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TRAIL Receptor-targeted therapeutics: Resistance mechanisms and strategies to avoid them

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Abstract

Tumor Necrosis factor-Related Apoptosis-Inducing Ligand (TRAIL) receptors are attractive therapeutic targets in cancer because agents that activate these receptors directly induce tumor cell apoptosis and have low toxicity to normal tissues. Consequently, several different drugs that target these receptors (recombinant TRAIL and various agonistic antibodies that activate one of the two TRAIL receptors) have been developed and are being tested in human clinical trials. However, *in vitro* and *in vivo* data suggest that resistance to these agents may limit their clinical effectiveness. In this review, we discuss recent findings about some of the ways these resistance mechanisms arise, potential biomarkers to identify TRAIL resistance in patients (Six1, GALNT14, XIAP, certain microRNAs) and potential ways to circumvent resistance and resensitize tumors.

Keywords

TRAIL; DR4; DR5; apoptosis; Six1; GALNT14; XIAP; mapatumumab; resistance; cancer

1. Introduction

TRAIL (also known as Apo2L and TNFSF10) is Type II transmembrane protein belonging to the Tumor Necrosis Factor (TNF) superfamily that is expressed on the surface of Natural Killer (NK) and T cells, macrophages and dendritic cells. As with other cytokines, the protein is synthesized in a pro-form with a signal sequence that is removed in the mature secreted protein. TRAIL can also be anchored in the membrane via hydrophobic amino acids or released as a soluble protein. All forms of the protein are believed to function as trimers and can induce apoptosis by binding to and activating signaling by trimeric death receptors in a manner that is similar to that by other “death ligands” such as FasL or TNFα (Mollinedo and Gajate, 2006). Humans have five distinct TRAIL receptors (Ashkenazi, 2002) that are encoded by separate genes. DR4 (TNFRSF10a, TRAILR1) and DR5 (TNFRSF10b, TRAILR2) contain an intracellular death domain (death domains are structurally conserved protein interaction domains consisting of six anti-parallel alpha helices) and are capable of signaling apoptosis, and have been shown to form both homomeric and heteromeric complexes (Kischkel et al., 2000). Two membrane-bound decoy receptors called DcR1 (TNFRSF10c) and DcR2

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(TNFRSF10d) lack a functional death domain and are unable to activate apoptotic signaling and instead inhibit TRAIL signaling. The fifth TRAIL-binding receptor is Osteoprotogerin (TNFRSF11b), which is a soluble protein that may also function as a decoy/inhibitor by sequestering TRAIL extracellularly.

Much of the current interest in TRAIL signaling comes from its use in cancer treatment and at least 6 drugs (antibodies and recombinant TRAIL) that activate signaling by DR4 and/or DR5 (mapatumumab, lexatumumab, Apomab, AMG-655, LBY-135 and rhApo2L/TRAIL) have already been used in humans (Bouralexis et al., 2005; Camidge, 2007; Koschny et al., 2007b). Other potential clinical agents including additional antibodies, at least one of which may trigger a distinct death mechanism that involves autophagic cell death rather than apoptosis (Park et al., 2007; Moretti et al., 2007), recombinant TRAIL molecules that also target growth factor receptors (Bremer et al., 2005) and gene therapy agents that express TRAIL (Carlo-Stella et al., 2007; Lin et al., 2003; Seol et al., 2003) have also been developed. Anti-TRAIL Receptor antibodies can also cause long term anti-tumor responses by promoting tumor-specific T cell-mediated immunity (Takeda et al., 2004) indicating that it may be feasible to increase the anti-tumor responses of these agents by not only directly killing cancer cells but also promoting anti-tumor immune responses. These developments have led to the idea that we may be seeing the hopes of clinical application of TRAIL receptor-directed therapeutics coming to fruition (Gajewski, 2007).

2. Mechanism of TRAIL Receptor-induced apoptosis

Several reviews have discussed the mechanisms by which TRAIL signaling occurs (Almasan and Ashkenazi, 2003; LeBlanc and Ashkenazi, 2003; Thorburn, 2007; Wang and El-Deiry, 2003). In brief, ligand or agonistic antibody binding to the extracellular domain of the receptor trimer leads (via a molecular mechanism that is not understood but probably involves structural changes that are transmitted to the intracellular domain of the receptor) to the recruitment of an adaptor protein called FADD to the intracellular death domain of the receptor; this leads to formation of a protein complex called the Death Inducing Signaling Complex (DISC) that contains (at a minimum) the receptor, FADD and caspase-8. Caspase-8 forms dimers in the DISC and this dimerization leads to its catalytic activation (Boatright et al., 2003). The apoptotic signal from active caspase-8 is sufficient in some cells (designated Type I cells) to activate enough effector caspase activity to kill the cell. In other cells (designated Type II cells), amplification of the apoptotic signal occurs through cleavage of the BH3-only protein Bid and activation of the mitochondrial apoptotic pathway, which can be blocked by Bcl-2. The distinction between Type I and II cells may not be absolute because dose response experiments have demonstrated Bcl-2-dependent inhibition of TRAIL-induced death at low doses in cells that display no inhibitory effects at higher doses (Rudner et al., 2005). This kind of response could, in principal, lead to different resistance mechanisms at limiting doses compared with high doses– at lower doses, increased Bcl-2 would confer resistance but at higher doses effective resistance may require interference with the DISC.

Additionally, various protein kinase cascades leading to activation of MAP kinases ERK, JNK and p38 along with activation of the NFκB transcription factor are stimulated by TRAIL receptors. These pathways require the formation of other protein complexes, which arise subsequent to DISC formation and in different subcellular locations (Varfolomeev et al., 2005). The non-signaling decoy receptors DcR1 and DcR2 lack a functional death domain and, therefore, cannot interact with FADD or induce apoptosis. The decoy receptors can also block TRAIL-induced apoptosis by competing for ligand binding with DR4 and DR5 or by forming complexes with the signaling receptors to produce non-functional receptor heterocomplexes (Merino et al., 2006).

3. Physiological Functions of TRAIL Receptor signaling and the relationship to cancer and its treatment

The creation of TRAIL-deficient and TRAIL Receptor-deficient mice has allowed examination of the physiological functions of TRAIL. Knockout mice are viable and fertile with no obvious developmental defects. TRAIL-deficient mice display defects in the immune system indicating that the TRAIL pathway regulates innate immunity (Diehl et al., 2004) and memory T cell homeostasis (Janssen et al., 2005). From the cancer perspective, TRAIL signaling is important in T-cell- and natural killer cell-mediated tumor surveillance and metastasis suppression in various xenograft models (Cretney et al., 2002; Schmaltz et al., 2002; Seki et al., 2003; Takeda et al., 2001). Although TRAIL receptor-deficiency was reported to have no effect on intestinal tumor development caused by p53 or APC loss (Yue et al., 2005), it has been shown to promote susceptibility to chronic inflammation and tumorigenesis using autochthonous models (Finnberg et al., 2007) and to promote metastasis under circumstances where there is little effect on primary tumor development (Grosse-Wilde et al., 2007). In addition, TRAIL-deficient animals have more hematological malignancies (Zerafa et al., 2005) and are more susceptible to chemical carcinogens (Cretney et al., 2002). Together, these findings indicate that the TRAIL pathway has important roles in host anti-tumor and anti-metastasis defense. Thus an attractive aspect of targeting these receptors therapeutically is that one can consider this approach as being a means to take a tumor- and metastasis-suppression mechanism that works in healthy people and make it more effective in people with cancer. When one thinks about it in this way, it is not surprising that the toxicity associated with therapeutic targeting of TRAIL receptors should be quite low, and the initial clinical trials with these agents have indeed demonstrated low normal tissue toxicity such that unlike most other anti-cancer drugs, it may even be difficult to define a maximum tolerated dose (Tolcher et al., 2007). However, another more troubling, consequence of this idea is that if TRAIL signaling is a mechanism by which tumors are suppressed in healthy people, one should expect that, in people with cancer, tumors may have already developed mechanisms of resistance to TRAIL before we even begin with treatment.

TRAIL receptor signaling has also been implicated in the mechanism of action of various other anti-cancer agents. Strong evidence for this idea comes from studies of inducible silencing of DR5 in colon cancer cells, which was shown to increase the tumor growth rate and cause resistance to 5-fluoruracil (Wang and El-Deiry, 2004). In addition, expression of the decoy receptor DcR2 has been reported to determine chemosensitivity to various DNA damaging agents (Liu et al., 2005) such that higher levels of DcR2 caused reduced sensitivity to chemotherapy. TRAIL is also responsible for tumor cell killing by some oncolytic viruses (Clarke et al., 2000). Together, these data suggest that defects in TRAIL receptor signaling might determine the response to cytotoxic chemotherapy as well as determining the response to the therapeutics that are specifically targeted to TRAIL receptors. In tumor cells that are resistant to TRAIL-induced apoptosis, TRAIL treatment can cause increased growth (Baader et al., 2005; Ehrhardt et al., 2003) and metastasis (Trauzold et al., 2006). The underlying mechanism for these effects is likely related to the other signaling pathways (MAP kinase activation etc.) that are induced by TRAIL receptors along side the activation of the apoptosis machinery– i.e. in cells that cannot activate apoptosis, these other signals may increase tumor cell growth and survival. Therefore, identification of patients whose tumors have developed TRAIL resistance is critically important because not only might TRAIL resistance limit the usefulness of TRAIL Receptor-targeted drugs and chemotherapeutic agents that work indirectly through TRAIL Receptors; treatment with these agents may then actually promote tumor growth and metastasis in these patients.

4. TRAIL Resistance

Up to half of tumor cell lines may be TRAIL resistant (Walczak et al., 1999) and resistance may vary in primary human tumor cells. For example, it has been reported that primary colon cancer cells are usually sensitive to TRAIL (Koschny et al., 2007a) but that primary astrocytoma cells (Koschny et al., 2007a) and B cell chronic lymphocytic leukemia cells (MacFarlane et al., 2002) are not. Other tumor types, e.g. ovarian cancers show more variable responses with some primary tumor cells being effectively killed and others displaying resistance and this variation also being reflected in established cell lines (Lane et al., 2004). Some tumor cells appear to be inherently resistant to TRAIL and resistance can also be acquired in cells that were originally TRAIL sensitive. For example, in a cell line model of breast and ovarian cancers, resistance to the anti-DR5 antibody TRA-8 was induced by repeated exposure to non-apoptosis inducing doses (Li et al., 2006). Interestingly in this example, the resistance mechanism was selective for DR5-directed agonists and the resistant cells retained sensitivity to TRAIL and to an antibody that activates DR4. Recent studies demonstrate that the microRNAs miR-221 and miR-222 interfere with TRAIL signaling through their effects on the cell cycle regulator $p27^{kip1}$ raising the possibility that microRNA patterns can be used to predict TRAIL resistance or sensitivity (Garofalo et al., 2008). Resistance mechanisms (for review see (Koschny et al., 2007b; Shankar and Srivastava, 2004; Van Geelen et al., 2004)) to TRAIL receptor-induced apoptosis fall into two broad categories.

4.1. Resistance caused by anti-apoptotic mechanisms

One group of resistance mechanisms involve tumor characteristics that generally inhibit apoptosis such as reduced caspase expression (e.g. epigenetic silencing of caspase-8 expression in aggressive neuroblastoma (Hopkins-Donaldson et al., 2000) and some glioblastomas (Eramo et al., 2005)), increased expression of caspase inhibitors such as XIAP (Cummins et al., 2004), cIAP2 (Ricci et al., 2007) or overexpression of Bcl-2 (Fulda et al., 2002a) and other inhibitors of the mitochondrial apoptosis pathway such as Mcl-1 (Ricci et al., 2007; Rosato et al., 2007).

4.2. Resistance caused by defects in death receptor signaling

The second group of resistance mechanisms includes mechanisms that are more specific for TRAIL (or death receptor) signaling such as defects in the TRAIL receptors themselves or increased expression of inhibitors that are selective for death receptors such as FLIP or the decoy receptors DcR1 and DcR2. FLIP is a homolog of caspase-8 with mutations in the catalytic domain that prevent its activation as a protease. Its recruitment to the DISC can block TRAIL-induced apoptosis (Koornstra et al., 2003; Liao et al., 2001; Shivapurkar et al., 2004; Spierings et al., 2004). FLIP expression is controlled by other important oncogenic pathways; for example, Myc regulation of TRAIL sensitivity can be achieved through Myc's ability to repress FLIP expression (Ricci et al., 2004). The decoy receptors block TRAIL signaling both by competing for binding with TRAIL and by forming stable complexes with the signaling receptors to form inactive receptor complexes (Merino et al., 2006). Epigenetic silencing of TRAIL receptor expression has been reported (Horak et al., 2005) as has deficiencies in TRAIL receptor trafficking to the cell surface (Jin et al., 2004). Somatic mutations in TRAIL receptors have also been reported (Fisher et al., 2001; Lee et al., 1999; Lee et al., 2001; Park et al., 2001; Shin et al., 2001). Some of these mutations can have a "dominant negative" phenotype whereby not only is the mutant receptor unable to send signals that induce apoptosis it also inhibits the ability of wild-type receptors in the same cell to signal (Bin et al., 2007). Importantly it was also demonstrated that the underlying mechanism by which this dominant-negative effect was achieved predicted that in cells with mutant DR5 but functional DR4, the mutant receptor would block signaling by DR5-specific agonists and TRAIL but would not inhibit signaling by DR4-specific agonists. This provides a rationale for selection of mapatumumab (the

agonistic anti-DR4 antibody) rather than other therapeutic agents for killing of those cells (Bin et al., 2007). A similar strategy could potentially be adopted in tumor cells where resistance is caused by overexpression of decoy receptors and it has been shown that while decoy receptors confer resistance to TRAIL they do not affect anti-DR5-induced apoptosis (Merino et al., 2006).

Although tumor cells may express both DR4 and DR5, apoptosis signaling can occur preferentially through one or the other receptor even when the other receptor is present and not mutated. For example in chronic lymphocytic leukemia and mantle cell lymphoma, it was found that primary tumor cells that express both DR4 and DR5 could only be killed by agonists that activate DR4 (MacFarlane et al., 2005). Recent work shows however that it is possible to overcome this lack of apoptosis in response to DR5-directed antibodies by crosslinking them (Natoni et al., 2007).

4.3. Resistance caused by O-glycosylation of receptors

A novel method of resistance involving expression of the peptidyl O-glycosyltransferase GALNT14 was recently identified (Wagner et al., 2007). Loss of this enzyme correlated with reduced sensitivity to TRAIL because O-glycosylation of DR4 or DR5 promotes the ligand-stimulated clustering of receptors leading to more efficient recruitment and activation of caspase-8. Because GALNT14 expression in multiple cell lines appeared to be a better predictor of TRAIL sensitivity or resistance than other regulators of the pathway such as c-FLIP, Bcl-2 and XIAP, it was suggested that screening for expression of GALNT14 could be used as a strategy to select patients who are more or less likely to benefit from treatment– 10% of lobular breast tumors and up to 30% of lung tumors expressed high levels of GALNT14 and would therefore be expected to be particularly likely to be sensitive to TRAIL (Wagner et al., 2007). This last point exemplifies the benefits for optimal selection of patients who will or will not benefit from TRAIL receptor-targeted treatments that can be made if one can easily identify tumor markers that predict sensitivity or resistance and it is therefore important to determine if there are other markers that indicate sensitivity.

4.4. Resistance related to Six1 expression

Our groups recently identified one such marker that may affect large numbers of patients. We found that Six1, a homeobox transcription factor that is not expressed in most normal adult tissues but is often re-expressed in tumors causes marked resistance to TRAIL-induced apoptosis while having little effect on killing by another death receptor agonist, Fas ligand (Behbakht et al., 2007). Importantly Six1 expression is correlated with metastasis in breast cancer, where it is overexpressed in 50% of primary breast cancers, but an even greater 90% percent of metastatic lesions (Reichenberger et al., 2005). Similarly high Six1 expression in tumors occurs in more than 60% of women with metastatic ovarian cancer and is strongly associated with worse survival in these patients (Behbakht et al., 2007). Six1 is additionally associated with worsened survival in hepatocellular carcinoma (Ng et al., 2006). Thus Six1 expression may represent a mechanism of TRAIL resistance that is very common in advanced metastatic cancers. The most important question, of course, is what we can do about this. It is useful to identify resistance mechanisms and use this information to identify patients who may not benefit from treatment with TRAIL receptor agonists. However, it would obviously be far more useful to also have a way to reverse the resistance and thus make these tumors susceptible to TRAIL or the agonistic antibodies.

5. Strategies to boost efficacy and avoid resistance

A bewildering array of drugs can synergize with TRAIL and have often been suggested to provide a useful way to sensitize TRAIL-resistant tumors. For example many different DNA

damaging agents can increase TRAIL-induced killing (for review see (Shankar and Srivastava, 2004)). Other agents that can promote TRAIL-induced apoptosis include: Smac mimetics (Fulda et al., 2002b; Li et al., 2004), proteosome inhibitors (Landis-Piwowar et al., 2006; Liu et al., 2007), the multikinase inhibitor sorafenib (Ricci et al., 2007; Rosato et al., 2007), histone deacetylase inhibitors (Guo et al., 2004; Inoue et al., 2004; Inoue et al., 2006a; Singh et al., 2005), interferon (Park et al., 2004; Siegmund et al., 2005), PPAR gamma activators (Kim et al., 2002), Casein kinase I inhibitors (Izeradjene et al., 2004), cyclo-oxygenase 2 inhibitors (Martin et al., 2005), rapamycin (Panner et al., 2005), DNA methylation inhibitors (Eramo et al., 2005), epidermal growth factor receptor inhibitors (Gibson et al., 2002), cardiac glycosides (Frese et al., 2006), natural plant products (Frese et al., 2003), Rituximab (Daniel et al., 2007), curcumin (Wahl et al., 2007) and, tumor cell-targeted bacterial toxins (Horita et al., 2007). Most of these agents have been identified empirically, however, unbiased screening with, for example libraries of siRNAs can also provide a way to identify novel targets whose inhibition can increase TRAIL sensitivity (Aza-Blanc et al., 2003). In some cases, it may also be possible to sensitize resistant cells to TRAIL receptor-targeted therapeutics by using TRAIL Receptor-targeted drugs in different ways without adding other agents. A good example of this idea comes from work by Cohen's group who showed that chronic lymphocytic leukemia cells that are normally insensitive to DR5-directed agonists are sensitive to two DR5-specific antibodies (lexatumumab and LBY135) so long as those antibodies are cross-linked (Natoni et al., 2007).

When studying the interactions between TRAIL receptor agonists and other drugs, it is important to distinguish between *synergy* and *sensitization*. By definition, synergy between two drugs requires that both drugs have an effect on their own and that the effect of combining the two drugs at particular doses is greater than the sum of the parts at those doses. This is not the same as sensitization where one drug (e.g. TRAIL) has no effect on its own but becomes active when combined with the other agent. The distinction is potentially important and may be affected by the particular molecular mechanisms that apply. For example, synergy between TRAIL and a second drug might arise when the drug causes increased expression of TRAIL receptors– indeed this mechanism has been frequently suggested in tumor cells treated with ionizing radiation and DNA damaging chemotherapy (Shankar and Srivastava, 2004) as well as numerous other agents targeted to different signaling pathways. It is easy to see how this mechanism might cause synergy in cells that can undergo TRAIL-induced apoptosis – higher levels of TRAIL receptors in a particular tumor cell would be expected to increase the effectiveness of signaling for a given dose of the ligand and thus one should get synergy. It should be noted however that there is no strict correlation between receptor expression and TRAIL sensitivity when one compares different tumor cell lines and it has been suggested that even when one obtains increased receptor levels this may not be the underlying synergy/sensitization mechanism (Inoue et al., 2006b). However, even if this is a true mechanism of synergy, it would not necessarily lead to sensitization in tumor cells that are resistant to TRAIL. For example, the work from our group on the mutant TRAIL receptors suggests that if the resistance mechanism was caused by somatic mutation of the TRAIL receptor DR5, increasing the level of DR5 as a result of treating with a second drug would not only not help, it might even make things worse by increasing the dominant-negative effect of the mutant receptor (Bin et al., 2007). Similarly, increasing the amount of the receptor would not improve TRAIL receptor-induced apoptosis in cells that lack caspase-8. On the other hand, if the mechanism of TRAIL resistance was epigenetic reduced expression of wild-type DR4/5 or increased decoy receptors, one would anticipate that increasing DR5 levels would lead to true sensitization of the resistant tumor cells.

An indication of the complexity that may arise when we try to apply these ideas in a practical context can be seen if one takes four different established mechanisms of TRAIL resistance (DR5 mutation, epigenetic silencing of caspase-8, increased XIAP or increased DcR2

expression) and considers how current knowledge would predict whether three drugs (mapatumumab, lexatumumab and recombinant Apo2L/TRAIL) would be affected (Table 1). Further complexity is seen if we then ask whether combination treatment with other agents would be helpful. When we consider a quite simple question such as whether it might be useful to treat with DNA damaging agents that increase expression of DR5, or with sorafenib, which sensitizes to TRAIL by down-regulating Mcl-1 and FLIP or cIAP2 (Ricci et al., 2007;Rosato et al., 2007) and ask how these manipulation might be expected to affect the four resistance mechanisms for just one therapeutic agonist (Apo2L/TRAIL), we see that there may well be very variable effects (Table 2). These considerations demonstrate the importance of understanding the molecular mechanisms by which resistance arises in a particular tumor and the critical importance of having a good understanding of how the other drugs that will be combined with TRAIL alter DR4 and DR5 signaling.

6. Conclusions and future perspectives

There are already quite a large number of different TRAIL receptor agonists that are being tested in the clinic and the continuing development of other agents suggests that we will have many options to consider targeting these receptors therapeutically. However, while the progress that has been made is encouraging, we need to find tumor characteristics that will identify patients, who will be more or less likely to benefit from these drugs. The recent data that we have discussed indicate that there may be multiple biomarkers (e.g. Six1, GALNT14, XIAP etc.) that influence TRAIL sensitivity and which might be useful to select patients who are most likely to benefit from treatment. The practical issue, that will need to be determined in the case of TRAIL-receptor targeted therapeutics is similar to those for other current classes of (targeted) agents (Anderson et al., 2006), namely whether one or two of these markers will provide sufficient information to make informed treatment decisions or whether we will need to assess a large panel of such markers to optimize patient selection. Another question to be answered is, whether these markers will be associated with resistance or sensitivity to the various different drugs that could be used. The example described above with mutant TRAIL receptors shows that it may even be feasible to avoid a block of TRAIL receptor signaling that would occur with one drug if one simply chooses a different drug that targets the same TRAIL receptor. Additionally, the demonstration that chronic lymphocytic leukemia cells can become sensitive to DR5-directed antibodies if they are cross-linked, shows that it may be necessary to alter the way these drugs are prepared in order to increase their effectiveness for particular patients.

In conclusion, there is still much work to be done if we are to develop effective decision-making tools to decide who should and who should not be treated with these drugs and which drug to use for which person. The decisions that will need to be made as we try to move to the next step– i.e. to choose effective combination treatments that will allow us to avoid resistance mechanisms or increase the effectiveness of TRAIL receptor-targeted therapeutics may be more complicated still. What certainly seems clear is that if we are to apply these ideas to improve treatment of patients with cancer, it is unlikely that a “one-size-fits-all” approach will be effective, i.e. two patients who both have tumors that are resistant to TRAIL may not both benefit if they are treated with the same TRAIL Receptor agonist in combination with the same other agent. Instead, it will be necessary to determine which category of resistance mechanism a particular patient’s tumor falls into and tailor the combination therapies with TRAIL or the TRAIL receptor antibodies accordingly. Unfortunately, although combination therapies using TRAIL receptor-targeted drugs along with other agents are already underway, the clinical trials have not usually been designed to incorporate assessment of biomarkers that can be used to predict if patients are likely to have TRAIL-resistant tumors or how that resistance came about. There is therefore a real possibility that if these issues are not taken into consideration, we may obtain results suggesting that TRAIL receptor-targeted therapeutics alone and in combination

with other drugs are not effective, while better patient selection for particular combinations would have demonstrated clinical value. An encouraging thought, however, is that given the rapid progress that has already been made in this field, it is likely that future discoveries will help us better refine these ideas and come up with truly effective decision making tools to allow better patient selection and better combination treatments so that this class of drugs can be effectively used.

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Table 1

Anticipated effects of different TRAIL resistance mechanisms on sensitivity to different therapeutic agonists.

Resistance Mechanism	Expected response to Apo2L/TRAIL	Expected response to lexatumumab (anti-DR5)	Expected response to maptumumab (anti
DR5 mutation	No apoptosis	No apoptosis	Apoptosis
Caspase-8 silencing	No apoptosis	No apoptosis	No apoptosis
Increased XIAP	No apoptosis	No apoptosis	No apoptosis
Increased DcR2	No apoptosis	Apoptosis	Apoptosis

Table 2

Anticipated effects of different TRAIL resistance mechanisms on sensitivity to Apo2L/TRAIL when combined with other agents.

Resistance Mechanism	Expected effect on Apo2L/TRAIL sensitivity when treated in combination	
	DNA damaging agent that elevates DR5 expression	Reduced Mcl-1, FLIP and cIAP2 expression caused by sorafenib
DR5 mutation	Increased Resistance	No difference
Caspase-8 silencing	No difference	No difference
Increased XIAP	Increased sensitivity	Increased sensitivity
Increased DcR2	Increased sensitivity	No difference.