RASH AS A MARKER FOR THE EFFICACY OF GEMCITABINE PLUS ERLOTINIB-BASED THERAPY IN PANCREATIC CANCER: RESULTS FROM THE AViTA STUDY

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Updated abstract

Background: The EGFR inhibitor, erlotinib (E), in combination with gemcitabine (G), provides a significant survival benefit in metastatic pancreatic cancer. Rash, a common toxicity with EGFR inhibitors, has been proposed as a potential marker of erlotinib efficacy in multiple tumor types. The recent phase III study of GE ± bevacizumab (B)[1] provides a further opportunity to consider this topic.

Methods: Chemonaïve patients (pts) with metastatic pancreatic adenocarcinoma and KPS of 60–100 were randomized to GE-placebo (GE-P) or GE-B; pts received B/P 5mg/kg q2w plus E (100mg/d) and G (1,000mg/m^2) given weekly for 7 weeks during the first 8-weekly cycle, followed by weekly for 3 weeks during subsequent 4-weekly cycles. We retrospectively analyzed the impact of rash on patient outcomes.

Results: 607 pts were recruited; the arms were well balanced with respect to baseline characteristics. The addition of B to GE produced a significant benefit in PFS and a trend towards longer OS (median 7.1 mo vs 6.0 mo for GE-P). GE-B was well tolerated with no new safety signals observed. The incidence of rash was higher in the GE-B arm (73% vs 62% in the GE-P arm). There was a clear trend towards improved PFS and OS with increased grade of rash (see table); this trend was apparent in both arms of the study. There was no difference in OS between treatment groups for any rash grade.

Conclusions: The observed relationship between higher grades of rash and longer median OS supports the findings of the phase III PA.3 study of G ± E,[2] in pts with advanced pancreatic cancer. Studies are under way to prospectively investigate the relationship between rash and efficacy with erlotinib-based regimens in pancreatic cancer.

	Rash grade					
	0		1		≥2	
	GE-P (n=123)	GE-B (n=91)	GE-P (n=101)	GE-B (n=110)	GE-P (n=77)	GE-B (n=105)
Median OS (mo)	4.3	5.0	7.1	7.4	8.3	8.4
Median PFS (mo)	2.1	3.0	3.7	4.0	4.1	5.8

Introduction

- Pancreatic cancer represents a leading cause of cancer-associated mortality. Very few patients are diagnosed with early-stage disease suitable for resection, while disease recurrence is also common among those patients who are able to undergo surgery.[3,4]
- Gemcitabine has been the standard of care for patients with advanced pancreatic cancer for over 10 years; many phase III studies have subsequently failed to show any survival benefit with other therapies compared with gemcitabine alone.[5-8]
- The PA.3 study was the first study to demonstrate a significant improvement in overall survival (OS) with a biologic agent plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer. In this study, median OS was 6.24 months with gemcitabine/erlotinib and 5.91 months with gemcitabine monotherapy (hazard ratio [HR]=0.82; 95% confidence interval [CI]: 0.69–0.99; p=0.038)[2]
  - Cox regression analysis revealed that, if patients developed rash, they survived significantly longer: median survival rates in patients with grade 0, 1, and 2+ rash were 5.3, 5.8 and 10.5 months, respectively.[2]
- The association between erlotinib therapy, rash and favorable treatment outcomes has also been reported in patients with non-small-cell lung cancer. In the BR.21 study, there was a strong association between rash grade and survival among patients receiving erlotinib monotherapy (HR=0.34 for grade ≥2 vs grade 0, p<0.001).[9]
- AViTA was an international, placebo-controlled, phase III study designed to compare the combination of gemcitabine/erlotinib plus placebo (GE-P) with gemcitabine/erlotinib plus bevacizumab (GE-B) in patients with metastatic pancreatic cancer. The study found that the addition of bevacizumab to gemcitabine/erlotinib significantly improved progression-free survival (PFS) versus gemcitabine/erlotinib alone (HR=0.73; 95% CI: 0.61–0.86; p=0.0002); a trend to improved OS in the GE-B arm was also observed, but this did not reach statistical significance (HR=0.89; 95% CI: 0.74–1.07; p=0.2087)[1]
  - this retrospective analysis examined the incidence of rash in the AViTA study, to determine if there was a relationship between occurrence and severity of rash and patient outcomes when receiving either GE-P or GE-B
  - we also evaluated whether patients who developed rash had different baseline characteristics from those patients who did not develop rash.

Methods

Study design

- Patients with metastatic pancreatic adenocarcinoma and no prior systemic therapy for metastatic disease were randomized 1:1 to receive gemcitabine (1,000mg/m^2 on days 1, 8, 15, 22, 29, 36 and 43 for the first 8 weeks and then on days 1, 8, and 15 of subsequent 4-week cycles) plus erlotinib (100mg/day) in combination with either bevacizumab (5mg/kg once every 2 weeks) or placebo (Figure 1)
  - patients were stratified according to country, Karnofsky performance status (KPS), (<80% vs ≥80%) and albumin level (<2.9g/dL vs ≥2.9g/dL).

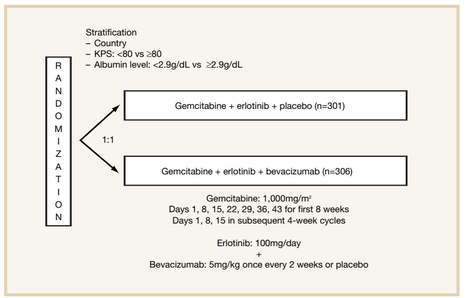

Figure 1. Study design.

- The primary endpoint was OS using an intent-to-treat analysis.
- Secondary endpoints included PFS, response rate, and safety. The safety population included all patients who received at least one dose of study protocol medication. Placebo recipients exposed to active treatment were analyzed in the bevacizumab treatment arm.
- This retrospective exploratory analysis analyzed OS, PFS, best response, and disease control rate (DCR) relative to occurrence and grade of rash
  - treatment outcomes were compared between patients with no rash and those with rash of grade 1, and grade ≥2.

Eligibility criteria

- Inclusion criteria: all patients had histologically confirmed metastatic disease, KPS ≥60% and had received no prior gemcitabine or anti-vascular endothelial growth factor (VEGF) therapy; the minimum allowable period since adjuvant therapy was 6 months; all patients were required to have adequate hematologic, hepatic, and renal function.
- Exclusion criteria: patients with tumors invading major blood vessels or with bleeding disorders, and those who had received surgery during the previous 28 days or had significant cardiovascular disease were excluded.

Safety assessments

- Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 3.0.

Results

Patient characteristics

- A total of 607 patients were enrolled. Patient characteristics were well balanced between treatment groups
  - approximately 60% of patients in each arm were male and median age was 61–62 years
  - in both treatment arms, >85% of patients had a KPS of ≥80%, and almost one-quarter had a KPS of 100%
  - pain rating, using the Memorial Pain Card Assessment Visual Analogue Scale, was >20mm in 39% of patients randomized to GE-P and in 36% of those randomized to GE-B.
- Rash of any grade was reported by 178 of 287 patients (62%) receiving GE-P and 215 of 296 patients (73%) receiving GE-B
  - of the 178 patients receiving GE-P who reported rash, 101 (56.7%) had, at worst, grade 1 rash and 77 (43.3%) had, at worst, grade ≥2 rash
  - of the 215 patients receiving GE-B who reported rash, 110 (51.2%) had, at worst, grade 1 rash and 105 (48.8%) had, at worst, grade ≥2 rash.
- Patient characteristics according to occurrence of rash are shown in Table 1
  - patients who developed rash were more likely to have baseline C-reactive protein (CRP) levels below the median (≥1.4mg/dL) in both treatment arms
  - current smokers were less likely to develop rash.
- Median time to occurrence of rash was 16 days in patients in the GE-P arm compared with 14 days in those receiving GE-B.

Table 1. Demographic characteristics according to severity of rash.

	Skin rash					
	NCI-CTC grade 0		NCI-CTC grade 1		NCI-CTC grade ≥2	
Intent-to-treat population	GE-P (n=123)	GE-B (n=91)	GE-P (n=101)	GE-B (n=110)	GE-P (n=77)	GE-B (n=105)
Gender, % Male/female	64/36	46/54	55/45	57/43	69/31	66/34
Race, % White/Asian/Black/other	85/11/0/5	87/10/1/2	85/12/0/3	91/7/0/2	86/10/0/4	87/8/<1/5
Age Median (range), years	62.0 (37–84)	63.0 (38–83)	60.0 (33–84)	62.0 (37–81)	60.0 (38–85)	61.0 (20–85)
<65 years/≥65 years, %	59/41	56/44	68/32	61/39	68/32	61/39
Smoking status Current/former/never, %	30/27/42	30/25/44	18/37/45	14/37/49	10/39/51	8/38/54
Pack years, median (range)	30.0 (3–162)	30.0 (3–120)	20.0 (0–105)	25.0 (0–100)	20.0 (0–80)	20.0 (1–135)
KPS, % 60/70/80/90/100	6/11/24/36/24	7/13/32/29/20	3/3/26/45/24	2/8/25/44/21	1/13/19/40/26	4/7/20/43/27
Laboratory parameters, % Albumin, < or ≥2.9g/dL	7/93	8/92	1/99	7/93	4/96	3/97
LDH, ≤ or >ULN	67/33	68/32	75/25	73/27	67/33	63/37
Alkaline phosphatase, ≤ or >4,84U/L	85/15	88/12	96/4	90/10	86/14	89/11
Platelet count, < or >ULN	86/14	78/22	93/7	81/19	91/9	84/16
CRP, ≤ or >1.4mg/dL	36/64	34/66	55/45	62/38	61/39	49/51
Total bilirubin, ≤ or >ULN	84/16	80/20	88/12	86/14	81/19	88/12
Hemoglobin, ≤ or >ULN	100/0	99/1	100/0	100/0	100/0	100/0
CA19, ≤ or >1,350kU/L	41/59	47/53	51/49	46/54	70/30	51/49
Neutrophils, ≤ or >ULN.	75/25	78/22	88/12	82/18	86/14	78/22

LDH = lactate dehydrogenase; ULN = upper limit of normal

Clinical efficacy and incidence of rash

- In the patient population evaluable for response to treatment (n=567), overall response rate (complete plus partial response) was 9.2% (17/185) in patients with no rash, 13.2% (27/205) in patients with grade 1 rash, and 11.9% (21/177) in those with rash grade ≥2
  - of the two patients who achieved a complete response, one had grade 1 rash and the other had rash grade ≥2
  - DCR (CR + PR + SD) was 43.2% (0% + 9.2% + 34.1%) in patients without rash versus 65.4% (0.5% + 12.7% + 52.2%) in patients with grade 1 rash (p<0.0001) and 72.9% (0.6% + 11.3% + 61.0%) in patients with rash grade ≥2 (p<0.0001).
- There was a clear relationship between occurrence and grade of rash and OS, in the overall study population (Table 2a and Figure 2a)
  - median OS was 4.8 months, 7.4 months, and 8.4 months in patients with rash grade 0, 1, and ≥2, respectively.

Table 2a. OS according to severity of rash.

	Median OS (months [95% CI])			
	No rash	Grade 1 rash	Grade ≥2 rash	Any rash
GE-P arm	4.3 (3.4–5.4)	7.1 (6.1–9.6) HR=0.56 (95% CI: 0.41–0.76) p=0.0001	8.3 (6.0–10.7) HR=0.50 (95% CI: 0.36–0.70) p<0.0001	8.1 (6.6–9.6) HR=0.53 (95% CI: 0.41–0.68) p<0.0001
GE-B arm	5.0 (3.9–6.4)	7.4 (5.8–9.1) HR=0.60 (95% CI: 0.44–0.83) p=0.0017	8.4 (7.2–10.2) HR=0.49 (95% CI: 0.35–0.69) p<0.0001	7.9 (7.1–9.1) HR=0.54 (95% CI: 0.41–0.72) p<0.0001
All patients	4.8 (3.7–5.4)	(7.4 [6.4–9.1) HR=0.59 (95% CI: 0.47–0.73) p<0.0001	8.4 (7.2–9.9) HR=0.50 (95% CI: 0.39–0.63) p<0.0001	8.0 (7.1–9.1) HR=0.54 (95% CI: 0.44–0.65) p<0.0001

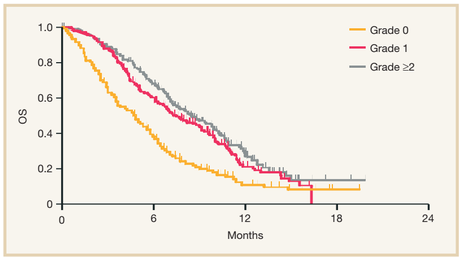

Figure 2a. Kaplan-Meier analysis of OS in all patients according to severity of rash.

- Similarly, in the overall study population, there was a clear relationship between occurrence and grade of rash and PFS (Table 2b and Figure 2b)
  - across both treatment arms, median PFS was 2.5 months, 3.8 months and 5.5 months among patients with rash grade 0, 1, and ≥2, respectively.

Table 2b. PFS according to severity of rash.

	Median PFS (months [95% CI])			
	No rash	Grade 1 rash	Grade ≥2 rash	Any rash
GE-P arm	2.1 (1.9–2.8)	3.7 (3.6–4.2) HR=0.67 (95% CI: 0.51–0.88) p=0.0033	4.1 (3.6–5.5) HR=0.47 (95% CI: 0.34–0.64) p<0.0001	3.8 (3.7–4.7) HR=0.56 (95% CI: 0.44–0.71) p<0.0001
GE-B arm	3.0 (2.1–3.9)	4.0 (3.4–5.4) HR=0.61 (95% CI: 0.45–0.83) p=0.0011	5.8 (5.4–7.3) HR=0.45 (95% CI: 0.33–0.62) p<0.0001	5.4 (4.5–5.8) HR=0.52 (95% CI: 0.40–0.68) p<0.0001
All patients	2.5 (2.0–3.0)	3.8 (3.6–4.4) HR=0.62 (95% CI: 0.51–0.76) p<0.0001	5.5 (4.7–6.0) HR=0.44 (95% CI: 0.35–0.55) p<0.0001	4.6 (3.9–5.3) HR=0.53 (95% CI: 0.44–0.63) p<0.0001

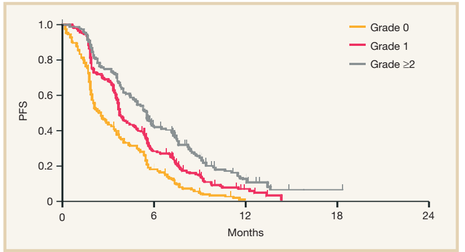

Figure 2b. Kaplan-Meier analysis of PFS in all patients according to severity of rash.

- Differences in OS and PFS between patients with no rash and those with rash of grade 1, ≥2 or any grade were also significant when analyzed by treatment arm.
- Median OS and PFS according to the severity of rash within each treatment arm are shown in Figure 3.

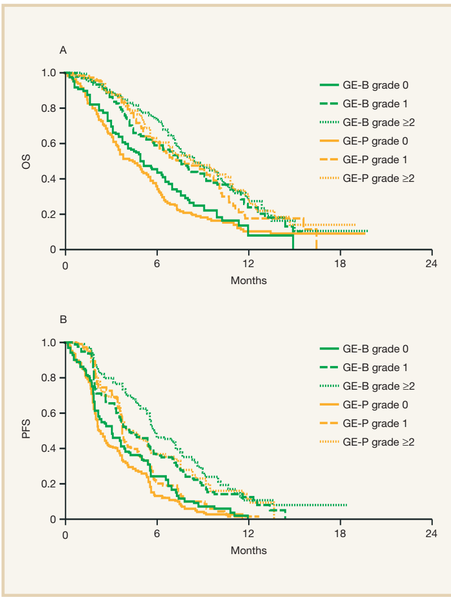

Figure 3. Kaplan-Meier analysis of OS (A) and PFS (B) by treatment arm according to severity of rash.

Conclusions

- AViTA was the second, large, phase III study to demonstrate that the combination of erlotinib with gemcitabine is effective and well tolerated in pancreatic cancer
  - the addition of bevacizumab to gemcitabine/erlotinib improved PFS and showed a trend towards improved OS.
- We conducted a retrospective exploratory analysis not corrected by multiple testing to explore the relationships between rash and efficacy in patients treated with erlotinib.
- Rash appeared to be a useful predictor of efficacy across both treatment arms, supporting its use as a marker for benefit with epidermal growth factor receptor (EGFR) inhibitors.
- Baseline laboratory values, e.g. CRP levels, or patient characteristics, e.g. smoking status, may help to predict which patients will develop rash; further research is needed to confirm this.

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