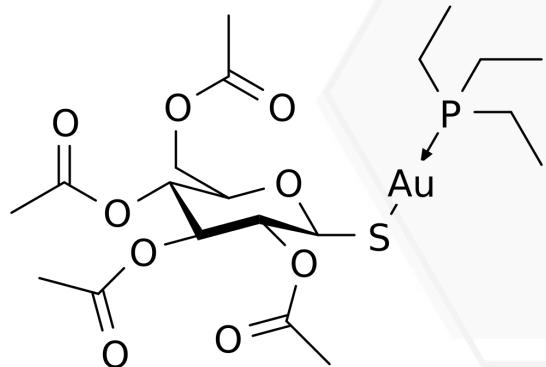


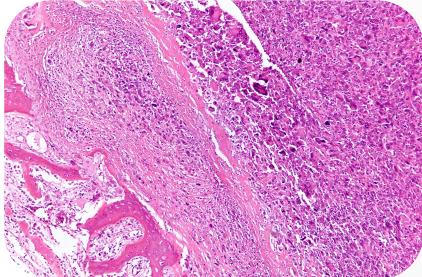
Comparative Oncology: Osteosarcoma



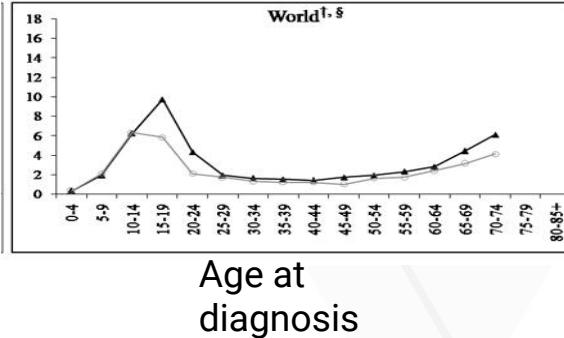
Arely Balderas, Stephanie Lee,
Kitty Liu, Lisa Rusali,
Kate Tanha, Jeffrey Zhong

Osteogenic Sarcoma

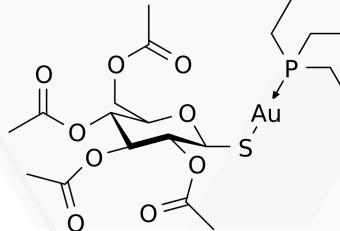
Osteosarcoma is an orphan disease that results in tumors in the bones.



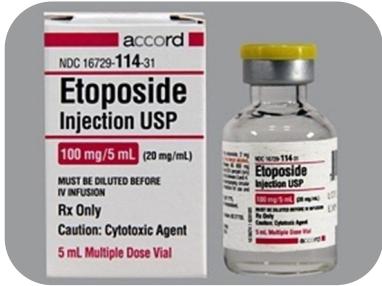
Rate per 1,000,000



Age at diagnosis



Current Treatment

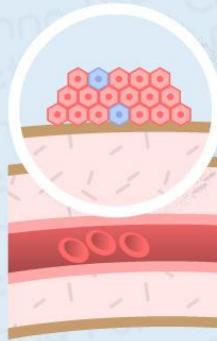


Current treatment involves chemotherapy and surgery, often limb amputation.

The disease will be categorized into a stage

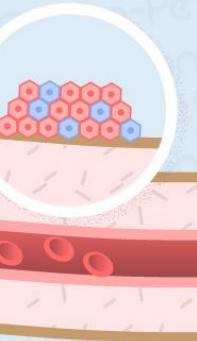
These stages include:

Stage I



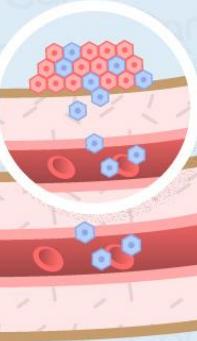
low-grade tumors
without evidence
of metastasis

Stage II



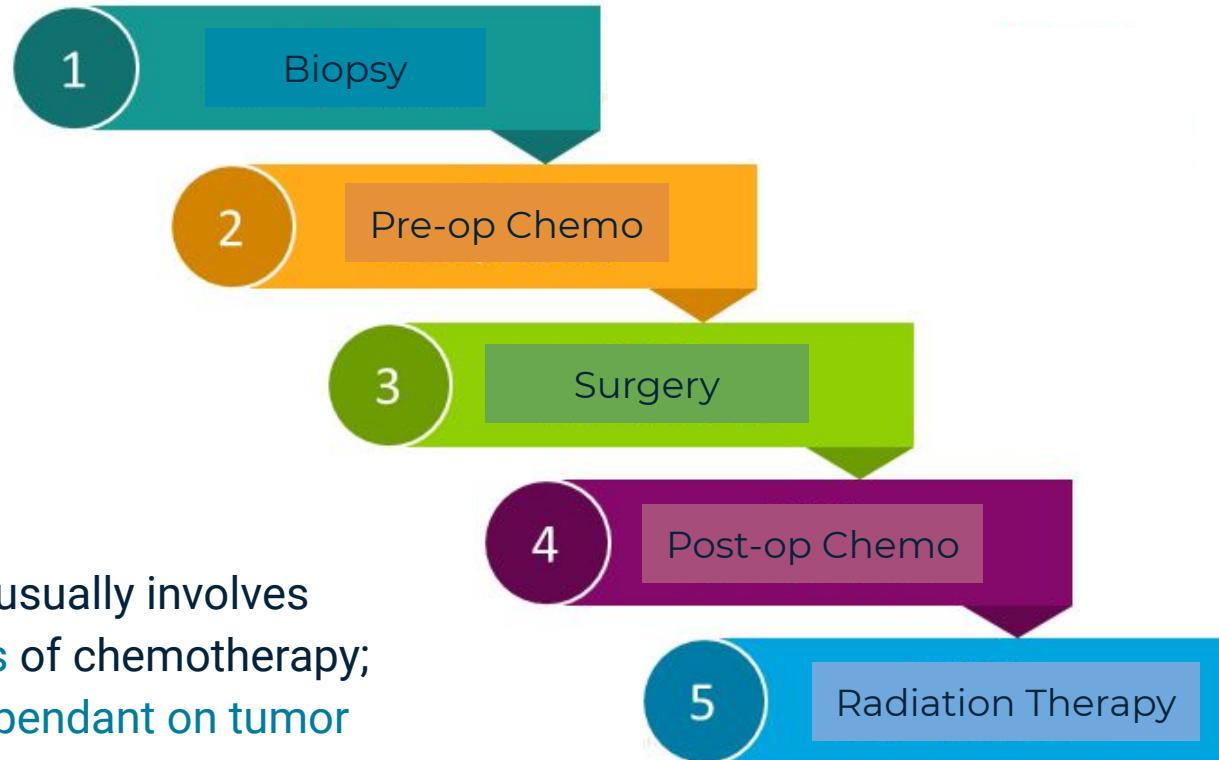
high-grade
tumors without
metastasis

Stage III



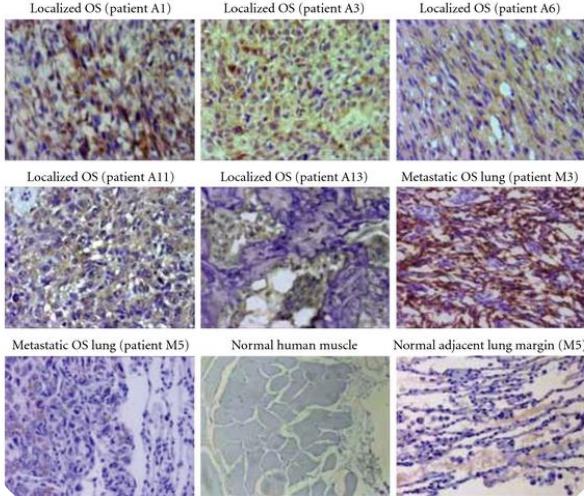
metastasis has
occurred

Steps for Treatment



Treatment usually involves several rounds of chemotherapy; surgery is dependant on tumor size.

Addressable Market



- **Metastatic Osteosarcoma Patients**
 - 15–20% at diagnosis
 - 15–30% long term survival
- **Localized Osteosarcoma Patients**
 - 80–85% at diagnosis
 - 60–80% survival over 5 year period
- **Total: 800 - 900 patients → 850 average**
 - 80-85% localized osteosarcoma → 82.5% average
- **$850 * 82.5\% = 701 \text{ patients}$**

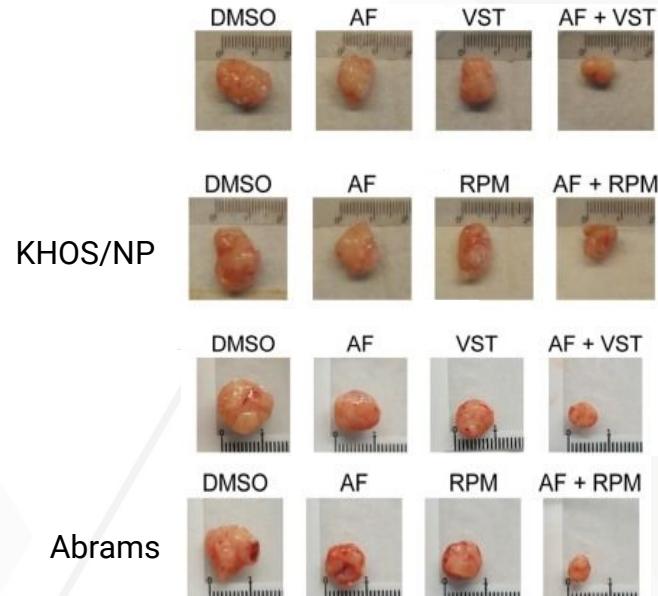


There are realistically **700 patients** on the market.

R&D Analysis: Stage 1 (Discovery)

- Primary drug screen
 - Screen FDA-approved drug library for growth inhibition
 - Auranofin showed specificity for OS in both human + canine cell lines
- *In silico* drug-drug interaction testing
 - Vorinostat + rapamycin showed synergistic effect
 - All 3 drugs well tolerated
- Proof-of-principle studies
 - *In vivo* tumor growth assay in mice
 - Decrease in Ki67 → less cell proliferation
 - Increase cleaved caspase-3 → more apoptosis

Auranofin + vorinostat/rapamycin significantly suppressed OS tumor growth.

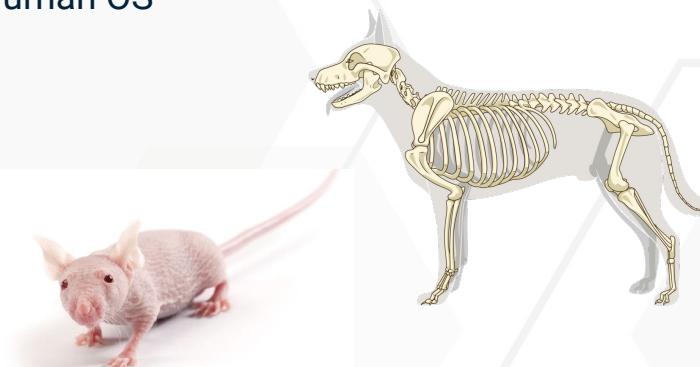


R&D Analysis: Stage 2 & 3 (Preclinical + Clinical Trials)

- Preclinical testing complete: murine + canine

- Currently in phase 1 trial in canine patients
 - Will assess maximum tolerated dosage
 - No phase 1 in humans because of potential heavy metal toxicity of auranofin
 - Also considered during original indication trials
 - Canine OS is similar to human OS

Preclinical testing in mouse and dog models is complete, progressing to Phase I clinical trials in canines.



R&D Analysis: Stage 3 (Clinical Trials)

Phase	Purpose	No. of participants	Notes
Phase 0/Phase I	Pharmacokinetics	~10 people	In-progress
Phase II	Assess efficacy and side effects	~20-30 patients	Determines drug's efficacy
Phase III	Assess efficacy, effectiveness and safety	~35-40 patients	Determines drug's therapeutic effect
Phase IV	Post-marketing surveillance	~350 patients	Monitors drug's long-term effects

Phases II - IV are still needed; costs are limited to Phases II and III.

Reference Pricing

Type of Surgery	Biopsy	Wide-Excision Surgery	Limb Removal/Amputation	Rotationplasty (OS in Femur Only)
Cost Breakdown	<ul style="list-style-type: none"> Fine Needle Aspiration: \$1,060 Open Biopsy: \$4,313 	<ul style="list-style-type: none"> Needed in 80% - 90% of patients after neoadjuvant chemo <ul style="list-style-type: none"> Tumor Removal: ~\$10k Average 7 day hospital stay: \$21k Endoprosthesis: \$51k OR Reconstruction: \$28k - \$58k 	<ul style="list-style-type: none"> Amputation: \$20k - \$60k (not including PT costs) <ul style="list-style-type: none"> Average 57 day hospital stay: \$171k Reconstruction: \$28k - \$58k 	<ul style="list-style-type: none"> Knee Replacement Surgery: \$49.5k <ul style="list-style-type: none"> Average 7-day hospital stay: \$21k Prosthetics: \$5k-\$50k
Cost	~\$1k - \$4.5k	~\$59k - \$89k	~\$215k - \$290k	~\$76k - \$121k

Biopsy and wide-excision surgery are required in all patients; amputation and rotationplasty may be required depending on tumor size/aggression.

Reference Pricing

Therapy	Chemotherapy	AF + VST	AF + RPM
Cost Breakdown	<ul style="list-style-type: none"> 15 day cycle, repeat every 21 days <ul style="list-style-type: none"> Dacarbazine: 250mg/m²/day CIV for 4 days → \$114.00 Doxorubicin: 15mg/m²/day CIV for 4 days → \$12.40 Ifosfamide: 2000mg/m²/day CIV for 3 days → \$200.03 Mesna: 2000mg/m²/day CIV for 4 days → \$2,483.60 	<ul style="list-style-type: none"> Significant tumor reduction generally found within 2.2 months <ul style="list-style-type: none"> Auranofin: 6mg/day PO → \$1,316.62/month Vorinostat: 150mg/day PO → \$5,760.60/month 	<ul style="list-style-type: none"> Significant tumor reduction generally found within 2.2 months <ul style="list-style-type: none"> Auranofin: 6mg/day PO → \$1,316.62/month Rapamycin: 6mg/day PO → \$817.70/month
Total Cost	<p>\$2,810 per cycle \$14,050 in 6 months</p>	<p>\$5,596 per month \$15,570 in 2.2 months</p>	<p>\$2,134 per month \$4,696 in 2.2 months</p>

Auranofin + Rapamycin is the ideal drug combination to pursue.

Value Analysis

- **Improvements and Reduced Opportunity Cost:**
 - Traditional chemo
 - 5 cycles, 15 days each → **\$225k**
 - **Auranofin + RPM/Auranofin + VST**
 - Not in hospital → **\$225k saved + \$10.8k earned** (work)
 - **Reduced probability** of major surgery
 - 57 days, \$171k (limb amputation)
 - 7 days, \$21k (wide-excision) → **\$150k saved**
- **Average economic value: \$385.8k**
 - Market equals = $\$385.8k * 700 = \$270m$



Auranofin + Rapamycin provide a **cheaper** and **faster** therapy, with a **higher quality** of treatment.

Market Value Estimates

- **Auranofin (AF) + Rapamycin (RPM)**
 - $700 * \$4,695.50 = \$3.3m$
- **Auranofin (AF) + Vorinostat (VST)**
 - $700 * \$15,569.88 = \$10.9m$
- **Traditional Chemotherapy**
 - $700 * \$14,050.15 = \$9.8m$
- **Pricing is not sensitive**
 - Less expensive than traditional chemotherapy
 - Current therapies are dated and limited



There is a **\$3.3 million market** for Auranofin + Rapamycin.

Product Development

- **Median duration: 7.3 years**
 - Range: 5.8 - 15.2 years
 - Accelerated approval based on tumor shrinkage
 - 10% chance of success (FDA Approval Rates)
- **Cost to develop:**
 - 14.3 years of market exclusivity
 - Repurposed: higher success rates + lower R&D costs
 - 50% tax credit for expenditures (Orphan Drug Act, 2013)

Phase Success	Phase I to Phase II		Phase II to Phase III		Phase III to NDA/BLA		NDA/BLA to Approval	
	Advanced or Suspended	Phase Success						
Hematology	86	73.3%	83	56.6%	64	75.0%	50	84.0%
Infectious disease	347	69.5%	286	42.7%	150	72.7%	133	88.7%
Ophthalmology	66	84.8%	101	44.6%	60	58.3%	40	77.5%
Other	96	66.7%	116	39.7%	46	69.6%	43	88.4%
Metabolic	95	61.1%	84	45.2%	35	71.4%	27	77.8%
Gastroenterology*	41	75.6%	56	35.7%	33	60.6%	26	92.3%
Allergy	37	67.6%	40	32.5%	14	71.4%	16	93.8%
Endocrine	299	58.9%	242	40.1%	143	65.0%	107	86.0%
Respiratory	150	65.3%	196	29.1%	45	71.1%	37	94.6%
Urology	21	57.1%	52	32.7%	21	71.4%	14	85.7%
Autoimmune	297	65.7%	319	31.7%	135	62.2%	86	86.0%
All Indications	3582	63.2%	3862	30.7%	1491	58.1%	1050	85.3%
Neurology	462	59.1%	465	29.7%	216	57.4%	161	83.2%
Cardiovascular	209	58.9%	237	24.1%	110	55.5%	76	84.2%
Psychiatry	154	53.9%	169	23.7%	70	55.7%	58	87.9%
Oncology	1222	62.8%	1416	24.6%	349	40.1%	176	82.4%

Due to its status as an orphan drug, Auranofin + Rapamycin may receive expedited FDA approval with benefits.

Cost/Revenue Analysis & Pricing (Per Patient)



- Combination of AF + RPM: **\$3,735.06 per month**
 - Manufacturing cost: \$2,134.32
 - Clinical trial/Development costs: 50% of manufacturing → \$1,067.16
 - Profit: 25% of manufacturing → \$533.58

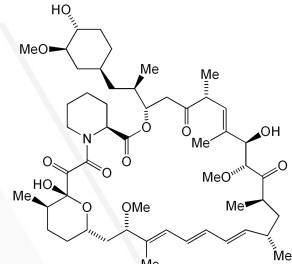
- US, Western Europe, Asia:

Phase II	\$12,291 * 100 Patients
Phase III	\$10,428 * 200 Patients
Estimated Total Cost:	\$3,319,189
Market Value	\$3,286,500

Per patient, Auranofin + Rapamycin would cost around **\$3.7k per month.**

Competition + Need for Improvement

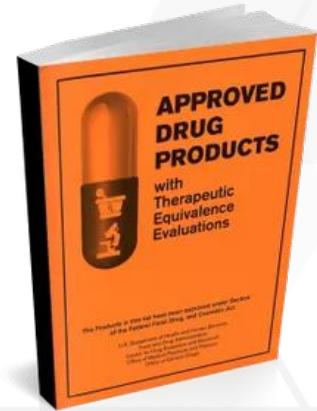
- **Chemotherapy is default treatment**
 - Most trials focus on improving current chemotherapies
 - Cyclophosphamide + Methotrexate
 - Methotrexate + Glucarpidase
 - Gemcitabine + Rapamycin
- **Auranofin + Rapamycin**
 - **Cheaper + quicker** than traditional chemo
 - **\$7,648.57 in 2.2 months vs \$12,845-15,255 in 6 months**
 - Novel approach → new mechanisms of action
 - Combination drug
 - More effective against chemoresistance tumors
 - Synergistic effect → lower dosing, fewer side effects



**Auranofin +
Rapamycin expands
the treatment options
available for OS.**

Intellectual property

- **FDA Orange Book: no unexpired patents or exclusivity**
 - Potential for utility patent
 - Novel claim: Osteosarcoma
 - Considered new combination drug with rapamycin
- **Risk if patent is rejected → not worth manufacturing**
 - No exclusivity
 - Orphan drug → greater significance if rejected



There is **no existing intellectual property conflict** for Auranofin + Rapamycin.

Market Adoption

- **Orphan drug → tax incentives, better patent protection/exclusivity, clinical research subsidies, etc.**
 - Small market size (700) → **only \$3.3 million**
 - Clinical case is strong enough for market adoption
 - Potentially **cheaper**
 - Lower price → greater incentive for insurance to pay
 - Potentially **higher efficacy**
 - Combats chemoresistant tumors
 - Less time required for treatment

With **lower prices** and **higher efficacy**,
Auranofin + Rapamycin stand to be adopted
into the market successfully.



Pursue Development?



Shorter treatment time



Shorter hospital stays



Canine model OS extremely similar to human OS



Similar competitors: longer, more costly



Reduced probability of major surgery



Auranofin + Rapamycin **should be pursued** as a treatment for osteosarcoma.

References

1. 5 Things About the Orphan Drug Act <https://www.ajmc.com/newsroom/5-things-about-the-orphan-drug-act> (accessed Jul 22, 2019).
2. 36B: Van Nes Rotation-Plasty in Tumor Surgery | O&P Virtual Library <http://www.oandplibrary.org/alp/chap36-02.asp> (accessed Jul 14, 2019).
3. Clinical Trial Evaluating Metronomic Chemotherapy in Patients With Metastatic Osteosarcoma - Full Text View - ClinicalTrials.gov
<https://clinicaltrials.gov/ct2/show/NCT03063983> (accessed Jul 22, 2019).
4. Connolly, K. M.; Stecher, V. J.; Pruden, D. J. Effect of Auranofin on Plasma Fibronectin, C Reactive Protein, and Albumin Levels in Arthritic Rats. *Annals of the Rheumatic Diseases* 1988, 47 (6), 515–521. <https://doi.org/10.1136/ard.47.6.515>.
5. Cost-utility of osteoarticular allograft versus endoprosthetic reconstruction for primary bone sarcoma of the knee: A markov analysis. - PubMed - NCBI
<https://www.ncbi.nlm.nih.gov/pubmed/28105636> (accessed Jul 14, 2019).
6. Current concepts in surgical treatment of osteosarcoma <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3872798/> (accessed Jul 14, 2019).
7. Drugs@FDA: FDA Approved Drug Products. (n.d.). Retrieved from <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>
8. Fine needle aspiration biopsy of primary bone tumors. - PubMed - NCBI <https://www.ncbi.nlm.nih.gov/pubmed/10810465> (accessed Jul 14, 2019).
9. Glucarpidase After High-Dose Methotrexate in Patients With Osteosarcoma - Full Text View - ClinicalTrials.gov
<https://clinicaltrials.gov/ct2/show/NCT03960177> (accessed Jul 22, 2019).
10. How Much Does Amputation Cost? - CostHelper.com <https://health.costhelper.com/amputation.html> (accessed Jul 14, 2019).
11. Ifex (ifosfamide) dose, indications, adverse effects, interactions... from PDR.net <https://www.pdr.net/drug-summary/Ifex-ifosfamide-2427> (accessed Jul 14, 2019).
12. Key Statistics for Osteosarcoma <https://www.cancer.org/cancer/osteosarcoma/about/key-statistics.html> (accessed Jul 9, 2019).
13. Losartan + Sunitinib in Treatment of Osteosarcoma - Full Text View - ClinicalTrials.gov <https://clinicaltrials.gov/ct2/show/NCT03900793> (accessed Jul 22, 2019).
14. Nie, Z.; Peng, H. Osteosarcoma in Patients below 25 Years of Age: An Observational Study of Incidence, Metastasis, Treatment and Outcomes. *Oncol Lett* 2018, 16 (5), 6502–6514. <https://doi.org/10.3892/ol.2018.9453>.
15. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations
https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=018689&Appl_type=N (accessed Jul 22, 2019).
16. Osteosarcoma - St. Jude Children's Research Hospital <https://www.stjude.org/disease/osteosarcoma.html> (accessed Jul 14, 2019).
17. Osteosarcoma | Genetic and Rare Diseases Information Center (GARD) – an NCATS Program
<https://rarediseases.info.nih.gov/diseases/7284/osteosarcoma> (accessed Jul 14, 2019).

References

18. Osteosarcoma ppt <https://www.slideshare.net/vidyaveer/osteosarcoma-ppt-34022546> (accessed Jul 14, 2019).
19. Parrales, A.; McDonald, P.; Ottomeyer, M.; Roy, A.; Shoenen, F. J.; Broward, M.; Bruns, T.; Thamm, D. H.; Weir, S. J.; Neville, K. A.; et al. Comparative Oncology Approach to Drug Repurposing in Osteosarcoma. *PLoS ONE* 2018, 13 (3), e0194224. <https://doi.org/10.1371/journal.pone.0194224>.
20. Patent Docs: Patenting Repurposed Drugs <https://www.patentdocs.org/2018/09/patenting-repurposed-drugs.html> (accessed Jul 22, 2019).
21. Prasad, V.; Mailankody, S. Research and Development Spending to Bring a Single Cancer Drug to Market and Revenues After Approval. *JAMA Intern Med* 2017, 177 (11), 1569–1575. <https://doi.org/10.1001/jamainternmed.2017.3601>.
22. Prevalence of metastasis at diagnosis of osteosarcoma: an international comparison <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4833631/> (accessed Jul 14, 2019).
23. Rapamycin | CAS 53123-88-9 (accessed Jul 14, 2019).
24. Research, C. for D. E. and. From Our Perspective: The Importance of the Physical Characteristics of Generic Drugs. FDA 2019.
25. Repurposing Existing Drugs for New Indications. <https://www.the-scientist.com/features/repurposing-existing-drugs-for-new-indications-32285> (accessed Jul 22, 2019).
26. Surgery for Osteosarcoma | – UNM Comprehensive Cancer Center <http://cancer.unm.edu/cancer/cancer-info/types-of-cancer/bone-cancer/osteosarcoma/surgery-for-osteosarcoma/> (accessed Jul 14, 2019).
27. Surgical Procedures: Rotationplasty | OncoLink <https://www.oncologink.org/cancers/sarcomas/sarcoma-bone/rotationplasty> (accessed Jul 14, 2019).
28. Surgical Procedures: Surgery and Staging for Osteosarcoma | OncoLink <https://www.oncologink.org/cancers/sarcomas/sarcoma-bone/surgical-procedures-surgery-and-staging-for-osteosarcoma> (accessed Jul 14, 2019).
29. Sweeney, B. 2015. The Cost Of Things: A Brain Tumor <https://www.thebillfold.com/2015/06/the-cost-of-things-a-brain-tumor/> (accessed Jul 14, 2019).
30. Topkas, E.; Cai, N.; Cumming, A.; Hazar-Rethinam, M.; Gannon, O. M.; Burgess, M.; Saunders, N. A.; Endo-Munoz, L. Auranofin Is a Potent Suppressor of Osteosarcoma Metastasis. *Oncotarget* 2015, 7 (1), 831–844.
31. Topotecan Prices, Coupons & Savings Tips - GoodRx <https://www.goodrx.com/topotecan> (accessed Jul 14, 2019).
32. Trial With Gemcitabine and Rapamycin in Second Line of Metastatic Osteosarcoma - Full Text View - ClinicalTrials.gov <https://clinicaltrials.gov/ct2/show/NCT02429973> (accessed Jul 22, 2019).
33. Vorinostat Prices, Coupons & Savings Tips - GoodRx <https://www.goodrx.com/vorinostat> (accessed Jul 14, 2019).
34. Western Blotting | MyBioSource Learning Center.

Thank you!



Orphan Drug Act (2013)

- Pharmaceutical manufacturers receive 7 years of marketing exclusivity
 - Several grants available to companies or academic-based researchers
 - Awarded annually
 - 50% tax credit for expenditures incurred during evaluation of therapeutic potential of orphan drugs



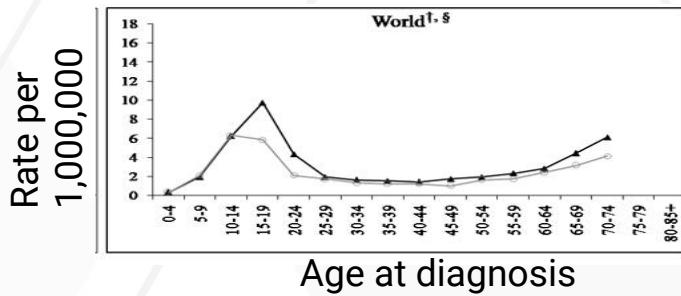
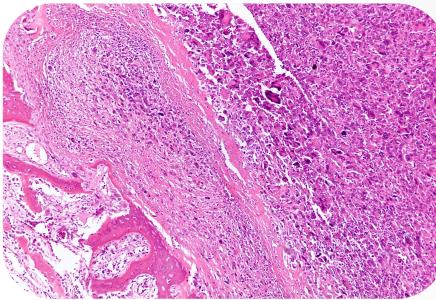
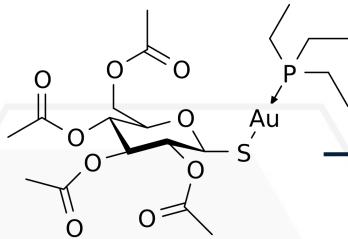
FDA Approval Rates

Phase Success	Phase I to Phase II		Phase II to Phase III		Phase III to NDA/BLA		NDA/BLA to Approval	
	Advanced or Suspended	Phase Success						
Hematology	86	73.3%	83	56.6%	64	75.0%	50	84.0%
Infectious disease	347	69.5%	286	42.7%	150	72.7%	133	88.7%
Ophthalmology	66	84.8%	101	44.6%	60	58.3%	40	77.5%
Other	96	66.7%	116	39.7%	46	69.6%	43	88.4%
Metabolic	95	61.1%	84	45.2%	35	71.4%	27	77.8%
Gastroenterology*	41	75.6%	56	35.7%	33	60.6%	26	92.3%
Allergy	37	67.6%	40	32.5%	14	71.4%	16	93.8%
Endocrine	299	58.9%	242	40.1%	143	65.0%	107	86.0%
Respiratory	150	65.3%	196	29.1%	45	71.1%	37	94.6%
Urology	21	57.1%	52	32.7%	21	71.4%	14	85.7%
Autoimmune	297	65.7%	319	31.7%	135	62.2%	86	86.0%
All Indications	3582	63.2%	3862	30.7%	1491	58.1%	1050	85.3%
Neurology	462	59.1%	465	29.7%	216	57.4%	161	83.2%
Cardiovascular	209	58.9%	237	24.1%	110	55.5%	76	84.2%
Psychiatry	154	53.9%	169	23.7%	70	55.7%	58	87.9%
Oncology	1222	62.8%	1416	24.6%	349	40.1%	176	82.4%

- BE FINAL

- Slides should look the same (format, size, font, color)
- Every slide--what is the purpose of it--needs a takeaway
 - 25 slides max for 18 min presentation
 - I just copied all of other slides just for ref right now
 - 1. Disease
 - 2. repurposing
 - 3. Need assessment
 - 4. Market
 - 5. Demand, cost, risk
 - 6. Where it needs to go, final recommendation

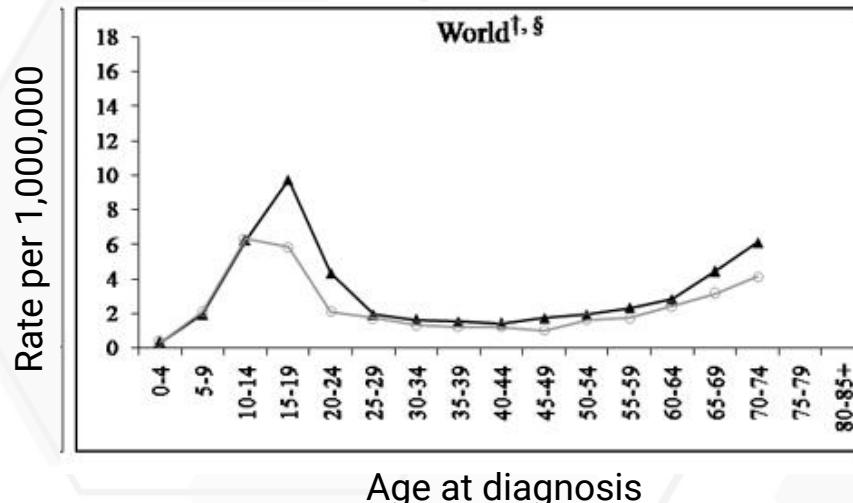
Osteosarcoma



Clinical Value

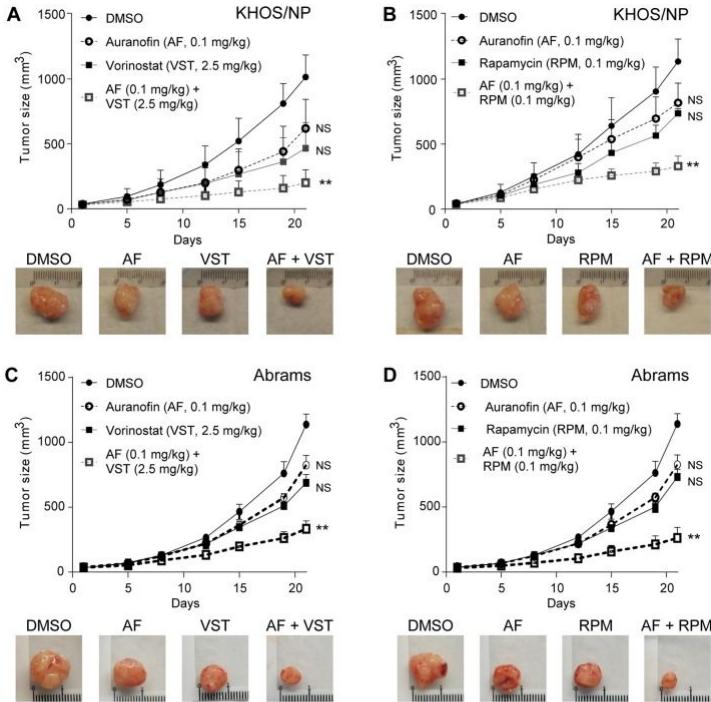
- **Osteosarcoma**

- Prevalence: ~800-900 new cases diagnosed each year
- Incidence: 4-5 per million persons



- Proof-of-principle studies:

- *In vivo* tumor growth assay in mice
 - Decrease in Ki67-positive cells, increase in cleaved caspase-3 positive cells

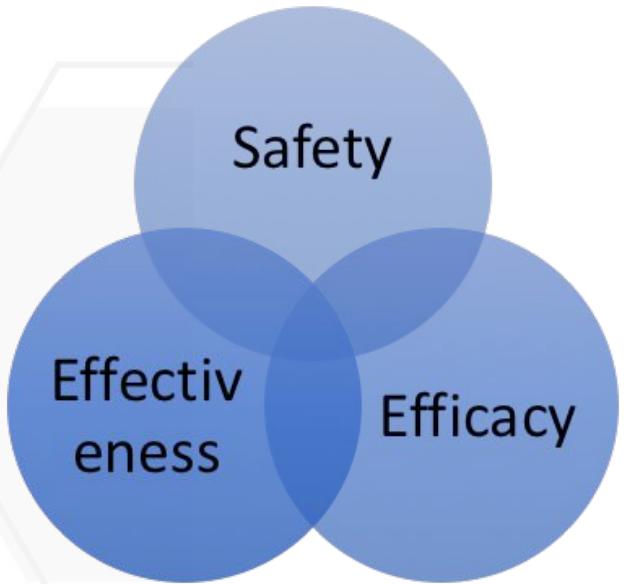


PLoS One. 2018; 13(3): e0194224.



Auranofin + vorinostat/rapamycin demonstrated significantly suppressed OS tumor growth

FDA-APPROVED DRUG CHARACTERISTICS



OTHER CHARACTERISTICS

- 
- Price
 - High likelihood of early adoption
 - Physical characteristics of drugs

Side-effects

- Usual adult dosage of RIDAURA (auranofin) is 6mg daily
 - Stomach cramping, nausea, loss of appetite, heartburn, and headache
 - Do not take if pregnant or if breastfeeding
 - Doses exceeding 9mg daily have not been studied



PRESCRIBING INFORMATION RIDAURA® Auranofin Capsules.
(2011, November). Retrieved from
<https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=05c34ddf-a0f7-4267-83f5-d02be3defc37&type=display>

Suggestions:

Patents: novel use or combination therapy?

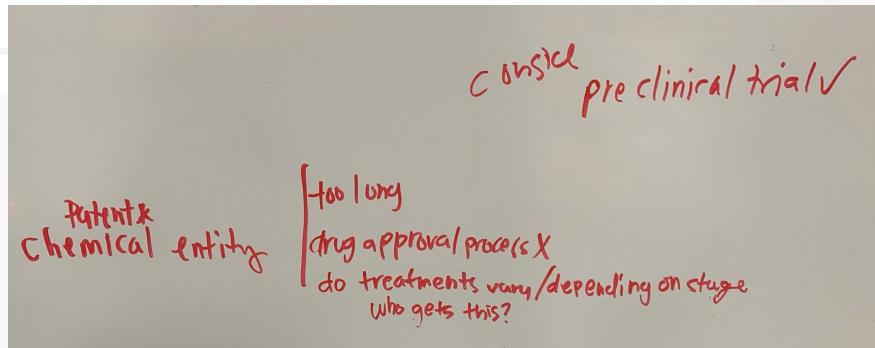
Cut scency bit shorter

- More on how treatment varies depending on stage of disease

Have everything add up to argument/conclusion, just bc have info, doesn't mean you need to use it

Don't overgeneralize

Incidence and prevalence super important for market assessment



R&D Analysis

1. Discovery

A

Performed screening in 5 cell lines (hFOB, MG63, KHOS/NNP, D17, Abrams) with 2,286 FDA compounds at concentration of 2.5 μM at 48 hours.



Over 40 drugs showed significant activities in multiple osteosarcoma cell lines.



Narrowed to 13, based on cytotoxicity profiles and possible clinical use.



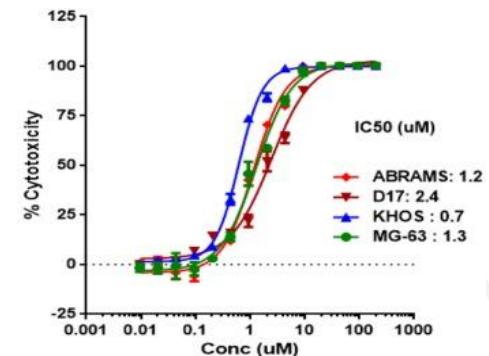
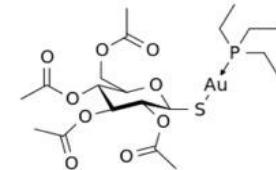
Repurchased 13 drugs and performed secondary confirmation at 16 concentrations at 48 hours in 6 cell lines.



Following a drug development and regulatory science gap analysis, selected auranofin for synergy testing and *in vitro/in vivo* confirmation.

B

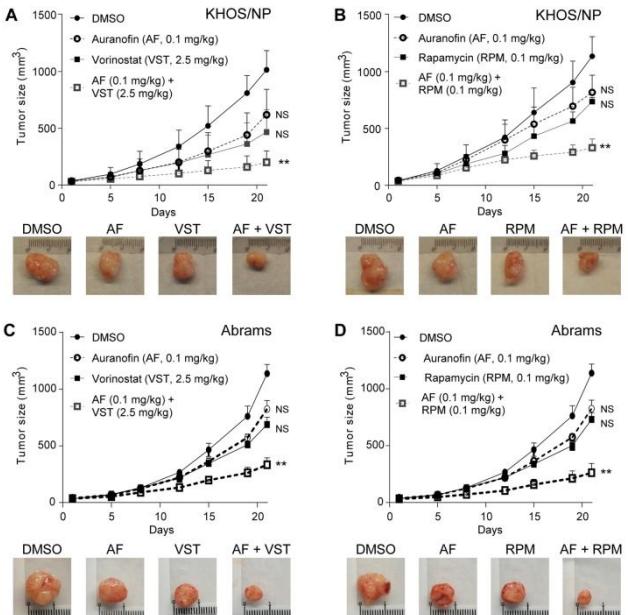
Auranofin



R&D Analysis: Stage 2 (Preclinical Trials)

2. Preclinical Trials

Stage A:



Stage B:

- All three drugs used were well tolerated by tumor-bearing nude mice

Next steps:

- Determine in vitro safety

Stage C:

- “Currently, evaluation of auranofin in canine cancer patients is on-going in a phase 1 trial to assess the maximum tolerated dose of auranofin in this population”

*IND Exemption

Objective Value

Complications of Auranofin	Incidence	Frequency	Cost Per Incidence	Average Cost per Patient
Rash	24%	2	\$9	\$5
Stomatitis	13%	5	\$10	\$7
Diarrhea	47%	6	\$12	\$34
Abdominal Pain	14%	9	\$10	\$13
Nausea (with or without vomiting)	10%	8	\$11	\$9
			TOTAL	\$68

Objective Value

Complications of Chemotherapy	Incidence	Frequency	Cost Per Incidence	Average Cost per Patient
Hair Loss	65%	1	\$2,000	\$1,300
Stomatitis	13%	5	\$10	\$7
Diarrhea	47%	6	\$12	\$34
Appetite/Weight Loss	40%	10	\$20	\$80
Nausea (with or without vomiting)	10%	10	\$11	\$11
			TOTAL	\$1,432

Object 3: Market Assessment (just for ref, will take out later)

- What is the addressable market for the repurposed drug?
- Number of patients: around the world?
- What price can you charge?
- Reference pricing: price being charged for existing drugs/treatments
- Economic/value pricing: based on value being created for patients or the healthcare system from the new drug (quality of life, reduced complications, reduced healthcare costs (stays in hospital, etc.)
- Market size = Number of patients/doses X price
- Likely market share the drug will achieve if successful
- Competitive analysis
 - Who are your competitors (both existing drugs)
 - How competitive will the market be in the future?
 - Hint: Look into www.clinicaltrials.org web-site for info on on-going trials within your indication – a good way to find potential competitors

The drugs used most often to treat osteosarcoma include:

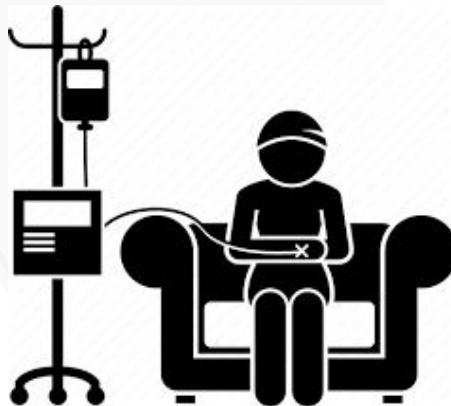
- Methotrexate (given in high doses along with leucovorin to help prevent side effects) (\$50.54 - 2.5mg)
- Doxorubicin (Adriamycin) (\$23.80 - 25ml of 2mg/ml)
- Cisplatin or carboplatin (\$237.94 - 200ml of 200mg/200ml)
- Epirubicin (prescription provided by doctor)
- Ifosfamide
- Cyclophosphamide (\$229.62 - 50mg)
- Etoposide (\$757.38 - 50mg)
- Gemcitabine (\$42.21 - 50ml of 2g)
- Topotecan (\$447.49 - 4mg)

Usually, 2 or more drugs are given together. Some common combinations of drugs include:

- High-dose methotrexate, doxorubicin, and cisplatin (sometimes with ifosfamide)
- Doxorubicin and cisplatin
- Ifosfamide and etoposide
- Ifosfamide, cisplatin (or carboplatin), and epirubicin

Addressable Market

- 800 - 900 patients → 850 average
 - 80-85% localized osteosarcoma → 82.5% average
- Addressable market = $850 * 82.5\% = 701$ patients
 - **~700 patients** realistically using this treatment



Reference Pricing

Therapy	Chemotherapy	AF + RPM	AF + VST
Cost Breakdown	<ul style="list-style-type: none"> 15 day cycle, repeat every 21 days <ul style="list-style-type: none"> Dacarbazine: 250mg/m²/day CIV for 4 days → \$104.00 - \$124.00 Doxorubicin: 15mg/m²/day CIV for 4 days → \$11.32 - \$13.45 Ifosfamide: 2000mg/m²/day CIV for 3 days → \$182.88 - \$217.17 Mesna: 2000mg/m²/day CIV for 4 days → \$2,270.72 - \$2,696.48 	<ul style="list-style-type: none"> Significant tumor reduction generally found within 2.2 months <ul style="list-style-type: none"> Auranofin: 3mg/m²/month PO → \$1,316.62 Rapamycin: 180mg/m²/month PO → \$2,160.00 	<ul style="list-style-type: none"> Significant tumor reduction generally found within 2.2 months <ul style="list-style-type: none"> Auranofin: 3mg/m²/month PO → \$1,316.62 Vorinostat: 4500mg/m²/month PO → \$4,279.63
Total Cost	<p>\$2,570 - \$3,050 per cycle \$12,845 - \$15,255 in 6 months</p>	<p>\$3,476.62 per month \$7,648.57 in 2.2 months</p>	<p>\$5,596.25 per month \$12,311.76 in 2.2 months</p>

Pricing

- **Combination of AF + RPM: \$3,735.06 per month**
 - Manufacturing cost: \$2,134.32
 - Clinical trial/Development costs: 50% of manufacturing → \$1,067.16
 - Profit: 25% of manufacturing → \$533.58
- **Conservative estimate**
 - Can be adjusted according to investor buy-in



Potential Savings from Previous R&D

- **Auranofin is an Repurposed Drug**
 - Self-selected for success → higher success rates than self-originated drugs
 - Lower R&D spending → Median: \$328.1m vs. \$899.2m
- **Mean length of market exclusivity for oncologic drugs: 14.3 years**
 - Revenues will continue to increase over time
- **Some companies boast more than a 10-fold higher revenue than R&D spending**



Criticism

- Dosing schedule for repurposed drugs not specified in paper
 - Estimated using data from graphs
- Pricing must be calculated based on treatment regimen
 - Repurposed drug regimen exceeds average → traditional chemotherapy may be more cost efficient

Objective #4: R&D Analysis

- Please identify as carefully as possible the scientific steps your technology would need to achieve in order to become a product (i.e. medicine). Please break these steps into two groups of activities: research (or 'discovery') and development:
- Research: the key scientific tasks you must accomplish to translate the 'basic research'...into a molecule that can be put into the drug development pipeline. This includes preclinical trials.
- Development: the clinical trials needed to gain approval to market your product. Try to estimate the likely size (# people enrolled) and costs of the clinical trials needed to prove efficacy of typical drugs in your therapeutic area.
- **Analysis.** The time, risk, and cost of product development will strongly influence your ultimate recommendation of whether your technology is an attractive opportunity.
- How long do you think it will take for your product to reach the market?
- What is the probability that your technology will make it to market. Note, a supplement containing clinical trials success rates will be provided.
- How much will it cost to develop your product?
- How does the drug-repurposing opportunity impact this analysis
- Identify potential cost and time savings created by previous R&D on the earlier indication

Project Objective 5: Risk Analysis

- Please identify key obstacles to the development and commercial success of your repurposed drug.

Please investigate these three risks:

Future competition

Intellectual property

Adoption

• For each risk that you determined to be 'major', be sure to assess potential strategies to overcome the risk.

• There might be other risks associated with your repurposed drug. If so, please consider them. But please be sure to assess risks associated with: intellectual property, market adoption, and regulatory approval

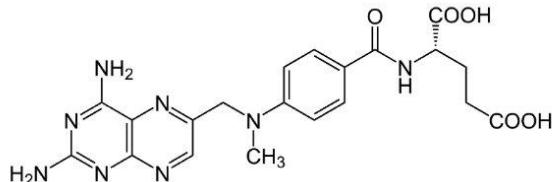
Pricing

- Combination of AF + RPM: **\$3,735.06 per month**
 - Manufacturing cost: \$2,134.32
 - Clinical trial/Development costs: 50% → \$1,067.16
 - Profit: 25% → \$533.58
- Conservative estimate
 - Can be adjusted according to investor buy-in

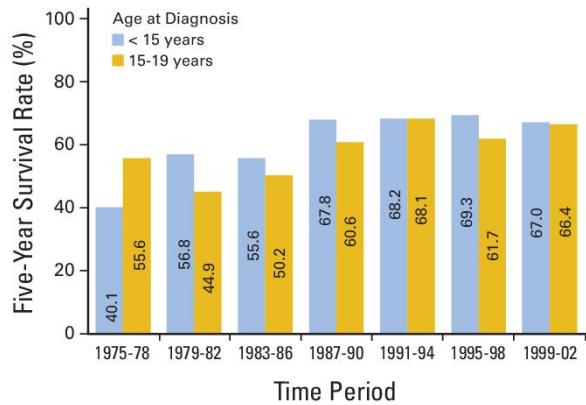


Notable Competitors

- Cyclophosphamide + Methotrexate
 - May be effective against **chemotherapy-resistant** tumor
 - 2 year treatment
- Methotrexate + Glucarpidase
 - Glucarpidase may reduce toxicity in patients taking methotrexate
- Gemcitabine + Rapamycin
 - Another study using rapamycin



Clinical Need for Improvement



- AF + RPM expands treatment options

- Cheaper + quicker than traditional chemo
 - Estimated price: **\$7,648.57 in 2.2 months** vs **\$12,845-15,255 in 6 months**
- Novel approach → new mechanisms of action
 - Combination drug that inhibits TXNRD expression (potentially effective against chemoresistance tumors)
 - Synergistic effects with some chemotherapy drugs (e.g. vorinostat and rapamycin)
 - May increase survival rates through combination therapy

IMG CITE: A Smith, Malcolm & Seibel, Nita & Altekroose, Sean & Ries, Lynn & L Melbert, Danielle & O'Leary, Maura & O Smith, Franklin & Reaman, Gregory. (2010). Outcomes for Children and Adolescents With Cancer: Challenges for the Twenty-First Century. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 28. 2625-34. 10.1200/JCO.2009.27.0421.



Future Competition

- **Improvements to existing chemotherapies**
 - Most trials focus on **improving current chemotherapies or new combinations**
 - Orphan disease
- Auranofin + Rapamycin improve treatment
 - **Cheaper + quicker** vs traditional chemo treatment
 - Estimated price: **\$7,648.57 in 2.2 months** vs **\$12,845-15,255 in 6 months**
 - Novel approach → new mechanisms of action
 - Combination drug that inhibits TXNRD expression (potentially effective against chemoresistance)



Orphan Drug Act (2013)

- Pharmaceutical manufacturers receive 7 years of marketing exclusivity
 - Several grants available to companies or academic-based researchers
 - Awarded annually
 - 50% tax credit for expenditures incurred during evaluation of therapeutic potential of orphan drugs



FDA Approval Rates

Phase Success	Phase I to Phase II		Phase II to Phase III		Phase III to NDA/BLA		NDA/BLA to Approval	
	Advanced or Suspended	Phase Success						
Hematology	86	73.3%	83	56.6%	64	75.0%	50	84.0%
Infectious disease	347	69.5%	286	42.7%	150	72.7%	133	88.7%
Ophthalmology	66	84.8%	101	44.6%	60	58.3%	40	77.5%
Other	96	66.7%	116	39.7%	46	69.6%	43	88.4%
Metabolic	95	61.1%	84	45.2%	35	71.4%	27	77.8%
Gastroenterology*	41	75.6%	56	35.7%	33	60.6%	26	92.3%
Allergy	37	67.6%	40	32.5%	14	71.4%	16	93.8%
Endocrine	299	58.9%	242	40.1%	143	65.0%	107	86.0%
Respiratory	150	65.3%	196	29.1%	45	71.1%	37	94.6%
Urology	21	57.1%	52	32.7%	21	71.4%	14	85.7%
Autoimmune	297	65.7%	319	31.7%	135	62.2%	86	86.0%
All Indications	3582	63.2%	3862	30.7%	1491	58.1%	1050	85.3%
Neurology	462	59.1%	465	29.7%	216	57.4%	161	83.2%
Cardiovascular	209	58.9%	237	24.1%	110	55.5%	76	84.2%
Psychiatry	154	53.9%	169	23.7%	70	55.7%	58	87.9%
Oncology	1222	62.8%	1416	24.6%	349	40.1%	176	82.4%

REFERENCES

1. Key Statistics for Osteosarcoma
<https://www.cancer.org/cancer/osteosarcoma/about/key-statistics.html> (accessed Jul 9, 2019).
2. Nie, Z.; Peng, H. Osteosarcoma in Patients below 25 Years of Age: An Observational Study of Incidence, Metastasis, Treatment and Outcomes. *Oncol Lett* 2018, 16 (5), 6502–6514.
<https://doi.org/10.3892/ol.2018.9453>.
3. Parrales, A.; McDonald, P.; Ottomeyer, M.; Roy, A.; Shoenen, F. J.; Broward, M.; Bruns, T.; Thamm, D. H.; Weir, S. J.; Neville, K. A.; et al. Comparative Oncology Approach to Drug Repurposing in Osteosarcoma. *PLoS ONE* 2018, 13 (3), e0194224.
<https://doi.org/10.1371/journal.pone.0194224>.
4. Research, C. for D. E. and. From Our Perspective: The Importance of the Physical Characteristics of Generic Drugs. FDA 2019.
5. Topkas, E.; Cai, N.; Cumming, A.; Hazar-Rethinam, M.; Gannon, O. M.; Burgess, M.; Saunders, N. A.; Endo-Munoz, L. Auranofin Is a Potent Suppressor of Osteosarcoma Metastasis. *Oncotarget* 2015, 7 (1), 831–844.
6. Western Blotting | MyBioSource Learning Center.

References

1. 36B: Van Nes Rotation-Plasty in Tumor Surgery | O&P Virtual Library
<http://www.oandplibrary.org/alp/chap36-02.asp> (accessed Jul 14, 2019).
2. Cost-utility of osteoarticular allograft versus endoprosthetic reconstruction for primary bone sarcoma of the knee: A markov analysis. - PubMed - NCBI <https://www.ncbi.nlm.nih.gov/pubmed/28105636> (accessed Jul 14, 2019).
3. Current concepts in surgical treatment of osteosarcoma <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3872798/> (accessed Jul 14, 2019).
4. Fine needle aspiration biopsy of primary bone tumors. - PubMed - NCBI <https://www.ncbi.nlm.nih.gov/pubmed/10810465> (accessed Jul 14, 2019).
5. How Much Does Amputation Cost? - CostHelper.com <https://health.costhelper.com/amputation.html> (accessed Jul 14, 2019).
6. Ifex (ifosfamide) dose, indications, adverse effects, interactions... from PDR.net
<https://www.pdr.net/drug-summary/Ifex-ifosfamide-2427> (accessed Jul 14, 2019).
7. Osteosarcoma - St. Jude Children's Research Hospital <https://www.stjude.org/disease/osteosarcoma.html> (accessed Jul 14, 2019).
8. Osteosarcoma | Genetic and Rare Diseases Information Center (GARD) – an NCATS Program
<https://rarediseases.info.nih.gov/diseases/7284/osteosarcoma> (accessed Jul 14, 2019).
9. Osteosarcoma ppt <https://www.slideshare.net/vidyaveer/osteosarcoma-ppt-34022546> (accessed Jul 14, 2019).
10. Prevalence of metastasis at diagnosis of osteosarcoma: an international comparison
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4833631/> (accessed Jul 14, 2019).

References

References

11. Rapamycin | CAS 53123-88-9
<https://www.scbt.com/scbt/zh/product/rapamycin-53123-88-9/?jsessionid=ROHzZXn31D2P57fD2aVP4QhlrvAaAX1efRnnmHLAJsflaWtj033u!1930529085> (accessed Jul 14, 2019).
12. Side Effects Of Chemotherapy Set. Patient Suffer Stock Vector - Illustration of disease, concept: 133352965
<https://www.dreamstime.com/side-effects-chemotherapy-set-patient-suffer-side-effects-chemotherapy-set-patient-suffer-cancer-disease-hair-loss-image133352965> (accessed Jul 14, 2019).
13. Surgery for Osteosarcoma | – UNM Comprehensive Cancer Center
<http://cancer.unm.edu/cancer/cancer-info/types-of-cancer/bone-cancer/osteosarcoma/surgery-for-osteosarcoma/> (accessed Jul 14, 2019).
14. Surgical Procedures: Rotationplasty | OncoLink
<https://www.oncolink.org/cancers/sarcomas/sarcoma-bone/rotationplasty> (accessed Jul 14, 2019).
15. Surgical Procedures: Surgery and Staging for Osteosarcoma | OncoLink
<https://www.oncolink.org/cancers/sarcomas/sarcoma-bone/surgical-procedures-surgery-and-staging-for-osteosarcoma> (accessed Jul 14, 2019).
16. June 23, T. B.; 2015. The Cost Of Things: A Brain Tumor
<https://www.thebillfold.com/2015/06/the-cost-of-things-a-brain-tumor/> (accessed Jul 14, 2019).
17. Topotecan Prices, Coupons & Savings Tips - GoodRx <https://www.goodrx.com/topotecan> (accessed Jul 14, 2019).
18. Vorinostat Prices, Coupons & Savings Tips - GoodRx <https://www.goodrx.com/vorinostat> (accessed Jul 14, 2019).

References

1. 5 Things About the Orphan Drug Act <https://www.ajmc.com/newsroom/5-things-about-the-orphan-drug-act> (accessed Jul 22, 2019).
2. Clinical Trial Evaluating Metronomic Chemotherapy in Patients With Metastatic Osteosarcoma - Full Text View - ClinicalTrials.gov <https://clinicaltrials.gov/ct2/show/NCT03063983> (accessed Jul 22, 2019).
3. Connolly, K. M.; Stecher, V. J.; Pruden, D. J. Effect of Auranofin on Plasma Fibronectin, C Reactive Protein, and Albumin Levels in Arthritic Rats. *Annals of the Rheumatic Diseases* 1988, 47 (6), 515–521. <https://doi.org/10.1136/ard.47.6.515>.
4. Glucarpidase After High-Dose Methotrexate in Patients With Osteosarcoma - Full Text View - ClinicalTrials.gov <https://clinicaltrials.gov/ct2/show/NCT03960177> (accessed Jul 22, 2019).
5. Losartan + Sunitinib in Treatment of Osteosarcoma - Full Text View - ClinicalTrials.gov <https://clinicaltrials.gov/ct2/show/NCT03900793> (accessed Jul 22, 2019).
6. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=018689&Appl_type=N (accessed Jul 22, 2019)
7. Patent Docs: Patenting Repurposed Drugs <https://www.patentdocs.org/2018/09/patenting-repurposed-drugs.html> (accessed Jul 22, 2019).
8. Prasad, V.; Mailankody, S. Research and Development Spending to Bring a Single Cancer Drug to Market and Revenues After Approval. *JAMA Intern Med* 2017, 177 (11), 1569–1575. <https://doi.org/10.1001/jamainternmed.2017.3601>.
9. Repurposing Existing Drugs for New Indications <https://www.the-scientist.com/features/repurposing-existing-drugs-for-new-indications-32285> (accessed Jul 22, 2019).
10. Trial With Gemcitabine and Rapamycin in Second Line of Metastatic Osteosarcoma - Full Text View - ClinicalTrials.gov <https://clinicaltrials.gov/ct2/show/NCT02429973> (accessed Jul 22, 2019).
11. Drugs@FDA: FDA Approved Drug Products. (n.d.). Retrieved from <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>
12. Parrales, A., McDonald, P., Ottomeyer, M., Roy, A., Shoenen, F. J., Broward, M., . . . Fulbright, J. M. (2018, March 26). Comparative oncology approach to drug repurposing in osteosarcoma. Retrieved from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5868798/> Phases of clinical research. (2019, January 29)

SIDE EFFECTS OF CURRENT TREATMENT

