EXAMPLE OF A CLINICAL TRIAL SYNOPSIS

Title: Effect of enzalutamide dose reduction on fatigue, cognition, and drug trough levels in patients with prostate cancer (EFFECT study)

Background and Rationale

- Enzalutamide is a potent anti-androgen that gives a survival benefit in patients with metastatic castrate-resistant prostate cancer.
- Toxicity from enzalutamide is generally low. However, evidence from phase-3 trials and also from clinical investigators shows that a minority of patients experience fatigue and/or cognition change, severe enough to trouble the patient. Sometimes these side effects lead to cessation of enzalutamide use.
- There is anecdotal evidence that these side effects respond to dose reduction of enzalutamide indicating a dose (or systemic exposure) – toxicity relationship.
- Pharmacokinetic data from two phase-3 studies show that trough levels of enzalutamide (and the active metabolite N-desmethyl enzalutamide) range from 0.82 to 42.4 ng/mL in individuals.
- Quartile analysis of the AFFIRM study data shows that those patients in the lowest quartile of enzalutamide exposure maintained the survival advantage over placebo.
- The approved product information for Enzalutamide states: "If a patient experiences a ≥ Grade 3 toxicity or an intolerable adverse reaction, withhold dosing for one week or until symptoms improve to ≤ Grade 2, then resume at the same or a reduced dose (120 mg or 80 mg) if warranted."

Research questions/aim/hypothesis

To determine whether dose reduction of enzalutamide in patients with Grade 3 and/or cognition change will lead to an improvement in symptoms while maintaining effective drug levels.

Objectives/ Endpoints

Primary objective:

1. Determine the proportion of patients who have an improvement in cognition/ fatigue symptoms.
2. Determine whether the median TTL (enzalutamide + N-desmethyl enzalutamide) of the dose reduced group is not significantly different from the published median of the lowest quartile of the AFFIRM study (~19.35 mg/L).

Secondary endpoints:

1. Compare enzalutamide and N-desmethyl enzalutamide trough levels in patients with significant cognition changes and/or fatigue with published population PK results.

2. Changes in serum PSA level in patients undergoing dose reduction of enzalutamide.

Hypothesis

We hypothesise that the fatigue and cognition changes seen in a subset of patients treated with enzalutamide is due to high systemic exposure of the drug and its active metobilite. Furthermore, we hypothesise that dose reduction of enzalutamide will lead to an improvement in symptoms and that the drug trough levels will remain within a potentially effective range in those patients.

Overview of research methods/ study design

Prospective multiple-centre phase II clinical trial.

Intervention

Patients receiving enzalutamide as standard of care, within 6 months of starting therapy. Patients will undergo dose reduction of enzalutamide.

Participants and recruitment

1. Patients with prostate cancer treated with enzalutamide.
2. Patients may have hormone sensitive or castrate resistant disease.
3. Patients may have metastatic (M1) or non-metastatic (M0) disease.
4. ECOG 0 or 1
5. Cognition and/ or fatigue changes due to enzalutamide and severe enough to warrant a dose reduction (Grade 3).
6. No other cause for cognition change or fatigue (such as change in narcotics, recent infection, use of sedative etc)

Participant numbers

47 patients will be recruited by a Research assistant at MQ Health Cancer Clinic.

Study Procedures

After signing the consent form, eligible patients will complete the validated questionnaires for cognition and fatigue. To allow immediate dose reduction and collection of blood for enzalutamide and metabolite assay, consent will be permitted to be taken on the day of review. Enzalutamide dose will be reduced by 40mg for moderate, and 40 or 80mg for severe cognition/fatigue impairment. Drug cessation until symptoms' resolution will also be allowed before recommencement at the lower dose. Assessments will be undertaken and 4 and 8 weeks after dose reduction for clinical review, cognition/fatigue questionnaires and blood for drug level assay and PSA. If symptoms have been adequately reduced, enzalutamide dose will be continued at that same dose and the patient is off study. If symptoms have not improved adequately, then a further dose reduction will be allowed with follow-up, as above, at 4 and 8 weeks.

Resources

The study will be conducted at MQ Health Cancer Clinic by the Clinical Trials Unit staff. PC2 laboratory will be used for standard blood work. There are already space arrangements in place for this type of blood work.

Data management – Data will be collected directly from the patients. All paper patient records will be kept in locked filing cabinet in the Chief Investigator's office. Electronic files will be saved on password protected folder on MQ Health network.

Significance

If it is demonstrated that cognition and/or fatigue induced by enzalutamide resolve after dose reduction, and that effective drug levels are maintained, this will give clinicians and patients confidence in allowing dose reduction for these side effects without negatively influencing efficacy. This project is cancer research, which is one of the key areas of clinical and research activity of MQ Health.

Budget

Items	Per unit cost	Number	total
Enzalutamide will be supplied on the PBS	0	0	$0
Imaging and lab tests as per standard care	0	0	$0
Ethics submissions		1	$0
Enzalutamide and metabolite trough level analysis (Netherlands)	$115	175	$20,125
Transport cost of PK samples to Netherlands and within Australia	300	21	$6,300
Site costs -(visits, application of questionnaires, data collection etc)	$3,085	47	$144,995
Training in use of Questionnaire and PK handling	$1,000	10	$10,000
Brief Fatigue Inventory Licence and Training manuals	$50	10	$500
Hopkins Learning Licence and Training manuals	$500	10	$5,000
Trail making A+B Licence and Training manuals	$50	10	$500
Controlled Word Association Licence and Training manuals	$684	10	$6,840
Central data management	$20,000	1	$20,000
Statistical analysis and safety monitoring	$10,000	1	$10,000
Web Database (eCRF design) and site training	$20,000	1	$20,000
SUBTOTAL			$244,260
25% Macquarie University overhead	25% overhead		$61,065
TOTAL			**$305,325**