

A Randomized Phase 2 Study of MEDI0680 in Combination With Durvalumab Versus Nivolumab Monotherapy in Patients With Advanced or Metastatic Clear Cell Renal Cell Carcinoma

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Statement of Translational Relevance

In this Phase 2 study, patients with clear cell renal cell carcinoma (ccRCC) treated with the programmed death receptor 1 (PD-1) inhibitor MEDI0680 plus the programmed death receptor ligand-1 (PD-L1) inhibitor durvalumab had similar objective response rates compared to patients who received the PD-1 inhibitor nivolumab alone. The safety profile of MEDI0680 plus durvalumab was consistent with the known toxicity of PD-1/PD-L1 antibodies. In the combination arm, lower circulating tumor DNA (ctDNA) fraction was associated with improved progression-free survival, but not overall survival. ctDNA genomic alterations were not associated with response. Tumor-infiltrated immune cell profiles showed an association between immune cell activation and objective response in the combination arm. Combined blockade of PD-1 and PD-L1 does not result in additive efficacy over inhibition of PD-1 alone, suggesting that the PD-L1-CD80 interaction has a limited role in tumor immune evasion in ccRCC. Future combination strategies should explore targeting separate pathways.

1

2 Clinical Trials.gov: **NCT02118337**

3

4 **Abstract**

5 **Background:** MEDI0680 is a humanized anti-programmed cell death-1 (PD-1) antibody and
6 durvalumab is an anti-PD-L1 antibody. Combining treatment using these antibodies may
7 improve efficacy versus blockade of PD-1 alone. This phase 2 study evaluated antitumor activity
8 and safety of MEDI0680 plus durvalumab versus nivolumab monotherapy in immunotherapy-
9 naïve patients with advanced clear cell renal cell carcinoma who received at least one prior line
10 of anti-angiogenic therapy.

11 **Methods:** Patients received either MEDI0680 (20 mg/kg) with durvalumab (750 mg) or
12 nivolumab (240 mg), all IV Q2W. The primary endpoint was investigator-assessed objective
13 response rate (ORR). Secondary endpoints included best overall response, progression-free
14 survival (PFS), safety, overall survival (OS), and immunogenicity. Exploratory endpoints
15 included changes in circulating tumor DNA (ctDNA), baseline tumor mutational burden (TMB),
16 and tumor-infiltrated immune cell profiles.

17 **Results:** Sixty-three patients were randomized (combination, n = 42; nivolumab, n = 21). ORR
18 was 16.7% (7/42; 95% CI, 7.0–31.4) with combination treatment and 23.8% (5/21; 95% CI, 8.2–
19 47.2) with nivolumab. Median PFS was 3.6 months in both arms; median OS was not reached in
20 either arm. Due to AEs, 23.8% of patients discontinued MEDI0680 and durvalumab and 14.3%
21 of patients discontinued nivolumab. In the combination arm, reduction in ctDNA fraction was
22 associated with longer PFS. ctDNA mutational analysis did not demonstrate an association with
23 response in either arm. Tumor-infiltrated immune profiles showed an association between
24 immune cell activation and response in the combination arm.

25 **Conclusions:** MEDI0680 combined with durvalumab was safe and tolerable; however, it did not
26 improve efficacy versus nivolumab monotherapy.

27

28 Introduction

29 Renal Cell Carcinoma (RCC) encompasses a range of malignancies derived from renal
30 tubular epithelial cells and represents 2–3% of all cancers with 338,000 new diagnoses each
31 year (1,2). The most common subtype is clear cell renal cell carcinoma (ccRCC), which
32 accounts for the majority of deaths due to kidney cancer (2). Multiple targeted therapies have
33 been developed to treat ccRCC (1). Targets of approved agents include vascular endothelial
34 growth factor (VEGF) receptor, the mammalian target of rapamycin (mTOR), and immune
35 checkpoint proteins such as cytotoxic T-lymphocyte associated protein 4 (CTLA4), programmed
36 death receptor 1 (PD-1), and programmed death receptor ligand-1 (PD-L1) (1). In recent years,
37 immune checkpoint inhibitors used in combination (e.g., nivolumab plus ipilimumab) or with anti-
38 angiogenic tyrosine kinase inhibitors (TKI), (e.g., axitinib plus avelumab or pembrolizumab;
39 cabozantinib plus nivolumab) have become the first line standard of care for RCC in the United
40 States, resulting in improved clinical benefit and prolonged survival for patients with metastatic
41 disease (3,4).

42 Nivolumab is a human IgG4 anti-PD-1 antibody. The randomized phase 3 clinical trial
43 CheckMate 025 evaluated nivolumab versus the mTOR inhibitor everolimus in patients with
44 advanced RCC who had previously progressed on antiangiogenic therapy (5,6). Nivolumab
45 demonstrated improved efficacy and safety compared with everolimus (6). The results of the
46 Checkmate 025 trial led to the approval of nivolumab by the FDA in 2015 as a second line
47 treatment for metastatic ccRCC, following antiangiogenic treatment failure, shifting the standard-
48 of-care for metastatic ccRCC toward immunotherapy-based treatments (7). However, about
49 35% (142/410) of patients treated with nivolumab experienced progressive disease (PD) as a
50 best response, compared with 26% treated with everolimus (6), demonstrating a need for
51 additional or novel treatment combinations (6).

52 Durvalumab is a fully human IgG1 monoclonal antibody that blocks the binding of PD-L1
53 to PD-1 and CD80 (8). In clinical studies, durvalumab has been evaluated as a monotherapy or
54 in combination with other therapies for patients with various cancer types, demonstrating both
55 safety and efficacy (8). One disadvantage of using PD-L1 inhibitors as monotherapy is that they
56 do not block the binding of PD-L2 to PD-1 (9). A preclinical study demonstrated that PD-L2 was
57 upregulated on tumor-associated macrophages following treatment with a PD-L1 inhibitor (9).
58 Notably, PD-L1 targeted immuno-oncology agents have not demonstrated an OS benefit for
59 patients with RCC (10). This may be due to the potential of PD-L2 to promote T-cell tolerance
60 (10).

61 MEDI0680 is a humanized Immunoglobulin G (IgG) 4 κ monoclonal antibody that binds to
62 PD-1 expressed on the surface of T cells, blocking the interaction of PD-1 with PD-L1 and PD-
63 L2 on tumor cells (11). The binding of PD-L1 and PD-L2 to the inhibitory PD-1 receptor
64 expressed on T cells suppresses the cells' ability to mount an effective antitumor response
65 (1,12). In a first-in-human phase 1 study, MEDI0680 demonstrated a tolerable safety profile and
66 preliminary clinical activity in patients with advanced solid malignancies, including RCC (11).

67 Suboptimal response rates with PD-1-directed monotherapy may be due in part to
68 factors such as low PD-L1 expression and tumor mutational burden (13). Preclinical studies
69 have also demonstrated that blocking PD-1 can increase the release of the pro-inflammatory
70 cytokine interferon- γ (IFN- γ) at the tumor site, which may then increase the expression of PD-L1
71 in various cancer cells (14,15). Additionally, PD-L1, when left uninhibited, can limit the antitumor
72 response by binding to cluster of differentiation 80 (CD80) expressed on activated CD8⁺ T cells,
73 thereby restricting the role of CD80 in promoting T cell survival, proliferation, and cytokine
74 production (16). The hypothesis underlying the current trial was that simultaneous blockade of
75 PD-1 using MEDI0680 and PD-L1 using durvalumab has the potential to improve efficacy

76 relative to a blockade of PD-1 alone using nivolumab by blocking additional inhibitory
77 interactions within the tumor microenvironment.

78 In the dose-escalation phase of this multicenter, open label study in patients with
79 advanced solid tumors, the combination of MEDI0680 with durvalumab was well tolerated, and
80 a confirmed ORR of 30% (9/30), including 3 out of 4 patients with RCC was observed (17). In
81 the phase 2 (dose expansion) part of this study, we evaluated the antitumor activity and safety
82 of MEDI0680 in combination with durvalumab versus nivolumab monotherapy in adults with
83 ccRCC and assessed potential tumor-based biomarkers of response.

84 **Materials and Methods**

85 *Patients*

86 Eligible patients were aged ≥ 18 years and had advanced or metastatic RCC with a clear
87 cell component. Additional key inclusion criteria were an Eastern Cooperative Oncology Group
88 (ECOG) score of 0–1 and at least 1 measurable lesion. Patients had to have received 1–2 prior
89 anti-angiogenic therapy regimens, no prior immunotherapy, and a maximum of 3 systemic
90 treatment regimens in the advanced or metastatic setting. Patients had to have evidence of
91 radiographic progression on or after the last treatment regimen received and within 6 months
92 prior to study enrollment. Patients had adequate organ and marrow function (defined in the
93 Supplementary methods). Key exclusion criteria included concurrent malignancies, active/prior
94 autoimmune or inflammatory disorders within the past 3 years, and untreated central nervous
95 system metastatic disease. Additional inclusion and exclusion criteria are available in the
96 Supplementary Methods.

97 *Study Design*

98 This randomized phase 2, open label, multicenter study of MEDI0680 in combination
99 with durvalumab versus nivolumab monotherapy was conducted at 27 centers in 6 countries,
100 including Australia, Canada, France, the Netherlands, the United Kingdom, and the United
101 States. The study design is summarized in **Supplementary Figure 1**. Stratification factors
102 included the Memorial Sloan Kettering Cancer Center (MSKCC) risk group (prognostic score:
103 0 = favorable risk; 1 or 2 = intermediate risk; 3 = poor risk) (18) and the status of PD-L1
104 expression on tumor cells ($\leq 1\%$ and $> 1\%$). For determination of PD-L1 expression, archival
105 tumor tissues or fresh tumor biopsies were evaluated by a central laboratory using the Ventana
106 (SP263) immunohistochemistry assay (Roche Cat# 790-4905). Patients were randomly

107 assigned at a ratio of 2:1 to receive either 20 mg/kg of MEDI0680 with 750 mg of durvalumab or
108 240 mg nivolumab monotherapy. Each drug was administered intravenously every two weeks.

109 For patients receiving combination treatment, durvalumab was administered first.
110 MEDI0680 was given approximately 30 minutes after completion of durvalumab infusion. Dose
111 reductions of MEDI0680 and durvalumab were not permitted; however, holding doses or
112 discontinuation in the case of treatment-related toxicity was allowed. Nivolumab dosing was
113 based on the FDA-approved regimen described in the package insert. Patients could remain on
114 study treatment for up to 2 years while tolerable and effective. Disease assessments were
115 performed at baseline and every 8 weeks thereafter. Patients were followed for survival until the
116 end of the study, regardless of additional treatments.

117 This study was conducted in accordance with the ethical principles originating in the
118 Declaration of Helsinki and was consistent with the International Conference on
119 Harmonization/Good Clinical Practice and applicable regulatory requirements. The study
120 protocol was approved by an institutional review board or independent ethics committee at each
121 study site prior to initiation and enrollment. All patients provided written informed consent before
122 participating in the study. This study was registered with ClinicalTrials.gov, number
123 NCT03089645.

124 *Endpoints*

125 The primary endpoint was investigator-assessed ORR by Response Evaluation Criteria
126 in Solid Tumors (RECIST) version 1.1 criteria (19), defined as the proportion of patients with a
127 best overall response (BOR) category of confirmed complete response (CR) or partial response
128 (PR). Secondary endpoints included safety, BOR, disease control, time to response, duration of
129 response, progression-free survival (PFS), change from baseline in tumor size, overall survival,
130 and the detection of anti-drug antibodies (ADAs). Exploratory endpoints included blood tumor

131 mutational burden (bTMB), changes in circulating tumor DNA (ctDNA), baseline genomic
132 alteration profile, and baseline tumor infiltrated immune profile in association with objective
133 response.

134 Disease control was defined as the proportion of patients with a BOR of confirmed CR,
135 PR, or stable disease (SD) maintained for ≥ 24 weeks. Duration of response was defined as the
136 time from first documentation of objective response until first documentation of disease
137 progression or death. Time to response was defined as the time from randomization until the
138 first documentation of objective response. PFS was defined as the time from randomization until
139 first documentation of disease progression or death, regardless of subsequent anticancer
140 therapy received prior to progression. Change from baseline in tumor size was calculated as the
141 percent change in target lesion sum of diameters at every post-baseline disease assessment.
142 Overall survival was defined as the time from randomization until death due to any cause. For
143 PFS and OS analysis, patients free from progression and alive were censored at the last follow
144 up timepoint, respectively.

145 *Safety*

146 Safety was assessed by the presence of adverse events (AEs) and serious AEs, as well
147 as changes from baseline in laboratory parameters, vital signs, physical examination, and
148 electrocardiogram results. AEs were coded by the Medical Dictionary for Regulatory Activities
149 and preferred term, and adverse events and laboratory values were graded according to the
150 National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

151 *Statistics*

152 Up to 60 patients (40 patients in the MEDI0680 and durvalumab combination therapy
153 arm and 20 patients in the nivolumab monotherapy arm) were planned for randomization at the
154 selected combination dose. Assuming an ORR for nivolumab monotherapy of 21.5% (20), the

155 sample size was chosen to detect a difference in ORR of 26.0% (i.e., an objective response of
156 47.5%) with 76% power at a 1-sided significance level of 0.10. The 95% confidence interval (CI)
157 of an ORR of 47.5% (19 responders/40 patients) based on the exact probability method is
158 31.5%–63.9%. Efficacy and safety analyses were based on the as-treated population, defined
159 as all patients who received any dose of investigational product and were analyzed according to
160 the treatment they received. The difference in ORR between arms was tested for significance
161 using Fisher's exact test.

162 Patients with missing overall response were counted as non-responders. The median
163 PFS and overall survival, along with their 95% CIs, were summarized by Kaplan-Meier curves.
164 The differences in PFS and overall survival between treatment arms were tested for significance
165 using a log rank test. The hazard ratio with 95% CIs was estimated by Cox proportional hazard
166 model controlling for prespecified stratification factors as explanatory variables.

167 A joint Bayesian predictive probability approach was developed to allow for continuous
168 assessments of the delta (δ), or difference, of the ORR between the MEDI0680 and durvalumab
169 combination and nivolumab. The target δ was set so as to demonstrate a 20% increase in the
170 MEDI0680 and durvalumab combination ORR over the benchmark nivolumab ORR based on
171 investigator assessments. Categorical data was summarized by the number and percentage of
172 patients in each category. Continuous variables were summarized by descriptive statistics. SAS
173 version 9.4 (SAS Institute Inc., Cary NC) was used for data analyses.

174 *Immunogenicity*

175 Blood samples were assessed for the presence of ADAs in response to MEDI0680 using
176 a previously described validated immunoassay (11). For durvalumab, clinical samples were
177 evaluated for ADA via screening, confirmatory, titer, and neutralizing antibody assays. A
178 homogeneous double-bridging electrochemiluminescence assay was used for ADA screening.

179 Positive control (goat anti-durvalumab polyclonal antibody), negative control, and test samples
180 were incubated with biotin-conjugated durvalumab and ruthenium-conjugated durvalumab to
181 form an immunocomplex. The ADA immunocomplexes were captured on streptavidin-coated
182 standard 96 well plates and signals were measured by an MSD Sector Imager (Meso Scale
183 Diagnostics, Rockville, MD). A signal \geq the established cutoff indicated the presence of ADAs in
184 the sample. Samples for ADA assessment were collected during cycle 1 (study day 1), cycle 2
185 (study day 29 ± 3), cycle 5 (study day 113 ± 3), cycle 8 (study day 197 ± 3), cycle 11 (study day
186 281 ± 3), and during post-treatment and long term follow-up. Patients who received ≥ 1 dose of
187 both durvalumab and MEDI0680 and provided ≥ 1 post-treatment sample were evaluated, and
188 immunogenicity results were analyzed descriptively by summarizing the proportion of patients
189 who developed detectable anti-durvalumab or anti-MEDI0680 antibodies.

190 *Biomarker analysis*

191 *ctDNA, bTMB and Genomic alterations*

192 ctDNA was extracted centrally from plasma samples collected from both treatment arms,
193 as previously described (21-23), and assayed using a GuardantOMNI Research Use Only
194 (RUO) next generation sequencing (NGS) assay (Guardant Health, Redwood City, CA)(23).
195 This assay detects genomic alterations such as single nucleotide variants, insertions, deletions,
196 copy-number variants, fusions, and microsatellite instability (500 genes; 2.145 Mb) (23). bTMB
197 score was determined as previously described (23). Mean variant allelic frequency (VAF) was
198 calculated at baseline and at 4 weeks following treatment. Percent change in mean VAF from
199 baseline was determined, indicating percent change in ctDNA fraction. Reduction in ctDNA
200 fraction $\geq 50\%$ at 4 weeks versus baseline is defined as molecular response (MR) (21,24).
201 Reduction in ctDNA fraction $< 50\%$ at 4 weeks versus baseline is defined as non-molecular
202 response (non-MR) (21,24,25).

203 *Immunohistochemistry, multiplex immune fluorescence, and digital analysis*

204 Tumor tissue sections from formalin-fixed paraffin embedded (FFPE) blocks, derived
205 from tumor biopsies at baseline or archival tumor samples, were processed by
206 immunohistochemistry (IHC) for PD-L2 (Abcam; CAL28 clone) and by multiplex
207 immunofluorescence (mIF) for CD8 (Ventana; SP239 clone), PD-L1 (Ventana; SP263 clone),
208 PD-1 (CST; D4W2J clone), Ki-67 (Dako; MIB-1 clone), CD68 (Dako; PG-M1 clone), and
209 cytokeratin (Dako; AE1/AE3 clone). Briefly, automated IHC protocols were performed on
210 Ventana instruments (Roche Diagnostics, Ventana Medical Systems, Tucson, AZ) employing
211 3,3'-diaminobenzidine as the chromogen. Immunostained slides were digitally scanned using an
212 Aperio AT turbo scanner (Leica BioSystems, Wetzlar, Germany) at 20X magnification. Digital
213 images were viewed using Aperio ImageScope software version 12.1.0 (Leica BioSystems) or
214 VeriTrova software (AstraZeneca Computational Pathology GmbH, Munich, Germany). For mIF,
215 a BOND Rx automated staining platform (Leica BioSystems, Wetzlar, Germany) with a modified
216 Opal protocol (PerkinElmer, MA, United States) was used. Imaging was performed on a Vectra
217 Polaris multispectral imaging platform (Akoya Biosciences, CA, United States) in multispectral
218 instrument (MSI) mode. Digital images were imported into Developer XD software (AstraZeneca
219 Computational Pathology GmbH, Munich, Germany) and analyzed for marker positive cells,
220 which were reported as densities (cells/mm²) using the program's cognition network technology,
221 as previously described (26-28).

222

223 **Data Availability Statement**

224 The individual patient level data generated in this study are not publicly available to protect
225 patient privacy. Requests for data may be submitted through Vivli's web-based data request

226 platform (www.vivli.org). A comprehensive explanation of AstraZeneca's data sharing policies is
227 available at: <https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure>.

228

229 **Results**

230 *Patient Demographics and Clinical Characteristics*

231 As of June 12, 2020, 63 patients had been enrolled, randomly assigned a treatment, and
232 treated (**Supplementary Figure 2**). Forty-two patients were randomly assigned to receive
233 MEDI0680 and durvalumab, and 21 were randomly assigned to receive nivolumab. Early in the
234 study and prior to a protocol amendment, an additional 4 patients had been randomized to
235 receive MEDI0680 20 mg/kg as monotherapy; this arm of the study was subsequently closed
236 and replaced with the nivolumab arm due to a change in the standard of care treatment for
237 ccRCC shortly after initiation of the study. All 4 patients discontinued treatment due to PD,
238 withdrew from the study, and none of them were included in this analysis. The median duration
239 of exposure for the 4 patients on MEDI0680 monotherapy was 24.1 weeks (range, 10.1–40.1).

240 Patient demographics and baseline disease characteristics are summarized in **Table 1**.
241 Baseline patient and disease characteristics were generally well balanced between study arms,
242 with several relevant exceptions: the percent of patients with PD-L1 expression $\leq 1\%$ was
243 higher in the MEDI0680 and durvalumab combination arm than in the nivolumab arm (88.1% vs
244 61.9%), the median age was higher in the combination arm (64 years vs 58 years, respectively),
245 and the prevalence of MSKCC favorable disease risk was lower in the combination arm (23.8%
246 vs 33.3%, respectively) (**Table 1**). Additionally, patients in the combination arm had a longer
247 median time from initial diagnosis to study entry (38.3 months vs 14.1 months in the nivolumab
248 arm) (**Table 1**). The median number of prior anticancer treatments was 2.0 for both arms (**Table**
249 **1**).

250 *Antitumor Activity*

251 The primary endpoint of investigator-assessed ORR was 16.7% (95% CI, 7.0–31.4) with
252 MEDI0680 plus durvalumab and 23.8% (95% CI, 8.2–47.2) with nivolumab (**Table 2**), with no
253 significant difference between the two treatment arms ($p = 0.513$; **Table 2**). CR was observed in
254 4.8% (2/42) of patients in the combination arm, with response durations of 21.5 and 11.1
255 months (**Table 2**). One patient with CR had multiple disease sites at baseline (lymph nodes,
256 adrenal glands, nephrectomy bed, and diaphragm); the other patient with CR had renal fossa
257 lesions at baseline. No patients in the nivolumab arm had a CR (**Table 2**). The nivolumab arm
258 had a lower proportion of patients with PD (28.6% vs 40.5%). For patients who achieved an
259 objective response in the combination arm ($n = 7$) or in the nivolumab arm ($n = 5$), the median
260 time to response was 1.8 months (95% CI, 1.7–9.1 months) and 1.8 months (95% CI, 1.6–7.3
261 months), respectively. The median duration of response was not reached in either arm; the
262 longest duration of response was 23.5 months with the combination and 9.2 months with
263 nivolumab (**Table 2**). The disease control rate at 24 weeks was 38.1% (16/42) with the
264 combination and 38.1% (8/21) with nivolumab treatment (**Table 2**).

265 The ORR was not significantly different between treatment arms based on PD-L1 status
266 (**Supplementary Table 1**). In PD-L1 negative patients (defined as expression $\leq 1\%$), the ORR
267 was 13.5% (5/37) with combination treatment versus 15.4% (2/13) with nivolumab. In PD-L1
268 positive patients (defined as expression $> 1\%$), the ORR was 40.0% (2/5) with combination
269 treatment versus 37.5% (3/8), with nivolumab. Change in tumor burden over time is shown for
270 individual patients in **Figure 1**. The best change in the sum of target lesions from baseline for
271 each patient is shown in **Figure 2**. Progression-free survival was comparable between the
272 combination and nivolumab arms (**Table 2**; **Supplementary Figure 3a**). The median PFS for
273 the as-treated population in the MEDI0680 and durvalumab arm was 3.6 months (95% CI, 2.0–
274 5.5 months) versus 3.6 months (95% CI, 1.9–13.0 months) in the nivolumab arm (HR, 1.09;

275 95% CI, 0.58–2.04; $p = 0.789$). Median OS was not reached in either arm (**Table 2**;
276 **Supplementary Figure 3b**), and OS rates at 12 months were 75.2% (95% CI, 57.4%–86.4%) in
277 the MEDI0680 and durvalumab arm and 83.6% (95% CI, 56.8%–94.5%) in the nivolumab arm.

278 *Safety*

279 In the combination arm, 64.3% (27/42) patients discontinued treatment due to PD; in the
280 nivolumab arm, 61.9% (13/21) patients discontinued treatment due to PD (**Supplementary**
281 **Figure 2**). The median duration of exposure was 16.0 weeks (range, 2.0–120.0) for MEDI0680
282 and durvalumab and 29.7 weeks (range, 2.0–78.1) for nivolumab. In the combination arm, 8
283 (19%) patients had at least 1 dose delay for MEDI0680, and 7 (16.7%) patients had at least 1
284 dose delay for durvalumab. In the nivolumab arm, 3 (14.3%) patients had at least one dose
285 delay.

286 Treatment-related adverse events (TRAEs) of any grade occurred in 92.9% of patients
287 ($n = 39$) treated with the combination and 81.0% ($n = 17$) treated with nivolumab. TRAEs of
288 grade 3–4 severity are summarized in **Table 3**. In the combination arm, Grade 3–4 MEDI0680-
289 related AEs occurred in 26.2% ($n = 11$) of patients and Grade 3–4 durvalumab-related AEs
290 occurred in 23.8% ($n = 10$) of patients (**Table 3**). Grade 3–4 nivolumab-related AEs occurred in
291 23.8% ($n = 5$) of patients (**Table 3**). In total, 23.8% ($n = 10$) of patients discontinued MEDI0680
292 plus durvalumab due to an AE and 14.3% of patients ($n = 3$) discontinued nivolumab due to an
293 AE (**Supplementary Table 2**).

294 *Immunogenicity*

295 Baseline and post-baseline ADA measurements for MEDI0680 were available for 40 and
296 39 patients, respectively. A total of 4 (10.0%) patients had an ADA positive response at baseline
297 and a total of 2 (5.1%) patients had an ADA positive response to MEDI0680 post-baseline on
298 cycle 5, day 1 (study day 112) and on cycle 2, day 1 (study day 31). No ADA-persistent positive

299 responses were observed. Baseline and post-baseline ADA data for durvalumab were available
300 for 41 and 39 patients, respectively. One patient (2.4%) had an ADA positive response to
301 durvalumab at baseline and 2 (5.1%) patients had an ADA positive response to durvalumab
302 post-baseline. ADA persistent-positive responses were observed in 2 patients.

303 *Translational biomarker analysis*

304 Sample sizes for translational biomarker analyses are summarized in **Supplementary**
305 **Table 3**. Change in ctDNA was measured by percent change from baseline in mean VAF.
306 ctDNA reductions were observed in several patients with CR and PR, in both treatment groups
307 (**Figure 3a and 3b**). In the combination and nivolumab arms, 27.5% (8/29) and 30% (3/10) of
308 patients reported an MR, respectively (**Figure 3b**). Only one patient with MR in the combination
309 arm reported PD as their BOR (**Figure 3b**). A subgroup analysis based on MR in relation to
310 PFS and OS was performed in the MEDI0680 and durvalumab treatment arm only, due to
311 sufficient sample size (n = 29). MR was observed in 8 patients (27.6%) and tended to be
312 associated with a longer median PFS (7.7 months vs 3.4 months; log-rank $p = 0.06$); however,
313 no association with OS was observed (**Figure 3c and 3d**).

314 Across both arms, the median peripheral bTMB score at baseline was 6.65 mut/Mb
315 (combination arm: 6.700 mut/Mb [range, 0.96–14.36]; nivolumab arm: 6.285 mut/Mb [range,
316 1.10–8.69]), consistent with previous observations showing relatively low TMB in patients with
317 mRCC (29). No association between bTMB score at baseline as a continuous variable and
318 response (CR or PR) was observed in either arm (**Supplementary Figure 4a**). Applying a
319 bTMB median cutoff of 6.65 mut/Mb (above median, n = 10; below median, n = 10) did not
320 reveal an association with PFS or OS in the combination arm; this analysis could not be
321 performed for the nivolumab arm due to an insufficient sample size (n = 6) (**Supplementary**
322 **Figure 4b and 4c**).

323 The presence of genomic alterations derived from ctDNA analysis and obtained at
324 baseline was not associated with response in either arm (**Supplementary Figure 4d**). Pursuant
325 to the hypothesis that the combination of MEDI0680 and durvalumab provides a more complete
326 blockade targeting both PD-L2-PD1 and PD-L1-PD1 in comparison to anti-PD1 nivolumab
327 monotherapy, we evaluated the tumor-infiltrated immune profiles using mIF and IHC. Neither
328 PD-L1 nor PD-L2 expression were associated with response in either arm (**Supplementary**
329 **Figure 5**). Immune activated cells were associated with response in patients who received
330 combination treatment, but not nivolumab treatment, although sample-size differences between
331 the arms must be considered when interpreting these findings. Tumors of patients with CR or
332 PR were characterized by increased PD-1+ immune cell and PD-1+CD8+ T cell density
333 (cells/mm²) compared with patients who had SD (n = 38; *p* < 0.05), and a higher trend
334 compared with PD (**Supplementary Figure 5**). However, in patients who received nivolumab (n
335 = 21), CD8+ Ki67+ (± PD-1+) T cell density (cells/mm²) showed a trend of association with
336 response (**Supplementary Figure 5**). Due to the small sample sizes in both arms, translational
337 findings should be interpreted with caution, particularly in the nivolumab arm.

338 Discussion

339 The aim of the current study was to evaluate whether combined inhibition of PD-1 via
340 MEDI0680 plus PD-L1 via durvalumab could improve antitumor immune response over that of
341 PD-1 inhibition alone in patients with advanced or metastatic ccRCC. Treatment with the
342 combination of MEDI0680 and durvalumab was safe and tolerable; however, it did not improve
343 the ORR or PFS versus treatment with nivolumab alone. The ORR was numerically lower with
344 MEDI0680 and durvalumab (16.7%) than with nivolumab (23.8%), but the difference was not
345 statistically significant.

346 Differences in the ORR were not apparent between treatment arms when the analysis
347 was stratified by PD-L1 expression. Notably, and despite the study design, the combination

348 group enrolled patients with lower PD-L1 expression levels and less favorable MSKCC risk
349 status, which highlights the challenges of effectively allocating arms in smaller randomized
350 studies. Prior randomized studies of nivolumab in advanced RCC have shown a difference in
351 outcomes based on MSKCC risk group and PD-L1 expression. A randomized phase 3 study of
352 nivolumab monotherapy in patients with advanced RCC showed longer median OS in patients
353 with favorable MSKCC risk scores (not reached [NR]), versus patients with intermediate
354 MSKCC risk scores (21.8 months; 95% CI, 18.3-NR) and poor MSKCC risk (15.3 months; 95%
355 CI, 9.6-22.4); however, no significant differences in ORR were observed between MSKCC risk
356 groups (30). Additionally, in a randomized phase 2 study of nivolumab monotherapy in patients
357 with metastatic RCC, median OS in the PD-L1 \geq 5% subgroup (NR; 95% CI, 13.4 months-NR)
358 was longer compared with the PD-L1 < 5% subgroup (18.2 months; 95% CI, 12.7-26.0) (31).
359 Furthermore, ORR was higher for patients in the PD-L1 \geq 5% subgroup (31% versus 18%) (31).
360 However, a follow-up phase 3 study showed longer median OS in a subgroup of patients with
361 < 1% PD-L1 expression (27.4 months; 95% CI, 21.4-NE) compared with the > 1% PD-L1
362 expression subgroup (21.8 months; 95% CI, 16.5-28.1) (5). In the present study, a larger
363 proportion of patients in the nivolumab arm had > 1% PD-L1 expression levels and lower
364 MSKCC risk scores, which may have influenced the observed clinical outcomes. Therefore, the
365 efficacy results should be interpreted with caution.

366 Although this study did not demonstrate superior antitumor efficacy of MEDI0680 in
367 combination with durvalumab versus nivolumab in immunotherapy-naïve subjects with
368 advanced or metastatic ccRCC, some clinical activity was reported. Two patients (4.8%)
369 achieved CR with the combination treatment. Responses were durable, with the median
370 duration not reached in either arm. The longest duration was 23.5 months with MEDI0680 and
371 durvalumab and 9.2 months with nivolumab. While median PFS was 3.6 months in both arms,
372 the rate of discontinuations was slightly higher in the MEDI0680 and durvalumab arm. The most

373 frequently reported TRAEs were diarrhea, fatigue, pruritus, rash, and pyrexia. AST increased
374 was the only AE of special interest related to hepatotoxicity reported in $\geq 5\%$ patients
375 (combination arm, 4.8%; nivolumab arm, 14.3%). No hematologic toxicity or sustained hepatic,
376 metabolic, renal, or endocrine toxicity was observed in this study and no patients died due to
377 treatment-related toxicity.

378 Currently, there are no validated predictive biomarkers of response available for use in
379 patients with RCC in clinical practice (32). No tissue or peripheral blood-based biomarker
380 signature evaluated was clearly associated with favorable clinical outcomes in either arm.
381 Multiparametric analyses did not reveal associations between bTMB or T cell infiltration and
382 response, as the ability to investigate either of these thoroughly was limited by sample sizes.
383 The results of the ctDNA analysis, while not significant and limited by sample size, are of
384 interest and do warrant further investigation, particularly in larger clinical trials. Notably, we
385 observed a trend in the combination arm where tumors containing activated T cells were more
386 likely to respond to therapy. This is consistent with a previous study in mRCC demonstrating
387 that tumors with activated immune profiles were more likely to respond to immunotherapy
388 treatment compared with VEGF inhibitors (33). Based on the considerable complexity
389 underlying the response to immunotherapy, additional comprehensive and integrated
390 approaches to identify suitable biomarkers of response in patients with RCC are needed (32).

391 In conclusion, while the safety profile of MEDI0680 and durvalumab was manageable
392 and generally consistent with the known toxicity of the anti-PD-L1/PD-1 drug class, this study
393 did not meet its primary endpoint. The combined blockade of PD-1 and PD-L1 did not improve
394 efficacy over the inhibition of PD-1 alone for patients with advanced or metastatic ccRCC.
395 Moreover, previous studies of the anti-CD80 monoclonal antibody, galiximab, similarly
396 demonstrated favorable safety profiles but low ORRs in patients with relapsed and refractory
397 lymphomas when used as monotherapy. ORRs in those studies were 10.3% in patients with

398 Hodgkin lymphoma (34) and 11% in patients with follicular lymphoma (35). Taken together,
399 these results may suggest that the PD-L1-CD80 interaction does not have a significant role in
400 tumor immune evasion in ccRCC, or that MEDI0680 does not provide adequate inhibition of the
401 PD-1-CD80 interaction in patients with ccRCC. Future combination strategies could be explored
402 combining agents that target PD-1 with others targeting alternative immunomodulatory
403 pathways outside the PD-1/PD-L1 axis, such as CTLA-4 or VEGF.

404

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517

518

Tables

Table 1. Patient Demographics and Baseline Disease Characteristics

	MEDI0680 + durvalumab (n = 42)	Nivolumab (n = 21)
Median age (range), years	64.0 (39–80)	58.0 (38–80)
Sex, n (%)		
Male	33 (78.6)	15 (71.4)
Female	9 (21.4)	6 (28.6)
ECOG PS		
0	19 (45.2)	10 (47.6)
1	23 (54.8)	11 (52.4)
MSKCC risk classification, n (%)		
Favorable	10 (23.8)	7 (33.3)
Intermediate	30 (71.4)	13 (61.9)
Poor	2 (4.8)	1 (4.8)
PD-L1 expression, n (%)		
≤1%	37 (88.1)	13 (61.9)
>1%	5 (11.9)	8 (38.1)
Time from initial diagnosis to study entry		
n	40	19
Median (range), months	38.3 (2.9–236.8)	14.1 (6.7–155.2)
Number of prior anticancer therapies ^a		
Median (range)	2.0 (1–7)	2.0 (1–3)
Type of prior treatment		
n	42	21
Biologic	9 (21.4)	3 (14.3)
Immunotherapy	1 (2.4)	0
Chemotherapy	13 (31.0)	7 (33.3)
Radiation	15 (35.7)	5 (23.8)
Surgery	28 (66.7)	16 (76.2)
Other	21 (50.0)	12 (57.1)
Number of prior systemic therapies for metastatic disease ^a		
n	34	17
1	26 (76.5)	17 (100)
2	8 (23.5)	0

ECOG PS, Eastern Cooperative Oncology Group performance status; MSKCC, Memorial Sloan Kettering Cancer Center; PD-L1, programmed cell death ligand-1.

^aNumber of prior systemic therapies for metastatic disease is defined as number of lines of biologic, immunotherapy, chemotherapy, and other with treatment intent as definitive treatment or palliative for recurrent/metastatic disease.

Table 2. Disease Response (As-treated Population)

	MEDI0680 + durvalumab (n = 42)	Nivolumab (n = 21)
Best overall response, n (%)		
Complete response	2 (4.8)	0
Partial response	5 (11.9)	5 (23.8)
Stable disease	17 (40.5)	8 (38.1)
Unconfirmed partial response	2 (4.8)	0
Progressive disease	17 (40.5)	6 (28.6)
Not evaluable	1 (2.4)	2 (9.5)
Objective response, n (%)	7 (16.7)	5 (23.8)
95% CI	7.0, 31.4	8.2, 47.2
<i>p</i> value ^b	0.513	—
Median progression-free survival (95% CI), months	3.6 (2.0, 5.5)	3.6 (1.9, 13.0)
Median overall survival (95% CI), months	NR (NR, NR)	NR (12.0, NR)
Median time to response (range), months	1.8 (1.7–12.8)	1.8 (1.6–7.3)
Median duration of response (range), months	NR (9.5–23.5)	NR (1.9–9.2)
Disease control at ≥ 24 weeks, n (%)^a	16 (38.1)	8 (38.1)
95% CI	23.6, 54.4	18.1, 61.6

CI, confidence interval; NR, not reached.

^aComplete and partial responses plus stable disease.

^bAs compared to nivolumab.

Table 3. Treatment-related AEs of Grade 3-4 Severity by Drug (As-treated Population)

n (%)	MEDI0680 + Durvalumab (n = 42)				Nivolumab ^a (n = 21)	
	MEDI0680 ^a		Durvalumab ^a		Grade 3–4	Any Grade ^b
	Grade 3–4	Any Grade ^b	Grade 3–4	Any Grade ^b		
Patients with any treatment-related ^b AEs	11 (26.2)	39 (92.9)	10 (23.8)	39 (92.9)	5 (23.8)	17 (81.0)
Anemia	1 (2.4)	2 (4.8)	1 (2.4)	2 (4.8)	0	0
Immune-mediated enterocolitis	1 (2.4)	2 (4.8)	1 (2.4)	2 (4.8)	0	0
Immune-mediated pancreatitis	1 (2.4)	1 (2.4)	1 (2.4)	1 (2.4)	0	0
Hepatocellular injury	1 (2.4)	1 (2.4)	1 (2.4)	1 (2.4)	0	0
Amylase increased	1 (2.4)	2 (4.8)	1 (2.4)	2 (4.8)	1 (4.8)	0
Alanine aminotransferase increased	1 (2.4)	1 (2.4)	1 (2.4)	1 (2.4)	0	2 (9.5)
Aspartate aminotransferase increased	2 (4.8)	2 (4.8)	2 (4.8)	2 (4.8)	0	2 (9.5)
C-reactive protein increased	1 (2.4)	1 (2.4)	1 (2.4)	1 (2.4)	0	0
Lipase increased	2 (4.8)	2 (4.8)	2 (4.8)	2 (4.8)	2 (9.5)	2 (9.5)
Transaminases increased	1 (2.4)	1 (2.4)	1 (2.4)	1 (2.4)	0	0
Weight decreased	1 (2.4)	2 (4.8)	0	1 (2.4)	0	0
Hyponatremia	1 (2.4)	1 (2.4)	1 (2.4)	1 (2.4)	0	0
Arthralgia	1 (2.4)	6 (14.3)	1 (2.4)	6 (14.3)	0	2 (9.5)
Myalgia	1 (2.4)	6 (14.3)	1 (2.4)	6 (14.3)	0	2 (9.5)
Encephalitis autoimmune	1 (2.4)	1 (2.4)	1 (2.4)	1 (2.4)	0	0
Rash maculopapular	1 (2.4)	3 (7.1)	1 (2.4)	3 (7.1)	0	3 (14.3)
Rash papular	1 (2.4)	1 (2.4)	1 (2.4)	1 (2.4)	0	1 (4.8)
Adrenal insufficiency	0	0	1 (2.4)	1 (2.4)	0	0
Pancreatitis	0	0	1 (2.4)	1 (2.4)	0	1 (4.8)
Constipation	0	3 (7.1)	0	3 (7.1)	1 (4.8)	1 (4.8)
Hepatotoxicity	0	0	0	0	1 (4.8)	1 (4.8)
Hypophosphatemia	0	0	0	0	1 (4.8)	0
Renal tubular necrosis	0	0	0	0	1 (4.8)	1 (4.8)
Pneumonitis	0	1 (2.4)	0	1 (2.4%)	1 (4.8)	1 (4.8)

^aAs assessed by investigator; ^bNo treatment-related deaths were observed in this study. AE, adverse event.

Figures

Figure 1. Percentage Change From Baseline in Target Lesion Sum of Diameters (As-treated Population)

Figure 2. Best Percent Change From Baseline in Target Lesion Sum of Diameters for **(A)** MEDI0680 With Durvalumab, and **(B)** Nivolumab Monotherapy (As-treated Population).

*New lesion occurred at the time best change from baseline achieved.

CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

Figure 3. **(A)** Change in ctDNA Mean VAF From Baseline to Week 4 and **(B)** Percent Change From Baseline in Mean VAF by Clinical Response. Subgroup Analysis Based on Changes in ctDNA Fraction Using a 50% Change From Baseline Cutoff in Association With **(C)** PFS, and **(D)** OS in the MEDI0680-Plus-Durvalumab arm.

Reduction in ctDNA fraction $\geq 50\%$ at 4 weeks versus baseline is defined as MR and reduction ctDNA fraction $< 50\%$ at 4 weeks versus baseline is defined as non-MR.

AIC, Akaike Information Criteria; CI, confidence interval; CR, complete response; ctDNA, circulating tumor DNA; MR, molecular response; NA, not applicable; NS, not significant; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; VAF, variant allele frequency.

Figure 1

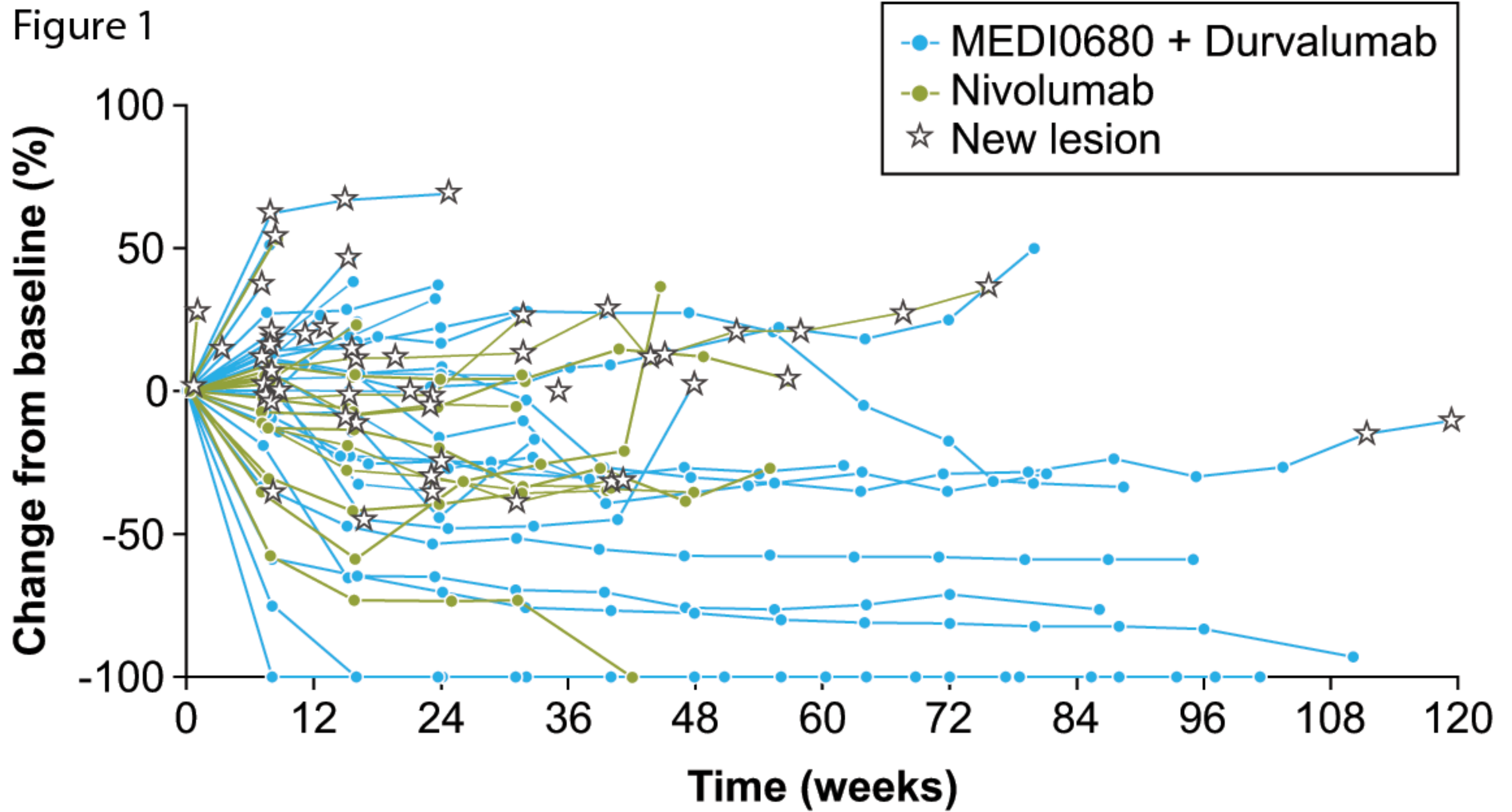


Figure 2

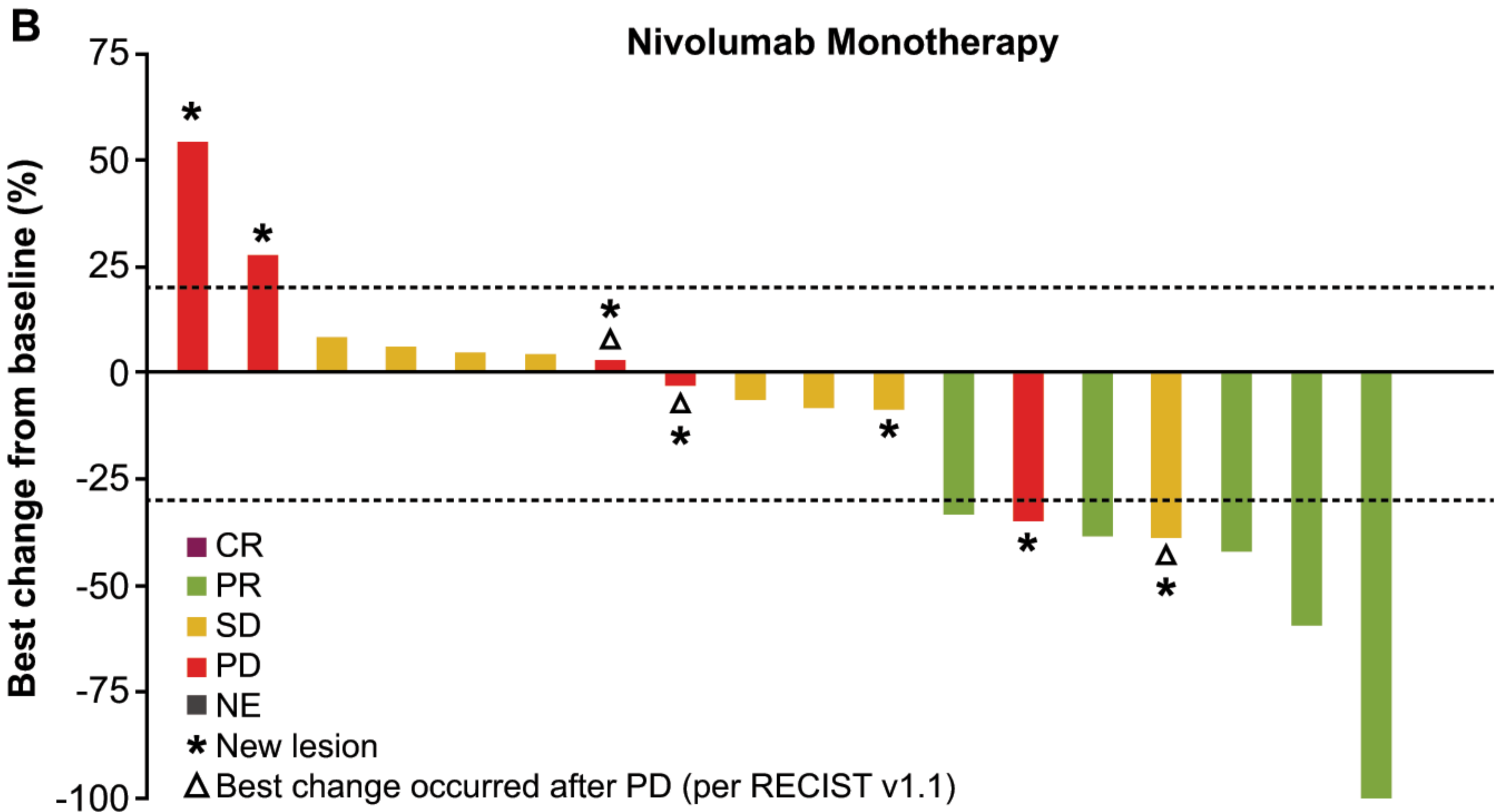
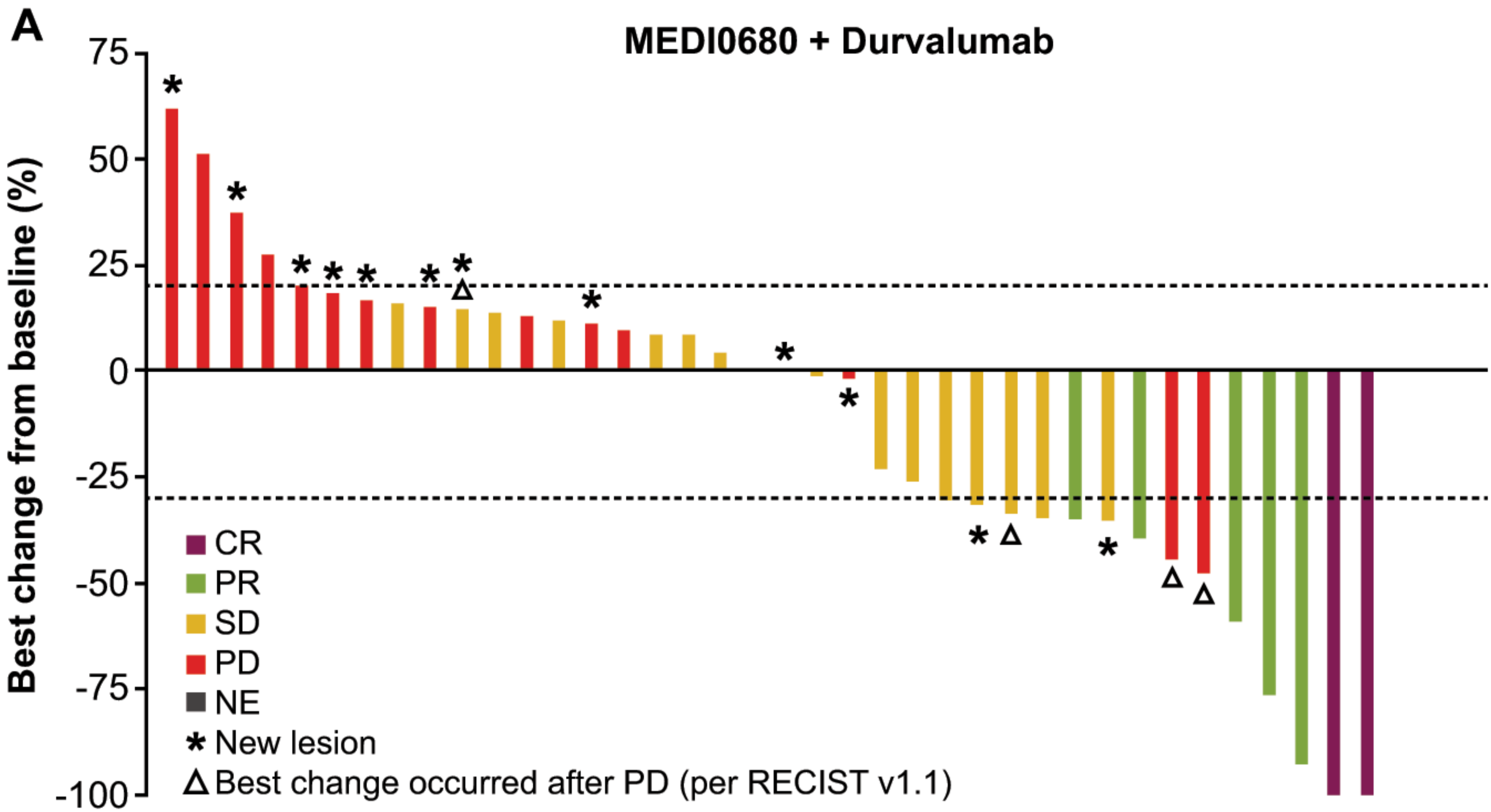
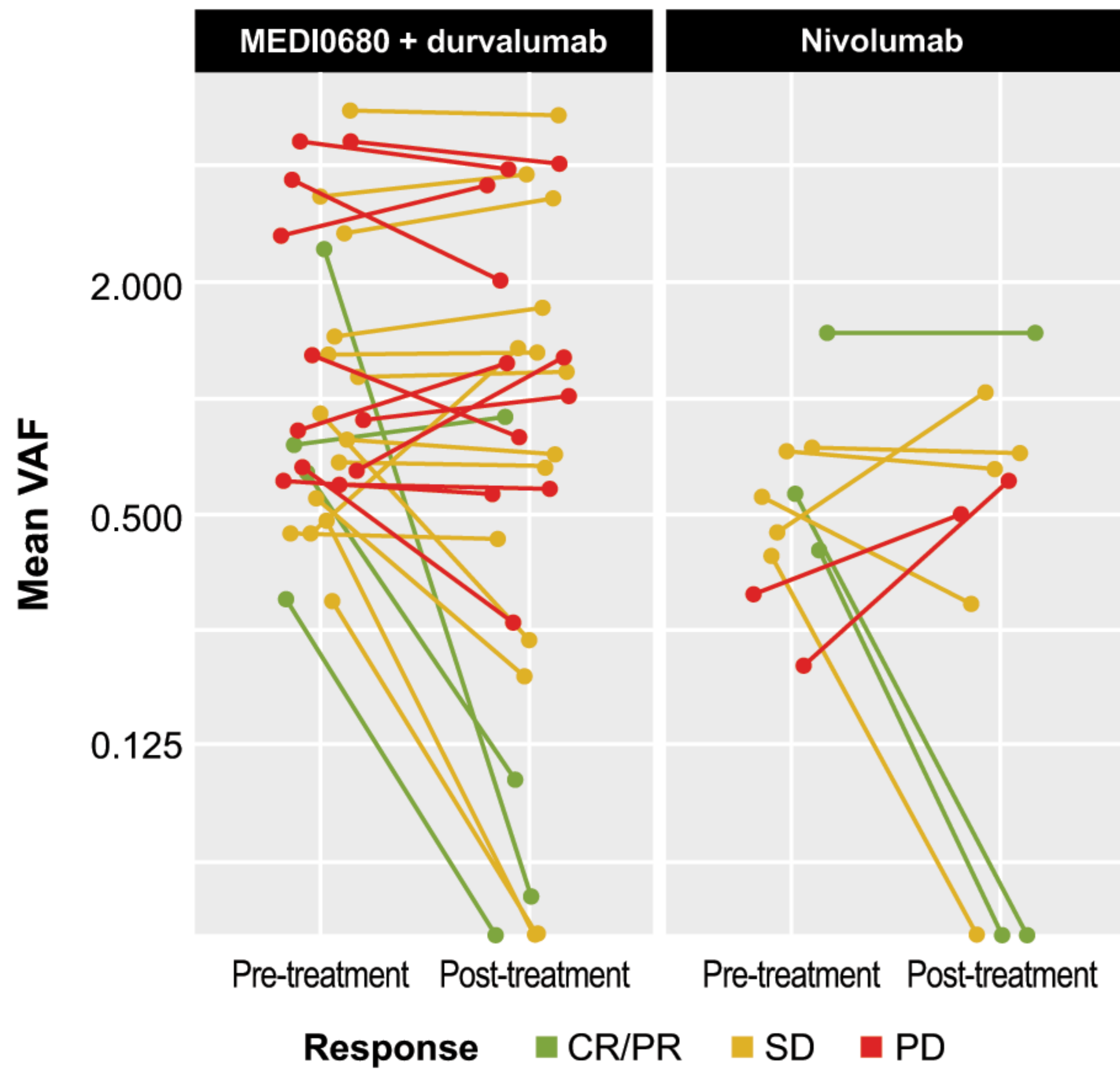
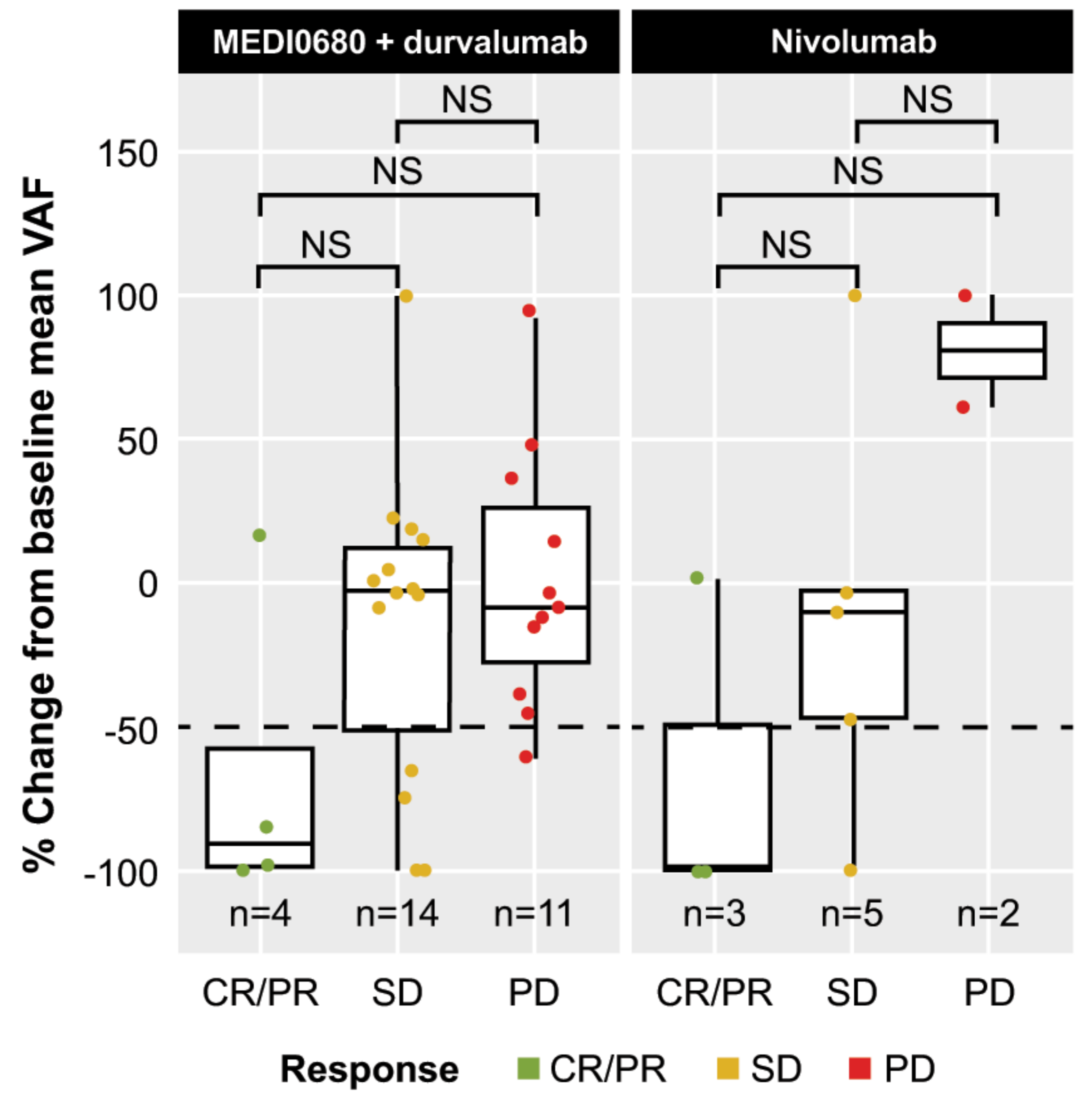


Figure 3

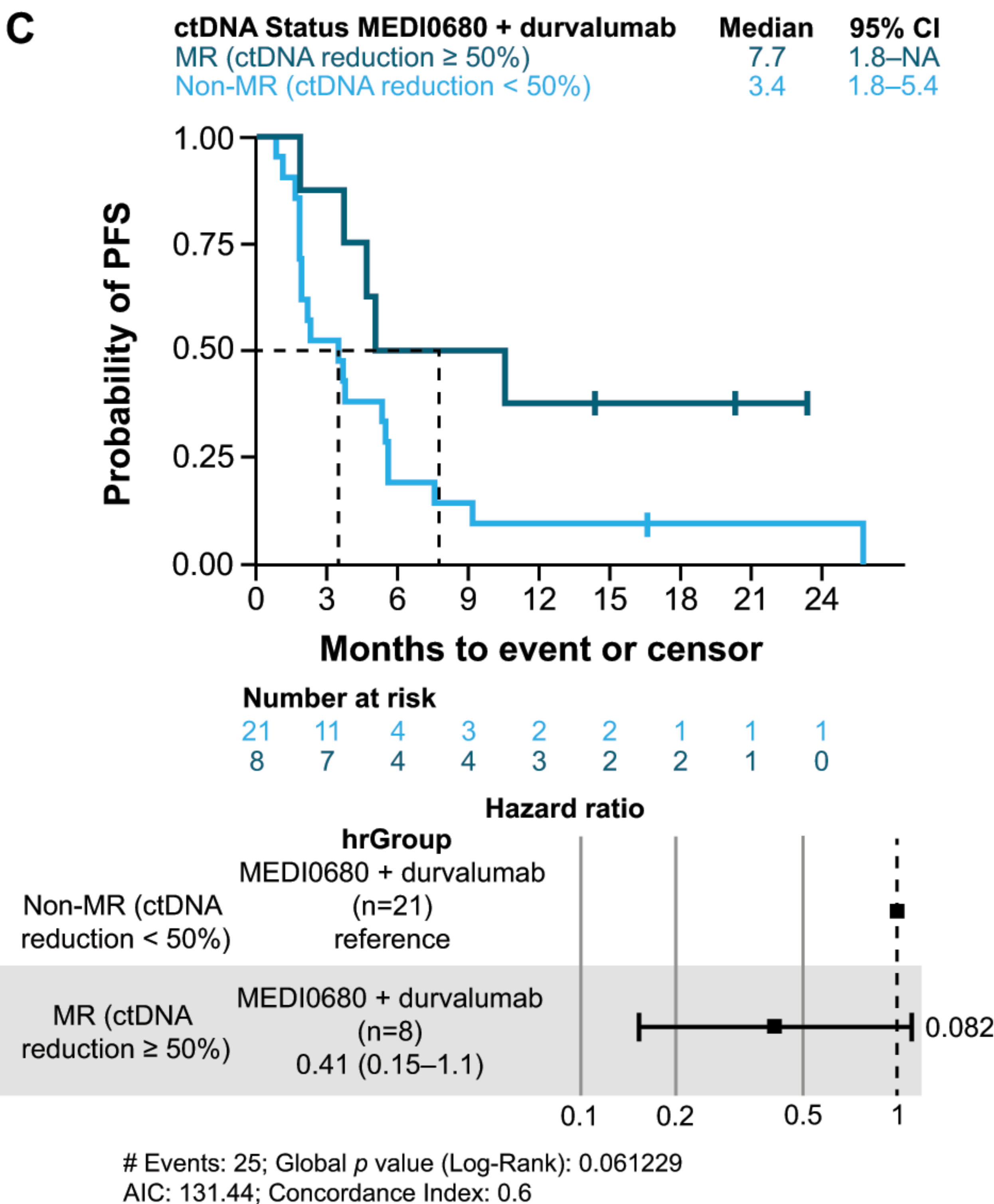
A



B



C



D

