ANZUP Cancer Trials Group Limited

ENZAMET & ENZARAD Trial News

www.anzup.org.au

Welcome to the March 2021 ENZAMET & ENZARAD newsletter

Dear ENZAMET and ENZARAD Investigators

Due to our incredible multidisciplinary global academic collaboration, we are clearly developing new data defining how best to treat patients with high risk localised and metastatic hormone sensitive prostate cancer. It should also be noted that the quality of our data has been reviewed by regulatory agencies and has been found to be at the highest quality. This newsletter is an opportunity for us to detail some high level plans for 2021, as well as express our gratitude.

ENZARAD UPDATE

As you will have seen, the ENZARAD primary endpoint has been amended to have "metastasis free survival (MFS)," be the primary endpoint to expedite the readout. This is possible by using metastasis free survival endpoints that are surrogates for overall survival using the ICECaP definition. To that end, metastatic events that are clearly identified on conventional CAT scan and Tc bone scan per RECIST criteria and as detailed in the protocol are the metastatic events that will be scored as "events" per the primary endpoint.

- To that end PSMA PET positive but conventional scan negative lesions will be documented but not scored as events for the primary endpoint. These lesions do not have the documented surrogacy for overall survival. We will also document any therapies such as hormonal therapy or SBRT that are instituted prior to the MFS event per ICECaP definition.

ENZARAD is a global collaborative investigator-initiated trial led by ANZUP and sponsored by the University of Sydney, in collaboration with the TROG Cancer Research, Dana-Farber Cancer Institute, and Cancer Trials Ireland (formally known as ICORG).

The University of Sydney NHMRC Clinical Trials Centre provided central study coordination. Astellas Pharma provided drug and financial support but was not involved in study conduct or data analysis. ANZUP receives valuable infrastructure support from the Australian Government through Cancer Australia.

Dana-Farber Cancer Institute

TROG CANCER RESEARCH

cancer trials ireland

NHMRC Clinical Trials Centre

Funding and support from:

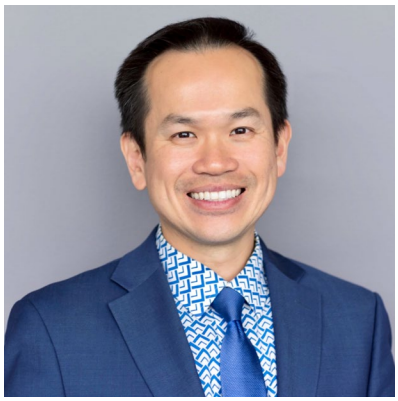
astellas ONCOLOGY

Australian Government Cancer Australia

- Although we are not scoring these as metastatic events per the MFS, endpoint we do believe they are metastatic events but do not reach the "cut point" to qualify as an MFS event with overall survival surrogacy. Specifically, many patients with these events that do not meet the ICECaP MFS criteria could live for many years and most likely do not have the same correlation with overall survival as the metastatic events per the ICECaP database. Many of these PSMA PET positive/conventional scan negative lesions are identified as part of an evaluation for a rising PSA and make up many of "event free survival (EFS)" events which is driven by PSA relapse. We have shown EFS is not viable as a surrogate for overall survival for clinical trial conduct.

ENZARAD STUDY CO-CHAIRS

Prof. Scott Williams



Prof. Paul Nguyen

ENZAMET UPDATE

The second major update to provide, relates to the next analysis of the ENZAMET database. Our **2019 New England Journal of Medicine paper** was based on the interim analysis being positive. The next survival analysis will be when the original planned 470 events is reached. This is likely to occur in the June to July 2021 timeframe. Two specific groups will be of particular interest with this long term follow-up:

- Patients with "metachronous metastases", i.e., those who are recorded as M0 at diagnosis in the database. Most of these patients have low volume disease and patients with low volume metachronous metastases have a median overall survival of about 8 years from the time of starting hormonal therapy. In March 2021, we submitted for publication data from the interim analysis that the HR(OS) for metachronous low volume was 0.4 and 3-year OS increased from 83% to 92%. This is the first direct evidence and quantification of benefit for this subgroup with a more favourable prognosis with testosterone suppression alone.

- Patients who were treated with ADT plus docetaxel per physician and patient choice and were also randomised to receive enzalutamide. There was a significant improvement of time-to-clinical progression but with a short follow up, the hazard ratio for overall survival was only approximately 0.9. To that end we will also report the outcome of this subgroup with this analysis. It is anticipated that we will be able to submit a late breaking abstract for ESMO 2021.

We are always appreciative of the diligence that everyone has provided to keeping the case report forms up to date so we can report accurate data in as timely a manner as possible.

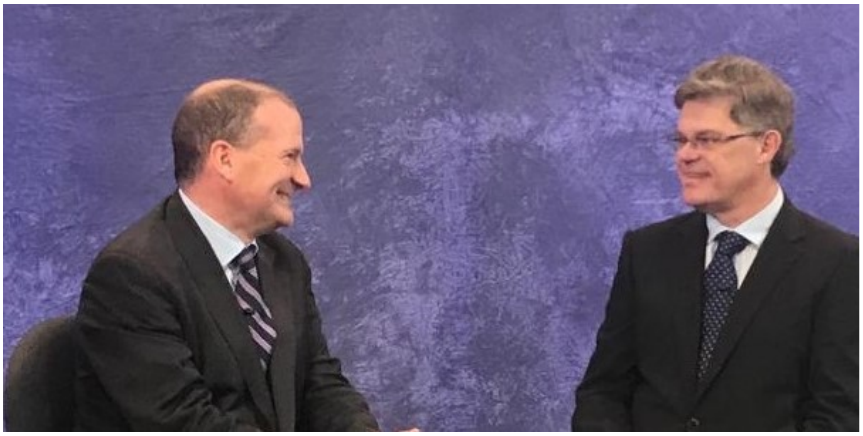
ENZAMET & ENZARAD (ANZUP 1304/1303)

ANZUP Cancer Trials Group Limited

It is also worth noting the ENZAMET Quality of Life paper has been drafted and we anticipate submitting to a journal for review in March 2021. We would also like to report that we have made great progress in collecting the biological specimens, tumor and blood, that will allow us to perform in-depth state of the art biomarker interrogation to hopefully define who is better treated with a combined hormonal versus chemotherapy approach and possibly even a triplet approach of adding enzalutamide to ADT and docetaxel.

Thank you so very much to everyone for your amazing support and collaboration. We truly believe our academic global collaboration is providing timely and informative information that is guiding how we need to treat patients. This is not possible without all of your efforts and the kind and compassionate care that you and your team provide to your patients and support them as they have supported our clinical trial efforts.

ENZAMET STUDY CO-CHAIRS



Prof. Chris Sweeney **Prof. Ian Davis**

ENZAMET STUDY HIGHLIGHTS

- **ENZAMET announced as ACTA Trial of the Year 2020**
- **ANZUP's ENZAMET trial results recognised as one of the most important clinical research advances of 2020**
- **Enzalutamide receives U.S. FDA approval for treatment of men with metastatic hormone-sensitive prostate cancer**
- **ENZAMET presented in the Plenary Session at ASCO in 2019** and simultaneous **NEJM publication**

ENZAMET is a global collaborative investigator-initiated trial led by ANZUP and sponsored by the University of Sydney, in collaboration with the Canadian Cancer Trials Group, Dana-Farber Cancer Institute, and Cancer Trials Ireland (enrolling patients from Ireland and the United Kingdom).

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Dana-Farber Cancer Institute

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Canadian Cancer Trials Group

NHMRC Clinical Trials Centre

Australian Government Cancer Australia

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