Indication-Based Pricing – Evidence from England, France, Canada, and Australia

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Research Questions

1. How do current practices of pricing multiple indication products in key markets affect manufacturer's launch sequencing?

2. What are the implications for patients, payers and the manufacturers?

3. What kind of policy changes are required to implement IBP in practice in a way that would be acceptable for these groups of stakeholders.

Some Hypotheses Based on Theory

1. In markets without IBP, manufacturers demonstrate a tendency to launch first in the indication where there is highest clinical benefit (which may be a niche indication), where budget constraints will have less of an impact on the initial price obtained.
2. Launch sequence depends on both the quality of clinical evidence and the relative clinical benefit demonstrated for an indication.
3. Economic and clinical uncertainties raised at HTA level are predictive of time from MA to launch.
4. Social value judgements, such as burden of disease and disease rarity, may accelerate time to launch and push an indication forward in launch sequence.

Analytical framework

TYPES OF MULTIPLE INDICATION PRODUCTS	
	Indications across different lines of therapy within the same disease area (e.g. adjuvant therapy vs advanced metastatic stage).
	Indications across different diseases within the same therapeutic areas (e.g. melanoma vs lung cancer)
	Indications across distinct therapeutic areas (e.g. Opthalmology vs Oncology)

Methodology

1. Landscape Scanning

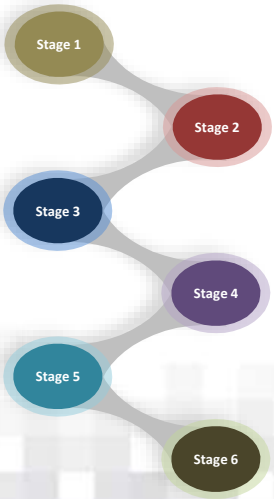
Scan FDA and EMA drug approvals to identify drugs that are suitable for analysis. Drugs must have multiple approved indications in one or more of the EMA, HC or the TGA from 2010-2019.

3. Drug Selection

Drugs will be chosen according to the analytical framework. A minimum of five drugs with multiple indications across therapeutic areas, ten drugs with multiple indications across diseases within the same therapeutic area, and ten drugs with multiple indications across different lines of therapy will be selected from those identified in Stage 1.

5. Primary Data Collection

Interviews will be conducted with decision makers across settings in order to address the questions surrounding practical IBP implementation, experiences with IBP, advantages, limitations, and best practices.



2. Country Selection

Research focuses on key markets in Europe, North America and Australia. Country selection is based on public availability of HTA reports, in order understand how evidence is perceived and how decisions are made. This includes Germany, France, England, Scotland, Sweden, Canada, and Australia.

4. Secondary Data Extraction

The unit of analysis will be drug-indication pairs. Data will be extracted on target population, degree of unmet need, MA dates, HTA dates, resubmissions, HTA decision, HTA restrictions, clinical trial design, type of clinical endpoints, performance of clinical endpoints, uncertainties (both clinical and economic), social value judgements, and funding arrangements

6. Impact Analysis and Recommendations

Secondary data analysis will attempt to address project research questions and test hypothesis. Based on the results across jurisdictions a series of policy recommendations will be made .

Variables

Dependent Variable	Description
Launch Sequence	The sequence in which multiple indications of a single molecule are launched within an individual setting
Explanatory Variables	**Description**
Prevalence	The estimated eligible population to receive a drug within a defined indication
Managed Entry Agreement	Outcomes-based or financial managed entry agreement
Clinical Trial Design	The design of the pivotal trial used to support HTA submissions, defined based on phase of study, randomization, blinding, number of arms, and type of comparator
Type of Primary Endpoints	Surrogate or clinical
Performance of Endpoints	Endpoint performance is based on the pre-defined criteria within the clinical trial.
Clinical Uncertainties	Includes uncertainties relating to clinical benefit, comparators, indirect comparisons, generalizability, clinical practice, and safety.
Economic Uncertainties	Includes uncertainties relating to type of model, extrapolation, costs, utilities, cost-effectiveness, budget impact, and sensitivity analysis.
Social Value Judgements	Includes burden of disease, disease rarity, unmet need, mechanism of action, equity, and administration advantage

3 Case Studies – Evidence from England, France, Canada and Australia

1. Abiraterone Acetate (Zytiga)
   - Multi-indication across different lines of therapy

2. Pembrolizumab (Keytruda)
   - Multi-indications across different diseases within same therapeutic area

3. Nintedanib (Ofev/Vargatef)
   - Multi-indication across therapeutic areas

Zytiga – Abiraterone Acetate

3 indications launched across different lines of therapy

Indication	Date of First MA (Agency)	Time to 2nd MA (days)	Time to 3rd MA (days)	Time to 4th MA (days)
1. 2nd Line MCRPC	28/04/2011 (FDA)	90 (HC)	130 (EMA)	308 (TGA)
2. 1st Line MCRPC	15/11/2012 (EMA)	25 (FDA)	194 (HC)	433 (TGA)
3. 1st Line MCSPC	15/11/2017 (EMA)	84 (FDA)	90 (HC)	275 (TGA)

FDA and EMA consistently first to approve indications, followed by HC and then TGA

Zytiga HTA Recommendations

Indication		(SMR, ASMR)		
2nd Line MCRPC	LWC 27/06/2012 #1	Important, III 29/02/2012 #1	No Submission	LWC 01/11/2012 #1
1st Line MCRPC	LWC 27/06/2016 #2	Important, IV 17/06/2015 #2	LWC 22/10/2013 #1	DNL 01/07/2014
1st Line MCSPC	No Submission	Important, III 16/05/2018 #3	No submission	No submission

Zytiga – Time from first MA to HTA

Indication	Average Time to Launch (days)	(days)	(days)	(days)	(days)
1. 2nd Line MCRPC	429	426	307	NS	553
2. 1st Line MCRPC	868	1320	944	341	DNL
3. 1st Line MCSPC	182	NS	182	NS	NS

Average launch time longer for second indication

Initial launch in smaller indication for both UK and France

Indication	Launch Sequence in UK	Time from 1st MA to HTA in UK (days)	Eligible Patients in UK	Launch Sequence in France	Time from 1st MA to HTA in UK (days)	Eligible Patients in France
2nd Line MCRPC	1 (27/06/2012)	426	3124	1 (29/02/2012)	307	4000
1st Line MCRPC	2 (27/06/2016)	1320	5900	2 (17/06/2015)	944	5400
1st Line MCSPC	NS	NS	NS	3 (16/05/2018)	182	2500

Initial launch in niche indication, followed by expansion to larger patient populations

Larger relative OS gain seen in first indication

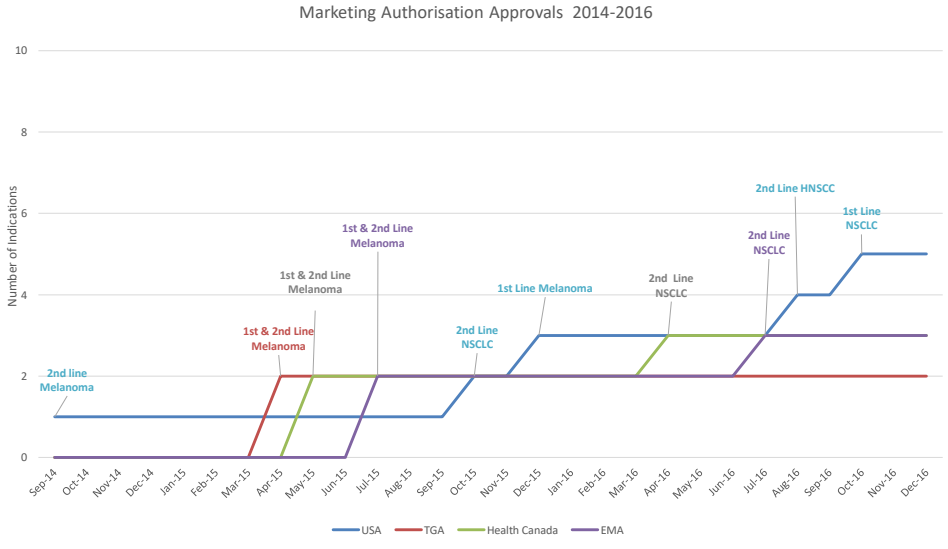
Indication	Pivotal Trial Design	Average Time to Launch	Primary Endpoint	Results
1. 2nd Line MCRPC	Phase III, DB, placebo-controlled RCT	429	OS	14.8 mo vs 10.9 mo*
2. 1st Line MCRPC	Phase III, DB, placebo controlled RCT	868	OS & PFS	OS 34.7 mo vs 30.3 mo* rPFS NR vs 8.28*
3. 1st Line MCSPC	Phase III, DB, placebo controlled RCT	182	OS & PFS	OS NR vs 34.7 mo* PFS 33.0 mo vs 14.8 mo*

Larger relative OS improvement in first indication (End-of-life indication) associated with shorter average launch time

Zytiga - Summary

Impact of Disease Prevalence
Within UK and France, **launched first in smaller population** relative to 2nd indication
Impact of Clinical Trial Design
No differences seen in pivotal trial design across indications.
Impact of Primary Endpoint Results
Smaller relative OS gains in 2nd indication may have contributed to **delays in launch** in England, France, and Canada and a **negative listing recommendation** in Australia.

Keytruda – Marketing Authorisation Approvals 23 Indications, 13 Cancer Types



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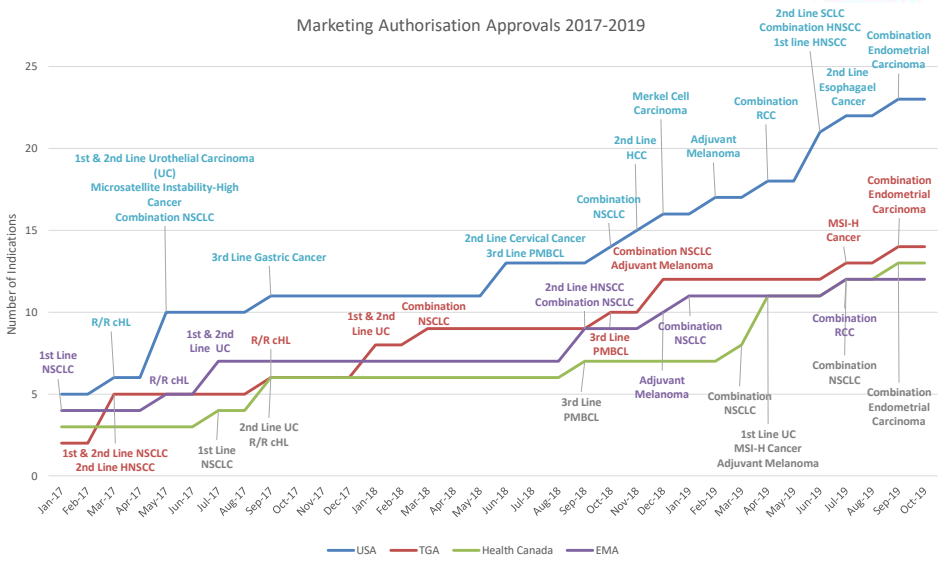


Keytruda – Summary of HTA Recommendations

UK	Canada
EMA – 12 Indications NICE 10 LWC, (6 through new CDF, involving discounted prices and additional evidence generation requirements) 2 No submission	Health Canada – 12 Indications CADTH (PCODR) 8 LWC (3 economic) 1 DNL 3 No submission
France	**Australia**
EMA – 12 Indications HAS SMR – 8 Important, 1 Insufficient ASMR – 3 III, 4 IV, 1 V 3 No submission	TGA – 13 Indications PBAC 5 LWC (5 economic and clinical) 6 DNL 2 No submission

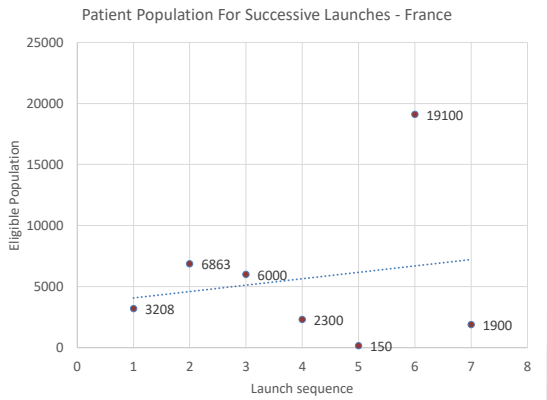
HTA success varies considerably across settings, despite similar number of indications approved

Number of launches and launch sequence varies across settings (England =10 France = 8, Canada =8, Australia =5)

Indications in order of FDA launch				
2nd Line Metastatic Melanoma	1	T1	T1	T1
2nd Line Metastatic NSCLC	3	3	3	
1st line Metastatic Melanoma	2	T1	T1	T1
2nd Line Metastatic HNSCC				
1st line Metastatic NSCLC	5	4	4	T4
Relapsed/Refractory cHL	7	6	5	3
Combination 1st Line NSCLC	9	7	7	
1st line Metastatic Urothelial Carcinoma	6			
2nd line Metastatic Urothelial Carcinoma	4	5	6	T4
2nd Line - Microsatellite Instability-High Cancer (MSI-H)				
3rd line Metastatic Gastric Cancer				
2nd line Cervical Cancer				
3rd line Primary Mediastinal Large B-Cell Lymphoma (PMBCL)				
Combination 1st Line NSCLC	10			
2nd Line Hepatocellular Carcinoma (HCC)				
Metastatic Merkell Cell Carcinoma				
Adjuvant Treatment Melanoma	8	8	8	
Combination 1st line Renal Cell Carcinoma				
2nd Line Small Cell Lung Cancer (SCLC)				
Combination 1st line HNSCC				
1st line HNSCC				
2nd line Metastatic Esophageal Cancer				
Combination 2nd line advanced endometrial carcinoma				

L
LWC
DNL
No Submission
No MA

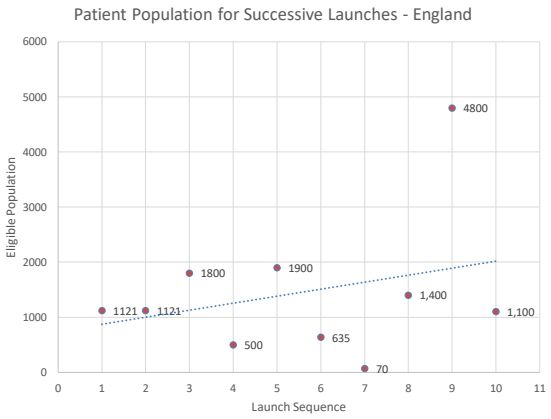
Keytruda – Impact of Disease Prevalence – France



1	Metastatic Melanoma
2	2nd Line NSCLC
3	1st Line NSCLC
4	2nd Line Urothelial Carcinoma
5	R/R cHL
6	Combination 1st Line NSCLC
7	Adjuvant Treatment for Melanoma

Initial launch in niche indication, followed by expansion to larger patient populations

Keytruda – Impact of Disease Prevalence - England



1	2nd Line Melanoma
2	1st Line Melanoma
3	2nd Line NSCLC
4	2nd Line Urothelial Carcinoma
5	1st Line NSCLC
6	1st Line Urothelial Carcinoma
7	R/R cHL
8	Adjuvant Treatment for Melanoma
9	Combination 1st Line NSCLC
10	Combination 1st Line NSCLC

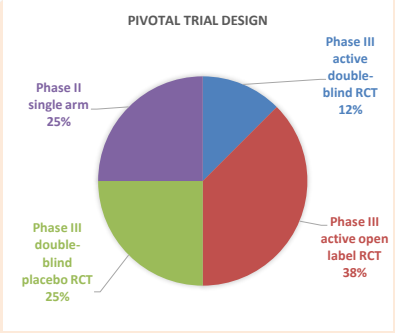
Initial launch in niche indication, followed by expansion to larger patient populations

Keytruda – Pivotal Trial Design

First Indication

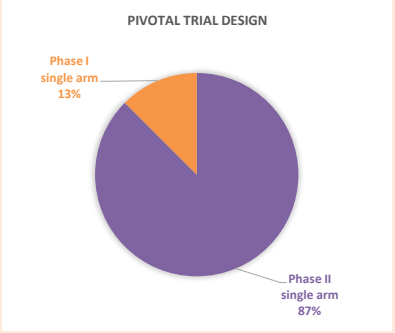
Pivotal Trial Design: Phase III, open label RCT
Primary endpoints: PFS and OS
Results: OS 32.7 months vs 15.9 months p<0.001, PFS 8.4 mo vs 3.4 mo p<0.001

Subsequent Indications (N=8)*



*With MA in one or more of EMA, HC, TGA

US Only Indications** (N=7)



**Excludes indications approved in 2019

Indications approved only in US supported predominantly by phase II single arm pivotal trials

Keytruda – Primary Endpoints

First Indication

Pivotal Trial Design: Phase III, open label RCT
Primary endpoints: PFS and OS
Results: OS 32.7 months vs 15.9 months p<0.001, PFS 8.4 mo vs 3.4 mo p<0.001

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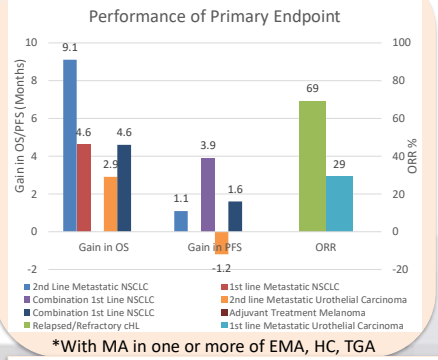

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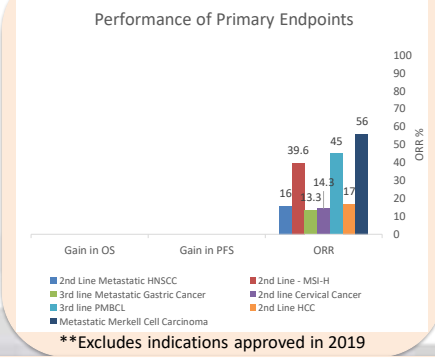
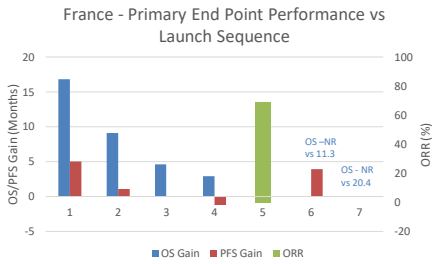
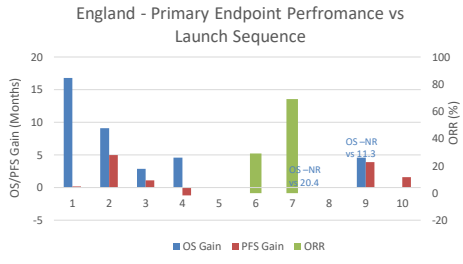


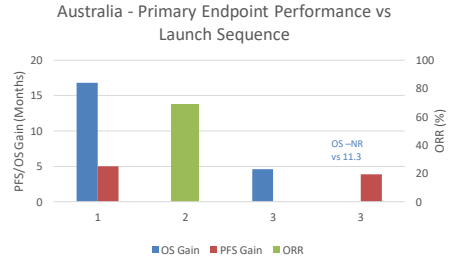
**Excludes indications approved in 2019

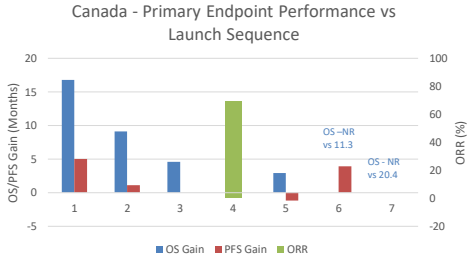
Indications approved only in US exclusively used ORR as primary endpoint in pivotal trial

How does clinical performance in primary endpoint relate to launch sequence?



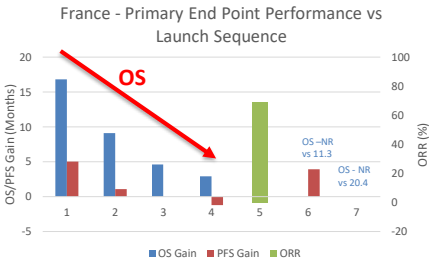


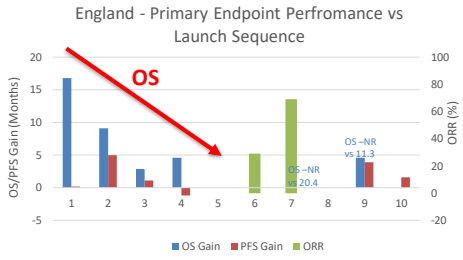


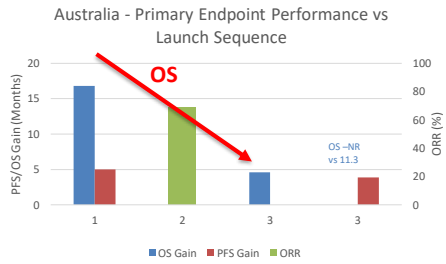


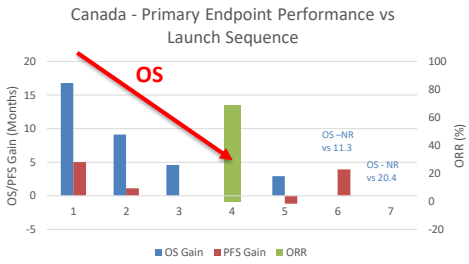
Diminishing performance of primary end point from subsequent indications

How does clinical performance in primary endpoint relate to launch sequence?









Diminishing performance of primary end point from subsequent indications

Keytruda Key Messages

Impact of Disease Prevalence
Slight increasing trend in disease prevalence with successive launches in UK and France
Impact of Clinical Trial Design
Products supported only by **phase II single arm trials** with ORR as primary endpoint **less likely to launch** in England, France, Canada, or Australia
Impact of Primary Endpoint Results
Evidence shows **higher OS and PFS gains** in early indications. Tendency for non-launched or late indications supported by ORR data.

Ofev/Vargatef - Nintedanib

3 indications launched across therapeutic areas

Indication	Date of First MA (Agency)	Time to 2nd MA (days)	Time to 3rd MA (days)	Time to 4th MA (days)
1. Idiopathic Pulmonary Fibrosis (IPF)	15/10/2014 (FDA)	91 (EMA)	253 (HC)	321 (TGA)
2. 2nd line combination therapy for NSCLC	21/11/2014 (EMA)	284 (TGA)	N/A	N/A
3. Systemic Sclerosis-associated Interstitial Lung Disease (SSc-ILD)	06/09/2019 (FDA)	N/A	N/A	N/A

Second Indication only available in EMA and TGA

Nintedanib HTA Recommendations

Indication		 **(SMR, ASMR)**		
For the treatment of idiopathic pulmonary fibrosis (IPF)	LWC **27/01/2016 #2**	Moderate, IV **20/05/2015 #1**	LWC **13/03/2015 #1**	LWC **01/11/2016 #1**
2nd line combination therapy for NSCLC	LWC **22/07/2015 #1**	Insufficient 01/07/2015	Not Authorised	DNL 01/03/2015

Multiple launches only present in UK. HTA rejections seen in France and Australia

Nintedanib – Time from first MA to HTA

Indication	Average Time to Launch (days)	(days)	(days)	(days)	(days)
Idiopathic Pulmonary Fibrosis (IPF)	316	149	217	149	748
2nd line combination therapy for NSCLC	469	469	Insuff-icient	N/A	DNL

Average time to launch longer for 2nd indication

Nintedanib – Disease Prevalence and Clinical evidence

Indication	Launch Sequence	Time from 1st MA to HTA	Eligible Patient Population (UK)	Pivotal Trial(s)	Primary Endpoint	Results
Idiopathic Pulmonary Fibrosis (IPF)	2 (27/01/2016)	149	4410	Phase II, DB, placebo-controlled RCT	annual rate of decline in Forced Vital Capacity (FVC) (mL/year)	-60 vs -191*
				Phase III, DB, placebo-controlled RCT	annual rate of decline in Forced Vital Capacity (FVC) (mL/year)	-115 vs -240*
				Phase III, DB, placebo-controlled RCT	annual rate of decline in Forced Vital Capacity (FVC) (mL/year)	-114 vs -207*
2nd line combination therapy for NSCLC	1 (22/07/2015)	469	600	Phase III, DB, placebo-controlled RCT	PFS	4.0 months vs 2.8 months, HR 0.77 (0.62-0.96)**

*Statistically significant difference. Note the **normal FVC range** for an adult is between 3.0 liters and 5.0 liters.
** Demonstrated a small but statistically significant improvement in OS as a secondary endpoint (2.3 months)

Nintedanib Key Messages

Impact of Disease Prevalence
Within UK, launched **first in smaller patient population** (2nd Line NSCLC)
Impact of Clinical Trial Design
No differences seen in clinical trial design across indications
Impact of Primary Endpoint Results
Acceptability of clinical evidence varies at both regulatory and HTA level. **Limitations in clinical benefit** in 2nd indication may be a **barrier to launching** in France, Australia, and Canada.

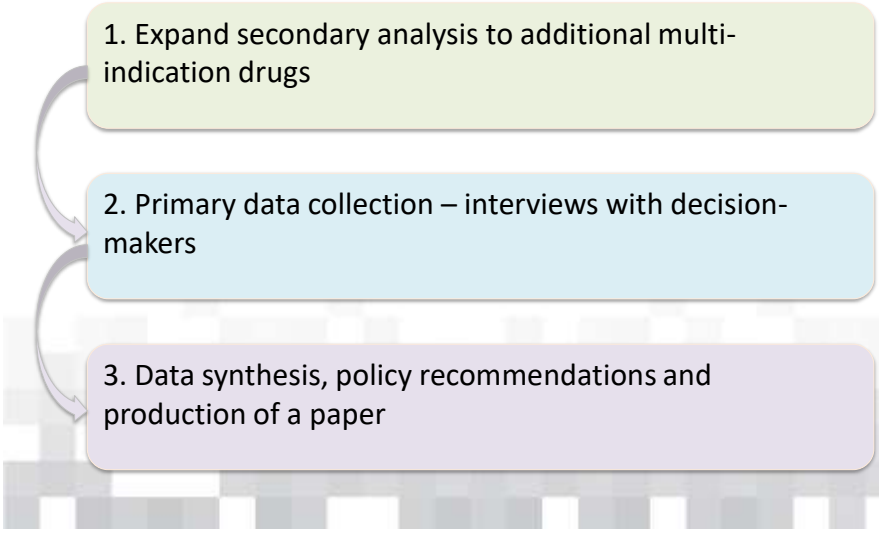
Preliminary Conclusions

1. With some exceptions, indications with evidence based on ORR from single arm phase II trials, are unlikely to be launched in Europe, Canada, or Australia.

2. Manufacturers show a tendency to launch first in areas with highest relative clinical benefit in primary endpoint.

3. Manufacturers show a tendency to launch first in niche indications, before expanding to indications with larger patient populations

Next Steps



Thank you!