Tumor biopsy and patient enrollment in clinical trials for advanced hepatocellular carcinoma

Lorenza Rimassa, Maria Reig, Giovanni Abbadesa, Markus Peck-Radosavljevic, William Harris, Vittorina Zagonel, Davide Pastorelli, Elena Rota Caremoli, Camillo Porta, Nevena Damjanov, Hitendra Patel, Bruno Daniele, Maria Lamar, Brian Schwartz, Terri Goldberg, Armando Santoro, Jordi Bruix

Lorenza Rimassa, Medical Oncology and Hematology Unit, Humanitas Cancer Center, Humanitas Clinical and Research Center, 20089 Rozzano, Italy

Maria Reig, Jordi Bruix, Barcelona Clinic Liver Cancer Group, Liver Unit, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERehd, 08036 Barcelona, Spain

Giovanni Abbadesa, Maria Lamar, Brian Schwartz, Clinical Development, ArQule, Inc, Burlington, MA 01803, United States

Markus Peck-Radosavljevic, Department of Gastroenterology, Hepatology, Endocrinology, and Nephrology, Klinikum Klagenfurt am Wörthersee, 9020 Klagenfurt, Austria

William Harris, Department of Medicine, Oncology Division, University of Washington School of Medicine, Seattle, WA 98195, United States

Vittorina Zagonel, Department of Clinical and Experimental Oncology, Medical Oncology 1, Veneto Institute of Oncology-IRCCS, 35128 Padua, Italy

Davide Pastorelli, Department of Oncology, Santa Maria del Prato Hospital, 32032 Feltre, Italy

Elena Rota Caremoli, Department of Oncology, Papa Giovanni XXIII Hospital, 24125 Bergamo, Italy

Camillo Porta, Department of Oncology, Fondazione IRCCS Policlinico San Matteo, 27100 Pavia, Italy

Nevena Damjanov, Division of Gastrointestinal Oncology, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA 19104, United States

Hitendra Patel, Department of Medicine, The University of Arizona Cancer Center, Tucson, AZ 85724, United States

Bruno Daniele, Department of Oncology, G. Rummo Hospital, Via Dell’Angelo, 82100 Benevento, Italy

Terri Goldberg, Clinical Development, Daiichi Sankyo, Edison, NJ 08837, United States

Armando Santoro, Medical Oncology and Hematology Unit, Humanitas Cancer Center, Humanitas Clinical and Research Center, Humanitas University, 20089 Rozzano, Italy

Author contributions: Rimassa L, Reig M, Abbadesa G, Santoro A and Bruix J wrote the manuscript; Peck-Radosavljevic M, Harris W, Zagonel V, Pastorelli D, Rota Caremoli E, Porta C, Damjanov N, Patel H, Daniele B, Lamar M, Schwartz B and Goldberg T contributed to the preparation, editing, and final approval of the manuscript.

Conflict-of-interest statement: Authors report no conflict of interest with the subject discussed in this article.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Unsolicited manuscript

Correspondence to: Dr. Lorenza Rimassa, Deputy Director, Medical Oncology and Hematology Unit, Humanitas Cancer Center, Humanitas Clinical and Research Center, Via Manzoni 56, 20089 Rozzano, Italy. lorenza.rimassa@cancercenter.humanitas.it

Telephone: +39-2-82244573
Fax: +39-2-82244590

Received: January 20, 2017
Peer-review started: January 22, 2017
First decision: February 10, 2017
Revised: February 24, 2017
TO THE EDITOR

Liver cancer was estimated to be responsible for almost 746000 deaths worldwide in 2012 (WHO), with hepatocellular carcinoma (HCC) being the most common type\[1\]. Sorafenib, a multi-targeted tyrosine kinase inhibitor (TKI), is the only approved first-line systemic therapy for HCC\[2,3\]. Recently regorafenib, a similar multi-targeted TKI, was shown to benefit HCC patients who tolerated and progressed on sorafenib\[4\]. It is still unclear which patient sub-populations may benefit more from these drugs although interestingly, development of dermatological adverse events and AFP decrease during treatment may be associated with improved outcomes on sorafenib\[5,6\].

Many efforts to develop new therapies for unselected HCC populations have failed: in first-line, sunitinib\[7\], brivanib\[8\], linifanib\[9\] when compared to sorafenib; and erlotinib\[10\] and doxorubicin\[11\] in combination with sorafenib; in second-line, brivanib\[12\], everolimus\[13\], ramucirumab\[14\], and ADI-PEG 20\[15\]. Studies looking for alternative approaches for HCC, such as immunotherapy, are ongoing\[16,17\].

While for other solid tumors prognostic and predictive molecular biomarkers are already used in clinical practice, for HCC biomarker research has not produced conclusive results\[18-20\]. The many disappointing clinical trial failures due to excessive toxicity, lack of efficacy, study design problems, or lack of biological population enrichment, emphasize the need to identify predictive molecular biomarkers for selection of treatment in patients with HCC.

Circulating biomarker analyses from the sorafenib approval study suggested that the angiogenesis biomarkers angioptin-2 (Ang2) and vascular endothelial growth factor (VEGF) were independent prognostic factors, while none of the tested biomarkers were predictive of sorafenib efficacy\[21\]. On the contrary, on the basis of positive efficacy and biomarker results in tumor MMNG HOS transforming gene (MET)-High patients in a randomized phase II study\[22,23\], tivantinib has been tested in two phase III studies selecting only MET-High patients, one in western countries and the other in Japan (NCT01755767, NCT02029157); while the study in the western world has recently been announced to be negative\[24\], results are still awaited for the Japanese study. Recently, second-line ramucirumab was shown to offer a significant survival benefit in a pre-specified subgroup of patients with elevated alpha-fetoprotein (AFP)\[14\] and a confirmatory phase III clinical trial is ongoing in this sub-population (NCT02435433).

Challenges of enrolling patients into clinical trials for second-line HCC

Most patients with advanced, unresectable HCC who are eligible for clinical trials with systemic therapies have a
relatively short life expectancy, with rapid progression of
disease, especially if they have progressed on sorafenib
and have distant metastases\textsuperscript{[25,26]}. To optimize timely
and proper recommendations for the care of these
patients, their cases should be discussed periodically by
multidisciplinary teams including medical oncologists,
gastroenterologists/hepatologists, surgeons, inter-
ventional radiologists, radiation oncologists, and
pathologists. Such meetings would ideally take place
weekly, or every two weeks: a longer delay of the proper
therapeutic decision may undermine the possibilities of
trial enrolment for patients.

Patients who are not followed in research centers
may find it challenging to seek further treatment
options, other than best supportive care, after failing
standard treatments. On the other hand, many
physicians have difficulties in identifying proper patients
for second line clinical trials. Set up of webpages listing
available clinical trials, and of inter-hospital networks
to prime referrals for research studies can provide a key
support to reduce the gap time for the comprehensive
evaluation of these patients and speed up recruitment.
Considering all this, with due exceptions, the best
hospitals to involve in clinical trials for second-line HCC
and to refer these patients to seem to be the larger
academic centers, where HCC care is jointly pursued
by at least oncologists and hepatologists.

Finally, study characteristics can make a difference
in enabling trial enrolment, and involvement of active
investigators from multiple relevant disciplines in the
early phases of the protocol design can be beneficial to
the scope.

Importance of analyzing tumor biomarkers to guide
development of novel therapies

Analyzing HCC tumor specimens is essential to improve
the knowledge about development, biology under-
pinning progression and treatment of HCC. Particularly,
clarifying the tumor biology may lead to identifying biomarkers that would predict response or resistance to
therapies.

Hepatology guidelines recommend that the diagnosis
of HCC may be established via radiographic studies in
the appropriate patient population\textsuperscript{[27]}, therefore not
all patients with hepatic tumors have available biopsy
material allowing for molecular profiling of their disease,
at diagnosis. Furthermore, as tumors progress, they
accumulate genetic alterations developing heterogeneity
and drug resistance\textsuperscript{[28]}. Studies suggest that VEGF
pathway inhibition, as with sorafenib, produces a
hypoxic microenvironment with oxidative stress that
selects for highly aggressive, invasive tumor cells
driving overexpression of proliferation factors, HCC
progression, and induction of an immunosuppressive
microenvironment\textsuperscript{[29,30]}. Therefore, if in the future any
molecular classifiers have an impact in clinical decision
making, routine biopsy will become part of the standard
of care. Considering the current treatment landscape,
and clinical rationale to select patient populations based on the drug target, success rate might increase and adverse events would be avoided to patient populations estimated not to benefit from the experimental drug. Biological understanding of the treated population can be relevant even in trials where the target expression is not used as an entry criterion, providing key information to design subsequent target-selected studies. The historically low rates of biopsy confirmation of patients with HCC has presented a barrier to development of experimental therapeutics in this disease. With such frail patient population, multidisciplinary case discussions and inter-hospital networks can enable a seamless transition from standard care to tumor biology analysis for a clinical trial. Hopefully, as more targeted therapies are developed, the biological characteristics of tumors, including histology and more specific molecular markers, will be evaluated in the therapeutic decision process for HCC patients as currently occurs for other tumor types.

ACKNOWLEDGMENTS

We thank Hazem Hallak (CHEMC Global IIC, Philadelphia, PA, United States) for his medical editorial assistance, and Kathleen Farren (ArQule) for her editorial assistance.

REFERENCES

1. Torre LA, Bray F, Siegel RL, et al. Cancer statistics, 2012. CA Cancer J Clin 2012; 62: 5-29. [PMID: 22601354 DOI: 10.3324/caac.21184]

2. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008; 359: 378-390. [PMID: 18565014 DOI: 10.1056/NEJMoa0708857]

3. Cheng AL, Kang YK, Chen Z, Tao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, Wang J, Tak WY, Pan H, Barook C, Zou J, Voliotis D, Guan Z. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009; 10: 25-34. [PMID: 19095497 DOI: 10.1016/S1470-2045(08)70285-7]

4. Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, Peichl M, Yokosuka O, Rosmorduc O, Breder V, Gerolami R, Masi G, Ross PJ, Song T, Chen LT. Phase III randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with advanced hepatocellular carcinoma. J Clin Oncol 2008; 26: 2451-2457. [PMID: 18091698 DOI: 10.1200/JCO.2008.19.5041]

5. Reig M, Torres F, Rodriguez-Lopez C, Forner A, LLarch N, Rimola J, Darnell A, Rios J, Ayuso C, Bruix J. Early dermatologic adverse events predict better outcome in HCC patients treated with sorafenib. J Hepatol 2014; 61: 318-324. [PMID: 24703956 DOI: 10.1016/j.jhep.2014.03.030]

6. Personeni N, Bozzarelli S, Pressiani T, Rimassa L, Tironi MC, Scala F, Cartoni C, Pedicini V, Giordano L, Santoro A. Feasibility of alpha-fetoprotein response in patients treated with sorafenib for advanced hepatocellular carcinoma. J Hepatol 2012; 57: 101-107. [PMID: 22414760 DOI: 10.1016/j.jhep.2012.06.016]

7. Cheng AL, Kang YK, Lin DY, Park JW, Kudo M, Qin S, Chung HC, Song X, Xu J, Poggi G, Omata M, Pitman Lowenthal S, Llanza Solang Y, Lecuaga MJ, Raymond E. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. J Clin Oncol 2013; 31: 4067-4075. [PMID: 24081937 DOI: 10.1200/JCO.2012.45.8372]

8. Johnson PJ, Qin S, Park JW, Poon RT, Raoul JL, Philip PA, Hsu CH, Hu TH, Heo J, Xu J, Lu L, Chao Y, Boucher E, Han KH, Pak SW, Robles-Avila J, Kudo M, Yan L, Sobhonsilpasuk A, Komov D, Decaens T, Tak WY, Jeng LB, Liu D, Ezzeddine R, Walters I, Cheng AL. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. J Clin Oncol 2013; 31: 3517-3524. [PMID: 23980684 DOI: 10.1200/JCO.2012.48.4410]

9. Cainap C, Qin S, Huang WT, Chung JH, Pan H, Cheng Y, Kudo M, Kang YK, Chen PJ, Toh H, Gorbonova V, Ewansky F, Qin J, McKeel MD, Rieker JL, Carlson DM, El-Noewiem S. Linifanib versus Sorafenib in patients with advanced hepatocellular carcinoma: results of a randomized phase III trial. J Clin Oncol 2015; 33: 172-179. [PMID: 25488963 DOI: 10.1200/JCO.2013.54.3298]

10. Zhu AX, Rosmorduc O, Evans TR, Ross PJ, Santoro A, Camillo P, Buix A, Qin S, Thuluvath PJ, Llovet JM, Leberre MA, Jensen M, Meinhardt G, Kang YK, Tak WY, SEARCH: a phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with advanced hepatocellular carcinoma. J Clin Oncol 2015; 33: 559-566. [PMID: 25547503 DOI: 10.1200/JCO.2013.53.7746]

11. Abou-Alfa G, Niedzwiecki D, Knox J, Kausibach A, Posey J, Tan BR, Kavan P, Goel R, Murray JJ, Bekaii-Saab TS, Van YC, Rajdev L, Keliy RK, Sngel A, Balfitt J, Harding J, Schwartz LH, Goldberg RM, Bertagnoli MM, Venook AP. Phase III randomized study of sorafenib plus doxorubicin versus sorafenib in patients with advanced hepatocellular carcinoma (HCC): CALGB 80802 (Alliance). Gastrointestinal Cancers Symposium; 2016, Jan 21-23; San Francisco, CA. J Clin Oncol 2016; 34: 192.

12. Llovet JM, Decaens T, Raoul JL, Boucher E, Kudo M, Chang C, Kang YK, Assenat E, Lin HY, Boige V, Mathurin P, Fartoux L, Lin DY, Bruix J, Poon RT, Sherman M, Blanc JF, Fins RS, Tak WY, Chao Y, Ezzeddine R, Liu D, Walters I, Park JW. Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized phase III BRISK-PS study. J Clin Oncol 2013; 31: 3509-3516. [PMID: 23980900 DOI: 10.1200/JCO.2012.47.3009]

13. Zhu AX, Kudo M, Assenat E, Cattan S, Kang YK, Lin HY, Poon RT, Blanc JF, Vogel A, Chen CL, Dorval E, Peck-Radosavljevic M, Santoro A, Daniele B, Furse J, Papar A, Aenak O, Sellami BM, Chen LT. Effect of everolimus on survival in advanced hepatocellular carcinoma after failure of sorafenib: the EVOLVE-1 randomized clinical trial. JAMA 2014; 312: 57-67. [PMID: 25058218 DOI: 10.1001/jama.2014.7189]

14. Zhu AX, Park JO, Rooy BY, Yen CJ, Poon R, Pastorelli D, Blanc JF, Chang HC, Baror AD, Piffier TE, Okusaka T, Kubakova K, Trojan J, Sastre J, Chau I, Jiang SC, Abada PB, Yang L, Schwartz JD, Kudo M. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib: the RAMOS study. J Clin Oncol 2015; 33: 4017-4025. [PMID: 25912448 DOI: 10.1200/JCO.2014.63.7336]

15. Abou-Alfa GK, Qin S, Rooy BY, Lu SN, Yen CJ, Feng YH, Lim HY, Izzo F, Colombo M, Sarker D, Bolondi L, Vaccaro GM, Harris WP, Chen Z, Hubner R, Meyer T, Akabshie A, Ruck PJ, Anak O, Sellami BM, Chen LT. Effect of everolimus on survival in advanced hepatocellular carcinoma after failure of sorafenib: the EVOLVE-1 randomized clinical trial. JAMA 2014; 312: 57-67. [PMID: 25058218 DOI: 10.1001/jama.2014.7189]
Welling T, Yeo W, Chopra A, Anderson J, Dela Cruz CM, Lang L, Neely J, Melero I. Phase I/II safety and antitumor activity of nivolimab (nivo) in patients (pts) with advanced hepatocellular carcinoma (HCC): Interim analysis of the CheckMate-040 dose escalation study. ASCO Annual Meeting; 2016 June 3-6; Chicago, IL, USA. J Clin Oncol 2016; 34: 4012

17 Gong XL, Qin SK. Progress in systemic therapy of advanced hepatocellular carcinoma. World J Gastroenterol 2016; 22: 6582-6594 [PMID: 27547002 DOI: 10.3748/wjg.v22.i29.6582]

18 Bruix J, Han KH, Gores G, Llovet JM, Mazzaferro V. Liver cancer: Approaching a personalized care. J Hepatol 2015; 62: S144-S156 [PMID: 25920083 DOI: 10.1016/j.jhep.2015.02.007]

19 Niu ZS, Niu XJ, Wang WH. Genetic alterations in hepatocellular carcinoma: An update. World J Gastroenterol 2016; 22: 9069-9095 [PMID: 27895396 DOI: 10.3748/wjg.v22.i41.9069]

20 Scaglione B, Kazemi M, Pozzato G, Papas B, Farra R, Grassi M, Zanconati F, Grassi G. Novel hepatocellular carcinoma molecules with prognostic and therapeutic potentials. World J Gastroenterol 2014; 20: 1268-1288 [PMID: 24574801 DOI: 10.3748/wjg.v20.i5.1268]

21 Llovet JM, Peña CE, Lathia CD, Shan M, Meinhardt G, Bruix J. Plasma biomarkers as predictors of outcome in patients with advanced hepatocellular carcinoma. Clin Cancer Res 2012; 18: 2290-2300 [PMID: 22374331 DOI: 10.1158/1078-0432.CCR-11-2175]

22 Santoro A, Rimassa L, Borbath I, Daniele B, Salvaggi S, Van Laethem JL, Van Vlierberghe H, Trojan J, Kolligs FT, Weiss A, Miles S, Gasbarrini A, Lencioni M, Cicalese L, Sherman M, Gridelli C, Buggisch P, Gerken G, Schmid RM, Boni C, Personeni N, Hassoun Z, Abbadessa G, Schwartz B, Von Roemeling R, Lamar ME, Chen Y, Porta C. Tivantinib for second-line treatment of advanced hepatocellular carcinoma: a randomised, placebo-controlled phase 2 study. Lancet Oncol 2013; 14: 55-63 [PMID: 23182677 DOI: 10.1016/S1470-2045(12)70490-4]

23 Rimassa L, Abbadessa G, Personeni N, Porta C, Borbath I, Daniele B, Salvaggi S, Van Laethem JL, Van Vlierberghe H, Trojan J, De Toni EN, Weiss A, Miles S, Gasbarrini A, Lencioni M, Lamar ME, Wang Y, Shuster D, Schwartz BE, Santoro A. Tumor and circulating biomarkers in patients with second-line hepatocellular carcinoma from the randomized phase II study with tivantinib. Oncotarget 2016; 7: 72622-72633 [PMID: 27579536 DOI: 10.18632/oncotarget.11621]

24 ArQule, Inc. Daiichi Sankyo and ArQule Announce the Completion of the METIV-HCC Phase 3 Study of Tivantinib in Second-Line Treatment of MET-Overexpressing Hepatocellular Carcinoma. Available from: http://investors.arqule.com/releasedetail.cfm?ReleaseID=1012374

25 Reig M, Rimola J, Torres E, Darnell A, Rodriguez-Lopez C, Forner A, Llarch N, Rios J, Ayuso C, Bruix J. Postprogression survival of patients with advanced hepatocellular carcinoma: rationale for second-line trial design. Hepatology 2013; 58: 2023-2031 [PMID: 23787822 DOI: 10.1002/hep.26586]

26 Iavarone M, Cabiibbo G, Biotato M, Della Corte C, Maida M, Barbaro M, Basso M, Vavassori S, Craxi A, Gricco A, Cammà C, Colombo M. Predictors of survival in patients with advanced hepatocellular carcinoma who permanently discontinued sorafenib. Hepatology 2015; 62: 784-791 [PMID: 25645399 DOI: 10.1002/hep.27729]

27 Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011; 53: 1020-1022 [PMID: 21374666 DOI: 10.1002/hep.24199]

28 Gerlinger M, Rowan AJ, Horswell S, Larkin J, Endesfelder D, Gronroos E, Martinez P, Matthews N, Stewart A, Tarpey P, Varela I, Philimore B, Begum S, McDonald NQ, Butler A, Jones D, Raine K, Latimer C, Santos CR, Nohadani M, Eklund AC, Spencer-Dene B, Clark G, Pickering L, Stamp G, Gore M, Zalasli Z, Downward J, Futreal PA, Swanton C. Intra-tumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med 2012; 366: 883-892 [PMID: 22397650 DOI: 10.1056/NEJMoa1113205]

29 Jahangiri A, De Lay M, Miller LM, Carbonell WS, Hu YL, Lu K, Tom MW, Paquette J, Tokuyasu TA, Tsao S, Marshall R, Perry A, Bjorgan KM, Chauvel MM, Ronen SM, Bergers G, Aghi MK. Gene expression profile identifies tyrosine kinase c-Met as a targetable mediator of antiangiogenic therapy resistance. Clin Cancer Res 2013; 19: 1773-1783 [PMID: 23307858 DOI: 10.1158/1078-0432.CCR-12-1281]

30 Ye LY, Chen W, Bai XL, Xu XY, Zhang Q, Xia XF, Sun X, Li GG, Hu QD, Fu QH, Liang TB. Hypoxia-Induced Epithelial-to-Mesenchymal Transition in Hepatocellular Carcinoma Induces an Immunosuppressive Tumor Microenvironment to Promote Metastasis. Cancer Res 2016; 76: 818-830 [PMID: 26837767 DOI: 10.1158/0008-5472.CAN-15-0977]

31 Eisai Co., Ltd. Phase III trial of anticancer agent Lenvima® as first-line treatment for unresectable hepatocellular carcinoma meets primary endpoint. Available from: http://www.eisai.com/news/enews201706pdf.pdf

P- Reviewer: Gkretsi V, Varona MA S- Editor: Qi Y L- Editor: A E- Editor: Zhang FF
