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Results of a phase 1 trial combining ridaforolimus and MK-0752 in patients with advanced solid tumors

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Abstract

Background—The phosphatidylinositol 3-kinase/protein kinase-B/mammalian target of rapamycin (PI3K-AKT-mTOR) signaling pathway is aberrantly activated in several cancers. Notch signaling maintains cell proliferation, growth, and metabolism in part by driving the PI3K pathway. Combining the mTOR inhibitor ridaforolimus with the Notch inhibitor MK-0752 may increase blockade of the PI3K pathway.

Methods—This phase I dose-escalation study (NCT01295632) aimed to define the dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD) of combination oral ridaforolimus (rising doses starting at 20 mg, 5 days/week) and oral MK-0752 (1800 mg once weekly) in patients with solid tumors. No intrapatient dose escalation was permitted.

Results—28 patients were treated on study. Ridaforolimus doses were escalated from 20 to 30 mg/day. Among 14 evaluable patients receiving ridaforolimus 20 mg, one DLT (grade 2 stomatitis, second episode) was reported. Among 8 evaluable patients receiving ridaforolimus 30 mg, three DLTs were reported (1 each grade 3 stomatitis, grade 3 diarrhea, and grade 3 asthenia). The MTD was 20 mg daily ridaforolimus 5 days/week + 1800 mg weekly MK-0752. The most common

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Conflict of Interest Statement

S.A. Piha-Paul, A. Hollebecque, G. Argilés, O. Dajani, and S. Gupta have nothing to disclose. P.N. Munster received research support from Merck & Co., Inc. J.D. Cheng, R. Wang, A. Swift, and A. Tosolini are employees of Merck & Co., Inc.

drug-related adverse events included stomatitis, diarrhea, decreased appetite, hyperglycemia, thrombocytopenia, asthenia, and rash. Two of 15 (13%) patients with head and neck squamous cell carcinoma (HNSCC) had responses: one with complete response (CR) and one with partial response (PR). In addition, one patient experienced stable disease ≥6 months.

Conclusions—Combined ridaforolimus and MK-0752 showed activity in HNSCC. However, a high number of adverse events were reported at the MTD, which would require careful management during future clinical development.

Keywords

Ridaforolimus; mTOR inhibitor; MK-0752; Notch inhibitor; head and neck cancer; Phase I

Introduction

The phosphatidylinositol-3-kinase (PI3K) signaling pathway is dysregulated in many human malignancies [1–3]. The PI3K pathway links growth factor ligand-receptor interactions on the cell surface to downstream effectors such as the mammalian target of rapamycin (mTOR), which regulates cell cycle progression and cellular growth processes, and is involved in tumor progression for many cancers [4–6]. The mTOR inhibitor ridaforolimus has demonstrated preclinical antitumor activity *in vitro* and *in vivo* [7–10]. Its clinical safety and efficacy is being explored in patients with advanced malignancies as both a single agent and in combination with other targeted agents or chemotherapy [11–21]. To date, ridaforolimus has been generally well tolerated and has demonstrated antitumor activity in several cancers [3, 8]. The most frequently reported adverse effects associated with ridaforolimus have been mucositis, nausea, pruritus, anemia, thrombocytopenia, hypokalemia, and hyponatremia [8]

MK-0752 inhibits γ-secretase, an aspartic protease that activates the Notch receptor by cleaving the Notch ligand/receptor complex [22]. MK-0752 has shown single-agent clinical activity in patients with high-grade gliomas in a dose-escalation trial of weekly MK-0752 doses up to 4200 mg; the dose-limiting toxicities (DLTs) were fatigue and diarrhea [23]. The maximum tolerated dose (MTD) of MK-0752 was 3200 mg given once weekly (QW), and the biologically effective dose was 1800 mg QW [23]. MK-0752 was also well-tolerated in a dose-escalation trial in pediatric patients, and although no objective responses were observed, 2 patients (1 with ependymoma and 1 with glioblastoma multiforme) experienced prolonged stable disease (≥3 months) [24].

We hypothesized that combining ridaforolimus with MK-0752 could lead to complementary blockade of the PI3K pathway (Fig. 1). The combined activity of a Notch inhibitor and an mTOR inhibitor is expected to produce improved efficacy by targeting the tumor directly as well as blocking the recruitment of new blood vessels on which tumors depend. Notch signaling maintains cell proliferation, growth, and metabolism in part by driving PI3K pathway signaling. As mTOR is downstream in this pathway, mTOR inhibitors can constrain some of the oncogenic signaling initiated by Notch. The mTOR inhibitor could also restore inhibition of PI3K signaling in cells that are resistant to γ-secretase inhibition as a result of mutations in the phosphatase and tensin homolog (PTEN) gene, through which γ-secretase

inhibition acts, in part, to inhibit growth and proliferation. Preclinical data have demonstrated that targeting both Notch and mTOR can result in antitumor activity in cell lines and prolonged survival in a mouse leukemia model [25]. In pancreatic cancer cells coadministration of a Notch inhibitor with rapamycin inhibited cell proliferation to a greater degree than either agent alone [26]. The present study investigated the safety and tolerability of the ridaforolimus plus MK-0752 combination in patients with advanced solid tumors, characterizing the DLTs and identifying the MTD.

Methods

Study Design

This was an international, multicenter, open-label, nonrandomized, phase 1 study to determine the DLTs and MTD for the combination of oral ridaforolimus with oral MK-0752 (ClinicalTrial.gov identifier, NCT01295632). This study also evaluated the combination of ridaforolimus + MK-2206 (a protein kinase-B [AKT] inhibitor); results will be disseminated in a separate manuscript.

The study protocol was approved by the Institutional Review Board or Independent Ethics Committee at each participating site and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and all local and federal regulatory guidelines. Patients provided written informed consent.

Patients

Adult (≥18 years old) male or female patients were eligible for the study if they had histologically confirmed metastatic or locally advanced solid tumors that had failed to respond to standard therapy, that had progressed despite standard therapy, or for which standard therapy does not exist. Patients could only enroll in 1 dose group, and were not permitted to have any medical conditions that could affect compliance with the protocol, limit interpretation of study results, or pose an unacceptable medical risk. The number of prior treatments permitted was not limited. Patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, and adequate organ function. Patients had to have at least 1 measurable recurrent or metastatic lesion according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1) [27], with the exception of patients with prostate cancer which did not require measurable disease if PSA level >10 ng/mL.

Exclusion criteria included treatment with chemotherapy or radiotherapy within 4 weeks prior to study day 1, biological therapy (excluding antibodies) within 2 weeks prior to study day 1, or lack of recovery to ≤ grade 1 or baseline from adverse events due to agents administered more than 4 weeks earlier. Patients with known symptomatic or progressing central nervous system (CNS) metastases or with prior exposure to related agents, were also excluded.

Treatments

Ridaforolimus was administered as monotherapy for 5 days prior to beginning combination dosing. During combination treatment, ridaforolimus was administered orally for 5 consecutive days followed by 2 consecutive days off each week, and MK-0752 (fixed dose 1800 mg) was administered orally once per week on cycle day 1, in repeating 28-day treatment cycles. The starting dose of ridaforolimus was 20 mg (DL1), with planned sequential dose increases to 30 mg (DL2) and 40 mg (DL3) using a 3+3 patients dose-escalation scheme. The fixed dose of MK-0752 was chosen based on the phase 1 trial that found 1800 mg/wk to be a biologically effective dose [23]. Additional dose increases up to 3200 mg/wk did not result in additional drug exposure, so a fixed dose for MK-0752 was selected rather than dose escalation. DLTs observed in cycle 1 were used to determine escalation (or de-escalation).

End Points and Assessments

The DLT rate (primary end point) was assessed in the DLT-evaluable population, which included all patients who had a cycle 0 or cycle 1 DLT or who completed both cycle 0 and cycle 1 without a DLT. The MTD was defined as the dose level for which <1/3 or <2/6 patients developed a DLT.

Adverse events were graded and recorded throughout the study according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v4.0). Assessments included vital signs, electrocardiogram (at screening and 2 hours after dose on day 2, cycle 1), ECOG performance status, comprehensive ophthalmologic examination, laboratory measures, and medical history.

A secondary end point was response rate, defined as the proportion of patients whose best response was partial response (PR) or complete response (CR). Response was evaluated according to RECIST v1.1, using either computed tomography (CT) or magnetic resonance imaging (MRI) at baseline, then every 2 cycles (±5 days) during treatment, and at the time of treatment discontinuation. Image analysis was undertaken both locally by the investigator and centrally by an independent imaging laboratory.

Statistics

No formal statistical hypothesis was tested for the primary objective of defining DLT and MTD. Adverse events were summarized using descriptive statistics per NCI CTCAE v 4.0. The safety analysis population consisted of all patients who received at least 1 dose of study treatment. The primary efficacy population consisted of all patients who received at least 1 dose of study treatment and who had baseline data for those analyses that required baseline data.

The study utilized a 3+3 dose-escalation scheme; a maximum of 6 patients could be enrolled per dose level during dose escalation. A cohort of 3 patients was enrolled at the initial dose level. If 0/3 patients developed a DLT, escalation to the next dose level would occur. If 1/3 patients developed a DLT, another 3 patients would be enrolled at that dose level. Providing that 0 of these 3 new patients developed a DLT (giving a total of 1/6 patients with a DLT at

this dose level), escalation to the next dose level would occur. However, if ≥1 of the 3 new patients developed a DLT (giving a total of ≥2/6 patients [≥33%] with a DLT at that dose level), the dose escalation stage of the trial would be terminated and the dose(s) directly below the current dose would be considered the MTD. If ≥2/3 patients developed DLTs, the dose level will not be considered further and the dose(s) directly below the current dose would be explored.

Results

Disposition

Thirty patients were allocated and assigned to treatment, of whom 28 patients received at least 1 dose of ridaforolimus plus MK-0752. There were 7 trial centers in 4 countries (4 in the United States; 1 in France; 1 in Norway, and 1 in Spain).

The majority of patients discontinued the study because of progressive disease (19 of 30 allocated patients; 63.3%). Eight patients (26.7%) withdrew consent (6 of these 8 patients had a serious adverse event [SAE] and/or DLT), 1 patient (3.3%) discontinued because of an adverse event, and 1 patient discontinued per physician decision. The other patient, who has continued in the extension phase for >9 months after database lock, remains on therapy with no evidence of disease and is tolerating therapy well.

Baseline Demographics and Disease Characteristics

Most of the patients were white, and the median age was 63 years old (Table 1). The most common type of tumor was head and neck cancer, in 50% of the patients overall, followed by colorectal cancer in 17% of patients. Most patients had received prior chemotherapy (96.7%) or surgery (96.7%), and many had received biologic agents (53.3%) or radiation therapy (66.7%).

Dose-Limiting Toxicity and Maximum Tolerated Dose

Ridaforolimus doses were escalated from 20 mg/d ($n = 19$; DL1) to 30 mg/d ($n = 9$; DL2). Patients received a median of 3 (range, 1 to 21) cycles of ridaforolimus and 2 (range, 1 to 20) cycles of MK-0752 at DL1, and 3 (range, 2 to 11) cycles of ridaforolimus and 2 (range, 1 to 10) cycles of MK-0752 at DL2.

In DL1 there were 14 patients evaluable for DLTs; 1 DLT (grade 2 stomatitis, second episode) was reported. At DL2, 3 DLTs were reported among 8 evaluable patients (1 each of grade 3 stomatitis, grade 3 diarrhea, and grade 3 asthenia). Based on these results, the MTD was determined to be ridaforolimus 20 mg by mouth (PO) daily 5 days/week plus MK-0752 1800 mg PO QW (DL1).

Safety

Twenty-four of the 28 treated patients (85.7%) experienced 1 or more drug-related adverse events. At the MTD (DL1) approximately 42.1% of patients experienced a grade 3 adverse event versus 55.6% at DL2; no grade 4 adverse events were reported (Table 2). Fifteen of the 28 treated patients (53.6%) experienced ≥1 serious adverse event. At DL2, two of the 9

patients experienced a drug-related serious adverse event: grade 3 diarrhea (1 patient) and grade 3 asthenia (1 patient). None of the 19 patients treated at DL1 experienced a drug-related serious adverse event (Table 2). There were 2 deaths on study, neither of which was considered drug-related: malignant neoplasm progression during cycle 1 at DL2 (1 patient), and neoplasm progression during the safety follow-up period at DL1 (1 patient).

The most commonly reported drug-related adverse events included stomatitis, diarrhea, decreased appetite, hyperglycemia, thrombocytopenia, asthenia, and rash; most were mild to moderate in severity (Table 3). With the exception of diarrhea and decreased appetite, the incidence of these specific drug-related adverse events was 2 to 3 times greater in patients treated at DL2. At the MTD, the most common drug-related adverse events were diarrhea (32%), stomatitis (32%), and decreased appetite (32%). Adverse events of grade 3 severity that occurred at the MTD included anemia (3 patients) and stomatitis (2 patients), and 1 patient each experienced diarrhea, fatigue, alanine aminotransferase elevation, aspartate aminotransferase elevation, hypokalemia, and hypophosphatemia. These were not considered DLTs as they occurred beyond cycle 1.

Tumor Response

Eighteen patients were evaluable for tumor response per RECIST 1.1 (they had measurable target lesions and at least 1 postbaseline scan), of which 10 had HNSCC. The maximum percentage change from baseline in target lesions for all response-evaluable patients is presented in Fig. 2A, and Fig. 2B shows maximum percentage change from baseline in target lesions for patients with HNSCC only. One patient with HNSCC, who did not have measurable lesions per RECIST 1.1 but was evaluable for disease response, had a CR and remained on therapy for >20+ months (Fig. 3). Another patient with HNSCC had a confirmed PR (Fig. 4). Stable disease ≥6 months was seen in a third patient with HNSCC.

Discussion

This phase 1 study, novel in that it assessed the combination of 2 investigational targeted therapies, demonstrated the feasibility of combining the mTOR inhibitor ridaforolimus with the Notch inhibitor MK-0752 for treating advanced solid malignancies, and identified the MTD for the combination. Indications of clinical activity were observed in patients with HNSCC, but there were issues with tolerability even at the MTD, with 42% of patients experiencing grade 3 drug-related adverse events.

There is some overlap in the toxicity profiles of ridaforolimus and MK-0752, but not extensively. The most common adverse events associated with single-agent MK-0752 therapy were nausea, vomiting, diarrhea, fatigue, and rash [23, 24]. For ridaforolimus monotherapy, the most commonly reported adverse events were stomatitis/mucositis, rash, anemia, infection, and fatigue [12–16]. In combination, these agents resulted in a relatively high incidence of stomatitis, diarrhea, and decreased appetite (all around 32%) at the MTD. Interestingly, rash is a common adverse event for both agents as monotherapies, but was not a significant issue with combination therapy. Prophylactic strategies to reduce the occurrence of common adverse events could improve the tolerability of the regimen. In particular, stomatitis/mucositis is a class toxicity associated with mTOR inhibitor therapy

[28–30], with high incidence rates in clinical trials of other mTOR inhibitors in malignancies [31, 32]. Prevention or early treatment is crucial to avoid any dose interruptions or reductions that could compromise the efficacy of the therapy [30, 33, 34].

A previous study combining the mTOR inhibitor temsirolimus with the Notch inhibitor RO4929097 in patients with advanced solid tumors reported no objective responses, although 73% of patients experienced stable disease [35]. In the present study, combination ridaforolimus and MK-0752 produced clinical activity in 3 patients with HNSCC (1 CR, 1 PR, and 1 prolonged stable disease). Development of HNSCC is frequently associated with inactivating mutations in *Notch* or *PTEN*, and activating mutations in elements of the PI3K-AKT-mTOR pathway [36, 37]. In a mouse model of HNSCC, reduced PTEN expression and/or inactivation was associated with HNSCC progression [38]. In patients with HNSCC, tumor samples have shown evidence of transcriptional alterations in the Notch signaling pathway, suggesting that the Notch pathway may be driving tumor progression in a subset of HNSCC tumors [39]. Given these genetic associations with Notch and the PI3K-AKT-mTOR pathway and the clinical activity seen in this phase 1 trial, HNSCC would appear to be a good candidate for exploring further with this therapeutic combination.

In conclusion, the combination of ridaforolimus and MK-0752 demonstrated some clinical activity in HNSCC, but there were issues with tolerability leading to study discontinuation. Use of prophylactic strategies to prevent some of the common adverse events, careful patient education, and aggressive early intervention for patients who develop these adverse events may improve the balance between efficacy and safety of this combination.

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References

1. Granville CA, Memmott RM, Gills JJ, Dennis PA. Handicapping the race to develop inhibitors of the phosphoinositide 3-kinase/Akt/mammalian target of rapamycin pathway. Clin Cancer Res. 2006; 12:679–89. [PubMed: 16467077]
2. Baselga J. Targeting the phosphoinositide-3 (PI3) kinase pathway in breast cancer. Oncologist. 2011; 16(Suppl 1):12–9.
3. Dancey JE, Monzon J. Ridaforolimus: a promising drug in the treatment of soft-tissue sarcoma and other malignancies. Future Oncology. 2011; 7:827–39. [PubMed: 21732754]
4. Pal SK, Reckamp KL. Mammalian target of rapamycin, Akt, and phosphatidylinositol 3-kinase signaling. Journal of Thoracic Oncology. 2010; 5:S487–S489. [PubMed: 21102251]
5. Abraham RT, Gibbons JJ. The mammalian target of rapamycin signaling pathway: twists and turns in the road to cancer therapy. Clin Cancer Res. 2007; 13:3109–14. [PubMed: 17545512]
6. Hennessy BT, Smith DL, Ram PT, Lu Y, Mills GB. Exploiting the PI3K/AKT pathway for cancer drug discovery. Nature Reviews- Drug Discovery. 2005; 4:988–1004. [PubMed: 16341064]

7. Elit L. Drug evaluation: AP-23573–an mTOR inhibitor for the treatment of cancer. IDrugs. 2006; 9:636–44. [PubMed: 16952072]
8. Ridaforolimus. Vol. 10. Drugs R D; 2010. p. 165-78.
9. Rivera VM, Squillace RM, Miller D, Berk L, Wardwell SD, Ning Y, Pollock R, Narasimhan NI, Iuliucci JD, Wang F, Clackson T. Ridaforolimus (AP23573; MK-8669), a potent mTOR inhibitor, has broad antitumor activity and can be optimally administered using intermittent dosing regimens. Molecular Cancer Therapy. 2011; 10:1059–71.
10. Squillace RM, Miller D, Cookson M, Wardwell SD, Moran L, Clapham D, Wang F, Clackson T, Rivera VM. Antitumor activity of ridaforolimus and potential cell cycle determinants of sensitivity in sarcoma and endometrial cancer models. Molecular Cancer Therapy. 2011; 10:1959–68.
11. Berk L, Mita MM, Kreisberg J, Bedrosian CL, Tolcher AW, Clackson T, Rivera VM. Analysis of the pharmacodynamic activity of the mTOR inhibitor ridaforolimus (AP23573, MK-8669) in a phase 1 clinical trial. Cancer Chemother Pharmacol. 2012; 69:1369–77. [PubMed: 22231376]
12. Mita MM, Mita AC, Chu QS, Rowinsky EK, Fetterly GJ, Goldston M, Patnaik A, Mathews L, Ricart AD, Mays T, Knowles H, Rivera VM, Kreisberg J, Bedrosian CL, Tolcher AW. Phase I trial of the novel mammalian target of rapamycin inhibitor deforolimus (AP23573; MK-8669) administered intravenously daily for 5 days every 2 weeks to patients with advanced malignancies. J Clin Oncol. 2008; 26:361–7. [PubMed: 18202410]
13. Mita MM, Poplin E, Britten CD, Tap WD, Rubin EH, Scott BB, Berk L, Rivera VM, Loewy JW, Dodion P, Haluska F, Sarantopoulos J, Mita A, Tolcher A. Phase I/IIa trial of the mammalian target of rapamycin inhibitor ridaforolimus (AP23573; MK-8669) administered orally in patients with refractory or advanced malignancies and sarcoma. Ann Oncol. 2013; 24:1104–11. [PubMed: 23211938]
14. Amato RJ, Wilding G, Bubley G, Loewy J, Haluska F, Gross ME. Safety and preliminary efficacy analysis of the mTOR inhibitor ridaforolimus in patients with taxane-treated, castration-resistant prostate cancer. Clinical Genitourinary Cancer. 2012; 10:232–8. [PubMed: 22695254]
15. Chawla SP, Staddon AP, Baker LH, Schuetze SM, Tolcher AW, D'Amato GZ, Blay JY, Mita MM, Sankhala KK, Berk L, Rivera VM, Clackson T, Loewy JW, Haluska FG, Demetri GD. Phase II study of the mammalian target of rapamycin inhibitor ridaforolimus in patients with advanced bone and soft tissue sarcomas. J Clin Oncol. 2012; 30:78–84. [PubMed: 22067397]
16. Demetri GD, Chawla SP, Ray-Coquard I, Le CA, Staddon AP, Milhem MM, Penel N, Riedel RF, Bui-Nguyen B, Cranmer LD, Reichardt P, Bompas E, Alcindor T, Rushing D, Song Y, Lee RM, Ebbinghaus S, Eid JE, Loewy JW, Haluska FG, Dodion PF, Blay JY. Results of an international randomized phase III trial of the mammalian target of rapamycin inhibitor ridaforolimus versus placebo to control metastatic sarcomas in patients after benefit from prior chemotherapy. J Clin Oncol. 2013; 31:2485–92. [PubMed: 23715582]
17. Gore L, Trippett TM, Katzenstein HM, Boklan J, Narendran A, Smith A, Macy ME, Rolla K, Narashimhan N, Squillace RM, Turner CD, Haluska FG, Nieder M. A multicenter, first-in-pediatrics, phase 1, pharmacokinetic and pharmacodynamic study of ridaforolimus in patients with refractory solid tumors. Clin Cancer Res. 2013; 19:3649–58. [PubMed: 23659969]
18. Perotti A, Locatelli A, Sessa C, Hess D, Vigano L, Capri G, Maur M, Cerny T, Cresta S, Rojo F, Albanell J, Marsoni S, Corradino I, Berk L, Rivera VM, Haluska F, Gianni L. Phase IB study of the mTOR inhibitor ridaforolimus with capecitabine. J Clin Oncol. 2010; 28:4554–61. [PubMed: 20855840]
19. Rizzieri DA, Feldman E, DiPersio JF, Gabrail N, Stock W, Strair R, Rivera VM, Albitar M, Bedrosian CL, Giles FJ. A phase 2 clinical trial of deforolimus (AP23573, MK-8669), a novel mammalian target of rapamycin inhibitor, in patients with relapsed or refractory hematologic malignancies. Clin Cancer Res. 2008; 14:2756–62. [PubMed: 18451242]
20. Sessa C, Tosi D, Vigano L, Albanell J, Hess D, Maur M, Cresta S, Locatelli A, Angst R, Rojo F, Coceani N, Rivera VM, Berk L, Haluska F, Gianni L. Phase Ib study of weekly mammalian target of rapamycin inhibitor ridaforolimus (AP23573; MK-8669) with weekly paclitaxel. Ann Oncol. 2010; 21:1315–22. [PubMed: 19901013]
21. Meulenbeld HJ, de Bono JS, Tagawa ST, Whang YE, Li X, Heath KH, Zandvliet AS, Ebbinghaus SW, Hudes GR, de WR. Tolerability, safety and pharmacokinetics of ridaforolimus in combination

with bicalutamide in patients with asymptomatic, metastatic castration-resistant prostate cancer (CRPC). Cancer Chemother Pharmacol. 2013; 72:909–16. [PubMed: 23921574]

22. Kopan R, Ilagan MX. Gamma-secretase: proteasome of the membrane? Nature Reviews-Molecular Cell Biology. 2004; 5:499–504.
23. Krop I, Demuth T, Guthrie T, Wen PY, Mason WP, Chinnaiyan P, Butowski N, Groves MD, Kesari S, Freedman SJ, Blackman S, Watters J, Loboda A, Podtelezhnikov A, Lunceford J, Chen C, Giannotti M, Hing J, Beckman R, LoRusso P. Phase I pharmacologic and pharmacodynamic study of the gamma secretase (Notch) inhibitor MK-0752 in adult patients with advanced solid tumors. J Clin Oncol. 2012; 30:2307–13. [PubMed: 22547604]
24. Fouladi M, Stewart CF, Olson J, Wagner LM, Onar-Thomas A, Kocak M, Packer RJ, Goldman S, Gururangan S, Gajjar A, Demuth T, Kun LE, Boyett JM, Gilbertson RJ. Phase I trial of MK-0752 in children with refractory CNS malignancies: a pediatric brain tumor consortium study. J Clin Oncol. 2011; 29:3529–34. [PubMed: 21825264]
25. Cullion K, Draheim KM, Hermance N, Tammam J, Sharma VM, Ware C, Nikov G, Krishnamoorthy V, Majumder PK, Kelliher MA. Targeting the Notch1 and mTOR pathways in a mouse T-ALL model. Blood. 2009; 113:6172–81. [PubMed: 19246562]
26. Vo K, Amarasinghe B, Washington K, Gonzalez A, Berlin J, Dang TP. Targeting notch pathway enhances rapamycin antitumor activity in pancreas cancers through PTEN phosphorylation. Molecular Cancer. 2011; 10:138. [PubMed: 22074495]
27. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 11). Eur J Cancer. 2009; 45:228–47. [PubMed: 19097774]
28. Martins F, de Oliveira MA, Wang Q, Sonis S, Gallottini M, George S, Treister N. A review of oral toxicity associated with mTOR inhibitor therapy in cancer patients. Oral Oncol. 2013; 49:293–8. [PubMed: 23312237]
29. Pilotte AP, Hohos MB, Polson KM, Huftalen TM, Treister N. Managing stomatitis in patients treated with Mammalian target of rapamycin inhibitors. Clin J Oncol Nurs. 2011; 15:E83–E89. [PubMed: 21951751]
30. Boers-Doets CB, Raber-Durlacher JE, Treister NS, Epstein JB, Arends AB, Wiersma DR, Lalla RV, Logan RM, van Erp NP, Gelderblom H. Mammalian target of rapamycin inhibitor-associated stomatitis. Future Oncology. 2013; 9:1883–92. [PubMed: 24295418]
31. Baselga J, Campone M, Piccart M, Burris HA, Rugo HS, Sahmoud T, Noguchi S, Gnant M, Pritchard KI, Lebrun F, Beck JT, Ito Y, Yardley D, Deleu I, Perez A, Bachelot T, Vittori L, Xu Z, Mukhopadhyay P, Lebwohl D, Hortobagyi GN. Everolimus in postmenopausal hormone receptor-positive advanced breast cancer. N Engl J Med. 2012; 366:520–9. [PubMed: 22149876]
32. Bachelot T, Bourgier C, Cropet C, Ray-Coquard I, Ferrero JM, Freyer G, Abadie-Lacourtoisie S, Eymard JC, Debled M, Spaeth D, Legouffe E, Allouache D, El Kouri C, Pujade-Lauraine E. Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer with prior exposure to aromatase inhibitors: A GINECO study. J Clin Oncol. 2012; 30:2718–24. [PubMed: 22565002]
33. Boers-Doets CB, Epstein JB, Raber-Durlacher JE, Ouwerkerk J, Logan RM, Brakenhoff JA, Lacouture ME, Gelderblom H. Oral adverse events associated with tyrosine kinase and mammalian target of rapamycin inhibitors in renal cell carcinoma: a structured literature review. Oncologist. 2011
34. Kaplan B, Qazi Y, Wellen JR. Strategies for the management of adverse events associated with mTOR inhibitors. Transplant Rev. 2014; 28:126–33.
35. Diaz-Padilla I, Hirte H, Oza AM, Clarke BA, Cohen B, Reedjik M, Zhang T, Kamel-Reid S, Ivy SP, Hotte SJ, Razak AA, Chen EX, Brana I, Wizemann M, Wang L, Siu LL, Bedard PL. A phase Ib combination study of RO4929097, a gamma-secretase inhibitor, and temsirolimus in patients with advanced solid tumors. Invest New Drugs. 2013; 31:1182–91. [PubMed: 23860641]
36. Agrawal N, Frederick MJ, Pickering CR, Bettegowda C, Chang K, Li RJ, Fakhry C, Xie TX, Zhang J, Wang J, Zhang N, El-Naggar AK, Jasser SA, Weinstein JN, Trevino L, Drummond JA, Muzny DM, Wu Y, Wood LD, Hruban RH, Westra WH, Koch WM, Califano JA, Gibbs RA,

Sidransky D, Vogelstein B, Velculescu VE, Papadopoulos N, Wheeler DA, Kinzler KW, Myers JN. Exome sequencing of head and neck squamous cell carcinoma reveals inactivating mutations in NOTCH1. Science. 2011; 333:1154–7. [PubMed: 21798897]

37. Stransky N, Egloff AM, Tward AD, Kostic AD, Cibulskis K, Sivachenko A, Kryukov GV, Lawrence MS, Sougnez C, McKenna A, Shefler E, Ramos AH, Stojanov P, Carter SL, Voet D, Cortes ML, Auclair D, Berger MF, Saksena G, Guiducci C, Onofrio RC, Parkin M, Romkes M, Weissfeld JL, Seethala RR, Wang L, Rangel-Escareno C, Fernandez-Lopez JC, Hidalgo-Miranda A, Melendez-Zajgla J, Winckler W, Ardlie K, Gabriel SB, Meyerson M, Lander ES, Getz G, Golub TR, Garraway LA, Grandis JR. The mutational landscape of head and neck squamous cell carcinoma. Science. 2011; 333:1157–60. [PubMed: 21798893]
38. Squarize CH, Castilho RM, Abrahao AC, Molinolo A, Lingen MW, Gutkind JS. PTEN deficiency contributes to the development and progression of head and neck cancer. Neoplasia. 2013; 15:461–71. [PubMed: 23633918]
39. Sun W, Gaykalova DA, Ochs MF, Mambo E, Arnaoutakis D, Liu Y, Loyo M, Agrawal N, Howard J, Li R, Ahn S, Fertig E, Sidransky D, Houghton J, Buddavarapu K, Sanford T, Choudhary A, Darden W, Adai A, Latham G, Bishop J, Sharma R, Westra WH, Hennessey P, Chung CH, Califano JA. Activation of the NOTCH pathway in head and neck cancer. Cancer Res. 2014; 74:1091–104. [PubMed: 24351288]

Highlights

- Novel combination of 2 investigational agents, ridaforolimus and MK-0752
- Inhibiting mTOR and Notch could lead to complementary blockade of the PI3K pathway
- The MTD was ridaforolimus 20 mg PO daily 5 days/week plus MK-0752 1800 mg PO QW
- There were 2 responses (1 CR, 1 PR), both in patients with SCC of the head and neck

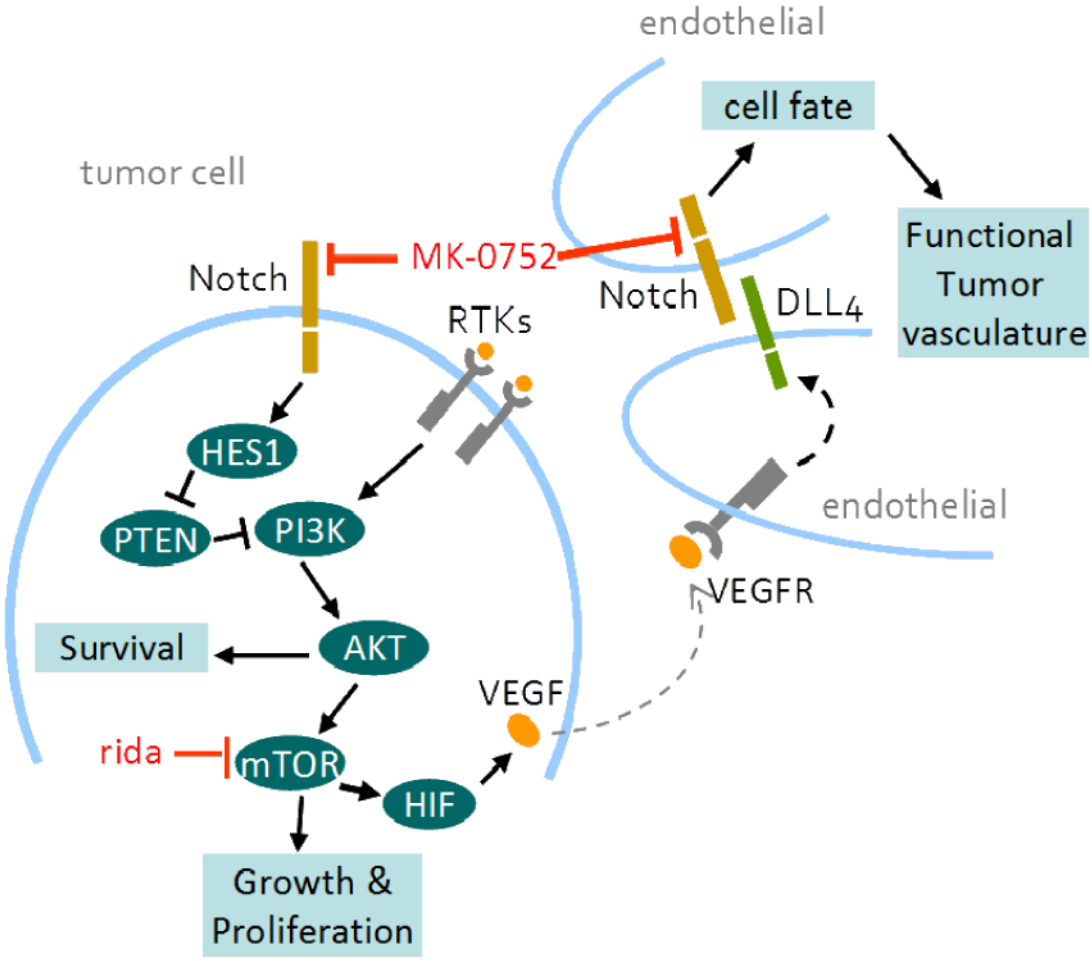

Fig. 1.

Rationale for mTOR inhibitor + NOTCH inhibitor combination. The PI3K/AKT/mTOR signaling pathway is aberrantly activated in a variety of cancers. Notch signaling has been shown to maintain cell proliferation, growth, and metabolism in part by driving PI3K pathway signaling. The combination of mTOR inhibitor ridaforolimus and Notch inhibitor MK-0752 may lead to complementary blockade of the PI3K pathway.

Abbreviations: AKT, protein kinase-B; DLL_4, Delta-like ligand 4; HES1, Hairy/enhancer of split 1; HIF, hypoxia-inducible factor; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog; rida, ridaforolimus; RTK, receptor tyrosine kinase; VEGFR, vascular endothelial growth factor receptor.

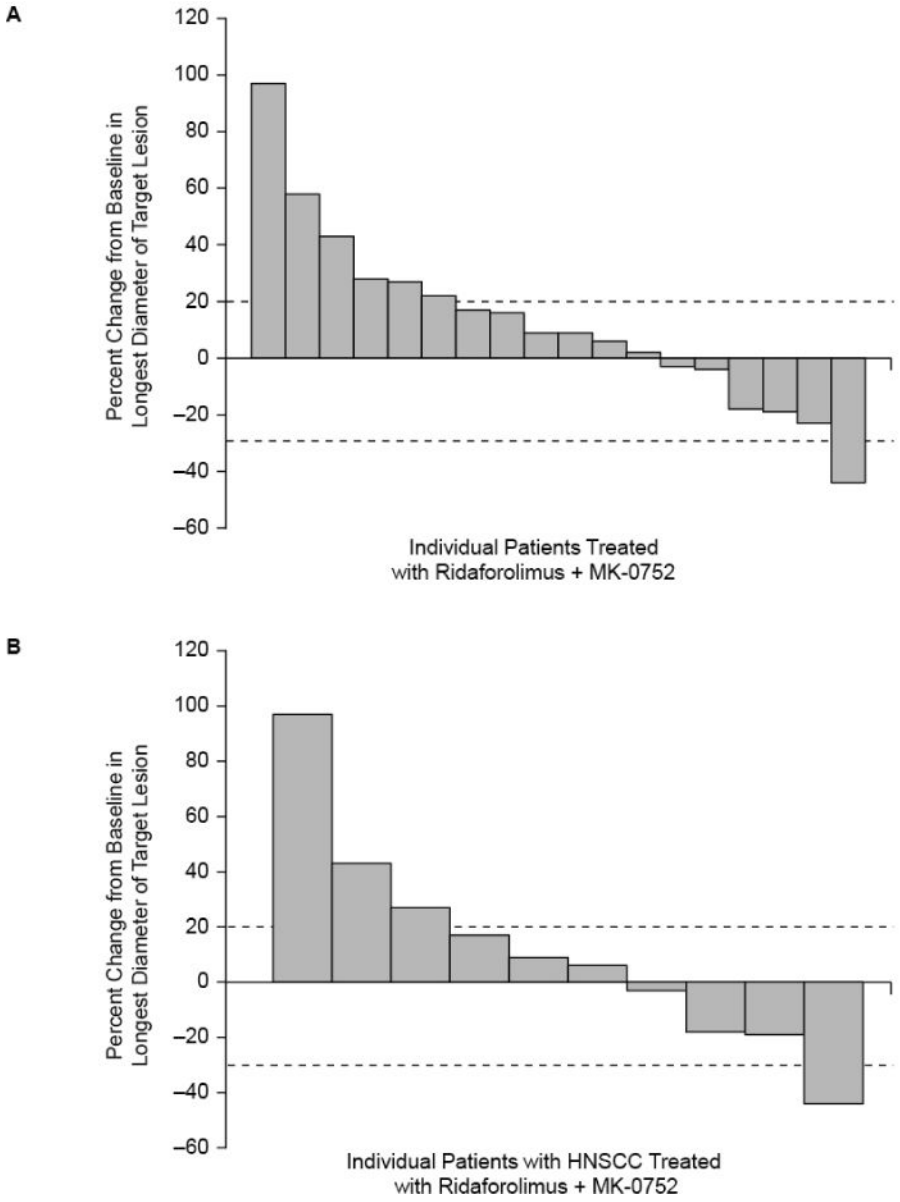

Fig. 2.

Maximum change from baseline in the size of target lesions in patients evaluable for response (at least 1 postbaseline scan available) as assessed per RECIST v1.1 by investigator review. A. All patients (n = 18). B. Patients with HNSCC (n =10).

Abbreviations: HNSCC, head and neck squamous cell carcinoma; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1.

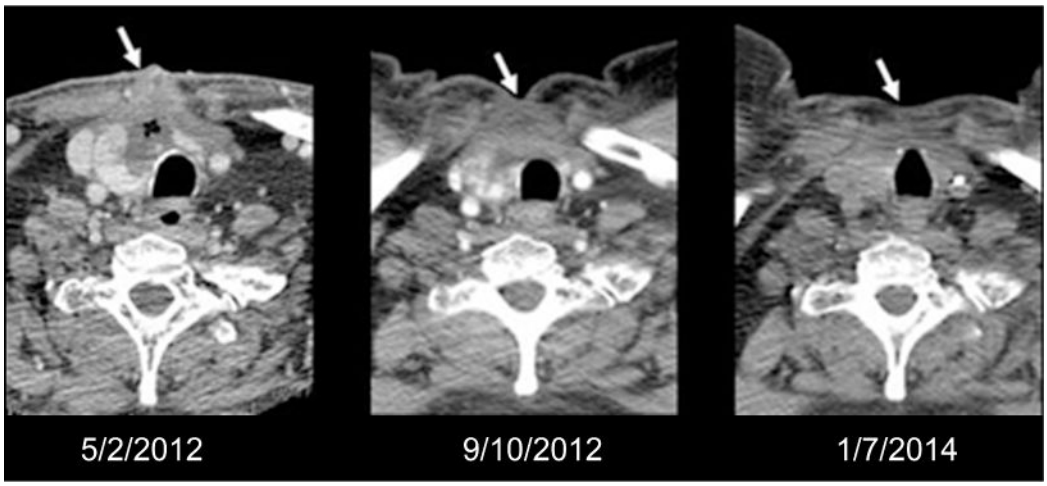

Fig. 3.

Imaging results for a patient with recurrent HNSCC obtained at baseline (5/2/2012), cycle 4, day 27 (9/10/12) and cycle 20, day 35 (1/7/14). The patient developed a contrast allergy, and CT of the neck done at baseline was later changed to PET-CT. The patient exhibits no evidence of disease and continues on therapy.

Abbreviations: CT, computed tomography; HNSCC, head and neck squamous cell carcinoma; PET, positron emission tomography.

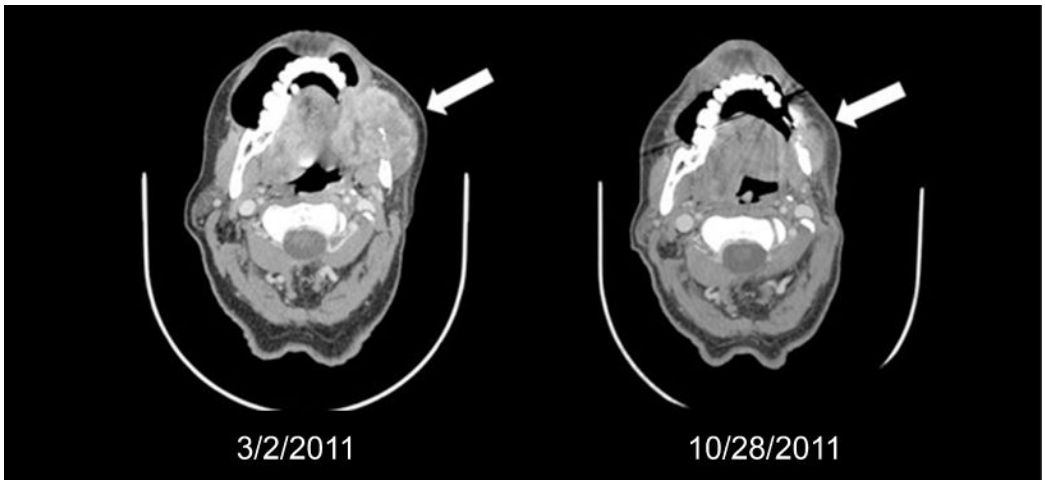

Fig. 4.

Imaging results for a patient with recurrent HNSCC obtained at baseline (3/2/11) and cycle 8, day 26 (10/28/11). The best response per RECIST v1.1 by local assessment was a decrease in target lesions of 46%.

Abbreviations: HNSCC, head and neck squamous cell carcinoma; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1.

Table 1

Baseline demographics and disease characteristics.

***n* (%)[a]**	**Ridaforolimus 20 mg QD × 5 d/wk + MK-0752 1800 mg weekly *n* = 21**	**Ridaforolimus 30 mg QD × 5 d/wk + MK-0752 1800 mg weekly *n* = 9**	**Total *N* = 30**
Age, y			
<65	13 (61.9)	6 (66.7)	19 (63.3)
Mean (SD)	62.0 ± 11.3	59.4 ± 8.7	61.2 ± 10.5
Median (range)	63 (38–80)	59 (42–70)	63 (38–80)
Gender			
Male	12 (57.1)	5 (55.6)	17 (56.7)
Female	9 (42.9)	4 (44.4)	13 (43.3)
Race			
White	18 (85.7)	9 (100.0)	27 (90.0)
Asian	1 (4.8)	0	1 (3.3)
Black or African American	1 (4.8)	0	1 (3.3)
Unknown	1 (4.8)	0	1 (3.3)
Ethnicity			
Hispanic or Latino	1 (4.8)	1 (11.1)	2 (6.7)
Tumor Type			
Breast	1 (4.8)	1 (11.1)	2 (6.7)
Colorectal	3 (14.3)	2 (22.2)	5 (16.7)
Glioblastoma multiforme	1 (4.8)	1 (11.1)	2 (6.7)
Head and neck	12 (57.1)	3 (33.3)	15 (50.0)
Ovarian	1 (4.8)	1 (11.1)	2 (6.7)
Other	3 (14.3)	1 (11.1)	4 (13.3)
Prior treatment			
Chemotherapy	20 (95.2)	9 (100.0)	29 (96.7)
Biologic	10 (47.6)	6 (66.7)	16 (53.3)
Radiation[b]	15 (71.4)	5(55.6)	20 (66.7)
Surgery	21 (100.0)	8 (88.9)	29 (96.7)
Number of prior systemic regimens			
Median (range)	2 (0–6)	3 (1–5)	2 (0–6)

Abbreviations: QD, once daily; SD, standard deviation.

[a] Unless otherwise specified, figures represent *n* (%).

[b] Includes chemoradiation treatment.

Table 2

AE summary.

***n* (%)**	**Ridaforolimus 20 mg QD × 5 d/wk + MK-0752 1800 mg weekly *n* = 19**	**Ridaforolimus 30 mg QD × 5 d/wk + MK-0752 1800 mg weekly *n* = 9**	**Total *N* = 28**
≥1 AE	18 (94.7)	9 (100.0)	27 (96.4)
Drug-related AE	15 (78.9)	9 (100.0)	24 (85.7)
Grade 3 AE	8 (42.1)	5 (55.6)	13 (46.4)
SAE	11 (57.9)	4 (44.4)	15 (53.6)
Drug-related SAE	0	2 (22.2)	2 (7.1)
Deaths	1 (5.3)	1 (11.1)	2 (7.1)
Discontinued because of AE	1 (5.3)	0	1 (3.6)
Discontinued because of drug-related AE	0	0	0
Discontinued because of SAE	1 (5.3)	0	1 (3.6)
Discontinued because of drug-related SAE	0	0	0

Abbreviations: AE, adverse event; QD, once daily; SAE, serious adverse event.

Table 3

Summary of drug-related adverse events occurring in ≥15% of patients (for all grades of severity) in either treatment group.

***n* (%)**	**Ridaforolimus 20 mg QD × 5 days/week + MK-0752 1800 mg weekly *n* = 19**		**Ridaforolimus 30 mg QD × 5 days/week + MK-0752 1800 mg weekly *n* = 9**		**Total *N* = 28**	
	All	**Grade 3 or 4**	**All**	**Grade 3 or 4**	**All**	**Grade 3 or 4**
Stomatitis	6 (31.6)	2 (10.5)[a]	7 (77.8)	1 (11.1)[a]	13 (46.4)	3 (10.7)*
Diarrhea	6 (31.6)	1 (5.3)[a]	4 (44.4)	1 (11.1)[a]	10 (35.7)	2 (7.1)[a]
Decreased appetite	6 (31.6)	0	3 (33.3)	0	9 (32.1)	0
Hyperglycemia	2 (10.5)	0	4 (44.4)	0	6 (21.4)	0
Thrombocytopenia	2 (10.5)	0	3 (33.3)	1 (11.1)[a]	5 (17.9)	1 (3.6)[a]
Asthenia	1 (5.3)	0	4 (44.4)	1 (11.1)[a]	5 (17.9)	1 (3.6)[a]
Rash	2 (10.5)	0	3 (33.3)	0	5 (17.9)	0
Hemoglobin decreased	3 (15.8)	1 (5.3)[a]	1 (11.1)	0	4 (14.3)	1 (3.6)[a]
Hypophosphatemia	3 (15.8)	1 (5.3)[a]	1 (11.1)	1 (11.1)[a]	4 (14.3)	2 (7.1)[a]
Vomiting	1 (5.3)	0	2 (22.2)	1 (11.1)[a]	3 (10.7)	1 (3.6)[a]
Hypomagnesemia	3 (15.8)	0	0	0	3 (10.7)	0
Hypertriglyceride mia	1 (5.3)	0	2 (22.2)	0	3 (10.7)	0
Weight decreased	1 (5.3)	0	2 (22.2)	0	3 (10.7)	0

Abbreviations: ALT, Alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; QD, once daily.

[a]All grade 3.