Abstract 1755

High activity of Nivolumab in patients with pathogenic exonucleasic domain POLE (edPOLE) mutated Mismatch Repair proficient (MMRp) advanced tumors

Type: Abstract

Category: Developmental therapeutics

Authors: B. Rousseau[1], I. Bieche[2], E. Pasmant[3], V. Simmet[4], N. Hamzaoui[3], J. Masliah-Planchon[5], D. Pouessel[6], A. Bruyas[7], P. Augereau[4], J.-J. Grob[8], F. Rolland[9], E. Saada-Bouzid[10], R. Cohen[11], O. Bouche[12], N. Hoog-Labouret[13], F. Legrand[13], C. Simon[14], A. Lamrani-Ghaouti[15], S. Chevret[16], A. Marabelle[17]; [1]Solid Tumors, Memorial Sloan Kettering Cancer Center, New York, NY, United States of America, [2]Molecular Biology, Institut Curie, Paris, France, [3]Service de Génétique et Biologie Moléculaires, HUPC, AP-HP, Cochin Hospital, Paris, France, [4]Department of Medical Oncology, Institut de Cancérologie de l'Ouest (ICO), Angers, France, [5]Genetics, Institut Curie, Paris, France, [6]Department of Medical Oncology, Institut Claudius Regaud / Cancer Comprehensive Center, Midi-Pyrénées, France, [7]Department of Medical Oncology, Hôpital de la Croix-Rousse, Lyon, France, [8]Dermatology And Oncology, Hôpital de la Timone, Marseille, France, [9]Department of Medical Oncology, ICO Institut de Cancerologie de l'Ouest René Gauducheau, Saint-Herblain, France, [10]Medical oncology, Centre Anticancer Antoine Lacassagne, Nice, France, [11]Medical Oncology Department, Hôpital Saint-Antoine, Paris, France, [12]Gastroenterology and Digestive Oncology, CHU de Reims - Hôpital Robert Debré, Reims, France, [13]Research and Innovation, Institut National du Cancer, Boulogne-Billancourt, France, [14]R&D Department, UNICANCER, Paris, France, [15]R&D, UNICANCER, Paris, France, [16]Biostatisitics, Hopital St Louis, Paris, France, [17]Drug Development Department, Institut Gustave Roussy, Villejuif, France

Background

Hotspots *edPOLE* mutations (mut) generate proofreading defects and hypermutated genomic profiles. While rare in advanced setting, most *edPOLE* mut pathogenicity and derived sensitivity to anti-PD-1 (aPD1) remain unclear. We aimed to investigate the efficacy of Nivolumab in MMRp tumors with *edPOLE* mut.

Methods

ACSé immunotherapy is a nationwide program launched by the French National Cancer Institute (INCa) and sponsored by the French network of comprehensive cancer centers (Unicancer) investigating in multiple phase II single arm cohorts the efficacy and tolerance of aPD1 in rare tumors. We report here the initial results of the *edPOLE* cohort, first trial selecting patients on a prospective assessment of missense *POLE* mut pathogenicity by an *ad hoc* molecular tumor board. Nivolumab (240 mg IV q2w) was administered until disease progression (PD), toxicity or up to 2 years. The primary endpoint was the objective response rate (ORR) assessed by RECIST v1.1 at 12 weeks.

Results

From Apr 2018 to Jan 2020, 15 pts (mean age, 59 years) were included with colorectal (6), endometrial (4), gastric (2), pancreas (1), biliary (1) and glial (1) tumors. Mean # of previous lines: 2.7. Median follow up was 74 days (Q1-Q3= 40.5-188.5). At the date of submission, Nivolumab safety was in accordance with data reported in other tumor types. ORR at 12 weeks out of 10 evaluable patients was 30% (PR: n=3; SD: n=4; PD:n=3).

Pathogenicity of *edPOLE* mut was confirmed by the *ad hoc* committee in 7 cases (47%): 2 P286R, 2 N363K, 2 V411L, 1 A463V. In the pathogenic mut group, ORR was 50% (3/6), DCR 83% (5/6) and mPFS was 161 days. Responses were observed in MMRp colorectal and endometrial cancers with P286R and V411L mutations. Conversely in the non-pathogenic group (n=4), only 2 SD were observed as best response and 2 pts died before first evaluation, and mPFS = 47 days.

Conclusions

We report the first clinical trial assessing aPD1 in *POLE* mutated MMRp tumors. Nivolumab activity appears promising in *edPOLE* mutated MMRp advanced cancer pts but limited to pathogenic mutations underlining the need for individual mutational functional assessment by a molecular tumor board. We will include the tumor evaluation of the last 5 additional patients at meeting.

Clinical trial identification

NCT03012581

Editorial acknowledgement

Print