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By Lynne Peterson

SUMMARY

Both Genta's Genasense and Allos's RSR-13 missed their primary endpoints. Genta tried to get approval on a secondary endpoint, and Allos wanted approval based on a subset analysis that was not pre-specified. The ODAC panel rejected both arguments, sending three strong messages to industry: (1) Don't expect approval of a drug that misses its primary endpoint, (2) slicing and dicing data won't turn a sow's ear into a silk purse or a failed drug into an approvable one, and (3) ODAC can make tough decisions even in the face of Congressional and patient pressure.

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FDA Oncologic Drugs Advisory Committee (ODAC) Rejects Genta's Genasense and Allos Therapeutics' RSR-13

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Genta's antisense cancer drug Genasense (oblimersen, G-3139) and Allos Therapeutics' radiosensitizer RSR-13 (efaproxiral) have several things in common: Both came before ODAC on the same day, both missed the primary endpoint in the pivotal trial, and both failed to get a recommendation for approval from the panel.

Patient pressure is nothing new. Occasionally, patients and patient advocates speak at FDA panel meetings, but the bar was raised when a large group of patients came to the ODAC panel on AstraZeneca's Iressa (gefitinib) to plead for approval. Several patients also came to this ODAC panel meeting.

Congressional pressure on an FDA advisory panel is more unusual and added a political factor to the deliberations. A front row of seats was reserved for members of the House Energy and Commerce Committee, which oversees the FDA. Panel members and FDA officials agreed that it was highly unusual to see legislators there, but they insisted they were not intimidated, though the legislators' presence made some people a little nervous.

Apparently, some legislators are upset that several years ago the FDA turned down Bristol-Myers Squibb's UFT (an oral combination of uracil and tegafur) as a treatment for colorectal cancer, against the advice of its ODAC panel. Surprising data from Japan recently showed the benefits of UFT in lung cancer, for which it was never tested in the U.S. The 979-patient Japanese study found that UFT extended survival in patients with early NSCLC (non-small-cell lung cancer) that has not metastasized outside the lung.

Five-Year Survival

Survival	UFT + Surgery	No chemotherapy
Patients with tumors >3 cm	85%	74%
Patients with tumors ≤3 cm but ≥2 cm	89%	86%
Patients with tumors <2 cm	Nss difference	

The legislators do not want the FDA to make the same mistake with other drugs, including Genasense. Congressman Peter Deutsch (D-FL), a member of the House Energy and Commerce Committee, told the panel that he has had basal cell carcinoma (not melanoma for which Genasense was being considered): "I am not

here to advocate for approval of this drug but that the mindset be your own mindset – that you, as clinical physicians, consider what is best for your patients. Would you want this drug available to your patients if they were diagnosed with metastatic carcinoma?…Dying patients need to be given access to every possible treatment…The Japanese found the effectiveness of UFT…and this same technology was rejected by the FDA…Thousands of cancer patients could be dying because their government failed them…The FDA turned down (UFT) even though this committee voted unanimously in favor…That is inexcusable." An aide to Congressman Mike Ferguson (R-NJ), another member of the House Energy and Commerce Committee, warned the panel against over-reliance on statistical analyses, saying, "One of my constituents, David Bernstein, had a grape-sized tumor in his chest...His chemotherapy was by Genasense, and six weeks later the tumor disappeared…That experimental drug was Genasense… For my mother (who had cancer) and David Bernstein, I hope you look favorably on Genasense."

Asked before the meeting why he was there, Ferguson's aide said, "I probably wouldn't be here if (Mark) McClellan were still head of FDA." He said Genta had not solicited his attendance, but he didn't know whether Genta had approached his boss, and he confirmed that Genta is located in Ferguson's district. The aide wondered how the panel and the FDA could ignore patients and "such a prominent Harvard expert" as Dr. Frank Haluska, an investigator and speaker for Genasense. After a 13 to 3 negative vote by the panel of oncology experts, the aide was much quieter and would only say, "I'm just trying to figure out what happened."

GENTA'S Genasense

Genta submitted a single, international, multi-center, unblinded, active control, randomized Phase III trial (GM-301) of Genasense plus dacarbazine (DTIC) vs. DTIC alone in advanced melanoma. The analysis occurred when the pre-specified 53 events were reached.

Dr. Richard Pazdur, Director of Oncology Drug Products for the FDA, opened the panel meeting and set the tone, saying: "This trial was originally designed as a survival improvement study…It did not demonstrate improvement in overall survival...We are asked to approve on secondary endpoints – on ***claims*** of improvement in PFS and response rates…A very small effect may raise questions about the very existence of an effect, especially when the trial is unblinded and there is not careful handling of missing assessments."

The Company Perspective

Speaking on behalf of Genta, Dr. John Kirkwood of the University of Pittsburgh, Chair of ECOG's Melanoma Committee, argued in favor of approval of Genasense. He noted that nothing works very well in melanoma, and Genasense works at least as well or better than what is available.

Genasense Pivotal Study GM-301

Measurement	Genasense+ DTIC n=386	DTIC n=385	p-value
Intent-to-Treat Analysis			
Overall survival (median)	9.1 months	7.9 months	0.18
Progression-free survival (median)	74 days	49 days	.006*
Durable response	3.4%	1.3%	0.057
Overall response by investigators	11.7%	6.8%	0.018
Overall response confirmed by independent review committee	6.7%	3.6%	.056
Response			
Complete response	1.3%	0.5%	N/A
Partial response	10.4%	6.2%	N/A
Stable disease	30.1%	27.5%	N/A
Progressive disease	39.4%	46.2%	N/A
Inevaluable	18.9%	19.5%	N/A
Safety			
Grade 3-4 thrombocytopenia	15.6%	6.4%	N/A
Serious thrombocytopenia	4.0%	1.1%	N/A
Grade 3-4 bleeding	2.2%	3.1%	N/A
Serious bleeding	1.3%	2.5%	N/A
Serious bleeding with thrombocytopenia	0.8%	0.8%	N/A
Platelet transfusions	3.8%	2.5%	N/A
Grade 3-4 neutropenia	21.3%	12%	N/A
Serious neutropenia	2.2%	0.3%	N/A
Adverse events leading to discontinuation	18.6%	10.8%	N/A
Injection site infection	4.0%	0.9%	N/A

*** This is FDA listed p-value. Genta claimed p-value of 0.0003.**

In February 2004, the FDA requested that the reading center, RadPharm, review an additional 80 cases. Genta said this produced new responses that improved the response rate. A Genta official said this review, using an intent-to-treat analysis, showed a statistically significant improvement in complete response.

ITT Re-Analysis of GM-301 Study
(Submitted to FDA 4-9-2004)

Measurement	Genasense+DTIC n=386	DTIC n=385
Overall response	12.4%	6.8%
Complete response*	2.8%	0.5% (p=.02)
Partial response	9.6%	6.2%
Stable disease	29.3%	27.5%

*** includes 3 surgical CRs in Genasense arm**

Genta Response to FDA Concerns

Issue	Genasense Response
Radiographic non-concordance	Concordance documented
Effect of interval assessments of PFS	Benefit maintained with aggressive sensitivity analyses
Baseline demographic differences	No effect on endpoints
Response rate driven by non-U.S. sites	Benefit observed U.S. and non-U.S.

Dr. Frank Haluska of Harvard/Mass General, Co-Chairman of the CALGB Melanoma Committee, also argued on behalf of approval of Genasense. He made several interesting points:

- "I think this drug is approvable despite the failure to meet the primary endpoint…I do think significant clinical benefit is strongly suggested by these data…We have nine patients alive, an increment that is not seen with IL-2 treatment…This trial sets itself apart from progress in the field in the last few years, and that is why it requires your consideration today."
- "Patients value responses…There are no melanoma drugs approved on anything else."
- In a direct reference to approval of AstraZenca's Iressa he said, "Patients value CR…The recent approval history and data on responses to targeted therapies underscore a clinical benefit in a subset of patients – a 10% response rate can change the field…A 10% response rate in and of itself doesn't argue against approval."
- "Patients value time free of disease progression even if that time is short – even a month is significant."
- "I'm supposed to be dispassionate, but I don't think I can do that…This represents progress…It is incremental progress – not a home run – but curing this disease requires incremental progress."

The FDA Perspective

The FDA expressed several problems with the Genasense data:

- The pivotal trial missed its primary endpoint. It showed no survival benefit.
- The PFS endpoint had a very small effect – "well under one month" – and it was not clear whether this was clinically meaningful. Assessments were done only at six-week intervals, but the PFS difference was only two to three weeks.
- The small increase in response rate with Genasense was somewhat uncertain because a central reading (particularly important in an open study) showed no significant difference.
- There was missing data: missing assessment visits and missing individual lesion measurements. This raised a question of bias, especially in an open study.
- Lesion assessments were done earlier in the DTIC alone group, which could lead to earlier documentation of progression. So, the concern was whether the observed difference was real.
- No difference in symptoms were observed between the study arms.
- The duration of the response was 126 days with Genasense vs. 127.5 days with DTIC alone.
- There was greater toxicity in the Genasense arm.

The Panel Perspective

REVISED QUESTION 1A: *(Is there a real response rate?)* Does the committee believe the observed differences in the response rates represent real effects of Genasense when added to DTIC?
VOTE: 11 yes, 5 no

REVISED QUESTION 1B: *(Is there an improvement in PFS?***)** Does the committee believe the observed differences in PFS represent real effects of Genasense when added to DTIC?
VOTE: 4 yes, 12 no

Panel members comments included:

- "I desperately want some drug to help with my patients…but, unfortunately, this drug is not the answer, at least the way it is administered."
- "To me some of this is rather disturbing, which is why I suppose it is before the committee…The general strategy of looking at secondary endpoints when the primary endpoint is not met is bothersome from a regulatory and scientific viewpoint…I'm very suspicious of the PFS because of the differential measurement, the timing, and the effect on attenuation…This might be a promising agent but probably at a ***very*** low level."
- "I feel we are being called on to make similar decisions (to Iressa) again, with a hint of a response in an agent that may disappear if not approved at this committee meeting. I am also troubled that response rates and methods for independent review were troublesome in this study...I feel that we are between a rock and a hard place."

QUESTION 2*: (Do benefits outweigh toxicity?)* Do the results of this study, in the absence of a survival improvement, provide substantial evidence of effectiveness that outweighs the increased toxicity of administering Genasense for the treatment of patients with metastatic melanoma who have not received prior chemotherapy?
VOTE: 3 yes, 13 no

QUESTION 3: *(Could PFS ever be a primary endpoint for approval?)* In the metastatic melanoma setting, do you believe that a PFS benefit of some magnitude represents clinical benefit that could support regular drug approval, even in the absence of an effect on survival?
VOTE: 16 yes, unanimous

ALLOS THERAPEUTICS' RSR-13

RSR-13 was submitted to the FDA in December 2003. In a Phase III trial, RSR-13, administered by 30-minute infusion through a central venous catheter, failed to meet its primary endpoint of overall survival, but Allos tried to save the agent by focusing on a statistically significant survival benefit in breast cancer patients, even though this was not a pre-specified subgroup. The FDA found that a stretch, and the agency also was not satisfied with the safety profile of RSR-13. **The panel agreed, voting 15 to 1 that the observed survival results from this single study in the subgroup of patients with breast cancer metastatic to the brain do not represent substantial evidence of RSR-13 efficacy in this subgroup.**

RSR-13 Results in RT-009 Phase III Trial

Measurement	Control n=250	RSR-13 n=265	p-value
Primary endpoint: Overall survival (all eligible patients)	4.4 months	5.4 months	p=.16
Subset analysis: Overall survival in eligible NSCLC/breast cancer patients	4.4 months	6.0 months	p=.07
Subset analysis: Overall survival in eligible breast cancer patients	4.5 months	9.0 months	p<.05
Breast cancer patients alive at 18-24 months	19.1%	18.5% (27.0% >24 months)	N/A
Protocol-Defined Response Rate in the Brain			
Overall	37%	45%	.061
NSCLC/ breast cancer patients	41%	53%	.013
Breast cancer patients	49%	72%	.016
Confirmed-Response Rate in the Brain			
Overall	17%	25%	.02
NSCLC/ breast cancer patients	20%	29%	.03
Breast cancer patients	20%	42%	<.01
Other Secondary Endpoints			
Time to radiographic tumor progression in the brain (% PF at 3 months)	64%	72%	.44
Cause of death (% neurologic)	15%	17%	.50
Overall quality of life: stable or improved at 3 months	18% KPS 21% Spitzer	24% KPS 23% Spitzer	.15 KPS .31 Spitzer
Quality of life: stable or improved at 3 months in breast cancer patients	18% KPS 24% Spitzer	35% KPS 37% Spitzer	.002 KPS .01 Spitzer
Safety			
Fatigue	43%	49%	---
Headache	33%	47%	---
Nausea	30%	47%	---
Radiation dermatitis	25%	26%	---
Dizziness	15%	22%	---
Vomiting	17%	38%	---

The Allos Perspective

An Allos official pointed out that 170,000 Americans develop brain metastases annually, and the incidence is rising due to longer survival resulting from earlier diagnosis, better systemic therapy for extracranial disease, and improved neuroimaging that increases the detection rate. From 20%-40% of cancer patients develop brain mets, with up to 35,000 breast cancer patients developing brain mets each year. Whole brain radiation therapy (WBRT) improves survival approximately 4.5 months and improves/stabilizes neurologic function.

He explained that tumor hypoxia is associated with radio-resistance, and RSR-13 reduces tumor hypoxia and increases radiosensitivity. He and other speakers admitted that RSR-13 did not show a statistically significant benefit overall or in the combination of NSCLC/breast patients. However, a subset analysis (not pre-specified) in breast cancer patients showed a clinically meaningful improvement in survival and improved quality of life, with a "very low" incidence of Grade 3-4 adverse events, and Allos hoped the panel would find that significant enough to warrant approval.

The FDA Perspective

FDA view of RSR-13 efficacy findings:

- No survival advantage in overall population (p=.1688)
- No survival advantage in NSCLC/breast co-populations (p=.1217)
- Survival advantage seen in non-pre-specified breast population is considered exploratory at this time (p=.0061)
- Majority of patients with brain mets died of non-neurologic causes, causes not influenced by RSR-13 – and there was a large number of undistinguished deaths
- Steroid use comparable in both treatment arms

FDA concerns with RSR-13:

- Given that there is no apparent advantage in response rate in the brain with RSR-13, WBRT, and oxygen vs. WBRT/oxygen, there does not appear to be a contribution of RSR-13 to tumor response.
- The designation of CR/PR was given irrespective of the appearance of a new brain parenchymal lesion
- No statistically significant difference between control and RSR-13 in:
  - Time to radiographic tumor progressions
  - Time to clinical tumor progression
  - Quality of life

- More than 90% of patients in both arms received steroids
- Response duration cannot be assessed since confirmatory imaging studies were not required.

FDA View of RSR-13 Side Effects

Measurement	Control n=264	RSR-13 n=268
Hypoxemia	4%	41%
Hypotension`	1%	13%
Vomiting	17%	38%
Nausea	30%	47%
Headache	33%	47%
Fatigue	43%	49%
Anemia	5%	12%
Taste perversion	4%	12%

An FDA statistician argued that the breast cancer subset was questionable because it has several problems, including:

- Small size – only 21% of the study population.
- The sample was from a single study.
- Post hoc, exploratory analysis.
- Imbalances possibly influenced the treatment effect.

The statistician also pointed out that the results from a single study are not always persuasive. She said inherent variability may produce a positive trial by chance (p=.05 means 1 in 40 studies will be a false positive, statistically).

The Panel Perspective

Among comments by panel members before the vote were:

- "There probably is something of value going on here… but is it enough to change the way we practice?…The company has another drug in the population of interest. If we decide to proceed today, what happens to that trial? The answer is that trial will not accrue, and we will never know an answer based on more substance than what we have today."
- "The ongoing study will be doomed if we over-interpret this study…and it would be an over interpretation… Reading too much into this data is wrong."
- "I know even small results can be significant to a patient or a few patients. Yet, I think these results are too preliminary, and I really think we should wait for the other trial, which has already slowed down because this drug came before the FDA."
- "If we approve, the ongoing trial is dead…And if we don't, it still may be."
- "Based on the data, I think there are too many questions with the post hoc aspect and the non-pre-specified subset."
- "I also have questions on efficacy from the data as presented…There were problems with methodology; no control for dexamethasone; >10% of scans were missing; and, of those missing scans, survival was in favor of control rather than the experimental arm."

QUESTION: Do the observed survival results from this single study in the subgroup of patients with breast cancer metastatic to the brain represent substantial evidence of RSR-13 efficacy in this subgroup?

VOTE: 1 yes (the chair), 15 no

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