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What is an innovative drug?

Barcelona, March 2014
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MPA

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No Conflict of Interest

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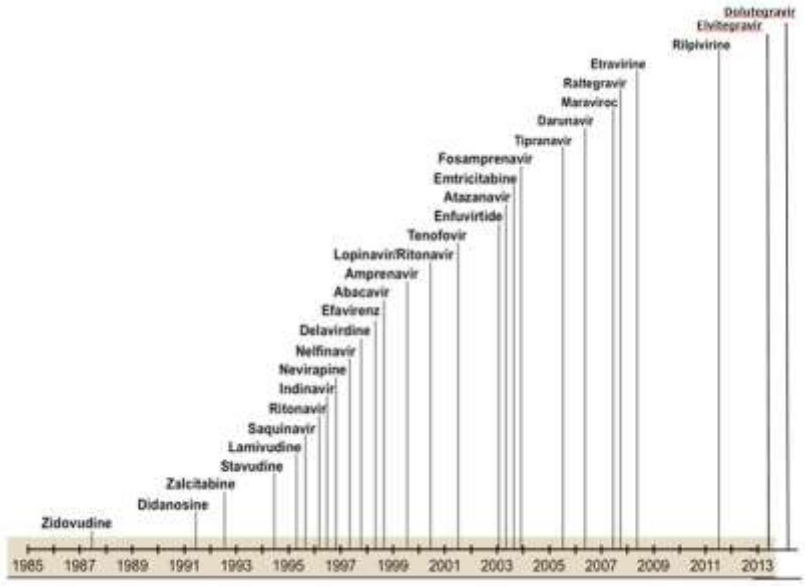

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Where is the innovation?

Benefit/Risk of new drugs.

”Efficacy”: 1995 – 2000

Multiresistance: - 2006

”Safety”: - 2014

Today no detectable virus at minimal risk.

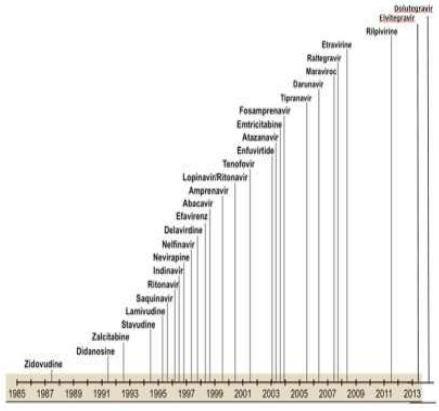
So where is the innovative drug?

Combination therapy (insight)

HIV RNA (technology)

Designed drug discovery (technology)

No individual drug, or?



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Another example

Chronic hepatitis C

1989 and for 20 years: interferon alpha and ribavirin.

2011: Telaprevir and boceprevir (direct acting anti-virals) as add-on to IFN + ribavirin.

2014: Cure within reach for the vast majority of HCV infected with IFN-free regimens and short duration of therapy.

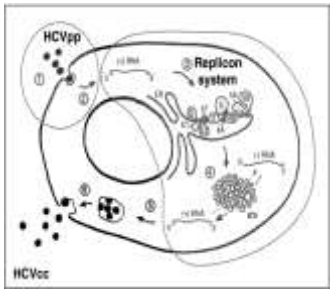
Five years not 25 as in HIV.

Why?

Expertise from HIV.

The **replicon** assay.

Self-replicating HCV **mini-genomes**, called replicons.



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Innovative drugs, how to define?

- Systematic review (Kesselheim et al, 2013, 42 studies included)
  - New molecular entitity.
  - Economic markers or patent
  - *Therapeutic value*

- Comparing Prescrire classification of innovatetiveness with Human Drug Advisory panel (HDA, Canada) (Joel Lexchin, 2012).
- 2004 - 2009

		HDA	
		Innovative	Non-innovative
Prescrire	Innovative	5	7
	non-innovative	7	65

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Innovative drugs, how to define?

- Transformative drugs, 1985 -**2009**, survey among physicians (Kesselheim, Avorn, 2013)
- "Both innovative and has had a groundbreaking effect on patient care and health-care delivery"
- Fifteen specialties, about 10 physicians per specialty, two rounds.
- First round 476 products, second round, 63 drugs, 941 written responses

Oncology products only

- Improved efficacy (55%), rituximab (1998)
- Novel mechanism of action (37%), trastuzumab (2000)
- Impact on practice (24%)
- Scientific merits (15%) imatinib (2001)
- Improved safety (15%) temozolomide (glioma) (1999, 2006)
- Widespread use (12%)

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Innovative drugs, how to define?

Kwong and Norton (1995-2001)

"Creative products," defined as investigational (not yet approved) drugs with novel pharmacological mechanisms of action as compared with existing or investigational drugs for the same indication

- Among 328 investigational drug products currently in clinical trials in 8 therapeutic areas, 130 (40%) were creative products

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Toward a definition of pharmaceutical innovation

Steven Morgan, Ruth Lopert, Devon Greyson

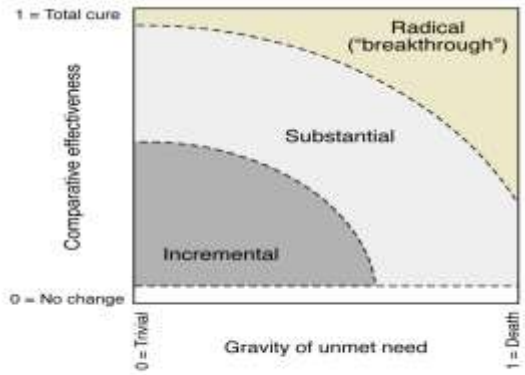

Figure 1: A model of pharmacological innovation

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Is ”innovation” of importance for HTA?

Floortje van Nooten et al. 2012

TABLE 1

Important parameters in the reimbursement process in individual countries [30]

	Australia	Netherlands	Canada	France	Germany	Sweden	Italy	UK
Clinical effectiveness	✔	✔	✔	✔	✔	✔	✔	✔
Cost-effectiveness	✔	✔	✔	✔ (post-launch)	✔ (only in specific cases)	✔	✔	✔
Innovation[a]				✔			✔	

Note: Please note that this table was up-to-date at the time of submitting; however, things keep evolving within healthcare systems, which means this table might change over time.
[a] The term 'innovation' lacks specificity and differs by country. Only Italy has published criteria for identifying an innovative product [31]. With this algorithm, pharmaceuticals are designated as an important, moderate, or modest therapeutic innovation based on (i) the availability of existing products or (ii) the extent of the therapeutic benefit. In France, an improvement of medical benefit (ASMR) level (major innovation, important improvement, significant improvement, minor improvement and no improvement) is assigned for each product, but the criteria used to determine these levels is not defined by the Haute Autorité de Santé. Despite the potential for unclear or conflicting definitions of innovation, the value of demonstrating innovation remains high for reimbursement authorities.

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Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

n engl j med 363;8 august 19, 2010

- Ipilimumab (MoAb IgG1) blocks cytotoxic T-lymphocyte-associated antigen.
  - Overcomes immune tolerance
- Gp100
  - ”Cancer vaccine”
- Three arms: Gp100, ipilimumab, Gp100+ipilimumab

• Median survival	Gp100:	6 months
•	ipilimumab:	10 months (HR 0.67)
•	Ipi + Gp100	10 months (HR 0.68)

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Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

n engl j med 364;26 june 30, 2011

- Non-resectable or metastatic melanoma
- Positive Cobas® 4800 BRAF V600 Mutation Test
- Vemurafenib (Zelboraf) vs. DTIC
- n=675

"After review of the interim analysis by an independent data and safety monitoring board, crossover from dacarbazine to vemurafenib was recommended."

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Vemurafenib, melanoma

Table 5: Overall survival in previously untreated patients with BRAF V600 mutation positive melanoma by study cut-off date (N=338 dacarbazine, N=337 vemurafenib)

Cut-off dates	Treatment	Number of deaths (%)	Hazard Ratio (95% CI)	Number of cross-over patients (%)
December 30, 2010	dacarbazine	75 (22)	0.37 (0.26, 0.55)	0 (not applicable)
	vemurafenib	43 (13)		
March 31, 2011	dacarbazine	122 (36)	0.44 (0.33, 0.59) [1]	50 (15%)
	vemurafenib	78 (23)		
October 3, 2011	dacarbazine	175 (52)	0.62 (0.49, 0.77) [1]	81 (24%)
	vemurafenib	159 (47)		
February 1, 2012	dacarbazine	200 (59)	0.70 (0.57, 0.87) [1]	83 (25%)
	vemurafenib	199 (59)		
December 30, 2012	dacarbazine	236 (70)	0.78 (0.64, 0.94) [1]	84 (25%)
	vemurafenib	242 (72)		

[1] Censored results at time of cross-over

Non-censored results at time of cross-over: March 31 2011: HR (95% CI) = 0.47 (0.35, 0.62); October 3 2011: HR (95% CI) = 0.67 (0.54, 0.84); February 1 2012: HR (95% CI) = 0.76 (0.63, 0.93); December 30 2012: HR (95% CI) = 0.79 (0.66, 0.95)

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Combined BRAF and MEK Inhibition in Melanoma with BRAF V600 Mutations

n engl j med 367; 2012

Endpoint/ assessment	Dabrafenib monotherapy N=54	150/1 Combination N=54	150/2 Combination N=54
Progression-free survival			
Investigator-assessed, median, months (95% CI)	5.8 (4.6, 7.4)	9.2 (6.4, 11.0)	9.4 (8.6, 16.7)
HR (95% CI)	–	0.56 (0.37, 0.87)	0.39 (0.25, 0.62)
p-value	–	0.0057	<0.0001
BICR-assessed, median, months (95% CI)	7.3 (5.5, 9.4)	8.3 (5.6, 11.3)	9.2 (7.6, -)
HR (95% CI)	–	0.73 (0.45, 1.19)	0.54 (0.32, 0.91)
p-value	–	0.1721	0.0121
Investigator-assessed 12-month PFS, % KM estimate, (95% CI)	9 (3, 20)	26 (15, 39)	41 (27, 54)
Overall response rate			
Investigator-assessed, % (95% CI)	54 (39.6, 67.4)	50 (36.1, 63.9)	76 (62.4, 86.5)
Difference, % (95% CI)	–	-4 (-23.1, 15.9)	22 (2.5, 40.7)
p-value	–	0.7730	0.0264
BICR-assessed, % (95% CI)	46 (32.6, 60.4)	39 (25.9, 53.1)	61 (46.9, 74.1)
Difference, % (95% CI)	–	-7 (-26.7, 12.3)	15 (-5.0, 33.7)
p-value	–	0.5008	0.1486
Duration of response			
Investigator-assessed, median, months (95% CI)	5.6 (4.5, 7.4)	9.5 (7.4, -)	10.5 (7.4, 14.9)
n	29	27	41
BICR-assessed, median, months (95% CI)n	7.6 (5.5, -)	11.3 (6.2, -)	7.6 (6.9, -)
n	25	21	33
Overall survival			
HR (95% CI)	–	0.98 (0.51, 1.87)	0.67 (0.34, 1.34)
p-value	–	0.9514	0.2591
12-month survival, KM estimate % (95% CI)	70 (55, 80)	68 (54, 79)	79 (66, 88)

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Confirmatory trial

	Investigator Assessment		BIRC Assessment	
	Dabrafenib+ Trametinib (N=211)	Dabrafenib+ Placebo (N=212)	Dabrafenib+ Trametinib (N=211)	Dabrafenib+ Placebo (N=212)
Number of subjects				
Progressed or died (event)	102 (48)	109 (51)	93 (44)	94 (44)
Censored, follow-up ended	14 (7)	22 (10)	24 (11)	40 (19)
Censored, follow-up ongoing	95 (45)	81 (38)	94 (45)	78 (37)
Estimates for progression-free survival(months)				
1st quartile	5.6	3.7	5.7	4.6
95% CI	(4.8, 6.5)	(3.6, 5.3)	(5.3, 7.1)	(3.7, 5.5)
Median	9.3	8.8	10.1	9.5
95% CI	(7.7, 11.1)	(5.9, 10.9)	(8.3, 11.8)	(7.3, 12.7)
3rd quartile		13.7	13.2	13.9
95% CI	(11.2,)	(12.0, 13.7)	(11.8, 13.2)	(12.7, 13.9)
Adjusted hazard ratio				
Estimate	0.75		0.78	
95% CI	(0.57, 0.99)		(0.59, 1.04)	
Stratified log-rank p-value	0.035		0.085	

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Oncology Drug of the Year, 2013

- Robert et al. (2013)
- Programmed death-1 receptor (PD-1)/its ligand (PD-L1) antibodies
- Breaking tolerance, inhibiting inhibitors
- In contrast to ipilimumab (anti-CTL4/B7), activity at the site of the tumour, not in the lymphnodes.
- Rapid onset of activity, autoimmune phenomenon less common.
- Melanoma, renal cell cancer, non-small cell lung cancer.

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”Four innovative melanoma drugs in four years”

- Ipilimumab
  - First to break tolerance +++
  - First showing survival benefit in melanoma ++
- Vemurafenib (BRAF V600 TK inhibitor)
  - First targeting the driving mutation BRAF V600 +
  - Survival benefit +
- Trametinib
  - Targeting resistance development to BRAFi ++
  - PFS benefit (+)
- Anti PD1 / PD1 ligand
  - Promising ++ (renal, melanoma, **NSCLC)**

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