ICE CREAM Lay Summary

Title
The Irinotecan Cetuximab Evaluation and the Cetuximab Response Evaluation Among Mutants (ICE CREAM) study: A randomised Phase II study of cetuximab alone or in combination with irinotecan in patients with KRAS WT metastatic CRC and patients harbouring a G13D mutation

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Study Background and Rationale
Most patients diagnosed with metastatic colon or rectal cancer still die from the disease, even though there are now many options for treatment which have extended the average lifespan to 18-24 months after diagnosis. More is being understood about how some colorectal cancers differ from others, particularly at the level of the cancer genes, which drive the behaviour of the tumour and can predict in some cases whether various treatments have a chance of working or not.

A major recent advance was the identification of a particular gene, the K-RAS (pronounced Kay-ras) gene, which predicts which cancers might respond to the group of drugs known as the anti-EGFR antibodies, of which there are two in clinical practice, cetuximab (Erbitux®) and panitumumab (Vectibix®). These antibodies are currently used in 3rd or 4th line treatment, that is, after the standard chemotherapy treatments are no longer working (treatment failures, also known as treatment refractory). The initial studies of cetuximab showed excellent results in some patients, and it was noticed that the patients who seemed to benefit most had a more dramatic rash on their face and body as a side effect than those who did not benefit from the treatment.

When trying to work out more who the patients were who benefited from the treatment, it was discovered that patients who did NOT have a mutation in the K-RAS gene (called K-RAS wild type) did better, and the AGITG-NCIC C0-17 trial showed that using cetuximab in these patients improved the survival of patients who had no other treatment options by 4.7 months, which at this end stage of the disease was highly significant and has not been shown by any other drug. Importantly this occurred with no reduction in quality of life. This drug, cetuximab, was recently made available on the PBS for treatment of metastatic K-RAS wild type (WT) colorectal cancer patients who have failed all other treatment. It is NOT available for patients with K-RAS mutations.

However, recent data shows that the story is not so simple and that some patients with mutations may benefit from cetuximab. It appears from retrospective data that patients with a particular mutation, known as the G13D K-RAS mutation, might benefit just as much as the K-RAS WT patients. These patients are currently missing out on access to the drug cetuximab. The ICECREAM study is looking at two groups of patients with metastatic colorectal cancer, those with K-RAS WT and those with K-RAS G13D mutations, to collect prospective data (of which there is none in existence) on how long these patients live without their cancer progressing (called Progression-free survival, which is the primary endpoint of the study). Both groups will get the drug cetuximab, so that we can compare whether the groups have similar benefit.

The ICECREAM trial is also asking another question, which is whether the cetuximab drug is better used by itself, or whether it will be even more effective when used in combination with a certain chemotherapy called...
irinotecan. Use with chemotherapy will increase side effects, so it is important to document how much better (if any) the combination is. We need to test this both in the WT and G13D mutation patients.

This trial was presented at the 2011 AGITG ASM and was well received as it is an example of translational research which aims at identifying the subgroup of patients who may benefit from a specific treatment, so that the treatment can be targeted at these patients and not given to patients in whom it will be ineffective. Two of our international guests, Professor Tabernero from Barcelona and Professor Hasan from London, both expressed an interest to be involved, which would make this the second-ever AGITG-led international trial. The comment from these eminent clinicians was that this was a unique trial worldwide which was seen as very important.

**Study aims**

1. To evaluate whether cetuximab should be given alone, or in combination with irinotecan chemotherapy in KRAS Wild type patients with progressing cancer who have progressed after treatment with oxaliplatin and irinotecan based chemotherapy
2. To evaluate whether this treatment approach has beneficial effects in patients with a specific KRAS mutation (G13D)

**Proposed study design**

Patients will be randomized (1:1) to receive cetuximab by itself (monotherapy) or cetuximab plus the chemotherapy drug irinotecan. They will be split (stratified) into separate groups based on the KRAS status of their cancers.

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KRAS WT *
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KRAS G13D MT
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* KRAS WT – Australian sites only

**Sample size**

100 patients (50 KRAS WT and 50 KRAS G13D mutations)

**Proposed Sites**

KRAS WT patients will be recruited from 8-10 Australian and New Zealand sites (each capital city). Patients with G13D mutations are rare (<10% of all patients with CRC) and in addition to the Australian sites, patients will be recruited from 2 large hospitals in Barcelona and London. Recruitment is expected to take 24 months based on AGITG previous experience with clinical trials in this patient population. As this drug will not be available to patients with G13D mutations outside the trial, it is anticipated that many patients would be willing travel within capital cities to enter the trial.

**Quality of life**

This study seeks to identify in particular the effect on QOL of the combination treatment versus the single drug, so that we can examine any trade off in QOL for any gain in benefit that may be seen. Subject to funding, we also want to compare the rash (and its impact on QOL) in patients with K-RAS WT versus K-RAS G13D mutations, to see if this is a good clinical indication of who may benefit. This will be very useful as the rash appears early (around 10-14 days), which predates any other evidence of the drug working.