Tisotumab Vedotin in Previously Treated Recurrent or Metastatic Cervical Cancer

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Abstract (250/250 words)

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

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

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

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

Translational Relevance (149/150 words)

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

Introduction

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

Available 2L+ therapies for recurrent or metastatic cervical cancer are characterized by low response rates (5,6). Before adoption of bevacizumab plus doublet chemotherapy in 1L, therapies administered in the 2L+ setting reported response rates in the range of 4.5–15%, with median survival <8 months (9-15). Data in the post-bevacizumab plus chemotherapy setting are limited, with a single-institution study showing single-digit response rates (0%–6%) for 2L treatment (7), suggesting prior vascular endothelial growth factor inhibition may negatively impact subsequent treatment response. Data in the third-line setting are further limited, with approximately 60% of patients not receiving third-line treatment and, when treated, response rates of 3% (8). Recently, pembrolizumab (anti–programmed death 1) was granted accelerated approval in the United States for the 2L+ treatment of patients with programmed death-ligand 1 (PD-L1)-positive (combined positive score ≥1%) recurrent or metastatic cervical cancer (16). However, only a fraction of these patients respond (objective response rate [ORR]: 14%) (16). In addition, efficacy in nonsquamous recurrent or metastatic cervical cancer is not yet known as 92% of the patients studied had squamous histology (16). These data underscore the high and immediate need for effective therapies that provide clinical benefit in a broader patient population.

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

Tisotumab vedotin delivers MMAE to TF-expressing cells to induce direct cytotoxicity and bystander killing of neighboring cells (17,18). In vitro studies demonstrated that tisotumab vedotin induces immunogenic cell death and efficiently engages with immune cells to promote tumor cell death through Fcγ receptor–mediated effector functions, such as antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis (18,27). Moreover, tisotumab vedotin was found to inhibit TF-activated factor VII (FVIIa)–dependent intracellular signaling while minimally impacting procoagulant activity (18). To our knowledge, tisotumab vedotin is the first drug to successfully target TF.

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

Methods

Study Oversight

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

Study Design and Patients

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

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

Eligible patients had measurable disease per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients with known coagulation defects, ongoing major bleeding, or Common Toxicity Criteria for Adverse Events (CTCAE) grade ≥2 neuropathy were excluded. A protocol amendment allowed for enrollment of patients on anticoagulants. Patients in the cervical cancer cohort had recurrent/metastatic disease, progressed on a platinum-based regimen, and received ≤4 prior treatments for advanced disease.

Treatment and Assessments

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

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

Protocol amendments implementing additional exclusion criteria and mitigation measures to reduce the risk for ocular events were introduced throughout the study. Patients with active ocular surface disease at baseline or a history of cicatricial conjunctivitis were excluded. Mitigation strategies included the application of preservative-free lubricating eye drops from the start of study treatment until the end of treatment, administration of local ocular vasoconstrictor eye drops immediately prior to the start of infusion, cooling eye pads worn during infusion, and application of steroid eye drops for 3 days beginning on the day of infusion. Furthermore, the use of contact lenses was avoided, and stricter dose modification guidance for ocular events was provided.

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

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

Study Outcomes

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

Statistical Analysis

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

Results

Patients

Between November 2015 and April 2018, 55 patients were enrolled into the cervical cancer expansion cohort of the innovaTV 201 study (**Supplementary Figure S1**). The demographics and baseline disease characteristics are presented in **Table 1**. Most patients had ECOG performance status of 1 (73%). Fifty-one percent of the patients had squamous cell carcinoma and 35% had adenocarcinoma. Fifty-one percent received ≥2 prior lines of treatment. Four patients did not receive 1L standard-of-care therapy because they were refractory to treatment for early stage disease (concurrent chemoradiation or neoadjuvant therapy) and were considered as having zero prior lines of treatment in the recurrent setting. Prior systemic therapies received included taxanes (91%) and bevacizumab plus doublet chemotherapy (67%). TF expression (≥1%) was confirmed in the majority of evaluable patients (membrane expression, 100%; cytoplasmic expression, 95%).

Safety

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

Treatment-emergent AEs regardless of causality and of any grade were reported in all patients, and AEs of grade ≥3 were reported in 31 patients (56%) (**Table 2**). The most common AEs were epistaxis (51%), fatigue (51%), nausea (49%), conjunctivitis (42%), and alopecia (40%) (**Table 2**). Of these, most were grade 1/2. The most common grade ≥3 AEs were anemia (11%), fatigue (9%), and vomiting (7%). Twenty-nine patients (53%) had serious AEs (**Supplementary Table S2**), the most common of which were vomiting (7%) and constipation (5%). Two fatal events occurred while on treatment, both due to disease progression, and were assessed as unrelated to treatment by investigator and study sponsor. No treatment-related deaths were observed.

No grade ≥4 AESIs were observed. Neuropathy AESIs occurred in 30 patients (55%); six of the AESIs (11%) were grade 3, and the most common was peripheral neuropathy (all grades: 36%; grade 3: 4%) (**Table 2**, additional information on neuropathy AESIs is summarized in **Supplementary Table S3**). Seventeen patients (31%) had neuropathy at baseline. Bleeding-related AESIs occurred in 40 patients (73%) and most were grade 1/2, with three patients (5%) experiencing a grade 3 bleeding-related event (two with vaginal hemorrhage and one with hematuria) (**Table 2**, additional information on bleeding-related AESIs is summarized in **Supplementary Table S4**). The most common bleeding-related event was epistaxis (51%); all were grade 1 except for one grade 2. Ocular AESIs of any type occurred in 36 patients (65%), and the most common were conjunctivitis (42%) and dry eye (24%) (**Table 2**, additional information on ocular AESIs is summarized in **Supplementary Table S5**). The incidence of ocular events was reduced from 80% in patients enrolled prior to the implementation of mitigation measures (n = 15) to 60% in patients enrolled after implementation (n = 40). The rates of conjunctivitis were reduced from 80% to 28% (**Figure 1**).

Antitumor Activity

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

4.2 months (range: 1.0^{+}−9.7) (**Table 3**). Four patients experienced a confirmed PR for ≥8 months (**Figure 2B**). The median PFS was 4.2 months (95% CI: 2.1−5.3), and the 6-month PFS rate was 29% (95% CI: 17%−43%) (**Table 3, Supplementary Figure S2**).

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

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

Subgroup and Biomarker Analysis

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

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

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

Discussion

In patients with advanced recurrent or metastatic cervical cancer, tisotumab vedotin, a first-in-class ADC designed to target TF, demonstrated a manageable safety profile and encouraging antitumor activity in a patient population for which no standard-of-care therapy exists. To our knowledge, tisotumab vedotin is the first ADC to successfully demonstrate meaningful clinical activity specifically targeting TF, a novel target overexpressed in many solid tumors associated with poor outcomes.

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

The ORR observed with tisotumab vedotin across histologies, line of therapy, and prior treatments, including bevacizumab plus doublet chemotherapy, is clinically important in a patient population that lacks effective therapies. Tisotumab vedotin demonstrated a notable response rate (24% by investigator assessment) and meaningful 6-month PFS rate in this previously treated patient population with advanced cervical cancer, including in patients with adenocarcinoma histology. In contrast, an ORR of 14% was observed in patients with PD-L1−positive cervical cancer treated with pembrolizumab (16). The efficacy of pembrolizumab in patients with nonsquamous histology has not been well established as the majority of patients (92%) enrolled in the clinical trial of pembrolizumab had squamous cell carcinoma (16), and although the median DOR was not reached, meaningful PFS benefit was not observed (34).

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

The majority of cervical cancer patient biopsies had detectable TF expression. Both membrane and cytoplasmic levels of TF expression were comparable across various cervical cancer histological types. Although median membrane and cytoplasmic TF H-score was higher in patients who achieved PR and stable disease compared to those with progressive disease, there was no statistically significant association with best confirmed response. That said, the majority of samples were from archival tissue, and the effect of previous lines of therapy on TF expression has yet to be explored. Further studies evaluating TF expression and other potential predictive biomarkers that associate with antitumor activity will be explored to determine whether certain patient populations may benefit more from tisotumab vedotin.

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

Recurrent or metastatic cervical cancer is a serious, life-threatening disease. The lack of effective treatments, high relapse risk, and low survival after 1L treatment demonstrate the need for novel, safe, and effective therapies that improve clinical benefit. The results of this study cohort have demonstrated the manageable safety profile and encouraging antitumor activity of tisotumab vedotin, supporting the further clinical development of this first-in-class ADC targeting the novel therapeutic target, TF, in patients with previously treated recurrent or metastatic cervical cancer.

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TABLES

Table 1. Baseline demographics and disease characteristics

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

3	6 (11)
4	5 (9)
Prior systemic therapies received, *n* (%)	
Taxane	50 (91)
Bevacizumab	40 (73)
Bevacizumab plus doublet chemotherapy[d]	37 (67)
TF expression positive, *n* (%)[e]	
Membrane	44 (100)
Cytoplasm	42 (95)

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

[a]Two patients were missing race information; percentage prevalence was calculated out of *n* = 53 for race.

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

[c]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).

[d]Doublet chemotherapy defined as paclitaxel plus cisplatin or paclitaxel plus topotecan.

[e]Positive TF expression was defined as ≥1%; percentage prevalence was calculated out of TF expression evaluable population (*n* = 44).

Table 2. Treatment-emergent adverse events

Incidence, *n* (%)	Cervical Cancer Cohort *N* = 55	
	All-grade	**Grade ≥3**
Patients with ≥1 AE	55 (100)	31 (56)
AEs With ≥20% Incidence	**All-grade**	**Grade ≥3**
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)
AESIs With ≥5% Incidence	**All-grade**	**Grade 3**

Neuropathy AESIs[a]	30 (55)	6 (11)
Peripheral neuropathy	20 (36)	2 (4)
Muscular weakness	4 (7)	0
Peripheral sensory neuropathy	4 (7)	0
Bleeding-related AESIs[b]	40 (73)	3 (5)
Epistaxis	28 (51)	0
Vaginal hemorrhage	7 (13)	2 (4)
Hematuria	5 (9)	1 (2)
Contusion	3 (5)	0
Ocular AESIs[c]	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.

[a]Defined as peripheral neuropathy SMQ.

[b]Defined as hemorrhage SMQ.

[c]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.

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

	Cervical Cancer Cohort *N* = 55	
Antitumor Activity	**Investigator-assessed**	**IRC-assessed**
ORR (95% CI), %[a]	24 (13–37)	22 (12–35)
CR, *n* (%)	0	1 (2)
PR, *n* (%)	13 (24)	11 (20)
SD, *n* (%)	21 (38)	19 (35)
Non-CR/Non-PD, *n* (%)	0	2 (4)
PD, *n* (%)	17 (31)	17 (31)
Not evaluable, *n* (%)	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[+]–9.7)	6.0 (1.0[+]–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.

[+]Indicates censored value due to ongoing response.

[a]Confirmed ORR by Response Evaluation Criteria In Solid Tumors v1.1 criteria.

FIGURE LEGENDS

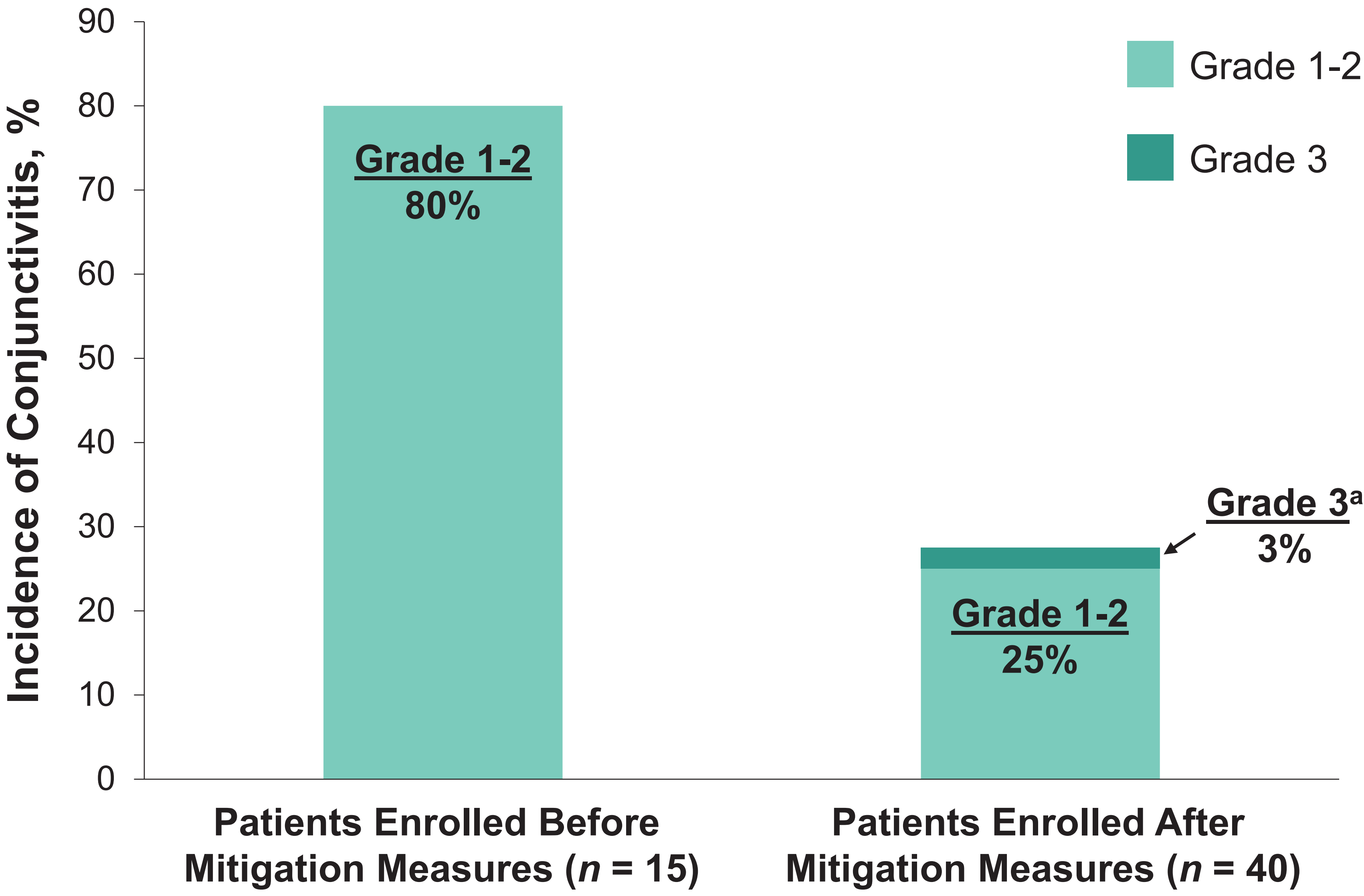
Figure 1. Conjunctivitis before and after mitigation measures. The percentage incidence of conjunctivitis by grade occurring in patients enrolled before and after the implementation of mitigation measures are shown. [a]One patient with grade 3 conjunctivitis after mitigation measures were implemented. No grade 3 events were observed before mitigation measures were implemented.

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

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

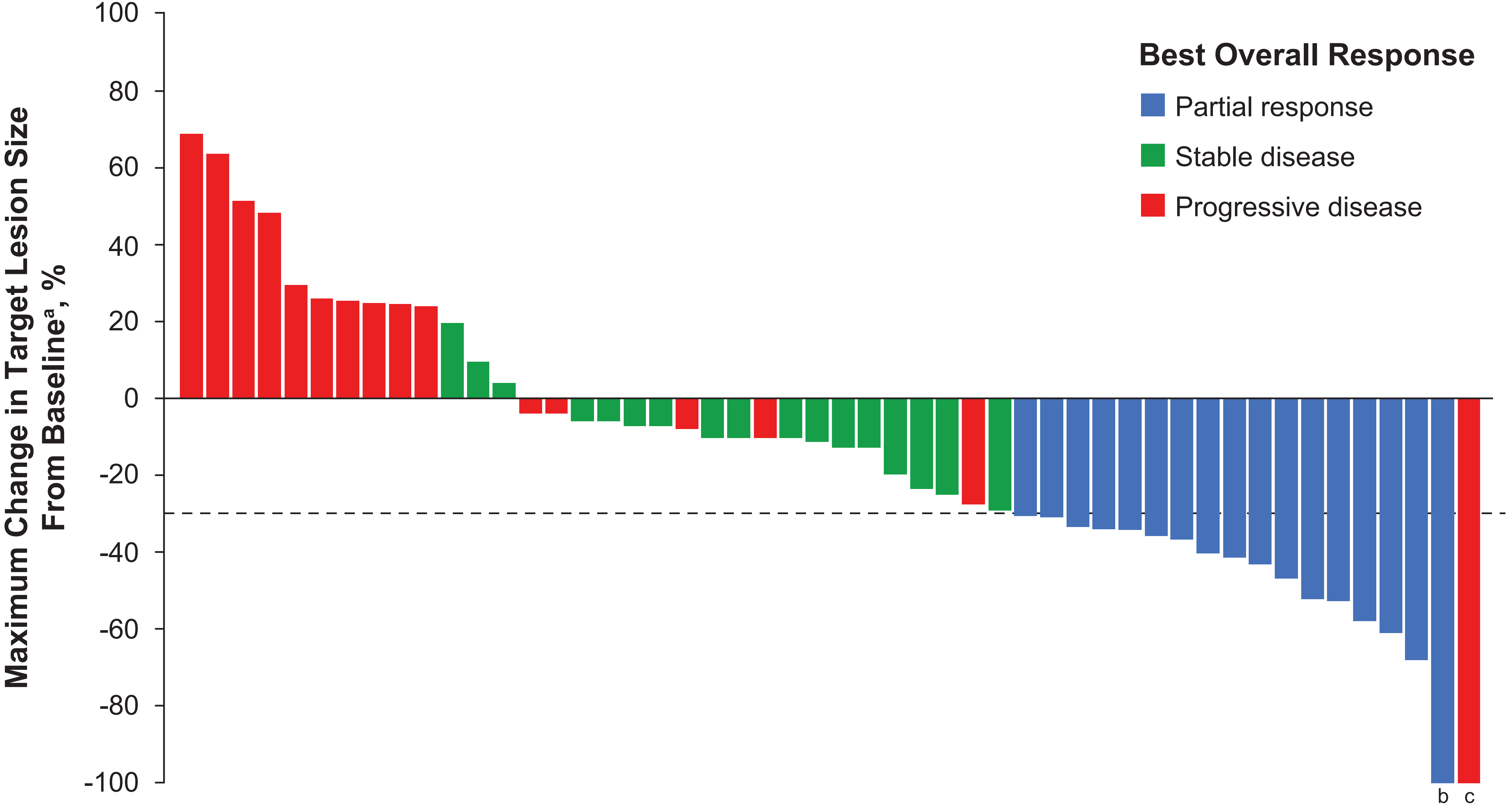
Figure 3. Response across baseline disease characteristic subgroups and by tissue factor expression. (**A**) The investigator-assessed confirmed ORR (95% CI) in patients with squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma; in patients who received 1, 2, or 3-4 prior lines of systemic treatment; and in patients who received prior taxanes, bevacizumab, or bevacizumab plus doublet chemotherapy. [a]Investigator-assessed confirmed response by RECIST v1.1. [b]Patients with other histology (n = 2) did not have confirmed response. [c]Doublet chemotherapy defined as paclitaxel plus cisplatin or paclitaxel plus topotecan. Membrane (**B**) and cytoplasmic (**C**) TF expression intensity as measured by H-score, in patients with adenocarcinoma, adenosquamous carcinoma, squamous carcinoma, or other histology. Membrane (**D**) and cytoplasmic (**E**) TF expression intensity as measured by H-score in patients who had investigator-assessed best confirmed PR, SD, or PD. P values are for descriptive purposes only. CI, confidence interval; H, histology; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria In Solid Tumors v1.1; SD, stable disease; TF, tissue factor.

Figure 1



Incidence of Conjunctivitis, %
90
80
70
60
50
40
30
20
10
0
Grade 1-2
Grade 3
Grade 1-2
80%
Grade 3[a]
3%
Grade 1-2
25%
Patients Enrolled Before Mitigation Measures (n = 15)
Patients Enrolled After Mitigation Measures (n = 40)

Figure 2A



Best Overall Response
Partial response
Stable disease
Progressive disease
Maximum Change in Target Lesion Size From Baseline[a], %
100
80
60
40
20
0
-20
-40
-60
-80
-100
b
c

Figure 2B

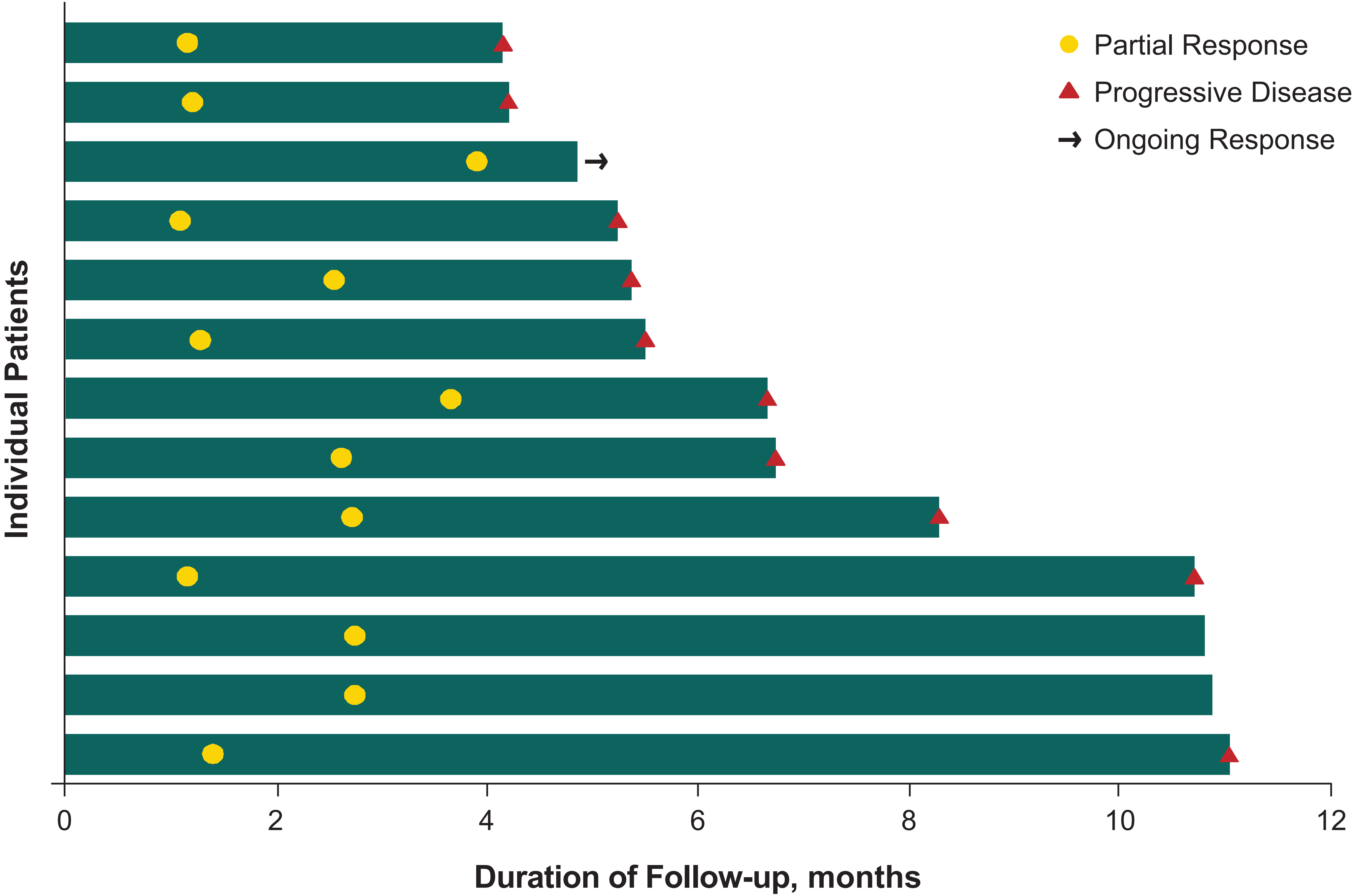
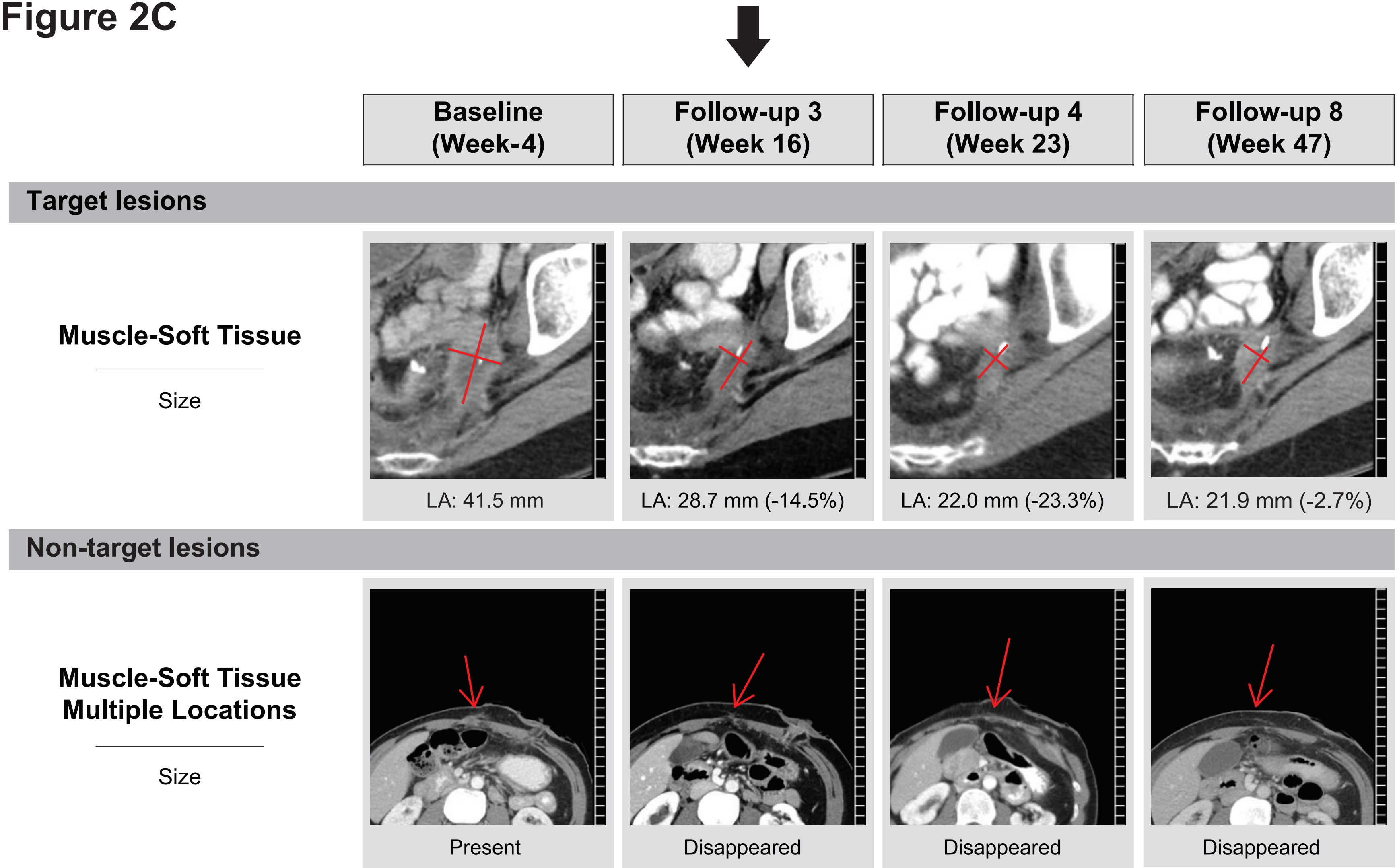
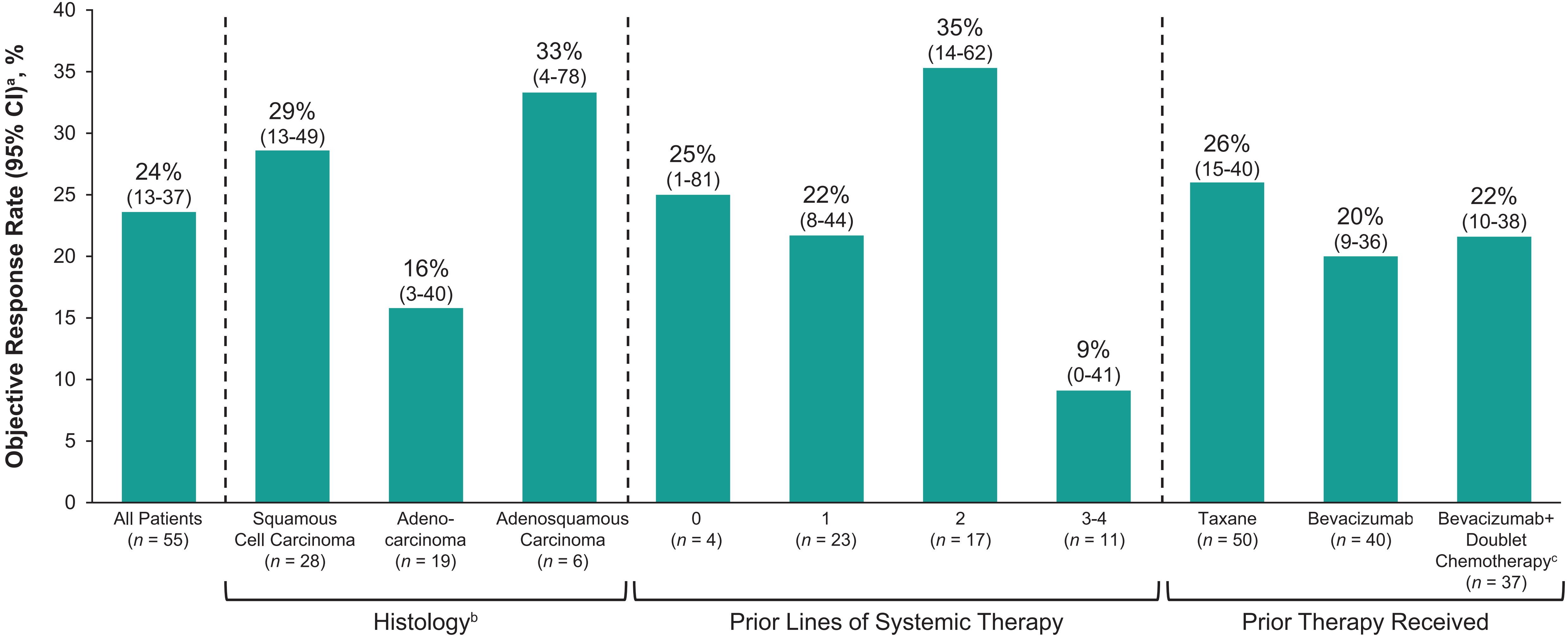

Partial Response
Progressive Disease
Ongoing Response
Individual Patients
0
2
4
6
8
10
12
Duration of Follow-up, months

Figure 2C



Baseline (Week-4)
Follow-up 3 (Week 16)
Follow-up 4 (Week 23)
Follow-up 8 (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



Objective Response Rate (95% CI)[a], %
40
35
30
25
20
15
10
5
0
24%
(13-37)
29%
(13-49)
16%
(3-40)
33%
(4-78)
25%
(1-81)
22%
(8-44)
35%
(14-62)
9%
(0-41)
26%
(15-40)
20%
(9-36)
22%
(10-38)
All Patients (n = 55)
Squamous Cell Carcinoma (n = 28)
Adeno-carcinoma (n = 19)
Adenosquamous Carcinoma (n = 6)
0 (n = 4)
1 (n = 23)
2 (n = 17)
3-4 (n = 11)
Taxane (n = 50)
Bevacizumab (n = 40)
Bevacizumab+ Doublet Chemotherapy[c] (n = 37)
Histology[b]
Prior Lines of Systemic Therapy
Prior Therapy Received

Figure 3B

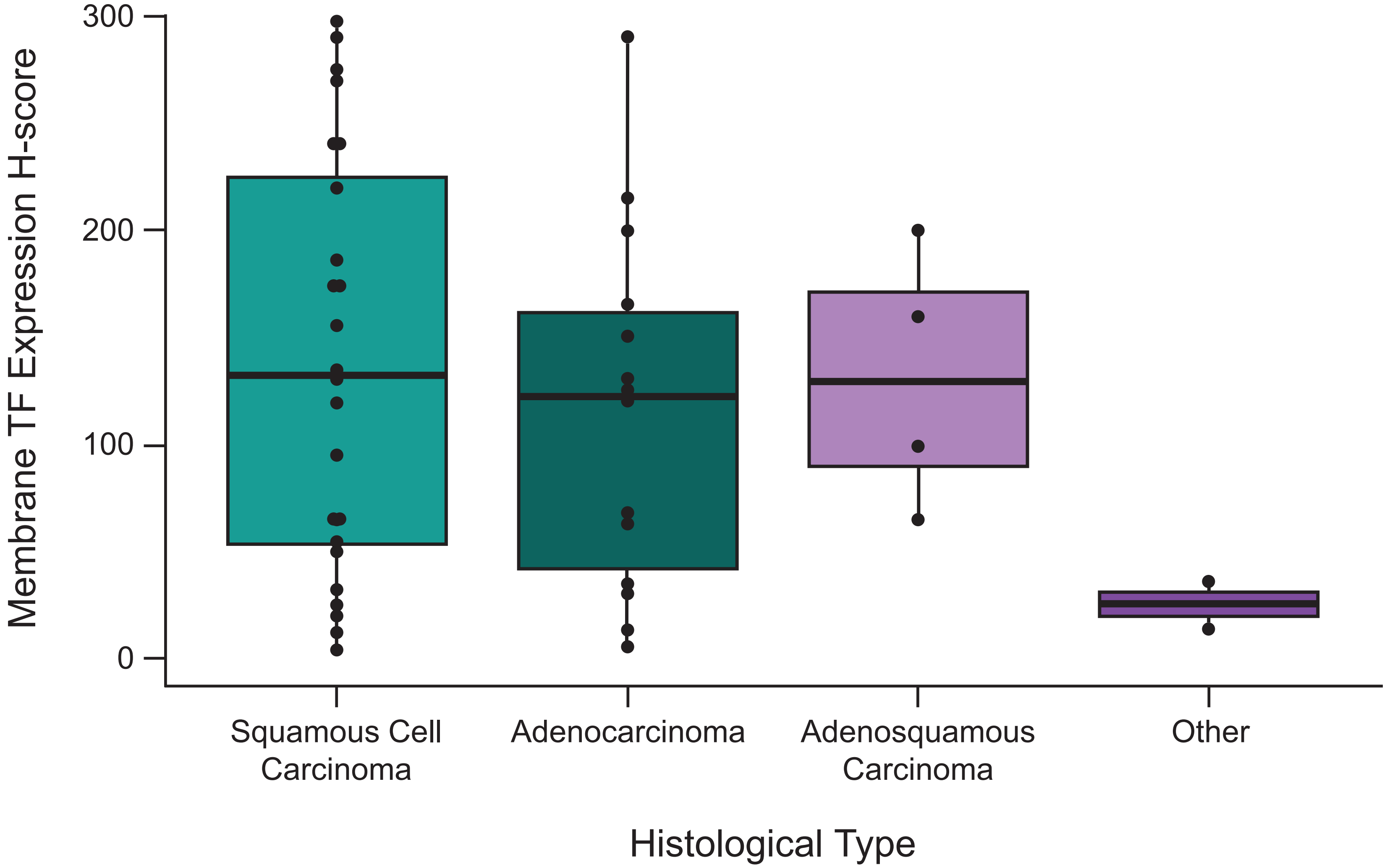
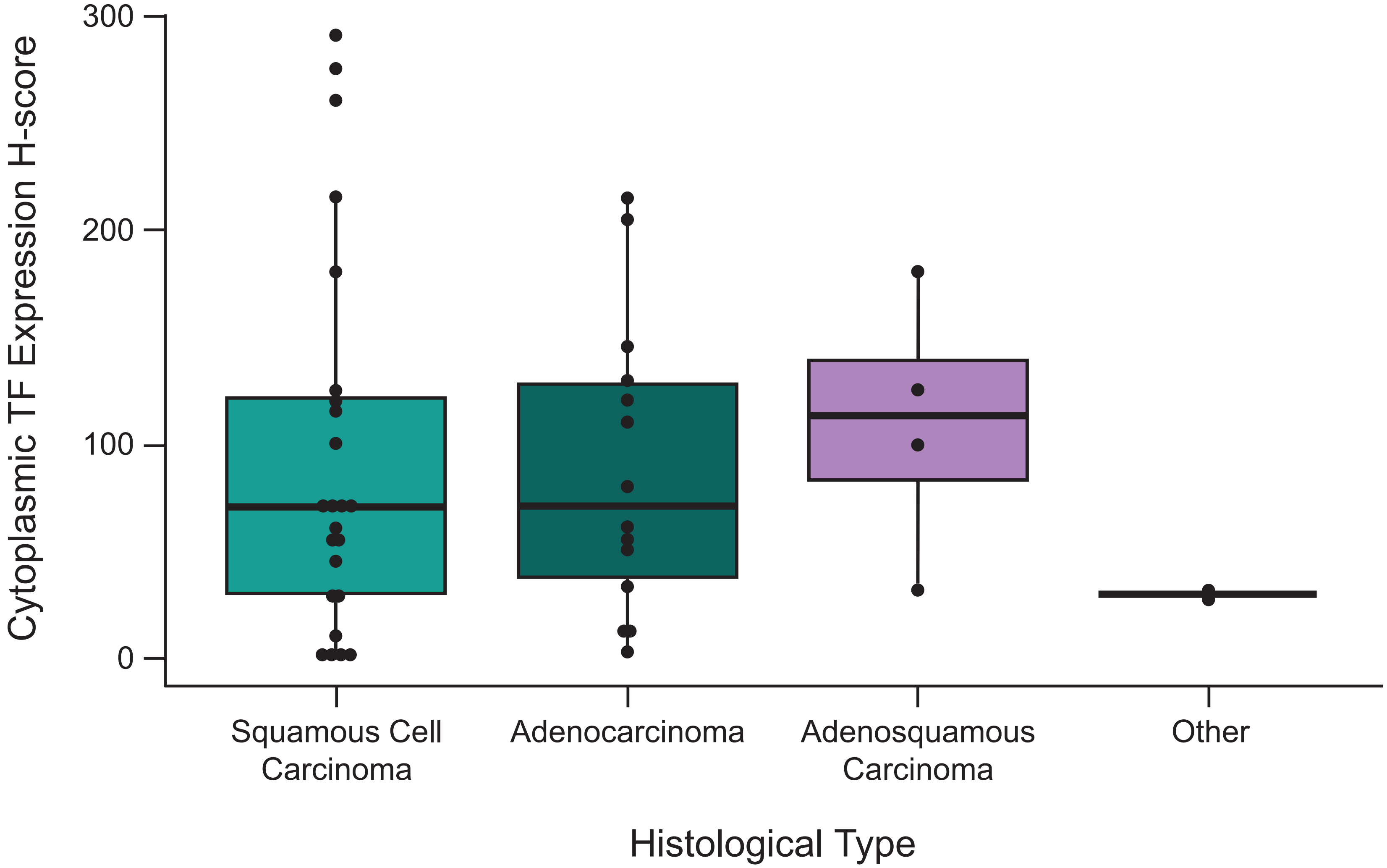
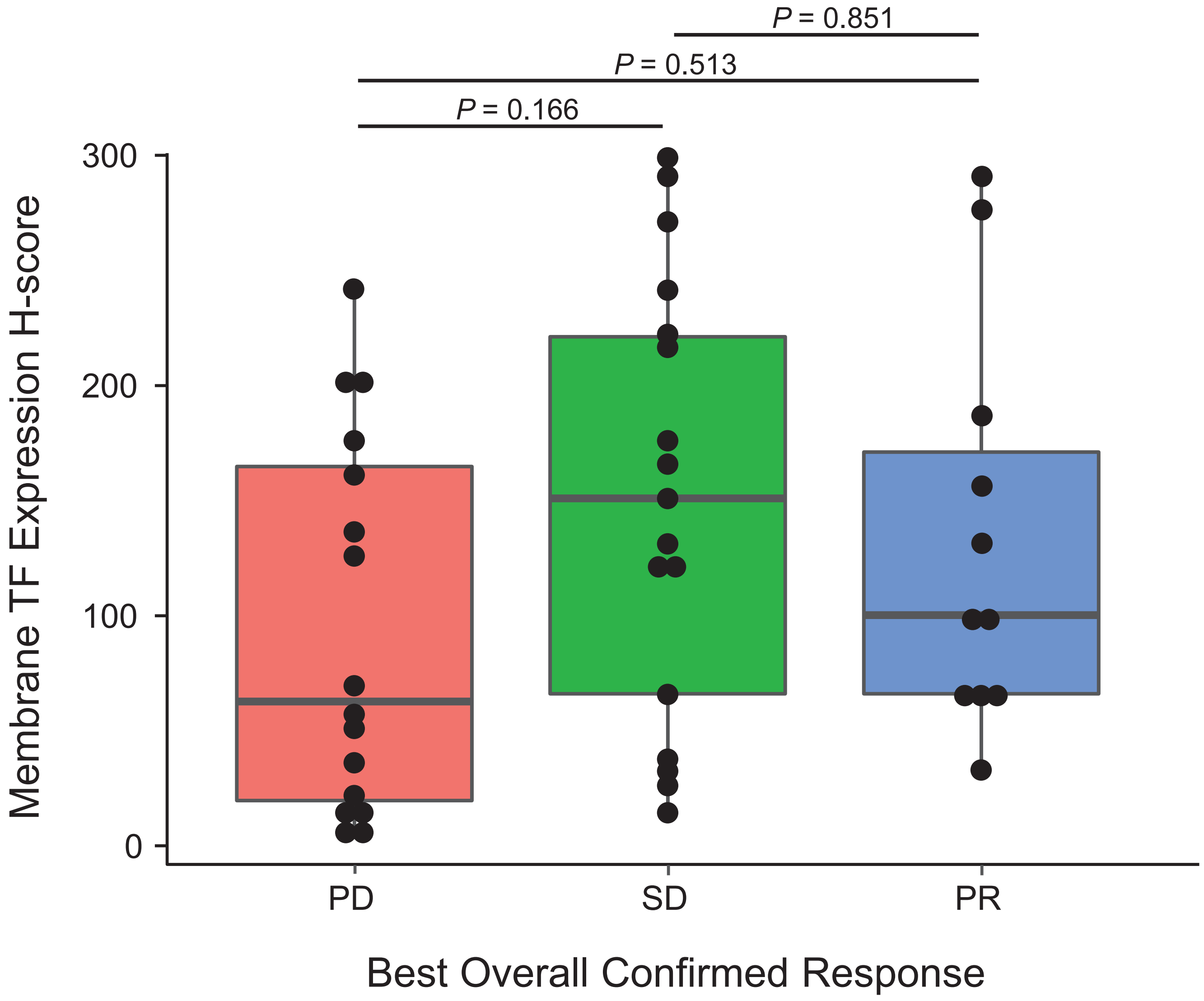

Membrane TF Expression H-score
300
200
100
0
Squamous Cell Carcinoma
Adenocarcinoma
Adenosquamous Carcinoma
Other
Histological Type

Figure 3C



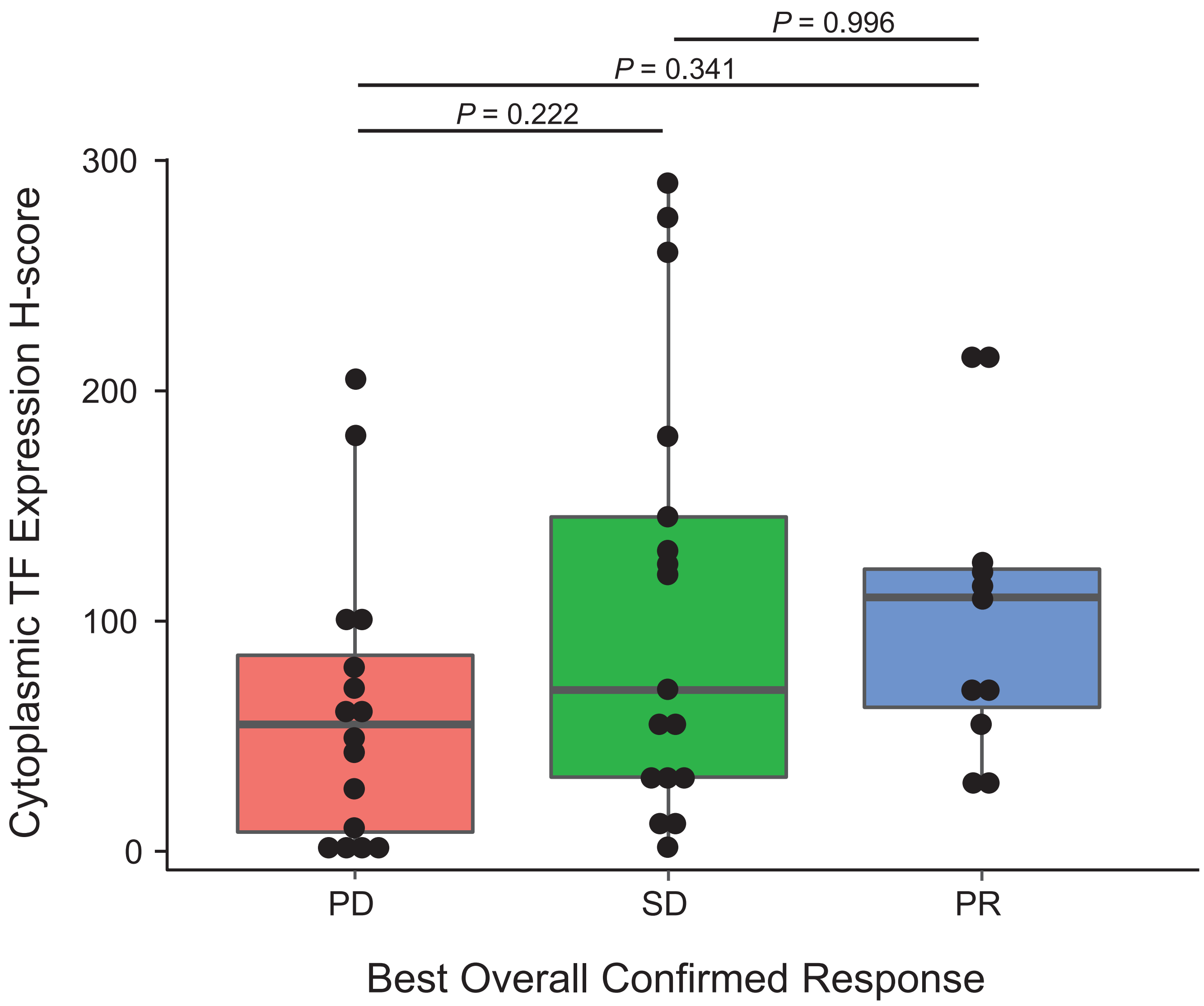
Cytoplasmic TF Expression H-score
300
200
100
0
Squamous Cell
Carcinoma
Adenocarcinoma
Adenosquamous
Carcinoma
Other
Histological Type

Figure 3D



P = 0.851
P = 0.513
P = 0.166
300
200
100
0
Membrane TF Expression H-score
PD
SD
PR
Best Overall Confirmed Response

Figure 3E



P = 0.996
P = 0.341
P = 0.222
300
200
100
0
Cytoplasmic TF Expression H-score
PD
SD
PR
Best Overall Confirmed Response