non-radiolabelled olaparib capsules to six patients. The primary aim was to investigate the metabolism, excretion and pharmacokinetics (PK) of olaparib in patients with advanced solid tumours.
Results: Six female patients (aged 34−72 years) were included. Data from one patient were excluded for PK analysis as she had received only half the total dose of olaparib with the planned dose of radioactivity (120 μCi). Absorption of olaparib was rapid, with maximum plasma concentrations (geometric mean 3556 ng/mL) observed at 1.5−2 hours (h) post dose. Following this, plasma concentrations declined polyphasically, and were below the limit of quantification by 16 to 24 h post dose. The geometric mean AUC was 19856 ng.h/mL, oral clearance was 4 to 14 L/h, apparent volume of distribution was 20 to 50 L, and the terminal half-life was between 2.4 and 4.7 h. Total plasma radioactivity concentrations were mostly higher than those of the parent compound, and these values declined in parallel. In addition, the mean ratio of the concentration of radioactivity in blood to plasma was 0.8, suggesting some association of olaparib-related material with cellular components of the blood. Mean total recovery (over 144 or 168 h) of the radioactive dose from all patients was 86%; 44% in the urine (15% as the parent compound) and 42% in the faeces. In most patients, the majority of the excreted radioactivity was recovered within 72 h of dosing.
Conclusions: After a single dose of olaparib 100 mg (50 mg contained [^{14}C]), absorption was rapid and elimination occurred relatively quickly, mainly via the urine and faeces. Furthermore, these data indicate the presence of circulating metabolites and suggest association of olaparib and/or metabolites with the cellular components of blood.

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Phase 2 study of XL184 in a cohort of patients (pts) with castration resistant prostate cancer (CRPC) and measurable soft tissue disease

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Background: XL184 is an oral potent inhibitor of MET, VEGFR2 and RET. Activation of the MET pathway promotes tumor growth, invasion, and metastasis. Overexpression of MET and/or its ligand HGF have been shown to correlate with prostate cancer metastasis to lymph nodes and bones, and disease recurrence. In addition, androgen ablation has been shown to upregulate MET signaling in preclinical studies. Targeting the MET pathway with XL184 may therefore be a promising treatment strategy. Preliminary data from the open label Lead-in Stage of a Phase 2 randomized discontinuation trial are presented showing the effects of XL184 in pts with CRPC.
Methods: Eligible pts have CRPC with measurable disease and have progressed on up to 1 prior non-hormonal systemic treatment after antiandrogen withdrawal. XL184 is administered open label at 100 mg free base equivalent (125 mg XL184-malate-salt) qd for 12 weeks (wks) (Lead-in Stage). Tumor response is assessed radiologically every 6 wks. Pts with partial or complete response (PR or CR) at wk 12 continue to receive XL184; pts with progressive disease (PD) discontinue XL184. Pts with SD at wk 12 are randomized 1:1 to receive XL184 or placebo. Cross-over from placebo to XL184 is allowed upon PD. Primary endpoints are objective response rate at wk 12 and progression free survival in the Randomized Stage. PSA levels will be correlated with clinical outcomes.
Results: A total of 16 pts have been enrolled with a median age of 69 years. The median number of prior non-hormonal systemic treatments was 1, with 7 pts receiving docetaxel. Of 9 pts who were evaluable (minimum 12 wks follow up) to date, 1 pt achieved a PR and 5 pts achieved SD for an overall disease control rate of 67% at wk 12. Two pts achieved a near complete resolution of tracer uptake on bone scan with one pt previously treated with docetaxel who attained a 41% reduction in measurable disease and a reduction of PSA > 50% at wk 12. Most frequently observed adverse events regardless of causality with CTCAE Grade ⩾3 in the Lead-in Stage were fatigue and asthenia (each n = 2).
Conclusions: Preliminary results suggest that XL184 is active in CRPC pts who failed prior treatment. XL184 was generally well tolerated. Updated efficacy and safety results will be presented.

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Phase 2 study of XL184 in a cohort of ovarian cancer patients (pts) with measurable soft tissue disease

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Background: XL184 is an oral, potent inhibitor of MET, VEGFR2 and RET. MET overexpression has been observed in advanced ovarian cancer (OC). Anti-VEGF pathway agents have shown clinical benefit in pts with OC. Co-targeting of the MET and VEGF signaling pathways using XL184 may therefore be a promising treatment strategy. Preliminary data from the open label Lead-in Stage of a Phase 2 randomized discontinuation trial are presented showing the effects of XL184 in pts with OC.
Methods: Eligible pts have advanced epithelial OC, primary peritoneal, or fallopian tube cancer with measurable disease. Up to 3 prior regimens are allowed for platinum-resistant (disease recurrence within 6 months after last platinum based chemotherapy [PBC]) and refractory pts, and up to 4 for platinum-sensitive (disease recurrence >6 months after last PBC) pts. XL184 is administered open label at 100 mg free base equivalent (125 mg XL184-malate-salt) qd for 12 weeks (wks) (Lead-in Stage). Tumor response is assessed radiologically every 6 wks. Pts with partial or complete response (PR or CR) at week (wk) 12 continue to receive XL184; pts with progressive disease (PD) discontinue XL184. Pts with stable disease (SD) at wk 12 are randomized 1:1 to receive XL184 or placebo (P). Cross-over from P to XL184 is allowed upon PD. Primary endpoints are objective response rate at wk 12 and progression free survival in the Randomized Stage. CA125 levels will be correlated with clinical outcomes.
Results: A total of 21 pts have been enrolled to date with a median age of 60 years. The median number of prior systemic treatments was 2. Of the 7 pts who were evaluable (minimum 12 wk follow up) to date, 3 pts achieved an unconfirmed PR and 4 pts achieved SD. One pt with platinum-sensitive serous adenocarcinoma (SAC) achieved a 34% tumor reduction at wk 12. One pt with platinum-resistant SAC experienced a CA125 response per GCIG criteria and a 24% tumor decrease at wk 12. A second pt with platinum-resistant SAC achieved re-stabilization of PD after cross-over from P to XL184. Most frequently observed adverse events regardless of causality with CTCAE Grade ⩾3 in the Lead-in Stage include rash, palmar-plantar erythrodysesthesia syndrome, pruritus, pulmonary embolism, staphylococcal infection (each n = 1).
Conclusions: Preliminary results suggest that XL184 is active in pts with advanced OC who failed prior treatment. XL184 was generally well tolerated. Updated efficacy and safety results will be presented.

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Phase 2 study of XL184 (BMS-907351) in a cohort of patients (pts) with hepatocellular carcinoma (HCC)

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Background: XL184 is an oral, potent inhibitor of MET, VEGFR2 and RET. MET overexpression has been found to correlate with an increased incidence of intrahepatic metastasis and inversely correlated with survival of HCC patients. In addition, HCC is a hypervascular malignancy. Thus co-targeting of the MET and VEGF signaling pathways by XL184 may be a promising treatment strategy. Preliminary data from the open label Lead-in Stage of a Phase 2 randomized discontinuation trial are presented showing the effects of XL184 in pts with HCC.
Methods: HCC pts with a Child–Pugh score of A who failed up to 1 prior treatment regimen are eligible. XL184 is administered open label at 100 mg free base equivalent (125 mg XL184-malate-salt) qd for 12 weeks (wks) (Lead-in Stage). Tumor response per mRECIST is assessed every 6 wks. Pts with partial or complete response (PR or CR) at week (wk) 12 continue to receive XL184; pts with progressive disease (PD) discontinue XL184.