Planning for the 2018 Specialty Drug Spend

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Disclosure for Nicole Trask

I have no actual or potential conflict of interest in relation to this presentation.

Objectives

- Identify high-impact specialty pipeline drugs expected to reach the market in 2018-2019
- Summarize efficacy data for high-impact specialty pipeline drugs and indicate their anticipated place in therapy
- Compare specialty pipeline drugs to currently available therapeutic options
- Predict the budgetary impact of specialty pipeline drugs and discuss strategies to mitigate costs

Identifying High-Impact Drugs

Two key drivers

- Clinical impact
  - Efficacy/effectiveness
  - Therapeutic alternatives
- Economic impact
  - Cost
  - Volume

Assessing Clinical Impact

Clinical trial data

- Placebo-controlled, head-to-head studies
- Adverse events
- Potential drug-drug interactions
- Target population
- Patient willingness to use medication

Therapeutic alternatives

- Me-too drug vs. first-in-class
- Market competition
- Consensus guidelines

Assessing Economic Impact

Cost

- NADAC, AWP, WAC
- Supplemental rebate
- Value-based contracts
- Value assessments (e.g., AHRQ, ICER, PCORI)

Volume

- Prevalence/incidence of disease
- Frequency of administration
- Duration of therapy

AHRQ=Agency for Healthcare Research and Quality, AWP=average wholesale price, ICER=Institute for Clinical and Economic Review, NADAC=national average drug acquisition cost, PCORI=Patient-centered Outcomes Research Institute, WAC=wholesale acquisition cost

Assessing Budget Impact

- **Proactive pharmaceutical pipeline monitoring**
  - Focus on high-cost disease states, specialty drugs (e.g., gene therapy, CAR-T therapy, NASH, monoclonal antibodies)
- **Budget impact analysis completed for drugs with potentially high clinical *and* economic impact**
  - Pharmacy and/or medical claims to evaluate prevalence
  - Estimate market share, uptake
  - Cost

CAR-T=chimeric antigen receptor-T, NASH=nonalcoholic steatohepatitis

Lessons Learned

Difficult to predict uptake of new drugs

- Skepticism surrounding safety/efficacy
- Clinical inertia, lack of consensus guideline updates
- Relative cost

Updates to process

- Project ***net*** cost increases
- Shifting utilization ("cannibalization")
- Calculate true cost of drugs, including rebate

HIGH-IMPACT PIPELINE DRUGS

Inherited Retinal Dystrophy[1,2]

Clinical features

- Rare eye disorders caused by inherited mutations in one of >220 genes
  - LCA is a severe subtype of retinitis pigmentosa caused by mutations in any of the ≥19 identified genes that cause LCA
- Significant vision loss or blindness at birth (LCA) or later in life (LCA2); all are blind by young adulthood

Prevalence

- RPE65-mediated IRD affects ~3,300 individuals in the US; LCA2 is most common (~600 patients)

LCA=Leber congenital amaurosis

Voretigene Neparvovec[1,2]

- **Proposed indication:** vision loss due to confirmed biallelic RPE65 mutation-associated retinal disease
- **MOA:** AAV2 gene therapy
  - Introduces normal copy of RPE65 gene
  - Subretinal injection to each eye, 6 to 18 days apart
  - May improve functional vision

AAV2=adeno-associated virus type 2, MOA=mechanism of action

Voretigene Neparvovec: Clinical Impact[1]

Phase III trial: Design

- Randomized, open-label, controlled
- Population: N=31; confirmed genetic diagnosis of biallelic RPE65 mutations
- Intervention: bilateral subretinal injection of 1.5×10^{11} vector genomes or no treatment
- Primary outcome: change in MLMT performance at one year

MLMT=multi-luminance mobility testing

Voretigene Neparvovec: Clinical Impact[1]

Phase III trial: Results

- Change in MLMT performance at one year
  - Significant improvement in MLMT performance in intervention group

    (1.8 vs. 0.2 light levels; P=0.0013)
  - More patients in the intervention group passed MLMT at 1 lux (65% vs. 0%, respectively)

Voretigene Neparvovec: Clinical Impact[1,3]

Therapeutic alternatives

- None

Gene therapy pipeline

- GS010
  - Investigational AAV2 gene therapy containing human wild-type ND4 gene
  - Being developed for treatment of LHON associated with ND4 mutation
  - Phase III trials ongoing

LHON=Leber Hereditary Optic Neuropathy

Voretigene Neparvovec: Clinical Impact[1]

Potential Advantages

- Demonstrated improvement in functional vision
- Side effects were mild and transient or treatable
- May be first gene therapy for treatment of IRD
- One-time administration

Potential Disadvantages

- Likely to be extremely costly
- Long-term durability of effect unknown
- Studied in subset of patients with LCA2

Voretigene Neparvovec: Economic Impact[2,4]

Cost

- Cost data not available
- ICER estimates $650,000 to $1 million/patient
- Supplemental rebate – no market competition
- Value-based contracts – improvement in MLMT, durability of response
- Innovative payment models – amortized payment plans

Voretigene Neparvovec: Economic Impact[2,5,6]

Volume

- Prevalence: 3,300 individuals with RPE65-mediated IRDs in US
- Duration: one-time administration
- Other key facts
  - Administration in hospital outpatient setting at specialized ophthalmic treatment centers
  - Some side effects may require surgical repair (e.g., cataracts)

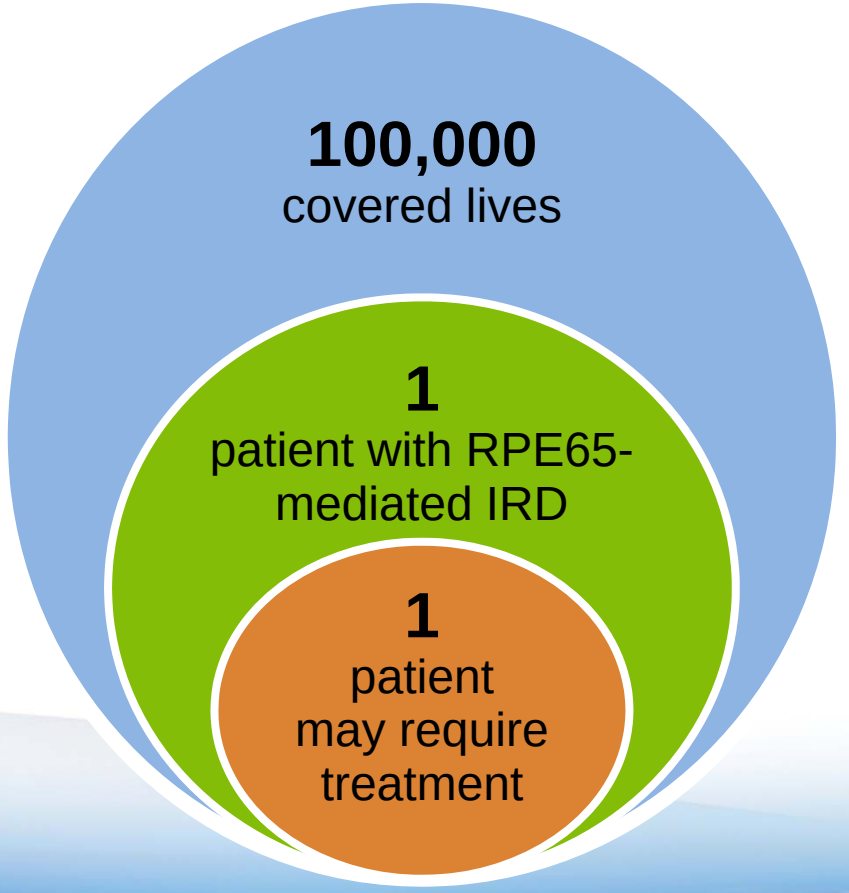
Voretigene Neparvovec: Budget Impact[2,5-8]

Commercial plan

- Approximately $1 million/patient for treatment
- **$1 million/year**

Timeline

- FDA decision expected 1/12/2018



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Non-Hodgkin Lymphoma (NHL)[9,10]

Clinical features

- Relapse rate following conventional chemotherapy >50%
- Five-year survival ~71%

Incidence/prevalence

- Seventh most common form of cancer in US
- New cases per year: 19.5 per 100,000
- Deaths per year: 5.9 per 100,000
- Approximately 662,000 people living with NHL

Axicabtagene Ciloleucel[11,12]

- **Proposed indication:** r/r aggressive NHL in patients ineligible for ASCT
- **MOA:** CAR-T therapy
  - T cells removed from patient, engineered to express CAR, multiplied in lab, and reinfused back into patient
  - Engineered cells target and attack CD19-expressing cancerous cells

ASCT=autologous stem cell transplant, CAR=chimeric antigen receptor, CAR-T=chimeric antigen receptor-T cell, r/r=relapsed/refractory

Axicabtagene Ciloleucel: Clinical Impact[13,14]

Phase I/II ZUMA-1 trial: Design

- Single-arm, open-label
- Population: N=111; adults with refractory DLBCL, TFL, or PMBCL
- Intervention: conditioning chemotherapy regimen followed by single IV infusion of axicabtagene ciloleucel*
- Primary outcome: ORR

*Conditioning chemotherapy regimen consisted of fludarabine plus cyclophosphamide
DLBCL=diffuse large B-cell lymphoma, IV=intravenous, ORR=objective response rate, PMBCL=primary mediastinal B-cell lymphoma, TFL=transformed follicular lymphoma

Axicabtagene Ciloleucel: Clinical Impact[13,14]

Phase I/II ZUMA-1 trial: Results

- ORR
  - After median follow-up of 8.7 months, 82% responded to treatment with 44% ongoing (P<0.0001)
  - CR observed in 54% of patients with 39% ongoing
  - Median duration of response of 8.2 months (not reached for patients with CR)

CR=complete response

Axicabtagene Ciloleucel: Clinical Impact[15,16]

Therapeutic alternatives

- Conventional chemotherapy
  - CHOP ± rituximab or obinutuzumab*
  - Bendamustine + rituximab or obinutuzumab, fludarabine-based regimens, CVP + rituximab or obinutuzumab†
- Radiation therapy
- Immunotherapy
  - Rituximab, obinutuzumab, ofatumumab, brentuximab
- Stem cell transplant

*CHOP=cyclophosphamide, doxorubicin, prednisone, vincristine
†CVP=cyclophosphamide, prednisone, vincristine

Axicabtagene Ciloleucel: Clinical Impact[17-21]

CAR-T pipeline

- Tisagenlecleucel-T
  - Treatment of children/young adults with r/r B-cell ALL
  - Phase II ELIANA study (N=50):

    82% of patients achieved complete remission ± incomplete blood count recovery three months post-infusion
  - FDA ODAC voted unanimously in favor of approval
  - Approved one month early on 8/30/17
  - Breakthrough Therapy designation for DLBCL

ALL=acute lymphoblastic leukemia, ODAC=Oncologic Drugs Advisory Committee

Axicabtagene Ciloleucel: Clinical Impact[12,22,23]

Potential Advantages

- May provide effective treatment option in patients who failed all alternatives
- Opportunity for expanded use across several types of hematologic malignancies

Potential Disadvantages

- Potential for serious, life-threatening CRS
- Complex manufacturing process (17 days vein-to-vein)
- Only available through specialized treatment centers

CRS=cytokine release syndrome

Axicabtagene Ciloleucel: Economic Impact[24,25]

Cost

- Cost data not yet available
- Analysts' cost predictions range from $300,000 to $750,000 per patient
  - NICE mock technology appraisal – CAR-T worth up to $649,000 in young patients with ALL
- Supplemental rebate – variation in indications, safety profile
- Value-based contracts – durability of response

NICE=National Institute for Health and Care Excellence

Axicabtagene Ciloleucel: Economic Impact[9,10,26,27]

Volume

- Incidence: 19.5 per 100,000 individuals in US
  - Estimated that 60% of cases are aggressive
  - Only ~20% of aggressive cases are cured with conventional treatment
- Duration: one-time administration
- Other key facts
  - Manufacturer anticipates having capacity to treat 4,000 to 5,000 patients per year

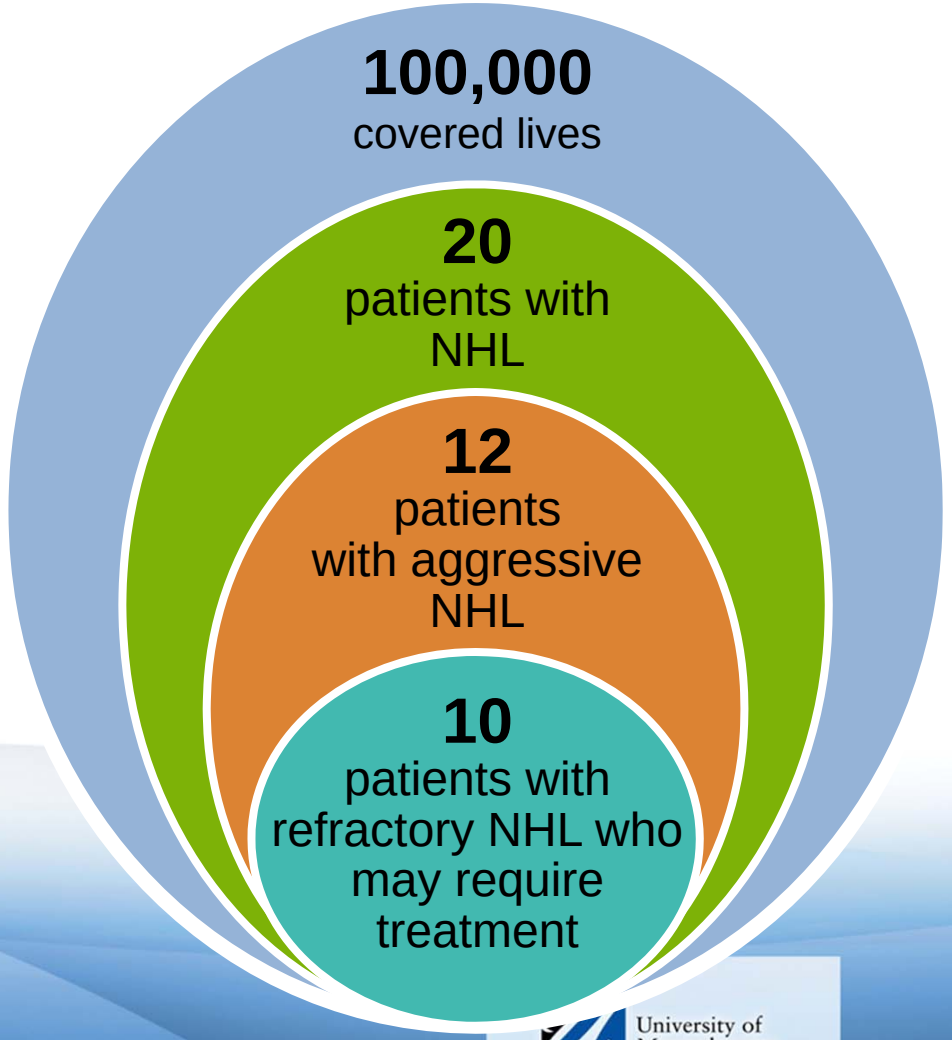
Axicabtagene Ciloleucel: Economic Impact[9,10,19,26,27]

Commercial plan

- Approximately $475,000/patient for treatment
- **$4.75 million/year**

Timeline

- FDA decision expected 11/29/2017



Duchenne Muscular Dystrophy (DMD)[28-30]

Clinical features

- Defective DMD gene, insufficient dystrophin production
- Muscle weakness beginning ~3 years of age
  - Loss of ambulation
  - Heart, respiratory muscles affected by teenage years
- Reduced life expectancy ~30 years of age

Incidence

- Approximately 1 in every 3,500 to 5,000 male births

Golodirsen[30]

- **Proposed indication:** DMD with mutations amenable to exon 53 skipping
- **MOA:** binds to exon 53 of dystrophin pre-mRNA, resulting in skipping of exon 53 during mRNA processing
  - Allows for creation of internally truncated dystrophin protein

mRNA=messenger ribonucleic acid

Golodirsen: Clinical Impact[30,31]

Phase I/II 4053-101 trial: Design

- Part 1 (randomized, double-blind)/Part 2 (open-label)
- Population: N=25; adolescent males with DMD amenable to exon 53 skipping
- Intervention: (Part 1 [n=12]) dose titration of golodirsen or placebo x 12 weeks, followed by (Part 2 [n=25]) golodirsen 30 mg/kg IV once weekly for ≥48 weeks or no treatment*
- Primary outcomes: change in mean dystrophin, 6MWT

*No treatment group included subjects with mutations not amenable to exon 53 skipping
6MWT=6 minute walk test

Golodirsen: Clinical Impact[30,32]

Phase I/II 4053-101 trial: Results

- Change in dystrophin level at 48 weeks
  - Mean dystrophin level increased to 1.019% of normal vs. 0.095% of normal at baseline (P<0.001)
  - Represents 10.7-fold increase from baseline
- All subjects receiving golodirsen experienced increased exon 53 skipping (P<0.001)
- Complete study results to be presented at future medical conference

Golodirsen: Clinical Impact[33]

Therapeutic alternatives

- Prednisone*
  - May improve strength, pulmonary function (Level B)
  - May improve timed motor function, reduce need for scoliosis surgery, delay cardiomyopathy onset (Level C)
- Deflazacort*
  - May improve strength, pulmonary function, timed motor function; reduce need for scoliosis surgery (Level C)
  - Delay cardiomyopathy onset, increase survival at 5 to 15 years of follow-up (Level C)
  - May delay age at loss of ambulation by 1.4 to 2.5 years (Level C)

*Recommendation level per American Academy of Neurology

Golodirsen: Clinical Impact[34,35]

Therapeutic alternatives

- Eteplirsen (Exondys 51™)
  - Received accelerated approval 9/2016 for treatment of DMD amenable to exon 51 skipping
  - Clinical benefit has not been established
  - Study 301 (N=13): mean dystrophin increased to 0.44% of normal at 48 weeks vs. 0.16% of normal at baseline ($P<0.005$)
  - Confirmatory trial ongoing – study completion ~5/2019

Golodirsen: Clinical Impact[36-39]

DMD pipeline*

- Ataluren
  - Oral protein restoration therapy for nmDMD
  - No significant difference in 6MWT vs. placebo for subjects with baseline <300m or ≥400m
  - FDA decision expected 10/24/17
- SRP-4045
  - DMD amenable to exon 45 skipping
  - Phase III ESSENCE trial ongoing

*Not an all-inclusive list
nmDMD=nonsense mutation DMD

Golodirsen: Clinical Impact[29,30]

Potential Advantages

- May provide a treatment alternative for patients with limited options
- Treatment resulted in 10-fold increase in dystrophin at 48 weeks

Potential Disadvantages

- Clinical benefit not yet established
- Currently available data is for surrogate endpoint
- Some clinicians suggest dystrophin levels of 10% may be needed for clinical benefit

Golodirsen: Economic Impact[40]

Cost

- Cost data not available
  - May be similar in cost to eteplirsen (~$650,000/year)*
- Supplemental rebate – limited market competition
- Value-based contracts
  - Short-term: improvement in 6MWT, dystrophin
  - Long-term: improvement in survival

*Assuming 55 lb (25 kg) patient

Golodirsen: Economic Impact[28,41-43]

Volume

- Incidence: 1 in 3,500 to 5,000 live male births
  - Point prevalence: 1.9 per 100,000 males
- Duration: chronic condition; treatment is indefinite
- Other key facts
  - ~8% of patients have mutations amenable to exon 53 skipping vs. 13% of patients have mutations amenable to exon 51 skipping

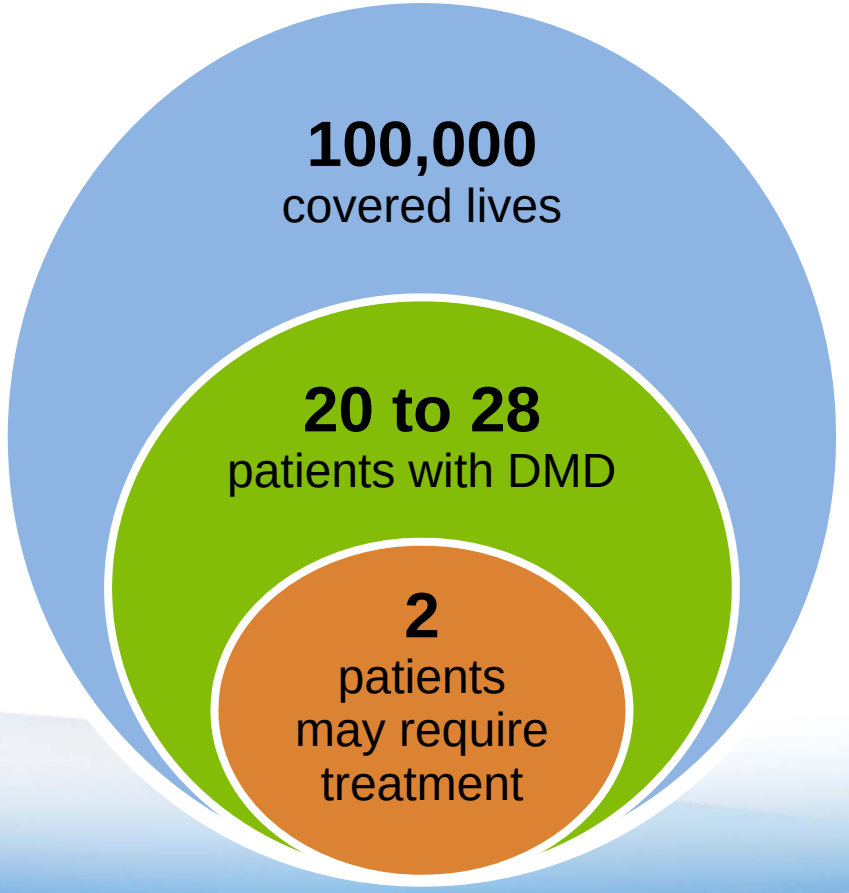
Golodirsen: Budget Impact[29]

Commercial plan

- Approximately $650,000/year for treatment
- **$1.3 million/year**

Timeline

- Regulatory submission may be anticipated ~2019



Cutaneous Squamous Cell Carcinoma (cSCC)[44-46]

Clinical features

- May develop on any cutaneous surface
- Head/neck most commonly affected
- Good prognosis when caught early
- Approximately 2-5% of cSCCs metastasize

Incidence

- One of the most common cancers in US
- Incidence: 100-200 cases per 100,000 individuals
  - Varies widely based on several risk factors (e.g., geographic location, age, gender)

Cemiplimab[47,48]

- **Proposed indication:** locally-advanced and unresectable cSCC, metastatic cSCC
- **MOA:** human MoAB targeting PD-1
  - None of the currently-available PD-1/PD-L1 agents are FDA-approved for the treatment of cSCC

MoAB=monoclonal antibody, PD-1=programmed death-1, PD-L1=programmed death ligand-1

Cemiplimab: Clinical Impact[48,49]

Phase I trial – expansion cohort: Design

- Non-randomized, parallel-group, open-label
- Population: N=26; patients with advanced cSCC
  - Metastatic (n=10), locally-advanced (n=16)
- Intervention: cemiplimab 3 mg/kg IV Q2W x 48 weeks
- Primary outcomes: ORR

Q2W=every two weeks, ORR=overall response rate

Cemiplimab: Clinical Impact[48,50]

Phase I trial expansion cohort: Results

At median of 7 months follow-up:

- Preliminary ORR: 46.2% (n=12)
- Complete response: 7.7% (n=2)
- Partial response: 38.5% (n=10)
- Disease control rate*: 69.2%
- Median PFS and OS not yet reached

*Disease control rate=proportion of patients with advanced/metastatic disease who achieve complete response or partial response and stable disease
OS=overall survival, PFS=progression-free survival

Cemiplimab: Clinical Impact[51-55]

Therapeutic alternatives*

Low-risk cSCC

- Surgical excision
- Cryotherapy
- Electrosurgery
- Topical therapy (5-FU, imiquimod)
- Radiation
- Photodynamic therapy

High-risk cSCC

- Surgical excision is the primary approach
- Radiation – not routinely used, relatively high rate of local recurrence
- Systemic therapy
  - Cisplatin, bleomycin, fluorouracil, cetuximab, vismodegib, sonidegib

*Not an all-inclusive list
5-FU=5-fluorouracil, MTX=methotrexate

Cemiplimab: Clinical Impact[48]

Potential Advantages

- Appears to be active across all levels of PD-L1 expression
- May be first PD-1/PD-L1 approved for cSCC
- Appears to be well-tolerated in clinical trials

Potential Disadvantages

- Number of patients studied may be too small to detect difference among PD-L1 levels
- Expansion of market share may be limited by well-established options

Cemiplimab: Economic Impact[56]

Cost

- Cost data not available
  - May be similar in cost to other PD-1/PD-L1 agents (~$150,000/year)*
- Supplemental rebate – limited market competition for cSCC
- Value-based contracts – improved survival

*Based on 70 kg patient

Cemiplimab: Economic Impact[45,46,57]

Volume

- Incidence: 2-10 in 100,000 individuals diagnosed with metastatic cSCC annually
- Duration: variable; treatment continues until disease progression or remission
- Other key facts
  - Phase II EMPOWER-CSCC1 trial ongoing
  - Also being studied in Phase III for first-line treatment of NSCLC

NSCLC=non-small cell lung cancer

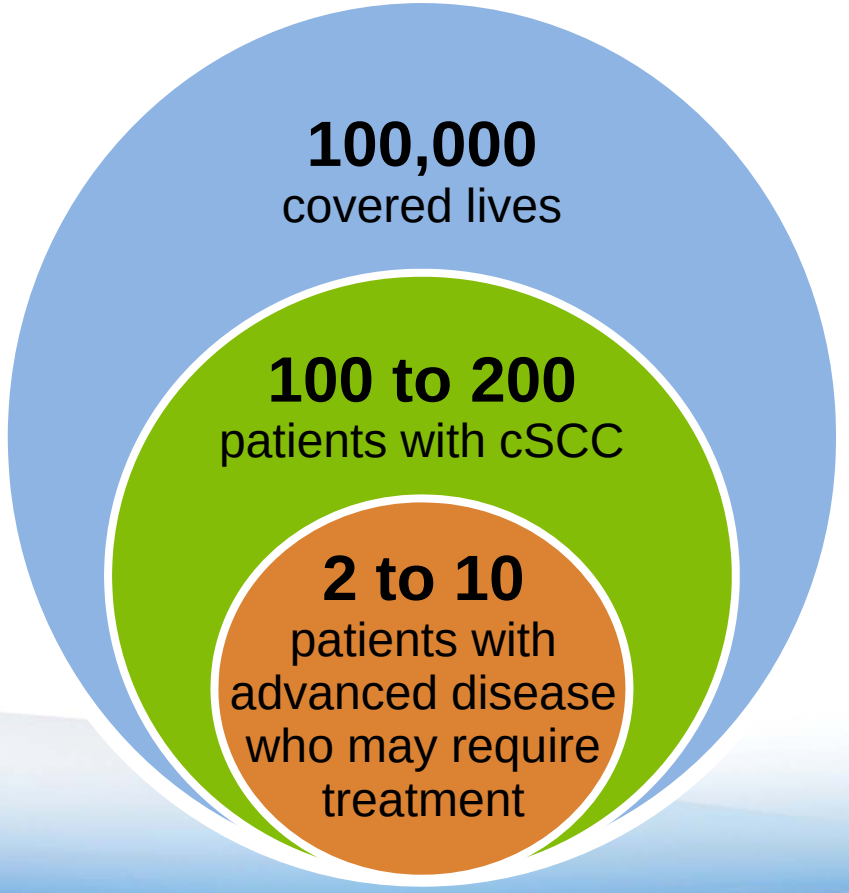
Cemiplimab: Budget Impact[57]

Commercial plan

- Approximately $150,000/year for treatment
- **$300,000 to $1.5 million/year**

Timeline

- Regulatory submission planned for Q1 2018
- Awarded Breakthrough Therapy designation



Q1=first quarter

Atopic Dermatitis[58,59]

Clinical features

- Chronic, inflammatory skin condition
- Characterized by rash, scaly patches on skin, intense itching
- May lead to skin infection

Prevalence

- Affects 7-30% of children and 1-10% of adults with 95% of cases starting before age 5
- 50% of patients with atopic dermatitis in childhood continue to have milder symptoms as an adult

Upadacitinib[60-62]

- **Proposed indication:** atopic dermatitis
- **MOA:** JAK1-selective inhibitor
  - Orally-available, once-daily dosing
  - JAK1 plays a key role in various immune-mediated inflammatory diseases

JAK=Janus kinase

Upadacitinib: Clinical Impact[61]

Phase IIb trial: Design

- Randomized, placebo-controlled, dose-ranging
- Population: N=167; adults with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical agents
- Intervention: upadacitinib 7.5 mg, 15 mg, or 30 mg once daily vs. placebo x 88 weeks
- Primary outcomes: change in EASI at 16 weeks

EASI=Eczema Area and Severity Index

Upadacitinib: Clinical Impact[61]

Phase IIb trial: Results at 16 weeks

Outcome	Upadacitinib			Placebo
	7.5 mg	15 mg	30 mg	
Mean percent change in EASI	39%*	62%**	74%***	23%
Proportion of patients achieving EASI75	29%*	52%**	69%***	10%
Proportion of patients achieving EASI90	14%*	26%**	50%***	2%
IGA score 0 or 1	14%*	31%***	50%***	2%

*P=0.05, **P=0.001, ***P<0.001
IGA=Investigator's Global Assessment

Upadacitinib: Clinical Impact[63-66]

Therapeutic alternatives*

- TCS, emollients
- Topical calcineurin inhibitors (e.g., tacrolimus, pimecrolimus)
- Phototherapy
- Systemic immunosuppressants (e.g., cyclosporine)
- First generation antihistamines – improve sleep
- Topical PDE-4 inhibitor (e.g., crisaborole)
- IL-4 MoAB (e.g., dupilumab)

*Not an all-inclusive list
IL=interleukin, PDE=phosodiesterase, TCS=topical corticosteroids

Upadacitinib: Clinical Impact[67-73]

Atopic dermatitis pipeline*

Drug name	MOA	Phase of development
Oral		
Apremilast	PDE-4 inhibitor	Phase II
Baricitinib	JAK inhibitor	Phase III
Injectable		
Lebrikizumab	IL-13 MoAB	Phase II
Mepolizumab	IL-5 MoAB	Phase II
Nemolizumab	IL-31 receptor A MoAB	Phase IIb
Tralokinumab	IL-13 MoAB	Phase III

*Moderate-to-severe disease; not an all-inclusive list

Upadacitinib: Clinical Impact[61,68,74-77]

Potential Advantages

- May be the first oral targeted therapy for underlying cause of disease
- Upadacitinib 30 mg/day appears to have similar efficacy compared to dupilumab*

Potential Disadvantages

- Likely to be significantly more costly than other oral treatment options
- Safety concerns with baricitinib, a JAK-1/2 inhibitor in development for RA

*Based on IGA and EASI75 data from LIBERTY AD CHRONOS trial

Upadacitinib: Economic Impact[56,61]

Cost

- Cost data not available
  - May be similar or lower in cost to dupilumab (~$35,000)
- Supplemental rebate – preferred atopic dermatitis agent
- Value-based contracts – improvements in EASI/IGA scores, patient adherence/persistence

Upadacitinib: Economic Impact[58,61,78-80]

Volume

- Prevalence: 10.7% of children, 10.2% of adults
  - Estimated that 33% of children with atopic dermatitis have moderate-to-severe disease
  - 7 to 8 million adults in US; approximately 1.6 million with uncontrolled disease per physician survey
- Duration: chronic condition; treatment is indefinite
- Other key facts
  - Also being studied in RA, PsA, UC, AS, and Crohn's

AS=ankylosing spondylitis, PsA=psoriatic arthritis, RA=rheumatoid arthritis, UC=ulcerative colitis

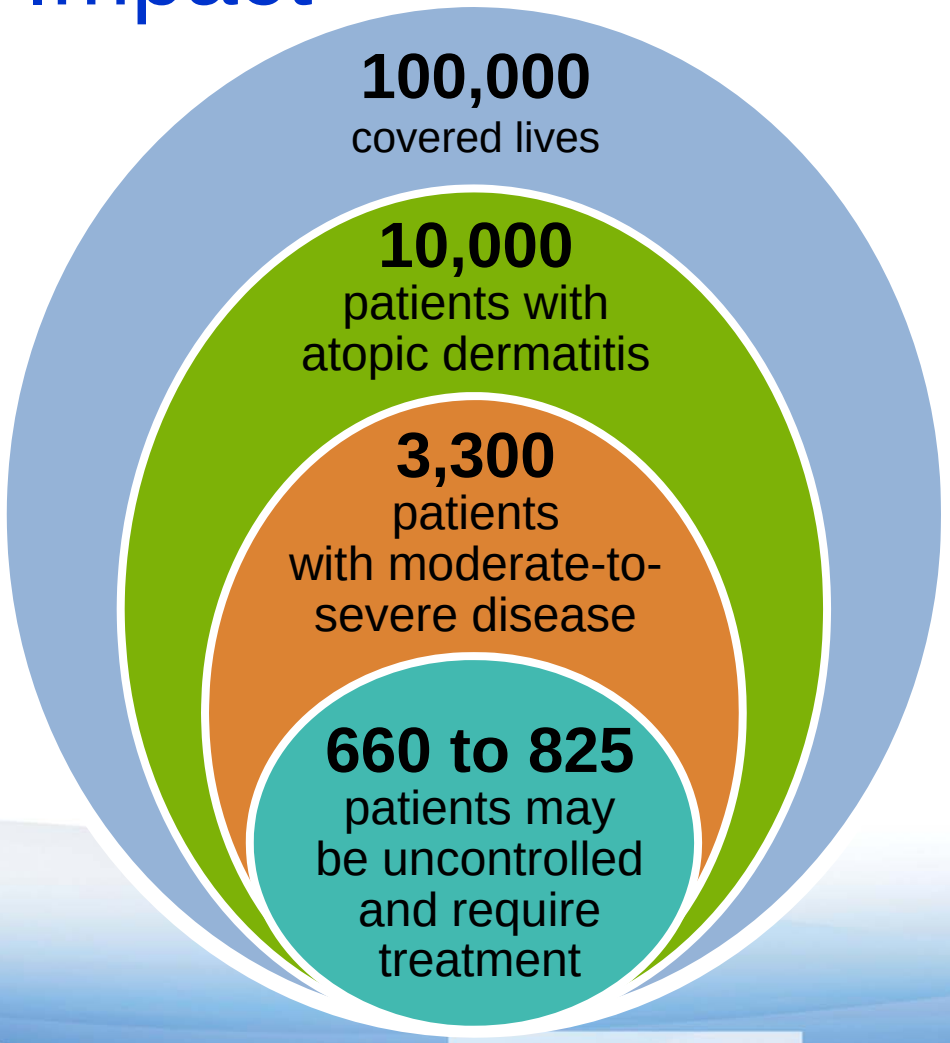
Upadacitinib: Budget Impact[81]

Commercial plan

- Approximately $35,000/patient for treatment
- Assume 10% uptake: **$2.3 to $2.9 million/year**

Timeline

- Phase III trial planned for 2018



Conclusions

- Specialty pipeline agents may offer important therapeutic, safety advantages
- Approval of high-cost specialty therapies highlight need for innovative management strategies
- Proactive pipeline monitoring and a solid understanding of plan membership are key to anticipating budget impact of new drugs