Abstract 9645

Phase 3 Trial of APF530 Versus Palonosetron in Preventing Chemotherapy-Induced Nausea and Vomiting: Efficacy in Breast Cancer Patients Receiving Moderately or Highly Emetogenic Chemotherapy

Ralph Boccia,[1] William Cooper,[2] Erin O'Boyle[3]

[1]Center for Cancer and Blood Disorders, Bethesda, MD; [2]TFS International, Flemington, NJ; [3]FibroGen, Inc., San Francisco, CA (previously an employee of A.P. Pharma, Inc, Redwood City, CA)

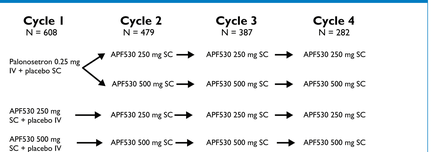
BACKGROUND

- Chemotherapeutic agents were first classified by Hesketh et al according to their emetogenic potential, with the risk of chemotherapy-induced nausea and vomiting (CINV) being 31% to 90% in patients receiving moderately emetogenic chemotherapy (MEC) and > 90% in patients receiving highly emetogenic chemotherapy (HEC)[1]
- Most patients with breast cancer receiving chemotherapy have, at minimum, MEC.[2] Importantly, anthracycline-based chemotherapy, commonly used to treat breast cancer, was recently reclassified by ASCO from MEC to HEC[3]
- APF530 is a novel formulation of 2% granisetron and a bioerodible tri(ethylene glycol) poly(ortho ester) polymer designed to provide slow, controlled hydrolysis resulting in slow and sustained release of granisetron for prevention of both acute (0-24 h after chemotherapy) and delayed (24-120 h) CINV associated with MEC and HEC[4]
- In clinical studies of patients receiving chemotherapy, a single dose of subcutaneous (SC) APF530 provided sustained therapeutic drug levels for > 120 hours.[4] A phase 3 trial demonstrated noninferiority of APF530 250 and 500 mg SC (granisetron 5 and 10 mg, respectively) compared with palonosetron 0.25 mg intravenously (IV), in control of acute CINV in patients receiving MEC or HEC and in prevention of delayed CINV in patients receiving MEC; however, it did not demonstrate superiority over palonosetron in delayed CINV with HEC[4,5]
- Here, we review data from the subpopulation of patients with breast cancer in this phase 3 trial, compared with the overall study population

METHODS

- In the original randomized, double-blind, placebo-controlled phase 3 trial (NCT00343460), adult patients with cancer scheduled to receive single doses of MEC or HEC were randomized to APF530 250 or 500 mg SC or palonosetron 0.25 mg IV prior to cycle 1 (C1) (**Figure 1**)
  - In C2-4, patients who received palonosetron in C1 were randomized, if they consented, to APF530 250 or 500 mg SC; those who received APF530 continued with their C1 APF530 dose
  - Standard doses of dexamethasone (8 mg IV with MEC, 20 mg IV with HEC) were given prior to chemotherapy on day 1; oral dexamethasone (8 mg bid) was given to HEC patients on days 2, 3, and 4
  - Primary objective: Establish noninferiority of APF530 to palonosetron for the prevention of acute CINV after MEC or HEC, and superiority of APF530 for the prevention of delayed CINV after HEC during C1 as measured by complete response (CR; no emetic episodes and no use of rescue medications) during C1
  - Secondary objectives included evaluating CR across each of 4 cycles
- Safety assessments included adverse events (AEs) during each treatment cycle (type, duration, severity, and relation to study drug)
- In this analysis, treatment group CR rates were compared (using Fisher's exact test) within cycle for the breast cancer subpopulation. Comparisons were exploratory in nature and not conducted to evaluate inferiority

Figure 1. Study Design



RESULTS

- There were 608 patients with breast cancer (423 MEC, 185 HEC) in the modified intent-to-treat (mITT) population (treated patients with postbaseline efficacy data [**Table 1**])

Table 1. Patient Demographics and Baseline Clinical Characteristics

	MEC			HEC		
	APF530 250 mg N = 149	APF530 500 mg N = 140	Palo 0.25 mg N = 134	APF530 250 mg N = 60	APF530 500 mg N = 67	Palo 0.25 mg N = 58
Age, mean (SD), y	53.5 (12.05)	54.3 (11.96)	55.0 (11.24)	50.3 (10.83)	49.8 (9.59)	52.6 (12.66)
Female, n (%)	149 (100)	137 (97.9)	132 (98.5)	60 (100)	67 (100)	58 (100)
ECOG PS 0-1, n (%)	145 (90.4)	140 (100)	131 (97.8)	59 (98.3)	65 (97)	56 (96.6)
Race/ethnicity, n (%)						
White or Caucasian	80 (53.7)	83 (59.3)	94 (70.1)	17 (28.3)	35 (52.2)	32 (55.2)
Black or African American	11 (7.4)	15 (10.7)	12 (9)	8 (13.3)	3 (4.5)	1 (1.7)
Native Hawaiian/ other Pacific Islander	2 (1.3)	1 (0.7)	0	2 (3.3)	1 (1.5)	0
American Indian/ Alaskan Native	1 (0.7)	0	0	-	-	-
Hispanic or Latino	12 (8.1)	9 (6.4)	6 (4.5)	6 (10)	6 (9)	5 (8.6)
Asian	42 (28.2)	30 (21.4)	22 (16.4)	25 (41.7)	22 (32.8)	20 (34.5)
Other	1 (0.7)	2 (1.4)	0	2 (3.3)	0	0
Hesketh class, n (%)						
1-2	0	0	1 (0.7)	0	0	0
3	3 (2.0)	6 (4.3)	6 (4.5)	0	0	0
4	145 (97.3)	131 (93.6)	127 (94.8)	2 (3.3)	3 (4.5)	1 (1.7)
5	1 (0.7)	3 (2.1)	0	58 (96.7)	64 (95.5)	57 (98.3)

ECOG PS = Eastern Cooperative Oncology Group performance status; MEC = moderately emetogenic chemotherapy; HEC = highly emetogenic chemotherapy; Palo = palonosetron.

- In C1, 78% of 423 MEC patients received cyclophosphamide plus doxorubicin or epirubicin (AC), and 75% of 185 HEC patients also received AC-containing chemotherapy (**Table 2**)

Table 2. Current Chemotherapy Regimens*

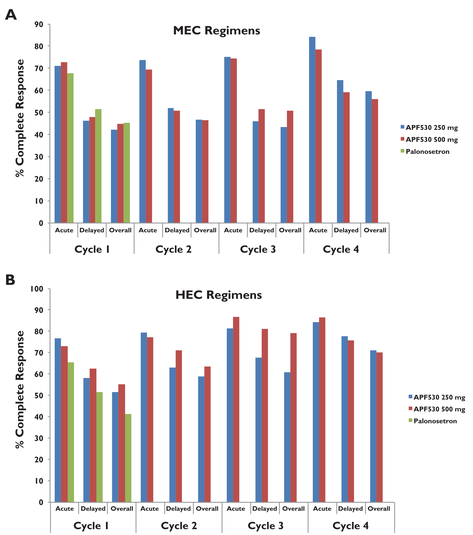
	Hesketh	APF530 250 mg	APF530 500 mg	Palo 0.25 mg
MEC regimens, n (%)		n = 149	n = 140	n = 134
Docetaxel-trastuzumab	3	0	1 (0.7)	2 (1.5)
Doxorubicin	3	1 (0.7)	1 (0.7)	1 (0.7)
Cyclophosphamide-doxorubicin	4	116 (77.97)	105 (75)	101 (75.4)
Cyclophosphamide-docetaxel	4	7 (4.7)	7 (5)	13 (9.7)
5-FU-cyclophosphamide-methotrexate	4	10 (6.7)	11 (7.9)	5 (3.7)
Docetaxel-epirubicin	4	4 (2.7)	3 (2.1)	3 (2.2)
Cyclophosphamide-doxorubicin	4	4 (2.7)	1 (0.7)	1 (0.7)
Cyclophosphamide-doxorubicin	5	1 (0.7)	1 (0.7)	2 (1.4)
HEC regimens, n (%)		n = 60	n = 67	n = 58
Cyclophosphamide-doxorubicin	4	2 (3.3)	3 (4.5)	0
5-FU-cyclophosphamide-doxorubicin	5	19 (31.7)	19 (28.4)	19 (32.8)
5-FU-cyclophosphamide-epirubicin	5	10 (16.7)	14 (20.9)	14 (24.1)
Cyclophosphamide-docetaxel-doxorubicin	5	15 (25)	10 (14.9)	7 (12.1)
Carboplatin-docetaxel-trastuzumab	5	5 (8.3)	5 (7.5)	5 (8.6)
Carboplatin-docetaxel	5	5 (8.3)	5 (7.5)	4 (6.9)
Carboplatin-paclitaxel	5	0	4 (6)	2 (3.4)
Carboplatin-gemcitabine	5	1 (1.7)	2 (3)	1 (1.7)

*Received by 3 or more patients.
5-FU = 5-fluorouracil; MEC = moderately emetogenic chemotherapy; HEC = highly emetogenic chemotherapy; Palo = palonosetron.

CR Rates During Acute, Delayed, and Overall Phases, Cycles 1 to 4, for Breast Cancer Population

- CR rates with APF530 250 mg and 500 mg in C1 were not significantly different from that of palonosetron in preventing both acute and delayed emesis with MEC and HEC
- No significant differences were seen in within-cycle CR rates between the 2 APF530 doses during acute and delayed CINV phases in patients receiving MEC or HEC in C1 (**Figure 2 A and B**) or in later cycles

Figure 2. Complete Response Rates of Patients With Breast Cancer Treated With MEC (A) and HEC (B) Regimens



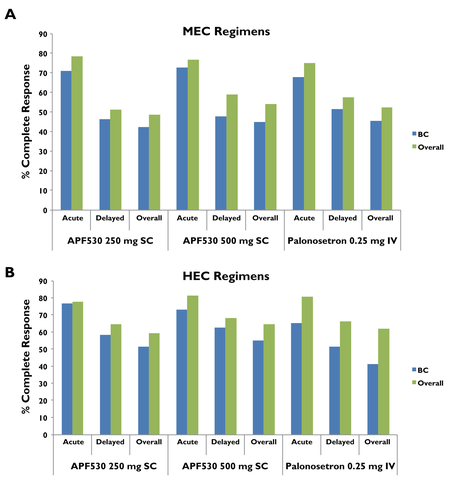
MEC = moderately emetogenic chemotherapy; HEC = highly emetogenic chemotherapy.

- CR rates remained high during the acute phase with both the APF530 250 and 500 mg doses through all 4 cycles: C2 (72% and 78%), C3 (75% and 84%), and C4 (82% and 85%) (MEC and HEC, respectively, combined 250 and 500 mg doses), revealing a trend toward higher CR rates in later cycles
- High and sustained CR rates were also achieved in C2-4 during the delayed phase and overall-risk period

CR Rate Comparison Between Breast Cancer Population and Overall Study Population

- CR rates were similar between patients with breast cancer and the overall study population (including breast [45.6%], lung [18.4%], and ovarian [10.7%]) from the original phase 3 study[4,5] (**Figure 3**)

Figure 3. Comparison of Complete Response Rates in Cycle 1 Between Patients With Breast Cancer and Overall Study Population With MEC (A) and HEC (B) Regimens



BC = patients with breast cancer; MEC = moderately emetogenic chemotherapy; HEC = highly emetogenic chemotherapy.

SAFETY

- The breast cancer safety population (n = 629) comprised all patients who were randomized and received study drug
- In the breast cancer population, 75% of patients experienced an AE, with similar frequency in each treatment group (**Table 3**)
- No notable differences in AEs were seen between the breast cancer population and the overall study population
- Excluding injection-site reactions (ISRs), the most common AEs across all groups were fatigue, constipation, and headache
- ISRs occurred across all treatment groups, and at a higher rate in the APF530 groups relative to palonosetron. The most frequent ISRs were bruising, erythema, and nodules
- After C1 there were 3 deaths, 1 in each group; none were treatment related
- Treatment-related AEs occurred in all groups (33% [APF530 250 mg]; 46% [APF530 500 mg]; 26% [palonosetron]) and were generally mild

Table 3. Treatment-Emergent Adverse Events (> 5%) in Any Group in Cycle 1

	APF530 250 mg SC		APF530 500 mg SC		Palonosetron 0.25 mg IV	
	n = 219	n = 464	n = 211	n = 468	n = 199	n = 463
Adverse Events	Breast Cancer	Overall	Breast Cancer	Overall	Breast Cancer	Overall
Preferred term,* n (%)						
Asthenia	11 (5.0)	23 (5.0)	10 (4.7)	22 (4.7)	15 (7.5)	30 (6.5)
Constipation	30 (13.7)	62 (13.4)	38 (18.0)	72 (15.4)	25 (12.6)	62 (13.4)
Diarrhea	24 (11.0)	49 (10.6)	25 (11.8)	44 (9.4)	20 (10.1)	39 (8.4)
Fatigue	42 (19.2)	62 (13.4)	37 (17.5)	62 (13.2)	32 (16.1)	52 (11.2)
Headache	24 (11.0)	31 (6.7)	33 (15.6)	47 (10.0)	28 (14.1)	45 (9.7)
Insomnia	12 (5.5)	20 (4.3)	10 (4.7)	25 (5.3)	3 (1.5)	11 (2.4)
Injection-site reactions, n (%)						
Bruising	41 (18.7)	78 (16.8)	54 (25.6)	93 (19.9)	21 (10.6)	41 (8.9)
Erythema	14 (6.4)	33 (7.1)	26 (12.3)	51 (10.9)	9 (4.5)	14 (3.0)
Nodule	12 (5.5)	22 (4.7)	32 (15.2)	50 (10.7)	1 (0.5)	3 (0.6)
Pain	11 (5.0)	16 (3.4)	25 (11.4)	33 (7.1)	3 (1.5)	5 (1.1)

*Excludes hematologic adverse events (anemia, leukopenia, neutropenia), abdominal pain, alopecia, nausea, and vomiting, which were assumed to be related to chemotherapy.

CONCLUSIONS

- APF530 demonstrated effective prevention of CINV over the entire 120-hour period following administration of MEC or HEC in patients with breast cancer
- No detectable differences were seen between APF530 250 mg and 500 mg SC in within-cycle CR rates in any CINV phase in patients with breast cancer receiving MEC or HEC
- CR rates for acute, delayed, and overall CINV periods were sustained across 4 chemotherapy cycles of all MEC and HEC regimens at each APF530 dose
- CR rates with APF530 tended to increase with subsequent cycles
- No differences in CR rates were seen between the breast cancer subset and the overall study population in the original phase 3 noninferiority study

REFERENCES

1. Hesketh et al. *J Clin Oncol.* 1997;15:103-109.
2. NCNN Clinical Practice Guidelines in Oncology: Breast Cancer—v2.2014.
3. Basch et al. *J Clin Oncol.* 2011;29:4189-4198.
4. Grous et al. ASCO 2009. Abstract 9627.
5. Charu et al. MASCC 2012. Abstract 1109.

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