EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

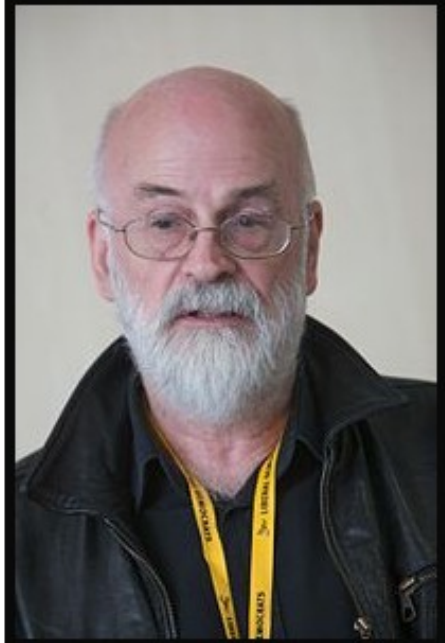
Personalised medicines: what does experience tell us so far?

Regulatory challenges and opportunities

PCWP/HCPWP workshop on personalised medicines

Presented by Rob Hemmings on 14 March 2017
MHRA; CHMP co-opted member; SAWP chair.

MHRA



The way to deal with an impossible task was to chop it down into a number of merely very difficult tasks, and break each one of them into a group of horribly hard tasks, and each of them into tricky jobs, and each of them...

(Terry Pratchett)

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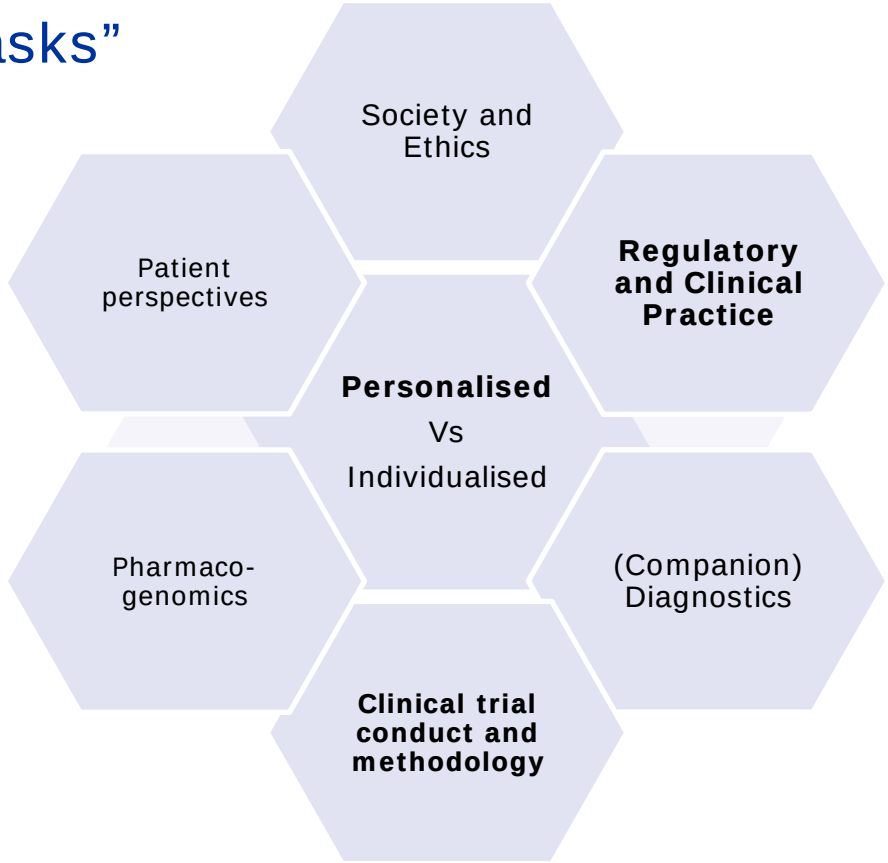
1 Rob Hemmings, Personalised Medicine, EMA

“Very difficult tasks”



“Horribly hard tasks”

- Personalised: genotype / phenotype, intrinsic and extrinsic factors, personal preferences and perceptions (e.g. of risks and benefits). Focus on disease subsets.

- Regulatory: Orphan drugs, B-R decisions, Labelling, Post-Authorisation
- Clinical practice: treatment decisions, costs
- CE marking and CDx

- Clinical trials: Authorisations, Logistics, Interpretation

“Tricky jobs” from SAWP and CHMP

- Context and guidelines
- SAWP
  - Biomarker ‘generation’
  - Impact on drug development and clinical trials
- CHMP
  - Interpretation of clinical data
  - Labelling
  - Impact of labelling on clinical practice
  - Post-authorisation requirements and ‘lifecycle’

Context

Context

Figure 2: Number of medicinal products and ratio of medicinal products containing a genomic biomarker (gene) in their product label under "Therapeutic Indication" per year.

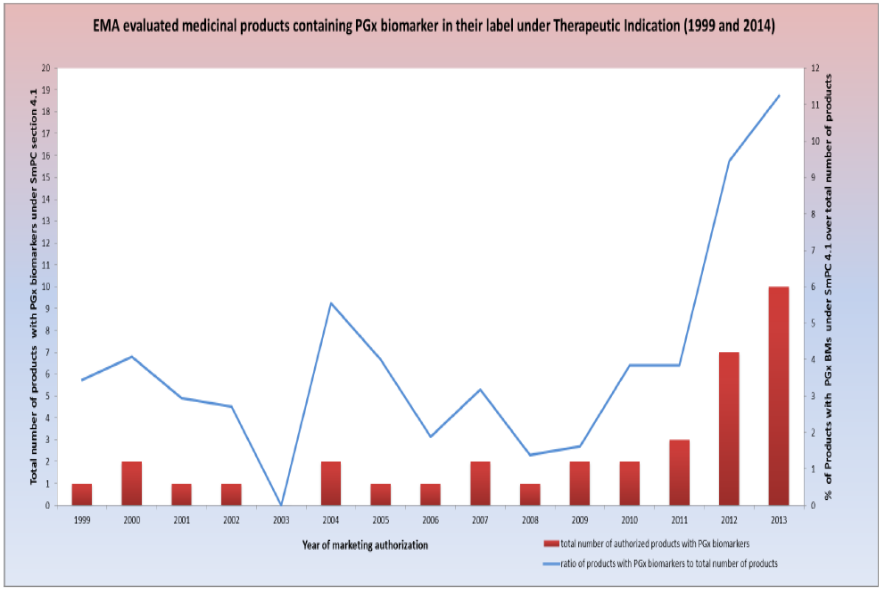


Table 4. Studied patient population (biomarker positive and/or negative) in pivotal clinical trial leading to initial marketing authorisation

PGx biomarker	*Active substance*	*Patient population studied in pivotal trial for initial MAA*
HLA-B*5701	Abacavir (Ziagen) Abacavir/lamivudine (Kivexa) Abacavir/lamivudine/zidovudine (Trizivir)	HLA-B*5701 positive and negative (not tested at time of MAA)
CD30	Brentuximab vedotin (Adcetris)	CD30 positive only
HER2	Everolimus (Afinitor) Trastuzumab (Herceptin) Lapatinib (Tyverb) Pertuzumab (Perjeta) Trastuzumab emtansine (Kadcyla)	HER negative only HER positive only
RAS	Panitumumab (Vectibix) Cetuximab (Erbitux)	Wild-type and mutant
EGFR	Cetuximab (Erbitux) Gefitinib (Iressa) Erlotinib (Tarceva) Afatinib (Giotrif)	EGFR positive only EGFR positive and negative EGFR positive only
ALK	Crizotinib (Xalkori)	ALK-positive and negative
BRAF V600	Vemurafenib (Zelboraf) Dabrafenib (Tafinlar)	BRAF V600 mutation positive only
BCR-ABL	Imatinib (Glivec) Dasatinib (Sprycel) Nilotinib (Tasigna) Bosutinib (Bosulif) Imatinib (actavis, accord, medac, teva) Ponatinib (Iclusig)	Philadelphia chromosome (bcr-abl) positive (Ph+) only Bioequivalence studies T315I+ mutation only
Kit CD117	Imatinib (Glivec)	Kit (CD 117) positive only
CFTR *G551D*	Ivacaftor (Kalydeco)	G551D positive mutation only
FIP1L1-PDGFR	Imatinib (Glivec)	FIP1L1-PDGFRα positive rearrangement only
T315I	Ponatinib (Iclusig)	T315I positive mutation only
RET mutation	Vandetanib (Caprelsa)	RET mutation positive and negative
PML/RAR-α	Arsenic trioxide (Trisenox)	t(15;17) translocation and/or PML/RAR-α positive and negative

Context

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 June 2011
EMA/446337/2011
Committee for Medicinal Products for Human Use (CHMP)

Reflection paper on methodological issues associated with pharmacogenomic biomarkers in relation to clinical development and patient selection

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 June 2010
EMA/CHMP/641298/2008
Committee for Medicinal Products for Human Use (CHMP)

Reflection paper on co-development of pharmacogenomic biomarkers and Assays in the context of drug development

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 December 2012
EMA/CHMP/205/95/Rev.4
Oncology Working Party

Guideline on the evaluation of anticancer medicinal products in man

"Irrespective of pharmacological class, it is assumed that entrance into clinical development of new molecule today is guided by translational research."

Issues at SAWP

Identification of marker
- e.g. PD1, PDL1
- Which one? Which measure? When?

Understanding of marker
- Prognostic, Predictive

Performance of the diagnostic

Selection of “cut-off”

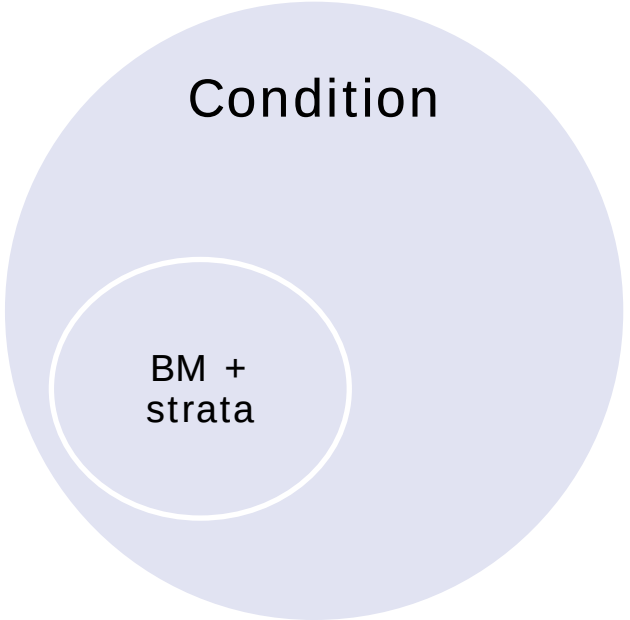
Issues at SAWP; what shape for drug development?

Issues at SAWP – population for confirmatory development

- Primary analysis is usually based on a population of patients that is as close as possible to ‘all randomised’
- Where there is uncertainty about the choice of ‘cut-off’:
  - the sponsor might prioritise a ‘successful’ study by choosing a conservative cut-off
  - this misses the opportunity to generate data to reduce the uncertainty
- Recruit more broadly, with primary analysis based on a pre-defined subset (and as close as possible to ‘all randomised’ within that subset)
- Interpret based on the primary analysis unless the totality of evidence to restrict or extend is compelling
- How important to patients and prescribers is the inclusion of BM-ve patients?

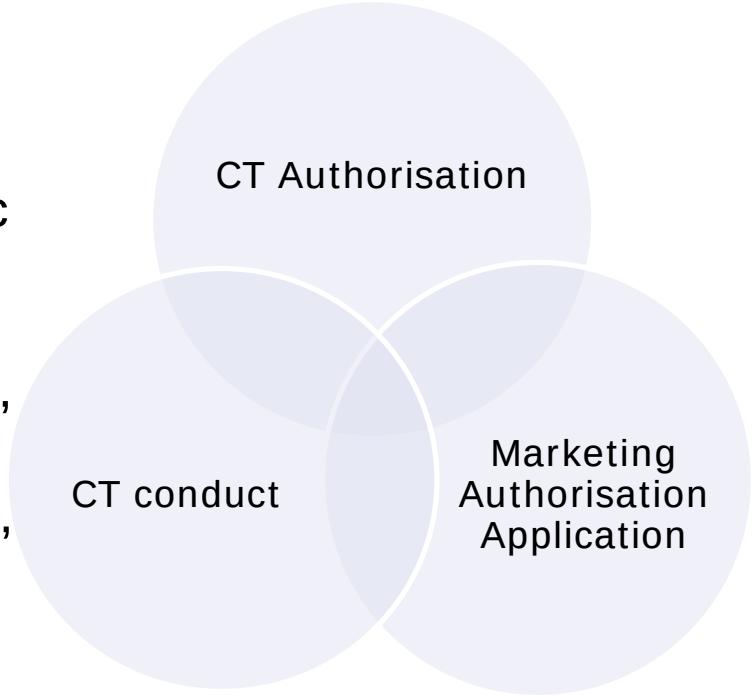
Issues at SAWP – planning for development in rare strata

- Regulatory aspects, e.g.:
  - Unmet medical need?
  - Orphan designation, ‘Similarity’
- Consequences for clinical development
  - Nature of BM difficult to determine
  - Challenges to fully powered RCTs
  - External control data not available
    - Untreated vs Standard of care
    - Time to event endpoints
    - Safety?

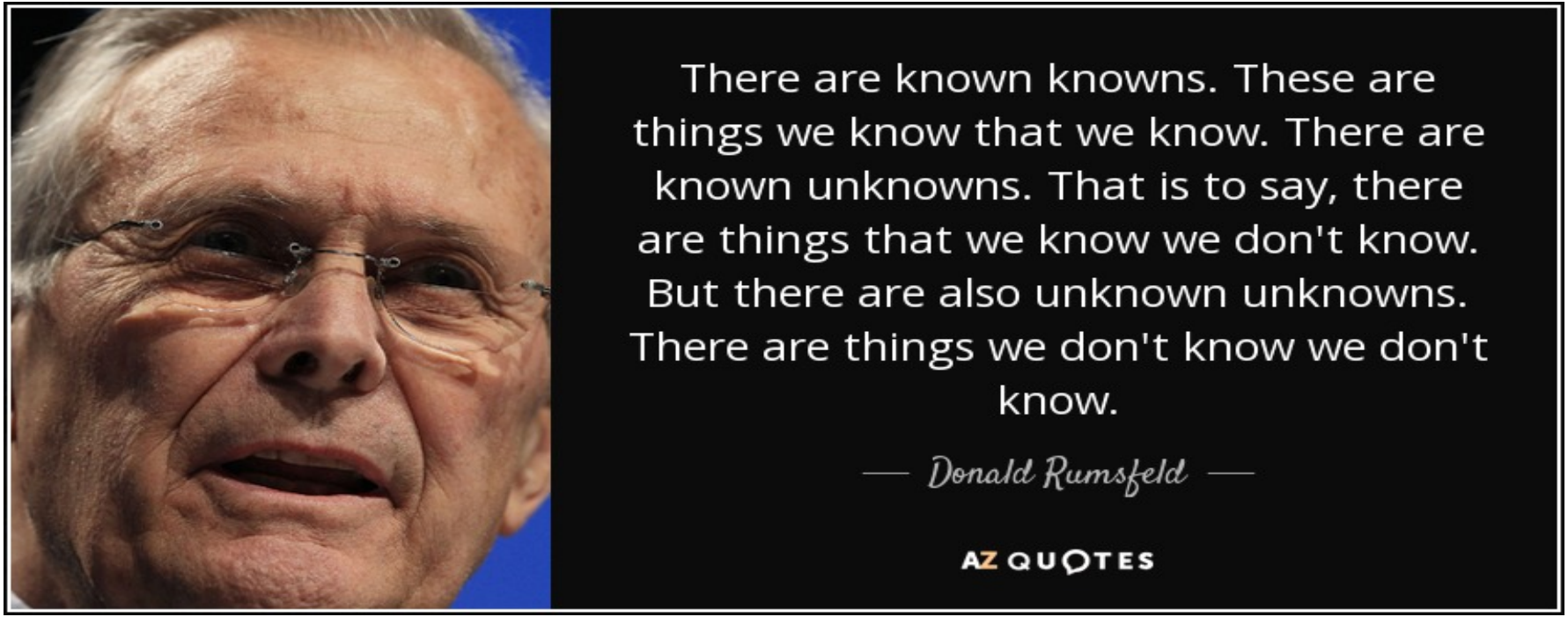


Issues at SAWP – clinical trials

- ‘Umbrella’ trials; e.g. one tumour type, multiple genetic biomarker strata, each with targeted therapeutic
- ‘Platform’ trials; a type of adaptive trial designed to evaluate multiple treatments efficiently (e.g. multi-arm, multi-stage trials).
- ‘Basket’ trials; one genetic biomarker, multiple anatomical locations, one targeted therapeutic

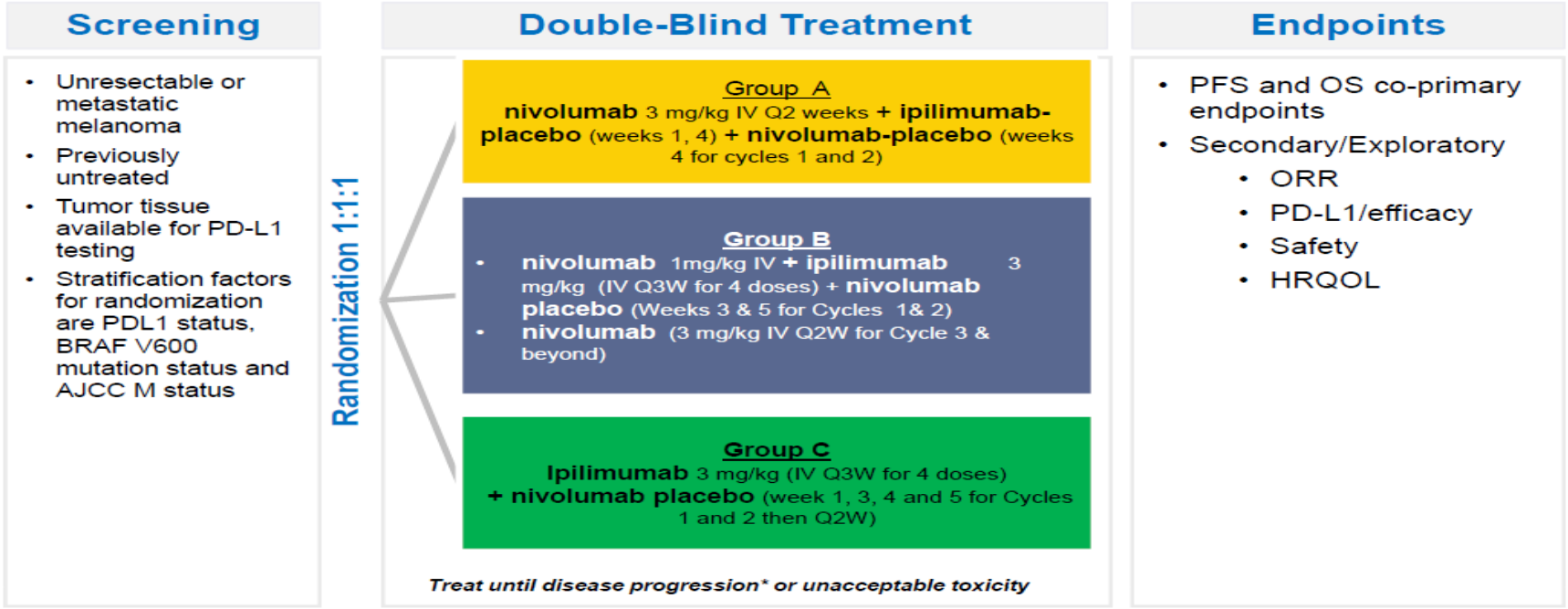


Issues at CHMP



Issues at CHMP

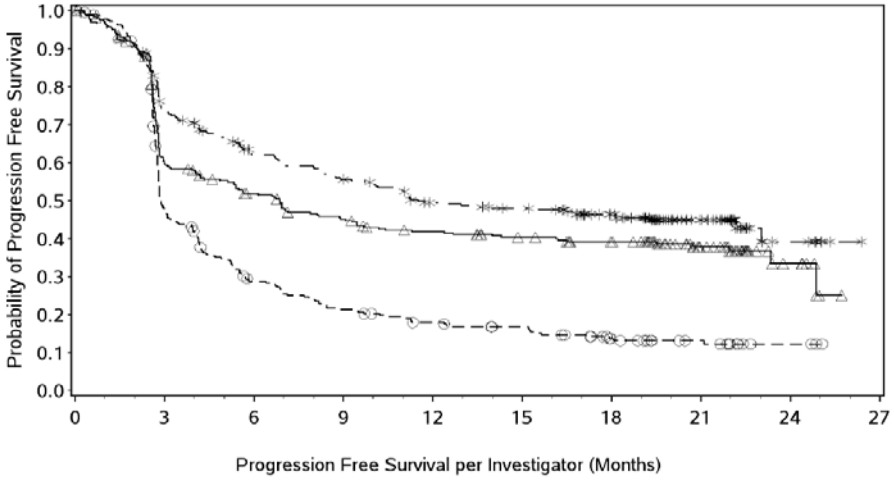
Illustration through Opdivo



A DMC will provide oversight of safety and efficacy considerations

**Patients could be treated beyond progression provided they had a clinical benefit without clinical deterioration, as assessed by investigator*

PFS / OS All Randomized Subjects CA209067

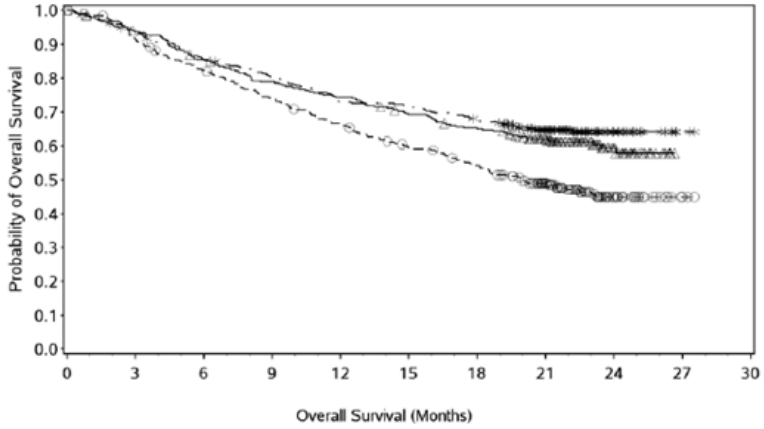


Number of Subjects at Risk

Nivolumab									
316	177	148	127	114	104	94	46	8	0
Nivolumab + Ipilimumab									
314	219	174	156	133	126	103	48	8	0
Ipilimumab									
315	137	78	58	46	40	25	15	3	0

Nivolumab (events: 183/316), median and 95% CI: 6.87 (4.34, 9.46)
Nivolumab + Ipilimumab (events: 161/314), median and 95% CI: 11.50 (8.90, 22.18)
Ipilimumab (events: 245/315), median and 95% CI: 2.89 (2.79, 3.42)

Figure 5.1-1: Kaplan-Meier Plot of OS - All Randomized Subjects - CA209067



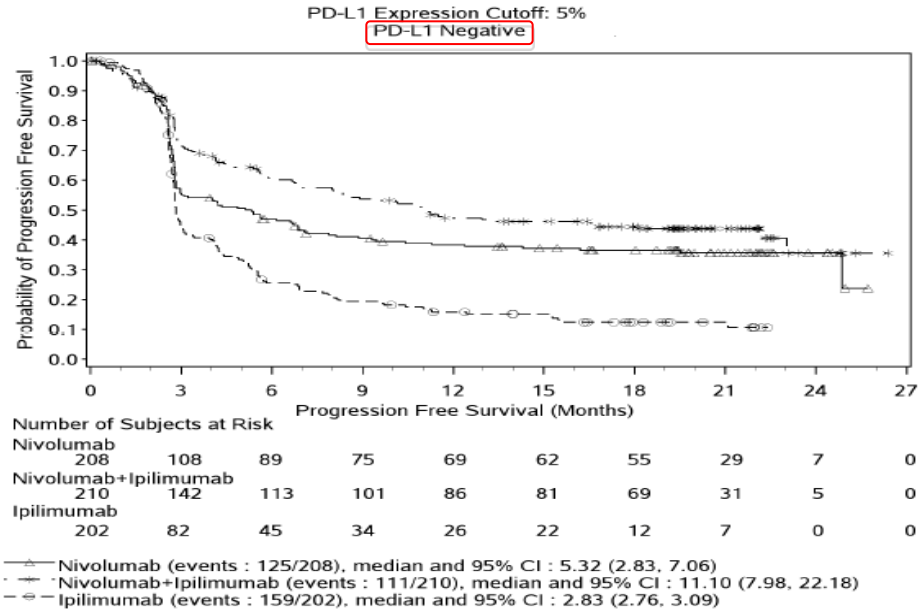
Number of Subjects at Risk

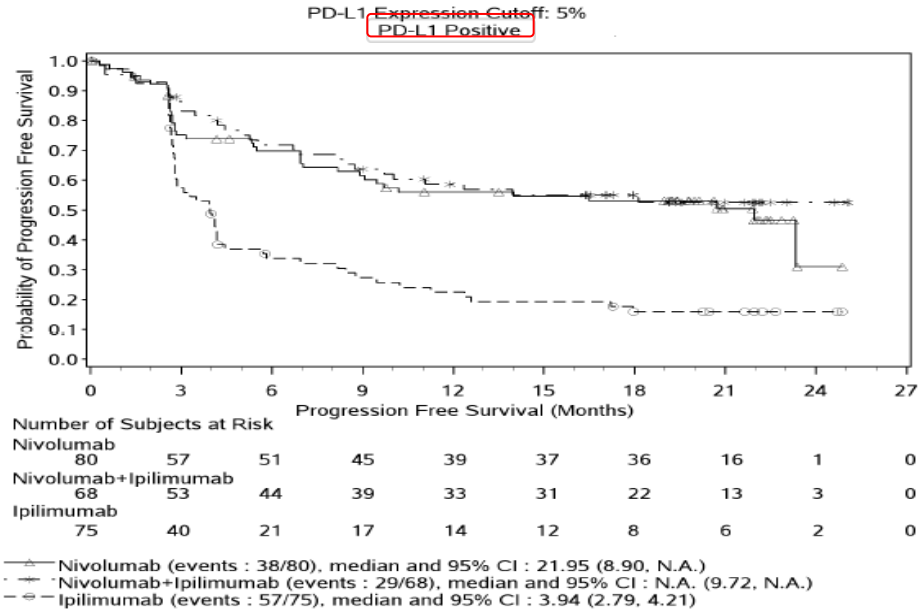
Nivolumab											
316	293	266	245	231	213	200	159	41	0	0
Nivolumab + Ipilimumab											
314	292	265	247	226	221	208	162	44	2	0
Ipilimumab											
315	285	254	228	204	179	161	118	32	3	0

Nivolumab (events: 123/316), median and 95% CI: N.A.
Nivolumab + Ipilimumab (events: 110/314), median and 95% CI: N.A.
Ipilimumab (events: 163/315), median and 95% CI: 19.94 (17.12, N.A.)

Nivolumab vs Ipilimumab - hazard ratio and 99.9% CI: 0.68 (0.46, 1.00)
Nivolumab + Ipilimumab vs Ipilimumab - hazard ratio and 99.9% CI: 0.60 (0.40, 0.91)
Nivolumab + Ipilimumab vs Nivolumab - hazard ratio and 99.9% CI: 0.90 (0.58, 1.38)

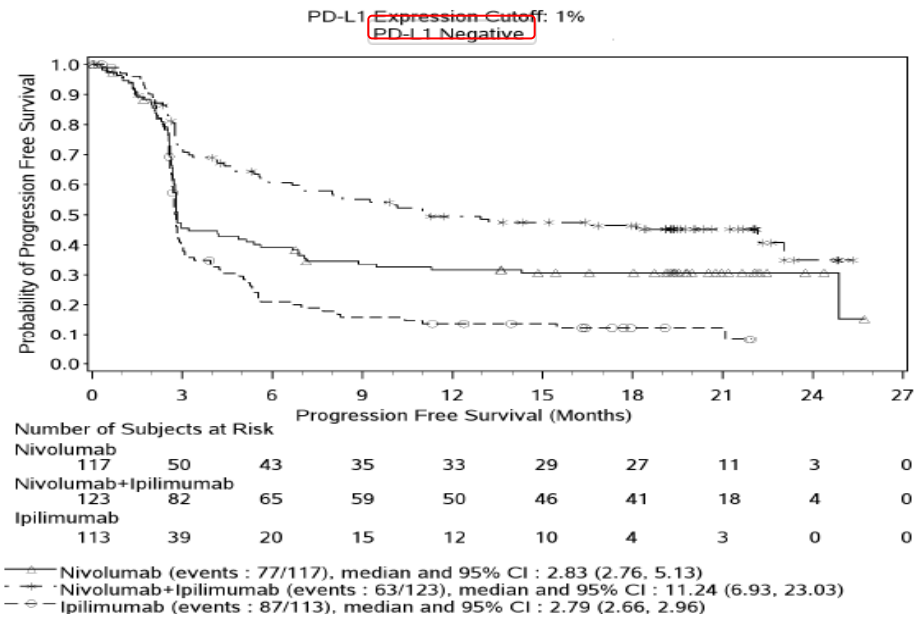
PFS according to PD-L1 CA209067 **Cut-off 5 %**

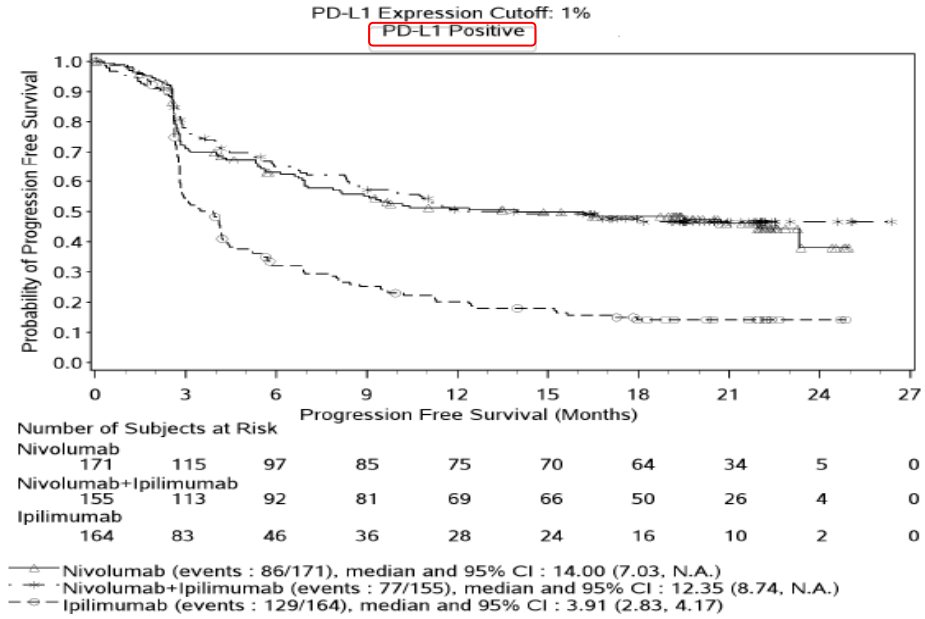




ORR PD-L1-positive (>5 %) (72 % vs 57.5 % combo vs nivo)

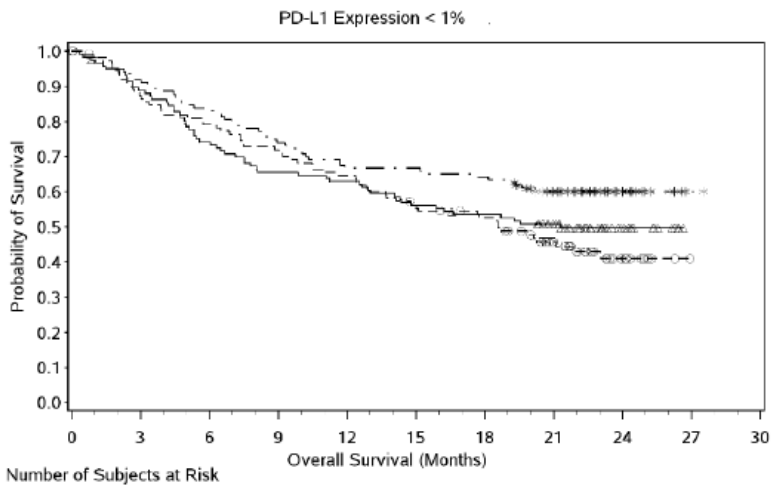
PFS according to PD-L1 CA209067 **Cut-off 1%**





ORR PD-L1-positive (>1%) (64.5% vs 54.4% combo vs nivo)

OS according to PD-L1 CA209067 **Cut-off 1 %**

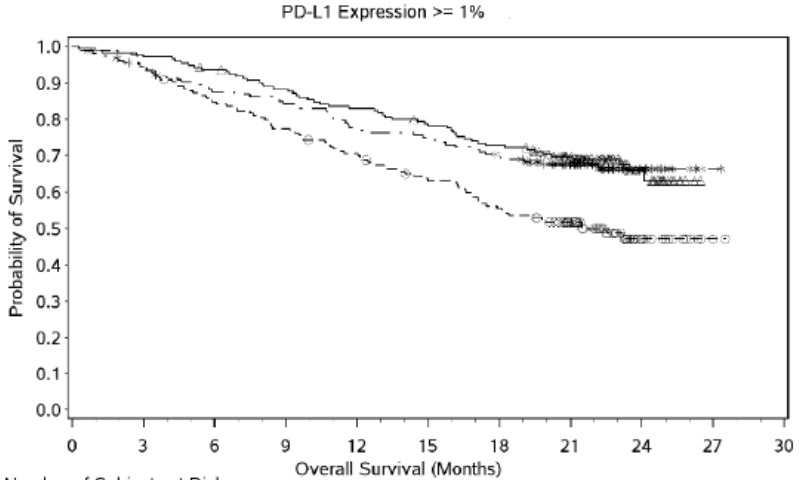


Number of Subjects at Risk

Nivolumab	117	103	86	76	73	65	61	48	13	0	0
Nivolumab+Ipilimumab	123	113	102	91	82	82	79	59	19	1	0
Ipilimumab	113	96	87	79	71	60	55	37	13	0	0

Nivolumab (events : 58/117), median and 95% CI : 21.29 (13.01, N.A.)
Nivolumab+Ipilimumab (events : 49/123), median and 95% CI : N.A.
Ipilimumab (events : 62/113), median and 95% CI : 18.56 (13.67, N.A.)

Nivolumab vs. Ipilimumab - hazard ratio: 0.89 (0.62, 1.27)
Nivolumab+Ipilimumab vs. Ipilimumab - hazard ratio: 0.65 (0.45, 0.94)
Nivolumab+Ipilimumab vs. Nivolumab - hazard ratio: 0.73 (0.50, 1.07)



Number of Subjects at Risk

Nivolumab	171	166	159	149	140	131	122	98	25	0	0
Nivolumab+Ipilimumab	155	144	132	127	116	112	104	82	22	1	0
Ipilimumab	164	155	138	126	114	100	88	69	16	2	0

Nivolumab (events : 55/171), median and 95% CI : N.A.
Nivolumab+Ipilimumab (events : 50/155), median and 95% CI : N.A.
Ipilimumab (events : 82/164), median and 95% CI : 21.49 (17.12, N.A.)

Nivolumab vs. Ipilimumab - hazard ratio: 0.55 (0.39, 0.78)
Nivolumab+Ipilimumab vs. Ipilimumab - hazard ratio: 0.59 (0.41, 0.84)
Nivolumab+Ipilimumab vs. Nivolumab - hazard ratio: 1.07 (0.73, 1.56)

Illustration through Opdivo

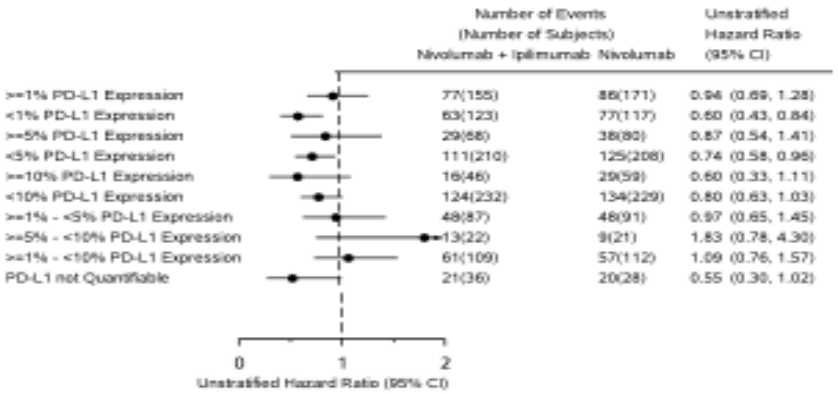
Table 3: ORR by PD-L1 Intervals - All Randomized Subjects in CA209067

	No. of Subjects: (%)				
PD-L1 Expression	**Nivolumab+ ipilimumab**	**Odds Ratio (95% CI)[a,b]**	**Nivolumab**	**Odds Ratio (95% CI)[c]**	**Ipilimumab**
Post-hoc Analyses					
≥1% to <3%	24/50 (48.0)	4.72 (1.77, 13.18)	28/59 (47.5)	4.62 (1.79, 12.55)	9/55 (16.4)
		1.02 (0.45, 2.32)			
≥3% to <5%	27/37 (73.0)	12.60 (3.58, 47.18)	19/32 (59.4)	6.82 (1.96, 25.34)	6/34 (17.6)
		1.85 (0.60, 5.77)			
≥5% to <10%	10/22 (45.5)	2.67 (0.61, 12.50)	12/21 (57.1)	4.27 (0.96, 20.24)	5/21 (23.8)
		0.63 (0.16, 2.44)			
Pre-specified Analyses					
<1%	64/123 (52.0)	4.75 (2.54, 9.04)	39/117 (33.3)	2.19 (1.14, 4.26)	21/113 (18.6)
		2.17 (1.25, 3.79)			
≥1%	100/155 (64.5)	7.80 (4.55, 13.47)	93/171 (54.4)	5.12 (3.04, 8.67)	31/164 (18.9)
		1.52 (0.95, 2.44)			

PD-L1 expression and PFS

Figure 2: **Plot of PFS per Investigator Hazard Ratios by PD-L1 Expression Interval at Baseline - All Randomized Subjects**

A. Pre-specified Analysis:



PD-L1 expression results from validated assay.
Program Source: /gbs/prod/clin/programs/ca/209/067/curia07/rpt/sas/20160119
Program Name: rg-bm-pfs-forest-v01.sas 21JAN2016:22:31:46

B. Post-hoc analysis

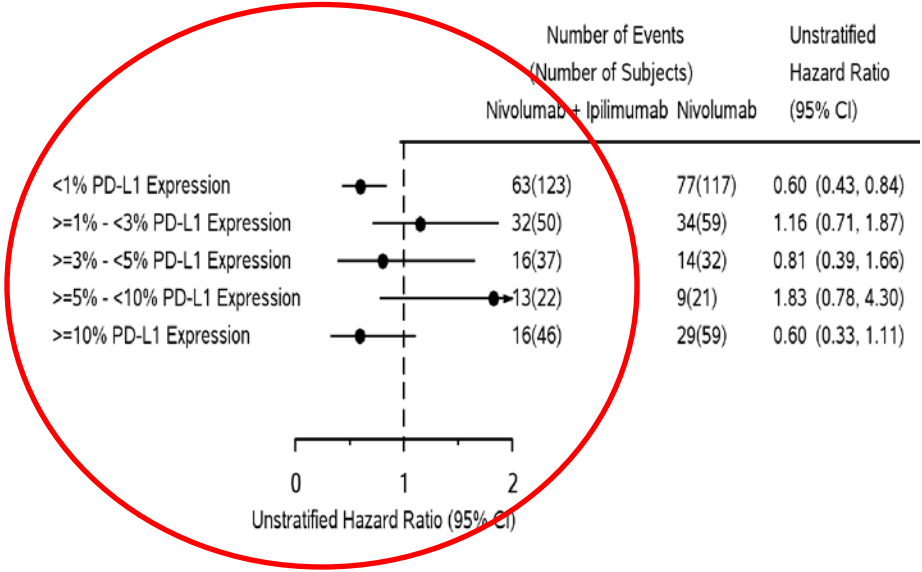


Illustration through Opdivo

- Benefit-Risk Balance?
  - Positive broad indication, with warnings
  - Positive for a restricted indication, with warnings
    - Indicated for patients with low PD-L1 expression
    - Broad indication + qualifying statement
  - Negative until mature OS data become available (by end 2016)

- Pros and Cons for use in practice?

Labelling

- XXX is a targeted antibody-drug conjugate for B cell ALL
- The target is expressed on the surface of B cells and on the blast surface of over 90% of patients with B-cell ALL.
- Does it help to specify in the Indication (4.1) that the patient should be positive for the target?
- What consequences are there from HTA and for clinical practice?

Illustration through Vectibix

An open–label, randomised, phase 3 clinical trials of Vectibix plus best supportive care vs. best supportive care in patients with metastatic colorectal cancer.

Figure 7. Study 20020408: Kaplan–Meier plot of PFS (ITT, IRC assessment)

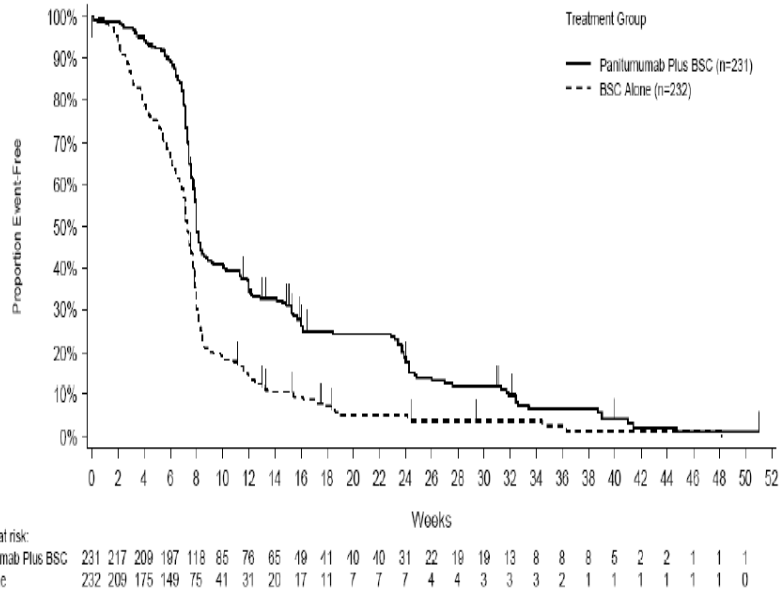


Illustration through Vectibix

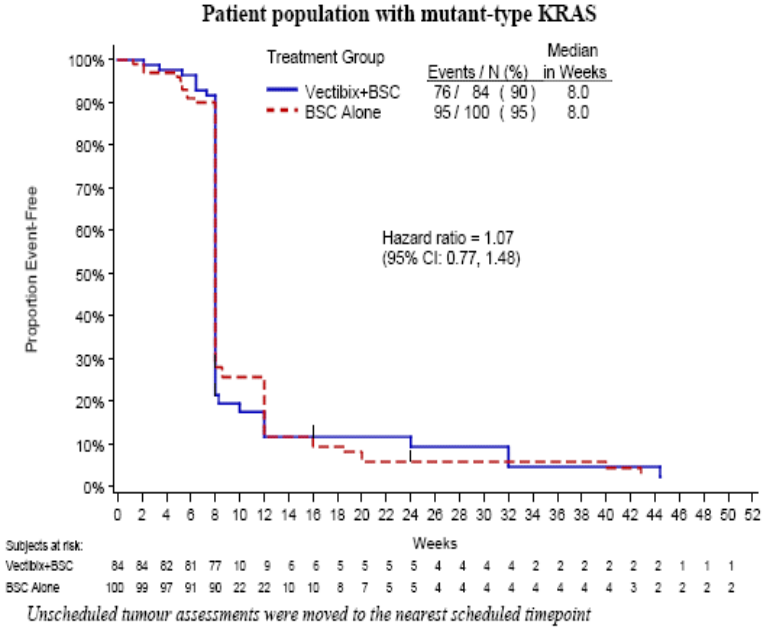
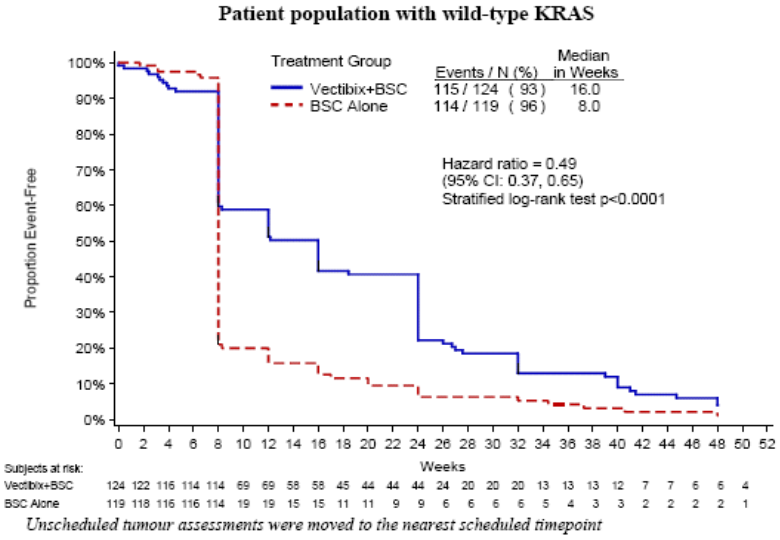


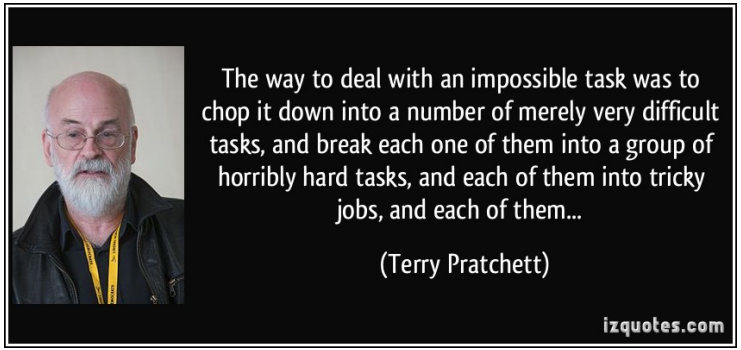
Figure 16. Study 20020408 – Kaplan–Meier plot of PFS (ITT, time adjusted, IRC assessment)

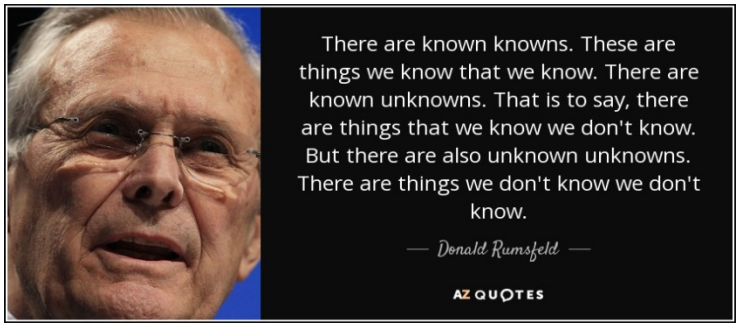


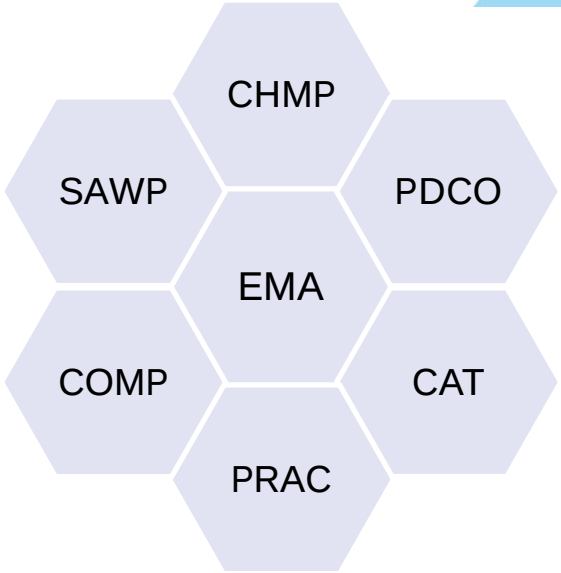
Then post-authorisation……

- Is KRAS being tested in the clinic?
  - How?
  - B-R if not?
  - Is use being restricted to wild-type KRAS?
  - MAH survey and educational materials
  - Who takes responsibility?
- Restriction to RAS wild-type
- New diagnostic identified
  - Does it identify the same patients?
  - B-R on the patient level
  - B-R on the population level
  - Who takes responsibility?

Summary


The way to deal with an impossible task was to chop it down into a number of merely very difficult tasks, and break each one of them into a group of horribly hard tasks, and each of them into tricky jobs, and each of them...
(Terry Pratchett)
izquotes.com


There are known knowns. These are things we know that we know. There are known unknowns. That is to say, there are things that we know we don't know. But there are also unknown unknowns. There are things we don't know we don't know.
— Donald Rumsfeld —
AZ QUOTES


CHMP
SAWP
PDCO
EMA
COMP
CAT
PRAC

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EMA support and contact:

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http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/genera
eneral_content_000059.jsp&mid=WC0b01ac05800240cc

CHMP/ Innovation Task Force (ITF)
itfsecretariat@ema.europa.eu
Briefing meetings with EMA Committees /FDA/PMDA
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/gen
l_content_000334.jsp&mid=WC0b01ac05800ba1d9

CHMP Scientific Advice and **Novel methods qualification** scientificadvice@ema.europa.eu
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/gene
l_content_000049.jsp&mid=WC0b01ac05800229b9