A first in human phase I study of the proteasome inhibitor CEP-18770 in patients with advanced solid tumours and multiple myeloma

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BACKGROUND
The safety, pharmacokinetics (PK) and pharmacodynamics of CEP-18770, a new peptide boronic acid proteasome inhibitor, have been investigated after intravenous administration on days 1, 4, 8 and 11 of every 21d cycle in patients with solid tumours and multiple myeloma (MM).

PATIENTS AND METHODS
Thirty-eight patients were treated with CEP-18770 at escalating doses from 0.1 to 1.8mg/m(2) where 2 out of 5 patients showed dose limiting toxicities. The maximum tolerated/recommended dose (MTD/RD) of 1.5mg/m(2) was tested in 12 additional patients. Skin rash was dose-limiting and occurred in 53% of patients; other frequent toxicities were asthenia (29%), stomatitis (21%) and pyrexia (16%). No significant peripheral neuropathy was observed. PK in plasma was linear with a half-life of the elimination phase of 62.0±43.5h. Proteasome inhibition in peripheral blood mononuclear cells was dose related in MM patients; it was of 45.4±11.5% at the RD.

CONCLUSIONS
CEP-18770 showed a favourable safety profile with lack of neurotoxicity and linear plasma PK. The definition of the optimal biological dose and schedule of treatment is actively pursued because of the high incidence of skin toxicity of the twice a week schedule.