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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Evaluating Use in Pancreatic Cancer: Efficacy and Safety Data for ON-State RAS Inhibitors

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Dr. O'Reilly:
This is CE on ReachMD and I'm delighted to be here today. My name is Dr. Eileen O'Reilly, and in this episode I'm going to review the efficacy and the safety data of the ON-state RAS inhibitors in pancreas cancer.

So we'll start with daraxonrasib, also known as RMC-6236, which is the ON-state inhibitor that binds the GTP-bound version of RAS and is, I think, going to have a huge impact on how we treat this disease.

So the development started as a phase 1 in extensively previously treated individuals with pancreas cancer, so primarily in the second- and third-line setting. And here, the results here—and I'm going to say they were unprecedented in this disease to see a response rate of almost 30% and maybe even a little bit higher when we restrict it completely to the second line, with a median progression-free survival of 8.8 months, a disease control rate in the high 80s in terms of percentage of patients with cancer control, and survival in the second-line setting of 14+ months.

And to reference the significance of what these data compare to, if you think about the frontline setting of pancreas cancer, sadly, most patients will succumb in a year or less. And acknowledging the selection that goes into studies for this type of drug development, but these are significant results.

And with that, this moved very quickly into phase 3 testing as part of the RASolute 302 trial. And this was a phase 3, designed in the second-line setting. So individuals with 1 prior regimen for metastatic disease, comparing daraxonrasib to a menu of limited standard chemotherapy choices.

And based on the initial phase 1 experience, this led to a breakthrough therapy designation and orphan drug designation and fast track potential approval in pancreas cancer.

So that was the second-line and previously treated disease setting, but there are 2 other major studies that are—one is activated already and the other is set to do so shortly. The one that's activated is called RASolute 304. This is in the adjuvant setting. So individuals with pancreas cancer who've received all of their standard therapy, be it surgery, be it neoadjuvant, adjuvant, as long as they're without evidence of disease on completion of standard therapy, potentially eligible for enrollment in this trial, comparing a multi-selective pan-RAS inhibitor, daraxonrasib, to observation, where the standard of care after completion of standard therapy would be observation. So that's very exciting. And think about it this way, right? If we're seeing notable promising signals in the bulk disease setting of later-stage disease, the potential for impact may be even larger in the resected setting.

The other study that is shortly to activate will be in the frontline setting called the RASolute 303 trial, and this will compare a chemotherapy reference with a gemcitabine and nab-paclitaxel on a standard day 1, 8, and 15 schedule as the control arm, and 2

experimental arms compared to that of single-agent daraxonrasib. And daraxonrasib with gemcitabine and nab-paclitaxel on an every-other-week schedule. So, again, exciting to see these drugs move to frontline therapy in metastatic disease, but also earlier-stage disease.

So let's look at the highlights on the pan-RAS inhibitor. There are, like in non-small cell lung cancer, there's allele-specific or mutant-specific inhibitors in development as well with zoldonrasib, or RMC-9805. And we have a little bit less data on this. Last presented in early 2025, but similarly, I think, very potent signal with a response rate of about 30% in previously treated pancreas cancer, high disease control rate, again, in the high 80s, and notable reductions in circulating DNA as a biomarker of response in this setting. So we look forward to seeing further development of this in pancreas cancer along with the pan-RAS inhibitors.

So, exciting times in pancreas cancer. That summarizes where we are today. Thank you so much for listening.

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