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# Identification of more potent imipridones, a new class of anti-cancer agents

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ONC201 is a member of a new class of anti-cancer therapy called imipridones. ONC201 was originally identified from a NCI chemical library in a phenotypic cell-based screen for small molecule inducers of TNF-related apoptosis-inducing ligand (TRAIL) expression.[1] Preclinically, it had broad spectrum activity, a benign toxicity profile, and favorable pharmacological properties, and a recent first-in-human trial confirmed that it was well tolerated while achieving micromolar plasma concentrations. In early trials, tumor regressions have been observed and several patients have had prolonged stability.[2,3] At the time of its discovery as an anti-cancer agent, ONC201s mechanism of action and direct molecular target were unknown, however it has since been shown to be a selective antagonist of dopamine receptor D2.[4] Downstream, ONC201 activates the integrated stress response (ISR), inactivates Akt and ERK signaling, and activates Foxo3a with subsequent upregulation of TRAIL.[4] Recent structural studies confirmed ONC201 to be a unique heterocyclic pharmacophore possessing anti-cancer activity.[4,5]

In this manuscript, Wagner et al. aimed to identify novel, more potent compounds based on the original imipridone core structure of ONC201.[6] They manipulated substituents on the peripheral benzyl moieties and found that halide benzyl groups replacing the 2-methylbenzyl group at the R1 position produced compounds with much greater potency in cell viability assays than ONC201. Two compounds, ONC206 and ONC212, with sub-micromolar GI50 values in an expanded set of cell lines (GI50 values for ONC201 were between 1–10 uM) and wide therapeutic indices were further developed. Importantly, the downstream signaling profile (ISR, TRAIL, and Akt/Erk) for ONC206 and ONC212 were similar to ONC201, although notably the effects were observed at much lower concentrations with ONC206 and ONC212 (50 nM and 10 nM, respectively) versus ONC201 (10 uM). Additionally, signaling effects were more rapid with ONC212 than with ONC201, and partially for this reason ONC212 was further explored.

In the cancer cell line panel of > 1000 cancer cell lines, ONC212 was effective against most hematological and solid malignancies with GI50 values in the low nanomolar range. It appeared that skin cancer cell lines were particularly sensitive, and that efficacy was independent of *BRAF* V600E status. ONC212 displayed overall favorable safety and pharmacokinetic profiles in mice and *in vivo* efficacy against various cancer types with an apparently stronger effect on cell proliferation than apoptosis.

Given the greater potency observed *in vitro* and *in vivo*, ONC212 appears to be a promising candidate for further development, although a few potential limitations were observed. ONC212 had a slightly shorter half-life ($T_{1/2}$ of 4.3 hours) in mice than ONC201. Despite this, the *in vivo* efficacy was greater in head-to-head comparison with ONC201 using the same dose and schedule. Additionally, ONC212 inhibited only invasion and not migration *in vitro* while ONC201 inhibited both, however the relevance of this *in vitro* finding to the clinic is unknown. Nonetheless, this difference, along with the different kinetics of downstream signaling, indicate there may be slightly different anti-cancer effects between ONC212 and ONC201 which may manifest as altered clinical activity profiles. Interestingly, ONC212 displayed the same delayed time course of apoptosis, suggesting a prolonged mechanism of action similar to ONC201. Another limitation is that ONC212 was not effective against a cell line with acquired ONC201 resistance, indicating cross-resistance, however this suggests the biologic activity between the 2 compounds are consistent.

Nevertheless, the significantly greater *in vitro* potency and *in vivo* efficacy of ONC212 vs. ONC201 may warrant further development. Although ONC201 has exhibited preliminary signs of clinical activity in early stage clinical trials, only a subset of patients appears to derive prolonged benefit. The greater potency and rapid signaling kinetics of ONC212 may result in broader clinical efficacy vs. ONC201, although it remains to be determined whether the increased potency will result in greater toxicity in humans. Additionally, it will be critical to identify the determinants of sensitivity and resistance to maximize the therapeutic potential of ONC201 and/or any analogs in the clinic. As a class, imipridones are of interest as they target pathways that are either underdeveloped or emerging in oncology, namely G protein coupled receptors and dopamine signaling.[7] Despite significant recent advances in cancer treatment, most patients with advanced or metastatic cancer don't derive benefit from current therapies and there remains significant unmet oncology need.

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## Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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