FDA (Over-)Regulation of Off-Label Product Communications: A Risk/Benefit Analysis

Presentation to FDLJ Symposium, "FDA and Health Behavior Regulation"

October 20, 2017

Jeffrey Chasnow
Sr. VP & Assoc. General Counsel, Pfizer Inc
Chief Counsel, Pfizer Innovative Health

capsules SUTENT® sunitinib malate

DOSING OVERVIEW

Recommended dose for advanced RCC is one 50-mg capsule taken orally once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off

WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5	WEEK 6
on	on	on	on	off	off

- Remind patients to disclose any prescription or nonprescription medications they are taking, including bisphosphonates, vitamins, and herbal supplements, which can interact with SUTENT in different ways
- SUTENT may be taken with or without food
- Dose modification and/or dose interruption is recommended based on individual patient safety and tolerability

When tolerability is a concern…

Dose modification per FDA label

For illustrative purposes only.

- The dose of SUTENT may be adjusted in 12.5-mg increments or decrements, based on individual patient safety and tolerability
- Dose adjustments are recommended when SUTENT is administered with CYP3A4 inhibitors or inducers. During treatment with SUTENT, patients should not drink grapefruit juice, eat grapefruit, or take St John's Wort
- No dose adjustment is recommended based on age, race, gender, body weight, creatinine clearance, ECOG performance status score, or hepatic impairment (Child-Pugh Class A or B)

Dose interruption considerations from retrospective studies

WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5	WEEK 6
on	on	off	on	on	off

- In patients with advanced RCC who are unable to tolerate Schedule 4/2, consider the dose reduction described in the FDA-approved label or, as an alternative, consider modifying the schedule to 2 weeks on treatment followed by 1 week off (Schedule 2/1) using the same dose
  - Studies supporting Schedule 2/1 have not been reviewed by the FDA. For most studies, the patient population was small and/or analysis was post hoc, and therefore susceptible to bias. The efficacy of any particular alternative dosing schedule has not been established[6-10]

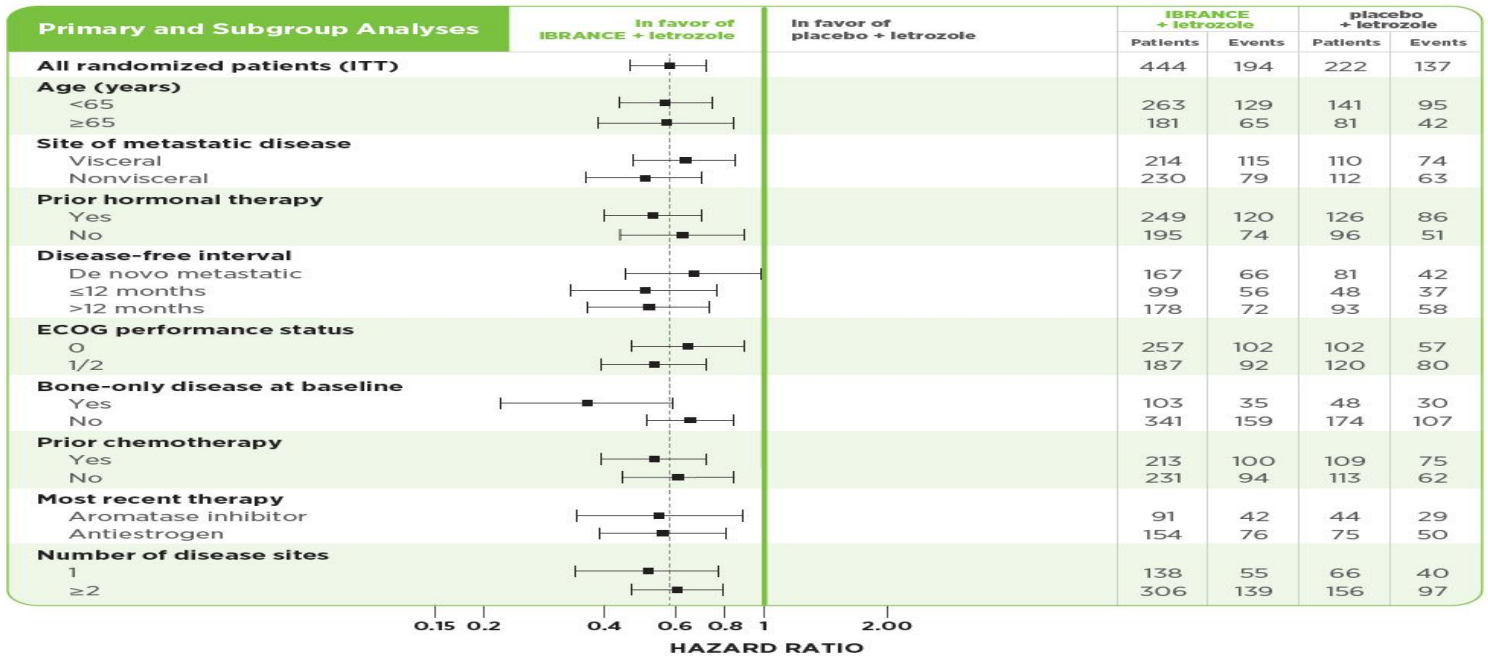
IMPORTANT SAFETY INFORMATION

- **The most common ARs** occurring in ≥20% of patients receiving SUTENT for treatment-naïve metastatic RCC (all grades, vs IFNα) were diarrhea (66% vs 21%), fatigue (62% vs 56%), nausea (58% vs 41%), anorexia (48% vs 42%), altered taste (47% vs 15%), mucositis/stomatitis (47% vs 5%), pain in extremity/limb discomfort (40% vs 30%), vomiting (39% vs 17%), bleeding, all sites (37% vs 10%), hypertension (34% vs 4%), dyspepsia (34% vs 4%), arthralgia (30% vs 19%), abdominal pain (30% vs 12%), rash (29% vs 11%), hand-foot syndrome (29% vs 1%), back pain (28% vs 14%), cough (27% vs 14%), asthenia (26% vs 22%), dyspnea (26% vs 20%), skin discoloration/yellow skin (25% vs 0%), peripheral edema (24% vs 5%), headache (23% vs 19%), constipation (23% vs 14%), dry skin (23% vs 7%), fever (22% vs 37%), and hair color changes (20% vs <1%)

PREPLANNED SUBGROUP ANALYSES FOR PFS IN PALOMA-2

Consistent results were observed across patient subgroups of disease site, disease-free interval, and prior therapy[1,2]

The graph below depicts preplanned subgroup analyses from the overall trial population in PALOMA-2. Small patient numbers can be a limitation of subgroup analyses. These analyses are not intended to demonstrate efficacy in particular subgroups.



Primary and Subgroup Analyses	IBRANCE + letrozole		placebo + letrozole	
	Patients	Events	Patients	Events
All randomized patients (ITT)	444	194	222	137
Age (years)				
<65	263	129	141	95
≥65	181	65	81	42
Site of metastatic disease				
Visceral	214	115	110	74
Nonvisceral	230	79	112	63
Prior hormonal therapy				
Yes	249	120	126	86
No	195	74	96	51
Disease-free interval				
De novo metastatic	167	66	81	42
≤12 months	99	56	48	37
>12 months	178	72	93	58
ECOG performance status				
0	257	102	102	57
1/2	187	92	120	80
Bone-only disease at baseline				
Yes	103	35	48	30
No	341	159	174	107
Prior chemotherapy				
Yes	213	100	109	75
No	231	94	113	62
Most recent therapy				
Aromatase inhibitor	91	42	44	29
Antiestrogen	154	76	75	50
Number of disease sites				
1	138	55	66	40
≥2	306	139	156	97

Adapted from Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med*. 2016;375(20):1925-1936. ECOG=Eastern Cooperative Oncology Group; ITT=intent to treat.

Selected Safety Information

Avoid concurrent use of **strong CYP3A inhibitors**. If patients must be administered a strong CYP3A inhibitor, reduce the IBRANCE dose to 75 mg/day. If the strong inhibitor is discontinued, increase the IBRANCE dose (after 3-5 half-lives of the inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor. Grapefruit or grapefruit juice may increase plasma concentrations of IBRANCE and should be avoided. Avoid concomitant use of **strong CYP3A inducers**. The dose of **sensitive CYP3A substrates** with a narrow therapeutic index may need to be reduced as IBRANCE may increase their exposure.

Please see Selected Safety Information throughout and accompanying full Prescribing Information.

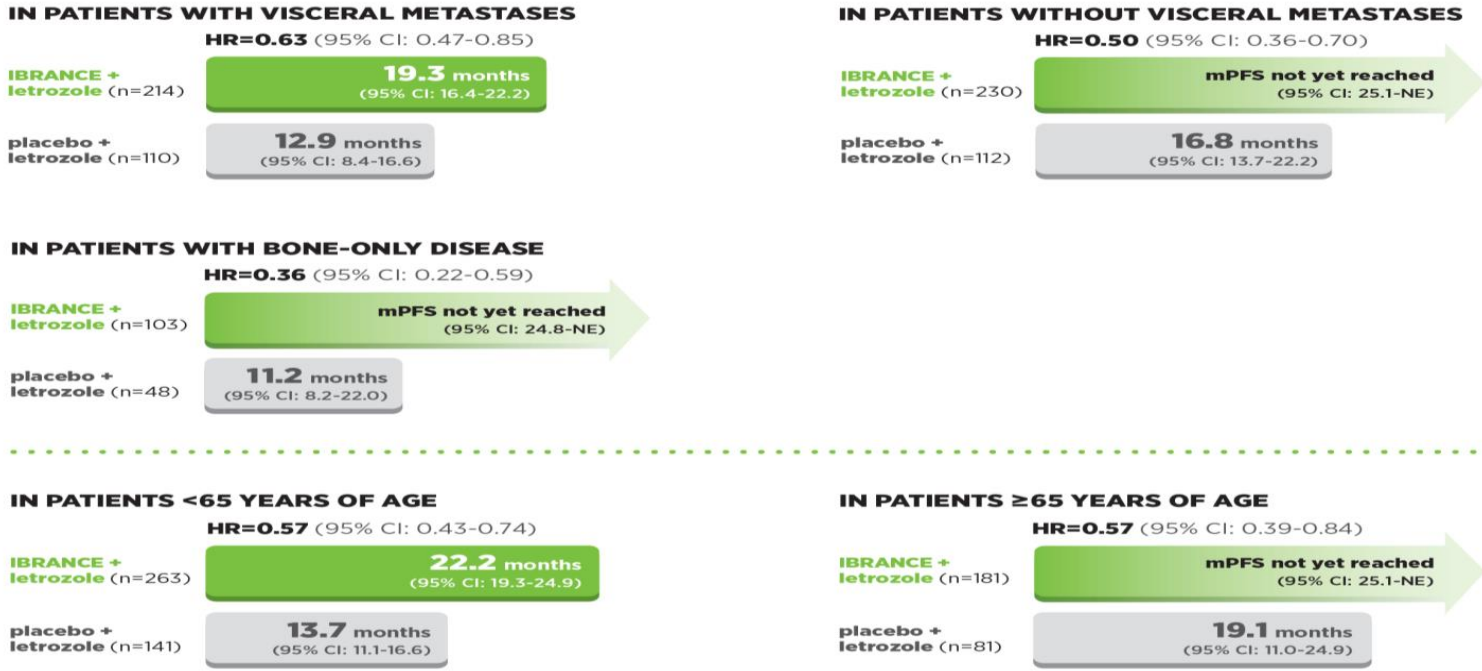
PFS SUBGROUP ANALYSES

IBRANCE™ palbociclib | 125 mg capsules
FIRST IN CLASS

These figures report the mPFS for selected subgroups. The degree of benefit in PFS observed as a result of the addition of IBRANCE to letrozole was consistent in all subgroups analyzed and was consistent with that seen in the overall study population.

- These analyses are considered exploratory. No adjustments were made for multiple comparisons in the subgroup analyses
- Small patient numbers can be a limitation of subgroup analyses. These analyses are not intended to demonstrate efficacy in particular subgroups

Analyses of disease site and age subgroups[1]



NE=not estimable.

Selected Safety Information

IBRANCE **has not been studied** in patients with **moderate to severe hepatic impairment** or in patients with **severe renal impairment** (CrCl <30 mL/min).

Prevnar 13 – Initial FDA Approvals vs. Initial ACIP Recommendation

- Initial FDA approval – February 24, 2010
  - Prevention of invasive disease and otitis media caused by strep pneumoniae in infants and young children six weeks to five years of age
- Supplemental FDA Approval – January 25, 2013
  - Expanded to older children and adolescents up to age 17
- ACIP Recommendation – February 20, 2013
  - Children aged 6-18 years with immunocompromising conditions

Prevnar 13 –
Pfizer Letter to prescribers (February 26, 2013)

For Your Information: FDA Approves Use of Prevnar 13® in Vaccine-Naïve Children and Adolescents Aged 6 Years through 17 Years

Dear Valued Customer,

We are pleased to announce that on January 25, 2013, the U.S. Food and Drug Administration (FDA) granted approval for the expansion of Pfizer's pneumococcal conjugate vaccine, Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein]), for use in older children and adolescents aged 6 years through 17 years for active immunization for the prevention of invasive disease caused by the 13 *Streptococcus pneumoniae* serotypes contained in the vaccine. For this age group, Prevnar 13® is administered as a one-time dose to patients who have never received Prevnar 13®.

Prevnar 13 –
Excerpt of Reply Email from CDC/ACIP Official (March 2013)

From: [CDC/ACIP Official]
Date: March 1, 2013, 12:45:51 AM GMT+01:00
To: [Pfizer Vaccines Medical Lead]
Subject: FW: Misleading Message

* * *

When FDA approves a vaccine as safe and effective, there is the implicit assumption that the use of the vaccine will come from recommendation(s) of the ACIP. This is a case where the ACIP recommendation was not communicated specifically in the attached letter, leaving the possibility that health care professionals may misinterpreting how the vaccine should be used as recommended by the ACIP, even though the letter from Ms Raphael is accurate with regards to the label. So, the issue concerns future communication from Pfizer regarding use of PCV13 in the 6 through 17 year old population. We hope that information provided by Pfizer will be the same as the ACIP recommendations and therefore avert potential confusion. I will be happy to discuss this issue with you and appreciate your discussion this afternoon.

Prevnar 13 – Reply Email from Academic Physician (March 15, 2013)

- “Discordant FDA and ACIP approaches . . . creates confusion for the practicing physicians as discussion of the uses recommended by the ACIP become off label discussions.”

- “It would appear sensible that discussion about its use in high risk individuals that are consistent with published and peer reviewed data should be able to be discussed.”

  - [Typos have been corrected]