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Oncolytic immunotherapeutic virus in HCC: Can it compete with molecular therapies?

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COMMENTARY ON:

Randomized dose-finding clinical trial of oncolytic immunotherapeutic vaccinia JX-594 in liver cancer. Heo J, Reid T, Ruo L, Breitbach CJ, Rose S, Bloomston M, Cho M, Lim HY, Chung HC, Kim CW, Burke J, Lencioni R, Hickman T, Moon A, Lee YS, Kim MK, Daneshmand M, Dubois K, Longpre L, Ngo M, Rooney C, Bell JC, Rhee BG, Patt R, Hwang TH, Kirn DH. Nat Med 2013 March;19(3):329–36. Copyright (2012). Abstract reprinted by permission from Macmillan Publishers.

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Abstract: *Oncolytic viruses and active immunotherapeutics have complementary mechanisms of action (MOA) that are both self amplifying in tumors, yet the impact of dose on subject outcome is unclear. JX-594 (Pexa-Vec) is an oncolytic and immunotherapeutic vaccinia virus. To determine the optimal JX-594 dose in subjects with advanced hepatocellular carcinoma (HCC), we conducted a randomized phase 2 dose-finding trial (n = 30). Radiologists infused low- or high-dose JX-594 into liver tumors (days 1, 15, and 29); infusions resulted in acute detectable intravascular JX-594 genomes. Objective intrahepatic Modified Response Evaluation Criteria in Solid Tumors (mRECIST) (15%) and Choi (62%) response rates and intrahepatic disease control (50%) were equivalent in injected and distant noninjected tumors at both doses. JX-594 replication and granulocyte–macrophage colony-stimulating factor (GM-CSF) expression preceded the induction of anticancer immunity. In contrast to tumor response rate and immune endpoints, subject survival duration was significantly related to dose (median survival of 14.1 months compared to 6.7 months on the high and low dose, respectively; hazard ratio 0.39; P = 0.020). JX-594 demonstrated oncolytic and immunotherapy MOA, tumor responses and dose-related survival in individuals with HCC.*

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HCC is a major public health problem, ranking as the 3rd cause of cancer-related death and the 16th absolute cause of death globally [1]. Its incidence is rising worldwide and besides major improvements in HCC management during the past 30 years, sorafenib remains the only approved systemic treatment for advanced tumors [2]. Considering that no biomarkers are able to predict response to sorafenib [3] and recent trials in first and second line have not provided treatment alternatives [4], the development of novel and innovative therapies is crucial [5,6].

The study from Heo *et al.* points towards a completely new potential treatment option for HCC. The JX-594 virus has an inactivation of its thymidine kinase further engineered to express β-galactosidase, a surrogate marker for detecting viral gene expression and human granulocyte–macrophage colony-stimulating factor (GM-CSF) to stimulate anti-tumor immunity [7,8]. Replication of the virus is dependent on the EGFR–RAS pathway, achieving a satisfactory high local concentration in the tumor due to selective targeting of tumor cells. JX-594 infects cells with activation of the EGFR/RAS pathway and uses the pathway to replicate and eventually kill the infected cells (Fig. 1) [7,8].

The study is a dose finding trial in which the authors compared low-dose (10^8 plaque-forming units (PFU)) versus high dose (10^9 PFU) intratumoral delivery of JX-594 virus in 30 patients with advanced HCC. Thus, low dose patients are receiving 10% of the viral load compared to high-dose patients. The trial is a multicenter randomized 1:1 trial assigning patients to receive either high or low dose, stratified by viral or non-viral infection. JX-594 virus was administered by imaging-guided intratumoral injection on day 1, 15, and 29 and the dose was distributed among up to five intrahepatic tumors. The objectives of this trial were to compare safety and efficacy measured as response rate assessed by expert radiologist blinded to treatment group and overall survival. Concentration of JX-594 in the blood was maximum 15 min after injection and virus replication was assessed by β-gal levels and hGM-CSF induction together with detection of JX-594 genomes in the blood followed by induction of humoral and cellular anticancer immunity. Both doses were well-tolerated and no treatment-related deaths were reported, being the most frequent adverse event flu-like symptoms in all subjects, and the most severe adverse event lymphopenia (grade 3–4) in 14% of patients in both treatments groups. Serial dynamic magnetic resonance imaging scans were used to assess tumor response

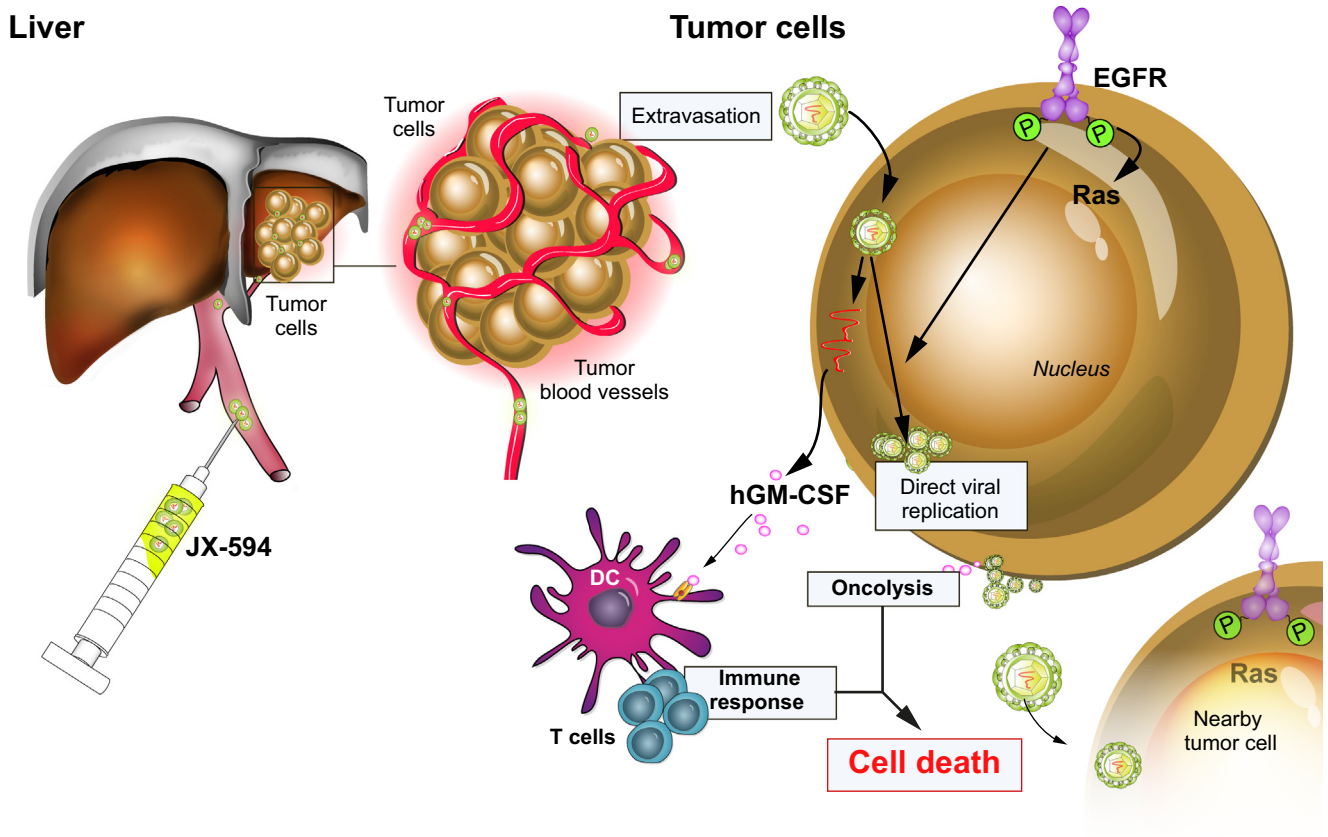

Fig. 1. JX-594 mechanism of action and tumoral selectivity. Genetically-modified viral particles (JX-594) are capable of replicating inside the tumor cell with active EGFR–RAS kinase pathway. After replication, viral-induced oncolysis triggers tumor cell death. At the same time, JX-594 expresses GM-CSF which triggers immune-induced cell death.

by mRECIST and Choi response, achieved in around 15% and 62% of patients, respectively. Patients in the high dose group had significantly better overall survival (OS) (14.1 months *vs.* 6.7 months). The study was halted early because of these survival differences.

The study deserves special attention due to several positive aspects. First, this is a novel treatment approach with a triple mechanism of action: (1) direct viral replication inducing oncolysis of cancer cells with activated Ras signaling, (2) immunotherapeutic, due to the expression of GM-CSF by the virus, which stimulated toll-like receptors, activating dendritic cells and the whole immune response related to T-cell activation [7,8], and (3) anti-angiogenic properties [7,8]. Second, the treatment is quite selective targeting tumoral cells. This phenomenon is explained both due to the fact that tumoral blood vessels allow extravasation of the viral particle [8] – as opposed to normal vessels – and also due to the selective replication in cells showing activation of Ras, very uncommon in normal cells. In addition, the group nicely demonstrated, in a phase I trial, that intravenous injection of the JX-594 virus selectively target cancer tissue without affecting normal tissues in patients with advanced, treatment-refractory solid tumors [7]. Its ability to spread within the tissue carrying large therapeutic transgenes and its stability in the blood, made the JX-594 a good candidate for intravenous infusion, as well. Third, the studies have shown lack of severe toxicity or treatment-related death cases. This is particularly important considering that more than 80% of patients with HCC have cirrhosis, and thus non-tumoral toxicity may induce liver failure, as has been reported with sunitinib therapies [9]. Finally, tumoral lysis was detected in cancer cells not-directly inoculated with the oncolytic virus, suggesting effective mechanisms resulting from immune response or distant viral replication. Thus, the approach looks promising and results from additional studies are expected.

The oncolytic virus therapeutic approach reported has also some limitations. First, the authors did not include sorafenib or placebo as control arm for first or second-line therapies, respectively. It is obvious that they aimed at exploring a dose-dependent effect, which seems identified with the higher dose, but the median 14.1 months of survival of the active arm is difficult to put in context. Although most of the patients had advanced disease (BCLC C), some of them already received sorafenib as first line therapy, and thus mixed populations have been included. The randomized nature of the study aids in defining a median survival for the control arm (low-dose therapy) of 6.7 months. The study is clearly underpowered to establish survival benefits, but the data can be interpreted in the context of previously reported large-phase III investigations. Overall survival reported from sorafenib trials in first line established a median survival of 10–11 months, whereas this figure can decrease to 8–9 months in second line studies, as the BRISK trial, which included patients who failed or were intolerant to sorafenib and evaluated the effect of brivanib in second line [10]. Therefore, although a random error effect cannot be

discarded, we consider the survival reported as a signal of efficacy, which needs further consideration.

Once established that the results reported in *Nature Medicine* represent a signal of efficacy, the question is now how further research needs to be moved forward. It seems that the high dose is adequate in achieving anti-tumoral and OS effects without major toxicities. The limitation of intratumoral-only administration can be overcome by testing the effect of a combined JX-594 systemic administration (clinicalTrials.gov, NCT01636284). Nonetheless, the critical question is whether the therapy should be moved ahead in first *vs.* second line. Data on the combination with sorafenib is not available so far, and would be crucial for further exploring this path in first line. Alternatively, ongoing trials in second line comparing high-dose *vs.* placebo/best supportive care in patients who failed to sorafenib (clinicalTrials.gov, NCT01387555) can provide additional evidence for decision-making. A final approach would be to select biomarkers defining a specific target population, for instance those patients with RAS activation. Nonetheless, in this specific case trial enrichment would have a minor impact since at advanced HCC stages Ras activation seems universal [11], as opposed to what has been described at more early phases of the disease [12].

Conflict of interest

Dr. Llovet has a consultancy agreement with Jennerex.

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