Novel pan-TEAD inhibitor ODM-212 Demonstrates Broad Combination Potential with KRAS and Pan-RAS Inhibitors in Preclinical Models of Multiple Tumor Types

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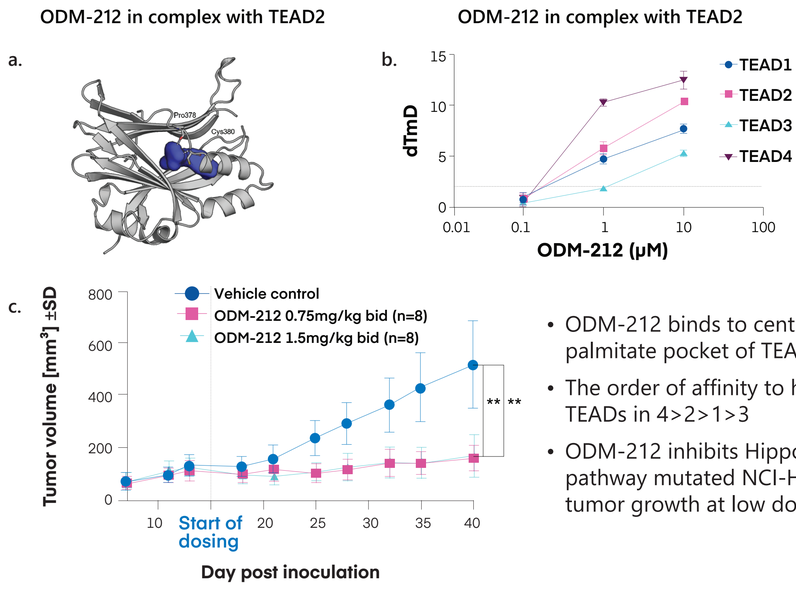
INTRODUCTION

- The Hippo pathway regulates cell proliferation and organ size through nuclear YAP/TAZ-mediated activation of TEAD1–4. Dysregulation of this pathway can sustain YAP/TAZ–TEAD signaling and drive the expression of genes that promote cancer cell survival and progression. YAP/TAZ–TEAD signaling can also be activated following KRAS inhibition and has been identified as a potential mechanism of resistance to KRAS inhibitors, highlighting TEAD as a potential target for combination strategies[1-5].
- ODM-212 is a novel, orally bioavailable pan-TEAD inhibitor with a safety and drug–drug interaction profile suitable for combination therapy[6].
- ODM-212 is currently being evaluated in Phase 1/2 trials as monotherapy (NCT06725758) and in combination regimens (NCT07563738).

ODM-212 is a potent pan-TEAD inhibitor with demonstrated single-agent efficacy in Hippo pathway-altered cancers



- ODM-212 binds to central palmitate pocket of TEADs
- The order of affinity to human TEADs in 4>2>1>3
- ODM-212 inhibits Hippo pathway mutated NCI-H226 tumor growth at low doses

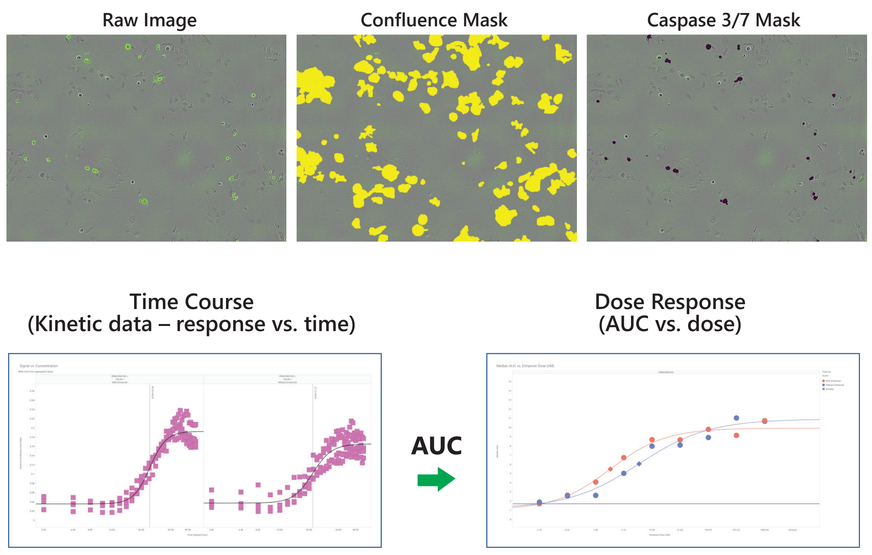
METHODS

ODM-212 combinations with RAS inhibitors were evaluated in 9 × 9 dose matrices across cancer cell lines (72 h). Cell viability was measured with CellTiter-Glo® 2.0 and inhibition was calculated as I = 1 – T/U (T, treated; U, vehicle control). Combination sensitivity (CSS) and Highest Single Agent (HSA) synergy scores were calculated from inhibition data. CSS > 40 and HSA > 5 were considered indicative of synergy.

	Lung cancer models tested	CRC models tested	Pancreatic cancer models tested	Other cancer models tested
ODM-212 + Sotorasib (KRAS G12Ci)	9	0	0	0
ODM-212 + Adagrasib (KRAS G12Ci)	12	1	1	4
ODM-212 + Daraxonrasib (RAS-ONi)	53	23	25	0
ODM-212 + Zoldonrasib (KRAS G12Di)	3	4	9	0

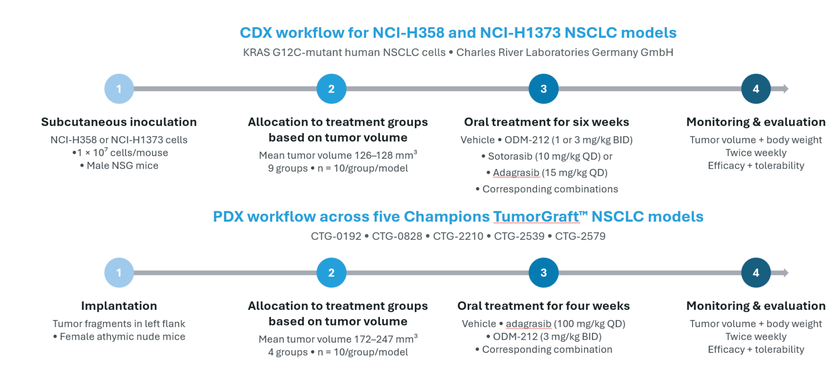
KRAS G12C-mutant lung cancer cells lines (n=6) were treated with KRAS inhibitors ± 1 μM ODM-212 and Caspase-3/7 Green Dye for 72 h. Apoptosis was monitored by Incucyte® live-cell imaging system, and relative apoptosis was quantified as the Green-to-Confluence Area Ratio (GCAR). AUC values derived from kinetic GCAR measurements were plotted against inhibitor concentration to generate dose-response curves.

Apoptosis Measured by Green -to-Confluence Area Ratio (GCAR)



Example of curve fits used for AUC calculation for one **KRAS inhibitor concentration** with and without enhancee

AUC from kinetic data plotted against all KRAS inhibitor doses, with (red) or without (blue) enhancer

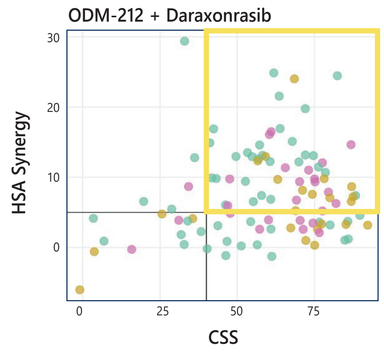


RESULTS

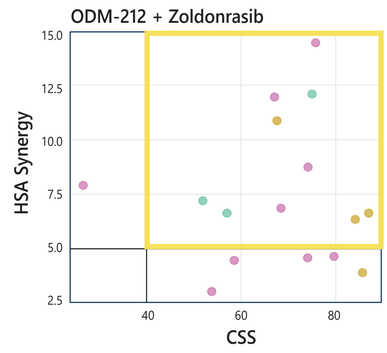
ODM-212 + sotorasib or adagrasib was synergistic in 75% of KRAS^G12C lung models (9/12)



ODM-212 + daraxonrasib was synergistic in lung (28/53), pancreatic (15/25), and colorectal (12/23) models



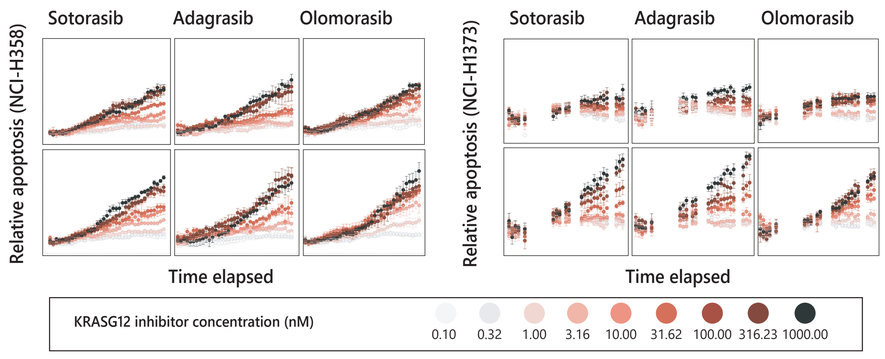
ODM-212 + zoldonrasib was synergistic in 63% of KRAS^G12D-mutated models: lung (3/3), pancreatic (4/9) and colorectal (3/4)



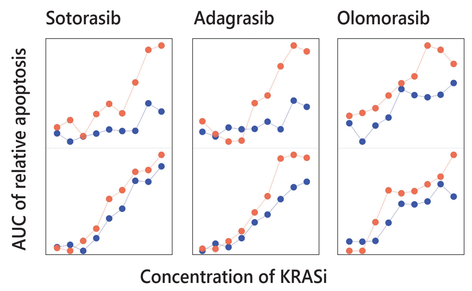
Drug: ●Adagrasib ▲Sotorasib

Primary Disease: Colorectal Endometrium Esophagus Lung Myeloma Ovary Pancreas

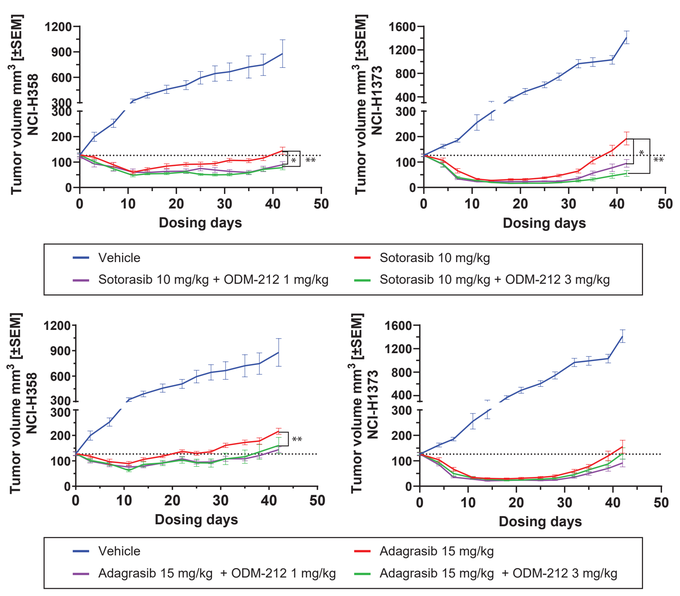
Apoptosis increased over time in NCI-H358 and NCI-H1373 NSCLC cell lines by KRAS inhibitor alone (top) and was enhanced with 1 μM ODM-212 combination (bottom). Apoptosis was enhanced also in NCI-H2122 and Calu-1. ODM-212 showed no apoptosis enhancement in LU-65 and KRAS inhibitors did not induce apoptosis in NCI-H2030 (data not shown)



ODM-212 (1 μM; red) enhanced KRAS G12C inhibitor-induced apoptosis (blue) in NCI-H1373 (top) and NCI-H358 (bottom) cells

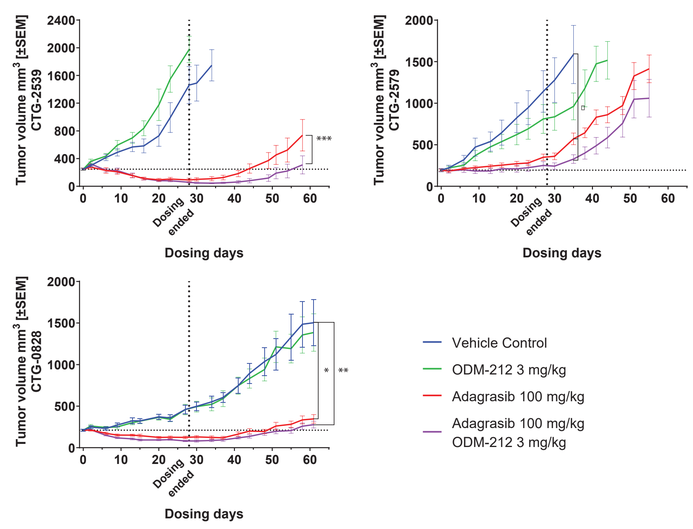


Enhanced antitumor activity of ODM-212 in combination with KRAS G12C inhibitors in KRAS G12C-mutant NSCLC xenograft models



Tumor volume was monitored during treatment with sotorasib (10 mg/kg QD) or adagrasib (15 mg/kg QD) alone or in combination with ODM-212 (1 mg/kg or 3 mg/kg BID). In both NCI-H358 and NCI-H1373 models, the addition of ODM-212 enhanced tumor growth inhibition compared with KRAS G12C inhibitor monotherapy, resulting in delayed tumor regrowth and improved antitumor activity. Data are presented as mean ± SEM. Statistical significance was determined versus KRAS G12C inhibitor monotherapy (*p < 0.05, **p < 0.01).

ODM-212 improved the durability of KRAS G12C inhibitor responses and delayed tumor regrowth in selected NSCLC patient-derived xenograft models



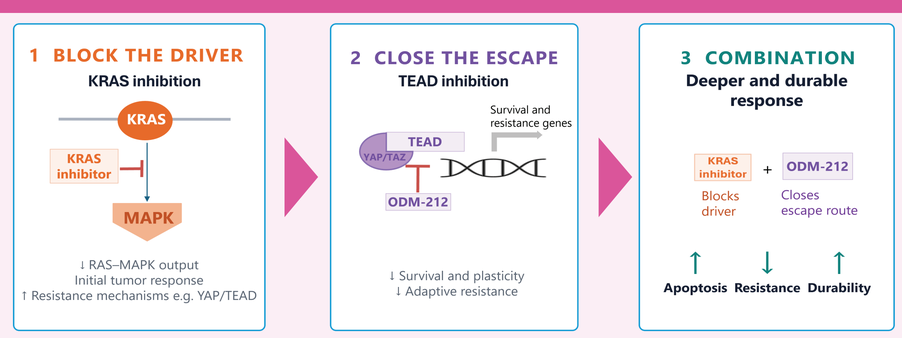
Treatment with ODM-212 (3 mg/kg BID) alone showed limited efficacy, whereas adagrasib (100 mg/kg QD) induced tumor regressions or inhibition across models. The combination treatment resulted in improved and more durable tumor growth control compared with adagrasib monotherapy in several models, including sustained suppression after treatment discontinuation. In models with complete adagrasib response, no additional benefit was seen with combination (data not shown). Data are presented as mean ± SEM. Statistical significance is indicated as follows: *p < 0.05, **p < 0.01, ***p < 0.001.

SUMMARY OF RESULTS

- ODM-212 demonstrated synergistic activity in 9/12 KRAS^G12C NSCLC models (75%) when combined with sotorasib or adagrasib. This was associated with increased apoptosis.
- Synergistic effects were also observed with the RAS(ON) inhibitor daraxonrasib in 28/53 lung (53%), 15/25 pancreatic (60%), and 12/23 colorectal (52%) models.
- Combination with zoldonrasib was synergistic in 63% of KRAS^G12D-mutated models: NSCLC (3/3), pancreatic (4/9) and colorectal (3/4).
- ODM-212 enhanced the in vivo efficacy of the KRAS^G12C inhibitors adagrasib and sotorasib in NSCLC CDX models.
- Combination of ODM-212 with adagrasib provided an efficacy benefit in PDX models that showed an incomplete response to adagrasib monotherapy.

CONCLUSIONS

These findings identify ODM-212 as a promising combination partner for RAS inhibitors including but not limited to daraxonrasib, sotorasib, adagrasib and zoldonrasib, with a potential to enhance efficacy and prolong the response of RAS inhibitors. ODM-212 is currently tested in phase 1/2 combination trial (NCT07563738).



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A first-in-human Phase I/II clinical trial: TEADES, NCT06725758, A 2-part Phase 1/2 Open-label Trial on ODM-212: TEADCO, NCT07563738