بسم الله الرحمن الرحيم

HANAA ALY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

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The Prognostic Impact Philadelphia Like (CRLF2) Gene on the Outcome of Adult Acute Lymphoblastic Leukaemia

Thesis

Submitted for Partial Fulfillment of
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By

Abdallah Sami Soliman Elkomy
M.B.B.Ch.

Under Supervision of

Prof. Dr/ Amal Mostafa Elafifi
Professor of Internal Medicine, Clinical Haematology and BMT
Faculty of Medicine, Ain Shams University

Prof. Dr/ Nermeen Adel Nabih
Assistant Professor of Internal Medicine, Clinical Haematology and BMT
Faculty of Medicine, Ain Shams University

Prof. Dr/ Haydi Sayed Mohamed
Lecturer of Internal Medicine- Clinical Haematology and BMT
Faculty of Medicine, Ain Shams University

Prof. Dr/ Yasser Hassan Elnahas
Professor of Clinical Pathology and Hematology
Faculty of Medicine, Ain Shams University

Faculty of Medicine – Ain Shams University

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بسم الله الرحمن الرحيم

قَالُوا

سبحانك لا علم لنا إلا ما علمتنا إنك أنت العليم الحكيم

صدق الله العظيم

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Abdallah Sami Soliman Elkomy

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List of Abbreviations

Abb.	Full term
± SD	± Standard deviation
6-MP	6-mercaptopurine
ADCC	Antibody-dependent cell-mediated cytotoxicity
ALL	Acute lymphoblastic leukemia
Allo-SCT	Allogeneic stem cell transplantation
AML	Acute myeloid leukemia
AMLs	Acute myeloid leukemias
AYA	Adolescent and young adults
AYAs	Adolescents and young adults
BLNK	B-cell linker
CAR	Chimeric antigen receptor
CDC	Complement-dependent cytotoxicity
CI	Confidence interval
CNS	Central nervous system
COG	Children's Oncology Group
CR	Complete remission
CRLF2	Cytokine receptor-like factor 2
CSF1R	Colony stimulating factor 1 receptor
CVL	Central Venous Line
DFS	Difference of disease-free
DFS	Disease-free survival
DGKH	Diacylglycerol kinase eta
E2A	Transcription factor 3
EBF1	Early B-cell factor 1
EPOR	Erythropoietin receptor
FAB	French American British
FISH	Fluorescence in situ hybridization
FLT3	Fms-related tyrosine kinase 3
GEP	Gene expression profiling
HC	Hierarchical clustering
HCVAD	Hyper-CVAD

List of Abbreviations cont...

Abb.	Full term
HR	Hazards ratio
HSCT	Hematopoietic stem cell transplant
HSP90	Heat shock protein 90
Ig	Immunoglobulin
IKZF1	IKAROS family zinc finger 1
IKZF3	IKAROS family zinc finger 3
IL-2 R	Interleukin-2 receptor
InO	Inotuzumab ozogamicin
JAK	Janus Activated Kinase
LBLs	Lymphoblastic lymphomas
LDA	Low Density Microarray
LDH	Lactic acid dehydrogenase
MDS	Myelodysplastic syndrome
MHC	Major histocompatibility complex
MMAF	Microtubule-disrupting agent monomethyl auristatin F
MPO	Myeloperoxidase
MRD	Minimal residual disease
MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin
NCCN	National Comprehensive Cancer Network
NGS	Next-generation sequencing
NHL	Non-hodgkin lymphoma
NTRK3	Neurotrophic receptor tyrosine kinase 3
OS	Overall survival
PAM	Prediction analysis of microarrays
PAX5	Paired box 5
PBD	Pyrrolobenzodiazepine
Ph+	Philadelphia positive
PI3K	Phosphoinositide 3-kinase
PI3K/AKT	Phosphatidylinositol 3-kinase/protein kinase B
PT	Prothrombin time

List of Abbreviations cont...

Abb.	Full term
PTK2B	Protein tyrosine kinase 2 beta
PTT	Partial thromboplastin time
rALL	Relapsed ALL
RFS	Relapse-free survival
RT-PCR	Reverse transcription polymerase chain reaction
SJCRH	St. Jude Children's Research Hospital
T-ALL	T-cell ALL
TCR	T-cell receptor
Tdt	Terminal deoxynucleotidyl transferase
TKIs	Tyrosine kinase inhibitors
TLSP	Thymic stromal lympho-poetin
TSLPR	Thymic stromal lymphopoietin protein receptor
VCR	Vincristine
WBC	White blood cell

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a heterogeneous disease characterized by the accumulation and proliferation of clonal lymphoid progenitor cells in the bone marrow, periphery, and/or extramedullary sites. The disease is frequently accompanied by suppression of normal hematopoiesis. B- and T-cell lymphoblastic leukemia cells express surface antigens that parallel their respective lineage developments *(Pui & Jeha, 2007).*

While ALL is known as a cancer success story in the pediatric setting, with cure rates approaching 90%, the same cannot yet be said in adults, with long-term disease-free survival (DFS) of around 40% to 45% *(Thomas et al., 2010),* depending on patient age and disease characteristics *(Sive et al., 2012).*

The inferior outcome of older patients has been linked to several factors, both disease-related (higher frequency of high-risk genomic subgroups such as Philadelphia chromosome [Ph+]) and patient-related (poor tolerance to chemotherapy). Recently, a high-risk subgroup of B-ALL called Ph-like ALL was identified in children and adolescents and young adults (AYAs), Ph-like ALL comprises up to 15% of childhood B-ALL, and 20% to 25% in AYAs *(Roberts et al., 2014).* Two broad genetic subgroups of Ph-like ALL have been identified. Approximately 50% of patients with Ph-like ALL have

overexpression of cytokine receptor-like factor 2 (CRLF2) *(Herold et al., 2016).* Almost half of the patients with CRLF2 overexpression have concomitant JAK-STAT mutations, most commonly JAK2 R683G, which result in JAK-STAT activation amenable to JAK inhibition *(Ravandi et al., 2015).*

In Ph-like ALL patients without CRLF2 overexpression, fusions involving JAK2, ABL1, ABL2, and many other tyrosine kinases are common, and many are amenable to ABL-type inhibitors (tyrosine kinase inhibitors [TKIs]) (fusions involving ABL1, ABL2, CSF1R, or PDGFRB) or JAK inhibitors (rearrangements of JAK2 and EPOR) *(Iacobucci et al., 2016).*

Several authors try to investigate Ph like mutation by several methods and explore the outcome with conflict results, there are conflicting data on the incidence and prognosis of Ph-like ALL in adults. Some authors reported that outcomes of adult patients with Ph-like ALL, and significantly worse outcomes in the CRLF2 subset of Ph-like ALL *(Perez-Andreu et al., 2015).* Thus, genomic characterization of Ph-like ALL has significant therapeutic implications with the emerging use of kinase inhibitors in this patient population *(Loh et al., 2015).*