Poster 657
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Abequolixron, a first-in-class oral immunotherapy targeting the liver-X receptor, in combination with docetaxel in recurrent advanced/metastatic non-small cell lung cancer

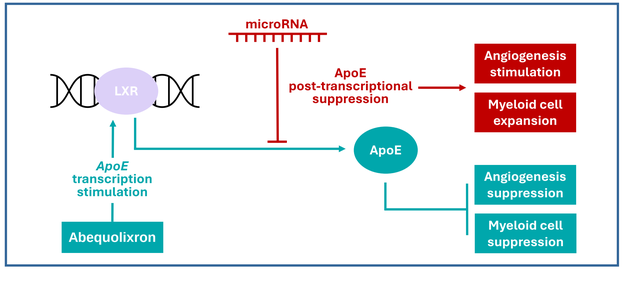
Monica M. Mita,[1] Alain C. Mita,[1] Pratibha Desai,[2] Eugenia Girda,[3] Erika Hamilton,[4] Daniel Johnson,[5] Melissa Johnson,[6] Sudhir Manda,[7] Abdul Rafeh Naqash,[8] Alexander Philipovskiy,[9] Karen L. Reckamp,[1] Erin L. Schenk,[10] Foster Gonsalves,[11] Kimberly Hoffman,[11] Steve Kaesshaefer,[11] Narayana Lebaka,[11] Michael Szarek,[11] Robert Wasserman,[11] Gerald S. Falchook.[12]

Inspirna

Introduction

- Apolipoprotein E (ApoE) was identified by the RNA-DRIVEr™ platform to be a microRNA-regulated tumor suppressor.[1]
- ApoE impedes cancer progression by inhibiting tumor angiogenesis and the expansion of myeloid-derived suppressor cells (MDSCs).[1,2]
- The Liver-X nuclear receptor (LXR) is the key transcriptional activator of ApoE gene expression and therefore represents an attractive target to reverse ApoE silencing in cancer.[3]
- RGX-104 (abequolixron) is an oral, first-in-class, small-molecule LXR agonist that can potently activate expression of ApoE via the LXR-β nuclear receptor (Fig 1).[4]

Figure 1. Abequolixron / ApoE activity in cancer



Phase 1/2b dose escalation and expansion study (RGX-104-001) key background[4-7]

- Dose escalation cohorts with abequolixron as monotherapy, and dose expansion cohorts as monotherapy and in combination with docetaxel.
- Included patients with relapsed / refractory solid tumors, as well as tumor-specific dose expansion cohorts.

Abequolixron monotherapy

- Dose escalation (n=26): abequolixron monotherapy (3 + 3 design) with 5 dose cohorts (abequolixron 120 mg once-daily to 200 mg twice-daily [BID]).
- Abequolixron was well tolerated: neutropenia was the most common treatment-related adverse event (TRAE). There were no treatment-related discontinuations or immune-related AEs. No maximum tolerated dose was reached.
- Clinical activity was observed in BID dosing cohorts, including 1 partial response (PR).
- Pharmacodynamic observations (e.g., induction of ApoE expression, depletion of MDSC) were in line with the mechanism of action.

Abequolixron + docetaxel

- Taxanes promote MDSC expansion by inducing expression of inflammatory cytokines, such as chemokine ligand 2 (CCL2), resulting in acquired taxane resistance.[8-12]
- Abequolixron + docetaxel, is highly efficacious in a mouse tumor model known to activate CCL2 in response to docetaxel.[9]
- Dose escalation in solid tumors (n=11): 2 PRs (melanoma; head and neck squamous cell carcinoma).
- Dose expansion in small cell lung cancer (n=12): 1 PR and 5 stable disease (SD).
- Dose expansion in non-small cell lung cancer (NSCLC): described in this poster.

Study rationale

- Docetaxel remains a standard of care (SOC) for 2nd/3rd-line advanced / metastatic NSCLC.[13]
- In a Phase 3 trial (REVEL), in patients with Stage IV NSCLC, 2nd-line docetaxel (in the non-squamous population) was associated with an overall response rate (ORR) of 15% and median progression-free survival (mPFS) of 3.7 months.[14]
- In a Phase 3 study (TROPION-LUNG01), in patients previously treated for advanced or metastatic NSCLC, docetaxel (in the non-squamous population) was associated with an ORR of 12.8%, mPFS of 3.7 months and median duration of response (mDOR) of 5.6 months.[15]
- MDSCs are associated with resistance to both checkpoint inhibitors (CPIs) and chemotherapy, providing a rationale for combining abequolixron with docetaxel.

Methods

Key eligibility criteria

- Non-squamous, NSCLC; metastatic (Stage 4) or locally advanced (Stage 3B) and unresectable.
- Had progressive disease (PD) after CPI and platinum-based chemotherapy and/or targeted agents (Table 1).
- (Neo)-adjuvant taxanes allowed as long as a > 6-month progression-free interval since the last taxane dose.
- Measurable disease by Response Evaluation Criteria in Solid Tumor (RECIST) version (v) 1.1.
- Eastern Cooperative Oncology Group (ECOG) ≤ 1.
- Treated brain metastases without evidence of new or enlarging lesions.

Study treatment
- Abequolixron (120 mg BID for 5/7 days continuously) and docetaxel (35 mg/m^2 weekly x 3 on a 28-day cycle).

Primary objectives
- Estimate the antitumor activity and characterize the safety profile of abequolixron in combination with docetaxel.

Secondary objective
- Evaluate the pharmacokinetic profile of abequolixron.

Endpoints
- Efficacy endpoints were ORR, PFS, and DOR per RECIST v 1.1 (Investigator assessment).
- Safety endpoints determined using Common Terminology Criteria for Adverse Events v 4.03.

Results

Table 1. Baseline characteristics (n=21)

Age	n (%)
Years (median)	65
Race	
White	15 (71)
Black or African American	3 (14)
Asian	2 (10)
Other	1 (5)
Gender	
Female	9 (43)
Male	12 (57)

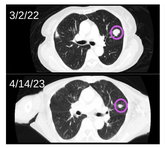
ECOG	
0	9 (43)
1	12 (57)
Prior lines of therapy	**n (%)**
1	15 (71)
2	6 (29)
Prior treatment therapies	
CPI + platinum-based	18 (86)
Targeted + platinum-based	2 (10)
CPI + platinum-based + targeted	1 (5)

Open database August 5, 2024.

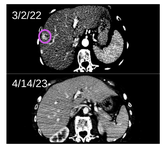
Results - efficacy

Case study: PR in patient with CPI-resistant NSCLC

- 67-year-old female; prior 1st-line pembrolizumab / carboplatin / pemetrexed; best response of PD.
- Initial PR at Week 16 (40% reduction in target lesions) with abequolixron + docetaxel.
- Confirmed PR at Week 20 scans (57% reduction of target lesions).
- Maximum shrinkage (63%) of target lesions (including disappearance of target liver lesion) at Week 56.
- Patient remained on study until PD at Week 65.



Left upper lobe nodule

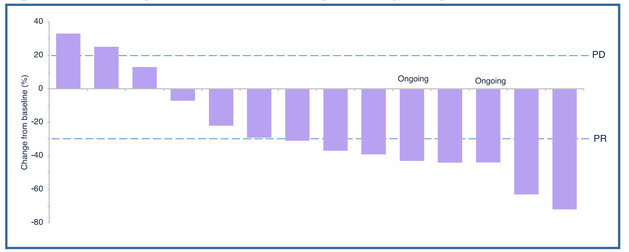


Liver, right hepatic mass

- The ORR in the intent-to-treat (ITT) population (n=21) was 38%, and 53% in the evaluable population* (n=15).
- The mDOR was 5.8 months.
- ORR (both ITT and evaluable) markedly exceeded that observed with recently reported SOC docetaxel-based regimens, and mDOR was comparable.
- Long-term follow-up data (not shown) indicate that 6/21 (~29%) patients were alive at 1 year or later from the start of dosing, with 9 patients still potentially informative.

* Evaluable patients must have received ≥ 66% of first cycle doses with an on-treatment scan. Remaining patients (n=6) not evaluable for efficacy due to insufficient dosing and/or never received on treatment scan.

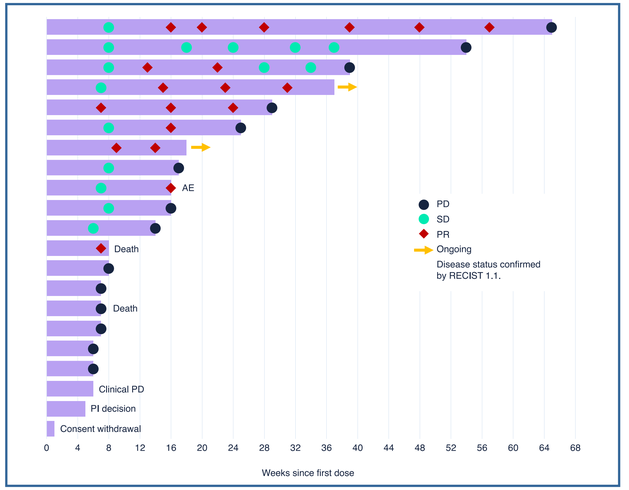
Figure 2. Best response in all evaluable patients (n=15*)



* One patient (not shown) was evaluable but one of the target lesions was not assessed on the first on-treatment scan. However, the overall response was PD due to radiographic progression in a non-target lesion.

- Of the evaluable population, 8 patients had PR (5 of which were confirmed), 4 patients had SD, and 3 patients had PD.

Figure 3. Duration of treatment response in all patients (n=21)



Author affiliations: 1. Cedars-Sinai Medical Center, Los Angeles, CA. **2.** Comprehensive Hematology Oncology, St. Petersburg, FL. **3.** Rutgers Cancer Institute of New Jersey, New Brunswick, NJ. **4.** Sarah Cannon Research Institute, Nashville, TN. **5.** Ochsner MD Anderson Cancer Center, New Orleans, LA. **6.** Tennessee Oncology (SCRI-N), Nashville, TN. **7.** Arizona Oncology Associates (USO), Tucson, AZ. **8.** Stephenson Cancer Center (University of Oklahoma), Oklahoma City, OK. **9.** Florida Cancer Specialists & Research Institute, Sarah Cannon Research Institute, Lake Mary, FL. **10.** University of Colorado - Anschutz Medical Campus, Aurora, CO. **11.** Inspirna, Inc., Long Island City, NY. **12.** Sarah Cannon Research Institute at HealthONE, Denver, CO.

Figure 4. Change in tumor size (n=17)

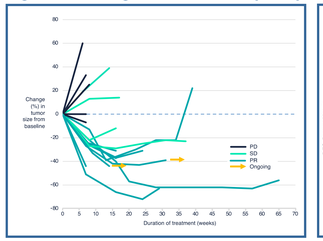
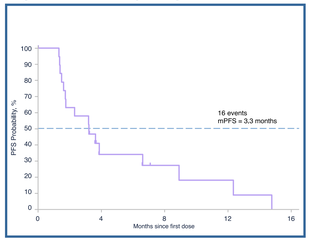
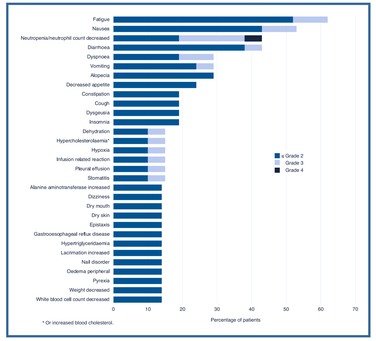


Figure 5. mPFS (n=21)



Results - safety

Figure 6. TEAEs in > 10% of all patients (n=21)



- Abequolixron + docetaxel was well tolerated.
- The most common Grade ≤ 2 treatment-emergent adverse events (TEAEs) were fatigue (52%), nausea (43%) and diarrhea (38%) (Figure 6).
- There were no episodes of febrile neutropenia.
- The most frequent Grade ≥ 3 TEAE was neutropenia (14%).
- Other Grade 3 TEAEs (each occurring in a total of 2 patients) were fatigue, nausea, dyspnea, fall, hypertension and pneumonia.
- There were no Grade 4 TEAEs that occurred in more than 1 patient.

Conclusion

- The combination provides promising preliminary efficacy in 2nd/3rd-line in non-squamous NSCLC, with an ORR of 38% (ITT) and a mDOR of 5.8 months.
- ORR (both ITT and evaluable) markedly exceeded that observed with recently reported SOC docetaxel-based regimens, and mDOR was comparable.
- Abequolixron + docetaxel was well tolerated. The frequency of Grade ≥ 3 neutropenia was lower than that observed with docetaxel monotherapy in prior Phase 3 studies.[14,15] This may be due to differences in dosing regimens.
- A Phase 2 randomized trial is planned in patients with recurrent advanced / metastatic NSCLC after previous treatment with CPI / platinum-based therapy.

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