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1 **Tisotumab Vedotin in Previously Treated Recurrent or Metastatic Cervical Cancer**

2

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116 **Running Head (60/60 characters including spaces):**

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126 **Abstract** (250/250 words)

127 **Purpose:** Tissue factor (TF) is a potential target in cervical cancer as it is frequently  
128 highly expressed and associated with poor prognosis. Tisotumab vedotin, a first-in-class  
129 investigational antibody-drug conjugate targeting TF, has demonstrated encouraging  
130 activity in solid tumors. Here we report data from the cervical cancer cohort of innovaTV  
131 201 phase 1/2 study (NCT02001623).

132 **Experimental Design:** Patients with recurrent or metastatic cervical cancer received  
133 tisotumab vedotin 2.0 mg/kg every 3 weeks until progressive disease, unacceptable  
134 toxicity, or consent withdrawal. The primary objective was safety and tolerability.  
135 Secondary objectives included antitumor activity.

136 **Results:** Of the 55 patients, 51% had received  $\geq 2$  prior lines of treatment in the  
137 recurrent or metastatic setting; 67% had prior bevacizumab+doublet chemotherapy.  
138 51% of patients had squamous cell carcinoma. The most common grade 3/4 treatment-  
139 emergent adverse events (AEs) were anemia (11%), fatigue (9%), and vomiting (7%).  
140 No grade 5 treatment-related AEs occurred. Investigator-assessed confirmed objective  
141 response rate (ORR) was 24% (95% confidence interval [CI]: 13%–37%). Median  
142 duration of response (DOR) was 4.2 months (range: 1.0<sup>+</sup>–9.7); four patients responded  
143 for >8 months. The 6-month progression-free survival (PFS) rate was 29% (95% CI:  
144 17%–43%). Independent review outcomes were comparable, with confirmed ORR of  
145 22% (95% CI: 12%–35%), median DOR of 6.0 months (range: 1.0<sup>+</sup>–9.7), and 6-month  
146 PFS rate of 40% (95% CI: 24%–55%). TF expression was confirmed in most patients;  
147 no significant association with response was observed.



148 **Conclusions:** Tisotumab vedotin demonstrated a manageable safety profile and  
149 encouraging antitumor activity in patients with previously treated recurrent or metastatic  
150 cervical cancer.

151 **Translational Relevance** (149/150 words)

152 Treatment of recurrent or metastatic cervical cancer upon disease progression on or  
153 after first-line therapy is variable, and current treatment options provide minimal benefit  
154 with no current second-line standard of care. Tissue factor is aberrantly expressed in  
155 cervical cancer and is associated with poor prognosis, making it a potential therapeutic  
156 target. In this final analysis of the full cervical cancer cohort from the innovaTV 201  
157 study ( $N = 55$ ), tisotumab vedotin showed a manageable safety profile and encouraging  
158 antitumor activity in this advanced, previously treated cervical cancer population.  
159 Responses with tisotumab vedotin were observed across histological types and prior  
160 treatment type received, including bevacizumab in combination with doublet  
161 chemotherapy. This study provides evidence to support the continued investigation of  
162 tisotumab vedotin as a potential treatment option for the cervical cancer patient  
163 population that currently lacks effective therapies, has high risk of relapse, and has low  
164 survival after first-line treatment.

165 **Introduction**

166 Cervical cancer is a common cancer in women, with an estimated 570,000 new cases  
167 globally in 2018, and represents the third-leading cause of cancer-related death in  
168 women worldwide (1). Approximately 15,500 and 61,000 new cases of cervical cancer  
169 were estimated in North America and in Europe in 2018, respectively, resulting in  
170 approximately 5,800 and 25,800 deaths (2). Recurrent or metastatic cervical cancer has  
171 a poor prognosis, with a 5-year survival rate of 17% (3). Bevacizumab and doublet  
172 chemotherapy (paclitaxel and cisplatin or paclitaxel and topotecan) was adopted as  
173 first-line (1L) standard-of-care therapy for recurrent or metastatic cervical cancer in the  
174 past 5 years (4-6). However, nearly all patients relapse after 1L treatment, and single-  
175 institution experiences indicate that the percentage of patients who receive a second-  
176 line (2L) therapy varies (30%–70%) as many patients die before receiving treatment  
177 (7,8).

178

179 Available 2L+ therapies for recurrent or metastatic cervical cancer are characterized by  
180 low response rates (5,6). Before adoption of bevacizumab plus doublet chemotherapy in  
181 1L, therapies administered in the 2L+ setting reported response rates in the range of  
182 4.5–15%, with median survival <8 months (9-15). Data in the post-bevacizumab plus  
183 chemotherapy setting are limited, with a single-institution study showing single-digit  
184 response rates (0%–6%) for 2L treatment (7), suggesting prior vascular endothelial  
185 growth factor inhibition may negatively impact subsequent treatment response. Data in  
186 the third-line setting are further limited, with approximately 60% of patients not receiving  
187 third-line treatment and, when treated, response rates of 3% (8). Recently,

188 pembrolizumab (anti-programmed death 1) was granted accelerated approval in the  
189 United States for the 2L+ treatment of patients with programmed death-ligand 1 (PD-  
190 L1)-positive (combined positive score  $\geq 1\%$ ) recurrent or metastatic cervical cancer (16).  
191 However, only a fraction of these patients respond (objective response rate [ORR]:  
192 14%) (16). In addition, efficacy in nonsquamous recurrent or metastatic cervical cancer  
193 is not yet known as 92% of the patients studied had squamous histology (16). These  
194 data underscore the high and immediate need for effective therapies that provide  
195 clinical benefit in a broader patient population.

196

197 Tisotumab vedotin is a first-in-class investigational antibody-drug conjugate (ADC)  
198 comprising a tissue factor (TF)-specific, fully human monoclonal antibody conjugated to  
199 the clinically validated microtubule-disrupting agent monomethyl auristatin E (MMAE)  
200 using a protease-cleavable linker (17,18). Under normal physiological conditions, TF is  
201 central to the coagulation pathway (19). In oncogenesis, TF plays a role in tumor-  
202 associated angiogenesis, progression, and metastasis (20-23). TF is aberrantly  
203 expressed across many solid tumors, including cervical cancer (20,24-26), and has  
204 been associated with poor clinical outcomes (20). The expression of TF across tumor  
205 types and its role in oncogenesis make it an appealing therapeutic target.

206

207 Tisotumab vedotin delivers MMAE to TF-expressing cells to induce direct cytotoxicity  
208 and bystander killing of neighboring cells (17,18). In vitro studies demonstrated that  
209 tisotumab vedotin induces immunogenic cell death and efficiently engages with immune  
210 cells to promote tumor cell death through Fc $\gamma$  receptor-mediated effector functions,

211 such as antibody-dependent cellular cytotoxicity and antibody-dependent cellular  
212 phagocytosis (18,27). Moreover, tisotumab vedotin was found to inhibit TF-activated  
213 factor VII (FVIIa)–dependent intracellular signaling while minimally impacting  
214 procoagulant activity (18). To our knowledge, tisotumab vedotin is the first drug to  
215 successfully target TF.

216

217 innovaTV 201 (NCT02001623) is a phase 1/2 dose-escalation and expansion trial  
218 evaluating tisotumab vedotin in patients with previously treated locally advanced or  
219 metastatic solid tumors. In the dose-escalation phase, tisotumab vedotin showed a  
220 manageable safety profile, and 2.0 mg/kg every 3 weeks was established as the  
221 recommended phase 2 dose (28). Here, we report the safety and antitumor activity of  
222 tisotumab vedotin in the cervical cancer expansion cohort.

223

## 224 **Methods**

### 225 *Study Oversight*

226 Genmab A/S sponsored the study, provided study drug, and collaborated with academic  
227 investigators on study design, data analysis/interpretation, and manuscript writing. The  
228 trial was conducted in accordance with the International Conference on Harmonization  
229 Good Clinical Practice Guidelines, Declaration of Helsinki, and all applicable regulatory  
230 requirements. The trial protocol was approved by an independent ethics committee or  
231 institutional review board prior to initiation. All patients gave written informed consent.

232 All authors confirm the accuracy of the data and adherence of the trial to the protocol.

233

234 *Study Design and Patients*

235 innovaTV 201 is an open-label, multi-cohort, phase 1/2 dose escalation and expansion  
236 study of tisotumab vedotin for the treatment of locally advanced and/or metastatic solid  
237 tumors known to express TF.

238  
239 The dose escalation phase of the innovaTV 201 study followed a standard 3+3 design  
240 to evaluate tisotumab vedotin at doses of 0.3 mg/kg up to 2.2 mg/kg administered  
241 intravenously every 3 weeks. The dose of tisotumab vedotin used in the expansion  
242 cohort was based on the safety and efficacy data from the dose escalation phase (28).  
243 The expansion phase included patients with locally advanced and/or metastatic cervical,  
244 ovarian, prostate, bladder, esophageal, endometrial, and non–small cell lung cancer  
245 who have progressed on or are ineligible for standard treatments (28). The cervical and  
246 ovarian cancer cohorts were expanded from the initial 14 patients to approximately 30  
247 patients each based on preliminary clinical activity and safety observed. After an  
248 amendment to the protocol, up to an additional 25 patients could be enrolled in the  
249 cervical cancer cohort for a maximum of 55 patients in total.

250  
251 Eligible patients had measurable disease per Response Evaluation Criteria In Solid  
252 Tumors (RECIST) v1.1 and an Eastern Cooperative Oncology Group (ECOG)  
253 performance status of 0 or 1. Patients with known coagulation defects, ongoing major  
254 bleeding, or Common Toxicity Criteria for Adverse Events (CTCAE) grade  $\geq 2$   
255 neuropathy were excluded. A protocol amendment allowed for enrollment of patients on  
256 anticoagulants. Patients in the cervical cancer cohort had recurrent/metastatic disease,

257 progressed on a platinum-based regimen, and received  $\leq 4$  prior treatments for  
258 advanced disease.

259

### 260 *Treatment and Assessments*

261 Patients in the cervical cancer cohort received tisotumab vedotin 2.0 mg/kg intravenous  
262 infusion every 3 weeks for four cycles. Patients with clinical benefit (stable disease or  
263 better) at the end of four cycles had the option to continue treatment for an additional  
264 eight cycles (up to 12 cycles total), or until disease progression or unacceptable toxicity.  
265 After 12 cycles, patients with clinical benefit could continue in an extension study  
266 (NCT03245736).

267

268 Safety was monitored throughout the study and for up to 30 days after the last dose.  
269 Adverse events (AEs) were graded according to the National Cancer Institute CTCAE  
270 v4.03 and coded according to Medical Dictionary for Regulatory Activities (MedDRA)  
271 v17.0. AEs of special interest (AESIs) were identified during the dose escalation phase  
272 of the study and for which pooled standardized MedDRA queries were applied included  
273 neuropathies (known MMAE-related AEs), bleeding-related events (because of TF's  
274 role in coagulation), and ocular events (conjunctivitis, conjunctival ulceration, keratitis,  
275 symblepharon).

276

277 Protocol amendments implementing additional exclusion criteria and mitigation  
278 measures to reduce the risk for ocular events were introduced throughout the study.  
279 Patients with active ocular surface disease at baseline or a history of cicatricial

280 conjunctivitis were excluded. Mitigation strategies included the application of  
281 preservative-free lubricating eye drops from the start of study treatment until the end of  
282 treatment, administration of local ocular vasoconstrictor eye drops immediately prior to  
283 the start of infusion, cooling eye pads worn during infusion, and application of steroid  
284 eye drops for 3 days beginning on the day of infusion. Furthermore, the use of contact  
285 lenses was avoided, and stricter dose modification guidance for ocular events was  
286 provided.

287

288 Tumor responses were assessed by investigator and independent review committee  
289 (IRC) using magnetic resonance imaging or computed tomography scans at baseline  
290 and every 6 weeks during the study. Responses were confirmed by subsequent repeat  
291 imaging performed  $\geq 4$  weeks after initial response.

292

293 Tumor biopsies were requested upon enrollment in the study. Fresh biopsies were  
294 requested, but the most recent archived sample could be used. If no archived biopsies  
295 were available, a fresh biopsy was taken prior to dosing. Biopsy samples were  
296 retrospectively assessed for membrane and cytoplasmic TF tumor expression in a  
297 central laboratory using an analytically validated immunohistochemistry assay. TF  
298 histology-score (H-score) was calculated based on the percentage of tumor tissue that  
299 had membrane or cytoplasmic TF expression intensity of low (1+), intermediate (2+),  
300 and high (3+) on evaluable samples using the following equation:  $H\text{-score} = (1 \times [\% \text{ cells } 1+]) + (2 \times [\% \text{ cells } 2+]) + (3 \times [\% \text{ cells } 3+])$ .

302



303 *Study Outcomes*

304 The primary objective of this study was to evaluate the safety and tolerability of  
305 tisotumab vedotin. Key secondary endpoints included ORR (defined as complete  
306 response [CR] or partial response [PR] as assessed by the investigator or IRC),  
307 duration of response (DOR), and progression-free survival (PFS) per RECIST v1.1.

308

309 *Statistical Analysis*

310 All patients who received at least one dose of tisotumab vedotin were included in the  
311 safety and antitumor activity analyses. ORR was determined with a corresponding two-  
312 sided 95% exact binomial confidence interval (CI). IRC-assessment utilized a 2 readers  
313 plus adjudication method. Agreement between investigator- and IRC-assessment with  
314 respect to confirmed objective response was determined using Cohen's kappa. Median  
315 PFS and DOR were determined using the Kaplan–Meier method and were presented  
316 with a two-sided 95% CI. Prespecified subgroup factors included TF expression.  
317 Association between TF expression and response was analyzed using analysis of  
318 variance with Tukey's multi-comparison post hoc test.

319

320 **Results**

321 *Patients*

322 Between November 2015 and April 2018, 55 patients were enrolled into the cervical  
323 cancer expansion cohort of the innovaTV 201 study (**Supplementary Figure S1**). The  
324 demographics and baseline disease characteristics are presented in **Table 1**. Most  
325 patients had ECOG performance status of 1 (73%). Fifty-one percent of the patients had

326 squamous cell carcinoma and 35% had adenocarcinoma. Fifty-one percent received  $\geq 2$   
327 prior lines of treatment. Four patients did not receive 1L standard-of-care therapy  
328 because they were refractory to treatment for early stage disease (concurrent  
329 chemoradiation or neoadjuvant therapy) and were considered as having zero prior lines  
330 of treatment in the recurrent setting. Prior systemic therapies received included taxanes  
331 (91%) and bevacizumab plus doublet chemotherapy (67%). TF expression ( $\geq 1\%$ ) was  
332 confirmed in the majority of evaluable patients (membrane expression, 100%;  
333 cytoplasmic expression, 95%).

334

### 335 *Safety*

336 At data cutoff (September 30, 2018), the median follow-up was 3.5 months (range: 0.6–  
337 11.8). The median number of doses of tisotumab vedotin received was 4.0 (range: 1.0–  
338 14.0). Ten patients (18%) discontinued treatment due to an AE, the most common of  
339 which was peripheral neuropathy (9%). Seven patients (13%) had an AE leading to  
340 dose reduction (**Supplementary Table S1**).

341

342 Treatment-emergent AEs regardless of causality and of any grade were reported in all  
343 patients, and AEs of grade  $\geq 3$  were reported in 31 patients (56%) (**Table 2**). The most  
344 common AEs were epistaxis (51%), fatigue (51%), nausea (49%), conjunctivitis (42%),  
345 and alopecia (40%) (**Table 2**). Of these, most were grade 1/2. The most common grade  
346  $\geq 3$  AEs were anemia (11%), fatigue (9%), and vomiting (7%). Twenty-nine patients  
347 (53%) had serious AEs (**Supplementary Table S2**), the most common of which were  
348 vomiting (7%) and constipation (5%). Two fatal events occurred while on treatment,

349 both due to disease progression, and were assessed as unrelated to treatment by  
350 investigator and study sponsor. No treatment-related deaths were observed.  
351  
352 No grade  $\geq 4$  AEs were observed. Neuropathy AEs occurred in 30 patients (55%);  
353 six of the AEs (11%) were grade 3, and the most common was peripheral neuropathy  
354 (all grades: 36%; grade 3: 4%) (**Table 2**, additional information on neuropathy AEs is  
355 summarized in **Supplementary Table S3**). Seventeen patients (31%) had neuropathy  
356 at baseline. Bleeding-related AEs occurred in 40 patients (73%) and most were grade  
357 1/2, with three patients (5%) experiencing a grade 3 bleeding-related event (two with  
358 vaginal hemorrhage and one with hematuria) (**Table 2**, additional information on  
359 bleeding-related AEs is summarized in **Supplementary Table S4**). The most  
360 common bleeding-related event was epistaxis (51%); all were grade 1 except for one  
361 grade 2. Ocular AEs of any type occurred in 36 patients (65%), and the most common  
362 were conjunctivitis (42%) and dry eye (24%) (**Table 2**, additional information on ocular  
363 AEs is summarized in **Supplementary Table S5**). The incidence of ocular events was  
364 reduced from 80% in patients enrolled prior to the implementation of mitigation  
365 measures ( $n = 15$ ) to 60% in patients enrolled after implementation ( $n = 40$ ). The rates  
366 of conjunctivitis were reduced from 80% to 28% (**Figure 1**).

367

### 368 *Antitumor Activity*

369 The investigator-assessed confirmed ORR was 24% (95% CI: 13%–37%) (**Table 3**).  
370 Maximum changes in target lesion size from baseline are shown in **Figure 2A**. The  
371 median time to response was 2.6 months (range: 1.1–3.9) and the median DOR was

372 4.2 months (range: 1.0<sup>+</sup>–9.7) (**Table 3**). Four patients experienced a confirmed PR for  
373 ≥8 months (**Figure 2B**). The median PFS was 4.2 months (95% CI: 2.1–5.3), and the 6-  
374 month PFS rate was 29% (95% CI: 17%–43%) (**Table 3, Supplementary Figure S2**).

375

376 The IRC-assessed confirmed ORR was 22% (95% CI: 12%–35%) (**Table 3**), which  
377 included one patient who had a CR by IRC-assessment. Four patients were refractory  
378 to prior treatment for early stage disease and did not receive standard of care (doublet  
379 chemotherapy ± bevacizumab) for first-line treatment of recurrent or metastatic disease.  
380 In these patients ( $n = 51$ ), the IRC-assessed confirmed ORR was 24% (95% CI: 13%–  
381 38%). The overall agreement between investigator- and IRC-assessment with respect  
382 to ORR was 95% (Cohen’s kappa 0.84). The median IRC-assessed DOR was 6.0  
383 months (range: 1.0<sup>+</sup>–9.7), and the 6-month PFS rate was 40% (95% CI: 24%–55%)  
384 (**Table 3, Supplementary Figure S3**).

385

386 **Figure 2C** shows the target and non-target lesion baseline and follow-up scans of a 43-  
387 year-old female patient with squamous cell carcinoma previously treated with paclitaxel  
388 plus carboplatin. This patient achieved PR after 16 weeks of treatment and discontinued  
389 tisotumab vedotin due to an AE at that time. The decreased target lesion size persisted  
390 after treatment discontinuation up to week 47.

391

### 392 *Subgroup and Biomarker Analysis*

393 Investigator-assessed responses with tisotumab vedotin were observed across  
394 histologic types (squamous cell carcinoma ORR, 29% [8/28 patients]; adenocarcinoma

395 ORR, 16% [3/19]) and for patients who received zero (25% [1/4]), one (22% [5/23]), two  
396 (35% [6/17]), or 3–4 (9% [1/11]) prior lines of therapy (**Figure 3A**). Patients who  
397 previously received bevacizumab plus doublet chemotherapy demonstrated a similar  
398 ORR to the overall population (22% [8/37]).

399

400 TF expression in relation to clinical response was evaluable in tissue samples from 44  
401 of the 55 patients (80%), as three patients had no biopsy, four were not evaluable for  
402 response by RECIST v1.1, and five had insufficient tumor material (one patient not  
403 evaluable for response also had insufficient tumor material). Of the evaluable cases, 37  
404 patients (84%) had archival biopsies and seven (16%) had fresh biopsies. Seventeen of  
405 the 37 patients (46%) with archived tissue had no prior treatment at the time of biopsy.  
406 There was no statistically significant difference in TF expression between biopsy  
407 samples taken with no prior treatment compared to recurrent cervical cancer biopsy  
408 samples (data not shown). Twenty-seven biopsies (61%) were from primary tumors and  
409 17 (39%) were from metastatic lesions. Membrane and cytoplasmic TF expression (H-  
410 score) were comparable across histological types (**Figure 3B-C**). Investigation of  
411 membrane or cytoplasmic TF expression did not show a statistically significant  
412 association with investigator-assessed best overall confirmed response (**Figure 3D-E**).

413

## 414 **Discussion**

415 In patients with advanced recurrent or metastatic cervical cancer, tisotumab vedotin, a  
416 first-in-class ADC designed to target TF, demonstrated a manageable safety profile and  
417 encouraging antitumor activity in a patient population for which no standard-of-care

418 therapy exists. To our knowledge, tisotumab vedotin is the first ADC to successfully  
419 demonstrate meaningful clinical activity specifically targeting TF, a novel target  
420 overexpressed in many solid tumors associated with poor outcomes.

421  
422 The safety profile of tisotumab vedotin was generally consistent with other MMAE-  
423 based ADCs, except for epistaxis and conjunctivitis (29,30). Almost all epistaxis events  
424 were grade 1, and none required clinical intervention. Moreover, as TF is highly  
425 expressed in the nasal epithelium (31), this observation may reflect a local disruption of  
426 the nasal mucosa rather than an underlying treatment-induced coagulopathy. The  
427 incidence of other bleeding-related events was consistent with the expected incidence  
428 observed in patients with advanced cervical cancer. Most ocular events were grade 1/2,  
429 except for one patient with grade 3 conjunctivitis. The incidence of ocular events,  
430 including conjunctivitis, was reduced in the patients enrolled after implementation of  
431 mitigation measures. Although the mechanism of the ocular events is not known, TF  
432 expression has been demonstrated in the ocular epithelium (32,33), which may result in  
433 treatment-emergent toxicity in these cells. The understanding of TF-related epistaxis  
434 and ocular events is continuing to evolve, and further studies are needed to optimize  
435 mitigation strategies, as well as to assess the long-term effects of tisotumab vedotin, the  
436 duration of these AEs, and the mechanisms by which they occur.

437  
438 The ORR observed with tisotumab vedotin across histologies, line of therapy, and prior  
439 treatments, including bevacizumab plus doublet chemotherapy, is clinically important in  
440 a patient population that lacks effective therapies. Tisotumab vedotin demonstrated a

441 notable response rate (24% by investigator assessment) and meaningful 6-month PFS  
442 rate in this previously treated patient population with advanced cervical cancer,  
443 including in patients with adenocarcinoma histology. In contrast, an ORR of 14% was  
444 observed in patients with PD-L1–positive cervical cancer treated with pembrolizumab  
445 (16). The efficacy of pembrolizumab in patients with nonsquamous histology has not  
446 been well established as the majority of patients (92%) enrolled in the clinical trial of  
447 pembrolizumab had squamous cell carcinoma (16), and although the median DOR was  
448 not reached, meaningful PFS benefit was not observed (34).

449  
450 The antitumor activity of tisotumab vedotin is further supported by the concordance  
451 between the investigator- and IRC-assessed ORR and prolonged responses. The  
452 durability of response with tisotumab vedotin is highlighted by the four patients with  
453 response >8 months and the patient case demonstrating persistent PR despite  
454 tisotumab vedotin discontinuation. The durable responses observed may be indicative  
455 of the multiple proposed mechanisms of action of tisotumab vedotin, including direct  
456 cytotoxicity, bystander killing, and immunogenic cell death induced by MMAE, as well as  
457 Fcγ receptor–mediated effector functions and inhibition of TF/FVIIa signaling (17,18,27).

458  
459 The majority of cervical cancer patient biopsies had detectable TF expression. Both  
460 membrane and cytoplasmic levels of TF expression were comparable across various  
461 cervical cancer histological types. Although median membrane and cytoplasmic TF H-  
462 score was higher in patients who achieved PR and stable disease compared to those  
463 with progressive disease, there was no statistically significant association with best

464 confirmed response. That said, the majority of samples were from archival tissue, and  
465 the effect of previous lines of therapy on TF expression has yet to be explored. Further  
466 studies evaluating TF expression and other potential predictive biomarkers that  
467 associate with antitumor activity will be explored to determine whether certain patient  
468 populations may benefit more from tisotumab vedotin.

469

470 This study demonstrated the antitumor activity of tisotumab vedotin in patients with  
471 advanced, previously treated recurrent or metastatic cervical cancer. However, overall  
472 survival was not a specified endpoint, and thus further studies are needed to establish  
473 the impact of tisotumab vedotin on survival in these patients. The ongoing phase 2  
474 innovaTV 204 study (NCT03438396; ENGOT-cx6; GOG-3032) is investigating the  
475 antitumor activity and safety of tisotumab vedotin in approximately 100 patients with  
476 previously treated recurrent or metastatic cervical cancer. Additionally, the phase 1/2  
477 innovaTV 205 study (NCT03786081; ENGOT-cx8; GOG-3024) is investigating the  
478 combination of tisotumab vedotin with pembrolizumab, bevacizumab, or carboplatin in  
479 the 1L and 2L+ settings in patients with recurrent or metastatic cervical cancer.

480

481 Recurrent or metastatic cervical cancer is a serious, life-threatening disease. The lack  
482 of effective treatments, high relapse risk, and low survival after 1L treatment  
483 demonstrate the need for novel, safe, and effective therapies that improve clinical  
484 benefit. The results of this study cohort have demonstrated the manageable safety  
485 profile and encouraging antitumor activity of tisotumab vedotin, supporting the further



486 clinical development of this first-in-class ADC targeting the novel therapeutic target, TF,  
487 in patients with previously treated recurrent or metastatic cervical cancer.

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497

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505 **References**

506

- 507 1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global Cancer  
508 Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for  
509 36 Cancers in 185 Countries. *CA Cancer J Clin* **2018** doi 10.3322/caac.21492.
- 510 2. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, *et al.* (2018). Global  
511 Cancer Observatory: Cancer Today. Lyon, France: International Agency for  
512 Research on Cancer. Available from: <https://gco.iarc.fr/today>, accessed 07  
513 October 2019.
- 514 3. Institute NC. 2018 SEER Cancer Statistics Review 1975-2015: Cancer of the  
515 Cervix Uteri. <[https://seer.cancer.gov/results\\_single/sect\\_05\\_table.08.pdf](https://seer.cancer.gov/results_single/sect_05_table.08.pdf)>.
- 516 4. Tewari KS, Sill MW, Long HJ, 3rd, Penson RT, Huang H, Ramondetta LM, *et al.*  
517 Improved survival with bevacizumab in advanced cervical cancer. *N Engl J Med*  
518 **2014**;370(8):734-43 doi 10.1056/NEJMoa1309748.
- 519 5. Boussios S, Seraj E, Zarkavelis G, Petrakis D, Kollas A, Kafantari A, *et al.*  
520 Management of patients with recurrent/advanced cervical cancer beyond first line  
521 platinum regimens: Where do we stand? A literature review. *Crit Rev Oncol*  
522 *Hematol* **2016**;108:164-74 doi 10.1016/j.critrevonc.2016.11.006.
- 523 6. Marth C, Landoni F, Mahner S, McCormack M, Gonzalez-Martin A, Colombo N.  
524 Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and  
525 follow-up. *Ann Oncol* **2017**;28(suppl\_4):iv72-iv83 doi 10.1093/annonc/mdx220.
- 526 7. Zamorano AS, Wan L, Powell MA, Massad LS. Repeating platinum/bevacizumab  
527 in recurrent or progressive cervical cancer yields marginal survival benefits.  
528 *Gynecol Oncol Rep* **2017**;22:48-51 doi 10.1016/j.gore.2017.09.003.

- 529 8. McLachlan J, Boussios S, Okines A, Glaessgen D, Bodlar S, Kalaitzaki R, *et al.*  
530 The Impact of Systemic Therapy Beyond First-line Treatment for Advanced  
531 Cervical Cancer. *Clin Oncol (R Coll Radiol)* **2017**;29(3):153-60 doi  
532 10.1016/j.clon.2016.10.002.
- 533 9. Bookman MA, Blessing JA, Hanjani P, Herzog TJ, Andersen WA. Topotecan in  
534 squamous cell carcinoma of the cervix: A Phase II study of the Gynecologic  
535 Oncology Group. *Gynecol Oncol* **2000**;77(3):446-9 doi 10.1006/gyno.2000.5807.
- 536 10. Muggia FM, Blessing JA, Method M, Miller DS, Johnson GA, Lee RB, *et al.*  
537 Evaluation of vinorelbine in persistent or recurrent squamous cell carcinoma of  
538 the cervix: a Gynecologic Oncology Group study. *Gynecol Oncol* **2004**;92(2):639-  
539 43 doi 10.1016/j.ygyno.2003.10.045.
- 540 11. Schilder RJ, Blessing J, Cohn DE. Evaluation of gemcitabine in previously  
541 treated patients with non-squamous cell carcinoma of the cervix: a phase II study  
542 of the Gynecologic Oncology Group. *Gynecol Oncol* **2005**;96(1):103-7 doi  
543 10.1016/j.ygyno.2004.09.027.
- 544 12. Miller DS, Blessing JA, Bodurka DC, Bonebrake AJ, Schorge JO. Evaluation of  
545 pemetrexed (Alimta, LY231514) as second line chemotherapy in persistent or  
546 recurrent carcinoma of the cervix: a phase II study of the Gynecologic Oncology  
547 Group. *Gynecol Oncol* **2008**;110(1):65-70 doi S0090-8258(08)00203-5  
548 [pii];10.1016/j.ygyno.2008.03.009 [doi].
- 549 13. Garcia AA, Blessing JA, Vaccarello L, Roman LD, Gynecologic Oncology Group  
550 S. Phase II clinical trial of docetaxel in refractory squamous cell carcinoma of the

- 551 cervix: a Gynecologic Oncology Group Study. *Am J Clin Oncol* **2007**;30(4):428-  
552 31 doi 10.1097/COC.0b013e31803377c8.
- 553 14. Monk BJ, Sill MW, Burger RA, Gray HJ, Buekers TE, Roman LD. Phase II trial of  
554 bevacizumab in the treatment of persistent or recurrent squamous cell carcinoma  
555 of the cervix: a gynecologic oncology group study. *Journal of clinical oncology :*  
556 *official journal of the American Society of Clinical Oncology* **2009**;27(7):1069-74  
557 doi JCO.2008.18.9043 [pii];10.1200/JCO.2008.18.9043 [doi].
- 558 15. Lorusso D, Ferrandina G, Pignata S, Ludovisi M, Vigano R, Scalone S, *et al.*  
559 Evaluation of pemetrexed (Alimta, LY231514) as second-line chemotherapy in  
560 persistent or recurrent carcinoma of the cervix: the CERVIX 1 study of the MITO  
561 (Multicentre Italian Trials in Ovarian Cancer and Gynecologic Malignancies)  
562 Group. *Ann Oncol* **2010**;21(1):61-6 doi 10.1093/annonc/mdp266.
- 563 16. Corp. MSD. KEYTRUDA® (pembrolizumab) for injection, for intravenous use.  
564 Whitehouse Station, NJ: Merck & Co., Inc.; 06/2018.
- 565 17. de Goeij BE, Satijn D, Freitag CM, Wubbolts R, Bleeker WK, Khasanov A, *et al.*  
566 High turnover of tissue factor enables efficient intracellular delivery of antibody-  
567 drug conjugates. *Mol Cancer Ther* **2015**;14(5):1130-40 doi 10.1158/1535-  
568 7163.MCT-14-0798.
- 569 18. Breij EC, de Goeij BE, Verploegen S, Schuurhuis DH, Amirkhosravi A, Francis J,  
570 *et al.* An antibody-drug conjugate that targets tissue factor exhibits potent  
571 therapeutic activity against a broad range of solid tumors. *Cancer Res*  
572 **2014**;74(4):1214-26 doi 10.1158/0008-5472.CAN-13-2440.

- 573 19. Lwaleed BA, Cooper AJ, Voegeli D, Getliffe K. Tissue factor: a critical role in  
574 inflammation and cancer. *Biol Res Nurs* **2007**;9(2):97-107 doi  
575 10.1177/1099800407305733.
- 576 20. Forster Y, Meye A, Albrecht S, Schwenger B. Tissue factor and tumor: clinical  
577 and laboratory aspects. *Clin Chim Acta* **2006**;364(1-2):12-21 doi  
578 10.1016/j.cca.2005.05.018.
- 579 21. Ruf W, Disse J, Carneiro-Lobo TC, Yokota N, Schaffner F. Tissue factor and cell  
580 signalling in cancer progression and thrombosis. *J Thromb Haemost* **2011**;9  
581 Suppl 1:306-15 doi 10.1111/j.1538-7836.2011.04318.x.
- 582 22. Anand M, Brat DJ. Oncogenic regulation of tissue factor and thrombosis in  
583 cancer. *Thromb Res* **2012**;129 Suppl 1:S46-9 doi 10.1016/S0049-  
584 3848(12)70015-4.
- 585 23. Han X, Guo B, Li Y, Zhu B. Tissue factor in tumor microenvironment: a  
586 systematic review. *J Hematol Oncol* **2014**;7:54 doi 10.1186/s13045-014-0054-8.
- 587 24. Cocco E, Varughese J, Buza N, Bellone S, Glasgow M, Bellone M, *et al.*  
588 Expression of tissue factor in adenocarcinoma and squamous cell carcinoma of  
589 the uterine cervix: implications for immunotherapy with hI-con1, a factor VII-  
590 IgGFc chimeric protein targeting tissue factor. *BMC Cancer* **2011**;11:263 doi  
591 10.1186/1471-2407-11-263.
- 592 25. Zhao X, Cheng C, Gou J, Yi T, Qian Y, Du X, *et al.* Expression of tissue factor in  
593 human cervical carcinoma tissue. *Exp Ther Med* **2018**;16(5):4075-81 doi  
594 10.3892/etm.2018.6723.

- 595 26. Pan L, Yu Y, Yu M, Yao S, Mu Q, Luo G, *et al.* Expression of fITF and asTF  
596 splice variants in various cell strains and tissues. *Mol Med Rep* **2019**;19(3):2077-  
597 86 doi 10.3892/mmr.2019.9843.
- 598 27. Alley SC, Harris JR, Cao A, den Heuvel EG-V, Velayudhan J, Satijn D, *et al.*  
599 Tisotumab vedotin induces anti-tumor activity through MMAE-mediated, Fc-  
600 mediated, and Fab-mediated effector functions in vitro. AACR 2019.
- 601 28. de Bono JS, Concin N, Hong DS, Thistlethwaite FC, Machiels J-P, Arkenau H-T,  
602 *et al.* First-in-human study of tisotumab vedotin in advanced and/or metastatic  
603 solid tumours: a multicentre, phase 1/2 trial. *Lancet Oncol* **2019**;20(3):383-93.
- 604 29. Prince HM, Kim YH, Horwitz SM, Dummer R, Scarisbrick J, Quagliano P, *et al.*  
605 Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell  
606 lymphoma (ALCANZA): an international, open-label, randomised, phase 3,  
607 multicentre trial. *Lancet* **2017**;390(10094):555-66 doi 10.1016/S0140-  
608 6736(17)31266-7.
- 609 30. Bendell J, Saleh M, Rose AA, Siegel PM, Hart L, Sirpal S, *et al.* Phase I/II study  
610 of the antibody-drug conjugate glembatumumab vedotin in patients with locally  
611 advanced or metastatic breast cancer. *J Clin Oncol* **2014**;32(32):3619-25 doi  
612 10.1200/JCO.2013.52.5683.
- 613 31. Shimizu S, Ogawa T, Takezawa K, Tojima I, Kouzaki H, Shimizu T. Tissue factor  
614 and tissue factor pathway inhibitor in nasal mucosa and nasal secretions of  
615 chronic rhinosinusitis with nasal polyp. *Am J Rhinol Allergy* **2015**;29(4):235-42  
616 doi 10.2500/ajra.2015.29.4183.

- 617 32. Ando R, Kase S, Ohashi T, Dong Z, Fukuhara J, Kanda A, *et al.* Tissue factor  
618 expression in human pterygium. *Mol Vis* **2011**;17:63-9.
- 619 33. Cho Y, Cao X, Shen D, Tuo J, Parver LM, Rickles FR, *et al.* Evidence for  
620 enhanced tissue factor expression in age-related macular degeneration. *Lab*  
621 *Invest* **2011**;91(4):519-26 doi 10.1038/labinvest.2010.184.
- 622 34. Chung HC, Schellens JHM, Delord J-P, Perets R, Italiano A, Shapira-Frommer  
623 R, *et al.* Pembrolizumab treatment of advanced cervical cancer: Updated results  
624 from the phase 2 KEYNOTE-158 study. *J Clin Oncol* **2018**;36(15\_suppl):5522-  
625 doi 10.1200/JCO.2018.36.15\_suppl.5522.
- 626



627 **TABLES**

628

629 **Table 1. Baseline demographics and disease characteristics**

| <b>Characteristic</b>  | <b>Cervical Cancer Cohort<br/>N = 55</b> |
|--|--|
| Age, median (range), years   | 46 (21–73)                               |
| Race, <i>n</i> (%) <sup>a</sup>  |  |
| White  | 49 (92)                                  |
| Asian  | 3 (6)                                    |
| Black or African American  | 1 (2)                                    |
| ECOG performance status, <i>n</i> (%)  |  |
| 0  | 15 (27)                                  |
| 1  | 40 (73)                                  |
| Histology, <i>n</i> (%)  |  |
| Squamous cell carcinoma  | 28 (51)                                  |
| Adenocarcinoma   | 19 (35)                                  |
| Adenosquamous carcinoma  | 6 (11)                                   |
| Other <sup>b</sup>   | 2 (4)                                    |
| Prior lines of systemic therapies for recurrent/metastatic disease, <i>n</i> (%) |  |
| 0 <sup>c</sup>   | 4 (7)                                    |
| 1  | 23 (42)                                  |
| 2  | 17 (31)                                  |

|  |          |
|--|----------|
| 3  | 6 (11)   |
| 4  | 5 (9)    |
| Prior systemic therapies received, <i>n</i> (%)    |          |
| Taxane   | 50 (91)  |
| Bevacizumab  | 40 (73)  |
| Bevacizumab plus doublet chemotherapy <sup>d</sup> | 37 (67)  |
| TF expression positive, <i>n</i> (%) <sup>e</sup>  |          |
| Membrane   | 44 (100) |
| Cytoplasm  | 42 (95)  |

ECOG, Eastern Cooperative Oncology Group; TF, tissue factor.

<sup>a</sup>Two patients were missing race information; percentage prevalence was calculated out of *n* = 53 for race.

<sup>b</sup>Following the data cutoff date, patients with other histology were resolved as having adenosquamous (*n* = 1) and neuroendocrine (*n* = 1) histology.

<sup>c</sup>Patients did not receive standard-of-care therapy in the first-line recurrent setting because they were refractory to treatment administered for early-stage disease (concurrent chemoradiation therapy or neoadjuvant therapy).

<sup>d</sup>Doublet chemotherapy defined as paclitaxel plus cisplatin or paclitaxel plus topotecan.

<sup>e</sup>Positive TF expression was defined as  $\geq 1\%$ ; percentage prevalence was calculated out of TF expression evaluable population (*n* = 44).

631 **Table 2. Treatment-emergent adverse events**

| Incidence, <i>n</i> (%)         | Cervical Cancer Cohort<br><i>N</i> = 55 |                 |
|---------------------------------|---|-----------------|
|                                 | All-grade                               | Grade ≥3        |
| Patients with ≥1 AE             | 55 (100)                                | 31 (56)         |
| <b>AEs With ≥20% Incidence</b>  | <b>All-grade</b>                        | <b>Grade ≥3</b> |
| Epistaxis                       | 28 (51)                                 | 0               |
| Fatigue                         | 28 (51)                                 | 5 (9)           |
| Nausea                          | 27 (49)                                 | 3 (5)           |
| Conjunctivitis                  | 23 (42)                                 | 1 (2)           |
| Alopecia                        | 22 (40)                                 | 0               |
| Decreased appetite              | 21 (38)                                 | 0               |
| Constipation                    | 20 (36)                                 | 1 (2)           |
| Peripheral neuropathy           | 20 (36)                                 | 2 (4)           |
| Vomiting                        | 19 (35)                                 | 4 (7)           |
| Diarrhea                        | 16 (29)                                 | 1 (2)           |
| Abdominal pain                  | 15 (27)                                 | 3 (5)           |
| Anemia                          | 13 (24)                                 | 6 (11)          |
| Dry eye                         | 13 (24)                                 | 0               |
| Hypokalemia                     | 11 (20)                                 | 3 (5)           |
| Pruritus                        | 11 (20)                                 | 0               |
| Pyrexia                         | 11 (20)                                 | 1 (2)           |
| Urinary tract infection         | 11 (20)                                 | 1 (2)           |
| <b>AESIs With ≥5% Incidence</b> | <b>All-grade</b>                        | <b>Grade 3</b>  |

|   |         |        |
|---|---------|--------|
| <b>Neuropathy AESIs<sup>a</sup></b>       | 30 (55) | 6 (11) |
| Peripheral neuropathy                     | 20 (36) | 2 (4)  |
| Muscular weakness                         | 4 (7)   | 0      |
| Peripheral sensory neuropathy             | 4 (7)   | 0      |
| <b>Bleeding-related AESIs<sup>b</sup></b> | 40 (73) | 3 (5)  |
| Epistaxis                                 | 28 (51) | 0      |
| Vaginal hemorrhage                        | 7 (13)  | 2 (4)  |
| Hematuria                                 | 5 (9)   | 1 (2)  |
| Contusion                                 | 3 (5)   | 0      |
| <b>Ocular AESIs<sup>c</sup></b>           | 36 (65) | 1 (2)  |
| Conjunctivitis                            | 23 (42) | 1 (2)  |
| Dry eye                                   | 13 (24) | 0      |
| Ulcerative keratitis                      | 4 (7)   | 0      |
| Blepharitis                               | 3 (5)   | 0      |
| Keratitis                                 | 3 (5)   | 0      |

AE, adverse event; AESI, adverse event of special interest; SMQ, standardized Medical Dictionary for Regulator Activities queries.

<sup>a</sup>Defined as peripheral neuropathy SMQ.

<sup>b</sup>Defined as hemorrhage SMQ.

<sup>c</sup>Defined as conjunctival disorders SMQ, corneal disorders SMQ, scleral disorders SMQ, retinal disorders SMQ, periorbital disorders SMQ, ocular infections SMQ, and optic nerve disorders SMQ.

633 **Table 3. Investigator- and independent review committee–assessed antitumor**  
 634 **activity of tisotumab vedotin**

|                              | <b>Cervical Cancer Cohort<br/>N = 55</b> |                             |
|------------------------------|--|-----------------------------|
| <b>Antitumor Activity</b>    | <b>Investigator-assessed</b>             | <b>IRC-assessed</b>         |
| ORR (95% CI), % <sup>a</sup> | 24 (13–37)                               | 22 (12–35)                  |
| CR, <i>n</i> (%)             | 0  | 1 (2)                       |
| PR, <i>n</i> (%)             | 13 (24)                                  | 11 (20)                     |
| SD, <i>n</i> (%)             | 21 (38)                                  | 19 (35)                     |
| Non-CR/Non-PD, <i>n</i> (%)  | 0  | 2 (4)                       |
| PD, <i>n</i> (%)             | 17 (31)                                  | 17 (31)                     |
| Not evaluable, <i>n</i> (%)  | 4 (7)                                    | 5 (9)                       |
| Median TTR (range), months   | 2.6 (1.1–3.9)                            | 2.1 (1.1–4.6)               |
| Median DOR (range), months   | 4.2 (1.0 <sup>+</sup> –9.7)              | 6.0 (1.0 <sup>+</sup> –9.7) |
| Median PFS (95% CI), months  | 4.2 (2.1–5.3)                            | 4.1 (1.7–6.7)               |
| 6-month PFS rate, % (95% CI) | 29 (17–43)                               | 40 (24–55)                  |

CI, confidence interval; CR, complete response; DOR, duration of response; IRC, independent review committee; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TTR, time to response.

<sup>+</sup>Indicates censored value due to ongoing response.

<sup>a</sup>Confirmed ORR by Response Evaluation Criteria In Solid Tumors v1.1 criteria.

635

636 **FIGURE LEGENDS**

637

638 **Figure 1. Conjunctivitis before and after mitigation measures.** The percentage  
639 incidence of conjunctivitis by grade occurring in patients enrolled before and after the  
640 implementation of mitigation measures are shown. <sup>a</sup>One patient with grade 3  
641 conjunctivitis after mitigation measures were implemented. No grade 3 events were  
642 observed before mitigation measures were implemented.

643

644 **Figure 2. Investigator-assessed antitumor activity of tisotumab vedotin in patients**  
645 **with cervical cancer. (A)** The maximum percentage change from baseline in target  
646 lesion size as assessed by the investigator and colored by best overall response  
647 according to RECIST v1.1. <sup>a</sup>Four patients did not have postbaseline scans and one  
648 patient did not have postbaseline assessments of sum of target lesions; these patients  
649 were excluded from this analysis. <sup>b</sup>Patient had lymph node disease and persistent non-  
650 target lesions for overall assessment of PR. <sup>c</sup>Patient had regression of nodal lesions to  
651 <10 mm short axis diameter of their target lesions and persistent non-target lesions, but  
652 was classified as PD due to a new lesion. **(B)** Investigator-assessed time to response  
653 and duration of response for patients with confirmed PR as measured by RECIST v1.1  
654 ( $n = 13$ ). **(C)** Target and non-target lesion scans at baseline and follow-up visits for a 43-  
655 year-old female patient with squamous cell carcinoma previously treated with paclitaxel  
656 and carboplatin. Weeks are measured from cycle 1 day 1 of tisotumab vedotin. The  
657 patient achieved a PR and discontinued tisotumab vedotin due to an adverse event at

658 week 16 (black arrow). PD, progressive disease; PR, partial response; RECIST v1.1,  
659 Response Evaluation Criteria In Solid Tumors v1.1.

660

661 **Figure 3. Response across baseline disease characteristic subgroups and by**

662 **tissue factor expression. (A)** The investigator-assessed confirmed ORR (95% CI) in

663 patients with squamous cell carcinoma, adenocarcinoma, or adenosquamous

664 carcinoma; in patients who received 1, 2, or 3-4 prior lines of systemic treatment; and in

665 patients who received prior taxanes, bevacizumab, or bevacizumab plus doublet

666 chemotherapy. <sup>a</sup>Investigator-assessed confirmed response by RECIST v1.1. <sup>b</sup>Patients

667 with other histology ( $n = 2$ ) did not have confirmed response. <sup>c</sup>Doublet chemotherapy

668 defined as paclitaxel plus cisplatin or paclitaxel plus topotecan. Membrane (**B**) and

669 cytoplasmic (**C**) TF expression intensity as measured by H-score, in patients with

670 adenocarcinoma, adenosquamous carcinoma, squamous carcinoma, or other histology.

671 Membrane (**D**) and cytoplasmic (**E**) TF expression intensity as measured by H-score in

672 patients who had investigator-assessed best confirmed PR, SD, or PD. *P* values are for

673 descriptive purposes only. CI, confidence interval; H, histology; ORR, objective

674 response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response

675 Evaluation Criteria In Solid Tumors v1.1; SD, stable disease; TF, tissue factor.

676

677

678

**Figure 1**

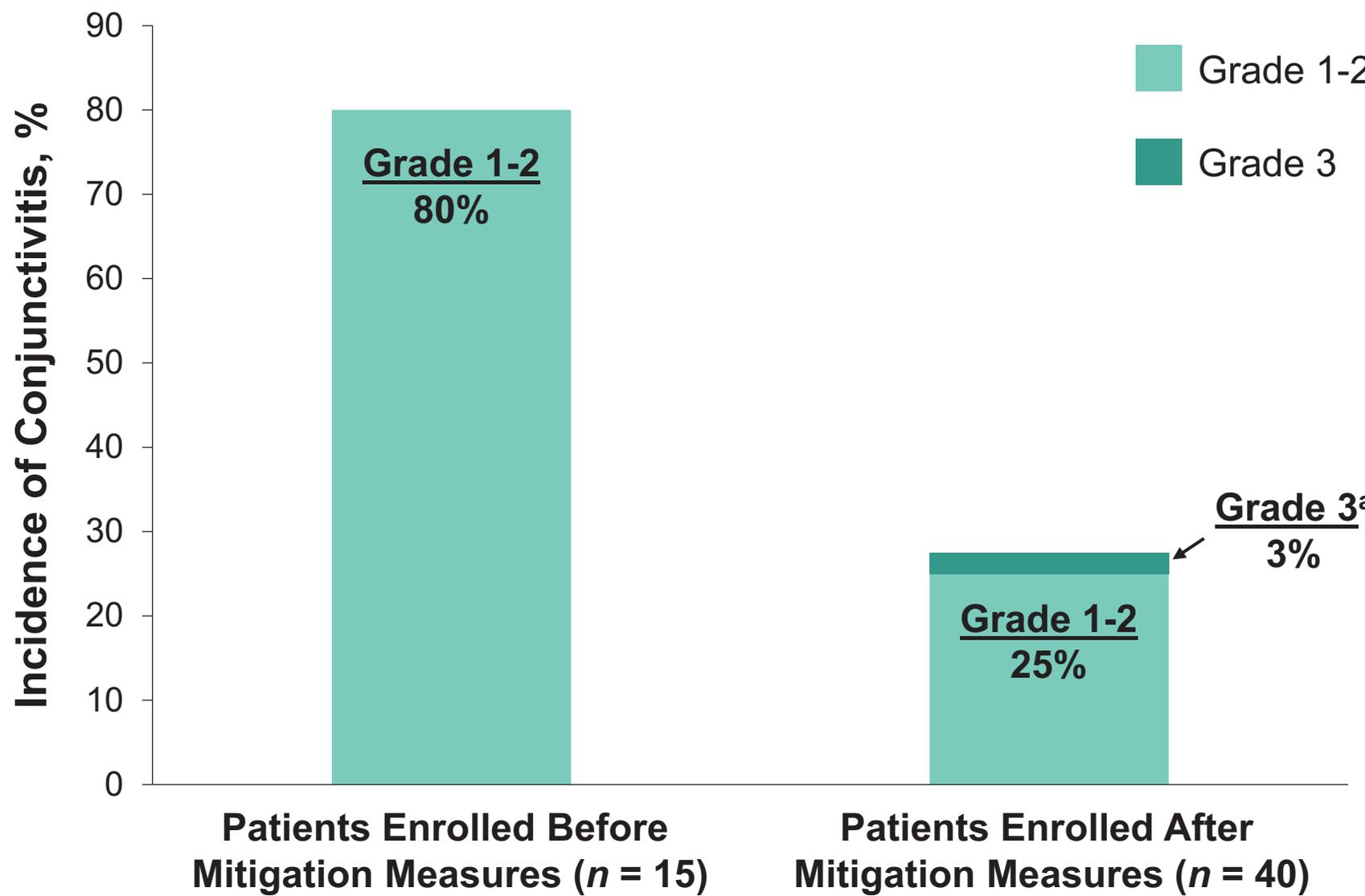
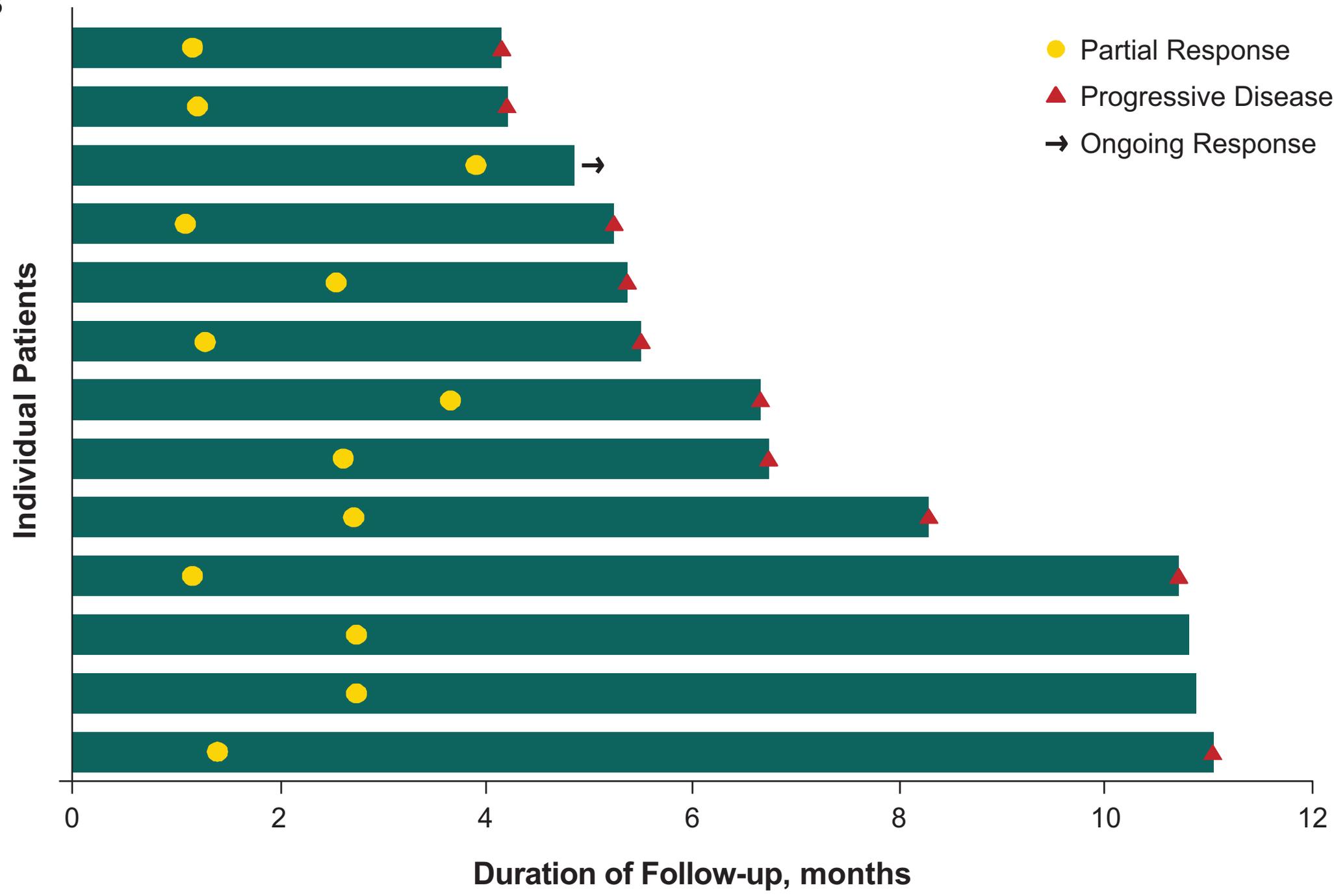






Figure 2B



**Figure 2C**



| Baseline<br>(Week-4) | Follow-up 3<br>(Week 16) | Follow-up 4<br>(Week 23) | Follow-up 8<br>(Week 47) |
|----------------------|--------------------------|--------------------------|--------------------------|
|----------------------|--------------------------|--------------------------|--------------------------|

**Target lesions**

**Muscle-Soft Tissue**

Size



LA: 41.5 mm



LA: 28.7 mm (-14.5%)



LA: 22.0 mm (-23.3%)



LA: 21.9 mm (-2.7%)

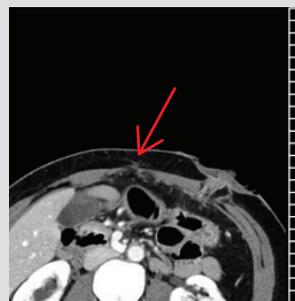
**Non-target lesions**

**Muscle-Soft Tissue  
Multiple Locations**

Size



Present



Disappeared



Disappeared



Disappeared

**Figure 3A**

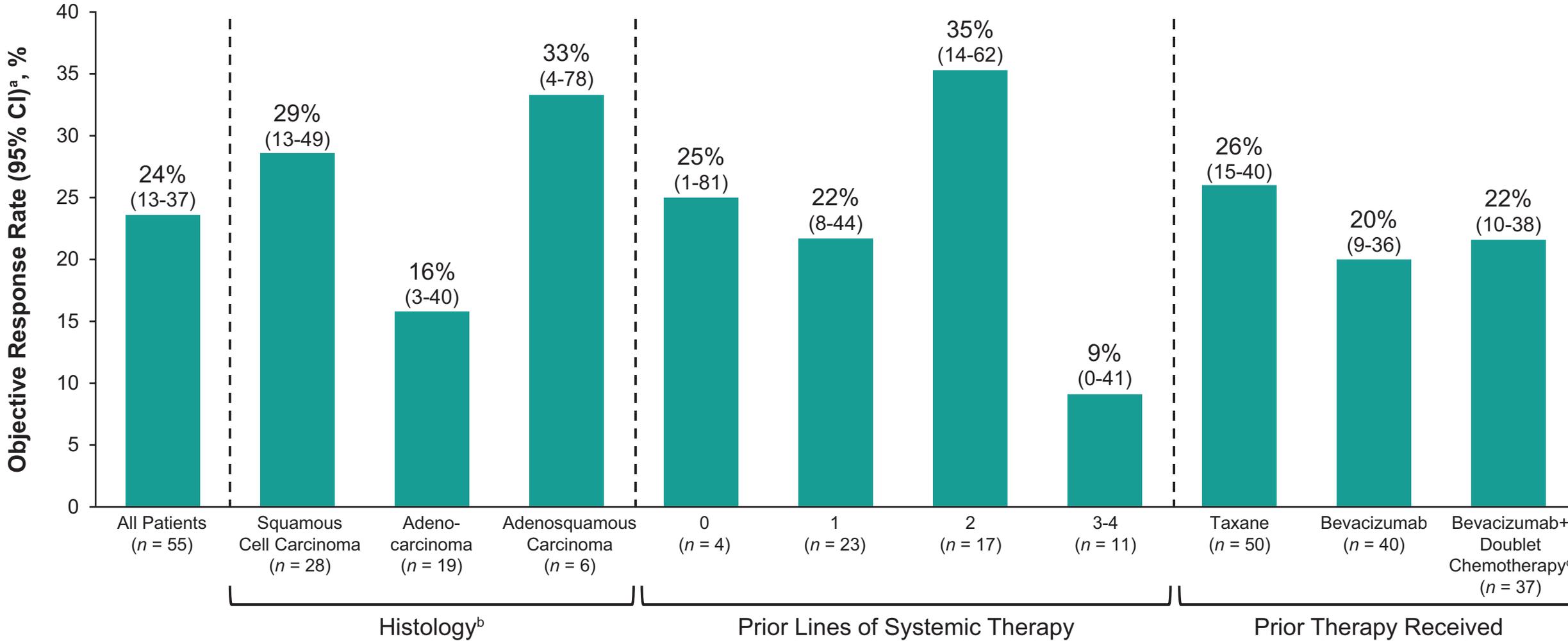


Figure 3B

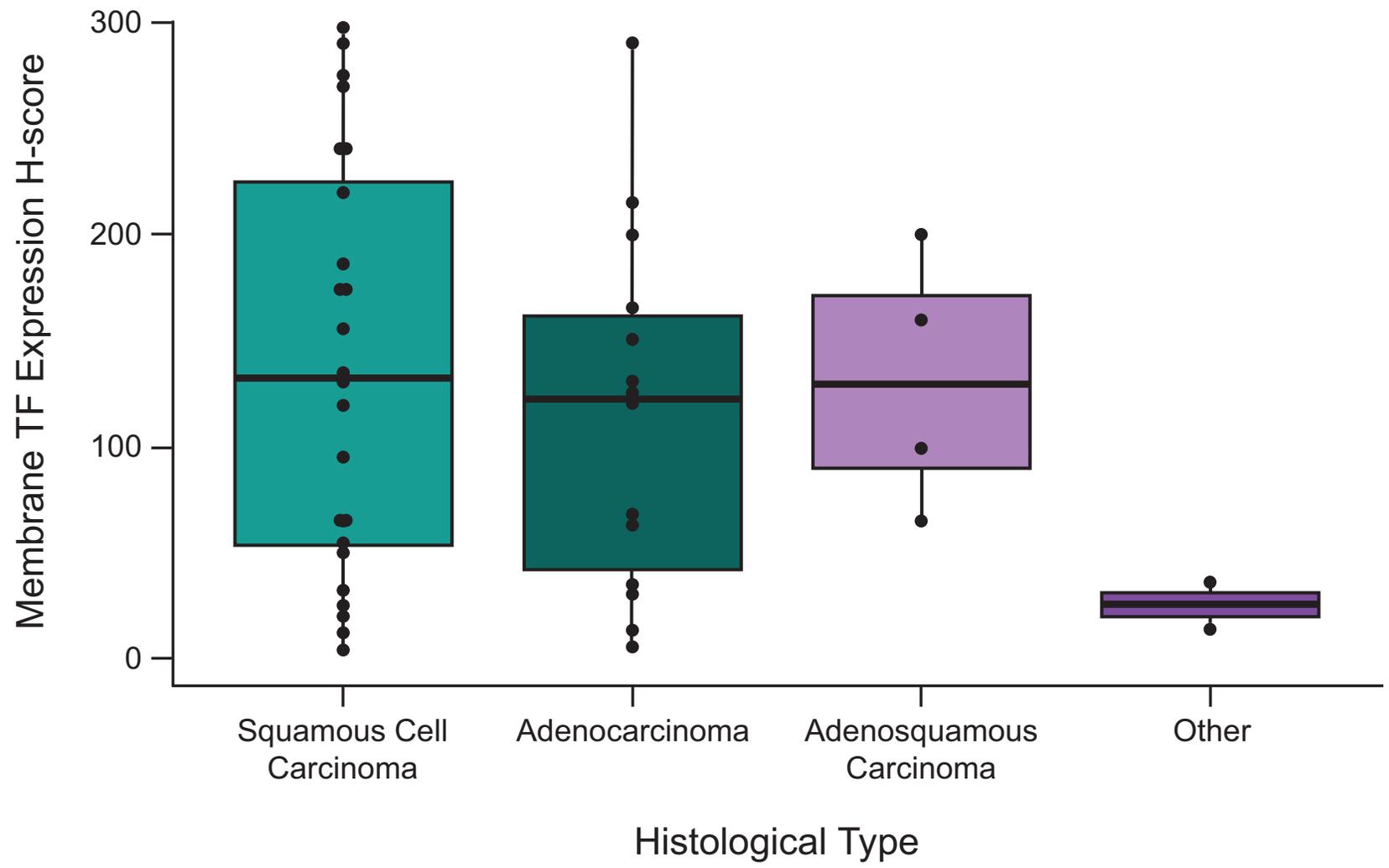


Figure 3C

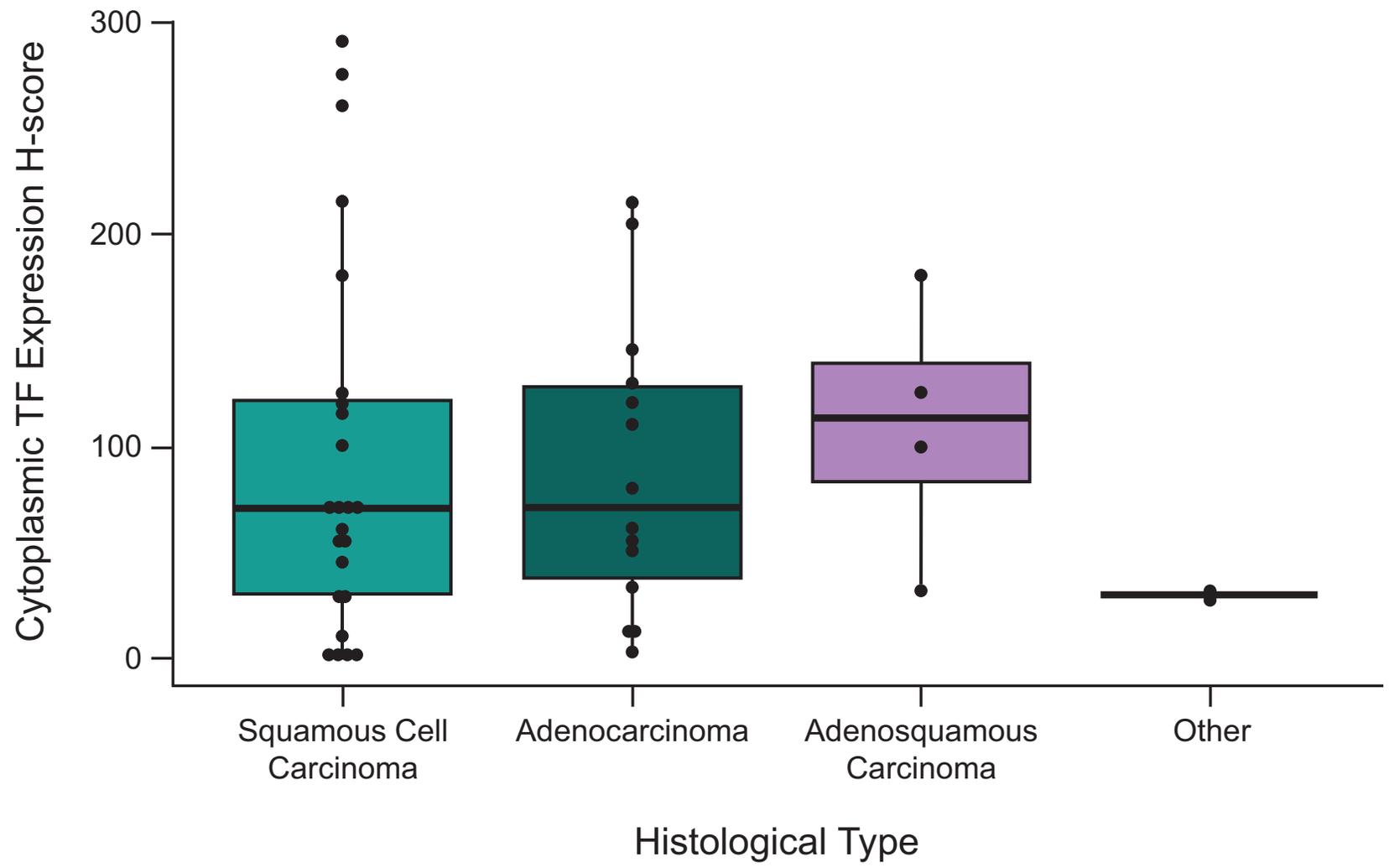


Figure 3D

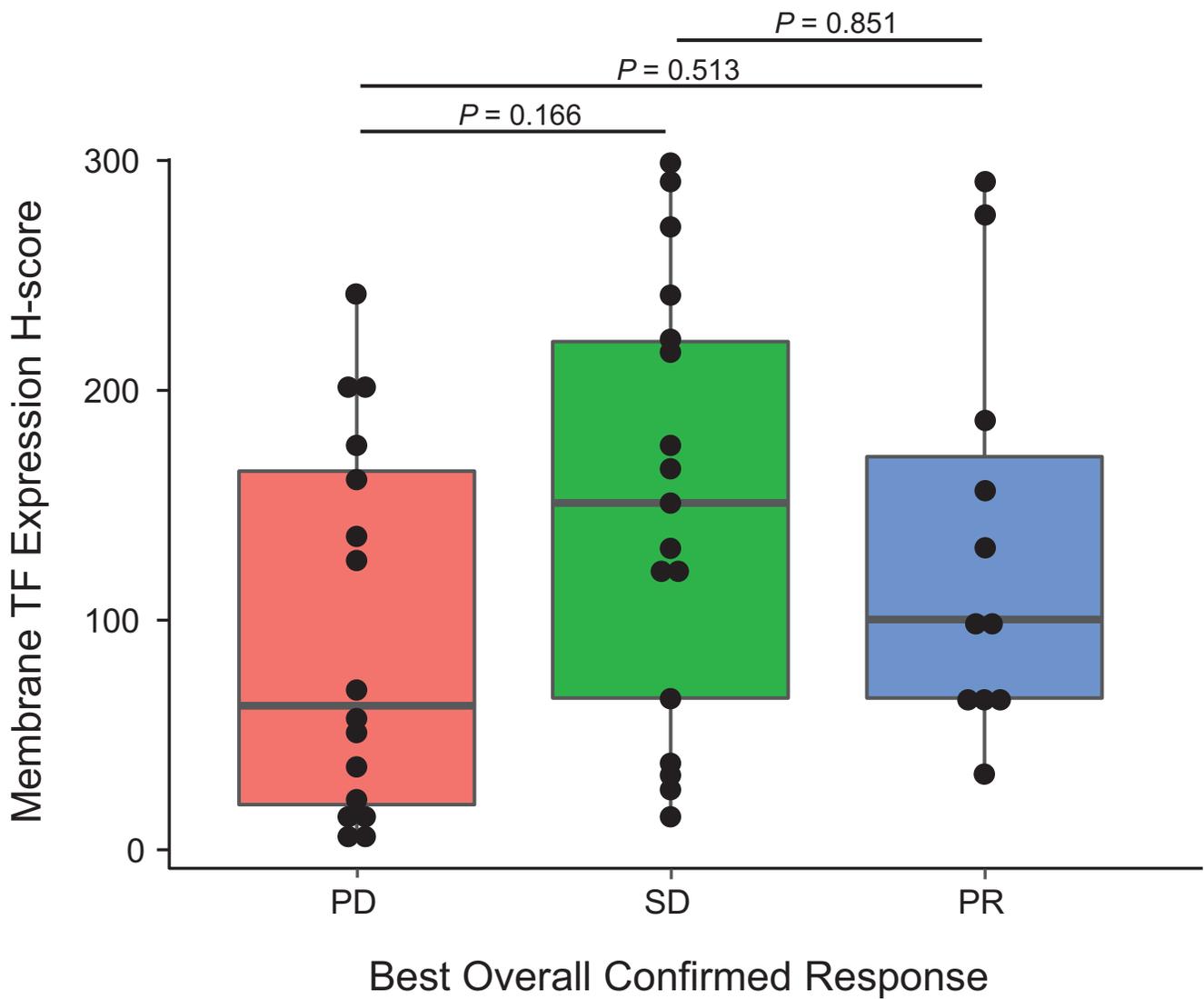


Figure 3E

