

# Evaluation of Toxicity and Effect on Growth and Sexual Development in Children with MAPK Pathway Driven Tumors Treated with BRAF and MEK Inhibitors – A Single Center Experience

Shani Caspi<sup>1</sup>, Gadi Abebe Campino<sup>1</sup>, Shoshana Greenberger<sup>1</sup>, Dalit Modan-Moses<sup>2</sup>, Talya Finke<sup>1</sup>, Michal Lurye<sup>1</sup>, Uriel Katz<sup>1</sup>, Michael Kinori<sup>1</sup>, Eve Stern<sup>1</sup>, Michal Ben-Ami<sup>1</sup>, Michal Golan<sup>1</sup>, Sharon Armarnik<sup>1</sup>, Michalle Soudack<sup>3</sup>, Ariel Hirchorn<sup>1</sup>, Renana Gross<sup>1</sup>, Amos Toren<sup>1</sup>, and Michal Yalon<sup>1</sup>

<sup>1</sup>Sheba Medical Center at Tel Hashomer

<sup>2</sup>Sheba Medical Center

<sup>3</sup>Edmond and Lili Safra Children Hospital, Sheba Medical Center, Tel Hashomer, Israel

October 9, 2020

## Abstract

**Background** The MAPK pathway, is a signal transduction pathway involved in the oncogenesis of a variety of pediatric tumors. The clinical use of BRAF inhibitors and MEK inhibitors is increasingly used in oncology practice. The toxicity profile of these drugs in the pediatric population, particularly in relation to development, growth and sexual maturation remains insufficiently studied. **Procedure** This study includes 22 pediatric patients with molecularly confirmed MAPK pathway driven tumors treated with MEK or BRAF between August 2014 and March 2020. Throughout treatment they underwent regular laboratory, endocrine, cardiac, ophthalmic and dermatologic evaluation. Toxicity was recorded and evaluated according to CTCA v4. **Results** Overall an adverse event frequency of 86% was encountered. Dermatological disorders accounted for 68% of the adverse events. Overall 8 patients suffered from severe adverse events including Erythema Nodosum, PLEVA-like rash, osteoporosis, Sarcoid-like massive lymphadenopathy, retinal toxicity and elevated liver enzymes & CPK. Four patients discontinued treatment as a result of adverse events. In this cohort we did not encounter any treatment-related abnormalities of sexual maturation or gonadal function nor statistically significant growth retardation, however a slower than expected growth rate was observed in one patient. In addition dose-dependent, non-symptomatic and within normal range for age decreased cardiac SF% was noted in two patients treated with MEK inhibitor. **Conclusion** Treatment with BRAF and MEK inhibitors was shown to be generally safe, we report drug tolerability of 82%. However, further prospective studies should be performed to are characterize the full scope of side effects in the pediatric population.

*Evaluation of Toxicity and Effect on Growth and Sexual Development in Children with MAPK Pathway Driven Tumors Treated with BRAF and MEK Inhibitors – A Single Center Experience*

*Shani Caspi<sup>1</sup>, Gadi Abbebe Campino<sup>\*1</sup>, Shoshana Grinberger<sup>2</sup>, Dalit Modan-Moses<sup>3</sup>, Talya Finke<sup>1</sup>, Michal Hazut-Lurye<sup>1</sup>, Michael Kinori<sup>4</sup>, Uriel Katz<sup>5</sup>, Michal Ben-Ami<sup>3</sup>, Eve Stern<sup>3</sup>, Michal Golan-Malki<sup>1</sup>, Sharon Armarnik<sup>4</sup>, Michalle Soudack<sup>6</sup>, Ariel Hirschhorn<sup>7</sup>, Renana Gross<sup>8</sup>, Amos Toren<sup>9</sup> and Michal Yalon<sup>10</sup>*

*\*The first, second and last authors have contributed equally to this article*

*1Department of pediatric oncology, Neuro-oncology service The Edmond and Lily Safra children's hospital, Chaim Sheba medical center and Sackler Faculty of Medicine Tel-Aviv university, Tel-Aviv, Israel*

2 The department of Dermatology, Chaim Sheba medical center and Sackler Faculty of Medicine Tel-Aviv university, Tel-Aviv, Israel

3. Pediatric Endocrinology, The Edmond and Lily Safra children's hospital, Chaim Sheba medical center and Sackler Faculty of Medicine Tel-Aviv university, Tel-Aviv, Israel

4. Department of ophthalmology and vision sciences, The Edmond and Lily Safra children's hospital, Chaim Sheba medical center and Sackler Faculty of Medicine Tel-Aviv university, Tel-Aviv, Israel

5. Department of pediatric cardiology, The Edmond and Lily Safra children's hospital, Chaim Sheba medical center and Sackler Faculty of Medicine Tel-Aviv university, Tel-Aviv, Israel

6. Department of pediatric radiology, The Edmond and Lily Safra children's hospital, Chaim Sheba medical center and Sackler Faculty of Medicine Tel-Aviv university, Tel-Aviv, Israel

7. Department of oral and maxillofacial surgery, Chaim Sheba medical center and Sackler Faculty of Medicine Tel-Aviv university, Tel-Aviv, Israel

8. Department of clinical research, Pediatric Oncology, The Edmond and Lily Safra children's hospital, Chaim Sheba medical center

9. Head of pediatric hemato-oncology and Bone Marrow Transplantation, The Edmond and Lily Safra children's hospital, Chaim Sheba medical center and Sackler Faculty of Medicine Tel-Aviv university, Tel-Aviv, Israel

10. Head of the pediatric Neuro-Oncology Service The Edmond and Lily Safra children's hospital, Chaim Sheba medical center and Sackler Faculty of Medicine Tel-Aviv university, Tel-Aviv, Israel

Corresponding author: Shani Caspi pediatric oncology department

Address: The Edmond and Lily Safra children's hospital, Chaim Sheba medical center

pediatric oncology department, Ramat Gan 52621, Israel

Phone: +972544749733

Email: shanicaspi@yahoo.com

Fax: +97235307263

Word count:

1. Abstract: 250 words
2. Main text – 3490 words

TABLES-3

FIGURES- 3

Keywords: MAPK pathway, MEK inhibitors, BRAF inhibitors, toxicity, pediatric oncology

Short running title: *MAPK Inhibitors safety – A Single Center Experience*

**Abbreviation key**

CTCA	Common terminology criteria for adverse events
SAE	Severe adverse event
AE	adverse event
SF	Shortening fraction
MAPK	Mitogen activated protein kinase
NF1	Neurofibromatosis type 1

CTCA	Common terminology criteria for adverse events
LGG	Low grade gliomas
HGG	High grade gliomas
LCH	Langerhans cell histiocytosis
MAKER	MEK inhibitors associated retinopathy
BMI	Body mass index
JPA	Juvenile pilocytic astrocytoma
GBM	Glioblastoma multiforme
PXA	Pleomorphic Xanthoastrocytoma
PLEVA	Pityriasis Lichenoides et Varioliformis acuta
SCC	Squamous cell carcinoma
GH	Growth hormone
DEXA	Dual energy Xray absorptiometry
TBS	Trabecular bone score
LVSF	Left ventricular fractional shortening
AMN	Acute macular neuroretinopathy
OCT	Optical coherence tomography
EN	Erythema nodosum
N#	NUMBER

#### Hosted file

abstract-final.pdf available at <https://authorea.com/users/365698/articles/485708-evaluation-of-toxicity-and-effect-on-growth-and-sexual-development-in-children-with-mapk-pathway-driven-tumors-treated-with-braf-and-mek-inhibitors-a-single-center-experience>

#### Hosted file

main-text-final.pdf available at <https://authorea.com/users/365698/articles/485708-evaluation-of-toxicity-and-effect-on-growth-and-sexual-development-in-children-with-mapk-pathway-driven-tumors-treated-with-braf-and-mek-inhibitors-a-single-center-experience>

#### Hosted file

Reference.pdf available at <https://authorea.com/users/365698/articles/485708-evaluation-of-toxicity-and-effect-on-growth-and-sexual-development-in-children-with-mapk-pathway-driven-tumors-treated-with-braf-and-mek-inhibitors-a-single-center-experience>

#### Hosted file

tables.pdf available at <https://authorea.com/users/365698/articles/485708-evaluation-of-toxicity-and-effect-on-growth-and-sexual-development-in-children-with-mapk-pathway-driven-tumors-treated-with-braf-and-mek-inhibitors-a-single-center-experience>



