PLATFORM Trial – MEDI4736 Management

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By:	Oncology Staff
For:	Oncology Staff
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PLATFORM Trial

Arm A: HER-2 Negative Patients with oesophagogastric adenocarcinomas.
Arm B: HER-2 Positive Patients with oesophagogastric adenocarcinomas.

Indication, no. cycles

- **ARM A2**: Capecitabine indefinitely until the occurrence of either disease progression, unacceptable toxicity, or patient withdrawal for another reason.
- **ARM A3**: MED14736 12 cycles in the absence of disease progression, unacceptable toxicity, or patient withdrawal for another reason.
- **ARM B1**: Trastuzumab indefinitely until the occurrence of either disease progression, unacceptable toxicity, or patient withdrawal for another reason.

The management of Capecitabine and Trastuzumab are covered by policies C.023 and C.031.

This document therefore covers management of the trial drug MEDI4736.

MEDI4736 (ANTI PD-L1) MAINTENANCE (ARM A3)

MEDI4736 is a fully human monoclonal antibody which is able to relieve PD-L1 mediated suppression of T cell activation. It therefore potentially allows reactivation of the normal immune surveillance within the tumour microenvironment, leading to meaningful tumour shrinkage in a number of solid organ tumours. It is therefore hoped that following chemotherapy, MEDI4736 mayfacilitate a prolonged disease control through its effects on the host immune system.

MEDI4736 is supplied in 200mg vials as a lipophilised powder for reconstitution. Each 200mg vial should be reconstituted with 4.0ml of water for injection, creating a 50 mg/ml solution. MEDI4736 should then be added to a 250ml bag of sterile 0.9% saline for administration as an IV infusion, and infused into the patient using a sterile infusion set. Subjects will receive the dose of MEDI4736 as an IV infusion over 60 minutes (± 10 minutes) through a 0.2µ in-line filter. The MEDI4736 solution should not be infused through an IV line in which other solutions or medications are being administered. If MEDI4736 administration has to be delayed, temporally interrupted or the infusion rate decreased for any reason, the total time between reconstitution and completion of the infusion should not exceed 6 hours. The date, start time, interruption, and completion time of MEDI4736 administration must be recorded in the source documents.

MEDI4736 Dosage Adjustments

Based on the mechanism of action of MEDI4736 leading to T-cell activation and proliferation, there is the possibility of observing immune-related AEs (irAEs) during the conduct of this study. In the absence of any alternate aetiology (e.g. infection or PD) signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune-related.
In general, for grade 1 adverse events there will be no requirement for MEDI4736 to be held or dose-reduced. For grade > 2 AEs and irAEs please follow the advice outlined in tables below:

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Grading

Infusion reactions will be graded according to the CTCAE (Version 4.0) definition of an allergic reaction/infusion reaction and anaphylaxis, as below:
• Grade 1: Transient flushing or rash, drug fever <38º C (<100.4º F); intervention not indicated.
• Grade 2: Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for <24 hours.
• Grade 3: Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension.
• Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade	Action and Dose Modification
Any	In case of doubt please consult with the trial physician
1 or 2	Temporarily interrupt infusion until resolution of the event (up to 4 hours) and reinitiate at 50% of the initial rate until completion of the infusion. Monitor patient every 15 minutes for worsening of condition Symptomatic treatment including chlorpheniramine 10mg IV (or equivalent antihistamine) and/or hydrocortisone 100mg IV (or equivalent corticosteroid) may be administered at the discretion of the investigator. Consider premedication prior to subsequent doses or administration of MEDI4736 at a reduced rate (over 90 minutes). Hold MEDI4736 until resolution to Grade 1 or baseline. If resolution to Grade 1 does not occur within 30 days, discontinue MEDI4736. No MEDI4736 dose modifications are required when resuming treatment.
3	Stop Infusion and disconnect infusion tubing from patient. Administer symptomatic treatment including chlorpheniramine 10mg IV (or equivalent anti-histamine), hydrocortisone 100mg IV (or equivalent corticosteroid), bronchodilators for bronchospasm, and other medications or oxygen as medically necessary. Permanent discontinuation of MEDI4736 treatment (no further treatment with MEDI4736 will be permitted).
4	Stop Infusion and disconnect infusion tubing from patient. Administer intramuscular adrenaline 1 in 1000 (1 mg/ml), bronchodilators or oxygen as indicated for bronchospasm. Administer chlorpheniramine 10mg IV (or equivalent anti-histamine) and hydrocortisone 100mg IV (or equivalent corticosteroid). Consider hospital admission for observation. Permanent discontinuation of MEDI4736 treatment (no further treatment with MEDI4736 will be permitted).

Management of Toxicity Related to MEDI4736

MEDI4736 leads to T-cell activation and proliferation, giving rise to the possibility of observing immune-related AEs (irAEs) during the conduct of this study. Potential irAEs include immune mediated enterocolitis, dermatitis, hepatitis/hepatotoxicity, neuropathy/neuromuscular toxicity, endocrinopathy, dermatitis, nephritis and pancreatitis. Subjects should therefore be monitored for signs and symptoms of irAEs and an immune-mediated cause of symptoms should be considered

in the absence of an alternate aetiology (e.g. infection or PD).

General Management Advice for irAEs

In addition to the specific advice, the following general advice should be followed (described by Weber et al, 2012):

1) Subjects should be thoroughly evaluated to identify any alternative aetiology

2) In the absence of clear alternative aetiology, all events of an inflammatory nature should be considered to be immune-related

3) Symptomatic and topical therapy should be considered for low-grade events < grade 2

4) For persistent (greater than 3 to 5 days) low grade (grade 2) or severe (grade 3 or >) events promptly start prednisolone PO 1-2mg/kg/day or IV equivalent.

5) If symptoms recur or worsen during steroid tapering (28 days of tapering) increase the steroid dose (prednisolone dose up to 2-4mg/kg/day or IV equivalent) until stabilisation or improvement of symptoms, then resume steroid tapering at a slower rate (> 28 days of tapering)

6) More potent immuno-suppressives should be considered for events not responding to systemic steroids (e.g. infliximab, mycophenolate)

7) Discontinuation of study drug is not mandated for grade 3/4 inflammatory reactions attributed to local tumour response (e.g. inflammatory reaction at sites of metastatic disease, lymph nodes etc).

Dose modifications will not be required for AEs that are clearly not attributed to MEDI4736 (such as an accident) or for laboratory abnormalities that are not deemed to be clinically significant. Dosing may continue despite concurrent vitiligo or alopecia of any AE grade. Dose reductions of MEDI4736 are not permitted.

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Guidance for MEDI4736 Dose Interruptions

Adverse Event	Severity	Action Taken
Endocrinopathy	Grade 2	Hold MEDI4736 dose if patient has evidence of uncontrolled endocrinopathy (based on either symptoms or biochemical results). Resume treatment once endocrinopathy is controlled. Patients with endocrinopathies may require prolonged steroid replacement, they can be recommenced on MEDI 4736provided: 1) The endocrinopathy is controlled 2) Patient is clinically stable 3) Doses of prednisolone are at less than or equal to 10mg/day of prednisolone.
	Grade 3 or 4	Hold MEDI 4736 until endocrinopathy is controlled. Then as for grade 2.
Gastrointestinal (Diarrhoea)	Grade 2	Hold MEDI4736 until resolution to < grade 1 or baseline. MEDI 4736 can be resumed at the next scheduled dose once events ≤ 1and 5-7 days have passed after completion of steroid taper
	Grade > 3	Discontinue MEDI4736
Elevated liver transaminases (ALT or AST) and / or elevated Bilirubin	Grade 2 (ALT/ AST 3-5 xULN) (bilirubin1.5-3 xULN)	Hold MEDI4736 until resolution to < grade 1 or baseline. MEDI 4736 can be resumed at the next scheduled dose once events ≤1and 5-7 days have passed after completion of steroid taper
	Grade > 3 (AST/ ALT>5-20 xULN) Bilirubin (>3-10 xULN)	For elevations < 8x ULN or elevations in bilirubin of _ 5 x ULN, hold MEDI4736 until resolution to < grade 1 or baseline. If elevations downgrade to ≤ Grade 1 or baseline within 14 days resume MEDI4736 administration at next scheduled dose. Otherwise discontinue MEDI4736. For AST/ ALT elevations > 8x ULN or elevations in bilirubin > 5 x ULN – discontinue MEDI4736
	Grade 4	Permanently discontinue MEDI 4736
Pneumonitis	Grade 2	Hold MEDI4736 until resolution to < grade 1 or baseline. If toxicity improves to baseline, MEDI 4736 can be resumed at the next scheduled dose once events ≤1and 5-7 days have passed after completion of steroid taper
	Grade ≥ 3	Discontinue MEDI4736

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Guidance for MEDI4736 Dose Interruptions cont.

Adverse Event	Severity	Action Taken
Nephritis	Grade 2 (creatinine >1.5 – 3.0 x baseline or >1.5-3.0 x ULN)	Hold MEDI 4736 until resolution to ≤ grade 1. MEDI 4736 can be resumed at the next scheduled dose once events ≤1and 5-7 days have passed after completion of steroid taper
	Grade 3/4 (Creatinine >3.0 x baseline or > 3.0-6.0x ULN) Or grade 4 (creatinine> 6.0x ULN)	Permanently discontinue MEDI 4736
Rash (excluding bullous skin formation)	Grade 2	For persistent (> 1-2 weeks) grade 2 events, hold MEDI 4736 until resolution to grade 1 or baseline. MEDI 4736 can be resumed at the next scheduled dose once events ≤ 1and 5-7 days have passed after completion of steroid taper
	Grade 3	Hold MEDI 4736 until resolution of grade 1 or baseline. If temporarily holding the drug does not provide improvement of the grade 3 skin rash to ≤ grade 1 or baseline within 30 days, then permanently discontinue MEDI 4736,
	Grade 4	Permanently discontinue MEDI 4736
Neurotoxicity	Grade 2	Hold MEDI 4736 until ≤ grade 1. MEDI 4736 can be resumed at the next scheduled dose once events _ 1and 5-7 days have passed after completion of steroid taper. For Guillain Barre or myasthenia gravis permanently discontinue if not < grade 1 within 30 days.
	Grade 3	Hold MEDI 4736 until resolution to ≤ grade 1. Permanently discontinue if not resolved to ≤ grade 1 within 30 days.
	Grade 4	Permanently discontinue
All other AEs	Grade 2	Hold MEDI4736 until resolution to < grade 1 or baseline. If resolution to < grade 1 or baseline occurs within 30 days, resume MEDI4736. If resolution to < grade 1 or baseline does not occur within 30days – discontinue MEDI4736.
	Grade 3	Hold MEDI 4736 until resolution to ≤ grade 1 or baseline. For AEs that downgrade to ≤ grade 2 within 7 days or resolve to ≤ grade 1 or baseline within 14 days, resume study drug at next scheduled dose. Otherwise, discontinue MEDI 4736.

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	Grade 4	Discontinue MEDI 4736

AMENDMENT HISTORY

A record of changes in this document

Date	Updated version number	Previous version number	Page Number/Section (updated version)	Details
28.02.17	1	1		New Document