



شبكة المعلومات الجامعية  
التوثيق الإلكتروني والميكروفيلم

# بسم الله الرحمن الرحيم



**HANAA ALY**



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# شبكة المعلومات الجامعية التوثيق الإلكتروني والميكروفيلم



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# جامعة عين شمس

## التوثيق الإلكتروني والميكروفيلم

### قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها  
علي هذه الأقراص المدمجة قد أعدت دون أية تغييرات



### يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار



**HANAA ALY**



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

**Thesis**

*Submitted for Partial Fulfillment of  
M.Sc. Degree in Clinical Haematology*

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

# قَالَ

سُبْحَانَكَ لَا عِلْمَ لَنَا  
إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ  
الْعَلِيمُ الْعَظِيمُ

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# List of Abbreviations

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

# List of Abbreviations cont...

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

# INTRODUCTION

**A**cute 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*).