SourceData – bridging scientific publishing and open science

Dr. Thomas Lemberger
EMBO

1. Open Science
2. SourceData
3. Outlook
1. Open science
Data are from the Survey of scholarly communication tool usage.
https://101innovations.wordpress.com/2016/04/04/support-for-open-science-in-eu-member-states/
Data & publishing: separate worlds

Research data → Database → Users
Data & publishing: separate worlds

Research data

Database

Users

Research data

Journals

Graph: Number of published papers/year
Bridging publishing and open data

Research data → Journals → Databases
Improved Overall Survival in Melanoma with Combined Dabrafenib and Trametinib

Caroline Robert, M.D., Ph.D., Regislawa Korzewska, M.D., Jacob Schachter, M.D., Piotr Rutkowski, M.D., Ph.D., Andrzej Mackiewicz, M.D., Ph.D., Danil Stroblowski, M.D., Michael Kiehlstein, M.D., Reinhard Dunner, M.D., Florent Goerg, M.D., Ph.D., Laurent Mortier, M.D., Vannina Chiorion-Sileni, M.D., Kamill Drucis, M.D., Ph.D., Irina Krajewska, M.D., Axel Hauschild, M.D., Ph.D., Paul Longo, M.D., Pascal Walter, M.D., Georgina V. Long, M.D., Ph.D., Keith Flaherty, M.D., Paul Nathan, M.D., Ph.D., Antonio Ribas, M.D., Ph.D., Anne-Marie Martin, Ph.D., Peng Sun, Ph.D., Wendy Crist, B.A., Jeff Leggo, Ph.D., Stephen D. Rubin, M.D., Shosha M. Little, M.P.H., and Dirk Schadendorf, M.D.

ABSTRACT

BACKGROUND

The BRAF inhibitors vemurafenib and dabrafenib have shown efficacy as monotherapies in patients with previously untreated metastatic melanoma with a BRAF V600E or V600K mutation. Combining dabrafenib and the MEK inhibitor trametinib, as compared with dabrafenib alone, enhanced antitumor activity in this population of patients.

METHODS

In this open-label, phase 3 trial, we randomly assigned 794 patients with metastatic melanoma with a BRAF V600E or V600K mutation to receive either a combination of dabrafenib (150 mg twice daily) and trametinib (2 mg once daily or vemurafenib (960 mg twice daily) orally as first-line therapy. The primary end point was overall survival.

RESULTS

At the preplanned interim overall survival analysis, which was performed after 77% of the total number of expected events occurred, the overall survival rate at 12 months was 72% (95% confidence interval [CI], 67 to 77) in the combination-therapy group and 69% (95% CI, 64 to 74) in the vemurafenib group (hazard ratio for death in the combination-therapy group was 0.69; 95% CI, 0.53 to 0.89; P=0.005). The prespecified interim stopping boundary was crossed, and the study was stopped for efficacy in July 2014. Median progression-free survival was 11.4 months in the combination-therapy group and 7.7 months in the vemurafenib group (hazard ratio, 0.56; 95% CI, 0.46 to 0.69; P<0.001). The objective response rate was 64% in the combination-therapy group and 51% in the vemurafenib group (P=0.04). Rates of severe adverse events and study-drug discontinuations were similar in the two groups. Cutaneous squamous-cell carcinoma and keratoacanthoma occurred in 1% of patients in the combination-therapy group and 2% in the vemurafenib group.

CONCLUSIONS

Dabrafenib plus trametinib, as compared with vemurafenib monotherapy, significantly improved overall survival in previously untreated patients with metastatic melanoma with a BRAF V600E or V600K mutation, without increased overall toxicity. (Funded by GlaxoSmithKline; ClinicalTrials.gov number, NCT01979096.)
Improved Overall Survival in Melanoma with Combined Dabrafenib and Trametinib

Caroline Robert, M.D., Ph.D., Bogusława Korzeczkowska, M.D., Jacob Schachter, M.D., Piotr Rublowski, M.D., Ph.D., Andrzej Mackiewicz, M.D., Ph.D., Davoril Stërman, M.D., Michael Schindler, M.D., Reinhard Dunauer, M.D., Florent Grange, M.D., Ophélie Lambert, M.D., Laurent Mortier, M.D., Vannina Chapron-Silini, M.D., Kamal Ducrè, M.D., Ph.D., Irina Krupczak, M.D., Axel Hauschild, M.D., Ph.D., Paul Longan, M.D., Pascal Wolter, M.D., Georgina V. Long, M.D., Ph.D., Keith Flaherty, M.D., Paul Nathan, M.D., Christof Nickel, M.D., Ph.D., Anne-Marie Martin, Ph.D., Peng Sun, Ph.D., Wendy Crist, B.A., Jeff Legos, Ph.D., Stephen D. Rubin, M.D., Shoshita Little, M.P.H., and Dirk Schadendorf, M.D.

ABSTRACT

BACKGROUND

The BRAF inhibitors vemurafenib and dabrafenib have shown efficacy as monotherapies in patients with previously untreated metastatic melanoma with a BRAF V600E or V600K mutation. Combining dabrafenib and the MEK inhibitor trametinib, as compared with dabrafenib alone, enhanced antitumor activity in this population of patients.

METHODS

In this open-label, phase 3 trial, we randomly assigned 794 patients with metastatic melanoma with a BRAF V600E mutation to receive either a combination of dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) or vemurafenib (960 mg twice daily) orally as first-line therapy. The primary end point was overall survival.

RESULTS

At the planned interim overall survival analysis, which was performed after 77% of the total number of expected events occurred, the overall survival rate at 12 months was 72% (95% confidence interval [CI], 67 to 77) in the combination-therapy group and 65% (95% CI, 59 to 70) in the vemurafenib group (hazard ratio for death in the combination-therapy group, 0.66; 95% CI, 0.53 to 0.84; P=0.005). The prespecified interim stopping boundary was crossed, and the study was stopped for efficacy in July 2014. Median progression-free survival was 11.4 months in the combination-therapy group and 7.7 months in the vemurafenib group (hazard ratio, 0.56; 95% CI, 0.46 to 0.69; P<0.001). The objective response rate was 64% in the combination-therapy group and 32% in the vemurafenib group (P=0.003). Rates of severe adverse events and study drug discontinuations were similar in the two groups. Cutaneous squamous-cell carcinoma and keratoacanthoma occurred in 1% of patients in the combination-therapy group and 10% of those in the vemurafenib group.

CONCLUSIONS

Dabrafenib plus trametinib, as compared with vemurafenib monotherapy, significantly improved overall survival in previously untreated patients with metastatic melanoma with BRAF V600E or V600K mutations, without increased overall toxicity. (Funded by GlaxoSmithKline; ClinicalTrials.gov number, NCT01397984.)
What is a figure?
What is a figure?

Clinical data (from 700 patients) converted into pixels...
2. SourceData
Facilitate discovery and browsing of data and papers
- Facilitate discovery and browsing of data and papers
- Couple discoverability with data availability
Facilitate discovery and browsing of data and papers
Couple discoverability with data availability
Bridge scientific publishing with open science

sourcedata.embo.org
Directed Search

Perturbation: Does Forskolin influence Huntingtin?
Directed Search

Perturbation: Does Forskolin influence Huntingtin?

Search results:

Forskolin → Huntingtin
5 Experiments

Novel targets for Huntington's disease in an mTOR-independent autophagy pathway
Williams E et al.
Nature Chemical Biology 2008
How it works

Forskolin concentration

Huntingtin aggregates after treatment with forskolin.
How it works

Perturbation
Manipulated

Forskolin X

Y Huntingtin

Measured entity
Observed
DataSearch

Data search

Perturbation

Does glucose affect insulin of type: small molecule?

Try: does insulin influence glucose? or does glucose influence insulin?

Fission and selective fusion govern mitochondrial segregation and elimination by autophagy
Gilad Tzuri, Alvaro Pironi, Anthony JA Fulginiti, Hiba Mohamed, Jakob D Wikstrom, Gill Walter, Lindsey Sillers, Sarah E Hong, Steve Krotz, Guy Lash, Joseph Aikou, Min Wu, Benedetto F Fy, Junying Yuan, Jule T Deeney, Barbara E Cynober, Gihan S Sharshar
The EMBO journal 2007

Abstract:
Accumulation of depolarized mitochondria within beta-cells has been associated with oxidative damage and development of diabetes. To determine the source and fate of depolarized mitochondria, individual mitochondria were photobleached and tracked through fusion and fission. Mitochondria were found to go through frequent cycles of fusion and fission in a noisy and random pattern. Fission events often generated a new daughter, while the other had decreased membrane potential and a reduced probability for a fusion event. Together, these patterns generated a population of non-fusing mitochondria that were found to have reduced delta psi and decreased levels of the fusion protein OPA1. Inhibition of the fission machinery through DRP1 (DRP1) or FIS1 (FIS1) decreased mitochondrial autophagy and resulted in the accumulation of depolarized mitochondria, reduced respiration and impaired insulin secretion. Pulsed choline and arrest of autophagy at the pre-autophagosome stage revealed that before autophagy mitochondrial hexokinase (HK) and OPA1, and the coregin expression of OPA1 decreases mitochondrial autophagy. Together, these findings suggest that fission followed by selective fusion segregates dysfunctional mitochondria and permits their removal by autophagy.

Dual melanocortin-4 receptor and GLP-1 receptor agonism amplifies metabolic benefits in diet-induced obese mice.
Clemmensen C et al.
EMBO molecular medicine 2015

Pharmacological correction of obesity-induced autophagy arrest using calcium channel blockers
Hei Jin-Woo H, H Park et al.
Nature communications 2014

sourcedata.embo.org
Defective NOD2 peptidoglycan sensing promotes diet-induced inflammation, dysbiosis, and insulin resistance.
EMBO molecular medicine: 2015

Abstract:
Pattern recognition receptors link metabolite and bacteria-derived inflammation to insulin resistance during obesity. We demonstrate that NOD2 detection of bacterial cell wall peptidoglycan (PGN) regulates metabolic inflammation and insulin sensitivity. An obesity-promoting high-fat diet (HFD) increased NOD2 in hepatocytes and adipocytes, and NOD2+/− mice have increased adipose tissue and liver inflammation and exacerbated insulin resistance during a HFD. This effect is independent of altered adiposity or NOD2 in hematopoietically-derived immune cells. Instead, increased metabolic inflammation and insulin resistance in NOD2+/− mice is associated with increased commensal bacterial translocation from the gut into adipose tissue and liver. An intact PGN-NOD2 sensing system regulated gut mucosal bacterial colonization and a metabolic tissue dysbiosis that is a potential trigger for increased metabolic inflammation and insulin resistance. Gut dysbiotics in HFD-fed NOD2+/− mice is an independent and transmissible factor that contributes to metabolic inflammation and insulin resistance when transferred to WT, germ-free mice. These findings warrant scrutiny of bacterial component detection, dysbiotics, and protective immune responses in the links between inflammatory gut and metabolic diseases, including diabetes.

Fatty acid-induced NLRP3-ASC inflammasome activation interferes with insulin signalling
Hätalo H Wen et al.
Nature Immunology: 2011

sourcedata.embo.org
This hormone, insulin, causes the liver to convert more glucose into glycogen (this process is called glycogenesis), and to force about 2/3 of body cells (primarily muscle and fat tissue cells) to take up glucose from the blood through the GLUT4 transporter, thus decreasing blood sugar.

Blood sugar regulation - Wikipedia
Overexpression of Atg5 in mice activates autophagy and extends lifespan

Reproduced from 10.1038/ncomms3300 with permissions

(h) Enhanced insulin sensitivity of Atg5 Tg mice. WT and Atg5 Tg mice were starved for 6h and then i.p injected with 0.75 IU soluble insulin. *P<0.01, **P<0.001 versus control; Student’s t-test.

spectrophotometry method
Overexpression of Atg5 in mice activates autophagy and extends lifespan

Pyo JO et al. Nature communications 2013
Reproduced from 10.1038/ncomms13300 with permissions
Common mechanisms for selective autophagy

To extend the model proposed for Atg30 and the autophagic core machinery proteins, we subjected *P. pastoris* Atg32 mutants to mitophagy assays. Mitophagy was followed by Tom20 localization (Tom20–mCherry) and Tom20 degradation (free GFP appearance from Tom20–GFP). Atg32 and Tom20 colocalized to mitochondria during growth condition in YPL medium (mid-log growth phase) and were degraded only after cells had reached stationary phase or shifted to SD-N (Figs 4A,B; supplementary Fig S5 online). Tom20 degradation was depended on Ypt7, Atg5 and Atg32 (Figs 4A,B), as expected for mitophagy.
Integration with data repositories

https://wwwdev.ebi.ac.uk/biostudies/studies/S-SCDT-MSB-16-7412
An AI approach to semantic analysis

Training set
(20’000 examples)

Artificial neural network

SmartTag engine
An AI approach to semantic analysis

(a) Macrophages were treated with control (Ctrl), Drp1, or Mfn1 siRNA for 72 hr in presence of absence of FK506. Mitochondria and autophagosome lysates were probed as in (b) by immunoblot for Drp1 and Mfn1 to show the efficiency of depletion. (b) We also observed a reduced expression of Bcl-2 expression levels in the brain, heart and kidney of Drp1-deficient mice. (c) GFP-Dr levels are significantly reduced.
An AI approach to semantic analysis

(a) Macrophages were treated with control (Ctrl), Drp1, or Mfn1 siRNA for 72 hr in presence of absence of FK506. Mitochondria and autophagosome lysates were probed as in (b) by immunoblot for Drp1 and Mfn1 to show the efficiency of depletion. (b) We also observed a reduced expression of Bcl-2 expression levels in the brain, heart and kidney of Drp1-deficient mice. (c) GFP-Dr levels are significantly reduced.
Disseminating knowledge

Machine → Manuscript → Knowledge → Author
3. Outlook
‘Smart’ papers
Accelerating science with Open Science

Reliability
Value

Peer Review
Curation

Journals: >1 Mio papers / yr

Preprints
Databases

‘Dark’ Data
Quality Open Science: how to make it work?
Quality Open Science: how to make it work?

Distributed responsibilities:

- Journals
Quality Open Science: how to make it work?

Distributed responsibilities:
- Journals
- Institutions
**Quality Open Science:** how to make it work?

Distributed responsibilities:
- Journals
- Institutions
- Individual researchers
CALLS on the Commission, the Member States and the stakeholders to take the necessary actions needed for making open science a reality and to advocate the need for concerted actions in relevant national, EU, multilateral and international fora; CALLS on the
THANK YOU!

thomas.lemberger@embo.org