Supplemental Data

The Influence of Anemia on Clinical Outcomes in Venous Thromboembolism: Results from GARFIELD-VTE

Shinya Goto, MD, PhD1, Alexander GG Turpie, MD2, Alfredo E. Farjat, PhD3, Jeffrey I. Weitz, MD4, Sylvia Haas, MD, PhD5, Walter Ageno, MD6, Samuel Z. Goldhaber, MD7, Pantep Angchaisuksiri, MD8, Gloria Kayani9, Peter MacCallum, MD10, Sebastian Schellong, MD11, Henri Bounameaux, MD12, Lorenzo G Mantovani, DSc13, 14, Paolo Prandoni, PhD15,Ajay K Kakkar, PhD16 on behalf of the GARFIELD-VTE investigators

1Shinya Goto, Department of Medicine (Cardiology), Tokai University School of Medicine, Japan

2Alexander GG Turpie, McMaster University, Hamilton, Canada

3Alfredo E. Farjat, Thrombosis Research Institute, London, United Kingdom

4Jeffrey I. Weitz, McMaster University and the Thrombosis and Atherosclerosis Research Institute, Hamilton, Ontario, Canada

5Sylvia Haas, Formerly Technical University of Munich, Munich, Germany

6Walter Ageno, Department of Medicine and Surgery, University of Insubria, Varese, Italy

7Samuel Z. Goldhaber, Harvard Medical School, Boston, USA

8Pantep Angchaisuksiri, Department of Medicine, Ramathibodi Hospital, Mahidol University, Thailand

9Gloria Kayani, Thrombosis Research Institute, London, United Kingdom

10Peter MacCallum, Thrombosis Research Institute, London, United Kingdom

11Sebastian Schellong, Medical Department 2, Municipal Hospital Dresden, Germany

12Henri Bounameaux, Faculty of Medicine, University of Geneva, Switzerland

13Lorenzo G Mantovani, IRCCS Multimedica, Milan, Italy;

14University of Milano, Bicocca, Milan, Italy

15Paolo Prandoni, Arianna Foundation on Anticoagulation, Bologna, Italy

16Ajay K. Kakkar, University College London, London, United Kingdom

Corresponding Author:

Professor Shinya Goto, M.D, Ph.D. Department of Medicine (Cardiology), Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan;

Email: [shinichi@is.icc.u-tokai.ac.jp](mailto:shinichi@is.icc.u-tokai.ac.jp); Phone: +81-463-93-1121

Supplemental Table S1. Confounders for adjusted hazard ratios

|  |  |
| --- | --- |
| **Outcome** | **Confounders** |
| **Mortality** | Age, sex, ethnicity, BMI, VTE type, smoking, creatinine serum, cancer, chronic heart failure, acute medical illness, surgery, chronic immobilization, history of cancer, and anticoagulation treatment. |
| **Recurrent VTE** | Age, sex, ethnicity, BMI, VTE type, smoking, creatinine serum, cancer, acute medical illness, surgery, family history of VTE, oral contraception, and anticoagulation treatment. |
| **Major bleeding** | Age, sex, ethnicity, BMI, VTE type, smoking, creatinine serum, cancer, acute medical illness, chronic immobilization, history of cancer, and anticoagulation treatment. |
| **Any bleeding** | Age, sex, ethnicity, BMI, VTE type, smoking, creatinine serum, cancer, chronic heart failure, acute medical illness, surgery, chronic immobilization, history of cancer, and anticoagulation treatment. |
| **Cancer** | Age, sex, ethnicity, BMI, VTE type, smoking, creatinine serum, cancer, history of cancer, and anticoagulation treatment. |
| **MI/ACS** | Age, sex, ethnicity, BMI, VTE type, smoking, creatinine serum, cancer, and anticoagulation treatment. |
| **Stroke/TIA** | Age, sex, ethnicity, BMI, VTE type, smoking, creatinine serum, cancer, and anticoagulation treatment. |

Supplemental Table S2. Hemoglobin by anemia status Mild/Moderate vs Severe

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| --- | --- | --- |
|  | **Mild/Moderate (N=1958)** | **Severe (N=813)** |
| **Haemoglobin [g/dL], median (IQR)** | 11.3 (10.7, 11.9) | 8.9 (8.0, 9.4) |
| **Haemoglobin categories [g/dL]** |  |  |
| **Low (males: <13·0; females: <12·0)** | 1958 (100.0%) | 813 (100.0%) |

Supplemental Table S3. Daily dosages of DOACs according to anticoagulant type

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **OAC Type,**  **n (%)** | |  | **Daily Dose of OAC (mg)** | | | | | | | | | | | | | |
|  |  | | 2.5 | 5 | 10 | 15 | 20 | 30 | 40 | 60 | 75 | 110 | 150 | 220 | 330 |
| **Apixaban** | Anemia (n=2,771) | | 0 (0.0) | 12 (1.2) | 74 (7.1) | 0 (0.0) | 65 (6.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| No-anemia (n=4,927) | | 1 (0.0) | 17 (0.7) | 128 (5.0) | 0 (0.0) | 198 (7.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Dabigatran** | Anemia (n=2,771) | | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.2) | 3 (0.3) | 1 (0.1) | 11 (1.1) | 48 (4.6) |
| No-anemia (n=4,927) | | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.0) | 1 (0.0) | 11 (0.4) | 124 (4.8) |
| **Edoxaban** | Anemia (n=2,771) | | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (0.3) | 0 (0.0) | 14 (1.3) | 0 (0.0) | 10 (1.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| No-anemia (n=4,927) | | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.1) | 0 (0.0) | 10 (0.4) | 0 (0.0) | 26 (1.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Rivaroxaban** | Anemia (n=2,771) | | 0 (0.0) | 0 (0.0) | 23 (2.2) | 57 (5.5) | 228 (22.0) | 482 (46.4) | 4 (0.4) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| No-anemia (n=4,927) | | 0 (0.0) | 0 (0.0) | 17 (0.7) | 77 (3.0) | 358 (13.9) | 1,595 (61.8) | 15 (0.6) | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

Supplemental Table S4. Rate of major bleeding per 100 person years in VTE patients with anemia by treatment type

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Mild-Moderate Anemia**  **(n=1,962)** | | | **Severe Anemia**  **(n=817)** | | |
| **Treatment** | **No. of patients** | **Events** | **Rate % (95% CI)** | **No. of patients** | **Events** | **Rate % (95% CI)** |
| **Parenteral therapy** | 469 | 35 | 5.28 (3.79-7.36) | 255 | 21 | 7.01 (4.57-10.75) |
| **VKA** | 596 | 23 | 2.34 (1.56-3.53) | 255 | 29 | 8.21 (5.71-11.82) |
| **NOAC** | 789 | 27 | 1.96 (1.34-2.86) | 258 | 20 | 5.16 (3.33-8.00) |

Supplemental Table S5. Sites of major and non-major bleeds in anemia and no-anemia VTE patients

|  |  |  |
| --- | --- | --- |
| Site of bleed, n (%) | Anemia (n = 164) | No-anemia (n = 84) |
| Intra-Spinal | 1 (0·6) | 3 (3·6) |
| Subconjuctival | 0 (0·0) | 0 (0·0) |
| Intra-ocular/Retinal | 3 (1·9) | 5 (6·0) |
| GI upper | 28 (17·1) | 9 (10·7) |
| GI lower | 29 (17·7) | 11 (13·1) |
| Macroscopic haematuria | 11 (6·7) | 5 (6·0) |
| Abnormal uterine (metorrhagia and menorrhagia) | 21 (12.8) | 9 (10·5) |
| Intra-articular | 0 (0·0) | 0 (0·0) |
| Intra-muscular (no compartment syndrome) | 4 (2·4) | 3 (3·6) |
| Intra-muscular (with compartment syndrome) | 2 (1·2) | 1 (1·2) |
| Epistaxis | 1 (0·6) | 2 (2·4) |
| Gingival | 2 (1·2) | 0 (0·0) |
| Intra-peritoneal | 4 (2·4) | 0 (0·0) |
| Retro-peritoneal | 7 (4·3) | 2 (2·4) |
| Puncture site | 1 (0·6) | 0 (0·0) |
| Skin (Ecchymosis other than instrument site) | 1 (0·6) | 1 (1·2) |
| Haemoptysis | 4 (2·4) | 3 (3·6) |
| Haemopericardium | 0 (0·0) | 3 (3·6) |
| Haemothorax | 2 (1·2) | 0 (0·0) |
| Hemorrhagic stroke | 7 (4·3) | 8 (9·5) |
| Other | 27 (16·5) | 16 (19·0) |
| Unknown | 9 (5·5) | 3 (3·6) |

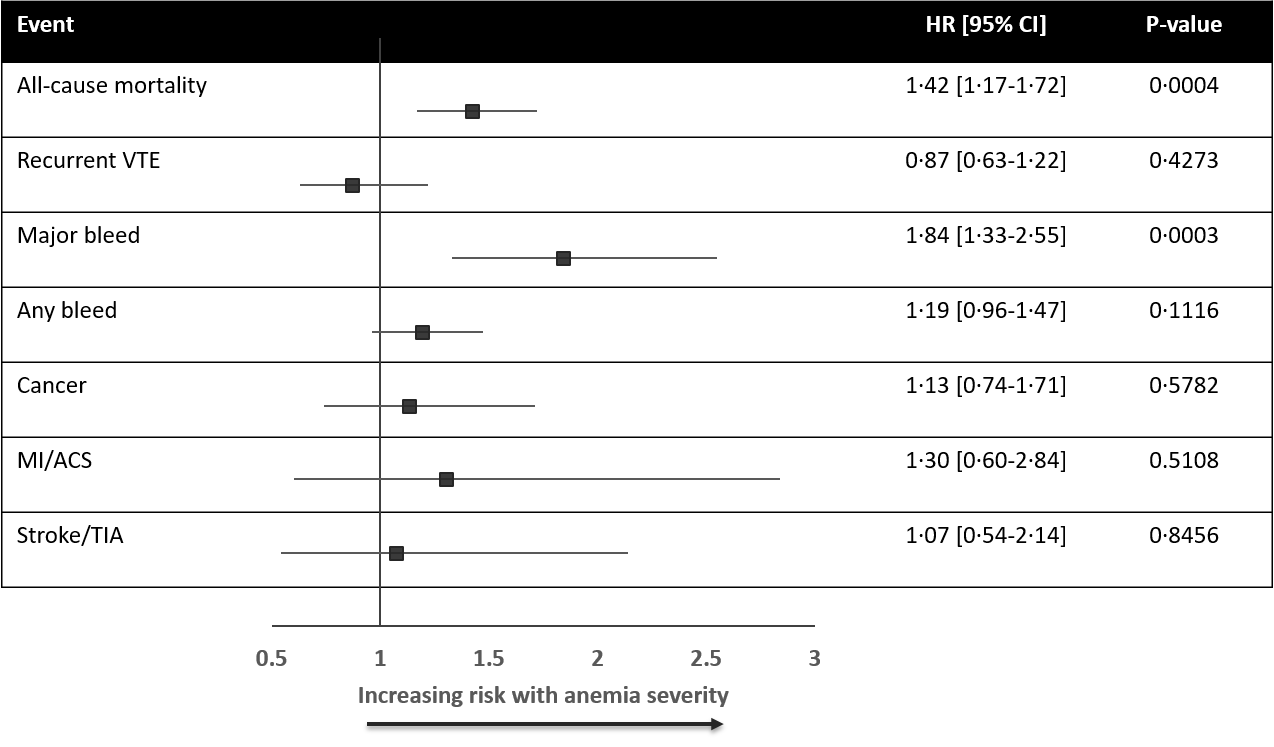
Supplemental table S6. Cause of death over 24-months follow-up

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| --- | --- | --- |
| Cause of death, n (%) | Anemia (n = 488) | No-anemia (n = 247) |
| Stroke | 12 (2·5) | 4 (1·6) |
| Cardiac | 35 (7·2) | 22 (8·9) |
| Cancer-related | 270 (55·3) | 117 (47·4) |
| Bleed | 7 (1·4) | 3 (1·2) |
| VTE | 13 (2·6) | 9 (3·6) |
| Other | 88 (18·0) | 46 (18·6) |
| Unknown | 63 (12·9) | 46 (18·6) |

Supplemental Table S7. Unadjusted 24-month clinical outcomes after VTE diagnosis in patients with mild/moderate anemia and severe anemia. Event rates are shown per 100 person-years (95% confidence interval). CI; confidence interval, VTE; venous thromboembolism, MI; myocardial infarction, ACS; acute coronary syndrome, TIA; transient ischemic attack.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Outcome |  | Mild/moderate anemia  (n = 1,958) |  | Severe anemia  (n = 813) |
| Event | n | Event rate (95% CI) | n | Event rate (95% CI) |
| All-cause mortality | 289 | 8·85 (7·89 to 9·94) | 199 | 17·10 (14·88 to 19·65) |
| Recurrent VTE | 144 | 4·64 (3·94 to 5·46) | 15 | 4·66 (3·54 to 6·13) |
| Major bleed | 91 | 2·86 (2·33 to 3·51) | 73 | 6·66 (5·30 to 8·38) |
| Any bleed | 287 | 9·80 (8·73 to 11·00) | 138 | 13·61 (11·51 to 16·08) |
| MI/ACS | 24 | 0·74 (0·50 to 1·11) | 10 | 0·87 (0·47 to 1·61) |
| Stroke/TIA | 33 | 1·02 (0·72 to 1·43) | 12 | 1·04 (0·59 to 1·82) |

Supplemental Figure S1. Adjusted hazard ratios for mortality with 95% CIs for 24-month outcomes after VTE diagnosis between patients with mild/moderate anemia (reference group) and severe anemia. Event rates are shown per 100 person-years. Abbreviations: VTE; venous thromboembolism, TIA; transient ischemic attack, MI; myocardial infarction, ACS; acute coronary syndrome, HR; hazard ratio, CI; confidence interval.



**A full list of GARFIELD-VTE Principal Investigators**

Ab Loualidi, Abbey Wilcox, Abdul Parwani, Abdurrahim Colak, Abraham Bezuidenhout, Abu, Abdool-Carrim, Addala Azeddine, Adriaan Beyers, Adriaan Dees, Ahmed Mohamed, Ahmet Aksoy, Akihiko,Abiko, Akinori Watanabe, Alan Krichell, Alberto Alfredo Fernandez, Alberto Tosetto, Alexander Tsaregorodtsev, Alexey Khotuntsov, Alisha Oropallo, Alison Slocombe, Allan Kelly, Amanda Clark, Amr Gad, Amy Arouni, Andor Schmidt, Andrea Berni, Andrei D. Vishniagov, Andres Javier Kleiban, Andrew Machowski, Andrew Rapule Ratsela, Andrey Kazakov, Andrey L. Komarov, Angel Galvez, Ann Lockman, Anna Falanga, Anoop Chauhan, Antoni Riera-Mestre, Antonino Mazzone, Armando D'Angelo, Artur Herdy, Atsushi Kato, Attilia Pizzini, Ayman Abd Elhamid, Ebrahim Mahmoud Salem, Azlan Husin, Barbara Erdelyi, Barry Jacobson, Beatrice Amann-Vesti, Bektas Battaloglu, Benedicte Wilson, Benilde Cosmi, Bergmann Jean Francois, Berremeli Toufek, Beverley Hunt, Bhavesh Natha, Binali Mavitaş, Bisher Mustafa, Bonnie Chi Shan Kho, Boulon Carine, Brian Zidel, Brisot Dominique, Brousse Christophe, Bruno Trimarco, Canhua Luo, Carlos Alberto Cuneo, Carlos Jerjes Sanchez Diaz, Carsten Schwencke, Cas Cader, Celal Yavuz, Cesar, Javier Zaidman, Charles Lunn, Charlotte Bomken, Chau-Chung Wu, Cheng Hock Toh, Chern-En Chiang, Chevrier Elisa, Chien-Hsun Hsia, Chien-Lung Huang, Chi-Hang Kevin Kwok, Chih-Cheng Wu, Chi-Hung Huang, Chooi Kheng Chiew, Chris Ward, Christian Opitz, Christina Jeanneret-Gris, Chung Yin Ha, Chun-Yao Huang, Claude Luyeye Bidi, Clifford Smith, Cornelia Brauer, Corrado Lodigiani, Couturaud Francis, Cynthia Wu, Daniel Theodoro, Daniel Staub, Daniela Poli, David Keeling, David - Riesco Acevedo, David Scott, David Adler, David Jimenez, Davide Imberti, Desmond Creagh, Desmurs-Clavel Helene, Dirk Hagemann, Dirk Le Roux, Dirk Skowasch, Dmitry Belenky, Dmitry Dorokhov, Dmitry Petrov, Dmitry Zateyshchikov, Domenico Prisco, Dorthe Møller, Dr. Bárbara Pagán, Dusan Kucera, Ehab M. Esheiba, Elena Kochmareva, Elena N. Dankovtseva, Elizaveta Panchenko, Elkouri Dominique, Emre Dogan, Emre Kubat, Enrique Diaz Diaz, Eric Wai Choi Tse, Erik Yeo, Erman Hashas, Ernst Grochenig, Eros Tiraferri, Erwin Blessing, Escande Orthlieb Michèle, Esther Usandizaga, Ettore Porreca, Eva Lichnerova, Fabian Ferroni, Falvo Nicolas, Félix Ayala-Paredes, Fitjerald Henry, Franco Cosmi, Frans Erdkamp, Frederic Baumann, Gadel Kamalov, Gaetano Paparella, Garcia-Bragado Dalmau, Garrigues Damien, Garry Klein, Gaurand Shah, Geert Hollanders, Geno Merli, Georg Plassmann, George Platt, Georgy V. Smirnov, Germain Poirier, German Sokurenko, Ghassan Haddad, Gholam Ali, Giancarlo Agnelli, Gin Gin Gan, Grace Kaye-Eddie, Gregoire Le Gal, Gregory Allen, Guillermo Antonio Llamas Esperón, Guillot Jean-Paul, Hagen Gerofke, Hallah Elali, Hana Burianova, Hans-Juergen Ohler, Haofu Wang, Harald Darius, Harinder S. Gogia, Harry Striekwold, Harry Gibbs, Hatice Hasanoglu, Hatice Turker, Hendrik Franow, Henri Bounameaux, Herbert De Raedt, Herman Schroe, Herman Sung Yu Liu, Hesham Salah ElDin, Hesham Zidan, Hiroaki Nakamura, Ho Young Kim, Holger Lawall, Hong Zhu, Hongyan Tian, Ho-Young Yhim, Hugo ten Cate, Hun Gyu Hwang, Hyeok Shim, Hyeon-Gyu Yi, Igor Kim, Igor Libov, Igor Sonkin, Igor Suchkov, Ik-Chan Song, Ilker Kiris, Ilya Staroverov, Irene Looi, Isabel M De La Azuela Tenorio, Ismail Savas, Ivan Gordeev, Ivo Podpera, Jae Hoon Lee, Jameela Sathar, James Welker, Jan Beyer-Westendorf, Jan Kvasnicka, Jan Van Meerbeeck, Jan Vanwelden, JangYong Kim, Jaromira Svobodova, Jaspal Gujral, Javier Tristan Galvar, Javier Claudio Marino, Jeannine Kassis, Jen-Yuan Kuo, Jhih-Yuan Shih, JiHyun Kwon, Jin Hyun Joh, Jin Hyun Park, Jin Seok Kim, Jinghua Yang, Jiri Krupicka, Jiri Lastuvka, Jiri Pumprla, Jiri Vesely, Joan Carlos Souto, João Antônio Correa, Johan Duchateau, John Perry Fletcher, Jorge del Toro, Jorge Guillermo Chavez Paez, Jørn Nielsen, Jose Dalmo Araujo Filho, Jose Maria Surinach, Jose Saraiva, Jose Antonio Diaz Peromingo, Jose Gomez Lara, Jose Luis Fedele, Joseph Chacko, Juan Carlos Álvarez Benitez, Juan Antonio Muntaner, Juan Moreno Hoyos Abril, Julian Humphrey, Julio Alberto Perez Sanchez, Julio Bono, Junji Kanda, Juree Boondumrongsagoon, Kai Hang Yiu, Kanchana Chansung, Karin Boomars, Kate Burbury, Katsuhiro Kondo, Kemal Karaarslan, Kensuke Takeuchi, Knut Kroeger, Konstantin Andreichuk, Konstantin Zrazhevskiy, Koscál Svatopluk, Kou-Gi Shyu, Kristel Vandenbosch, Kuan-Cheng Chang, Kuan-Ming Chiu, Kubina Jean-Manuel, Kwan Jing Wern, Kwo-Chang Ueng, Lalita Norasetthada, Laure Binet, Lee Ping Chew, Lei Zhang, Lidwine Tick, Lilia Beatriz Schiavi, Lily Lee Lee Wong, Lisbeth Andersen, Louis Botha, Luc Capiau, Luc Timmermans Luciano Eduardo López, Luigi Ria, Luis Manuel hernandez Blasco, Luis Alberto Guzman, Luis Flota Cervera, Magnus Thorsen Jensen, Mahe Isabelle, Manuel Monreal Bosch, Manuel de los Rios Ibarra, Manuel Núñez Fernandez, Marc Carrier, Marc Righini, Marcelo Raul Barrionuevo, Marco Antonio Alcocer Gamba, Marco Cattaneo, Marco Moia, Margaret Bowers, Mariam Chetanachan, Mario Alberto Berli, Mark Fixley, Markus Faghih, Markus Stuecker, Marlin Schul, Martin Banyai, Martin Koretzky, Martin Myriam, Mary Elizabeth Gaffney, Masao Hirano, Masashi Kanemoto, Mashio Nakamura, Meng Lee Chang, Mersel Tahar, Messas Emmanuel, Michael Kovacs, Michael Leahy, Michael Levy, Michael Munch, Michael Olsen, Michel De Pauw, Michel Gustin, Michiel Van Betsbrugge, Mikhail Boyarkin, Miroslav Homza, Modise Koto, Mohamed Abdool-Gaffar, Mohamed Ayman Fakhry Nagib, Mohamed El- Dessoki, Mohamed Khan, Monniaty Mohamed, Moo Hyun Kim, Moon-Hee Lee, Mosaad Soliman, Mostafa Shawky Ahmed, Mostafa Soliman Abd el Bary, Moustafa A. Moustafa, Muhammad Hameed, Muhip Kanko, Mujibur Majumder, Nadezhda Zubareva, Natasha Roseva-Nielsen, Ngyuen Dang, Nicola Mumoli, Nik Azim Nik Abdullah, Nisa Makruasi, Nishen Paruk, Nonglak Kanitsap, Norberto Duda, Nordiana Nordin, Oksana A. Zemlianskaia, Ole Nyvad, Olga Barbarash, Orcun Gurbuz, Oscar Gomez Vilamajo, Oscar Martin Lopez Ruiz, Oscar Nandayapa Flores, Oscar Sanz Peláez , Ove Østergaard, Ozcan Gur, Pablo Javier Marchena, Pantep Angchaisuksiri, Patrick Carroll, Paul Coughlin, Pavel Lang, Peter Verhamme, Peter Baron von Bilderling, Peter Blombery, Peter MacCallum, Petr Jansky, Peuch Bernadette, Philippe De Vleeschauwer, Philippe Hainaut, Piera Maria Ferrini, Piriyaporn Iamsai, Pol Ravez, Ponchaux Christian, Pongtep Viboonjuntra, Ponlapat Rojnuckarin, Prahlad Ho, Pramook Mutirangura, Rachel Wells, Rafael Martinez, Raimundo Tirado Miranda, Ralf Kroening, Raquel Lopez Reyes, Raul Franco Diaz de Leon, Raymond Siu Ming Wong, Raz Alikhan, Reinhold Jerwan-Keim, Remedios Otero, Renate Murena-Schmidt, Reto Canevascini, Richard White, Richard Ferkl, Rika Van Herreweghe, Rita Santoro, Robert Mendes, Robert Klamroth, Robert Prosecky, Roberto Cappelli, Rudolf Spacek, Rupesh Singh, Sam Griffin, Sang Hoon Na, Sanjeev Chunilal, Saskia Middeldorp, Satoshi Nakazawa, Sebastian Schellong, See Guan Toh, Seinturier Christophe, Selim Isbir, Selma Raymundo, Serge Motte, Sergey Gryaznov, Serhat Erol, Serir Ozkan Aktogu, Servaas Donders, Seung Ick Cha, Seung-Hyun Nam, Sevestre Pietri Marie-Antoinette (NCI), Shaun Maasdorp, Shenghua Sun, Shenming Wang, Sherif Mohamed Essameldin, Sherif Mohamed Sholkamy, Shintaro Kuki, Shinya Goto, Shuichi Yoshida, Shunzo Matsuoka, Simon McRae, Simon Watt, Siong Leng Hon, Siriwimon Patanasing, Siwe-Nana Jean-Léopold, Somchai Insiripong, Somchai Wongkhantee, Soo-Mee Bang, Sophie Testa, Stanislav Zemek, Steffen Behrens, Stephan Dominique, Stuart Mellor, Suaran Singh Gurcharan Singh, Sudip Datta, Sunee Chayangsu, Susan Solymoss, Tamara Everington, Tarek Ahmed Adel Abdel-Azim, Tawatchai Suwanban, Taylan Adademir, Terence Hart, Terriat Béatrice, Thifhelimbilu Luvhengo, Thomas Bieri, Thomas Horacek, Thomas Zeller, Tim Reynolds, Tim Boussy, Tina Biss, Ting-Hsing Chao, Tomas Smith Casabella, Tomoya Onodera, Tontanai Numbenjapon, Victor Gerdes, Vladimir Cech, Vladimir Krasavin, Vladimir Tolstikhin, W.A. Bax, Wagih Fawzy Abdel Malek, Wai Khoon Ho, Walter Ageno, Walter Pharr, Weihong Jiang, Wei-Hsiang Lin, Weihua Zhang, Wei-Kung Tseng, Weimar Kunz Sebba Barroso de Souza, Wen-Ter Lai, Wilfried De Backer, Wilhelm Haverkamp, Winston Yoshida, Wolfgang Korte, Won Il Choi, Yana Kazachek, Yang-Ki Kim, Yasuhiro Tanabe, Yasushi Ohnuma, Yeung-Chul Mun, Yohan Balthazar, Yong Park, Yoshisato Shibata, Yulia N. Moiseeva, Zdenek Coufal, Zhenwen Yang, Zhicheng Jing, Zhicheng Jing, Zhongqi Yang.