Antifungal Drugs to Address Unmet Medical Need

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The Rare Fungal Disease Company

Background on Olorofim

- Olorofim
  - Is a novel mechanism candidate antifungal drug[1]
    - It inhibits DHODH (pyrimidine biosynthesis pathway)
  - It shows broad microbiologic activity vs. mould fungi
    - Low MICs vs. *Aspergillus* spp., *Lomentospora prolificans, Scedosporium* spp., *Fusarium* spp., *Coccidioides* spp., and others
    - Fungicidal effects in vitro (*Aspergillus*) and in vivo (*Coccidioides*)[2,3]
  - Dosed by mouth (30-mg tablet), it has FDA Breakthrough Therapy Designation based on
    - "preliminary clinical evidence indicating that it may …
    - demonstrate substantial improvement over existing therapies …
    - on one or more clinically significant endpoints."
  - Now in an open-label Phase 2 study (NCT03583164) of mould IFD[4] in patients with limited treatment options

1. Oliver JD et al. (2016). "F901318 represents a novel class of antifungal drug that inhibits dihydroorotate dehydrogenase." PNAS USA 113: 12809-14.
2. du Pre, S., et al. (2018). "Effect of the Novel Antifungal Drug F901318 (Olorofim) on Growth and Viability of Aspergillus fumigatus." AAC 62(8): e00231-18.
3. Wiederhold, N. P., et al. (2018). "The Orotomide Olorofim Is Efficacious in an Experimental Model of Central Nervous System Coccidioidomycosis." AAC 62(9): e00999-18.
4. IFD = Invasive Fungal Disease

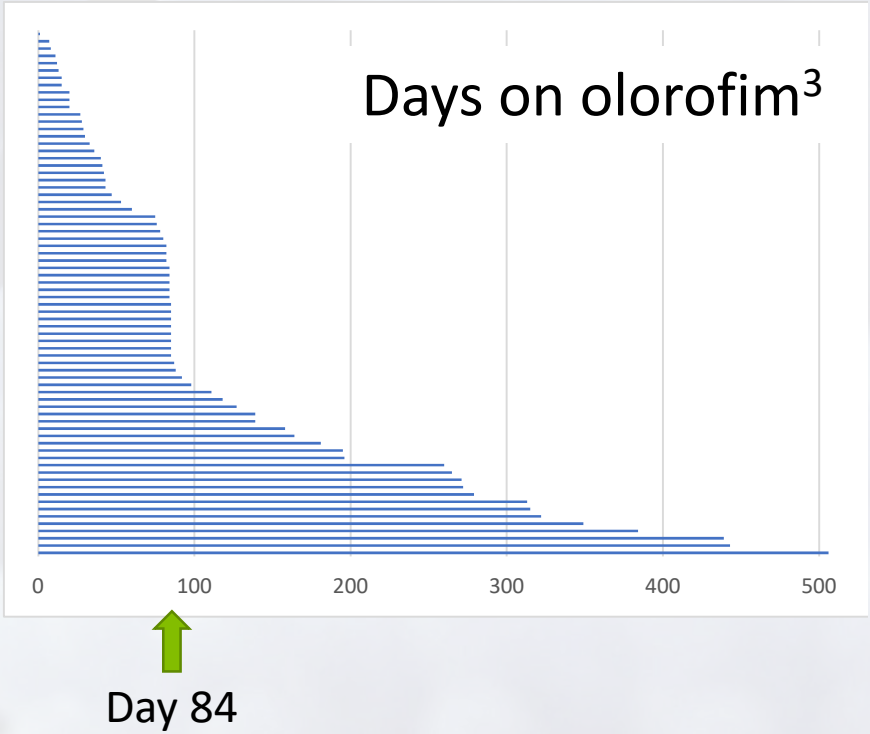
Endpoints: A trial design problem

- Day 42 All-Cause Mortality is OK for acute pulmonary IA[1]
  - But it is a blunt tool that gets entangled with underlying disease[2]
  - It doesn't work at all for infections that progress inexorably but slowly
- EORTC-MSG defined an Overall response endpoint[3]
  - Overall is built from clinical, radiological, & mycological responses
  - Overall Success logically requires improvement on all 3 sub-elements
  - Failure is likewise obvious
- But, the category of Stable is defined as a Failure
  - A patient with a Clinical Response but with < 25% radiologic improvement is scored as Failure-Stable
- This usually works for pulmonary IFD (especially IA)
  - But, extrapulmonary IFD can take months to respond
  - And even pulmonary IFD can sometimes be slow
  - Stable is the key prelude to Success: it enables further chemotherapy, transplantation, etc.

1. IA = Invasive Aspergillosis
2. Wingard, J. R., et al. (2008). "Changes in causes of death over time after treatment for invasive aspergillosis." Cancer 112(10): 2309-2312.
3. Segal BH et al. (2008). "Defining responses to therapy and study outcomes in clinical trials of invasive fungal diseases: Mycoses study group and European Organization for Research and Treatment of Cancer consensus criteria." Clin Infect Dis 47(5): 674-683.

Some invasive mould infections require lengthy therapy

- Olorofim Phase 2: Proven IFD[1]
  - ~75% highly immunosuppressed[2]
  - All with limited treatment options
  - Months of prior therapy in some
- Main phase duration: 84 days
  - Adequate for some, but not all
  - Extended dosing provided for infections that are responding but need more therapy for a complex or challenging infection

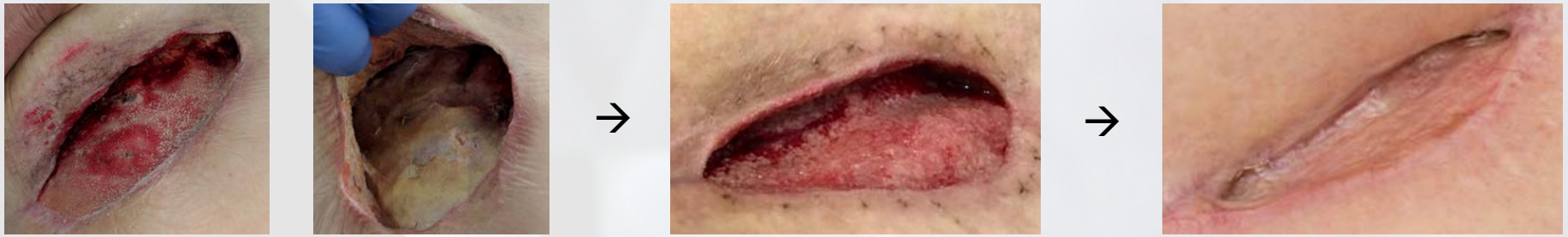


- Stable at Day 84
  - Has been a common finding
  - Has been the prelude to ultimate Success at end of therapy
- A case is instructive…

1. Probable IA per EORTC-MSG 2008/2019 is also permitted.
2. Hematologic malignancy, Hematopoietic Stem Cell Transplant (HSCT), or Lung Transplant
3. F2G, Limited, data on file: Duration of dosing from the ongoing Phase 2 study (clinicaltrials.gov: NCT03583164) as of 27 July 2020.

Chest-wall *L. prolificans* infection

- Aug ’18: 49-year-old healthy woman, breast augmentation
- Oct ’18: *L. prolificans* infection of right-sided breast implant
  - Spread to adjacent cartilage, sternum, and 4th-6th ribs
  - Voriconazole, terbinafine, miltefosine, posaconazole, and anidulafungin serially and in combination along with repeated debridement, hyperbaric oxygen
  - **The infection remained uncontrolled; fungal colonies seen in wound**
- Olorofim monotherapy begun 29 Nov 18
  - Day 84: EORTC-MSG Clinical Response of *Success-Partial* but Overall Response of ***Failure-Stable*** because of lag in radiologic improvement
  - Gradual wound closure over 322 days of therapy



Day -9 Day -5 Day 140 Day 243

Chen 2020 ECCMID Abstract #2585- A case of *L. prolificans* treated with the novel antifungal olorofim
See also Tio 2020 ECCMID Abstract #118: Olorofim for a case of severe disseminated L. prolificans infection

Conclusions

- Day 42 All-Cause mortality is but has limitations
- EORTC-MSG defined an Overall response endpoint[1]
  - It works well at Day 42 or 84 for most pulmonary IFD
  - It does not work for extrapulmonary (& some lung) infections)
  - Some infections take months to response radiologically
  - Staying alive to reach that point is a Success
- It is important that Stable be defined as a Success
  - Could argue that it "comes out in the wash" to continue to define Stable as Failure
  - But the inconsistency is inconsistent with clinical practice
    - Common problem: ~20-40% Stable-Failure rate in recent trials[2,3]
    - Scoring as Failure sends the wrong message to clinicians & payors: Stable can include substantial clinical improvement and better quality of life
    - Other causes of death arise during the 6-18 months needed to cure some infections … improved quality of life may be lost to the label of "Stable"

1. Segal BH et al. (2008). "Defining responses to therapy and study outcomes in clinical trials of invasive fungal diseases: Mycoses study group and European Organization for Research and Treatment of Cancer consensus criteria." Clin Infect Dis 47(5): 674-683.
2. Marty, F. M., et al. (2018). "Isavuconazole for treatment of invasive fungal diseases caused by more than one fungal species." Mycoses 61(7): 485-497.
3. Cornely, O. A., et al. (2018). "Isavuconazole for treatment of rare invasive fungal diseases." Mycoses 61(8): 518-533.