International Journal of Cancer Medicine

Clinical Research | Vol 6 Issue 3

Nivolumab Hepatocellular Carcinoma

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Received: May 22, 2023; Accepted: June 12, 2023; Published: June 19, 2023

ABSTRACT

INTRODUCTION

Current hepatocellular carcinoma (HCC) systemic treatment includes atezolizumab plus bevacizumab (A+B) or tremelimumab plus durvalumab as preferred first line therapy. Nivolumab is an option for patients with Child Pugh (CP) class B though there is limited data in real world cohorts in the first line setting.

METHODS

This retrospective study evaluated patients with HCC who were deemed not eligible for antiangiogenic therapy in the first line setting from 2017 to 2021. A second arm of patients treated with A+B who were initiated on atezolizumab monotherapy with a minimum of the first dose of bevacizumab held prior to getting an evaluation of esophageal varices were also included to evaluate this practice.

RESULTS

The median overall survival (OS) in the Nivolumab arm (n = 26) was 4.07 months (95% CI, 2.27-6.83). CP class was significantly associated with OS (p = 0.001) with a median OS of 8.9 months with a CP A, 3.7 months with a CP B, and 0.8 months with a CP C. In the A+B group 58.3% of patients (n = 12) never received bevacizumab.

CONCLUSION

Patients deemed not eligible for first line; antiangiogenic therapy derive minimal benefit from nivolumab. The practice of starting atezolizumab monotherapy led to many patients never starting bevacizumab.

KEYWORDS

Hepatocellular carcinoma; Hepatitis B; Atezolizumab monotherapy; Antiangiogenic therapies

INTRODUCTION

Hepatocellular carcinoma (HCC) deaths have continued to increase in multiple countries throughout the world even as new systemic therapies, and therapies that control major risk factors of HCC such as hepatitis B and C, have

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improved. Deaths in the United States increased by 34% from 2002 to 2012 [1]. In early-stage disease, curative tactics such as ablation, transplantation, and resection can be implemented, but in later stages, which are not amendable to locoregional therapy, palliative systemic therapy is often the best option [2]. Baseline liver dysfunction combined with the chemoresistance seen in HCC makes finding effective, tolerable regimens a challenge [3,4]. Since 2007, the antiangiogenic tyrosine kinase inhibitor sorafenib has been the standard of care first line option [5]. First line therapy for HCC has rapidly changed with the recent publications of data for atezolizumab plus bevacizumab (A+B) and tremelimumab plus durvalumab (T+D) [6,7]. A+B was compared to sorafenib which found that the combination of A+B had a significantly longer overall survival (OS). Due to the risk of gastrointestinal bleeding associated with bevacizumab in the setting of cirrhosis the trial required esophageal variceal evaluation within 6 months of initiation of therapy which may delay treatment initiation of bevacizumab [6]. Atezolizumab monotherapy was studied originally in a Phase Ib trial though the strategy of initiating patients on atezolizumab monotherapy prior to adding bevacizumab after esophageal evaluation has not been reported in the literature [8]. T+D was also compared to sorafenib and T+D was found to significantly improve OS [7]. Within this trial, OS between the durvalumab monotherapy arm and sorafenib was found to be non-inferior [7]. Lenvatinib has also been compared to sorafenib and shown non-inferiority [9]. Pembrolizumab has phase II data in the first line setting also making it a first line options though due to lower quality data it would not be a preferred option [10]. The tolerability of all the antiangiogenic regimens and T+D appears poor with grade 3 or 4 adverse event occurring in over half of the patients [6,7,9]. The first line options of A+B, T+D, durvalumab, sorafenib, and lenvatinib were all studied with strict inclusion and exclusion criteria including Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 1 and a Child Pugh (CP) class of A, and treatment or evaluation of varices prior to therapy among numerous other criteria [6,7,9].

In patients who are ineligible for first line antiangiogenic therapies due to adverse effect risk, CP class, or other criteria, monotherapy immunotherapy with durvalumab, pembrolizumab, or nivolumab may be an option [2]. Due to exclusion criteria of patients with a CP class of B or C among other criteria within the clinical trials for all three monotherapy immunotherapy options there is limited data on safety and efficacy with these options in real-world cohorts. Nivolumab was originally studied in the CheckMate 040 and CheckMate 459 trials [11,12]. In CheckMate 459 nivolumab failed to improve overall survival when compared to sorafenib though nivolumab performed numerically better [12]. Tolerability of nivolumab appeared significantly better than sorafenib which makes it a viable option in patients who are not candidates for first line antiangiogenic therapy [12]. While nivolumab appeared to be well tolerated based on the CheckMate 459 trial, the safety and efficacy in patients who were ineligible for clinical trials, and are not candidates for first line antiangiogenic therapy, is unclear [11,12]. A small retrospective cohort reviewed 14 patient outcomes who were started on monotherapy nivolumab as first line treatment. The median OS of the cohort was 8 months, and the tolerability was poor with 3 patient deaths due to immunotherapy-induced hepatitis [13]. Two other retrospective studies found numerically better outcomes, though low enrollment and heterogeneity of patients based online of therapy and CP class limits the utility of trials [14,15]. Similarly, the nivolumab dose expansion trial, CheckMate 040, only had a small subset of patients who were treated in the first line setting and 4 total patients with a CP class B [12].

This single center, retrospective study was devised to evaluate the safety and efficacy of first line nivolumab for HCC in patients who were deemed unfit for other standards of care, first line therapy. Secondary objectives were to evaluate prognostic baseline characteristics within the nivolumab cohort and to evaluate the practice at The Ohio State University of holding the first dose of bevacizumab and initiating atezolizumab monotherapy until esophageal variceal evaluation can be completed.

METHODS

The study was a single center, retrospective cohort performed among patients initiated on treatment at The James Cancer Hospital and Solove Research Institute and Martha Morehouse Outpatient Care at The Ohio State University (OSU). The study was approved by the institutional review board at The Ohio State University. Patients were included if they were a minimum of 18 years of age with confirmed HCC and no prior systemic lines of therapy. Patients were required to receive at least one dose of nivolumab monotherapy (cohort 1) or one dose of atezolizumab with a minimum of the first dose of bevacizumab held (cohort 2). Due to the restriction of esophageal variceal evaluation within 6 months of therapy initiation, physicians at The Ohio State University occasionally start monotherapy atezolizumab to initiate therapy earlier with the intention of adding bevacizumab on cycle 2 once an esophagogastroduodenoscopy has been performed and any varices banded. Currently no evidence supports this practice and thus this approach requires further evaluation.

The primary objective was to evaluate the safety and efficacy of nivolumab monotherapy in patients treated at OSU. These patients were deemed not to be candidates for standard of care, first-line, systemic therapy and thus required a less intensive regimen. The primary outcome was median overall survival (OS), defined as the date of first infusion to the date of death. Secondary endpoints included 12-months OS rate, median progression-free survival (PFS) (date of first infusion to confirmed radiographic progression or death), and median time-to-treatment failure (TTF) (date of first infusion to date of discontinuation of therapy, progression, or death). Patients who had not experienced a survival or progression event were censored at the date of last follow up. Efficacy endpoints were compared among key subgroups based on CP class, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and alphafetoprotein (AFP). An exploratory secondary endpoint compared the OS and PFS between cohort 1 and cohort 2. Safety outcomes included any grade immune-related adverse event (irAE), grade 3+ irAE, held therapy due to irAE, discontinuation of therapy due to irAE, and death correlated to an irAE. All adverse events were graded utilizing the common terminology criteria for adverse events (CTCAE) version 5 grading system.

All baseline characteristics were reported with descriptive statistics. OS and PFS curves were assessed by Kaplan Meier methods with between group differences determined through the log rank test. Safety endpoints were reported using descriptive statistics.

RESULTS

Between January 2017 and July 2021, a total of 26 patients met criteria for cohort 1 and 12 patients met criteria for cohort 2. Baseline characteristics are shown in Table 1. At data collection cut off a total of 22 patients (84.6%) in the nivolumab group had died. Median OS in cohort 1 was 4.07 months (95% confidence interval [CI], 2.27 to 6.83). The survival rate at 12 months was 12.4% (95% CI, 3.2 to 28.4). A total of 23 patients met the requirements for PFS at data cutoff with a median PFS of 3.33 months (95% CI, 1.43 to 4.7), and 24 patients met the requirement for TTF with a median TTF of 1.87 months (95% CI, 0.47 to 2.8) (Table 2).

Variable	Nivolumab	Atezolizumab + Bevacizumab (n = 12)
	(n = 26)	
Age, Median (IQR)	67.5 (62-72.75)	64 (61-71)
Ethnicity, n (%)		
Hispanic/Latino	0 (0)	1 (8.3)
African American	6 (23.1)	2 (16.7)
White	18 (69.2)	9 (75.0)
Asian	2 (7.7)	0 (0)
Gender, n (%)		
Male	20 (76.9)	9 (75.0)
Female	6 (23.1)	3 (25.0)
Child-Pugh Class, n (%)		
A (5-6)	11 (42.3)	6 (50.0)
B (7-9)	10 (38.5)	4 (33.3)
C (10-15)	5 (19.2)	2 (16.7)
Liver Disease Etiologies, n (%)		
Hepatitis B	1 (3.9)	3 (25.0)
Hepatitis C	12 (46.2)	6 (50.0)
Alcohol	10 (38.5)	5 (41.7)
Other	3 (11.5)	1 (8.3)
Unknown	5 (19.2)	1 (8.3)
ECOG Performance Status, n (%)		
0	2 (7.7)	2 (16.7)
1	10 (38.5)	6 (50.0)
2	12 (46.2)	4 (33.3)
3	1 (3.9)	0 (0)
Unknown	1 (3.9)	0 (0)
Prior Non-Pharm Treatments, n (%)		
Surgery	0 (0)	0 (0)
TA Chemoembolization	9 (34.9)	3 (25.0)
Y90 Radioembolization	6 (23.1)	4 (33.3)
EBRT	4 (15.4)	1 (8.3)
None	12 (46.2)	7 (58.3)
PD-L1 Expression, n/N (%)	1/26 (3.8)	1/12 (8.3)
Alpha-Fetoprotein, Median [IQR]	176.5 [5.9-2467.0]	156.5 [7.1-3825]

Table 1: Patient demographics compared by treatment type.**Note:** The PD-L1 expression of the nivolumab and atezolizumab plus bevacizumab patients were 0% and 1% respectively.

Outcome	Nivolumab	Atezolizumab + Bevacizumab (n = 12)	P Value
	(n = 26)		
Primary Outcome: Median OS			
Death, n (%)	22 (84.6)	6 (50.0)	
Median OS, months (95% CI)	4.07 (2.27-6.83)	7.13 (0.7-NR)	P = 0.17
1-year OS (95% CI)	12.4% (3.2-28.4)	46.3% (17.2-71.4)	
Secondary Outcome: Median PFS			
Progression or Death, n (%)	23 (88.5)	7 (58.3)	
Median PFS, Months (95% CI)	3.33 (1.43-4.7)	2.7 (1.7-NR)	P = 0.57
1-year PFS (95% CI)	9.6% (1.5-23.7)	23.8% (3.7-53.5)	
Secondary Outcome: Median TTF			
Treatment Failure, n (%)	24 (92.3)	11 (91.7)	
Median TTF, Months (95% CI)	1.87 (0.47-2.8)	1.47 (0-6.77)	
Secondary Outcome: Median OS by CP Class in the Nivolumab Cohort*			
CP Class A, Months (95% CI)	8.93 (2.27-NR)		
CP Class B, Months (95% CI)	3.7 (1.03-4.2)		
CP Class C, Months (95% CI)	0.8 (0.63-NR)		
CP Class A v B v C	P = 0.001		
Secondary outcome: Median PFS by CP Class in the Nivolumab Cohort**			

CP Class A, Months (95% CI)	4.8 (2.27-10.73)		
CP Class B, Months (95% CI)	2.77 (1.03-3.7)		
CP Class C, Months (95% CI)	0.8 (0.63-NR)		
Secondary Outcome: Median OS by ECOG PS in the Nivolumab Cohort			
ECOG PS 0 to 1 v ECOG PS 2 to 3, Months (95% CI); P Value	6.57 (1.43-11.37) v 2.67 (0.8-4.07); p = 0.07		
Secondary Outcome: Median OS by AFP in the Nivolumab Cohort			
AFP <400 v AFP 400+, Months (95% CI); P Value	3.9 (1.77-7.3) v 4.2 (1.03-6.83); p = 0.78		

Table 2: Efficacy outcomes. Note: *CP A v B/C p<0.001, CP A v B p = 0.009, CP A v C p = 0.006, CP B v C p = 0.70 ; **CP A v B v C p = 0.01, CP A v B/C p = 0.005

In our sample, CP score was demonstrated to be significantly associated with overall survival. The median OS for nivolumab patients with a CP class A was 8.93 months (95% CI, 2.27 to not reached [NR]), CP class B was 3.7 months (95% CI, 1.03 to 4.2), and CP class C was 0.8 months (95% CI, 0.63 to NR) (Figure 1). The median PFS for cohort 1 between CP class A versus B versus C was also found to be significantly different (p = 0.01). The median OS among patients with ECOG PS 0 to 1 versus ECOG PS 2+ in cohort 1 was 6.57 months (95% CI, 1.43 to 11.37) versus 2.67 (95% CI, 0.8 to 4.07) (p = 0.07). The median OS in cohort 2 was 7.13 months (95% CI, 0.7 to NR), and the median PFS was 2.7 months (95% CI, 1.7 to NR). The comparison of difference in OS and PFS between cohort 1 and 2 were not significantly different (p = 0.17 and p = 0.57 respectively).

A total of 8 irAEs of any grade were seen in cohort 1 with 73.1% of patients not having a reported irAE. One grade 3+ irAE was reported, therapy was held twice due to an irAE, therapy was discontinued once due to an irAE, and there were no deaths attributed to an irAE in cohort 1. In cohort 2, 9 patients (75%) did not have a reported irAE and 2 patients (16.7%) had grade 3+ irAE (Table 3). Initiation of bevacizumab after the first held dose at any point in therapy occurred in 5 patients (41.7%) (Table 4) (Figure 2).

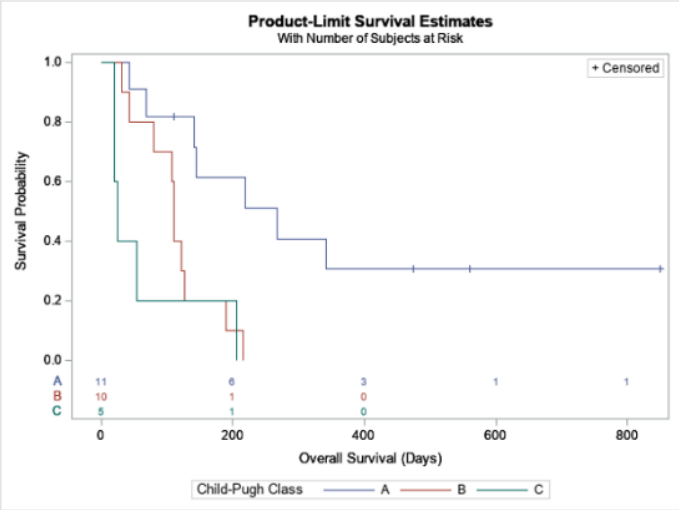

Figure 1: OS in nivolumab patients by CP class (log rank p = 0.001).

Adverse Event (Any Grade)	Nivolumab (n = 26)*	Atezolizumab + Bevacizumab (n = 12)
Dermatologic Toxicity	4 (15.4)	1 (8.3)
Diarrhea/Colitis	0 (0)	1 (8.3)
Hepatitis	1 (3.9)	1 (8.3)
Adrenal Insufficiency	1 (3.9)	0 (0)
Pneumonitis	0 (0)	0 (0)
Thyroid Dysfunction	2 (7.7)	0 (0)

No Adverse Events	19 (73.1)	9 (75.0)
Adverse Event (grade 3+)		
Dermatologic Toxicity	0 (0)	1 (8.3)
Hepatitis	0 (0)	1 (8.3)
Thyroid Dysfunction	1 (3.9)	0 (0)
irAE Outcomes		
Therapy held due to irAE	2 (7.7)	1 (8.3)
Therapy discontinued for irAE	1 (3.9)	0 (0)
Death Correlated to irAE	0 (0)	0 (0)

Table 3: Immune related adverse events during treatment. **Note:** *One patient in the Nivolumab group had 2 reported irAE.

Variable	Atezolizumab + Bevacizumab (n = 12)
Doses of Bevacizumab held	
1	4 (33.3)
2	3 (25.0)
3+	5 (41.7)
Bevacizumab Started after being held	
Yes	5 (41.7)
No	7 (58.3)

Table 4: Bevacizumab dosing information.

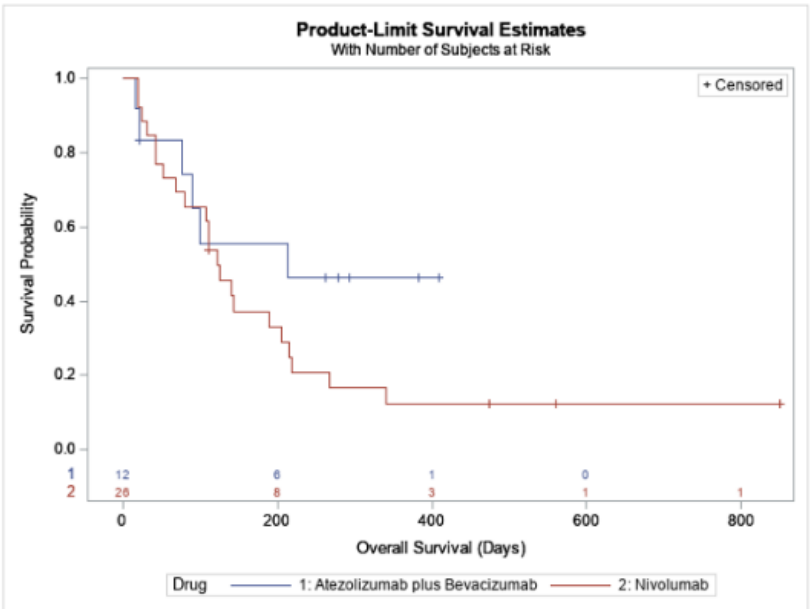

Figure 2: Overall survival by treatment type (log rank p = 0.17).

DISCUSSION

CheckMate 040 was a phase 1/2 trial that originally resulted in nivolumab monotherapy receiving accelerated FDA approval though the accelerated approval was eventually rescinded after no difference was found in OS in the CheckMate 459 trial between nivolumab and sorafenib [11,12]. The similar numerical efficacy to sorafenib from the CheckMate 459 clinical trial, the favorable toxicity profile, and the need for a first line therapy without an antiangiogenic medication or for patients with Child Pugh Class B liver dysfunction lead to the recommendation of nivolumab use in the first line setting (useful in certain circumstances for patients with a CP class B) from the National Comprehensive Cancer Network (NCCN) [2,11,12]. Efficacy and safety of nivolumab in the CheckMate 040 and CheckMate 459 trial were numerically similar with reported median overall survival of 15.0 months (dose-escalation phase) and 16.39 months respectively [11,12]. Grade 3+ adverse events were

also similar occurring in 18% of patients in the CheckMate 459 trial and 19% in the CheckMate 040 trial (dose expansion) [11,12]. Evidence of first line nivolumab use outside of clinical trials has variable reported safety and efficacy with median OS ranges between 8 months and 12.2 months along with grade 3+ irAE as low as 6.4% and reported grade 5 hepatotoxicity rates of 21% [13-15]. Our cohort's median OS is the lowest reported in literature to date at 4.07 months with the best tolerability having only 3.9% of patients having a reported grade 3+ irAE in a cohort that only includes patients who received nivolumab as first line therapy. The combination of overall poor baseline performance status and high CP scores likely contributed to the low median OS. The low rate of grade 3+ irAE in the nivolumab cohort is likely explained by the low median TTF of 1.87 months showing many patients only received 1 to 3 doses of nivolumab leading to lower risk of irAEs.

The exclusion of patients with a CP class of B and C in comparative clinical trials is a common standard in HCC [6,7,9,10]. This leads to very limited data for the safety and efficacy of treating patients with this level of hepatic impairment. Published clinical trials with nivolumab have only reported 10 total patients without a CP class A [11,12]. Literature of patients treated with nivolumab in the first line setting outside of clinical trials with baseline CP B and C is extremely limited and results are not always delineated between line of therapy [13-15]. This study found a statistically significant difference in OS and PFS based on CP class A versus B versus C solidifying CP class a primary prognostic marker for patients with HCC. Patients with a baseline CP class of B or C also had a significantly lower OS compared to patients with a CP class of A ($p < 0.001$). OS of patients with a CP class B and C were also numerically low with a median OS of 3.7 months and 0.8 months respectively. Additionally, a retrospective study evaluated real-world patients treated with A+B in patients with CP class B and also found a numerically low OS with this regimen at a median OS of 6.7 months which further brings into question the clinical benefit of treating this subset of patients with any systemic therapy as these regimens have not been compared to supportive care alone [16].

Eligibility criteria commonly restricts patients enrolled in clinical trials to an ECOG PS of 0 or 1 making it unclear if patients should be treated in practice with an ECOG PS of 2+ [17,18]. Another retrospective study of patients with HCC found a statistically significant difference in OS based on baseline ECOG PS 0 versus ECOG PS 1 to 3 when comparing patients treated with nivolumab outside of clinical trials.14 Our study did not find a difference in OS when comparing ECOG PS 0 to 1 versus ECOG PS 2+ ($p = 0.07$) though a strong trend towards better OS was seen in patients with an ECOG PS of 0 to 1. Baseline AFP level <400 versus 400+ also did not find a significant difference, though prior retrospective studies have also not found a difference giving further evidence AFP likely has minimal prognostic utility.

A+B was originally studied in a phase 1b trial which also included an atezolizumab monotherapy arm [8]. The combination of A+B was selected over monotherapy atezolizumab after the combination recorded a longer PFS in first line HCC patients [8]. Since the phase 1b trial, atezolizumab monotherapy has not been studied in clinical trials. The subsequent phase 3 trial found that A+B was superior to sorafenib making it a preferred first line option for unresectable HCC [6]. Due to the requirement for variceal evaluation and treatment prior to initiating A+B, physicians may have to decide on delaying therapy, selecting other first line therapy options such as T+D, or initiating atezolizumab monotherapy and adding bevacizumab after the evaluation as an off-label approach to initiate therapy sooner [6]. Our study sought to compare nivolumab to the practice of holding bevacizumab and starting atezolizumab monotherapy with the intention of

initiating bevacizumab once variceal evaluation was completed. The study did not find a statistically significant difference in OS or PFS between the nivolumab and the atezolizumab arm though this was in the setting of an underpowered cohort with large differences in baseline characteristics. A major takeaway is that it is uncommon for patients to start bevacizumab after initially being held with over half of the patients never receiving a dose of bevacizumab after atezolizumab initiation. This data brings into question the utility of this off label approach versus selecting an immunotherapy option such as T+D.

This study had several limitations including small sample size, retrospective design, and inability to evaluate overall response rate. The small sample size left outcomes underpowered limiting the evaluation of outcomes that did not find a statistically significant difference. Due to the small sample size, the statistical tests that were performed and corresponding p-values were not robust. Furthermore, while the recent expansion of other immunotherapy options such as T+D, durvalumab, and pembrolizumab in the NCCN guidelines may limit the use of nivolumab it is important to note that there is limited data on the safety and efficacy of these options in patients who do not meet the strict criteria required in the original clinical trials. Additional research is still needed to evaluate the safety and efficacy of other regimens in patients with HCC who would not have been eligible for clinical trials. Research evaluating CP score within each CP class with larger numbers may help further identify patients who may benefit from systemic therapy versus those who should consider supportive care measures only.

CONCLUSION

In conclusion, patients at our institution deemed not eligible for first line, standard of care therapy appear to derive minimal benefit from treatment with nivolumab monotherapy. CP class appears to be the best prognostic factor, and patients with a CP class B or C that would have been excluded from clinical trials should consider forgoing treatment due to the poor prognosis and limited benefit in addition to the cost of these medications. Further studies are still needed to evaluate the practice of initiating atezolizumab and holding bevacizumab until esophageal variceal evaluation has been completed especially with the option of T+D available. Our study highlights a major gap in effective treatment options for HCC patients with Child Pugh B and C hepatic impairment and ECOG 2+.

DECLARATION OF CONFLICTING INTERESTS

The authors declare that there is no conflict of interest.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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