THE LANCET

Supplementary appendix

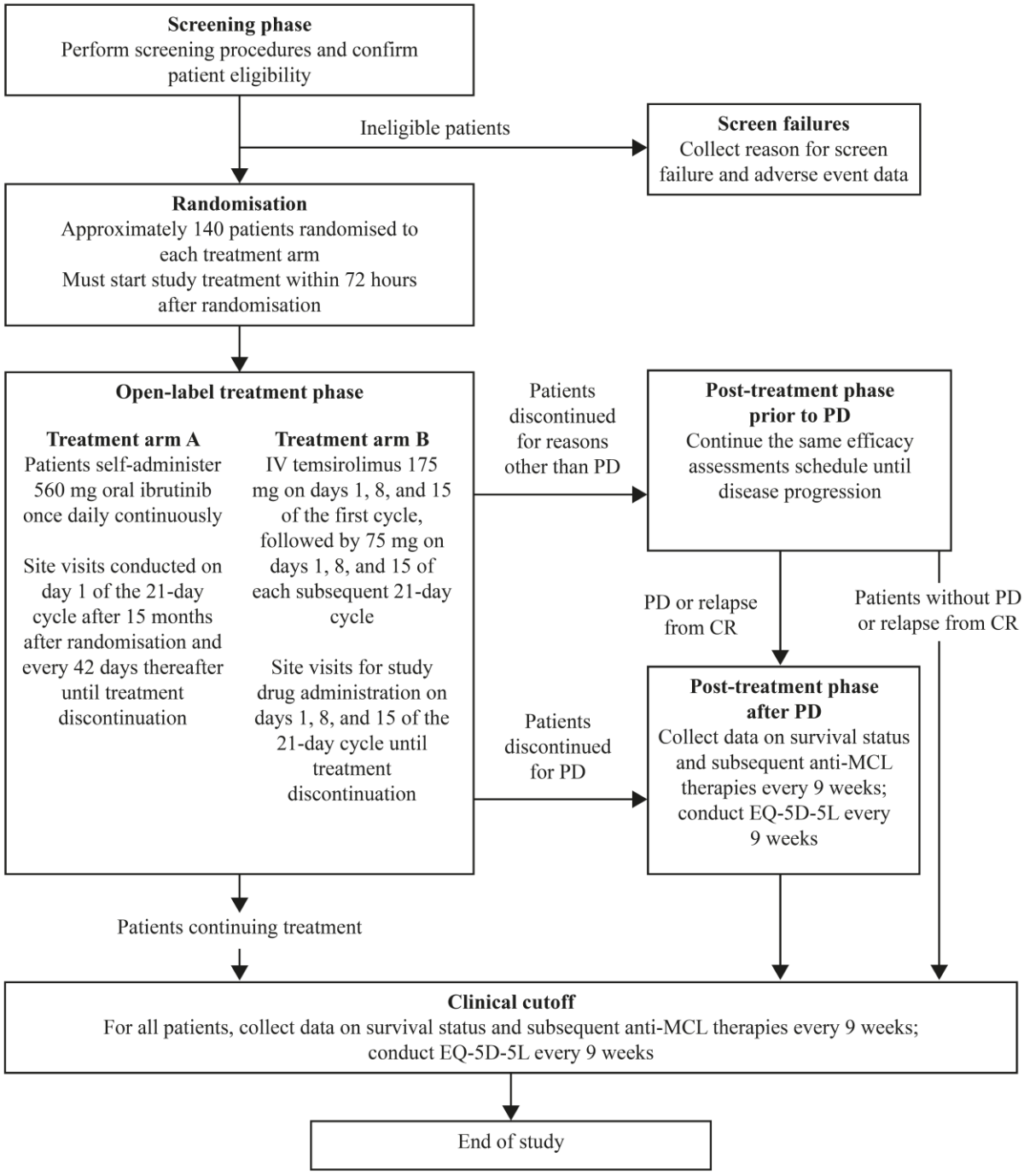
This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Dreyling M, Jurczak W, Jerkeman M, et al. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study. *Lancet* 2015; published online Dec 7. http://dx.doi.org/10.1016/S0140-6736(15)00667-4.

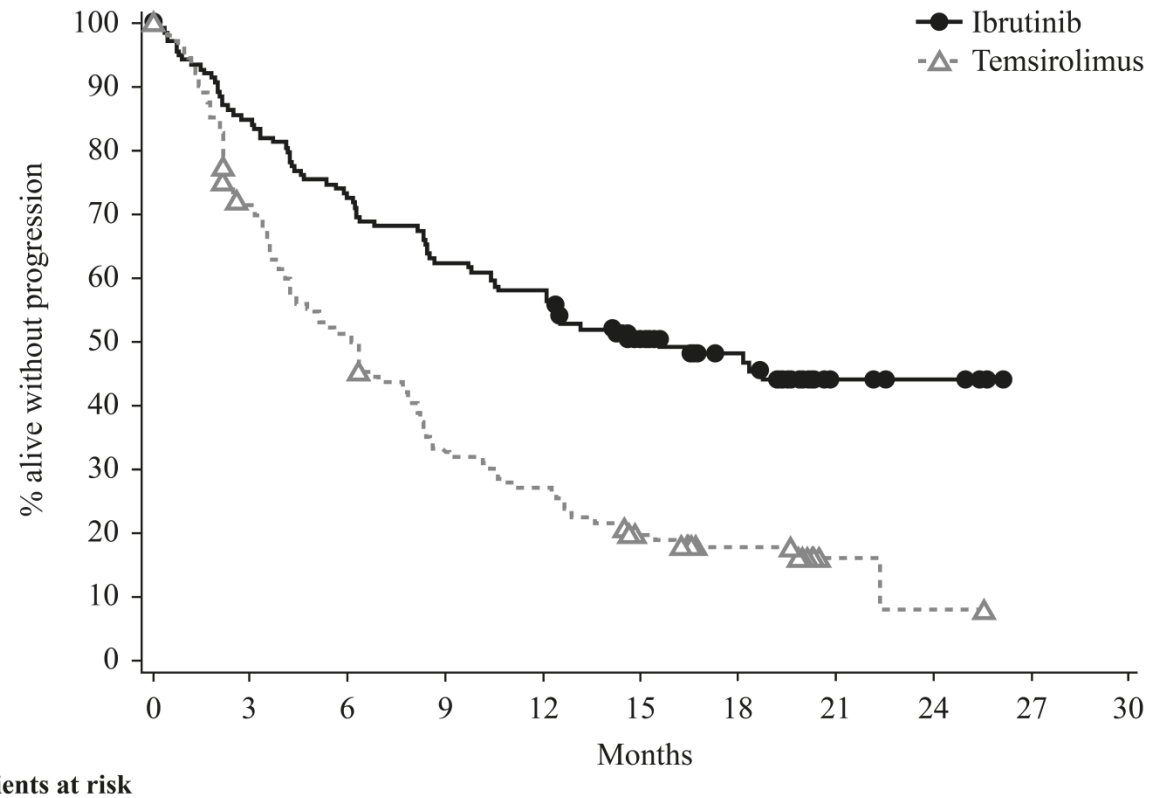
Web extra material

Supplementary Figure 1: **Study design schema**

PD=progressive disease. CR=complete response. MCL=mantle-cell lymphoma.



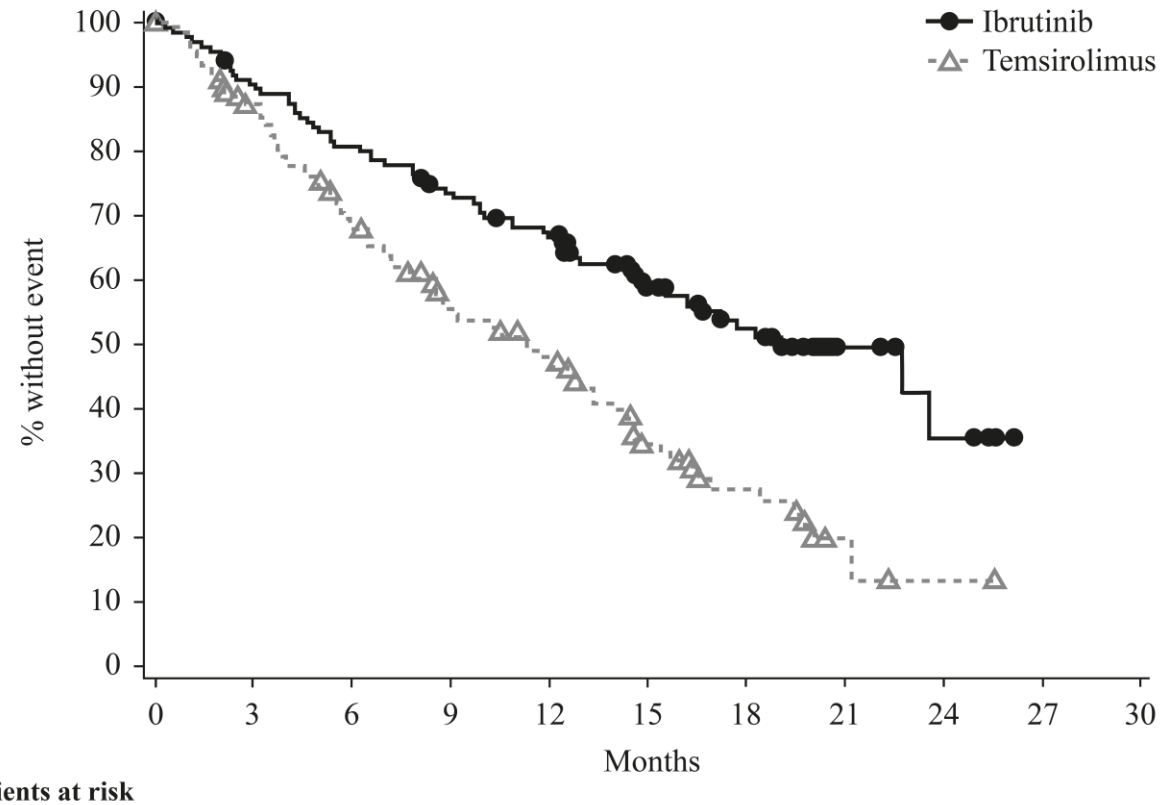
Supplementary Figure 2: **Progression-free survival by investigator**



Patients at risk

Ibrutinib	139	117	100	86	80	48	36	8	5	0	0
Temsirolimus	141	93	67	41	34	20	12	2	1	0	0

Supplementary Figure 3: **Progression-free survival 2 (PFS2)**



Patients at risk

Ibrutinib	139	123	110	98	88	54	38	10	5	0	0
Temsirolimus	141	109	84	60	49	28	16	3	1	0	0

Supplementary Table 1: **Extent of exposure**

	Ibrutinib	**Temsirolimus**
Analysis set: safety	n=139	n=139
Treatment duration (months)		
Median	14·39	3·02
Range	(0·0–28·2)	(0·0–27·0)
Total number of cycles		
Median	21·0	5·0
Range	(1–41)	(1–40)
Relative dose intensity (%)		
Median	99·85	81·82
Range	(30·3–100·0)	(30·0–100·0)
≥90%, n (%)	124 (89·2)	51 (36·7)

Percentages calculated with the number of patients in safety analysis set as denominator.

Supplementary Table 2: **Covariate-adjusted analysis for progression-free survival by independent review committee assessment**

	HR	95% CI for HR	p value
Treatment (ibrutinib *vs* temsirolimus)	0·41	(0·30–0·57)	<0·0001
Sex (male *vs* female)	0·82	(0·57–1·18)	0·2812
Age group (≥65 *vs* <65 years)	1·08	(0·74–1·58)	0·6713
Race (Caucasian *vs* non-Caucasian)	1·05	(0·57–1·93)	0·8808
Baseline ECOG PS (1 *vs* 0)	1·56	(1·13–2·16)	0·0069
Region (Europe *vs* non-Europe)	0·84	(0·53–1·34)	0·4688
Baseline extranodal disease (yes *vs* no)	0·91	(0·62–1·33)	0·6225
MIPI score (intermediate *vs* low)*	1·36	(0·90–2·03)	0·1400
MIPI score (high *vs* low)*	2·51	(1·55–4·07)	0·0002
Prior lines of therapy (≥3 *vs* <3)*	1·58	(1·14–2·19)	0·0066
Stage of disease (IV *vs* I-III)	1·08	(0·61–1·91)	0·7902
Prior bortezomib (yes *vs* no)	1·03	(0·70–1·53)	0·8641
Tumour bulk (≥5 *vs* <5 cm)	0·96	(0·66–1·40)	0·8309
Tumour burden	1·00	(1·00–1·00)	0·8147
Histology (blastoid *vs* non-blastoid)	2·49	(1·60–3·86)	<0·0001
Refractory disease (yes *vs* no)	1·21	(0·86–1·71)	0·2680
Bone marrow involvement (yes *vs* no)	0·96	(0·67–1·40)	0·8509

HR=hazard ratio. CI=confidence interval. ECOG PS=Eastern Cooperative Oncology Group performance status. MIPI=mantle-cell lymphoma international prognostic index. *From interactive web response system (IWRS) assignment.

Supplementary Table 3: **Sensitivity analysis using PFS by investigator**

PFS analysis / population	Median PFS (months)		Hazard ratio (95% CI)	p value
	Ibrutinib (95% CI)	Temsirolimus (95% CI)		
IRC-determined date of progression / ITT population (stratified log-rank test)*	14·6 (10·4–NE)	6·2 (4·2–7·9)	0·43 (0·32–0·58)	<0·0001
IRC-determined date of progression / ITT population (unstratified log-rank test)	14·6 (10·4–NE)	6·2 (4·2–7·9)	0·43 (0·32–0·58)	<0·0001
IRC determined date of progression censored at last disease assessment date prior to subsequent therapy / ITT population	18·3 (11·8–NE)	6·2 (4·4–8·3)	0·42 (0·30–0·57)	<0·0001
Investigator-determined date of progression / ITT population	15·6 (10·6–NE)	6·2 (4·2–7·8)	0·43 (0·32–0·58)	<0·0001

PFS=progression-free survival. CI=confidence interval. IRC= independent review committee. ITT=intent-to-treat. NE=not estimable. Hazard ratio is ibrutinib arm/temsirolimus arm. *Primary efficacy endpoint.

Supplementary Table 4: **Duration of response by IRC assessment**

	Ibrutinib	**Temsirolimus**
Analysis set: intent-to-treat	139	141
Responder (complete response or partial response)	100	57
Progressed or died (event)	39 (39·0%)	42 (73·7%)
Censored	61 (61·0%)	15 (26·3%)
Duration of response (months)*		
25% quantile (95% CI)	7·9 (4·7–12·4)	4·0 (2·1–5·1)
Median (95% CI)	NE (16·2–NE)	7·0 (4·2–9·9)
75% quantile (95% CI)	NE (NE–NE)	14·9 (9·5–23·5)
6-month DOR rate (95% CI)	0·83 (0·74–0·89)	0·60 (0·46–0·72)
12-month DOR rate (95% CI)	0·69 (0·59–0·77)	0·26 (0·15–0·38)
18-month DOR rate (95% CI)	0·58 (0·46–0·68)	0·20 (0·09–0·35)
24-months DOR rate (95% CI)	0·51 (0·35–0·65)	0·00 (NE–NE)

*Duration of response was derived for patients who achieved complete response or partial response.

Supplementary Table 5: **Subsequent antineoplastic therapy commonly used (≥2% of patients)**

	Ibrutinib	**Temsirolimus**
Analysis set: intent-to-treat	n=139	n=141
Antineoplastic systemic therapy	44 (31·7)	82 (58·2)
Rituximab	21 (15·1)	36 (25·5)
Bendamustine	15 (10·8)	22 (15·6)
Cyclophosphamide	12 (8·6)	19 (13·5)
Cytarabine	10 (7·2)	16 (11·3)
Dexamethasone	9 (6·5)	17 (12·1)
Prednisolone	8 (5·8)	7 (5·0)
Etoposide	7 (5·0)	12 (8·5)
Vincristine	5 (3·6)	6 (4·3)
Bortezomib	4 (2·9)	13 (9·2)
Doxorubicin	4 (2·9)	3 (2·1)
Temsirolimus	4 (2·9)	0
Cisplatin	3 (2·2)	4 (2·8)
Lenalidomide	3 (2·2)	5 (3·5)
Fludarabine	2 (1·4)	5 (3·5)
Mitoxantrone	2 (1·4)	3 (2·1)
Prednisone	2 (1·4)	5 (3·5)
Investigational drug	1 (0·7)	5 (3·5)
Melphalan	1 (0·7)	3 (2·1)
Methylprednisolone	1 (0·7)	5 (3·5)
Chlorambucil	0	3 (2·1)
Ibrutinib	0	32 (22·7)
Ifosfamide	0	4 (2·8)
Stem cell transplant	1 (0·7)	4 (2·8)

Values are n (%). Percentages calculated with the number of patients in the intent-to-treat analysis set as the denominator.

Supplementary Table 6: **Exposure-adjusted rates of major bleeding and atrial fibrillation**

	Ibrutinib			Temsirolimus		
	n	100 PMR*	EAIR†	N	100 PMR*	EAIR†
Safety analysis set	139			139		
Major bleeding (AE of special interest)						
Any grade	14	17·8	0·786	9	8·4	1·077
Grade ≥3	11	18·1	0·608	7	8·4	0·838
Atrial fibrillation (AE of heightened clinical interest)						
Any grade	6	17·8	0·337	3	8·4	0·358
Grade ≥3	5	17·9	0·280	2	8·4	0·239

PMR=patient-months at risk. EAIR=exposure-adjusted incidence rate. *PMR is the sum of the exposure times at the occurrence of the first TEAE for each subject. A patient's duration of exposure is given either by the time when the event has occurred (non-censored data) or by the total duration of treatment if the patient does not show the adverse event in question (censored data). †EAIR represents the number of subjects with the event divided by 100 PMR for that event. If a patient has multiple occurrences of an event, the patient is counted only once in the numerator.

Appendix A: Inclusion/exclusion criteria

Inclusion Criteria

Key inclusion criteria for the study were:

- Aged ≥18 years
- Diagnosis of MCL reviewed and approved by central pathology laboratory prior to randomisation
  - Diagnosis report from local laboratory must include morphology and expression of either cyclin D1 in association with one B-cell marker (eg, CD19, CD20, or PAX5) and CD5 or evidence of t(11;14) as assessed by cytogenetics, fluorescent in situ hybridisation, or polymerase chain reaction
  - If report from local laboratory is not available, diagnosis must be confirmed by central pathology laboratory based on the criteria above
- Received at least one prior rituximab-containing chemotherapy regimen (separate lines of therapy are defined as single or combination therapies that are either separated by disease progression or by a >6-month treatment-free interval)
- Documented relapse or disease progression following the last anti-MCL treatment
- ECOG performance status 0 or 1
- Haematology values within the following limits:
  - Absolute neutrophil count ≥1000/mm^3 independent of growth factor support
  - Platelet count ≥75 000/mm^3 or ≥50 000/mm^3 if bone marrow involvement independent of transfusion support
  - Haemoglobin level ≥8 g/dL, independent of transfusion support
- Biochemical values within the following limits:
  - Alanine aminotransferase and aspartate aminotransferase ≤3 × upper limit of normal (ULN)
  - Total bilirubin ≤1·5 × ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)
  - Serum creatinine ≤2 × ULN
  - Fasting serum cholesterol level ≤350 mg/dL
  - Fasting serum triglyceride level ≤400 mg/dL
- After protocol amendment 2 (July 2014), patients who received treatment with temsirolimus and had IRC-confirmed disease progression were eligible to cross over and receive ibrutinib treatment until disease progression, unacceptable toxicity, or study end

Exclusion Criteria

Patients were not to be enrolled into the study if upon pre-study screening they met any of the following key exclusion criteria:

- Received prior nitrosoureas within 6 weeks, chemotherapy within 3 weeks, therapeutic anticancer antibodies within 4 weeks, radio- or toxin-immunoconjugates within 10 weeks, radiation therapy or other investigational agents within 3 weeks, or major surgery within 4 weeks of randomisation
- Received prior treatment with temsirolimus, other mTOR inhibitors, ibrutinib, or other BTK inhibitors
- Had central nervous system lymphoma
- Had a history of stroke or intracranial haemorrhage within 6 months prior to first dose of study drug
- Required anticoagulation with warfarin or equivalent vitamin K antagonists or treatment with a strong CYP3A4/5 inhibitor
- Had a known history of human immunodeficiency virus, active infection with hepatitis C virus or hepatitis B virus, or any uncontrolled active systemic infection that required IV antibiotics

Appendix B: List of investigators

North America

Canada: S Assouline, A Fontaine, R Sangha, R Klasa, I Bence-Bruckler

Europe

Belgium: G Verhoef, F Offner, A Van Hoof, E Van Den Neste, J Lemmens, K L Wu, A Van de Velde

Czech Republic: J Mayer, J Novak, M Trneny

France: O Hermine, C Thieblemont, M Ojeda-Uribe, V Ribrag, K Bouabdallah, O Casasnovas, S LeGouill

Germany: M Dreyling, S Stilgenbauer, J Duerig, K Hübel, G Hess, M Kneba, C Pott, G Lenz, A Pezzutto, M Sökler, E Spaeth-Schwalbe, M Topp, M Witzens-Harig, C Scholz, W Brugger, M Pfreundschuh

Hungary: M David, A Szomor, J Demeter, A Illes, A Rosta, Z Borbenyi

Ireland: E Vandenberghe

Italy: U Vitolo, P Zinzani, AM Carella, E Morra, C Rusconi, F Zallio, M Maurizio, M Federico, C Visco

Netherlands: J Zijlstra, P Lugtenburg

Poland: S Grosicki, K Kuliczkowski, A Pluta, S Radwanski, H Hellmann, D Woszczyk, W Homenda, W Jurczak

*Portuga*l: J Raposo, R Alvarez, C Joao, M Gomes, JM Mariz, H Marques

Russia: N Khuazheva, T Shneider, E Osmanov, O Samoilova, S Voloshin, G Manikhas, V Pavlov, I Lysenko, O Serduk, N Fadeeva, O Gladkov, I Bulavina, D Udovitsa, A Proydakov

Spain: D Caballero, A Lopez, R Arranz, RJA Hernandez, RA Oriol, GA Lopez, MJ Terol, LJ Bargay, E Gonzalez-Barca

Sweden: M Jerkeman, M Sender, M Erlanson, A Laurell, E Kimby

Ukraine: E Karamanesht, G Rekhtman, Z Masliak, H Pylypenko, K Vilchevskaya, P Kaplan, I Dyagil

United Kingdom: P Johnson, J Radford, A Pettitt, R Johnson, K Ardeshna, R Auer, S Montoto, R Malladi, N Panoskaltsis, S Rule

Latin America

Brazil: R Santucci, J Pereira, L Viola, M Capra, A Scheliga, E Rego, R Tavares

Chile: M Rodriguez, C Salvo, M Capurro, M Sarmiento

Colombia: G Quintero, K Galvez, M Gomez

Mexico: D Gomez, E Ramirez, M Gonzalez

Asia

South Korea: C Suh, DH Yoon, SJ Kim, SG Cho, JW Cheong, HS Eom

Taiwan: BS Ko, YC Chen, CY Liu, YB Yu, PN Wang, TY Chen