Prolonged overall survival (OS) in patients with metastatic colorectal cancer (mCRC) in SPICE, a phase I study of enadenotucirev in combination with nivolumab

Abstract 329

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1. Background

Enadenotucirev (EnAd) is a tumor-selective chimeric Ad11/Ad3 group B oncolytic adenovirus that does not express any transgenes (a so called "unarmed virus") [Khun et al, 2008]. Following intravenous (IV) dosing of EnAd to patients with primary colon cancer in a phase I study, effective viral delivery has been demonstrated together with intra-tumoral CD8+ T-cell infiltrates [Garcia-Carbonero et al, 2017]. A further phase I clinical study identified a well-tolerated dose and regimen for EnAd monotherapy, including in patients with metastatic colorectal cancer (mCRC) [Machiels et al, 2019].

Immune checkpoint inhibitors (ICIs) have shown impressive clinical activity in several multiple types, including microsatellite instability (MSI) high mCRC [Le et al, 2015]. However, there is still a significant proportion of tumors which appear to have a primary resistance to ICI therapy, including MSI low and microsatellite stable (MSS) mCRC. Combination treatment strategies using ICIs together with immune stimulatory EnAd may help to overcome ICI resistance in MSI low / MSS mCRC and other ICI resistant tumor types.

The SPICE study is a phase I study to examine the safety and potential efficacy of the combination of EnAd and nivolumab in a range of epithelially derived solid tumor types previously shown to have primary or to have developed secondary ICI resistance (squamous cell head and neck (SCCHN), non-small cell lung (NSCLC), urothelial carcinoma (UCC) and MSI low / MSS mCRC).

Preliminary data has indicated promising survival in patients with mCRC resulting in a median OS of 14 months [Fakih 2019]. To further understand this OS signal, a comparison to historical patient-level data from the placebo arm of the CORRECT study [Grothey, 2013] was performed using data obtained from Project Data Sphere. The CORRECT study was a randomised, double-blind, placebo-controlled phase 3 study of regorafenib plus best supportive care (BSC) versus placebo plus BSC in patients with mCRC who have progressed after standard therapy.

2. Methods

In the SPICE study, EnAd was escalated in combination with ICI therapy in patients with metastatic epithelial tumors in a 3 + 3 design. Subjects received increasing dose levels and/or cycles of EnAd followed by up to 8 cycles of ICI as shown in Figure 1.

The objective of the comparison to the CORRECT study was to assess the extent to which OS outcomes with the combination of enadenotucirev and nivolumab were promising in comparison to a matched untreated colorectal cancer population.

Importantly, this analysis matched individual patients recruited into the SPICE study with patients in the placebo arm of the CORRECT study who they most resembled in terms of available reported patient characteristics (described throughout as covariates) that are known to be associated with OS (see Table 2). OS outcomes are then compared between the SPICE study and matched CORRECT placebo arm patients to minimise any bias due to patient selection.

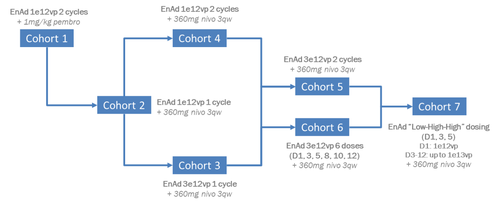
Individual patient data from the placebo arm of the CORRECT study were obtained from Project Data Sphere (for further information see https://www.projectdatasphere.org). It was not possible to perform a patient-matched comparison with the regorafenib arm of the CORRECT study as these data were not made available within Project DataSphere by the Sponsor.

Median OS in the available CORRECT dataset exactly matched the published outcomes [Grothey, 2013] although the dataset available appeared to be from a mature data-cut containing only 14 censored OS observations for the placebo arm.

Patients were matched according to patient characteristics previously shown to be potentially associated with OS and were reported in both studies. All of the selected covariates, apart from gender and age, were confirmed to be associated with OS within the placebo arm of the CORRECT study.

Figure 1: SPICE study design

The SPICE study is conducted at 6 clinical sites in the United States of America. The dose escalation phase of the study uses a 3+3 design to escalate the dose and regimen of enadenotucirev in combination with nivolumab. The progression through the 7 cohorts investigated to date are shown below:



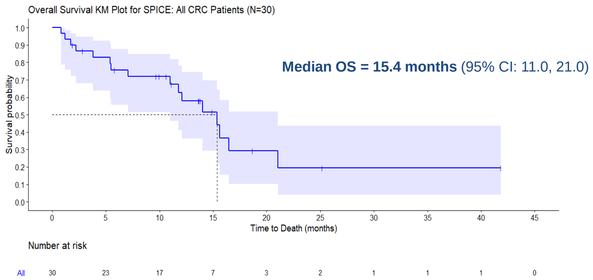
Treatment in each cohort consists of up to 8 x 21-day cycles.

Enadenotucriev is administered on
- Days 1, 3 & 5 of cycle 1 (cohorts 2, 3 & 7), or
- Days 1 ,3 & 5 of cycle 1 & 2 (in cohorts 1, 4, & 5)
- Days 1, 3, 5, 8, 10 & 12 of cycle 1 (cohort 6)

Nivolumab is administered on
- Day 8 of each cycle (cohorts 4 & 5), or
- Day 15 of each cycle (all other cohorts)

Figure 2: Overall survival in SPICE (all mCRC patients)

Thirty patients with mCRC who received at least one dose of enadenotucirev were included in the survival analyses. Of these, 25 patients had a confirmed microsatellite status of MSI-Low/MSS and the remaining 5 had unknown status. At the time of data cut-off 16 patients had died, with a median follow-up of 12.4 months amongst the censored patients.

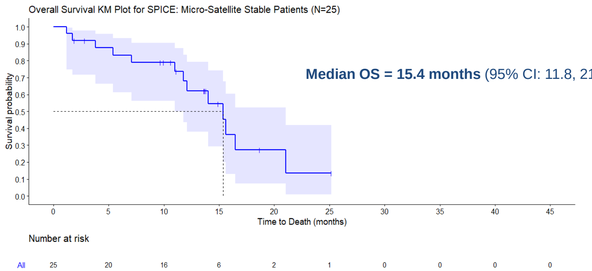


Median OS = 15.4 months (95% CI: 11.0, 21.0)

Note: Patients who were alive were censored at their last contact date and OS was measured from the date of the first enadenotucirev dose. Bands shown above represent 95% Cis.

Figure 3: Overall survival in SPICE (microsatellite stable mCRC patients)

Given the known differences in outcome for patients with MSI-high and MSI-low/MSS mCRC tumours, a subgroup analyses of OS was repeated in patients known to have an MSI-low or MSS tumour (n=25)



Median OS = 15.4 months (95% CI: 11.8, 21.0)

Note: Bands shown above represent 95% Cis.

Table 1: Comparison of SPICE & CORRECT studies

When comparing data with historical controls, it is important to bear in mind potential limitations.

The SPICE study and the CORRECT study are compared below, showing that these two mCRC studies conducted predominantly in research centres in the western world are comparable except on size.

	CORRECT	SPICE
Eligibility	Refractory late stage and metastatic CRC	Refractory late stage and metastatic CRC
Primary endpoint	OS	Safety but OS recorded
Median prior treatments	3	4
Date published	2013	2019
Study size	114 Centres, 16 countries, 760 patients randomised. (632 Patients from North America, Western EU, Israel and Australia)	34 Patients (currently) all USA.
Regulatory oversight	FDA and others	FDA

The SPICE study included patients with a greater median number of prior therapies, which tends to equate with shorter OS. This may reduce the likelihood of detecting a longer OS for patients in the SPICE, potentially biasing results in favour of the CORRECT study.

As there was no apparent dose effect on OS in the SPICE study, the survival data from all dose cohorts was pooled for the comparison with the CORRECT study.

Table 2: Comparison of patient characteristics

A comparison of the patient characteristics between SPICE and the placebo arm of CORRECT study is shown below

The distribution of the covariates were broadly similar between studies, at least for those found to be associated with OS within CORRECT, although median LDH and platelet count and the proportion of patients without liver metastases suggested the SPICE population may have had a better prognosis with respect to these particular covariates.

Covariate		SPICE N (%) N=30	CORRECT N (%) N=251	OS HR[1] (p-value) within placebo arm of CORRECT
AGE:	<60 years	15 (50%)	106 (42%)	0.925 (p=0.55) (<60: ≥60)
	≥60 years	15 (50%)	145 (58%)	
Sex:	Male	22 (73%)	149 (59%)	1.043 (p=0.75) (female:male)
	Female	8 (23%)	102 (41%)	
ECOG PS:	0	16 (53%)	143 (57%)	0.591 (p<0.001) (0: 1)
	1	14 (47%)	108 (43%)	
Liver Mets:	Y	18 (60%)	173 (69%)	0.548 (p<0.0001) N:Y
	N	12 (40%)	78 (31%)	
Haemoglobin:	<10.5 g/dL	4 (12%)	25 (10%)	0.854[2] (p<0.001)
	≥10.5 g/dL	16 (88%)	226 (90%)	
	Median	12.6 g/dL	12.7 g/dL	
Albumin:	<3.5 g/L	4 (12%)	17 (7%)	0.377[2] (p<0.001)
	≥3.5 g/L	26 (88%)	234 (93%)	
	Median	4 g/L	4.2 g/L	
LDH:	<618 IU/L	26 (88%)	214 (85%)	2.503[3] (p<0.001)
	≥618 IU/L	4 (12%)	37 (15%)	
	Median	218 IU/L	282 IU/L	
Platelet count:	<150 K/UL	5 (15%)	28 (11%)	2.321[3] (p<0.001)
	≥150 K/UL	25 (85%)	223 (89%)	
	Median	200 K/UL	236 K/UL	

PS=Performance Status; [1] Univariate HR for OS within placebo arm of CORRECT; [2] fitted as a continuous covariate, HR represents reduction in risk for every 1 unit increase in value; [3] log-transformed value fitted as a continuous covariate, HR represents increase in risk for every 1 unit increase in log-transformed value

Table 3: Results of matched statistical analyses

Three different statistical analyses were performed to compare the outcomes between the SPICE and CORRECT studies:

- **A comparison of OS having matched each SPICE patient to a maximum of 10 and an average of 5.5 placebo patients from CORRECT using M:1 variable nearest neighbour propensity score matching – 'NN PS Match'**
- **Stratified propensity score matching with 5 stratum – 'Stratified PS Match'**
- **Multivariate analysis of SPICE vs the CORRECT placebo arm having adjusted for all significant covariates in a Cox model – 'Regression model'**

The results of the analyses are presented below, along with additional technical details regarding the methods.

	HR (SPICE:CORRECT) and 95% CI
NN PS Match[1]	HR=0.314 (0.162, 0.606)
Stratified PS Match[2]	HR=0.208 (0.106, 0.407)
Regression Model[3]	HR=0.272 (0.155, 0.444)

[1] M:1 nearest neighbour variable matching, without replacement, to 165 patients in the CORRECT placebo arm. Each SPICE patient is matched to at least 1 up to a maximum of 10 and an average of 5.5 placebo patients, using log(LDH) and log(platelet count) with an exact match for ECOG and liver mets (Datasphere did not provide data for haemoglobin & albumin). Changing the number of matched patients produced similar results. The matched dataset was analysed using a weighted Cox Proportional Hazards model with covariates for study, ECOG, Liver mets, log(LDH) and log(platelet count), where CORRECT patients are weighted in inverse proportion to the number of nearest neighbours selected per SPICE observation.

[2] HR calculated separately in 5 stratum formed from quintiles for the propensity score of enrolment into the SPICE study based on ECOG, Liver mets, haemoglobin, albumin, log(LDH) and log(platelet count). HR within stratum estimated using a Cox Proportional Hazards model, adjusting for the same set of covariates, with results averaged over stratum by weighting in inverse proportion to the variance of the within stratum estimate of the HR.

[3] HR for study having adjusted for ECOG, Liver mets, haemoglobin, albumin, log(LDH) and log(platelet count)

Note: Models included covariates which were significant when fitted univariately to the placebo arm of the CORRECT study (see Table 2)

7. Discussion

- The combination of enadenotucirev and nivolumab in patients with heavily pre-treated MSI low or MSS mCRC has a manageable tolerability profile and is associated with preliminary but encouraging signals of efficacy [Fakih, 2019].
- Comparison of overall survival in the SPICE study with that of the placebo arm of the CORRECT study suggests a potential survival benefit with combination treatment using enadenotucirev and nivolumab in patients with metastatic colorectal cancer
- The OS HR from the regression model comparing OS outcomes between studies was 0.272 in favour of SPICE, with an upper 2-sided 95% confidence limit of 0.444, which was consistent with results when data were analysed using propensity score matching
  - The largest upper 95% confidence limit for the HR was 0.606
- Whilst the analyses cannot be regarded as definitive, due to the possible differential presence of unmeasured confounders between a small phase 1 open label study cohort with a large randomised double-blind phase 3 control group, the results appear promising particularly in a population that has historically shown little response to PD-1 intervention, and warrant further exploration.

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Clinical trial information: EUDRACT Number 2017-001231-39; ClinicalTrials.gov Identifier: NCT02636036