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PhD in Medical Sciences
2020-2021

INVITATION to the Public defence of

Gil AWADA

To obtain the academic degree of '**DOCTOR OF MEDICAL SCIENCES**'

Expanding the application of targeted therapies and immune checkpoint inhibitors in advanced melanoma and recurrent glioblastoma.

The defence will take place on Friday, 18 June 2021 at 6 p.m.

and will be organised online via Zoom meeting
accessible through the following link:

https://gf.vub.ac.be/redirects/PhD_defense_Gil_Awada.php

and in Auditorium Piet Brouwer

ADMITTANCE to the auditorium will only be granted upon presentation of the personal invitation from the PhD candidate.

Summary of the dissertation

The prognosis of patients with advanced melanoma that progresses after treatment with immune checkpoint inhibitors and BRAF-/MEK-inhibitors, and of patients with glioblastoma that recurs after radiation therapy and temozolomide chemotherapy is grim. In this research, we have explored new applications of molecular-targeted therapies and immune checkpoint inhibitors in these disease settings.

The phase 2 TraMel-WT trial investigated the efficacy and safety of the MEK-inhibitor trametinib in patients with advanced *BRAF^{V600}* wild-type, *NRAS^{Q61R/K/L}* mutant or *BRAF^{V600}* wild-type, *NRAS^{Q61R/K/L}* wild-type melanoma who were previously treated with immune checkpoint inhibitors. In order to prevent trametinib-related skin toxicity, a low dose of the BRAF-inhibitor dabrafenib was added to trametinib. We show that adding low-dose dabrafenib to trametinib effectively mitigates trametinib-related skin toxicity. Promising antitumor activity was observed with trametinib plus low-dose dabrafenib in patients with advanced *NRAS^{Q61R/K/L}* wild-type melanoma, especially when mutations known to activate the mitogen-activated protein kinase pathway were present. In *NRAS^{Q61R/K/L}* mutant melanoma however, this combination is insufficiently active.

The phase 1/2 COMBI-R 2 trial investigated the efficacy and safety of dabrafenib, trametinib and the autophagy inhibitor hydroxychloroquine in patients with advanced pretreated (with immune checkpoint inhibitors and BRAF-/MEK-inhibitors) *BRAF^{V600}* mutant melanoma. We did not observe a benefit of adding hydroxychloroquine to dabrafenib and trametinib in this setting.

The phase 2 GliAvAx trial investigated the efficacy and safety of the vascular endothelial growth factor receptor 1-3 inhibitor axitinib and the programmed cell death ligand 1 immune checkpoint inhibitor avelumab in patients with recurrent glioblastoma. Although this combination was sufficiently safe, the trial did not meet its primary endpoint of improving the progression-free survival rate at 6 months to more than 50%.

Finally, in a population of 183 advanced melanoma patients who were treated with the programmed cell death 1 immune checkpoint inhibitor pembrolizumab, we performed a multivariable analysis to determine which baseline characteristics and biomarkers are independently associated with progression-free and overall survival.

Curriculum Vitae

Gil Awada studied medicine at the Vrije Universiteit Brussel and graduated summa cum laude in 2015. He subsequently started his training in internal medicine at the Saint Pierre hospital and Universitair Ziekenhuis Brussel in Brussels. In 2017, he enrolled in a PhD project under the supervision of Prof. Dr. Bart Neyns with focus on the expansion of application of molecular-targeted therapies and immune checkpoint inhibitors in advanced melanoma and recurrent glioblastoma. He was awarded the Emmanuel van der Schueren starterbeurs by Kom op tegen Kanker and secured with his promotor grants from Kom op tegen Kanker and Stichting tegen Kanker for the conduct of his research. During his PhD, he published 6 manuscripts in peer-reviewed journals as first author and co-authored multiple other articles. His research has also been presented on international congresses for which he received a Merit Award and Best Poster Award (ESMO Immunology Congress 2018) and a Merit Award (ASCO Annual Meeting 2021). After his PhD, he will start his medical oncology training.