

2016

# Miglior articolo di Agosto



**RIVISTA:** Journal of Clinical Oncology (JCO)

**TITOLO:** Baseline Metabolic Tumor Volume Predicts Outcome in High-Tumor-Burden Follicular Lymphoma: A Pooled Analysis of Three Multicenter Studies

**AUTORI:** Meignan M, Cottereau AS, Versari A, Chartier L, Dupuis J, Boussetta S, Grassi I, Casanovas RO, Haioun C, Tilly H, Tarantino V, Dubreuil J, Federico M, Salles G, Luminari S, Trotman J

Published Ahead of Print on August 22, 2016 as 10.1200/JCO.2016.66.9440  
The latest version is at <http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2016.66.9440>

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

## Baseline Metabolic Tumor Volume Predicts Outcome in High-Tumor-Burden Follicular Lymphoma: A Pooled Analysis of Three Multicenter Studies

Michel Meignan, Anne Ségolène Cottereau, Annibale Versari, Loïc Chartier, Jehan Dupuis, Sami Boussetta, Ilaria Grazi, René-Olivier Casanovas, Corinne Haioun, Hervé Tilly, Vittoria Tarantino, Julien Dubreuil, Massimo Federico, Gilles Salles, Stefano Luminari, and Judith Trotman

### ABSTRACT

#### Purpose

Identifying patients at high risk of progression and early death among those with high-tumor-burden follicular lymphoma (FL) is unsatisfactory with current prognostic models. This study aimed to determine the prognostic impact of the total metabolic tumor volume (TMTV) measured at baseline with [<sup>18</sup>F]fluorodeoxyglucose/positron emission tomography-computed tomography (PET-CT) scans and its added value to these models.

#### Patients and Methods

A pooled analysis was performed by using patient data and centrally reviewed baseline PET-CT scans for 185 patients with FL who were receiving immunotherapy within three prospective trials. TMTV was computed by using the 41% maximum standardized uptake value thresholding method, and the optimal cutoff for survival prediction was determined.

#### Results

Median age was 55 years, 92% of patients had stage III to IV disease, 37% had a Follicular Lymphoma International Prognostic Index (FLIPI) score of 3 to 5, and 31% had a FLIPI2 score of 3 to 5. With a median follow-up of 64 months, overall 5-year progression-free survival (PFS) was 55% and overall survival (OS) was 92%. Median TMTV was 297 cm<sup>3</sup> (quartile 1 through quartile 3, 135 to 567 cm<sup>3</sup>). The optimal cutoff identified was 510 cm<sup>3</sup>, with a markedly inferior survival in the 29% of patients with TMTV > 510 cm<sup>3</sup>. Five-year PFS was 33% versus 65% (hazard ratio [HR], 2.90; *P* < .001), and 5-year OS was 85% versus 95% (HR, 3.45; *P* = .010). On multivariable analysis, TMTV (HR, 2.3; *P* = .002) and FLIPI2 score (HR, 2.2; *P* = .002) were independent predictors of PFS. In combination, they identify three risk groups: high TMTV and intermediate-to-high FLIPI2 score with 5-year PFS of 20% (HR, 5.0; *P* < .001), high TMTV or intermediate-to-high FLIPI2 score with 5-year PFS of 46% (HR, 2.1; *P* = .007), and low TMTV and low FLIPI2 with 5-year PFS of 69%.

#### Conclusion

Baseline TMTV is a strong independent predictor of outcome in FL. In combination with FLIPI2 score, it identifies patients at high risk of early progression. It warrants further validation as a biomarker for development of first-line PET-adapted approaches in FL.

*J Clin Oncol* 34. © 2016 by American Society of Clinical Oncology

### INTRODUCTION

Follicular lymphoma (FL) is the second most frequent non-Hodgkin lymphoma subtype in Western countries<sup>1</sup> and it accounts for approximately 20% to 25% of non-Hodgkin lymphomas diagnosed in Western Europe and the United States.<sup>2,3</sup> Approaches that use rituximab combined with chemotherapy have led to a remarkable improvement in survival over the last decade.

However, despite the advances in prolonging remission overall, 20% of those treated with immunotherapy have disease progression within 2 years and a 5-year overall survival (OS) of only 50%.<sup>4-10</sup> These patients are not easily identified by existing pretreatment prognostic indexes such as the Follicular Lymphoma International Prognostic Index (FLIPI)<sup>11</sup> and FLIPI2,<sup>12</sup> or by conventional computed tomography (CT)-based response assessment. In a recent pooled analysis of centrally reviewed scans and outcome data from

Michel Meignan, Anne Ségolène Cottereau, Jehan Dupuis, and Corinne Haioun, Université Paris-Est Créteil (France); Loïc Chartier, Sami Boussetta, and Julien Dubreuil, Centre Hospitalier Lyon-Sud; Gilles Salles, Université Claude Bernard Lyon 1; Pierre Béribé, René-Olivier Casanovas, Centre Hospitalier Universitaire-Dijon; Hervé Tilly, Université de Rouen, Rouen, France; Annibale Versari and Iaria Grazi, Santa Maria Nuova Hospital, Istituto di Ricovero e Cura a Carattere Scientifico, University of Modena and Reggio Emilia, Reggio Emilia; Vittoria Tarantino and Massimo Federico, University of Modena and Reggio Emilia, Modena, Italy; and Judith Trotman, University of Sydney, Concord, New South Wales, Australia.

Published online ahead of print at [www.jco.org](http://www.jco.org) on August 22, 2016.

Presented at the 57th American Society of Hematology Annual Meeting and Exposition, Orlando, FL, November 5-8, 2015.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Michel Meignan, MD, PhD, Lymphoma Study Association Imaging, Nuclear Medicine Department, Hôpital Henri Mondor, 51 Avenue du Maréchal de Lattre de Tassigny, Créteil, 94010, France; e-mail: michel.meignan@hmn.aphp.fr.

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0732-183X/16/34-0944-9440

DOI: 10.1200/JCO.2016.66.9440



**DIREZIONE SCIENTIFICA ASMN-IRCCS**

Tel.: 0522 296979 - Fax: 0522 295622  
E-mail: [massimo.costantini@asmn.re.it](mailto:massimo.costantini@asmn.re.it)  
Segreteria: [luca.pistolesi@asmn.re.it](mailto:luca.pistolesi@asmn.re.it)  
[Itala.rossi@asmn.re.it](mailto:Itala.rossi@asmn.re.it)