Final Efficacy Results of A3671009, a Phase III Study of Tremelimumab vs Chemotherapy (Dacarbazine or Temozolomide) in First-line Patients With Unresectable Melanoma

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Presented at: 25th Annual Meeting of the International Society for Biological Therapy of Cancer (iSBTc); October 2-4, 2010; Washington, DC. Late-breaking abstract 174.

Tremelimumab

- Fully human IgG2 antibody developed by Pfizer that is specific for CTLA4 (CD152) with a plasma half-life of 22.1 days[1,2]
- Promising activity was observed in phase I and II trials in patients with melanoma

- 1001: first-in-human, single-dose escalation, phase I clinical trial[2]
  - 4 (14%) objective responses
  - All responses lasted ≥ 18 months
- 1002: multidose phase I/II clinical trial[3]
  - 8 objective responses (9.5%) among 84 evaluable in phase II
  - 6 patients had responses lasting 15+ months
- 1008: multidose phase II clinical trial[4]
  - 16 (6.6%) objective responses
  - Response duration 8.9 to 29.8 months

Study	Phase	Patients with melanoma, n
A3671001[2]	**I**	**29**
A3671002[3]	**I/II**	**117**
A3671008[4]	**II**	**246**

Abbreviations: CTLA4, cytotoxic T-lymphocyte antigen 4; Ig, immunoglobulin.

1. Ribas A, et al. *Oncologist.* 2007;12(7):873-883; 2. Ribas A, et al. *J Clin Oncol.* 2005;23(35):8968-8977; 3. Camacho LH, et al. *J Clin Oncol*. 2009;27(7):1075-1081; 4. Kirkwood JM, et al. *Clin Cancer Res*. 2010;16(3):1042-1048.

Tremelimumab Phase III Study A3671009

Objective

- This phase III study was conducted to test the hypothesis that tremelimumab can improve survival in patients with surgically incurable metastatic melanoma

Primary Analysis of Survival

- 537 events would provide 90% power for 2-sided log-rank test at .045 significance when true HR ≥ 1.33 (chemotherapy over tremelimumab)

- 2 equally spaced interim analyses based on O'Brien-Fleming–type boundary were planned when ~1/3 and ~2/3 of events had been observed to stop the clinical trial for futility or to claim efficacy

Abbreviation: HR, hazard ratio.

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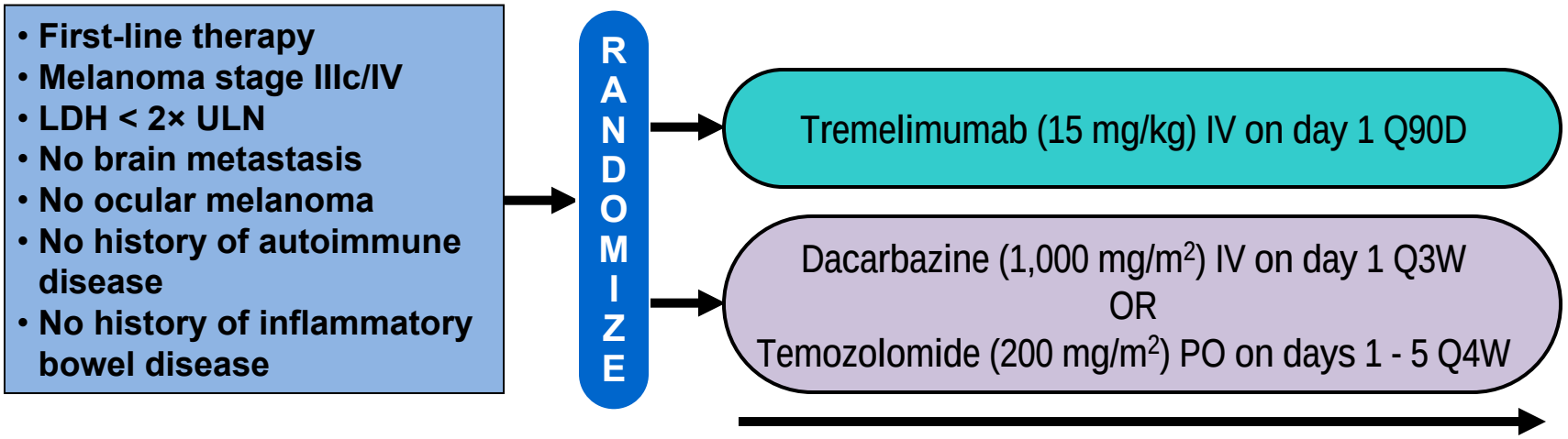
Schema and Endpoints

- Primary endpoint was overall survival
- Secondary endpoints included best overall response, durable response, duration of tumor response, PFS (at 6 months postrandomization) safety



- Accrual period: March 2006 - July 2007
- Crossed futility boundary at second interim analysis: March 2008

Abbreviations: IV, intravenous; LDH, lactate dehydrogenase; PFS, progression-free survival; PO, orally; ULN, upper limit of normal.

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Patient Characteristics

	Tremelimumab	Chemotherapy
Randomized patients, n	**328**	**327**
Male, %	**58**	**56**
White, %	**93**	**93**
Mean age, years (range)	**57 (22-90)**	**56 (22-90)**
Age ≥ 65 years, %	**34**	**28**
ECOG = 0, %	**68**	**70**
Disease stage, %		
IIIC	**6**	**4**
M1a	**14**	**15**
M1b	**23**	**21**
M1c	**57**	**59**
LDH ≥ ULN, %	**30**	**35**
Nonmeasurable disease, %	**6**	**6**

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

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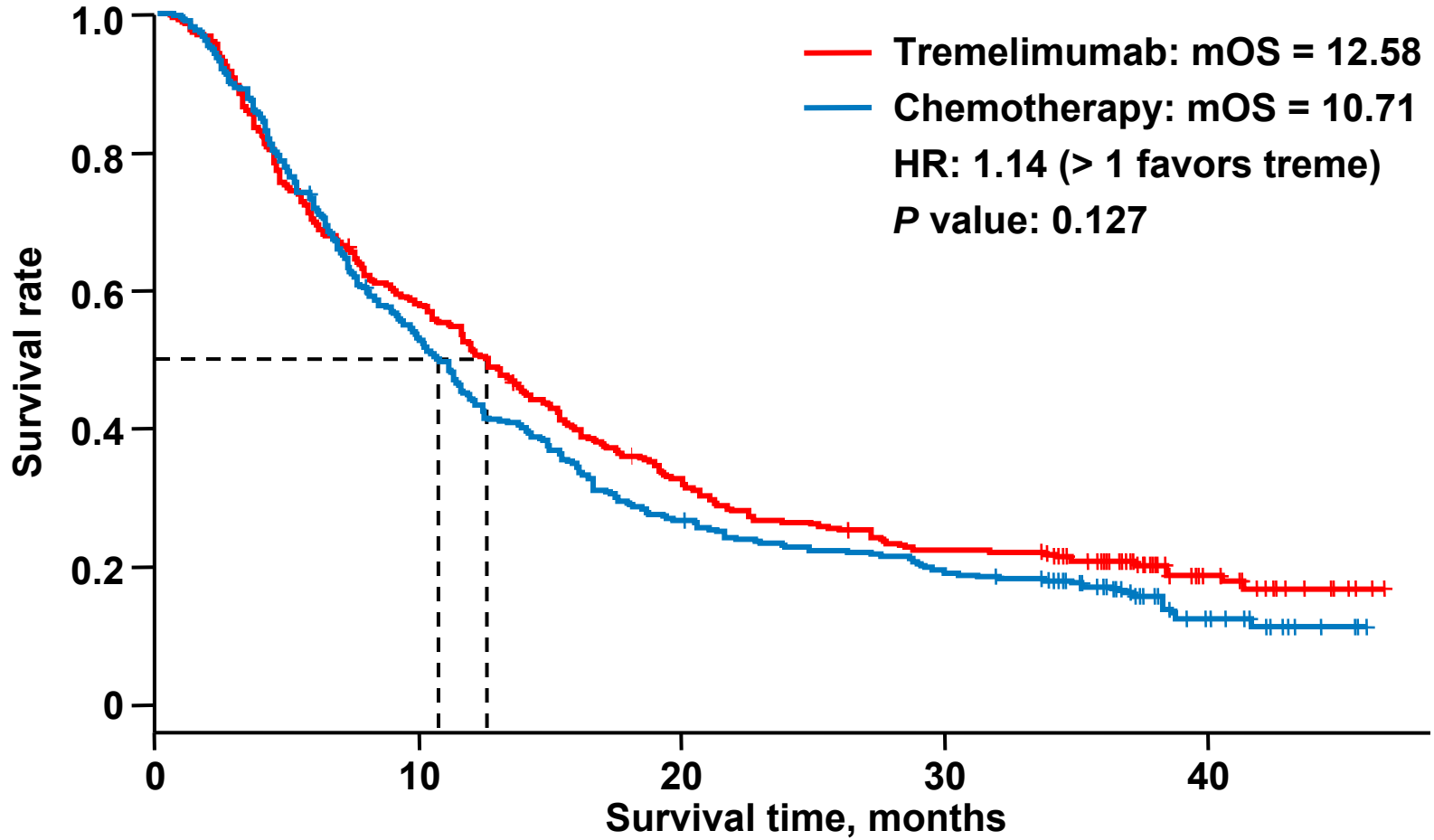
Kaplan-Meier Estimate of Overall Survival[a]



Patients at risk					
Tremelimumab	328	189	105	71	20
Chemotherapy	327	167	82	59	12

Abbreviation: mOS, median overall survival.
[a]Data from September 2010.

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Secondary Endpoint: Responses to Therapy and Progression-free Survival[a]

	Tremelimumab	Chemotherapy
Randomized patients, n	328	327
Complete response (CR),[b] n (%)	11 (3.4)	8 (2.4)
Partial response (PR),[b] n (%)	25 (7.6)	24 (7.3)
Objective response (CR + PR),[b] n (%)	36 (11.0)	32 (9.8)
95% CI for objective response rate[b] (%)	(7.8, 14.9)	(6.8, 13.5)
6-Month progression-free survival (PFS),[c] %	20.1	18.1

Abbreviation: CI, confidence interval.
[a]Best overall response as confirmed by sponsor.
[b]Data from September 2010.
[c]Data from May 2010.

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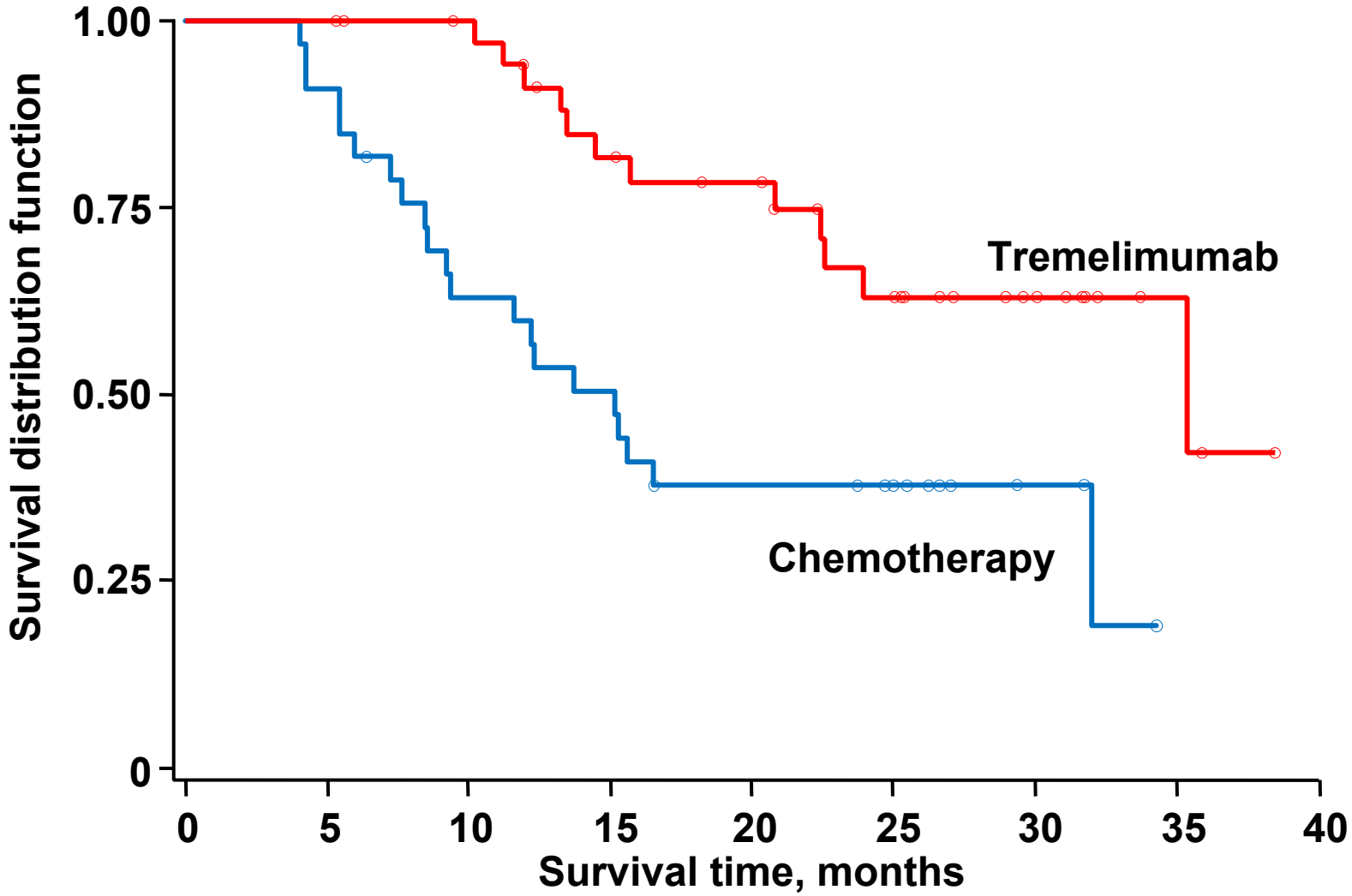
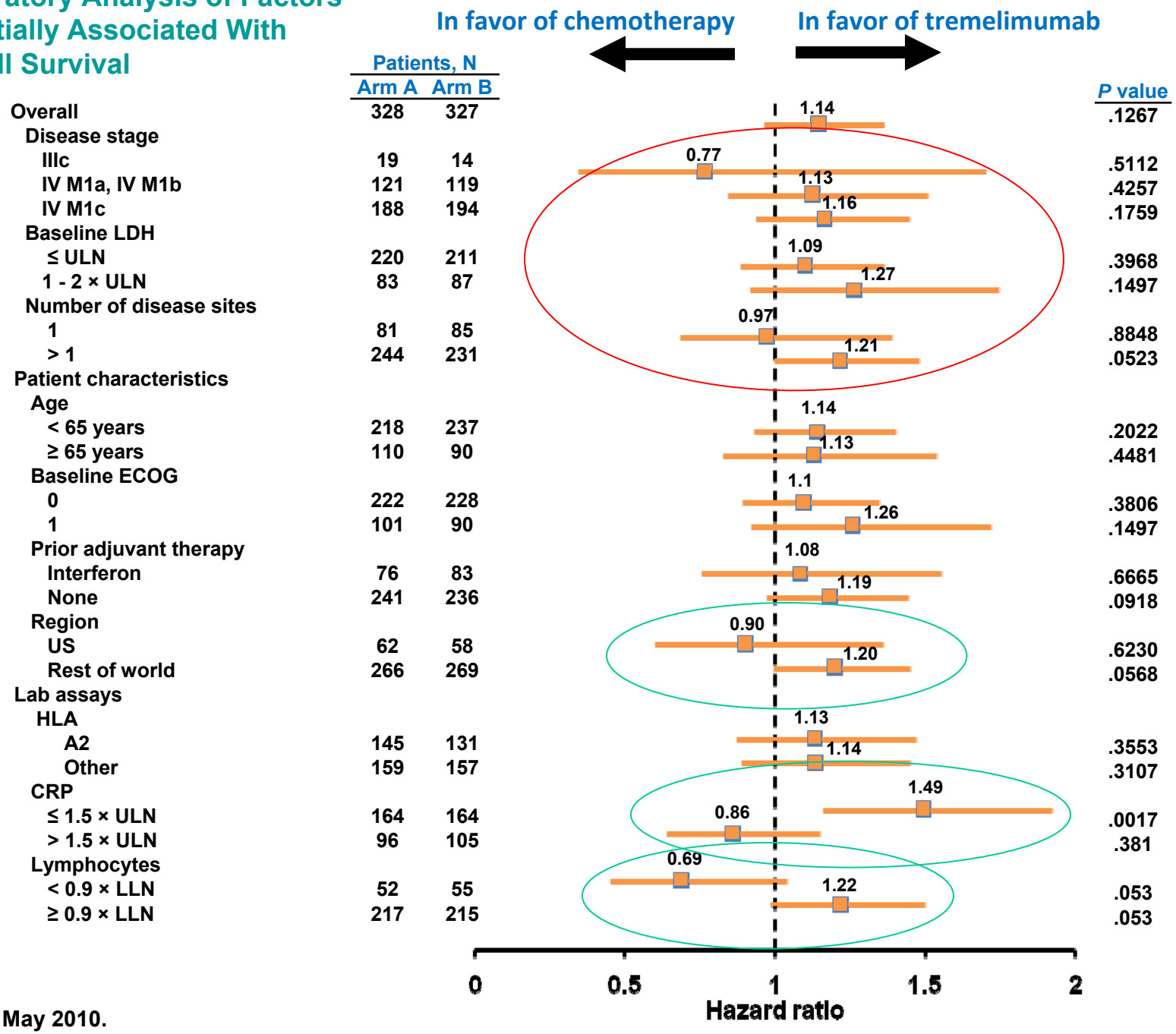
Secondary Endpoint: Duration of Objective Response[a,b]



[a]Duration of response from time of randomization.
[b]Data from September 2010.

Exploratory Analysis of Factors Potentially Associated With Overall Survival



Data from May 2010.

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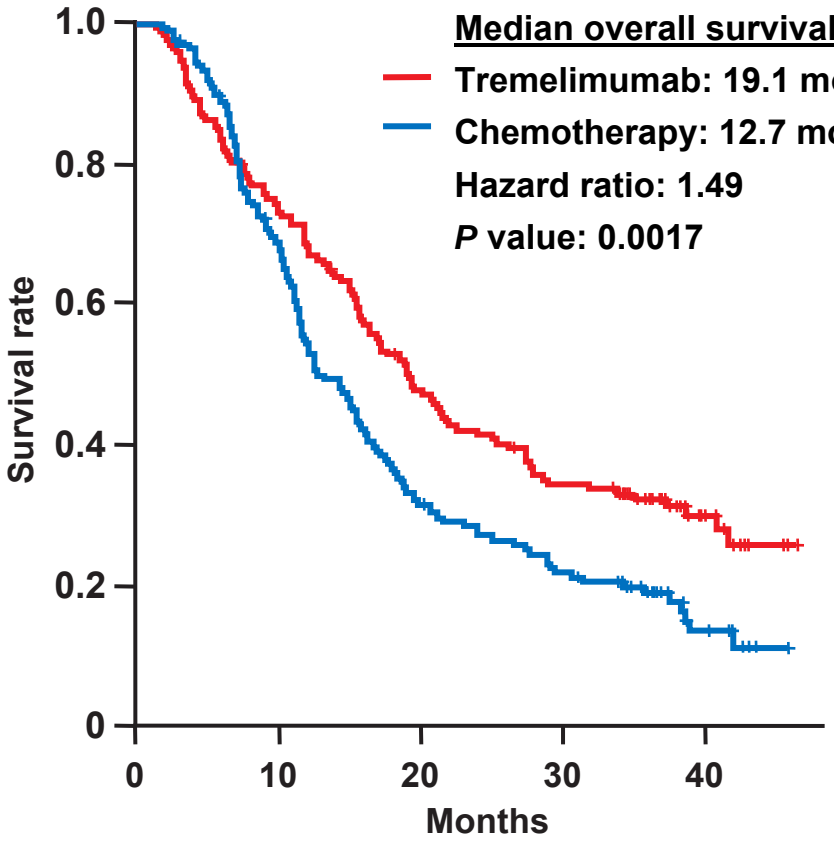
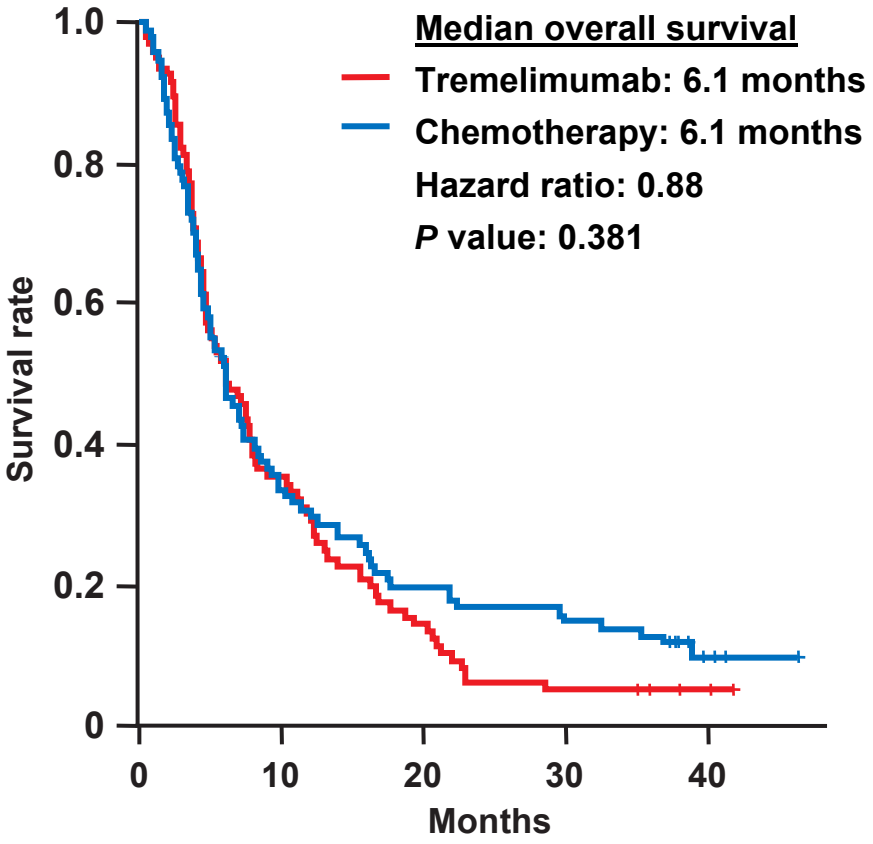
Survival by Baseline CRP

Subset of patients with CRP ≤ 1.5 × ULN



Subset of patients with CRP > 1.5 × ULN



Abbreviation: CRP, C-reactive protein.

Marshall MA, Ribas A, Huang B. Poster presented at: 46th Annual Meeting of the American Society of Clinical Oncology (ASCO); June 4-8, 2010; Chicago, IL. Abstract 2609.

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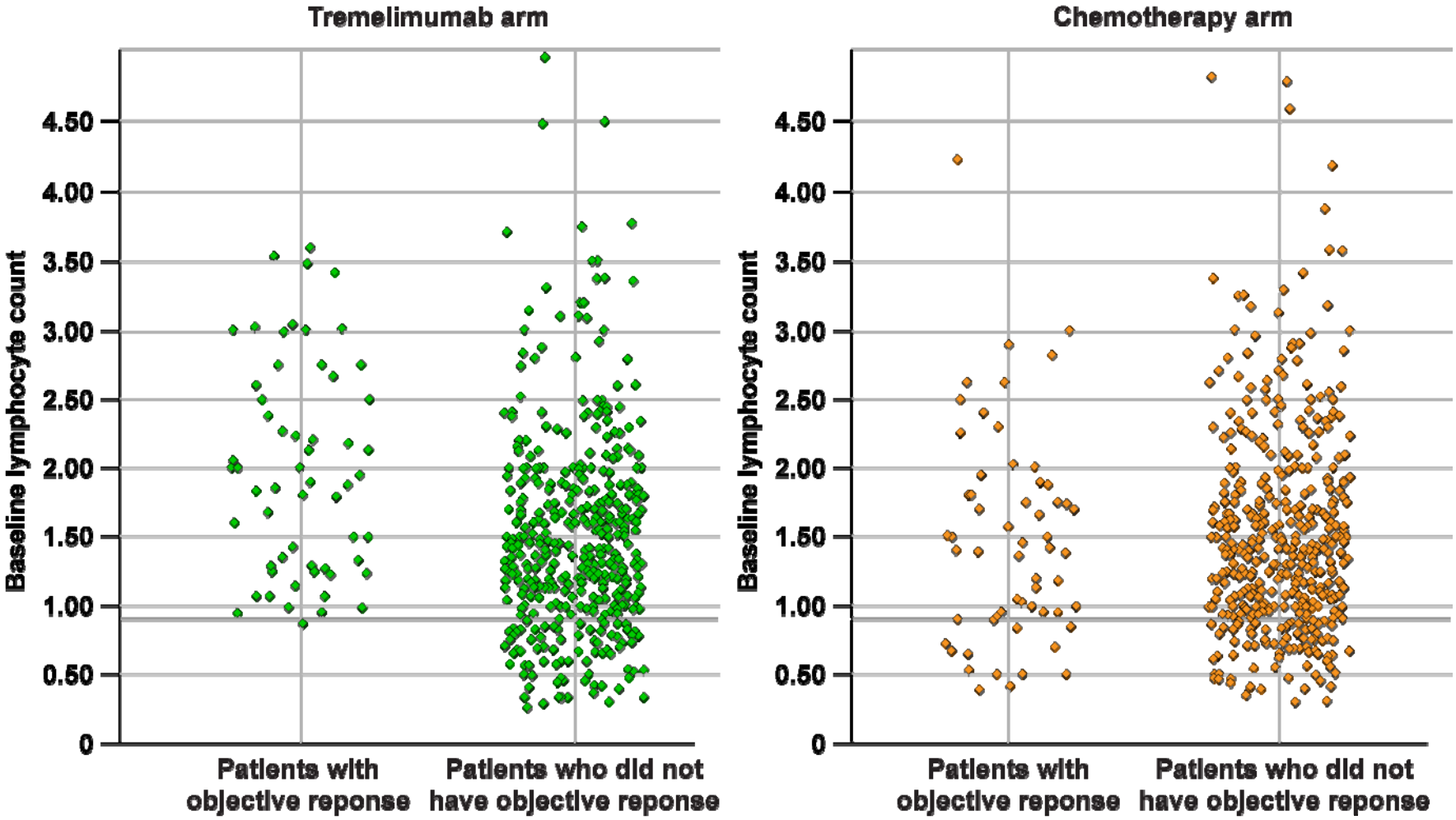
Distribution of Baseline Lymphocyte Count and Objective Tumor Response, by Treatment Arm



Data from May 2010.

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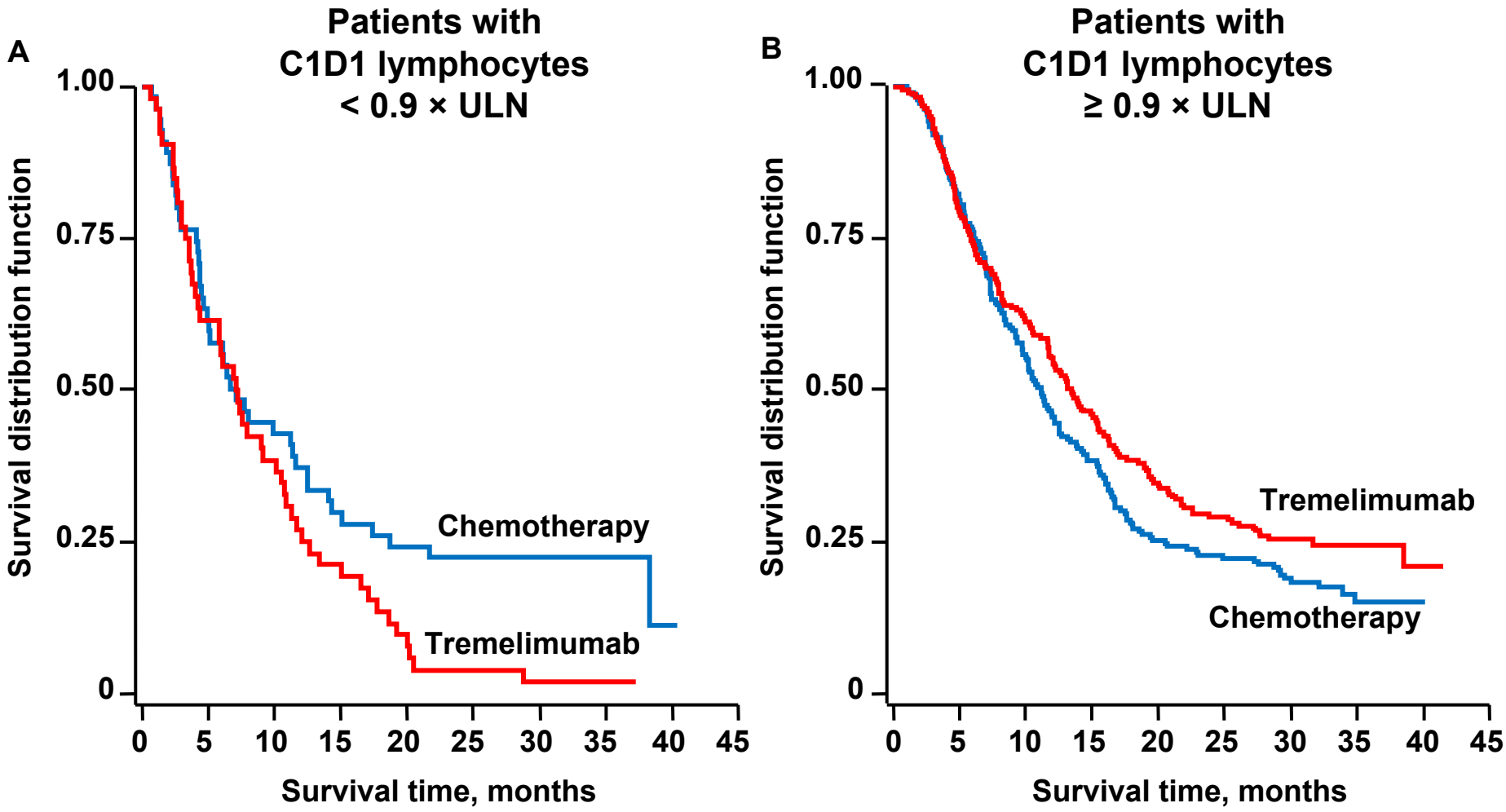
Survival by Baseline Lymphocytes Subset



Data from May 2010.

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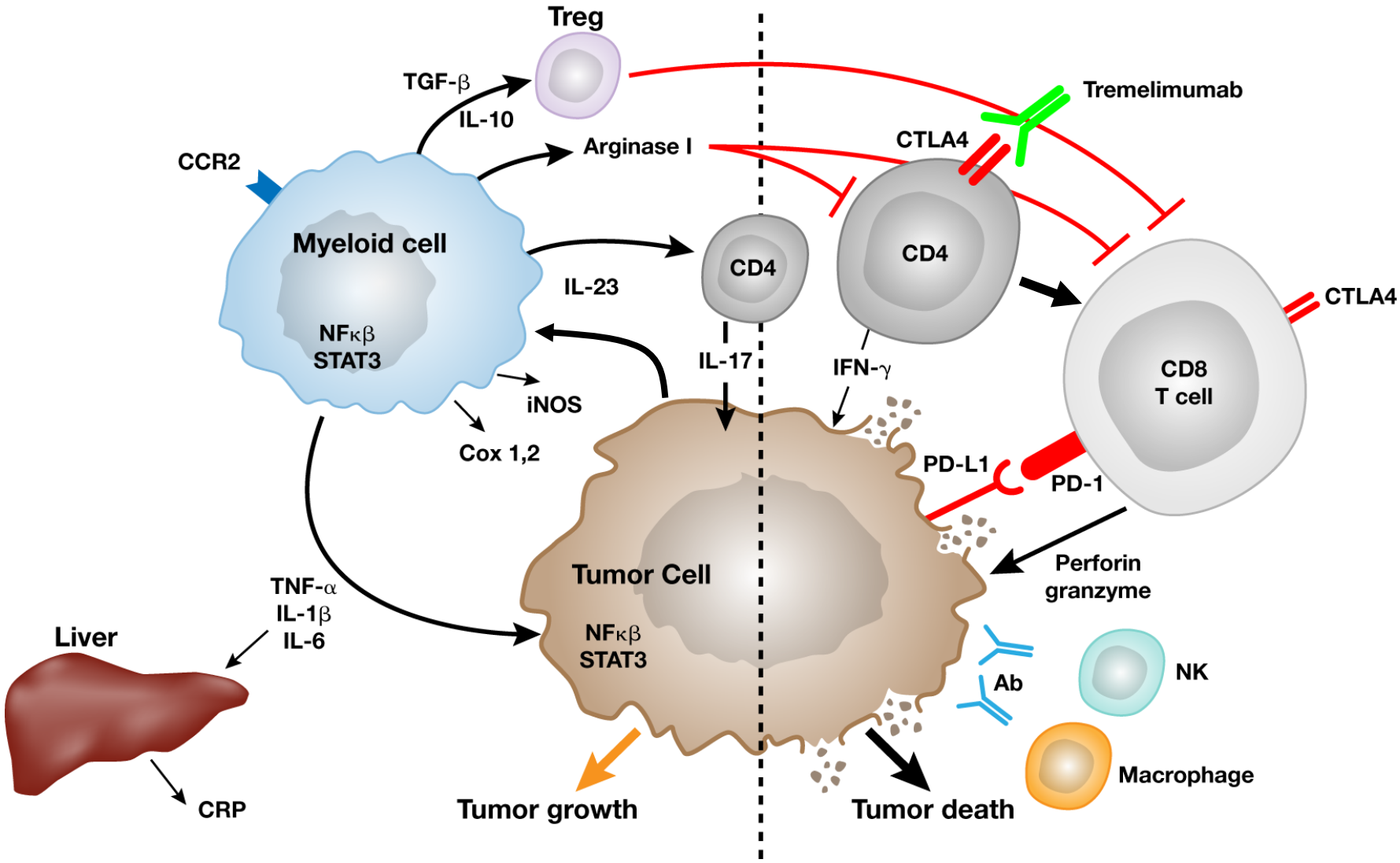
Treatment-Related Adverse Events (AEs)[a]

Patients	Tremelimumab, n (%)	Chemotherapy, n (%)
Evaluable for AEs	325	319
With grade 3 or 4 AEs	110 (33.8)	74 (23.2)
With serious adverse events	80 (24.6)	16 (5.0)
With grade 5 AEs	6 (1.8)	1 (0.3)
Discontinued because of AEs	39 (12.0)	8 (2.5)

[a]Data from September 2010.

Balancing Inflammation and Immunity in the Tumor Microenvironment



Tremelimumab Study A3671009
Conclusions

- Tremelimumab compared with chemotherapy resulted in a nonsignificant (P = 0.127) improvement in survival of patients with metastatic melanoma treated at first line

- The duration of first objective tumor responses to tremelimumab was significantly longer than responses to chemotherapy

- A low baseline CRP and a baseline absolute lymphocyte count in the normal range selected for a patient population with higher tumor response rate and better survival outcome with tremelimumab compared with chemotherapy
  - This may reflect an interaction between the tumor microenvironment, tumor inflammation, and an adaptive immune response

Acknowledgments

Pfizer GRD New London
J Gomez-Navarro (clinical lead)
M Marshall (study lead clinician)
D Pavlov (statistician)
Bo Huang (statistician)
P Carlson (study manager)
M Song (clinical protocol manager)

Christie Hosp
P Lorigan
Mount Vernon Hosp
P Nathan
Newcastle Ge'rl Hosp
E Plummer

U St. Radbound
CJA Punt
Netherlands Nat'l Cancer Inst
JBAG Haanen

U Tuebingen
C Garbe
U Kiel
A Hauschild
Charité-U Medicine Berlin
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Maria Sklodowska-Curie Mem Inst
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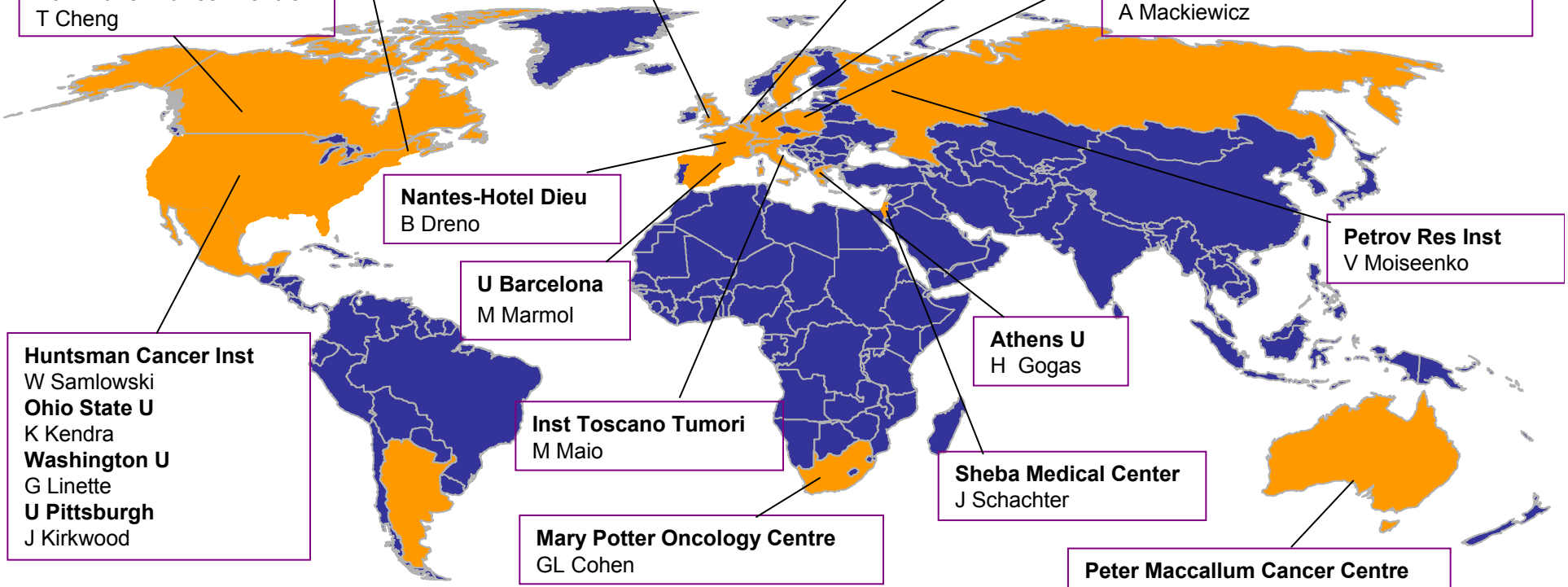
Great Poland Cancer Center
A Mackiewicz



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Patients, families, and caregivers from 24 countries

Listed are the 24 highest enrolling sites out of 114 sites open to patient accrual

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