Overview of 2019 CDER Drug Approvals in Hematology/Oncology

Michael E. Menefee, MD
Medical Officer
Office of Hematology and Oncology Products

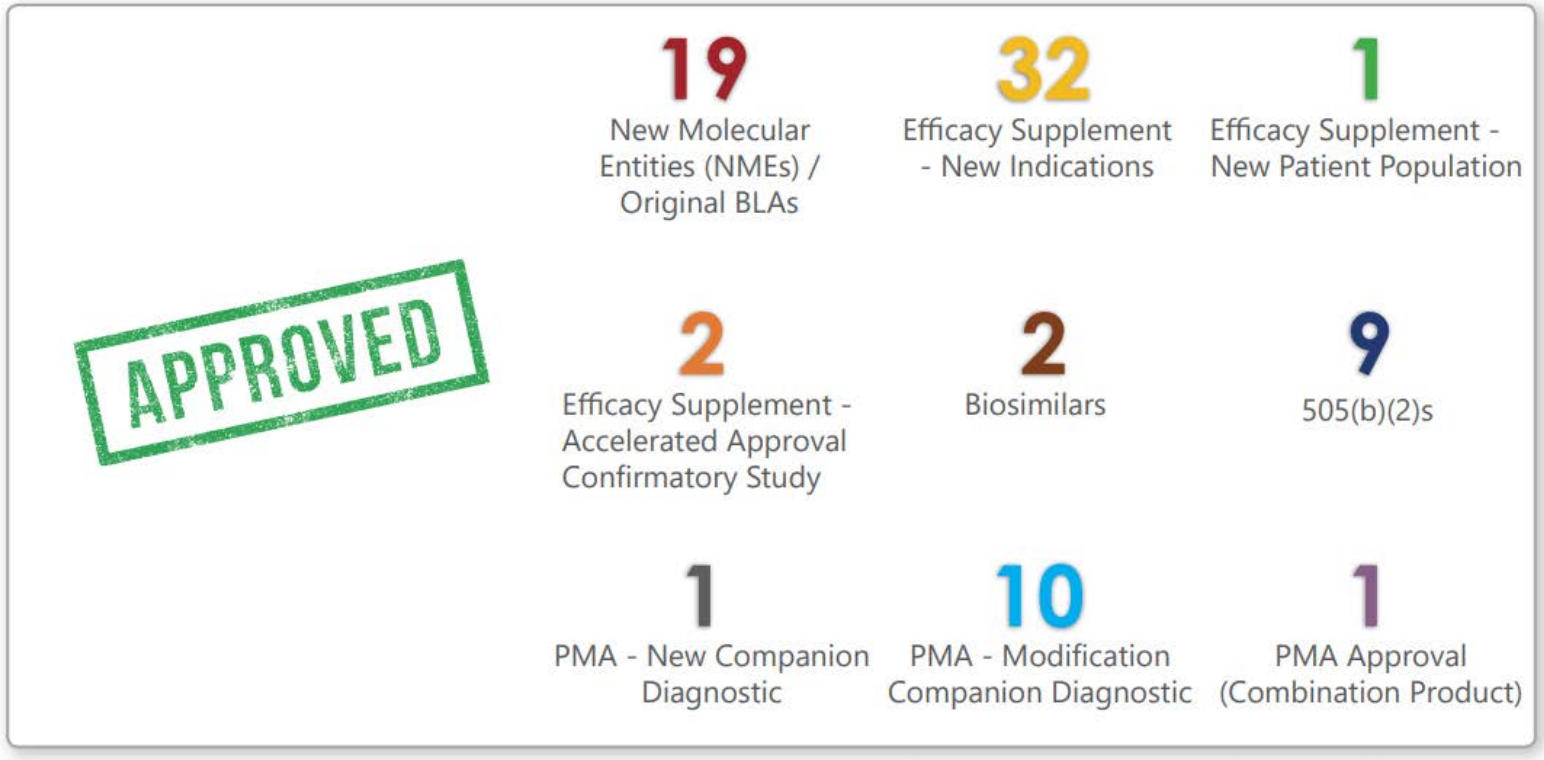
Disclosures

- I have no financial interests to disclose.
- I will not discuss off-label use of unapproved agents.

Speaking “FDA”

- NME: New Molecular Entity
  - A drug that contains an active component (ingredient) that has never been approved by the FDA or marketed in the US.
- MOA: Mechanism of Action
  - How a drug works to slow the cancers growth
- ORR: Overall Response Rate
  - The percentage of patients who had meaningful tumor shrinkage
- DOR: Duration of Response
  - How long did the response last before the tumor started to grow again
- Companion Diagnostic
  - a medical device, often an in vitro device, which provides information that is essential for the safe and effective use of a corresponding drug or biological product
- Accelerated Approval
  - Conditional approval, requiring additional studies to confirm the clinical benefit or safety

2018 Oncology Approvals



* Approval numbers reflect approvals from CBER, CDER and CDRH

2019 OHOP New Drug Approvals

- New Molecular Entities (NMEs): 10
  - Solid tumors: 6
  - Hematologic malignancies: 3
  - Benign Hematology: 1

Erdafitinib (Balversa)

- Mechanism of Action (MOA): Fibroblast Growth Factor Receptor (FGFR) kinase inhibitor

- Indication: locally advanced or metastatic urothelial carcinoma, with susceptible FGFR3 or FGFR2 genetic alterations, that has progressed during or following platinum-containing chemotherapy

- Patients are selected for therapy with erdafitinib based on an approved companion diagnostic

- Dosing: 8 mg by mouth once daily with or without food
  *Dose may be increased to 9 mg in patients with serum phosphate levels below the target range.

Erdafitinib (Balversa)

- Approval was based on data from a cohort of 87 patients enrolled on Study BLC2001, a multicenter, open-label, single-arm trial evaluating patients with:
  - locally advanced or metastatic urothelial carcinoma that had progressed on or after at least one prior chemotherapy
  - certain FGFR3 gene mutations or FGFR2 or FGFR3 gene fusions.

- Accelerated approval was granted based on:
  - overall response rate (ORR) of 32.2%
  - duration of response (DOR) of 5.4 months

- Side Effects: Ocular toxicity with retinopathy or retinal detachments resulting in visual field defects in 25% of patients.

Alpelisib (Piqray)

- MOA: Phosphatidyl Inositol-3-kinase (PI3K or PIK3CA) inhibitor

- Indication: ER or PR+, HER2-negative, **PIK3CA-mutated**, advanced or metastatic breast cancer in combination with fulvestrant after disease progression on at least one endocrine(hormonal)-based therapy

- Patients are selected for therapy with alpelisib based on an approved companion diagnostic (CTC plasma-based diagnostic)

- Dosing: 300 mg by mouth twice daily with food

Alpelisib (Piqray)

- Approval was based on SOLAR-1, a phase 3, randomized, double-blind, placebo-controlled trial fulvestrant with or without alpelisib in 572 patients.

- Results (PFS):
  - Alpelisib + fulvestrant: 11 months
  - Placebo + fulvestrant: 5.7 months

    (HR 0.65; 95% CI: 0.50, 0.85; p=0.001)

- Side Effects: Hyperglycemia (elevated blood glucose)

Selinexor (Xpovio)

- MOA: Selective Inhibitor of Nuclear Export (SINE)

- Indication: For patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies and whose disease is refractory to at least 2 proteasome inhibitors, at least 2 immunomodulatory agents, as well as an anti-CD38 monoclonal antibody (i.e. heavily pretreated).

- Dosing: 80 mg by mouth daily on days 1 and 3, weekly, in combination dexamethasone 20 mg

Selinexor (Xpovio)

- Accelerated approval based on a prespecified subgroup analysis of 83 patients of the 122 patients enrolled in Part 2 of the STORM trial, a multicenter, single-arm, open-label study of patients with RRMM who had previously received three or more anti-myeloma treatment regimens.

- Results:
  - ORR: 25.3%
  - DOR: 3.8 months

Darolutamide (Nubeqa)

- MOA: Androgen Receptor Inhibitor
- Indication: for the treatment of patients with non-metastatic castration-resistant prostate cancer.
- Approval was based on ARAMIS, a multicenter, double-blind, placebo-controlled study in 1,509 patients with non-metastatic castration resistant prostate cancer.
- Patients were randomized (2:1) to receive either 600 mg darolutamide orally twice daily (n=955) or matching placebo (n=554).

Darolutamide (Nubeqa)

- Results:
  - PFS: Darolutamide 40.4 months
    Placebo 18.4 months

  OS Data: not available

- Notable side Effects in Darolutamide arm:
  - Ischemic heart disease 4.3%
  - Heart failure 2.1%

  * More common than placebo group

Pexidartinib (Turalio)

- MOA: Multikinase inhibitor (**Colony stimulating factor 1 receptor**, FLT-3, c-kit)

- Indication: for adult patients with symptomatic tenosynovial giant cell tumor associated with severe morbidity or functional limitations and not amenable to improvement with surgery.

  **First drug approved for this disease*

- Dosing: 400 mg by mouth twice daily on an empty stomach

Pexidartinib (Turalio)

- Approval was based on durable ORR observed in an international, multicenter, randomized (1:1), double-blind, placebo-controlled trial that enrolled 120 patients with TGCT not amenable to surgical resection
- Results:
  - ORR (after 25 weeks of Tx):
    - 38% vs 0% (15% Complete responses)
    - Radiographic response and improved joint mobility/functionality

Entrectinib (Rozyltrek)

- MOA: Inhibitor of ROS1 and Neurotrophic tyrosine receptor kinase (NTRK) gene fusions

- Indications:
  - accelerated approval to entrectinib for adults and pediatric patients 12 years of age and older with metastatis solid tumors that have a *NTRK* gene fusion and without other treatment options.
  - adults with metastatic non-small cell lung cancer (NSCLC) whose tumors are *ROS1*-positive

- Dosing: 600 mg by mouth once daily

Entrectinib (Rozyltrek)

- Approval was based on investigations of *NTRK*-positive tumors in:
  - 54 adult patients who received entrectinib at various doses and schedules in one of three multicenter, single-arm, clinical trials: ALKA, STARTRK-1 and STARTRK-2 with 94% received entrectinib 600 mg orally once daily.
  - 51 patients with ROS1-positive, metastatic NSCLC received entrectinib at various doses and schedules in the same three trials with 90% receiving entrectinib 600 mg orally once daily.

Entrectinib (Rozyltrek)

- Results:
  - NTRK
    - ORR: 57%
    - DOR: 6 months or longer for 68%
  - ROS1
    - ORR: 78%
    - DOR: 12 months or longer for 55%
- Cancer types (NTRK)
  - sarcoma, NSCLC, mammary analogue secretory carcinoma, breast, thyroid, and colorectal
- Side Effects
  - Heart failure, CNS, skeletal fractures, liver toxicity, Visual disorders, and EKG changes

Fedratinib (Inrebic)

- MOA: Janus Kinase 2 (JAK2) inhibitor
- Indication: for adults with intermediate-2 or high-risk primary or secondary myelofibrosis (MF).
- Dosing: 400 mg by mouth with or without food

Fedratinib (Inrebic)

- Approval was based on JAKARTA, a double-blind, randomized, placebo-controlled study in 289 patients with MF with splenomegaly. Patients were randomized to receive either INREBIC 500 mg (N=97), 400 mg (n=96) or placebo (n=96) once daily for at least 6 cycles.

- Primary endpoint: proportion of patients achieving ≥35% reduction from baseline in spleen volume at the end of cycle 6 measured by MRI or CT

- Results:
  - 400 mg: 37%
  - Placebo: 1%

  - DOR: 18.2 months

More Information

- https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm

FDA U.S. FOOD & DRUG ADMINISTRATION

Thank you


FDA
U.S. FOOD & DRUG
ADMINISTRATION