K., Okamoto, T., Kameoka, S., Sato, A., Toi, M., Matsui, K., Mayumi, T., Saji, S., Miyazaki, M., Takatsuka, Y., Hirata, K.	Society of Clinical Oncology				
Yamakoshi, H., Kanoh, N., Kudo, C., Sato, A., Ueda, K., Muroi, M., Kon, S., Satake, M., Ohori, H., Ishioka, C., Oshima, Y., Osada, H., Chiba, N., Shibata, H., Iwabuchi, Y.	KSRP/FUBP2 Is a Binding Protein of GO-Y086, a Cytotoxic Curcumin Analogue	ACS Medicinal Chemistry Letters	1	273-276	2010
Yamakoshi, H., Ohori, H., Kudo, C., Sato, A., Kanoh, N., Ishioka, C., Shibata, H., Iwabuchi, Y.	Structure-activity relationship of C(5)-curcuminoids and synthesis of their molecular probes thereof	Bioorg Med Chem	18	1083-1092	2010
Sakamoto, Y., Kato, S., Takahashi, M., Okada, Y., Yasuda, K., Watanabe, G., Imai, H., Sato, A., Ishioka, C.	Contribution of autophagic cell death to p53-dependent cell death in human glioblastoma cell line SF126	Cancer Sci (2011)Apr	102 (4)	799-807	2011
Terui K,Takahata T, Sato J, Ishiguro A, Itoh J, Hayakari M, Saijo Y.	Enhancement of Warfarin Anticoagulant Activity by S-1.	Hirosaki Med J	62	80-85	2011
Katsha AM, Ohkouchi S, Xin H, Kanehira M, Sun R, Nukiwa T, Saijo Y.	Paracrine factors from Mesenchymal Stem Cells ameliorate lung injuries in elastase induced emphysema	MolTher	19	196-203	2011
Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, Gemma A, Harada M, Yoshizawa H, Kinoshita K, Fujita Y, Okinaga S, Hirano H,Yoshimori K, Harada T, Miyazawa H, Tanaka T, Saijo Y, Hagiwara K, Ogura T, Ando M, Morita S, and Nukiwa T	Gefitinib or Chemotherapy for Non-Small Cell Lung Cancer with Mutated EGFR.	New Engl J Med	362	2380-8	2010
Sakakibara T, Inoue A, Sugawara S, Maemondo M, Ishida T, Usui K, Abe T, Kanbe M, Watanabe H, Saijo Y, Nukiwa T	Randomized phase II trial of weekly paclitaxel combined with carboplatin versus standard paclitaxel combined with carboplatin for elderly patients with advanced non-small-cell lung cancer.	Ann Oncol	21	795-9	2010
佐藤淳也、照井一史、粟津朱美、小山基、伊東重豪、西條康夫、早狩誠	携帯型インフューザーポンプを使用した5-FU持続投与コンプライアンスの調査	癌と化学療法	第37巻4号	671-675	2010
西條康夫	肺癌と癌幹細胞	呼吸器内科	第17巻3号	228-233	2010
西條康夫	肺の stem cell と肺癌	Medical Practice	27巻	1177-1179	2010
吉岡孝志	変わりゆく大腸がんの化学療法 8 新しいレジメンの開発状況と臨床試験	臨床腫瘍プラクティス	6	178-181	2010
加藤俊介	希少がんの臨床 腹膜中皮腫	腫瘍内科	6	527-532	2010
加藤俊介	骨軟部肉腫	がん薬物療法エクスパートマニュアル	in press	in press	in press

加藤俊介	臓器別がん分子標的治療薬の解説 肝がん	がん治療レクチャー	in press	in press	in press
Shibata, H, et al.	KSRP/FUBP2 is a binding protein of GO-Y086, a cytotoxiccurcumin analogue	ACS Medicinal Chemistry Letters	6	273-276	2010
Shibata, H, et al.	Curcumin analog GO-Y030 is a novel inhibitor of IKK β that suppresses NF- κ B signaling and induces apoptosis.	Cancer Science	102	1045-1051	2011
Shibata, H, et al.	Phase II study of FOLFOX4 with "wait and go" strategy as first-line treatment for metastatic colorectal cancer	Cancer ChemotherPharmacol		Epub ahead of print	2011
Yasuda, K., Kato, S., Sakamoto, Y., Watanabe, G., Mashiko, S., Sato, A., Kakudo, Y., Ishioka, C.	Induction of apoptosis by cytoplasmically localized wild-type p53 and the S121F mutant super p53.	Oncology Letters	3	978-982	2012
福井忠久、伊藤由理子、吉岡孝志、武田弘明、河田純男	低用量ネダプラチン・5FU 併用放射線治療が著効した、重度肝障害をともない全身状態不良の肝転移を有する食道がんの 1 例	日本消化器病学会雑誌	108	813-818	2011
福井忠久、伊藤由理子、折原美佳、吉澤和哉、武田弘明、河田純男、吉岡孝志	食道癌化学療法におけるエレンタールの口内炎予防・軽減効果についての検討	癌と化学療法	38	2597-2601	2011
H Shibata, et al.	Curcumin analog GO-Y030 is a novel inhibitor of IKK β that suppresses NF- κ B signaling and induces apoptosis	Cancer Science	102	1045-1051	2011
H Shibata, et al.	Synthesis of 86 species of 1,5-diaryl-3-oxo-1,4-pentadienes analogs of curcumin can yield a good lead in vivo.	BMC Pharmacology	11		2011
H Shibata, et al.	Targeting colon cancer stem cells using a new curcumin analogue, GO-Y030	British Journal of Cancer	105	212-20	2011
H Shibata, et al.	18FDG-PET at 1-month intervals is a better predictive marker for GISTs that are difficult to be diagnosed histopathologically: a case report.	Case Reports in Oncological Medicine		pagesdoi: 10.1155/2011/638794	2011
H Shibata, et al.	Novel Curcumin Analogs, GO-Y030 and GO-Y078, Are Multi-targeted Agents with Enhanced Abilities for Multiple Myeloma	Anticancer Research	31	3719-3726	2011
H Shibata, et al.	Acquired/intratumor mutation of KRAS during metastatic progression of colorectal carcinogenesis	Oncology Letters	3	649-653	2012
柴田浩行	「Q26 消化管穿孔」	がん治療レクチャー	3	7-11	2011
蒲生真紀夫	がん診療連携拠点病院における腫瘍センターの役割	がん治療レクチャー	vol3 N01	p12-16	2012
Hanada N, Takahata T, Zhou Q, Ye X, Sun R, Itoh J, Ishiguro A, Kijima H, Mimura J, Itoh K, Fukuda S, Saijo Y	Methylation of the KEAP1 gene promoter region in human colorectal cancer.	BMC Cancer	12(1)	66.	2012
Ohkouchi S, Block GJ, Katsha AM, Kanehira M, Ebina M, Kikuchi T, Saijo Y, Nukiwa T, Prockop DJ.	Mesenchymal Stromal Cells Protect Cancer Cells From ROS-induced Apoptosis and Enhance the Warburg Effect by Secreting STC1	Mol Ther.	20(2)	417-423.	2012
Takahata T, Itoh J, Satoh T, Ishiguro A,	Sequential irinotecan hydrochloride/S-1 for S-1-resistant inoperable gastric cancer: A	Oncology Letters	3	89-93	2012

Matsumoto Y, Tanaka S, Saitoh S, Tohno H, Fukuda S, Saijo y, Satata Y.	feasibility study.				
Suzuki K, Sun R, Origuchi M, Kanehirra M, Takahata T, Itoh J, Umezawa A, Kijima H, Fukuda S, Saijo Y.	Mesenchymal Stromal Cells Promote Tumor Growth Through the Enhancement of Neovascularization.	Mol Med	17	579-87	2011
當麻景章 西條 康夫	新しい肺癌診療:ガイドラインの考え方	カレントテラピー	29	1052	2011
廣瀬千穂、石黒敦、高畑武功、伊東重豪、西條康夫	plasmablastic lymphomaの一例	内科	1082 011	1512-1516	2011
伊藤薫樹	WHO 分類 2008 に基づく急性混合性白血病の臨床像の解析	血液内科	63(5)	614-620	2011
Akagi T, Takahashi N, Yamaguchi K, Ishizawa K, Murai K, Tajima K, Ikeda K, Kameoka Y, Kameoka J, Ito S, et al.	Comparison of long-term clinical outcomes of CHOP chemotherapy between Japanese patients with nodal peripheral T-cell lymphoma and those with diffuse large B-cell lymphoma in the study group of the Tohoku Hematology Forum.	J Clin Exp Hematol.	51(1)	29-35	2011
Tachihara M, Misa K, Uematsu M, Minemura H, Katsuura Y, Ishida T, Munakata M.	Increase of ascites and pleural effusion misleading assessment of antitumor response to erlotinib in adenocarcinoma of the lung.	J Clin Oncol	29	675-7	2011
Ishida T, Asano F, Yamazaki K, Shinagawa N, Oizumi S, Moriya H, Munakata M, Nishimura M; for the Virtual Navigation in Japan (V-NINJA) trial group.	Virtual bronchoscopic navigation combined with endobronchial ultrasound to diagnose small peripheral pulmonary lesions: a randomised trial.	Thorax	66	1072-7	2011
Oshima K, Kanazawa K, Ishida T, Inokoshi Y, Sekine S, Tachihara M, Yokouchi H, Tanino Y, Munakata M.	Two cases of idiopathic subglottic stenosis.	ScienceMED	2	65-8	2011
立原素子、渡邉香奈、横内 浩、鈴木弘行、石田 卓、棟方 充	局所再発を繰り返し、外科切除にて混合型小細胞肺癌と診断した 1 例	肺癌	51	820-4	2011
秋山聖子, 佐竹宣明, 石岡千加史	分子標的薬-がんから他疾患までの治癒をめざして- II基礎研究 分子標的薬の作用機序・薬理作用／がん関連標的分子・標的経路 その他の受容体型チロシンキナーゼ(c-kit など)	日本臨牀	70巻	36-40	2012 年
石岡千加史	骨転移の治療-薬物療法を中心に-	癌と化学療法	第39巻	1169-1173	2012 年
秋山聖子, 佐竹宣明, 石岡千加史	災害後の抗がん剤治療	最新医学	6 月増刊号 67巻	1577-1586	2012 年
森隆弘, 石岡千加史	分子標的薬の副作用のトピックス、展望	臨床外科	67	862-868	2012 年

高橋信, 石岡千加史	乳癌(第 2 版)-基礎と臨床の最新研究動向ー化学療法の変遷と展望	日本臨牀	70巻	23-28	2012 年
石岡千加史	胃癌エキスパートフォーラム(GCEF)Web セミナーについて	日経メディカル Cancer Review	25		2012 年
石岡千加史	総論 1.最新のがん薬物療法の特徴と適応	Modern Physician	33	277-9	2013 年
Kais, Z., Chiba, N., Ishioka, C., Parvin, J. D.	Functional differences among BRCA1 missense mutations in the control of centrosome duplication	Oncogene	31	799-804	2012
Kato, S., Andoh, H., Gamoh, M., Yamaguchi, T., Murakawa, Y., Shimodaira, H., Takahashi, S., Mori, T., Ohori, H., Maeda, S., Suzuki, T., Kato, S., Akiyama, S., Sasaki, Y., Yoshioka, T., Ishioka, C., (T-CORE)., On behalf of Tohoku Clinical Oncology Research and Education	Safety Verification Trials of mFOLFIRI and Sequential IRIS plus Bevacizumab as First- or Second-Line Therapies for Metastatic Colorectal Cancer in Japanese Patients	Oncology	83	101-7	2012
Nomizu, T., Sakuma, T., Yamada, M., Matsuzaki, M., Katagata, N., Watanabe, F., Nihei, M., Ishioka, C., Takenoshita, S., Abe, R.	Three cases of kindred with familial breast cancer in which carrier detection by BRCA gene testing was performed on family members	Breast Cancer	19	270-4	2012
Saijo, K., Katoh, T., Shimodaira, H., Oda, A., Takahashi, O., Ishioka, C.	Romidepsin (FK228) and its analogs directly inhibit PI3K activity and potently induce apoptosis as HDAC/PI3K dual inhibitors	Cancer Sci	103:	1994-2001	2012
Shibahara, I, Sonoda, Y, Kanamori, M, Saito, R, Yamashita, Y., Kumabe, T, Watanabe, M, Suzuki, H, Kato, S., Ishioka, C.	IDH1/2 gene status defines the prognosis and molecular profiles in patients with grade III gliomas	Int J Clin Oncol	17	551-61	2012
Shiono, Masatoshi, Shimodaira, Hideki, Watanabe, Mika, Takase, Kei, Ito, Kiyoshi, Miura, Koh, Takami, Yuko, Akiyama, Shoko, Kakudo, Yuichi, Takahashi, Shin, Takahashi, Masanobu, Ishioka, Chikashi.	Multidisciplinary approach to a case of Lynch syndrome with colorectal, ovarian, and metastatic liver carcinomas.	INTERNATIONAL CANCER CONFERENCE JOURNAL	1	125-137	2012
Takahashi, M., Furukawa, Y., Shimodaira, H., Sakayori, M., Moriya, T., Moriya, Y., Nakamura, Y., Ishioka, C.	Aberrant splicing caused by a MLH1 splice donor site mutation found in a young Japanese patient with Lynch syndrome	Fam Cancer	11	559-64	2012
Yasuda, K., Kato, S., Sakamoto, Y., Watanabe, G., Mashiko, S., Sato, A., Kakudo, Y., Ishioka, C.	Induction of apoptosis by cytoplasmically localized wild-type p53 and the S121F mutant super p53	Oncol Lett	3	978-82	2012

Soeda, H., Shimodaira, H., Watanabe, M., Suzuki, T., Gamoh, M., Mori, T., Komine, K., Iwama, N., Kato, S., Ishioka, C.	Clinical usefulness of KRAS, BRAF, and PIK3CA mutations as predictive markers of cetuximab efficacy in irinotecan- and oxaliplatin-refractory Japanese patients with metastatic colorectal cancer	Int J Clin Oncol			2012
Watanabe, M., Baba, H., Ishioka, C., Nishimura, Y., Muto, M.	Recent advances in diagnosis and treatment for malignancies of the gastrointestinal tract	Digestion	85(2)	95-8	2012
Kawai, S., Kato, S, Imai, H, Okada, Y, C, Ishioka.	Suppression of FUT1 attenuates cell proliferation in HER2-overexpressing cancer cell line NCI-N87	Oncol Rep	29	13-20	2013
Takahash, M., Kakudo, Y., Takahashi, S., Sakamoto, Y., Kato, S., Ishioka, C.	Overexpression of DRAM enhances p53-dependent apoptosis	Cancer Medicine	2	1-10	2013
加藤俊介	がん医療におけるプライマリケア医の役割を考える-ここまで進歩した外来がん化学療法-『消化器癌(大腸癌・胃癌)』	日本医事新報	4627	53-56	2012年
加藤俊介	大腸がんに対する新しい分子標的薬(レゴラフェニブとアフリバセプト).	癌と化学療法	40	6-9	2013年
Tsushima, T., Taguri, M., Honma, Y., Takahashi, H., Ueda, S., Nishina, T., Kawai, H., Kato, S., Morita, S., Boku, N.	Multicenter Retrospective Study of 132 Patients with Unresectable Small Bowel Adenocarcinoma Treated with Chemotherapy.	Oncologist.	17	1163-70	2012年
Kawai, S., Kato, S., Imai, H., Okada, Y., Ishioka C.	Suppression of FUT1 attenuates cell proliferation in HER2-overexpressing cancer cell line NCI-N87.	Oncol Rep.	29	13-20	2013年
Kato S., Andoh H., Gamoh M., Yamaguchi T., Murakawa Y., Shimodaira H, Takahashi S., Mori T., Ohori H., Maeda S, Suzuki T., Kato S, Akiyama S., Sasaki Y, Yoshioka T., Ishioka C.	Safety verification trials of mFOLFIRI and sequential IRIS + bevacizumab as first- or second-line therapies for metastatic colorectal cancer in Japanese patients.	Oncology	83	101-107	2012年
Soeda H, Shimodaira H, Watanabe M, Suzuki T, Gamoh M, Mori T, Komine K, Iwama N, Kato S, Ishioka C.	Clinical usefulness of KRAS, BRAF, and PIK3CA mutations as predictive markers of cetuximab efficacy in irinotecan- and oxaliplatin-refractory Japanese patients with metastatic colorectal cancer. Int J Clin Oncol. 2012 May 26 [Epub ahead of print] 5) Shibahara I, Sonoda Y, Kanamori M, Saito R, Yamashita Y, Kumabe T, Watanabe M, Suzuki H, Kato S, Ishioka C, Tominaga T. IDH1/2 gene status defines the prognosis and molecular profiles in patients with grade III gliomas.	Int J Clin Oncol.	Epub ahead of print	Epub ahead of print	2012
Shibahara I, Sonoda Y, Kanamori M, Saito R, Yamashita Y, Kumabe T, Watanabe M, Suzuki H, Kato S, Ishioka C, Tominaga T	IDH1/2 gene status defines the prognosis and molecular profiles in patients with grade III gliomas.	Int J Clin Oncol.	17	551-561	2012
Kenji Nemoto, Misako Murakami,Mayumi Ichikawa, Ibuki Ohta, Takuma Nomiya, Mayumi Yamakawa, Yuriko Ito, Tadahisa	Influence of a Multidisciplinary cancer board on treatment decisions	International Journal of Clinical Oncology		Epub ahead of print	2012年

Fukui,TakashiYoshioka					
Kato S, Andoh H, Gamoh M, Yamaguchi T, Murakawa T, Shimodaira H, Takahashi S, Mori T, Ohori H, Maeda S, Suzuki T, Kato S, Akiyama S, Sasaki Y, Yoshioka T, Ishioka C	Safety Verification Trials of mFOLFIRI and Sequential IRIS + Bevacizumab as First- or Metastantic Colorectal Cancer in Japanese Patients	Oncology	83(2) :	101-107	2012 年
Kanbe M, Kikuchi H, Gamo M, Yoshioka T, Ohashi Y, Kanamaru R	Phase I study of irinotecan by 24 -h intravenous infusion in combination with 5-fluorouracil in metastatic colorectal cancer	International Journal of Clinical	17(2)	150-154	2012 年
Ito Y, Narimatsu H, Fukui T, A. Fukao A, Yoshioka T	Critical review of "Public domain application": a flexible drug approval system in Japan	Annals of Oncology		(in press)	2013 年
Suzuki S, Ito Y, Fukui T, Orihara M, Nakamura S, Takahashi M, Fujimoto H, Kimura W, Yoshioka T	Two cases of gastric cancer with peritoneal carcinomatosis successfully responding to combination chemotherapy of S-1 and cisplatin, leading to clinical complete response	International Cancer Conference Journa		(in press)	2013 年
柴田浩行	Q2 都道府県がん診療連携拠点病院の指定要件にみる標準的ながん薬物療法(化学療法)の実践	がん治療レクチャー	3	7-11	2012 年
柴田浩行	臨床医学の展望 2013「腫瘍内科学 Oncology」	日本医事新報	4632	42-47	2012 年
Otsuka K , Nanjo H , Soeda H, Shibata H.	The effect of XELOX plus bevacizumab on rectal hepatoid adenocarcinoma.	International Cancer Conference Journal		DOI 10.1007/s13691-012-0057-7	2012 年
Otsuka K, Imai H, Soeda H, Komine K, Ishioka C, Shibata H.	Practical utility of circulating tumour cells as biomarkers in cancer chemotherapy for advanced colorectal cancer.	Anticancer Res	33	625-9	2013 年
Anbai A, Koga M, Motoyama S, Jin M, Shibata H, Hashimoto M.	Outcomes of patients with stage IVA esophageal cancer (Japanese classification) treated with definitive chemoradiotherapy.	Japanese journal of radiology		DOI:10.1007/s11604-013-0180-1	2013 年
Satoshi Tanaka1, Naoto Suzuki, Akira Mimura, Maho Kurosawa, Yuriko Murai, Daisuke Saigusa, Makio Gamoh, Masuo Sato, Yoshihisa Tomioka1	Serum Chlorine Level as a Possible Predictive Factor for Oxaliplatin-Induced Peripheral Neuropathy	Pharmacology & Pharmacy	Vol. 3,No .1	p44-51	2012
Shunsuke Kato, Hideki Ando, Makio Gamoh, Takuhiro Yamaguchi, Yasuko Murakawa, Hideki Shimodaira, Shin Takahashi, Takahiro Mori6, Hisatsugu Ohori, Shun-ichi Maeda, Takao Suzuki, Satoshi Kato, Shoko Akiyama, Yuka Sasaki, Takashi, Yoshioka and Chikashi Ishioka	Safety verification trials of mFOLFIRI and sequential IRIS + bevacizumab as first- or second-line therapies for metastatic colorectal cancer in Japanese patients,	Oncology	83	101-107	2012
蒲生真紀夫	大腸がん(薬物療法)	Modern Physician	Vol. 33	294-297	2013

A. Inoue A, Kobayashi K, Maemondo M, Sugawara S, Oizumi S, Isobe H, Gemma A, Harada M, Yoshizawa H, Kinoshita I, Fujita Y, Okinaga S,Hirano H, Yoshimori K, Harada T, Saijo Y, Hagiwara K, Morita S, Nukiwa T	Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-Naïve non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002).	Ann Oncol	24	54-59	2013
Oizumi S, Kobayashi K, Inoue A, Maemondo M, Sugawara S, Yoshizawa H, Isobe H, Harada M, Kinoshita I, Okinaga S, Kato T, Harada T, Gemma A, Saijo Y, Yokomizo Y, Morita S, Hagiwara K, Nukiwa T	Quality of Life with Gefitinib in Patients with EGFR-Mutated Non-Small Cell Lung Cancer: Quality of Life Analysis of North East Japan Study Group 002 Trial.	Oncologist	17	863-870	2012
Hanada N, TakahataT, Zhou Q, Ye X, Sun R, Itoh J, Ishiguro A, Kijima H, Mimura J, Itoh K, Fukuda S, and Saijo Y.	Methylation of the KEAP1 gene promoter region in human colorectal cancer.	BMC Cancer	12	66	2012
Takahata T, Itoh J, Satoh T, Ishiguro A, Tanaka S, Saitoh S, Tohno H, Fukuda S, Saijo y, Satata Y	Sequential irinotecan hydrochloride/S-1 for S-1-resistant inoperable gastric cancer: A feasibility study.	Oncology Letters,	3	89-93	2012
石黒 敦、西條 康夫	＜小細胞肺癌治療の考え方と実践＞二次治療のエビデンス	内科	110	751-756	2012
三浦 理、各務 博、西條 康夫	肺癌治療と骨転移マネジメント	癌と化学療法	36	1183-1186	2012
西條康夫	日本におけるがん医療政策とがん薬物療法の進歩	新潟県医師会報	747	2-7	2012
Tachihara M, Nikaido T, Wang X, Sato Y, Ishii T, Saito K, Sekine S, Tanino Y, Ishida T, Munakata M.	Four cases of Trousseau's syndrome associated with lung adenocarcinoma	Intern Med	51 (9)	1099-1102	2012
Oshima K, Tanino Y, Sato S, Inokoshi Y, Saito J, Ishida T, Fukuda T, Watanabe K, Munakata M.	Primary pulmonary extranodal natural killer/T-cell lymphoma: nasal type with multiple nodules	Eur Respir J	40 (3)	795-798	2012
Yuki M, Sekine S, Takase K, Ishida T, Sessink PJM	Exposure of family members to antineoplastic drugs via excreta of treated cancer patients	J Oncol Phramacy Pract		Epub ahead of print	2012
石田 卓	【副作用のマネジメント】神経毒性(主に末梢神経障害)	がん治療レクチャー	3(1)	162-166	2012
立原素子、神尾淳子、佐藤丈晴、室井祥江、柴田眞一、森村 豊、石田卓、棟方 充	集検喀痰細胞診で発見された喉頭癌と早期中心型肺癌の細胞像の比較	日臨細誌	51 (1)	7-12	2012

Int J Clin Oncol
DOI 10.1007/s10147-010-0060-y

SPECIAL ARTICLE

Quality of guideline development assessed by the Evaluation Committee of the Japan Society of Clinical Oncology

Takuro Shimbo · Tsuguya Fukui · Chikashi Ishioka · Kohji Okamoto · Takahiro Okamoto · Shingo Kameoka · Atsushi Sato · Masakazu Toi · Kunihiko Matsui · Toshihiko Mayumi · Shigetoyo Saji · Masaru Miyazaki · Yuichi Takatsuka · Koichi Hirata

Received: 5 January 2010

Abstract
Background The Japan Society of Clinical Oncology started implementing clinical practice guidelines for cancer in 2001. It created a Guideline Committee and has published cancer-related information in collaboration with individual subspecialty cancer societies. The society then established an Evaluation Committee to assess the quality of guidelines.

Methods The quality of development and general characteristics of guidelines were reviewed using the AGREE instrument. The six standardized domain scores and 23-item crude scores were described, and items with a low median score or a wide inter-quartile range were explored. Kappa statistics for inter-rater reproducibility were also described.

T. Shimbo (✉)
Department of Clinical Research and Informatics,
Research Institute, International Medical Center of Japan,
1-21-1 Toyama, Shinjuku-ku, Tokyo, Japan
e-mail: tshimbo@ri.imcj.go.jp

T. Fukui
St. Luke's International Hospital, Tokyo, Japan

C. Ishioka
Department of Clinical Oncology, Institute of Development,
Aging and Cancer, Tohoku University, Sendai, Japan

K. Okamoto
First Department of Surgery, School of Medicine,
University of Occupational and Environmental Health,
Kitakyushu, Japan

T. Okamoto
Department of Endocrine Surgery, School of Medicine,
Tokyo Women's Medical University, Tokyo, Japan

T. Okamoto
Department of Hygiene and Public Health, School of Medicine,
Tokyo Women's Medical University, Tokyo, Japan

S. Kameoka
Second Department of Surgery, Tokyo Women's Medical
University, Tokyo, Japan

A. Sato
Division of Medical Oncology, Department of Internal
Medicine, Showa University School of Medicine, Tokyo, Japan

M. Toi
Department of Breast Surgery, Graduate School of Medicine,
Kyoto University, Kyoto, Japan

K. Matsui
Clinical Education Center, Kumamoto University Hospital,
Kumamoto, Japan

T. Mayumi
Department of Emergency and Critical Care Medicine,
Nagoya University Graduate School of Medicine, Nagoya, Japan

S. Saji
Department of Surgical Oncology, Gifu University Graduate
School of Medicine, Gifu, Japan

M. Miyazaki
Department of General Surgery, Graduate School of Medicine,
Chiba University, Chiba, Japan

Y. Takatsuka
Department of Breast Surgery, Kansai Rosai Hospital,
Amagasaki, Japan

K. Hirata
First Department of Surgery,
Sapporo Medical University, Sapporo, Japan

Published online: 24 March 2010

Results Domains in which the median score was >50 points in 18 guidelines developed between March 2005 and May 2009 included "scope and purpose," "rigor of development," and "clarity and presentation." Domains with a median score < 50 points were "stakeholder involvement," "applicability," and "editorial independence." Scores in all domains except "stakeholder involvement" were higher during the second half of the period than during the first half of the period, although *P* values were 0.10–0.93. Crude scores remained low for items 5, 7, 19, 20, 22, and 23, and the inter-quartile ranges of items 2, 6, 10, and 22 were wide. Kappa statistics ranged from –0.02 to 0.64, and they were especially low for items 3, 5, 7, 18, and 23.

Conclusion Guideline quality has tended to improve during the 10 years since the society started this activity. However, issues remain to be improved through continuous revisions.

Keywords Clinical practice guideline · AGREE instrument · Cancer

Introduction

The Japan Society of Clinical Oncology started implementing clinical practice guidelines (CPGs) for cancer in 2001 in collaboration with allied subspecialty societies. The society has developed summary versions of CPGs and flowcharts, and it has published them on the Internet with structured abstracts of important articles. Around 20 guidelines have been developed by subspecialty societies by November 2009, and 13 of them are presented on the society's homepage (http://www.jsco-cpg.jp/) [1].

The society established a Guideline Committee (GC) for this activity, as well as an Evaluation Committee (EC) to evaluate and ensure the quality of published guidelines. The aims of the present study were to identify issues requiring resolution from a summary of the assessment results generated by the EC.

Methods

Process before publishing the guidelines

The activity of CPG publishing and implementation in the society proceeds as follows. A subcommittee of the GC for a specific cancer writes a draft summary, algorithm, and structured abstract in accordance with the specific subspecialty society, and submits them, or sometimes a complete CPG, to the board of the GC. The board of the GC reviews and sends them to the EC. The EC evaluates them and reports the result to the chair of the GC and the members of GC subcommittee. If there is no major flaw, a homepage is developed. These tools for implementation of the CPG are then released to the public after the final approval of the GC and the board of the society.

The review in the EC

The EC has ten members, including a chair and four members from outside the society. All members individually review drafts under evaluation before attending a meeting where all members reach a consensus-based final assessment.

The AGREE instrument [2] was used for reviews that focus on the process of CPG development and the general characteristics of the CPGs, but not on the validity of specific statements. The AGREE instrument is a comprehensive tool for evaluation whose validity and reproducibility have been investigated [3, 4]. The EC did not require revision of the content and format of the draft after review, but revisions were expected for a subsequent version. The EC previously presented the appropriate methods for developing evidence-based CPGs to the GC.

Method of review

The present study summarizes the results of the review of the CPGs by the EC.

The AGREE instrument consists of 23 items that assess six domains of the CPG development process: "scope and purpose" (items 1–3), "stakeholder involvement" (items 4–7), "rigor of development" (items 8–14), "clarity and presentation" (items 15–18), "applicability" (items 19–21), and "editorial independence" (items 22–23). For each item, a crude score of 1–4 is assigned based on the reviewers' certainty of fulfilling the requirements of the items and the quantity of information contained in the CPG. A standardized domain score is calculated for the 6 domains after summing and adjusting the crude scores into a scale from 0 to 100 points. A global assessment could be given, but such global assessments were not recorded for all CPGs. Global quality was described as an aggregated score determined from the summation of all domain scores, although AGREE does not suggest using this strategy for global assessment.

The distributions of the crude scores for the items were determined. Low-score items in which the medians were ≤ 2 and dispersed items, for which the inter-quartile range of the crude score was 1–4, were identified. The dispersed items contained CPGs with both low and high scores, which led to the supposition that they could be easily improved.

Kappa statistics were calculated for each item to determine inter-rater reproducibility [5, 6]. Low kappa values

indicate a trend toward the item scoring differently among raters. When calculating kappa, crude scores of 1 and 2, as well as those of 3 and 4, were combined into one level. The EC used only one representative score based on consensus for evaluation at meetings and did not use the individual crude scores from which the kappa values were derived.

When members thought that determining a score was difficult, the committee used its own criteria to standardize

Table 1 Guidelines that have been reviewed by the evaluating committee

Type of cancer	Title	Version
Stomach[a]	Japanese Gastric Cancer Association: guidelines for the diagnosis and treatment of carcinoma of the stomach, April 2004 edition	2
Liver[b]	The Japan Society of Hepatology:[c] "clinical practice guidelines for hepatocellular carcinoma:" evidence-based clinical guidelines for the diagnosis and treatment of hepatocellular carcinoma in Japan (the print/web version)	1
GIST[a]	Japanese Gastric Cancer Association, Japan Society of Clinical Oncology, Japanese Study Group on GIST: clinical practice guidelines for gastrointestinal stromal tumors (GIST) in Japan	1
Oral cancer	Japan Society for Oral Tumors: clinical practice guidelines for oral cancer	1
Uterine cervix	The Japan Society of Gynecologic Oncology: treatment guidelines for cervical cancer, 2007 edition	1
Uterine body	The Japan Society of Gynecologic Oncology: treatment guidelines for uterine body cancer, 2006 edition	1
Children's leukemia	The Japanese Society of Pediatric Hematology: guidelines for the treatment of childhood leukemia/lymphoma, 2007 edition	1
Esophagus[d]	The Japan Esophageal Society: guidelines for the diagnosis and treatment of esophageal cancer	2
Kidney[d]	The Japanese Urological Association: clinical practice guidelines for managing renal carcinoma and the digest edition (web version)	1
Pancreas[d]	Japan Pancreas Society: evidence-based clinical practice guidelines for pancreatic cancer	1
Colon[d]	Japanese Society for Cancer of the Colon and Rectum: guidelines for the treatment of colon cancer, 2005 edition	1
Biliary tract[d]	Japanese Society of Hepato-Biliary-Pancreatic Surgery: clinical practice guidelines for the management of biliary tract and ampullary carcinomas (the print and web digest version)	1
Head and neck	Japan Society for Head and Neck Cancer: clinical practice guidelines for head and neck cancer	1
Breast[a]	The Japanese Breast Cancer Society: evidence-based clinical practice guidelines of the Japanese Breast Cancer Society (5 volumes) and web version	1
	1. Systemic therapy	
	2. Surgery	
	3. Radiation therapy	
	4. Screening and diagnosis	
	5. Epidemiology and prevention	
Lung	The Japan Lung Cancer Society: clinical practice guidelines for lung cancer, revised edition	2
Skin[d]	The Japanese Skin Cancer Society: clinical practice guidelines for the management of cutaneous malignancies	1
Ovary[d]	The Japan Society of Gynecologic Oncology: ovarian cancer treatment guidelines, 2004 edition	1
Ovary	The Japan Society of Gynecologic Oncology: ovarian cancer treatment guidelines, 2007 edition	2

Order in table reflects the list in the homepage of the Japan Society of Clinical Oncology (order of Japanese 50 sounds)

[a] Presentation was partly funded by the Scientific Study for the Third Term Comprehensive Control Research for Cancer of the Ministry of Health, Labour, and Welfare in 2007

[b] Development was funded by the Scientific Study for Supporting Clinical Practice Guidelines of the Ministry of Health, Labour, and Welfare in 2002–2003

[c] On October 2009

[d] Development and presentation was partly funded by the Scientific Study for the Research on the Medical Safety and Health Technology Assessment of the Ministry of Health, Labour, and Welfare in 2005–2006

Table 2 Domain scores determined using the AGREE instrument for clinical practice guidelines

Domain	Total ($n = 18$)		The first half, March 2005–March 2007 ($n = 10$)		The second half, April 2007–May 2009 ($n = 8$)		P value[a]
	Median	IQR[b]	Median	IQR	Median	IQR	
Scope and purpose	72.2	66.7–100	66.7	55.5–100	83.3	66.7–100	0.38
Stakeholder involvement	41.7	16.7–50.0	43.1	25.0–58.3	41.7	29.2–50.0	0.93
Rigor of development	66.7	38.9–83.3	44.4	16.7–72.2	72.2	61.1–86.1	0.13
Clarity and presentation	75.0	58.3–91.7	70.8	33.3–91.7	83.3	70.8–100	0.18
Applicability	33.3	0–66.6	16.7	0–33.3	50.0	25.0–66.7	0.10
Editorial independence	0	0–50.0	0	0–0	33.3	0–50.0	0.12
Aggregated	56.3	36.5–69.8	48.6	28.6–58.7	65.9	54.8–71.4	0.11

[a] Comparison of scores between the first half of the period and the second half of the period was tested using the Wilcoxon rank-sum test

[b] Inter-quartile range

the score among its members. Item 13 indicates a requirement for an external review of the CPG. This item was not scored because review by the EC is compatible with this. Item 21 requires the CPG to present key review criteria for monitoring or audit. This item was also omitted from scoring because quality indicators for measuring adherence to CPGs have not been developed.

Results

The EC started reviewing CPGs in March 2005, and 18 of them had been reviewed by May 2009 (Table 1). Table 2 shows the standardized domain scores of these CPGs. The domains with median scores > 50 points during the entire period of review were "scope and purpose," "rigor of development," and "clarity and presentation." The median scores for "stakeholder involvement," "applicability," and "editorial independence" were <50 points. All domain scores except "stakeholder involvement" were higher during the second half of the period than during the first half of the period, although the P values were 0.10—0.93.

Figure 1 shows the distribution of crude scores for each item in all CPGs. Item numbers with median crude scores $\leq$ 2.0 were 5 (emphasizing patients' perspectives), 7 (pre-test before publication), 19 (discussion about potential organizational barriers), 20 (considering cost implications), 22 (editorial independence from funding body), and 23 (records of conflicts of interest). The item numbers with widely distributed crude scores were 2 (description of clinical questions), 6 (target users defined clearly), 10 (presentation of methods for formulating recommendations), and 22 (editorial independence from funding body).

Table 3 shows the inter-rater reproducibility for each item. The kappa statistics were –0.02 to 0.64, and the null hypothesis that the consistency of the results occurred by chance alone could not be rejected for items 3 (target patients described specifically), 5 (emphasizing patients' perspectives), 7 (pre-test before publication), 18 (tools for application), and 23 (records of conflicts of interest).

Discussion

The present report describes the results of continuous evaluation of CPGs assembled by the Japan Society of Clinical Oncology. Changes in standardized domain scores indicated that the methods and organization for developing CPGs have improved slightly, although the differences were not statistically significant and the number of CPGs assessed was small. The domains with median scores > 50 points were "scope and purpose" (items 1–3), "rigor of development" (items 8–14), and "clarity and presentation" (items 15–18). Domains with median scores < 50 points were "stakeholder involvement" (items 4–7), "applicability" (items 19–21), and "editorial independence" (items 22–23). Developers must consider these findings when developing new guidelines or revising those that have been already established. For individual items, low scores were observed in items 5, 7, 19, 20, 22, and 23.

Item 5 emphasizes patients' perspectives. The values of individual patients with cancer should be considered in clinical decision making. Several guidelines seemed to specifically recommend a single option without providing alternatives. Representatives of patients or paramedical staff should be involved in these processes.

Item 7 addresses the pilot use of the CPG before formal publication. When a pilot is not used to improve the quality of the CPG, early feedback about its validity, implementation, and impact on routine practice after publication should be obtained.

Item 19 addresses potential organizational barriers. Alternatives should be discussed when barriers interfere with CPG implementation.

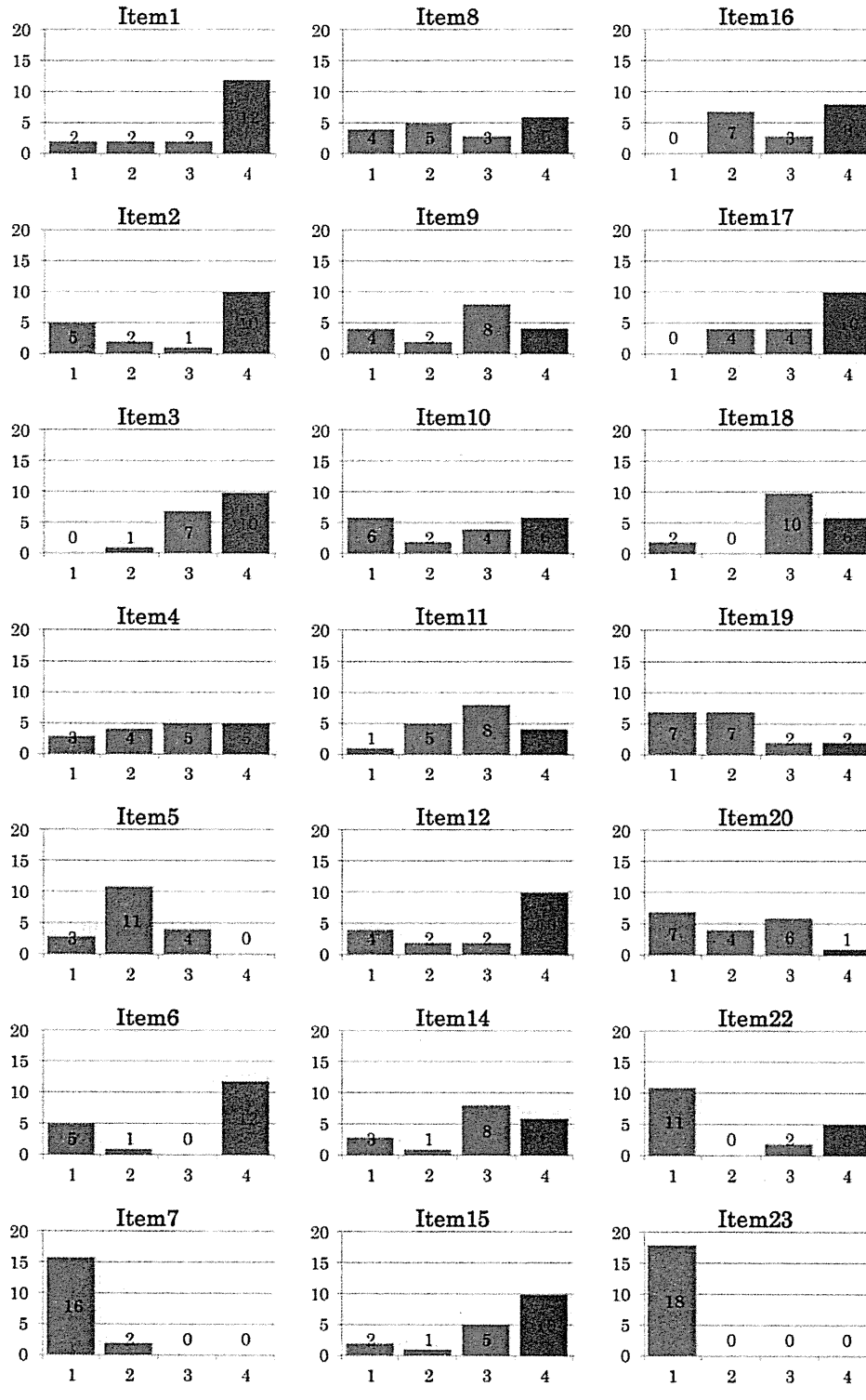

Fig. 1 Distribution of crude scores for each item. Crude scores of each item were reached by consensus after discussion in a committee meeting and are not simple means or medians of scores supplied by individual members of the Evaluation Committee

Item 20 refers to cost issues. The clinical practice of oncology must be individualized because it is based on patient status and value judgments. In general, the issue of cost is important, especially in preventive medicine and in the long-term management of prevalent chronic disorders such as hypertension or dyslipidemia. Cost is more urgent in preventive medicine than for oncologists whose patients have cancer.

Table 3 Inter-rater reproducibility of each item

Item	Kappa[a]	*P* value	Item	Kappa[a]	*P* value
1	0.23	<0.01	12	0.31	<0.01
2	0.64	<0.01	14	0.49	<0.01
3	0.00	0.49	15	0.15	<0.01
4	0.37	<0.01	16	0.20	<0.01
5	−0.02	0.61	17	0.15	<0.01
6	0.34	<0.01	18	0.05	0.18
7	0.04	0.23	19	0.19	<0.01
8	0.33	<0.01	20	0.28	<0.01
9	0.35	<0.01	22	0.14	0.01
10	0.33	<0.01	23	0.05	0.20
11	0.18	<0.01			

[a] Kappa statistics express agreement of several raters above the expected value

Item 22 requires editorial independence from funding bodies. The source of financial support should be documented. If pharmaceutical companies are the source, then the procedure for maintaining editorial independence should also be documented.

Item 23 asks about records of conflicts of interest. None of the CPGs described records for conflicts of interest, although the impact of CPGs on routine practice is substantial. Concern about conflicts of interest is increasing in Japan, where medical journals have not managed this issue as foreign journals have. The Japan Society of Clinical Oncology and the Japan Society of Medical Oncology have developed the "Clinical Oncology Research Conflict of Interest Policy (ver. 1)" [7, 8]. According to this policy, all members of the society must report their status regarding conflict of interest when they report and publish in the society, and these reports are centrally reviewed. This procedure must be followed when CPGs are developed, and records about conflicts of interest should be explicit.

The distribution of crude scores was wide for items 2, 6, 10, and 22, for which the same item scored low and high in several CPGs. Improving these points might not be difficult, although guideline-specific conditions might be involved. The involvement of experts specialized in the field of guidelines will be useful. Item 2 requires clear descriptions of clinical questions. When "Clinical Question" is first described for each CPG topic, it may help focus readers to understand the content more easily. This format of clinical question is preferable. Item 6 asks for a clear definition of the target users. It is important to define that clearly when developing and using CPGs. Item 10 addresses an explicit document that describes the methods of formulating recommendations; however, many CPGs did not provide this information. The impact of an assessment of benefits and harms after a systematic review on formulating a recommendation should be addressed. If disagreement about a recommendation arises, the methods used to reach consensus should be described.

Although the EC has reviewed a dozen CPGs, this report has some challenging issues as limitations. First, the inter-rater reproducibility of several items of the AGREE instrument was poor. Previous studies have identified good validity and reproducibility [3, 4], but we found that reproducibility was not easily achieved in our setting. Although AGREE is a good method of evaluation, the scoring remains subjective. We did not directly use the crude scores of individual members to reach the final assessment. Nevertheless, low reproducibility means that judgment by a member using the AGREE items is not a simple matter. Among low-score items, the score of items 5, 7, and 23 might be influenced by a difficult evaluation. Consensus will be achieved if the committee has criteria for scoring that maintain the original concept of the AGREE items.

Second, common scoring methods are not applicable to all CPGs, because solid evidence is not available in some fields of cancer. Although all CPGs of the society are related to cancer, each type of cancer has specific characteristics. AGREE itself does not recommend establishing a threshold to differentiate CPGs of "good" or "bad" quality.

The activity of CPG development is continuous, and CPGs of the subspecialty societies and the published material of the society (http://www.jsco-cpg.jp/) will be revised sequentially. These guidelines have also been published on the homepages of the subspecialty societies and of the Medical Information Network Distribution Service (MINDS), thus bringing the CPGs closer not only to medical professionals but also to patients. The activities of publishing and implementing CPGs within the society over the first decade seem to have begun well. Efforts to improve quality must be maintained, and users, including patients, should be able to easily understand the contents.

Acknowledgments The authors thank Ms. Misao Oda, who manages the affairs of the Evaluation Committee and maintains detailed records. We also acknowledge the assistance of Ms. Kaoruko Nakazawa, who helped with drafting the manuscript. This report was partly funded by the "Study for Development and Revision of Clinical Practice Guidelines for Cancer and Maintenance of Publishing," which is supported by the Ministry of Health, Labour, and Welfare, and by the fund for Scientific Studies for Cancer Clinical Research.

Conflict of interest statement M. Toi received honoraria from GlaxoSmithKline. The other authors have no conflict of interest.

References

1. Japan Society of Clinical Oncology (2007) Clinical practice guidelines for cancer. http://www.jsco-cpg.jp/, accessed on November 10, 2009
2. AGREE collaboration (2004) http://www.agreecollaboration.org/, accessed on July 6, 2009
3. AGREE collaboration (2003) Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. Qual Saf Health Care 12:18–23
4. MacDermid JC, Brooks D, Solway S et al (2005) Reliability and validity of the AGREE instrument used by physical therapists in assessment of clinical practice guidelines. BMC Health Serv Res 5:18
5. Fleiss JL (1981) Statistical methods for rates and proportion, 2nd edn. Wiley, New York, pp 212–236
6. Kappa-interrater agreement (2007) STATA base reference manual, vol 2, I-P, Release 10. STATA Press, Texas, pp 83–96
7. Joint Formulation Committee (Japan Society of Clinical Oncology/ Japan Society of Medical Oncology) (2009) Clinical Oncology Research Conflict of Interest Policy (ver.1). http://jsco.umin.ac.jp/outline/COI.html
8. Joint Formulation Committee (Japan Society of Clinical Oncology/ Japan Society of Medical Oncology) (2009) Bylaws to the Clinical Oncology Research Conflict of Interest Policy (ver.1). http://jsco.umin.ac.jp/outline/saisoku4.html#saisoku4

ORIGINAL ARTICLE

Gefitinib or Chemotherapy for Non–Small-Cell Lung Cancer with Mutated EGFR

Makoto Maemondo, M.D., Ph.D., Akira Inoue, M.D., Ph.D., Kunihiko Kobayashi, M.D., Ph.D., Shunichi Sugawara, M.D., Ph.D., Satoshi Oizumi, M.D., Ph.D., Hiroshi Isobe, M.D., Ph.D., Akihiko Gemma, M.D., Ph.D., Masao Harada, M.D., Ph.D., Hirohisa Yoshizawa, M.D., Ph.D., Ichiro Kinoshita, M.D., Ph.D., Yuka Fujita, M.D., Ph.D., Shoji Okinaga, M.D., Ph.D., Haruto Hirano, M.D., Ph.D., Kozo Yoshimori, M.D., Ph.D., Toshiyuki Harada, M.D., Ph.D., Takashi Ogura, M.D., Masahiro Ando, M.D., Ph.D., Hitoshi Miyazawa, M.S., Tomoaki Tanaka, Ph.D., Yasuo Saijo, M.D., Ph.D., Koichi Hagiwara, M.D., Ph.D., Satoshi Morita, Ph.D., and Toshihiro Nukiwa, M.D., Ph.D., for the North-East Japan Study Group*

ABSTRACT

BACKGROUND

Non–small-cell lung cancer with sensitive mutations of the epidermal growth factor receptor (EGFR) is highly responsive to EGFR tyrosine kinase inhibitors such as gefitinib, but little is known about how its efficacy and safety profile compares with that of standard chemotherapy.

METHODS

We randomly assigned 230 patients with metastatic, non–small-cell lung cancer and EGFR mutations who had not previously received chemotherapy to receive gefitinib or carboplatin–paclitaxel. The primary end point was progression-free survival; secondary end points included overall survival, response rate, and toxic effects.

RESULTS

In the planned interim analysis of data for the first 200 patients, progression-free survival was significantly longer in the gefitinib group than in the standard-chemotherapy group (hazard ratio for death or disease progression with gefitinib, 0.36; P<0.001), resulting in early termination of the study. The gefitinib group had a significantly longer median progression-free survival (10.8 months, vs. 5.4 months in the chemotherapy group; hazard ratio, 0.30; 95% confidence interval, 0.22 to 0.41; P<0.001), as well as a higher response rate (73.7% vs. 30.7%, P<0.001). The median overall survival was 30.5 months in the gefitinib group and 23.6 months in the chemotherapy group (P=0.31). The most common adverse events in the gefitinib group were rash (71.1%) and elevated aminotransferase levels (55.3%), and in the chemotherapy group, neutropenia (77.0%), anemia (64.6%), appetite loss (56.6%), and sensory neuropathy (54.9%). One patient receiving gefitinib died from interstitial lung disease.

CONCLUSIONS

First-line gefitinib for patients with advanced non–small-cell lung cancer who were selected on the basis of EGFR mutations improved progression-free survival, with acceptable toxicity, as compared with standard chemotherapy. (UMIN-CTR number, C000000376.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Inoue at the Department of Respiratory Medicine, Tohoku University Hospital 1-1, Seiryomachi, Aobaku, Sendai, 980-8574, Japan, or at akinoue@idac.tohoku.ac.jp.

*Contributing members of the North-East Japan Study Group are listed in the Appendix.

N Engl J Med 2010;362:2380-8.

NON–SMALL-CELL LUNG CANCER IS A major cause of death from cancer. The use of cytotoxic chemotherapy is associated with a response rate of 20 to 35% and a median survival time of 10 to 12 months among patients with advanced non–small-cell lung cancer.[1,2] Gefitinib is an orally administered tyrosine kinase inhibitor of the epidermal growth factor receptor (EGFR). In two phase 2 studies of patients with previously treated non–small-cell lung cancer, the response rate was 9 to 19%.[3,4] In subsequent phase 3 trials, the noninferiority of gefitinib as compared with docetaxel with respect to overall survival was shown in one study (hazard ratio, 1.02)[5] but not another (hazard ratio, 1.12).[6] Meanwhile, demographic and clinical factors such as Asian race, female sex, nonsmoking status, and adenocarcinoma were shown to be predictive of the efficacy of gefitinib, warranting a large comparative trial (First Line Iressa vs. Carboplatin/Paclitaxel in Asia [IPASS]; ClinicalTrials.gov number, NCT00322452) in which patients were selected in accordance with these factors.[7]

In May 2004, two pivotal studies showed that the presence of somatic mutations in the kinase domain of EGFR strongly correlates with increased responsiveness to EGFR tyrosine kinase inhibitors in patients with non–small-cell lung cancer.[8,9] It was later found that subgroups of patients with non–small-cell lung cancer who had sensitivity to gefitinib had a high incidence of EGFR mutations. In Japan, 30% or more of patients with mutated-EGFR non–small-cell lung cancer are male or have a history of smoking.[10,11] Therefore, we hypothesized that selecting patients on the basis of EGFR mutations rather than clinical factors would result in a population with a greater sensitivity to gefitinib.

Our previous prospective, phase 2 studies of gefitinib therapy in patients with advanced non–small-cell lung cancer and EGFR mutations[12-14] revealed a response rate of more than 70% and progression-free survival of 9 to 10 months. We also developed a rapid, sensitive method for detecting sensitive EGFR mutations: the peptide nucleic acid–locked nucleic acid (PNA-LNA) polymerase-chain-reaction (PCR) clamp method.[15] We then undertook a phase 3 study comparing gefitinib and standard carboplatin–paclitaxel chemotherapy in patients who had advanced non–small-cell lung cancer with sensitive EGFR mutations and who had not previously received chemotherapy.

METHODS

PATIENT POPULATION

This multicenter, randomized, phase 3 trial was approved by the institutional review board of each participating center. Eligibility criteria included the presence of advanced non–small-cell lung cancer harboring sensitive EGFR mutations, the absence of the resistant EGFR mutation T790M (in which threonine at amino acid 790 is substituted by methionine), no history of chemotherapy, and an age of 75 years or younger (because a benefit of a platinum-based regimen in patients >75 years of age is not established). Table 1 in the Supplementary Appendix (available with the full text of this article at NEJM.org) lists the detailed eligibility and exclusion criteria. The authors attest to the fidelity of the article to the full protocol and statistical-analysis plan.

DETECTION OF *EGFR* MUTATIONS

Cytologic or histologic specimens were examined for *EGFR* mutations by means of the PNA-LNA PCR clamp method. Briefly, genomic DNA fragments containing mutation hot spots of the *EGFR* gene were amplified with the use of a PCR assay in the presence of a peptide nucleic acid clamp primer synthesized from a peptide nucleic acid with a wild-type sequence. This method results in preferential amplification of the mutant sequence, which is then detected by a fluorescent primer that incorporates locked nucleic acids to increase the specificity. As a result, a mutant *EGFR* sequence is detected in specimens that contain 100 to 1000 excess copies of wild-type *EGFR* sequence. The sensitivity and specificity of the PNA-LNA PCR clamp method are 97% and 100%, respectively.[15,16]

STUDY DESIGN AND TREATMENT

Before randomization, patients were stratified according to sex, clinical stage of non–small-cell lung cancer (IIIB, IV, or postoperative relapse), and institution. Eligible patients were randomly assigned to receive either gefitinib (at a dose of 250 mg per day orally) or standard chemotherapy. The standard chemotherapy consisted of paclitaxel (at a dose of 200 mg per square meter of body-surface area, given intravenously over a 3-hour period) and carboplatin (at a dose equivalent to an area under the concentration–time curve [AUC] of 6, given intravenously over a 1-hour period), both administered on the first day of every 3-week cycle. The

carboplatin dose in milligrams was calculated by means of the Calvert formula (AUC × [the calculated creatinine clearance in milliliters per minute+25]; www.freekinetics.com/auccalc1.htm). The glomerular filtration rate was estimated according to the Cockcroft–Gault method ([140−age in years] × [actual weight in kilograms] ÷ [72 × serum creatinine level in milligrams per deciliter {× 0.85 in women}]). Chemotherapy was continued for at least three cycles. Gefitinib was administered until disease progression, development of intolerable toxic effects, or withdrawal of consent.

CLINICAL ASSESSMENTS

Assessments made before enrollment are summarized in Table 2 in the Supplementary Appendix. Assessment of the tumor for a response to treatment was performed by means of computed tomography (CT) every 2 months. Unidirectional measurements were adopted on the basis of the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.0).[17] Progression-free survival was evaluated for the period from the date of randomization to the date when disease progression was first observed or death occurred. Treatment response and progression-free survival were determined by external review of the CT films by experts who were not aware of the treatment assignments. Overall survival was evaluated for the period from the date of randomization to the date of death. Toxic effects were assessed according to the National Cancer Institute Common Terminology Criteria (NCI-CTC, version 3.0; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).

STATISTICAL ANALYSIS

The primary end point was progression-free survival, as a measure of the superiority of gefitinib over carboplatin–paclitaxel. From our previous data, we hypothesized that the progression-free survival with gefitinib was 9.7 months; from the results of the Iressa NSCLC Trial Assessing Combination Treatment (INTACT),[18] we hypothesized that the progression-free survival with standard chemotherapy was 6.7 months. We estimated that a total of 230 events would be needed for the study to have a power of 80% to confirm the superiority of gefitinib over standard chemotherapy, with the use of a log-rank test and a two-sided significance level of 5%. Setting the duration of enrollment to 2 years with a minimum follow-up period of 6 months, we initially planned to enroll 320 patients.

Kaplan–Meier survival curves were drawn for progression-free survival and were compared by means of a log-rank test. Hazard ratios (and 95% confidence intervals) were calculated with the use of a Cox proportional-hazards analysis. Prespecified adjustment factors included sex and clinical stage.

Secondary end points included overall survival, response rate, time to the deterioration of performance status (Eastern Cooperative Oncology Group [ECOG] performance status score of ≥3, capability of only limited self-care, or confinement to a bed or chair for >50% of waking hours[19]), and toxic effects. Overall survival and the time to ECOG performance status score of 3 or more were analyzed in the same way as progression-free survival. The response rate and rate of toxic effects were compared between the two groups with Fisher's exact test and the Wilcoxon test, respectively. Each analysis was performed with the use of a two-sided, 5% significance level and a 95% confidence interval by means of SAS for Windows software (release 9.1, SAS Institute).

One interim analysis was planned to analyze the primary end point (significance level, P=0.003). The Lan–DeMets method was used to adjust for multiple comparisons. The O'Brien–Fleming type alpha-spending function was also used.

RESULTS

PATIENT CHARACTERISTICS

The study was begun in March 2006. The preplanned interim analysis was performed 4 months after the 200th patient was enrolled (May 2009); it showed a significant difference in progression-free survival between the two treatment groups (P<0.001), and the independent data and safety monitoring committee recommended termination of the study. Therefore, the study was stopped at the end of May 2009.[20]

In total, 230 patients were enrolled from 43 institutions in Japan (Fig. 1). Half (115 patients) were randomly assigned to receive gefitinib and half to receive carboplatin–paclitaxel. Two patients were excluded because they were found to be ineligible. In the chemotherapy group, 1 patient was not evaluated for safety, owing to lack of receipt of the study drugs, and 3 others were excluded from the analysis of progression-free survival.

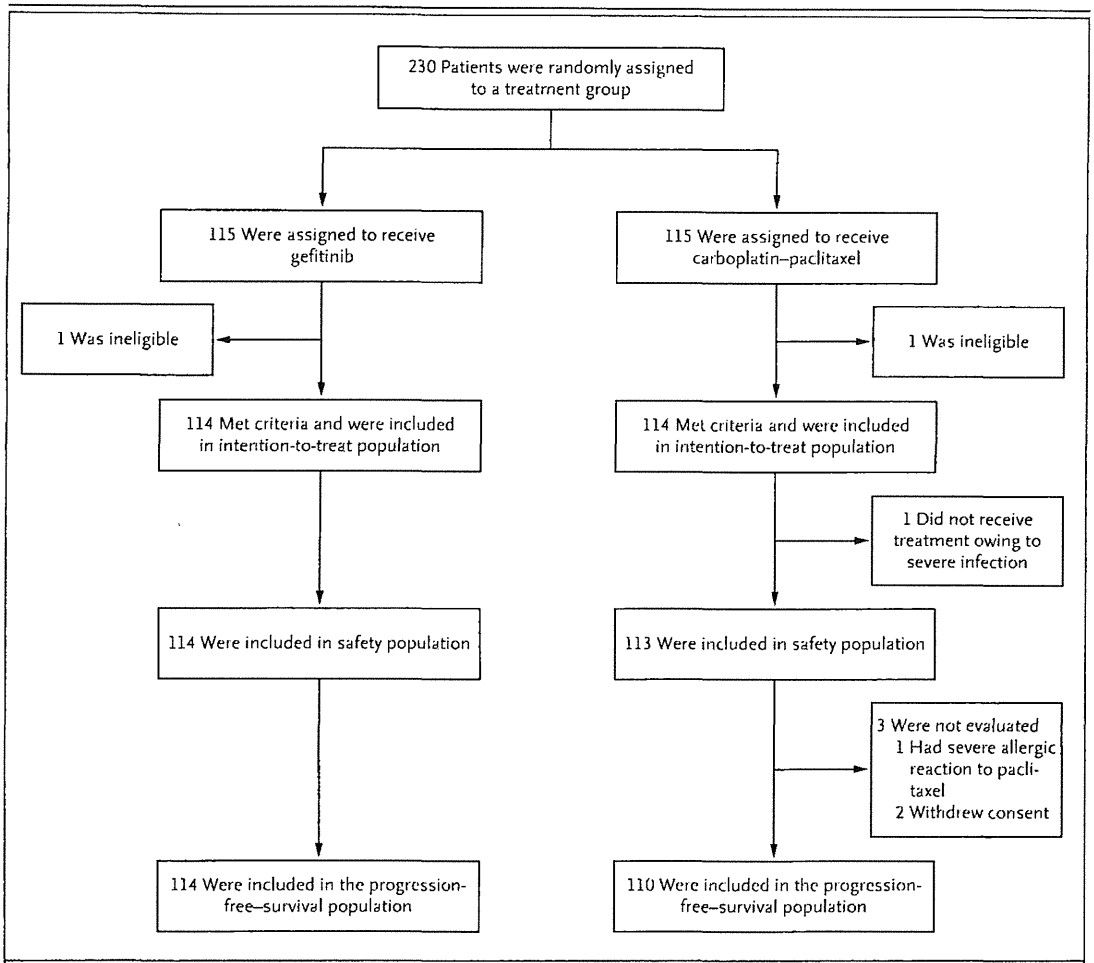

Figure 1. Randomization and Follow-up of the Study Patients, According to Treatment Group.

At the data cutoff point (early December 2009), the median follow-up period was 527 days (>17 months; range, 30 to 1261). The median duration of gefitinib treatment was 308 days (range, 14 to 1219); the median number of 3-week cycles of chemotherapy was 4 (range, 1 to 7). Three patients in the gefitinib group and 11 patients in the chemotherapy group received second-line treatment before they had RECIST-defined disease progression. The data on progression-free survival for these patients were censored at the time of the last CT evaluation at which they did not yet have evidence of disease progression. Demographic and disease characteristics at baseline were well balanced between the two groups (Table 1).

EFFICACY

The interim analysis performed in May 2009 showed that progression-free survival was significantly longer in the gefitinib group than in the chemotherapy group (median, 10.4 months vs. 5.5 months; hazard ratio for death or disease progression with gefitinib, 0.36; 95% confidence interval [CI], 0.25 to 0.51; P<0.001) (Fig. 1 in the Supplementary Appendix). A significant difference was again observed in the final analysis, performed in December 2009 (median progression-free survival, 10.8 months with gefitinib vs. 5.4 months with chemotherapy; hazard ratio, 0.30; 95% CI, 0.22 to 0.41; P<0.001) (Fig. 2A). The 1-year and 2-year rates of progression-free survival were 42.1% and 8.4%, respectively, in the gefitinib group and 3.2% and 0%, respectively, in the chemotherapy group. Subgroup analyses showed that women had significantly longer progression-free survival than men (median, 6.5 vs. 6.0 months; hazard ratio for death or disease progression, 0.68; 95% CI, 0.51 to 0.92; P=0.01). The objective response rate was significantly higher in the gefitinib group than the chemotherapy group (73.7% vs. 30.7%,

Table 1. Baseline Characteristics of the Intention-to-Treat Population, According to Treatment Group.*

Characteristic	Gefitinib (N=114)	Carboplatin–Paclitaxel (N=114)
Sex — no. (%)		
Male	42 (36.8)	41 (36.0)
Female	72 (63.2)	73 (64.0)
Age — yr		
Mean	63.9±7.7	62.6±8.9
Range	43–75	35–75
Smoking status — no. (%)		
Never smoked	75 (65.8)	66 (57.9)
Previous or current smoker	39 (34.2)	48 (42.1)
ECOG performance status score — no. (%)		
0	54 (47.4)	57 (50.0)
1	59 (51.8)	55 (48.2)
2	1 (0.9)	2 (1.8)
Histologic diagnosis — no. (%)		
Adenocarcinoma	103 (90.4)	110 (96.5)
Large-cell carcinoma	1 (0.9)	0
Adenosquamous carcinoma	2 (1.8)	1 (0.9)
Squamous-cell carcinoma	3 (2.6)	2 (1.8)
Other	5 (4.4)	1 (0.9)
Clinical stage — no. (%)		
IIIB	15 (13.2)	21 (18.4)
IV	88 (77.2)	84 (73.7)
Postoperative relapse	11 (9.6)	9 (7.9)
Type of EGFR mutation — no. (%)		
Exon 19 deletion	58 (50.9)	59 (51.8)
L858R	49 (43.0)	48 (42.1)
Other	7 (6.1)	7 (6.1)

* Plus–minus values are means ±SD. ECOG denotes Eastern Cooperative Oncology Group.

P<0.001) (Table 2). The median progression-free survival and response rate did not differ significantly between patients with the EGFR mutation consisting of an exon 19 deletion (11.5 months and 82.8%) and those with the L858R point mutation (in which leucine at amino acid 858 is replaced by arginine) (10.8 months and 67.3%) (Fig. 2B).

The overall survival did not differ significantly between the two treatment groups. The median survival time and the 2-year survival rate were 30.5 months and 61.4% for the gefitinib group, as compared with 23.6 months and 46.7%, respectively, for the carboplatin–paclitaxel group (P=0.31) (Fig. 2C). Neither sex nor clinical stage had a significant effect on overall survival. The time to an ECOG performance status score of 3 or more did not differ significantly between the two groups.

SAFETY

All patients who had received at least one dose of a study drug were included in the safety analysis. The most common adverse events in the gefitinib group were rash and elevated levels of aspartate aminotransferase or alanine aminotransferase, and in the chemotherapy group, appetite loss, neutropenia, anemia, and sensory neuropathy (Table 3, and Table 3 in the Supplementary Appendix). Interstitial lung disease was reported in six patients (5.3%) in the gefitinib group; three cases were severe, and one of the three was fatal. One grade 4 seizure in the gefitinib group and one grade 4 cerebral infarction and one grade 4 bowel obstruction in the chemotherapy group were observed. The incidence of severe toxic effects (NCI-CTC grade ≥3) was significantly higher in the chemotherapy group than in the gefitinib group (71.7% vs. 41.2%, P<0.001).

TREATMENT AFTER PROTOCOL DISCONTINUATION

Data on treatment given after the study protocol was discontinued were collected retrospectively. Though any treatment was permitted, the protocol recommended that the crossover regimen be used as second-line treatment. As of the data cutoff point, 37 patients in the gefitinib group had continued their first-line gefitinib therapy. Among the remaining 77 patients in the gefitinb group who had stopped receiving gefitinib, 52 (67.5%) were receiving carboplatin–paclitaxel as second-line treatment, with a response rate of 28.8%. Sixteen other patients in the gefitinib group were receiving other therapies such as carboplatin–gemcitabine. Among the 112 patients who had completed first-line carboplatin–paclitaxel, 106 patients (94.6%) received second-line gefitinib; 58.5% of these patients had a response.

DISCUSSION

Previous phase 2 studies have suggested that EGFR tyrosine kinase inhibitors are highly effective against mutated-EGFR non–small-cell lung cancer. The current phase 3, prospective, randomized study showed that the use of gefitinib results in progression-free survival that is twice as long

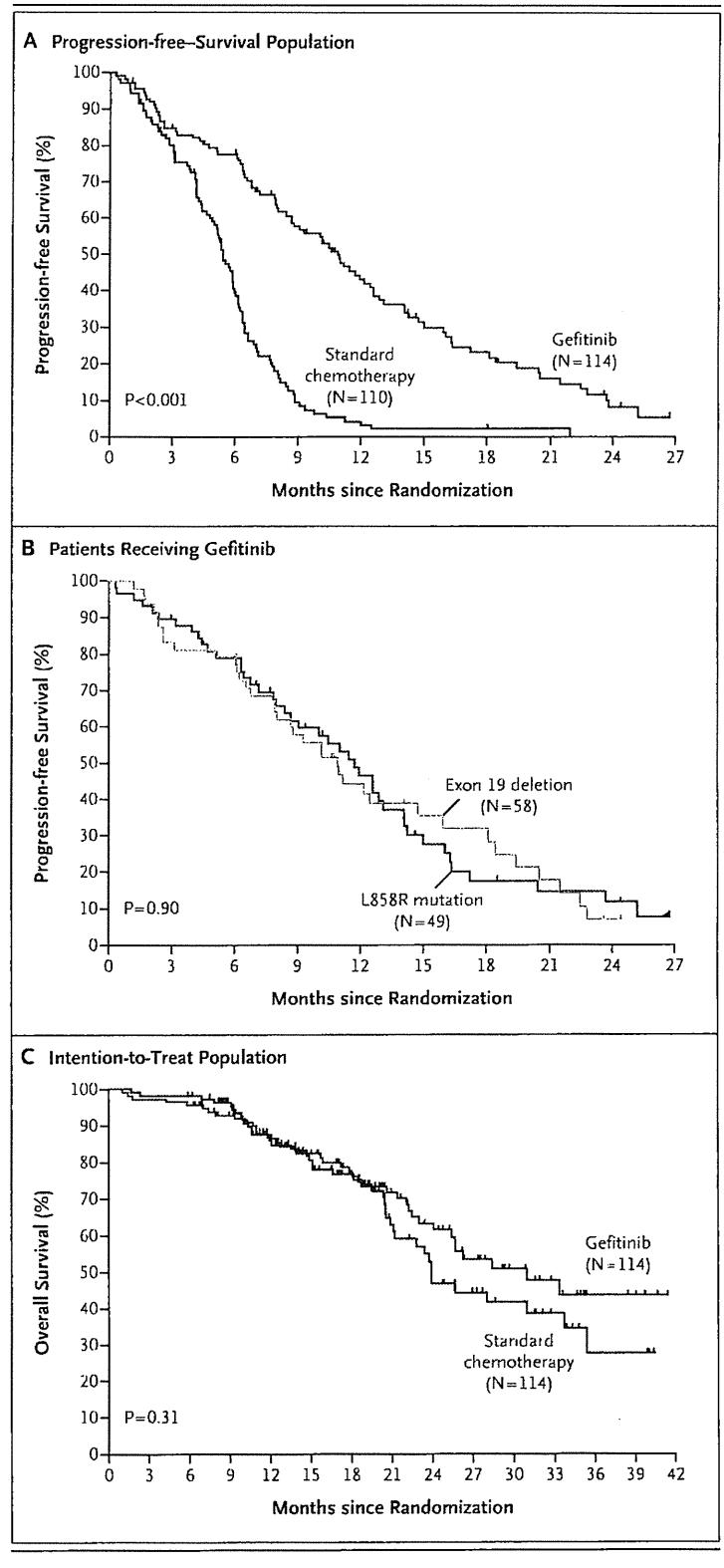

Figure 2. Progression-free Survival and Overall Survival among the Study Patients.

Kaplan–Meier curves for progression-free survival are shown for the progression-free–survival population (Panel A) and for the 107 patients in the gefitinib group with either of the two most common types of epidermal growth factor receptor (EGFR) mutation (Panel B). Kaplan–Meier curves for overall survival in the intention-to-treat population are shown in Panel C. In Panels B and C, tick marks indicate patients for whom data were censored at the data cutoff point (early December 2009).

as that obtained with the use of carboplatin–paclitaxel in patients with mutated-EGFR non–small-cell lung cancer, with a tolerable toxicity profile, including less hematologic toxicity and neurotoxicity than is seen with chemotherapy.

The IPASS, which was conducted in Asia, compared gefitinib with carboplatin–paclitaxel as the first-line treatment for advanced non–small-cell lung cancer in patients selected on the basis of clinical characteristics that included a history of no smoking or light smoking as well as histologic evidence of adenocarcinoma.[7] Although IPASS showed the overall superiority of gefitinib (rate of 1-year progression-free survival, 24.9%, vs. 6.7% with chemotherapy; hazard ratio for death or disease progression, 0.74; P<0.001), the most impressive result emerged from subgroup analysis: as compared with chemotherapy, gefitinib was effective in patients with mutant EGFR (hazard ratio for death or disease progression, 0.48) but was ineffective in those with wild-type EGFR (hazard ratio, 2.85). This finding suggested that the presence of EGFR mutations is the best criterion for selection of patients who benefit from gefitinib, an idea that is validated by the present study.[20] Recently, another Japanese phase 3 study (WJTOG3405; University Hospital Medical Information Network Clinical Trials Registry [UMIN-CTR] number, UMIN000000539) compared gefitinib to cisplatin–docetaxel as the first-line treatment for advanced non–small-cell lung cancer with EGFR mutations.[21] Although this study also showed the superiority of gefitinib over standard chemotherapy with respect to progression-free survival, the magnitude of the benefit was somewhat smaller than in our study, possibly because of differences in the characteristics of the patients (since 41% of patients in WJTOG3405 had had surgery, vs. only 9% in our study) and the duration of follow-up (median, 81 days in WJTOG3405 vs. 527 days in our study).

The standard end point of phase 3 trials of treatments for advanced non–small-cell lung cancer has been overall survival. However, when our trial was begun in 2006, we had data only on