A Randomized Phase II Study of GDC-0980 Versus Everolimus in Metastatic Renal Cell Carcinoma Patients After VEGF-Targeted Therapy


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METHODS

Study Design - Patients: Clear cell mRCC who progressed on or after VEGF-targeted therapy were randomized (1:1) to GDC-0980 (40 or 60 mg) or everolimus (10 mg). Patients were stratified by MSKCC prognostic score, prior number of VEGF-targeted therapies, and prior radiotherapy; patients were balanced across arms using random permuted block sizes of 6. - Primary endpoint: Overall Survival (OS). - Secondary endpoints: Progression-Free Survival (PFS), time to first dose reduction or treatment discontinuation, and tolerability. Key Selection Criteria - Measureable disease on RECIST v1.1. - Progression > 6 months after stopping VEGF-targeted therapy, which must be the most recent therapy before study entry ( > 6 months from first dose of study treatment). - Max. 3 prior systemic therapies, no prior PDK1 or mTOR inhibitors. Databases were excluded. RESULTS

Patient Characteristics, Patient Status - Date of 17, Jan, 2014. - Patients (n=43) were randomized and treated with GDC-0980 (n=22) or everolimus (n=21). - Baseline characteristics (Table 1) were generally comparable between treatment arms with the following exceptions: Imbalance in protocol-defined MSKCC prognostic score (see Table 1). - More prior systemic therapies (including greater number of prior VEGF-targeted therapy and use of sunitinib) and radiation in the GDC-0980 arm. Table 1: Patient Demographics and Baseline Characteristics. Characteristics GDC-0980 Everolimus Age, median years (range) 61 (49 – 76) 63 (59 – 81) BMI 29 (19 – 40) 29 (25 – 37) Region Europe 30 (65%) 31 (72%) USA 7 (17%) 5 (12%) mTORC1 inhibition 86 (93%) 42 (86%) HIF−1α expression 12 (25%) 16 (37%) NGS results: NRAS 12 (25%) 16 (37%) BRAF 2 (4%) 2 (4%) KRAS 11 (24%) 11 (24%) PI3KCA 2 (4%) 2 (4%) TP53 1 (2%) 1 (2%) VHL 1 (2%) 1 (2%) HR (Everolimus) 0.53 (0.22, 1.24) HR (GDC-0980) 0.53 (0.23, 1.22) Safety - GDC-0980 treatment was associated with a higher incidence of Grade 3-4 adverse events, particularly hyperglycemia (all grades) and rash (Table 2). Disposition and Dose Intensity - Patients treated with GDC-0980 had a higher rate of discontinuation from treatment due to an AE (37% vs. 12% for everolimus). - Dose reductions in both study arms were frequent in GDC-0980 (45% for GDC-0980, 40% for everolimus); however, median time to first dose reduction or treatment discontinuation was 28 days for GDC-0980 vs. 56 days for everolimus. - Hyperglycaemia and rash contributed most to a lower dose intensity for GDC-0980 (Figure 2). Pharmacokinetics - Consistent with data from the Phase I GDC-0980 dose escalation studies, PK analyses suggest a relationship between GDC-0980 exposure and risk of rash and hyperglycaemia. - Higher exposure to GDC-0980 was associated with treatment discontinuation for hyperglycaemia. - No clear associations between tumor responses and specific biomarkers were observed. - Patients with clear cell mRCC who progressed on or after VEGF-targeted therapy were included for enrollment on the study. - Dose reductions were common in both arms (45% for GDC-0980, 40% for everolimus); GDC-0980 treatment was associated with a higher incidence of Grade 3-4 adverse events, particularly hyperglycaemia and rash. - Higher exposure to GDC-0980 also correlated with treatment discontinuation for AEs. - Baseline characteristics (Table 1) were generally comparable between treatment arms with the following exceptions: Imbalance in protocol-defined MSKCC prognostic score (see Table 1). - More prior systemic therapies (including greater number of prior VEGF-targeted therapy and use of sunitinib) and radiation in the GDC-0980 arm. Conclusions - In the ROVER trial, everolimus produced a significantly longer PFS compared with GDC-0980. - The underling reasons for the observed PFS difference may be multifactorial and may have involved factors other than the primary endpoint of PFS. - Exposure-dependent hyperglycaemia and rash were major contributors to high frequencies of treatment discontinuation in both study arms. - VHL mutation and hyperglycaemia expression may be predictive of mTOR inhibitor benefit, warranting further evaluation. Acknowledgments - The authors and patients who participated in the study and their families, as well as the following contributing: Jennifer Lauchle, Mika Derynck, Stephanie Royer Joo, Bryan Hains, Hartmut Lackner, Svetlana Oudard, Thomas Powles, Christoph Beer, Daniel Fuchs, Benno Lucht, Robert Hoessli, James Lee, Joseph Yeh, Peter Ackland, Robert Jobon, Michael Staehler, Cristina Koeppen and Yulei Wang. - Genentech, Inc. provided support for the conduct of this trial and preparation of this poster. - ROVER Study Group: Jean Balducci, Janet Brown, John Busch, Daniel Fuchs, Bernard Escudier, Daniel Geiser, Vital Gruyraut, John Hanawalt, Robert Hoessli, James Lee, Joseph Yeh, Peter Ackland, Robert Jobon, Michael Staehler, Cristina Koeppen, Yulei Wang, Mika Derynck, Stephanie Royer Joo and Bryan Hains.