is significantly lower than reported for BTZ (Richardson, 2006), allowing responding pts to remain on CFZ for at least 1 year without dose modification. These data support the continuing evaluation of CFZ as a promising new agent in relapsed MM.

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Long-term outcomes for patients with limited stage, follicular lymphoma: involved regional radiotherapy versus involved nodal radiotherapy

B.A. Campbell[1], R. Woods[2], R.D. Gascoyne[3], J. Morris[1], T. Pickles[1], N. Voss[1], J.M. Connors[4], K.J. Savage[4]. *[1]BC Cancer Agency, Department of Radiation Oncology, Vancouver BC, Canada; [2]BC Cancer Agency, Department of Surveillance and Outcomes, Vancouver BC, Canada; [3]BC Cancer Agency, Department of Pathology, Vancouver BC, Canada; [4]BC Cancer Agency, Department of Medical Oncology, Vancouver BC, Canada*

Background: Approximately 25% of patients with follicular lymphoma (FL) present with stage I or II disease. Due to the indolent course of FL, it is controversial whether a subset is cured by radiotherapy (RT) alone. Further, it is unclear as to the optimal RT field size to maximize FL control and minimize toxicity. The aim of this study is to review the long-term outcomes of limited stage FL treated with RT alone at the British Columbia Cancer Agency (BCCA). Further, we assess the impact of reducing the RT field size, from involved regional radiotherapy (IRRT) to involved nodal radiotherapy (INRT$\leqslant$5cm), on patterns of relapse and survival.
Methods: Using the BCCA Lymphoid Cancer Database, we identified patients diagnosed with FL between 1986 and 2006. Inclusion criteria were: limited stage (stage I / II, no B symptoms, non-bulky disease <10 cm); grade 1−3A; treated with RT alone with curative intent. Era-specific guidelines for RT were: IRRT, 1986−1998; INRT $\leqslant$ 5 cm, 1998 - present. IRRT was defined as RT to the involved nodal group(s) and $\geqslant$1 adjacent uninvolved nodal group. INRT$\leqslant$5 cm was defined as RT to the involved node(s) with margins $\leqslant$5cm to account for physiological movement and set-up variation.
Results: 237 patients were eligible: median age 61 years; male 48%, stage IA 76%; extranodal disease 23%; elevated LDH 7%; grade 3A 12%; node size $\geqslant$5 cm 19%. The RT groups were: IRRT 142 (60%), INRT$\leqslant$5cm 95 (40%). Median follow-up of living patients was 7.3 years. Median time to relapse was 2.8 years. Only 2 patients relapsed after 10 years. 41% of all patients relapsed: IRRT 45%; INRT$\leqslant$5cm 35%. Distant-only relapse was the most common site of first failure: IRRT 38%; INRT$\leqslant$5cm 31%. Regional-only relapse occurred in only 1% after INRT$\leqslant$5cm. Infield-only relapse was uncommon: 1% in each group. At 10 and 15 years, progression-free survival (PFS) was 49% and 44%; and overall survival (OS) was 66% and 46%, respectively. In multivariate analysis (MVA), larger nodal size ($p = 0.013$), age >60 years ($p = 0.037$) and male sex ($p = 0.044$) were poor prognostic factors for PFS. For OS, age >60 years ($p < 0.001$), elevated LDH ($p = 0.007$), larger nodal size ($p = 0.016$) and grade 3A ($p = 0.036$) were poor prognostic factors. After adjusting for other significant predictors of outcome, the RT groups were not different for OS ($p = 0.328$) or PFS ($p = 0.070$) in final MVA models.