### Editorial

### Personalized and targeted therapy for esophageal squamous cell carcinoma

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Abbreviation: ESCC, esophageal squamous cell carcinoma; NGS, next-generation sequencing; OS, overall survival; WES, whole exome sequencing; WGS, whole genome sequencing

Esophageal cancer is the eighth most prevalent cancer in the world. Each year there are more than 480,000 incipient cases and 400,000 deaths with more than 80% occurring in developing countries [1]. Esophageal squamous cell carcinoma (ESCC) is the predominant histologic type worldwide. In China alone, more than 280,000 new cases and 200,000 deaths were estimated in 2010 [2]. Despite the many advances in diagnosis and treatment in past decades, the 5-year survival rate for patients with esophageal cancer ranges from 15-20% [3]. This is mainly due to late diagnosis, aggressiveness of this cancer, and lack of effective treatment strategies [4].

Surgery remains the mainstay of treatment for ESCC although surgery alone achieves poor locoregional control and poor long-term outcome. The 5-year survival rate for non-metastatic ESCC is 10~40% if treated with surgery alone [5]. Unfortunately esophagectomy itself is a complex procedure with significant morbidity and mortality. 2~25% patients die within 30 days after surgery [5].

Since 40%~50% surgical cases have stage III disease [4, 6, 7], most patients are given neoadjuvant chemotherapy with cisplatin/fluorouracil and carboplatin/paclitaxel. A recent meta-analysis showed a significant improvement in overall survival (OS) after neoadjuvant chemotherapy, with a 13% reduction of relative mortality risk and a 5.1% increase of 2-year survival. However, the difference was not statistically significant [7].

More than 50% of patients with ESCC present with unresectable or metastatic disease at the time of diagnosis [4]. Chemoradiotherapy is preferred as a non-surgical approach if there are no contraindications. This combination approach yields superior palliative outcome than radiotherapy alone and improves long-term progression-free survival [8], although its efficacy in locoregional control is inferior to surgery [9]. For chemotherapy, fluorouracil and cisplatin with or without a third drug (such as epirubicin, taxane) are known as the most efficacious combination [10].

Approximately 40% of patients for whom first-line treatment fails will be potential candidates for second-line therapy [11]. Unfortunately, salvage choices of second-line therapy are sparse, and there is no consensus on the optimum [10]. Survival of these patients is poor with a median OS of 5-10 months [12-22]. These data point to a great need of further understanding the mechanisms of ESCC and developing novel and effective approaches for early diagnosis, prevention and therapy.

Recently tremendous progress has been made in cancer genomics and epigenomics with the advent of high-throughput techniques like next-generation sequencing (NGS). Three groups have reported the genetic landscape of human ESCC with whole genome sequencing (WGS) and whole exome sequencing (WES) [23-25]. Genomic alterations include: (1) Single nucleotide variants of many genes with a relatively significant frequency (≥5%), such as p53, KMT2D, Notch1/2/3, FAT1/3, Syne1, EP300, Rb1, Nfe2l2, Cdkn2a, Ajuba, Crebbp, Kdm6A, Fbxw7, MLL2/3, Pik3ca, Pten, Arid2, Pbrm1, etc; (2) Copy number alterations of many genes with a relatively significant frequency (≥5%), such as CCND1, FGFs, CDKN2A, CDKN2B, Pik3ca, Dvl3, LRP5/6, KRas/MRas, EGFR, Akt1, Bcl2l1, Notch1/2/3, E2F1, SFRP4, SOS1/2, Birc5, Yap1, Sox2, Myc, IL7R, etc; (3) Alterations in multiple signaling pathways such as cell cycle regulation, apoptosis regulation, DNA damage control, RTK-Ras-MAPK-PI3K-Akt pathway, Hippo pathway, Notch pathway, Wnt pathway, Nfe2l2/Keap1 pathway, histone modifications, etc. The overall mutation pattern appears similar to that of head & neck SCC [26, 27], but different from those of esophageal adenocarcinoma [28, 29] and lung SCC [30].

In addition to these descriptive data, smoking was found not to be related with signature mutations [23], but non-drinking of alcohol was associated with a cluster of gene mutations [25]. Viral integration was not found in the genomes of 88 subjects [25]. Trinucleotide signature analysis suggested DNA cytidine deaminase (APOBEC3B) induced deamination was mainly responsible for mutations [31] [24]. Moreover, mutations of single genes or gene clusters were associated with patient survival, for example, EP300 mutation [23, 25]. Certain gene, for example, XPO1, was explored as a therapeutic target [24].

These landmark studies provided the research community enormous amount of information to better understand the molecular mechanisms of ESCC. This Editorial is aimed to gain insights from such studies, and propose personalized and targeted therapy as a research direction in the future.

1. **Interpretation of Genomics Data**

**Driver genes and driver mutations** Currently available bioinformatics tools have been designed to prioritize gene mutations at the nucleotide level, gene level, pathway level, and network level.The number of non-synonymous somatic mutations per ESCC averaged more than 80. If a solid tumor ordinarily requires 5 to 8 hits (not necessarily 5-8 mutations) as suggested by classical epidemiologic studies, most of these mutations should be “passengers” instead of “drivers” which can offer selective growth advantage to the tumor cell [32]. Therefore it is critical to identify which gene mutations are cancer drivers.

Since driver mutations may occur at high or low frequencies [33], it may not be safe to prioritize driver mutations according to their frequencies. However, as a clinically relevant parameter, a high frequency of a mutation does support its potential significance in carcinogenesis. Other than Mut-drivers (mutated drivers), Epi-driver is a class of driver genes that are not frequently mutated but aberrantly expressed in tumors through epigenetic alterations in DNA methylation or chromatin modification. Although epigenetics in ESCC has been studied for many years [34, 35], it is still not clear how to differentiate epigenetic alterations that bring forth a selective growth advantage from those that do not [32]. According to Vogelstein’s 20/20 rule, only 125 ‘Mut-driver’ genes of human cancers have been discovered to date, and the number is nearing saturation [32]. Tamborero *et al* reported a list of 291 high-confidence cancer driver genes and 144 candidate genes from 12 different types of cancer [36]. Several databases have become available, for example, Network of Cancer Genes (NCG 4.0) contains 537 experimentally supported genes and 1463 candidate genes inferred using statistical methods [37]. Candidate Cancer Gene Database contains cancer driver genes from forward genetic screens in mice [38]. Considering tissue specificity of ESCC, there is a need of compiling a cancer driver gene list to support future research on ESCC therapy. However, it should be pointed out that cancer driver genes may contain both driver mutations and passenger mutations in cancer. For example, Apc mutations truncating the N-terminal amino acids are driver mutations, while those affecting other regions are passenger mutations. Even for the same driver gene (e.g., K-Ras), different driver mutations (e.g., mutations at codon 12, 13 and 61) have different impact on carcinogenesis and clinical behaviors [39-41]. Because of these complexities, efforts need to be made in order to identify personalized driver genes in cancer [42].

**Pathways and network** Increasing evidence suggests that dysregulation of cellular signaling pathways, rather than individual mutations, contribute to ESCC [43-45]. Driver genes usually do not work in isolation, but together to alter cellular processes [46]. There is growing consensus that pathways rather than single genes are the primary target of mutations [47]. It is interesting that mutations in various components of a single pathway tend to be mutually exclusive [48]. Once driver genes or driver mutations are identified, the next step is to focus on driver pathways with genes grouped together according to the biochemical pathways that they play functional roles in. Pathway activity may be further validated by the downstream readouts, e.g., mRNA and protein expression, morphology, function. Incorporation of immunohistochemistry data or even proteomics data may help evaluation of the pathway activity [49, 50].

One major challenge in analyzing genomics data of ESCC is lack of information of esophagus-specific pathways. Pathway databases, e.g., KEGG, are fairly incomplete and lack tissue and cell-specificities. Applying such pathway information in analyzing ESCC data may generate misleading outcome. For example, using ChIP-seq analyses, Sox2-regulated genes in ESCC cells are different from those in embryonic stem cells because in ESCC Sox2 tends to interact with p63 as opposed to Oct4 in embryonic stem cells [51]. Identifying bona fide target genes and using expression profile of these genes to infer pathway activity in ESCC will be critical in the future [52].

Very few bioinformatics methods involves a principled procedure for taking account of pathway interactions, *i.e.* pathways that are mutated in the same sample, and that are mutated together across a large subset of samples [24]. Similar to expression-based stratification, network-based stratification of tumor mutations can identify cancer subtypes to guide treatment and prognosis [53]. Categorizing ESCC into multiple subtypes according to its molecular alterations may be a practical step leading to final personalization of ESCC therapy. In fact, subtyping has been shown to be a successful approach in managing other cancers [54].

**Drug selection** Selecting drugs according to genomics data has led to promising results in early studies on personalized and targeted therapy [55]. So far most clinically approved targeted drugs are directed against kinases. Some of these have been tried for ESCC (Table 1). Gefitinib, an EGFR inhibitor, has been tested as a second-line treatment for esophageal cancer. In unselected patients it does not improve OS, but has palliative benefits in a subgroup of difficult-to-treat patients with short-life expectancy [56]. Unfortunately only a few cancer drivers have enzymatic activities which are targetable in this fashion. Whether a target is druggable becomes a research question [57]. Once a drug target is verified, drugs or experimental compounds may be developed. Several databases are available for search, e.g., Therapeutic Target Database [58], DrugBank 4.0 [59].

If the target is not druggable, its regulatory proteins or functional pathway may be targeted. For example, Cyclin D1 amplification is commonly seen in human ESCC. Since cyclin D1 mainly functions through CDK activation, CDK4 and CDK6 can be targeted instead of cyclin D1 [60]. P53 is the most commonly mutated genes in human ESCC. Instead of targeting p53, many strategies have been tested to restore the functions of p53 by delivering wild-type p53, targeting MDM2-p53 interaction, restoring the functions of mutant p53, targeting p53 family proteins, eliminating mutation p53 [61, 62].

In addition to selecting drugs for targeted therapy, analysis of drug-metabolism genes in germ-line DNA can also optimize dosing and identify drug toxicity risk [63, 64]. With the help of a database, e.g., Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB), genetic variations can be associated with drug response [65].

1. **Issues in Targeted Therapy**

**Cancer heterogeneity** Various combinations of drivers and pathways result in intratumoral, intermetastatic, intrametastatic or interpatient heterogeneities. It may explain why the same treatment brings about favorable response or resistance in different patients, and why a patient responds well initially and develops resistance over time. Intratumoral heterogeneity has been validated using single-cell RNA-seq of primary glioblastoma [66]. Since the majority of cancer gene mutations do appear in multiple regions of the same tumor, single-region sequencing may be adequate to identify the majority of cancer gene mutations [67]. It can be predicted that most cancer cells in the same tumor may share the major alterations. If this is proven true in ESCC, it will make treatment more predictable.

Intermetastatic and intrametastatic heterogeneity may not be a big concern. Research of many years has failed to identify a group of so-called metastasis genes. Metastasis is probably stochastic depending on the environment in the metastatic site [68]. Therefore if we can understand genetic and epigenetic alterations in the primary tumor well, all cancer cells left at the primary site or metastatic sites are expected to behave in the same way. Nevertheless, the prevalence of different patterns of tumor heterogeneity needs to be more robustly assessed in large patient cohorts, and new patterns will probably be identified as the wealth of genomic data of ESCC is analyzed [69].

**Drug resistance** If carcinogenesis is regard as an evolutionary process with successive new mutations driven by Darwinian selection, chemotherapy, radiotherapy and target therapy may all provide a potent source of artificial selection to alter clonal dynamics. Consequently, the anti-tumor therapy may lead to resistance [70]. Indeed, targeted therapy is associated with a high rate of resistance at the very beginning when Vermurafeni, a BRAFV600E inhibitor, was clinically used for melanoma. Combination of a BRAFV600E inhibitor (dabrafenib) and a MEK inhibitor (trametinib) resulted in better response, yet did not prevent resistance from occurring. Distinct mechanisms include mutations in the target, reactivation of the targeted pathway, hyperactivation of alternative pathways, and cross-talk with the microenvironment [71]. Resistant cells may undergo a process called phenotype switching under the selection of targeted therapy [72]. Understanding these mechanisms has led to additional efforts in finding new therapy targeting the same target, the same pathway, or alternative pathways [73-75].

Three strategies are feasible measures in handling drug resistance. Before treatment, both bioinformatics and experimental modelling may inform heterogeneity [76-78]. There is a need to develop clinically useful measures of heterogeneity [79]. Secondly, during treatment, limited success can be achieved with a single agent. The combination strategy may be the best way to refrain from the inevitable development of resistance to single-drug targeted therapies [47]. Thirdly, longitudinal tumor sampling approaches will be essential to decipher the impact of tumor heterogeneity on cancer evolution, and developing minimally invasive methods to profile heterogeneous tumor genomes will play a major part in following clonal dynamics in real time [77]. For ESCC, repeated biopsy, circulating tumor DNA analysis [80, 81], exfoliative cells [82, 83] are all valid options for this purpose.

**Exceptional responders** As opposed to drug resistance, exceptional responders are patients who have a unique response to treatments that are not effective for most other patients. NCI has embarked on the Exceptional Responders Initiative to understand the molecular underpinnings of exceptional responses to treatment in cancer patients. The goal is to determine whether certain molecular features of the malignant tissue can predict responses to the same or similar drugs.

**Side effects**  As compared with traditional chemotherapy, targeted therapy is better tolerated. However, it does produce toxicities based on several major mechanisms, for example, on-target toxicity, off-target toxicity, hypersensitivity-related toxicities, metabolite-induced toxicities. VEGFR inhibitors cause hypertension and EGFR inhibitors cause toxicities in tissues where EGFR normally play an important functional role in tissue maintenance (e.g., skin, gastrointestinal epithelia). Some of these on-target toxicities may serve as surrogate biomarkers for clinical response [84-88]. Considering these potential side effects, clinical oncologists should be prepared to educate the patients and undertake respective preventive and therapeutic measures.

1. **Research Approaches for Targeted Therapy**

For genomics-guided research, cell line-based platforms have become an indispensable tool [89, 90]. Clarification of genetic and epigenetic alterations of established ESCC cell lines would be great tools for preclinical drug development [91, 92], in particular, KYSE series of ESCC cell lines which have been sequenced [23-25]. Patient-derived ESCC cells can be used for selection of potential individualized therapeutics [93, 94]. These cells are particularly useful in identifying effective drug combinations for acquired resistance [95].

Several models have been put into preclinical research and even clinical applications. Patient-derived xenograft model of ESCC is created when cancerous tissue from a patient’s primary tumor is implanted directly into immunodeficient mice. This model provides solutions to the translational challenges that researchers and clinicians face in cancer drug research and selection [96, 97]. Carcinogen-induced model, for example, N-nitrosomethylbenzylamine-induced model, is a classical model for ESCC research. It mimics human ESCC not only in etiology and histopathology, but also in molecular alterations (e.g., p53 mutations [98, 99]). However, exactly how well this model can mimic human ESCC at the genomics level has been well studied. WES has already shown that carcinogen-induced and genetically engineered models lead to carcinogenesis through different routes. Carcinogen-induced model is particularly important in understanding the complex mutation spectra seen in human cancers [100]. It is encouraging that genomic alterations in 4-nitroquinoline 1-oxide-induced mouse tongue cancer are well preserved [99].

Genetically engineered mouse models of human cancers have proven essential to dissect the molecular mechanisms behind carcinogenesis [101], and provide robust preclinical platforms for investigating drug efficacy [102] and resistance [103-105]. Using Sox2, an amplified oncogene in ESCC [106], as an example, transgenic Sox2 overexpression drives the complete process of carcinogenesis in mice [107]. This model can be readily used for preclinical drug development for Sox2-overexpressing ESCC. Although it may be difficult to target Sox2 itself, its downstream genes or pathways, e.g., Akt/mTOR pathway, can be targeted [94]. Biochemical outcome may be used for assessment of the efficacy of a Sox2-targeting therapy even when it does not reduce tumor incidence or size in mice. Genome engineering with CRISPR-Cas9 *in vivo* is an extremely promising technique in identifying cancer driver genes and testing drug targets [108]. It may ultimately be used for human gene therapy in the future [109].

As a hallmark of human cancer and stands for a crucial determinant of variable response to treatment [90], genomic heterogeneity calls for revision of clinical trial design currently in use in order to implement personalized therapy [110]. The majority of traditional prospective clinical trials are disease-based or histopathology-based. Genomics-driven trials, for example, mutation-based trial, pathway-based trial, subtype-based trial, will be more widely used in drug development [111]. Two genomics-based study designs are currently being utilized to develop targeted therapies, exploratory design and multi-agent sequential design [112]. ESCC fits both study designs very well because the esophagus can be biopsied before and after treatment.

1. **Future Perspectives**

The biggest challenge in ESCC treatment is the translation from genomic discoveries into personalized therapies based on strategies sketched from patients’ individual profiles [110]. Evasiveness of cancer cell has been a frustrating observation of clinical oncologists. Vogelstein *et al* proposed that “there is order in cancer” [32]. This view points to the need to tackling ESCC as a disease status with its own homeostatic mechanisms. From the perspective of ten hallmarks of human cancer [113], Hanahan proposed three strategically distinct “battlespace-guided plans” for cancer treatment, disruption of the enemy’s many capabilities, defense against cancer’s armed forces, and integration of the geographies of the battlefields [114]. It is clear that combination therapy targeting multiple mechanisms would be the only option in the future. Using immunotherapy as an example, tremelimumab (anti-CTLA4) has been tested as a second-line therapy for esophageal cancer. Although the clinical response was not impressive, its biological effect on T cell activation seemed to be associated with clinical response [115]. Recent development of immunotherapy based on Erbb2IP mutation-specific CD4+ T cells [116] and PD-L1 suppression is also quite promising. For patients in which pre-existing immunity is suppressed by PD-L1, blocking PD-L1 enhanced anti-cancer immunity including one case of esophageal cancer [117]. A realistic option in the near future can be a combination of target drugs and traditional chemoradiotherapy for ESCC. Target drugs are expected to kill cancer cells with specific genomic alterations, while traditional therapy acts in a much broader manner.

Technical issues of NGS and bioinformatics are still big hurdles and prevent us from gaining full insights into the mechanisms of carcinogenesis and metastasis of ESCC. WGS nonetheless correlates with incomplete coverage of inherited disease genes, low reproducibility of genetic variation with the highest potential clinical effects, and uncertainty about clinically reportable WGS findings [118]. WES is particularly prone to errors as only 61% of the mutated genes in ESCC are transcribed [24]. This is similar to what has been observed in pancreatic cancer: only 63% of the expected 251 driver gene mutations were identified, suggesting a 37% false negative rate. Marked discrepancies in the detection of missense mutations in identical cell lines (57.38%) have been reported due to inadequate sequencing of GC-rich areas of the exome [119]. The protein-coding genes account for only ~1.5% of the total genome. Although the vast majority of the alterations in noncoding regions are presumably passengers, some of these may be drivers, for example, mutations in Tert promoter [120, 121].

New computational and bioinformatics tools still need to be developed and improved due to low concordance of multiple variant-calling pipelines [122] [123]. Directly comparing genome sequence reads may improve data quality as compared with initial alignment of reads to a reference genome [124].

Apart from the logistic challenges, financial, social and ethical challenges are also posed by personalized and targeted therapy [55]. In addition to viewing a patient’s cancer as a biological phenomenon waiting for medical attention alone, personalized therapy emphasizes biopsychosocial care by including communication and information giving, psychological and emotional well-being, enhancing function, addressing financial concerns, symptom control, spiritual concerns, and social support [125]. If we look at one specific patient’s ESCC from all these perspectives, a tumor board should involve not only medical staff but also supporting staff (Figure 1).

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| Table 1. Clinical trials on targeted therapy of ESCC \*   |  |  |  | | --- | --- | --- | | Target | Agent | NCT Number (Phase) | | EGFR | Erlotinib | NCT00045526 (II), NCT00030498 (I), NCT00397384 (I), NCT00524121 (II), NCT01013831 (I), NCT01561014 (I), NCT01752205 (III) | | Gefitinib | NCT00093652 (I/II), NCT00258297 (II), NCT00258323 (II), NCT00268346 (II), NCT00290719 (I) | | Icotinib | NCT01973725 (II) | | Lapatinib | NCT00239200 (II), NCT01666431 (II) | | Nimotuzumab | NCT02272699 (II/III), NCT01232374 (II), NCT01336049 (II), NCT01402180 (II/III), NCT01486992 (II), NCT01688700 (II), NCT01993784 (I/II), NCT02011594 (II), NCT02034968 (II), NCT02041819 (II) | | Panitumumab | NCT01077999 (II), NCT01262183 (II), NCT01627379 (III) | | PF804 | NCT01608022 (II) | | IGFR | Cetuximab | NCT02123381 (II), NCT00109850 (II), NCT00165490 (II), NCT00381706 (II), NCT00397384 (I), NCT00397904 (II), NCT00425425 (I/II), NCT00445861 (I/II), NCT00509561 (II/III), NCT00544362 (I/II), NCT00655876 (III), NCT00757549 (0), NCT00815308 (II), NCT01034189 (II), NCT01107639 (III) | | Cixutumumab | NCT01142388 (II) | | PI3K | BKM120 | NCT01626209 (I), NCT01806649 (II) | | BYL719 | NCT01822613 (I/II) | | Rigosertib | NCT01807546 (II) | | HDAC | Entinostat | NCT00020579 (I) | | Vorinostat | NCT00537121 (I), NCT01249443 (I) | | HER3 | LJM716 | NCT01598077 (I), NCT01822613 (I/II) | | VEGFR | Vandetanib | NCT00732745 (I) | | Bevacizumab | NCT01212822 (II) | | RAF/VEGFR | Sorafenib | NCT00917462 (II) | | B7H1 | MEDI4736 | NCT01938612 (I) | | Bcl-2 mRNA | Oblimersen sodium | NCT00003103 (I/II) | | CDK | Alvocidib | NCT00006245 (II) | | CRM1 | Selinexor | NCT02213133 (II) | | FGFR | AZD4547 | NCT01795768 (II) | | KIF11 | Litronesib | NCT01059643 (II) | | TACSTD2 | IMMU-132 | NCT01631552 (I/II) | |  |  |  |  |  |  |  |  |  |

\* “Esophageal squamous cell carcinoma” was searched at the website ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)). Targeted therapy has been or is being tried in 62 of 204 studies.

Figure legend:

Figure 1. xxxx

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References

1 Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *International journal of cancer* 2010; **127**(12): 2893-2917

2 Zeng H, Zheng R, Guo Y, Zhang S, Zou X, Wang N, Zhang L, Tang J, Chen J, Wei K, Huang S, Wang J, Yu L, Zhao D, Song G, Chen J, Shen Y, Yang X, Gu X, Jin F, Li Q, Li Y, Ge H, Zhu F, Dong J, Guo G, Wu M, Du L, Sun X, He Y, Coleman MP, Baade P, Chen W, Yu XQ. Cancer survival in China, 2003-2005: A population-based study. *International journal of cancer Journal international du cancer* 2014 [PMID: 25242378 DOI: 10.1002/ijc.29227]

3 Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. *Lancet* 2013; **381**(9864): 400-412 [PMID: 23374478 DOI: 10.1016/s0140-6736(12)60643-6]

4 Enzinger PC, Mayer RJ. Esophageal cancer. *The New England journal of medicine* 2003; **349**(23): 2241-2252 [PMID: 14657432 DOI: 10.1056/NEJMra035010]

5 Kaifi JT, Gusani NJ, Jiang Y, Mackley HB, Dye CE, Mathew A, Kimchi ET, Reed MF, Staveley-O'Carroll KF. Multidisciplinary management of early and locally advanced esophageal cancer. *Journal of clinical gastroenterology* 2011; **45**(5): 391-399 [PMID: 21301357 DOI: 10.1097/MCG.0b013e3182049949]

6 Gebski V, Burmeister B, Smithers BM, Foo K, Zalcberg J, Simes J. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. *The Lancet Oncology* 2007; **8**(3): 226-234 [PMID: 17329193 DOI: 10.1016/s1470-2045(07)70039-6]

7 Sjoquist KM, Burmeister BH, Smithers BM, Zalcberg JR, Simes RJ, Barbour A, Gebski V. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *The Lancet Oncology* 2011; **12**(7): 681-692 [PMID: 21684205 DOI: 10.1016/s1470-2045(11)70142-5]

8 Kleinberg L, Gibson MK, Forastiere AA. Chemoradiotherapy for localized esophageal cancer: regimen selection and molecular mechanisms of radiosensitization. *Nature clinical practice Oncology* 2007; **4**(5): 282-294 [PMID: 17464336 DOI: 10.1038/ncponc0796]

9 Stahl M, Stuschke M, Lehmann N, Meyer HJ, Walz MK, Seeber S, Klump B, Budach W, Teichmann R, Schmitt M, Schmitt G, Franke C, Wilke H. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2005; **23**(10): 2310-2317 [PMID: 15800321 DOI: 10.1200/jco.2005.00.034]

10 Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, Middleton G, Daniel F, Oates J, Norman AR. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *The New England journal of medicine* 2008; **358**(1): 36-46 [PMID: 18172173 DOI: 10.1056/NEJMoa073149]

11 Thallinger CM, Raderer M, Hejna M. Esophageal cancer: a critical evaluation of systemic second-line therapy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2011; **29**(35): 4709-4714 [PMID: 22067408 DOI: 10.1200/jco.2011.36.7599]

12 Conroy T, Etienne P-L, Adenis A, Wagener D, Paillot B, Francois E, Bedenne L, Jacob J-H, Seitz J-F, Bleiberg H. Phase II trial of vinorelbine in metastatic squamous cell esophageal carcinoma. European Organization for Research and Treatment of Cancer Gastrointestinal Treat Cancer Cooperative Group. *Journal of clinical oncology* 1996; **14**(1): 164-170

13 Mafune K, Yamada K, Imamura K, Kubota K, Kaminishi M. Docetaxel, 5-fluorouracil and nedaplatin as second-line chemotherapy for patients with esophageal cancer after esophagectomy: a pilot study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2006; **24**: 14140

14 Yoshioka T, Sakayori M, Kato S, Chiba N, Miyazaki S, Nemoto K, Shibata H, Shimodaira H, Ohtsuka K, Kakudo Y. Dose escalation study of docetaxel and nedaplatin in patients with relapsed or refractory squamous cell carcinoma of the esophagus pretreated using cisplatin, 5-fluorouracil, and radiation. *International journal of clinical oncology* 2006; **11**(6): 454-460

15 Park B-B, Im Y-H, Hwang IG, Lee SC, Ahn JS, Ahn M-J, Lim H-Y, Kang WK, Park K. Salvage chemotherapy with mitomycin C, ifosfamide, and cisplatin (MIC) for previously treated metastatic or recurrent esophageal squamous cell carcinoma. *Investigational new drugs* 2008; **26**(4): 387-392

16 Nakajima Y, Suzuki T, Haruki S, Ogiya K, Kawada K, Nishikage T, Nagai K, Kawano T. A pilot trial of docetaxel and nedaplatin in cisplatin-pretreated relapsed or refractory esophageal squamous cell cancer. *Hepato-gastroenterology* 2007; **55**(86-87): 1631-1635

17 Yamazaki K, Hironaka S, Boku N, Yasui H, Fukutomi A, Yoshino T, Onozawa Y, Hasuike N, Inui T, Yamaguchi Y. A retrospective study of second-line chemotherapy for unresectable or recurrent squamous cell carcinoma of the esophagus refractory to chemotherapy with 5-fluorouracil plus platinum. *International journal of clinical oncology* 2008; **13**(2): 150-155

18 Jin J, Xu X, Wang F, Yan G, Liu J, Lu W, Li X, Tucker SJ, Zhong B, Cao Z. Second-line combination chemotherapy with docetaxel and nedaplatin for Cisplatin-pretreated refractory metastatic/recurrent esophageal squamous cell carcinoma. *Journal of Thoracic Oncology* 2009; **4**(8): 1017-1021

19 Shim H-J, Cho S-H, Hwang J-E, Bae W-K, Song S-Y, Cho S-B, Lee W-S, Joo Y-E, Na K-J, Chung I-J. Phase II study of docetaxel and cisplatin chemotherapy in 5-fluorouracil/cisplatin pretreated esophageal cancer. *American journal of clinical oncology* 2010; **33**(6): 624-628

20 Li X, Lin W, Wang H, Lin W, Lin S, Lin Y. Phase II trial of second-line chemotherapy with docetaxel and capecitabine in advanced esophageal squamous cell carcinoma. *Medical oncology (Northwood, London, England)* 2013; **30**(4): 746 [PMID: 24122256 DOI: 10.1007/s12032-013-0746-x]

21 Song Z, Zhang Y. Second-line docetaxel-based chemotherapy after failure of fluorouracil-based first-line treatment for advanced esophageal squamous cell carcinoma. *OncoTargets and therapy* 2014; **7**: 1875-1881 [PMID: 25342911 PMCID: Pmc4206393 DOI: 10.2147/ott.s66525]

22 Lee M, Jung KS, Kim HS, Lee JY, Lim SH, Kim M, Jung HA, Kim SM, Lee J, Lim DH, Park KW, Yi SY, Hwang IG, Lee S, Ahn HK, Park SH. Phase II study of a combination chemotherapy with weekly docetaxel and gemcitabine in previously treated metastatic esophageal squamous cell cancer. *Ann Oncol* 2014; **25**(Suppl 4): 680P

23 Gao YB, Chen ZL, Li JG, Hu XD, Shi XJ, Sun ZM, Zhang F, Zhao ZR, Li ZT, Liu ZY, Zhao YD, Sun J, Zhou CC, Yao R, Wang SY, Wang P, Sun N, Zhang BH, Dong JS, Yu Y, Luo M, Feng XL, Shi SS, Zhou F, Tan FW, Qiu B, Li N, Shao K, Zhang LJ, Zhang LJ, Xue Q, Gao SG, He J. Genetic landscape of esophageal squamous cell carcinoma. *Nature genetics* 2014; **46**(10): 1097-1102 [PMID: 25151357 DOI: 10.1038/ng.3076]

24 Lin DC, Hao JJ, Nagata Y, Xu L, Shang L, Meng X, Sato Y, Okuno Y, Varela AM, Ding LW, Garg M, Liu LZ, Yang H, Yin D, Shi ZZ, Jiang YY, Gu WY, Gong T, Zhang Y, Xu X, Kalid O, Shacham S, Ogawa S, Wang MR, Koeffler HP. Genomic and molecular characterization of esophageal squamous cell carcinoma. *Nature genetics* 2014; **46**(5): 467-473 [PMID: 24686850 PMCID: 4070589 DOI: 10.1038/ng.2935]

25 Song Y, Li L, Ou Y, Gao Z, Li E, Li X, Zhang W, Wang J, Xu L, Zhou Y, Ma X, Liu L, Zhao Z, Huang X, Fan J, Dong L, Chen G, Ma L, Yang J, Chen L, He M, Li M, Zhuang X, Huang K, Qiu K, Yin G, Guo G, Feng Q, Chen P, Wu Z, Wu J, Ma L, Zhao J, Luo L, Fu M, Xu B, Chen B, Li Y, Tong T, Wang M, Liu Z, Lin D, Zhang X, Yang H, Wang J, Zhan Q. Identification of genomic alterations in oesophageal squamous cell cancer. *Nature* 2014; **509**(7498): 91-95 [PMID: 24670651 DOI: 10.1038/nature13176]

26 Agrawal N, Frederick MJ, Pickering CR, Bettegowda C, Chang K, Li RJ, Fakhry C, Xie TX, Zhang J, Wang J, Zhang N, El-Naggar AK, Jasser SA, Weinstein JN, Trevino L, Drummond JA, Muzny DM, Wu Y, Wood LD, Hruban RH, Westra WH, Koch WM, Califano JA, Gibbs RA, Sidransky D, Vogelstein B, Velculescu VE, Papadopoulos N, Wheeler DA, Kinzler KW, Myers JN. Exome sequencing of head and neck squamous cell carcinoma reveals inactivating mutations in NOTCH1. *Science* 2011; **333**(6046): 1154-1157 [PMID: 21798897 PMCID: 3162986 DOI: 10.1126/science.1206923

27 Stransky N, Egloff AM, Tward AD, Kostic AD, Cibulskis K, Sivachenko A, Kryukov GV, Lawrence MS, Sougnez C, McKenna A, Shefler E, Ramos AH, Stojanov P, Carter SL, Voet D, Cortes ML, Auclair D, Berger MF, Saksena G, Guiducci C, Onofrio RC, Parkin M, Romkes M, Weissfeld JL, Seethala RR, Wang L, Rangel-Escareno C, Fernandez-Lopez JC, Hidalgo-Miranda A, Melendez-Zajgla J, Winckler W, Ardlie K, Gabriel SB, Meyerson M, Lander ES, Getz G, Golub TR, Garraway LA, Grandis JR. The mutational landscape of head and neck squamous cell carcinoma. *Science* 2011; **333**(6046): 1157-1160 [PMID: 21798893 PMCID: 3415217 DOI: 10.1126/science.1208130

28 Agrawal N, Jiao Y, Bettegowda C, Hutfless SM, Wang Y, David S, Cheng Y, Twaddell WS, Latt NL, Shin EJ, Wang LD, Wang L, Yang W, Velculescu VE, Vogelstein B, Papadopoulos N, Kinzler KW, Meltzer SJ. Comparative genomic analysis of esophageal adenocarcinoma and squamous cell carcinoma. *Cancer discovery* 2012; **2**(10): 899-905 [PMID: 22877736 PMCID: Pmc3473124 DOI: 10.1158/2159-8290.cd-12-0189]

29 Nones K, Waddell N, Wayte N, Patch AM, Bailey P, Newell F, Holmes O, Fink JL, Quinn MC, Tang YH, Lampe G, Quek K, Loffler KA, Manning S, Idrisoglu S, Miller D, Xu Q, Wilson PJ, Bruxner TJ, Christ AN, Harliwong I, Nourse C, Nourbakhsh E, Anderson M, Kazakoff S, Leonard C, Wood S, Simpson PT, Reid LE, Krause L, Hussey DJ, Watson DI, Lord RV, Nancarrow D, Phillips WA, Gotley D, Smithers BM, Whiteman DC, Hayward NK, Campbell PJ, Pearson JV, Grimmond SM, Barbour AP. Genomic catastrophes frequently arise in esophageal adenocarcinoma and drive tumorigenesis. *Nat Commun* 2014; **5**: 5224 [PMID: 25351503 DOI: 10.1038/ncomms6224

30 Network CGAR. Comprehensive genomic characterization of squamous cell lung cancers. *Nature* 2012; **489**(7417): 519-525 [PMID: 22960745 PMCID: 3466113 DOI: 10.1038/nature11404

31 Helleday T, Eshtad S, Nik-Zainal S. Mechanisms underlying mutational signatures in human cancers. *Nat Rev Genet* 2014; **15**(9): 585-598 [PMID: 24981601 DOI: 10.1038/nrg3729

32 Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA, Jr., Kinzler KW. Cancer genome landscapes. *Science* 2013; **339**(6127): 1546-1558 [PMID: 23539594 PMCID: 3749880 DOI: 10.1126/science.1235122]

33 Torkamani A, Schork NJ. Identification of rare cancer driver mutations by network reconstruction. *Genome research* 2009; **19**(9): 1570-1578 [PMID: 19574499 PMCID: Pmc2752121 DOI: 10.1101/gr.092833.109]

34 Komatsu M, Sasaki H. DNA methylation is a key factor in understanding differentiation phenotype in esophageal squamous cell carcinoma. *Epigenomics* 2014; **6**(6): 567-569 [PMID: 25531249 DOI: 10.2217/epi.14.56]

35 Cheng CP, Kuo IY, Alakus H, Frazer KA, Harismendy O, Wang YC, Tseng VS. Network-based analysis identifies epigenetic biomarkers of esophageal squamous cell carcinoma progression. *Bioinformatics* 2014; **30**(21): 3054-3061 [PMID: 25015989 DOI: 10.1093/bioinformatics/btu433]

36 Tamborero D, Gonzalez-Perez A, Perez-Llamas C, Deu-Pons J, Kandoth C, Reimand J, Lawrence MS, Getz G, Bader GD, Ding L, Lopez-Bigas N. Comprehensive identification of mutational cancer driver genes across 12 tumor types. *Scientific reports* 2013; **3**: 2650 [PMID: 24084849 PMCID: 3788361 DOI: 10.1038/srep02650]

37 An O, Pendino V, D'Antonio M, Ratti E, Gentilini M, Ciccarelli FD. NCG 4.0: the network of cancer genes in the era of massive mutational screenings of cancer genomes. *Database : the journal of biological databases and curation* 2014; **2014**: bau015 [PMID: 24608173 PMCID: 3948431 DOI: 10.1093/database/bau015]

38 Abbott KL, Nyre ET, Abrahante J, Ho YY, Isaksson Vogel R, Starr TK. The Candidate Cancer Gene Database: a database of cancer driver genes from forward genetic screens in mice. *Nucleic acids research* 2015; **43**(Database issue): D844-848 [PMID: 25190456 DOI: 10.1093/nar/gku770]

39 Alamo P, Gallardo A, Di Nicolantonio F, Pavón MA, Casanova I, Trias M, Mangues MA, Lopez-Pousa A, Villaverde A, Vázquez E, Bardelli A, Céspedes MV, Mangues R. Higher metastatic efficiency of KRas G12V than KRas G13D in a colorectal cancer model. *FASEB J* 2014: (Epub ahead of print)

40 Park JT, Johnson N, Liu S, Levesque M, Wang YJ, Ho H, Huso D, Maitra A, Parsons MJ, Prescott JD, Leach SD. Differential in vivo tumorigenicity of diverse KRAS mutations in vertebrate pancreas: A comprehensive survey. *Oncogene* 2014 [PMID: 25065594 DOI: 10.1038/onc.2014.223

41 Chen J, Ye Y, Sun H, Shi G. Association between KRAS codon 13 mutations and clinical response to anti-EGFR treatment in patients with metastatic colorectal cancer: results from a meta-analysis. *Cancer Chemother Pharmacol* 2013; **71**(1): 265-272 [PMID: 23090619 DOI: 10.1007/s00280-012-2005-9]

42 Hou JP, Ma J. DawnRank: discovering personalized driver genes in cancer. *Genome Med* 2014; **6**(7): 56 [PMID: 25177370 PMCID: 4148527 DOI: 10.1186/s13073-014-0056-8

43 Nevins JR. Pathway-based classification of lung cancer: a strategy to guide therapeutic selection. *Proceedings of the American Thoracic Society* 2011; **8**(2): 180-182 [PMID: 21543798 PMCID: Pmc3131836 DOI: 10.1513/pats.201006-040MS]

44 Gatza ML, Lucas JE, Barry WT, Kim JW, Wang Q, Crawford MD, Datto MB, Kelley M, Mathey-Prevot B, Potti A, Nevins JR. A pathway-based classification of human breast cancer. *Proceedings of the National Academy of Sciences of the United States of America* 2010; **107**(15): 6994-6999 [PMID: 20335537 PMCID: Pmc2872436 DOI: 10.1073/pnas.0912708107]

45 Bild AH, Yao G, Chang JT, Wang Q, Potti A, Chasse D, Joshi MB, Harpole D, Lancaster JM, Berchuck A, Olson JA, Jr., Marks JR, Dressman HK, West M, Nevins JR. Oncogenic pathway signatures in human cancers as a guide to targeted therapies. *Nature* 2006; **439**(7074): 353-357 [PMID: 16273092 DOI: 10.1038/nature04296]

46 Gonzalez-Perez A, Mustonen V, Reva B, Ritchie G, Creixell P, Karchin R, Vazquez M, Fink JL, Kassahn KS, Pearson JV. Computational approaches to identify functional genetic variants in cancer genomes. *Nature methods* 2013; **10**(8): 723-729

47 Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, Garbe C, Jouary T, Hauschild A, Grob JJ, Chiarion Sileni V, Lebbe C, Mandala M, Millward M, Arance A, Bondarenko I, Haanen JB, Hansson J, Utikal J, Ferraresi V, Kovalenko N, Mohr P, Probachai V, Schadendorf D, Nathan P, Robert C, Ribas A, DeMarini DJ, Irani JG, Casey M, Ouellet D, Martin AM, Le N, Patel K, Flaherty K. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. *The New England journal of medicine* 2014; **371**(20): 1877-1888 [PMID: 25265492 DOI: 10.1056/NEJMoa1406037]

48 Ciriello G, Cerami E, Sander C, Schultz N. Mutual exclusivity analysis identifies oncogenic network modules. *Genome research* 2012; **22**(2): 398-406

49 Shang L, Liu HJ, Hao JJ, Jiang YY, Shi F, Zhang Y, Cai Y, Xu X, Jia XM, Zhan QM, Wang MR. A panel of overexpressed proteins for prognosis in esophageal squamous cell carcinoma. *PLoS One* 2014; **9**(10): e111045 [PMID: 25337715 PMCID: 4206450 DOI: 10.1371/journal.pone.0111045]

50 Zhang B, Wang J, Wang X, Zhu J, Liu Q, Shi Z, Chambers MC, Zimmerman LJ, Shaddox KF, Kim S, Davies SR, Wang S, Wang P, Kinsinger CR, Rivers RC, Rodriguez H, Townsend RR, Ellis MJ, Carr SA, Tabb DL, Coffey RJ, Slebos RJ, Liebler DC, Nci C. Proteogenomic characterization of human colon and rectal cancer. *Nature* 2014; **513**(7518): 382-387 [PMID: 25043054 PMCID: 4249766 DOI: 10.1038/nature13438]

51 Watanabe H, Ma Q, Peng S, Adelmant G, Swain D, Song W, Fox C, Francis JM, Pedamallu CS, DeLuca DS, Brooks AN, Wang S, Que J, Rustgi AK, Wong KK, Ligon KL, Liu XS, Marto JA, Meyerson M, Bass AJ. SOX2 and p63 colocalize at genetic loci in squamous cell carcinomas. *J Clin Invest* 2014; **124**(4): 1636-1645 [PMID: 24590290 PMCID: 3973117 DOI: 10.1172/JCI71545

52 Verhaegh W, van Ooijen H, Inda MA, Hatzis P, Versteeg R, Smid M, Martens J, Foekens J, van de Wiel P, Clevers H, van de Stolpe A. Selection of personalized patient therapy through the use of knowledge-based computational models that identify tumor-driving signal transduction pathways. *Cancer Res* 2014; **74**(11): 2936-2945 [PMID: 24695361 DOI: 10.1158/0008-5472.CAN-13-2515

53 Hofree M, Shen JP, Carter H, Gross A, Ideker T. Network-based stratification of tumor mutations. *Nat Methods* 2013; **10**(11): 1108-1115 [PMID: 24037242 PMCID: 3866081 DOI: 10.1038/nmeth.2651

54 Sadanandam A, Lyssiotis CA, Homicsko K, Collisson EA, Gibb WJ, Wullschleger S, Ostos LC, Lannon WA, Grotzinger C, Del Rio M, Lhermitte B, Olshen AB, Wiedenmann B, Cantley LC, Gray JW, Hanahan D. A colorectal cancer classification system that associates cellular phenotype and responses to therapy. *Nat Med* 2013; **19**(5): 619-625 [PMID: 23584089 PMCID: 3774607 DOI: 10.1038/nm.3175

55 Roychowdhury S, Iyer MK, Robinson DR, Lonigro RJ, Wu YM, Cao X, Kalyana-Sundaram S, Sam L, Balbin OA, Quist MJ, Barrette T, Everett J, Siddiqui J, Kunju LP, Navone N, Araujo JC, Troncoso P, Logothetis CJ, Innis JW, Smith DC, Lao CD, Kim SY, Roberts JS, Gruber SB, Pienta KJ, Talpaz M, Chinnaiyan AM. Personalized oncology through integrative high-throughput sequencing: a pilot study. *Science translational medicine* 2011; **3**(111): 111ra121 [PMID: 22133722 PMCID: Pmc3476478 DOI: 10.1126/scitranslmed.3003161]

56 Dutton SJ, Ferry DR, Blazeby JM, Abbas H, Dahle-Smith A, Mansoor W, Thompson J, Harrison M, Chatterjee A, Falk S, Garcia-Alonso A, Fyfe DW, Hubner RA, Gamble T, Peachey L, Davoudianfar M, Pearson SR, Julier P, Jankowski J, Kerr R, Petty RD. Gefitinib for oesophageal cancer progressing after chemotherapy (COG): a phase 3, multicentre, double-blind, placebo-controlled randomised trial. *The Lancet Oncology* 2014; **15**(8): 894-904 [PMID: 24950987 DOI: 10.1016/S1470-2045(14)70024-5]

57 Chen Y, McGee J, Chen X, Doman TN, Gong X, Zhang Y, Hamm N, Ma X, Higgs RE, Bhagwat SV, Buchanan S, Peng SB, Staschke KA, Yadav V, Yue Y, Kouros-Mehr H. Identification of druggable cancer driver genes amplified across TCGA datasets. *PLoS One* 2014; **9**(5): e98293 [PMID: 24874471 PMCID: 4038530 DOI: 10.1371/journal.pone.0098293]

58 Qin C, Zhang C, Zhu F, Xu F, Chen SY, Zhang P, Li YH, Yang SY, Wei YQ, Tao L, Chen YZ. Therapeutic target database update 2014: a resource for targeted therapeutics. *Nucleic acids research* 2014; **42**(Database issue): D1118-1123 [PMID: 24265219 PMCID: 3964951 DOI: 10.1093/nar/gkt1129]

59 Law V, Knox C, Djoumbou Y, Jewison T, Guo AC, Liu Y, Maciejewski A, Arndt D, Wilson M, Neveu V, Tang A, Gabriel G, Ly C, Adamjee S, Dame ZT, Han B, Zhou Y, Wishart DS. DrugBank 4.0: shedding new light on drug metabolism. *Nucleic acids research* 2014; **42**(Database issue): D1091-1097 [PMID: 24203711 PMCID: 3965102 DOI: 10.1093/nar/gkt1068]

60 Musgrove EA, Caldon CE, Barraclough J, Stone A, Sutherland RL. Cyclin D as a therapeutic target in cancer. *Nature reviews Cancer* 2011; **11**(8): 558-572 [PMID: 21734724 DOI: 10.1038/nrc3090

61 Hong B, van den Heuvel AP, Prabhu VV, Zhang S, El-Deiry WS. Targeting tumor suppressor p53 for cancer therapy: strategies, challenges and opportunities. *Curr Drug Targets* 2014; **15**(1): 80-89 [PMID: 24387333 DOI: CDT-EPUB-58493 [pii]]

62 Khoo KH, Verma CS, Lane DP. Drugging the p53 pathway: understanding the route to clinical efficacy. *Nature reviews Drug discovery* 2014; **13**(3): 217-236 [PMID: 24577402 DOI: 10.1038/nrd4236

63 McLeod HL. Cancer pharmacogenomics: early promise, but concerted effort needed. *Science* 2013; **339**(6127): 1563-1566 [PMID: 23539596 PMCID: Pmc3900028 DOI: 10.1126/science.1234139]

64 Harper AR, Topol EJ. Pharmacogenomics in clinical practice and drug development. *Nat Biotechnol* 2012; **30**(11): 1117-1124 [PMID: 23138311 PMCID: 3819119 DOI: 10.1038/nbt.2424

65 Thorn CF, Klein TE, Altman RB. PharmGKB: the pharmacogenetics and pharmacogenomics knowledge base. *Methods in molecular biology* 2005; **311**: 179-191 [PMID: 16100408 DOI: 10.1385/1-59259-957-5:179]

66 Patel AP, Tirosh I, Trombetta JJ, Shalek AK, Gillespie SM, Wakimoto H, Cahill DP, Nahed BV, Curry WT, Martuza RL, Louis DN, Rozenblatt-Rosen O, Suva ML, Regev A, Bernstein BE. Single-cell RNA-seq highlights intratumoral heterogeneity in primary glioblastoma. *Science* 2014; **344**(6190): 1396-1401 [PMID: 24925914 PMCID: 4123637 DOI: 10.1126/science.1254257

67 Zhang J, Fujimoto J, Wedge DC, Song X, Seth S, Chow CW, Cao Y, Gumbs C, Gold KA, Kalhor N, Little L, Mahadeshwar H, Moran C, Protopopov A, Sun H, Tang J, Wu X, Ye Y, William WN, Lee JJ, Heymach JV, Hong WK, Swisher S, Wistuba, II, Futreal PA. Intratumor heterogeneity in localized lung adenocarcinomas delineated by multiregion sequencing. *Science* 2014; **346**(6206): 256-259 [PMID: 25301631 DOI: 10.1126/science.1256930

68 Komori J, Boone L, DeWard A, Hoppo T, Lagasse E. The mouse lymph node as an ectopic transplantation site for multiple tissues. *Nat Biotechnol* 2012; **30**(10): 976-983 [PMID: 23000933 PMCID: 3469750 DOI: 10.1038/nbt.2379

69 Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankin AV, Bignell GR, Bolli N, Borg A, Børresen-Dale A-L. Signatures of mutational processes in human cancer. *Nature* 2013

70 Greaves M, Maley CC. Clonal evolution in cancer. *Nature* 2012; **481**(7381): 306-313 [PMID: 22258609 PMCID: Pmc3367003 DOI: 10.1038/nature10762]

71 Ramos P, Bentires-Alj M. Mechanism-based cancer therapy: resistance to therapy, therapy for resistance. *Oncogene* 2014 [PMID: 25263438 DOI: 10.1038/onc.2014.314]

72 Kemper K, de Goeje PL, Peeper DS, van Amerongen R. Phenotype switching: tumor cell plasticity as a resistance mechanism and target for therapy. *Cancer Res* 2014; **74**(21): 5937-5941 [PMID: 25320006 DOI: 10.1158/0008-5472.CAN-14-1174]

73 Katayama R, Friboulet L, Koike S, Lockerman EL, Khan TM, Gainor JF, Iafrate AJ, Takeuchi K, Taiji M, Okuno Y, Fujita N, Engelman JA, Shaw AT. Two novel ALK mutations mediate acquired resistance to the next-generation ALK inhibitor alectinib. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2014; **20**(22): 5686-5696 [PMID: 25228534 PMCID: 4233168 DOI: 10.1158/1078-0432.CCR-14-1511]

74 Juric D, Castel P, Griffith M, Griffith OL, Won HH, Ellis H, Ebbesen SH, Ainscough BJ, Ramu A, Iyer G, Shah RH, Huynh T, Mino-Kenudson M, Sgroi D, Isakoff S, Thabet A, Elamine L, Solit DB, Lowe SW, Quadt C, Peters M, Derti A, Schegel R, Huang A, Mardis ER, Berger MF, Baselga J, Scaltriti M. Convergent loss of PTEN leads to clinical resistance to a PI(3)Kalpha inhibitor. *Nature* 2014 [PMID: 25409150 DOI: 10.1038/nature13948]

75 Martz CA, Ottina KA, Singleton KR, Jasper JS, Wardell SE, Peraza-Penton A, Anderson GR, Winter PS, Wang T, Alley HM, Kwong LN, Cooper ZA, Tetzlaff M, Chen PL, Rathmell JC, Flaherty KT, Wargo JA, McDonnell DP, Sabatini DM, Wood KC. Systematic identification of signaling pathways with potential to confer anticancer drug resistance. *Science signaling* 2014; **7**(357): ra121 [PMID: 25538079 DOI: 10.1126/scisignal.aaa1877]

76 Ding L, Ellis MJ, Li S, Larson DE, Chen K, Wallis JW, Harris CC, McLellan MD, Fulton RS, Fulton LL. Genome remodelling in a basal-like breast cancer metastasis and xenograft. *Nature* 2010; **464**(7291): 999-1005

77 Diaz Jr LA, Williams RT, Wu J, Kinde I, Hecht JR, Berlin J, Allen B, Bozic I, Reiter JG, Nowak MA. The molecular evolution of acquired resistance to targeted EGFR blockade in colorectal cancers. *Nature* 2012; **486**(7404): 537-540

78 Kreso A, O'Brien CA, van Galen P, Gan OI, Notta F, Brown AM, Ng K, Ma J, Wienholds E, Dunant C. Variable clonal repopulation dynamics influence chemotherapy response in colorectal cancer. *Science* 2013; **339**(6119): 543-548

79 Marusyk A, Almendro V, Polyak K. Intra-tumour heterogeneity: a looking glass for cancer? *Nature Reviews Cancer* 2012; **12**(5): 323-334

80 Spellman PT, Gray JW. Detecting cancer by monitoring circulating tumor DNA. *Nature medicine* 2014; **20**(5): 474-475

81 Bettegowda C, Sausen M, Leary RJ, Kinde I, Wang Y, Agrawal N, Bartlett BR, Wang H, Luber B, Alani RM, Antonarakis ES, Azad NS, Bardelli A, Brem H, Cameron JL, Lee CC, Fecher LA, Gallia GL, Gibbs P, Le D, Giuntoli RL, Goggins M, Hogarty MD, Holdhoff M, Hong SM, Jiao Y, Juhl HH, Kim JJ, Siravegna G, Laheru DA, Lauricella C, Lim M, Lipson EJ, Marie SK, Netto GJ, Oliner KS, Olivi A, Olsson L, Riggins GJ, Sartore-Bianchi A, Schmidt K, Shih l M, Oba-Shinjo SM, Siena S, Theodorescu D, Tie J, Harkins TT, Veronese S, Wang TL, Weingart JD, Wolfgang CL, Wood LD, Xing D, Hruban RH, Wu J, Allen PJ, Schmidt CM, Choti MA, Velculescu VE, Kinzler KW, Vogelstein B, Papadopoulos N, Diaz LA, Jr. Detection of circulating tumor DNA in early- and late-stage human malignancies. *Science translational medicine* 2014; **6**(224): 224ra224 [PMID: 24553385 PMCID: 4017867 DOI: 10.1126/scitranslmed.3007094]

82 Kadri S, Lao-Sirieix P, Fitzgerald RC. Developing a nonendoscopic screening test for Barrett's esophagus. *Biomark Med* 2011; **5**(3): 397-404 [PMID: 21657849 DOI: 10.2217/bmm.11.40]

83 Sepehr A, Razavi P, Saidi F, Salehian P, Rahmani M, Shamshiri A. Esophageal exfoliative cytology samplers. A comparison of three types. *Acta Cytol* 2000; **44**(5): 797-804 [PMID: 11015982]

84 Liu S, Kurzrock R. Toxicity of targeted therapy: Implications for response and impact of genetic polymorphisms. *Cancer Treat Rev* 2014; **40**(7): 883-891 [PMID: 24867380 DOI: 10.1016/j.ctrv.2014.05.003

85 Pessi MA, Zilembo N, Haspinger ER, Molino L, Di Cosimo S, Garassino M, Ripamonti CI. Targeted therapy-induced diarrhea: A review of the literature. *Crit Rev Oncol Hematol* 2014; **90**(2): 165-179 [PMID: 24373918 DOI: 10.1016/j.critrevonc.2013.11.008

86 Jensen SB, Peterson DE. Oral mucosal injury caused by cancer therapies: current management and new frontiers in research. *J Oral Pathol Med* 2014; **43**(2): 81-90 [PMID: 24261541 DOI: 10.1111/jop.12135]

87 Macdonald JB, Macdonald B, Golitz LE, LoRusso P, Sekulic A. Cutaneous adverse effects of targeted therapies: Part II: Inhibitors of intracellular molecular signaling pathways. *J Am Acad Dermatol* 2015; **72**(2): 221-236 [PMID: 25592339 DOI: S0190-9622(14)01764-2 [pii]

88 Macdonald JB, Macdonald B, Golitz LE, LoRusso P, Sekulic A. Cutaneous adverse effects of targeted therapies: Part I: Inhibitors of the cellular membrane. *J Am Acad Dermatol* 2015; **72**(2): 203-218 [PMID: 25592338 DOI: S0190-9622(14)01763-0 [pii]

89 Abaan OD, Polley EC, Davis SR, Zhu YJ, Bilke S, Walker RL, Pineda M, Gindin Y, Jiang Y, Reinhold WC. The exomes of the NCI-60 panel: a genomic resource for cancer biology and systems pharmacology. *Cancer research* 2013; **73**(14): 4372-4382

90 Sharma SV, Haber DA, Settleman J. Cell line-based platforms to evaluate the therapeutic efficacy of candidate anticancer agents. *Nature reviews Cancer* 2010; **10**(4): 241-253 [PMID: 20300105 DOI: 10.1038/nrc2820]

91 Ahmed D, Eide PW, Eilertsen IA, Danielsen SA, Eknaes M, Hektoen M, Lind GE, Lothe RA. Epigenetic and genetic features of 24 colon cancer cell lines. *Oncogenesis* 2013; **2**: e71 [PMID: 24042735 PMCID: 3816225 DOI: 10.1038/oncsis.2013.35]

92 Martin D, Abba MC, Molinolo AA, Vitale-Cross L, Wang Z, Zaida M, Delic NC, Samuels Y, Lyons JG, Gutkind JS. The head and neck cancer cell oncogenome: a platform for the development of precision molecular therapies. *Oncotarget* 2014; **5**(19): 8906-8923 [PMID: 25275298 PMCID: 4253406]

93 Shimada Y, Maeda M, Watanabe G, Yamasaki S, Komoto I, Kaganoi J, Kan T, Hashimoto Y, Imoto I, Inazawa J, Imamura M. Cell culture in esophageal squamous cell carcinoma and the association with molecular markers. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2003; **9**(1): 243-249 [PMID: 12538476]

94 Gen Y, Yasui K, Nishikawa T, Yoshikawa T. SOX2 promotes tumor growth of esophageal squamous cell carcinoma through the AKT/mammalian target of rapamycin complex 1 signaling pathway. *Cancer science* 2013; **104**(7): 810-816 [PMID: 23510069 DOI: 10.1111/cas.12155]

95 Crystal AS, Shaw AT, Sequist LV, Friboulet L, Niederst MJ, Lockerman EL, Frias RL, Gainor JF, Amzallag A, Greninger P, Lee D, Kalsy A, Gomez-Caraballo M, Elamine L, Howe E, Hur W, Lifshits E, Robinson HE, Katayama R, Faber AC, Awad MM, Ramaswamy S, Mino-Kenudson M, Iafrate AJ, Benes CH, Engelman JA. Patient-derived models of acquired resistance can identify effective drug combinations for cancer. *Science* 2014; **346**(6216): 1480-1486 [PMID: 25394791 DOI: 10.1126/science.1254721]

96 Wu X, Zhang J, Zhen R, Lv J, Zheng L, Su X, Zhu G, Gavine PR, Xu S, Lu S, Hou J, Liu Y, Xu C, Tan Y, Xie L, Yin X, He D, Ji Q, Hou Y, Ge D. Trastuzumab anti-tumor efficacy in patient-derived esophageal squamous cell carcinoma xenograft (PDECX) mouse models. *Journal of translational medicine* 2012; **10**: 180 [PMID: 22935382 PMCID: Pmc3485623 DOI: 10.1186/1479-5876-10-180]

97 Zhang J, Jiang D, Li X, Lv J, Xie L, Zheng L, Gavine PR, Hu Q, Shi Y, Tan L, Ge D, Xu S, Li L, Zhu L, Hou Y, Wang Q. Establishment and characterization of esophageal squamous cell carcinoma patient-derived xenograft mouse models for preclinical drug discovery. *Laboratory investigation; a journal of technical methods and pathology* 2014; **94**(8): 917-926 [PMID: 24999713 DOI: 10.1038/labinvest.2014.77]

98 Wang D, Weghorst CM, Calvert RJ, Stoner GD. Mutation in the p53 tumor suppressor gene in rat esophageal papillomas induced by N-nitrosomethylbenzylamine. *Carcinogenesis* 1996; **17**(4): 625-630 [PMID: 8625469]

99 Onken MD, Winkler AE, Kanchi KL, Chalivendra V, Law JH, Rickert CG, Kallogjeri D, Judd NP, Dunn GP, Piccirillo JF, Lewis JS, Jr., Mardis ER, Uppaluri R. A surprising cross-species conservation in the genomic landscape of mouse and human oral cancer identifies a transcriptional signature predicting metastatic disease. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2014; **20**(11): 2873-2884 [PMID: 24668645 PMCID: Pmc4096804 DOI: 10.1158/1078-0432.ccr-14-0205]

100 Westcott PM, Halliwill KD, To MD, Rashid M, Rust AG, Keane TM, Delrosario R, Jen KY, Gurley KE, Kemp CJ, Fredlund E, Quigley DA, Adams DJ, Balmain A. The mutational landscapes of genetic and chemical models of Kras-driven lung cancer. *Nature* 2014 [PMID: 25363767 DOI: 10.1038/nature13898]

101 Tuveson DA, Jacks T. Technologically advanced cancer modeling in mice. *Current opinion in genetics & development* 2002; **12**(1): 105-110 [PMID: 11790563]

102 Sharpless NE, Depinho RA. The mighty mouse: genetically engineered mouse models in cancer drug development. *Nature reviews Drug discovery* 2006; **5**(9): 741-754 [PMID: 16915232 DOI: 10.1038/nrd2110]

103 Pirazzoli V, Nebhan C, Song X, Wurtz A, Walther Z, Cai G, Zhao Z, Jia P, de Stanchina E, Shapiro EM, Gale M, Yin R, Horn L, Carbone DP, Stephens PJ, Miller V, Gettinger S, Pao W, Politi K. Acquired resistance of EGFR-mutant lung adenocarcinomas to afatinib plus cetuximab is associated with activation of mTORC1. *Cell reports* 2014; **7**(4): 999-1008 [PMID: 24813888 PMCID: Pmc4074596 DOI: 10.1016/j.celrep.2014.04.014]

104 Bergers G, Hanahan D. Modes of resistance to anti-angiogenic therapy. *Nature reviews Cancer* 2008; **8**(8): 592-603 [PMID: 18650835 PMCID: Pmc2874834 DOI: 10.1038/nrc2442]

105 Rottenberg S, Nygren AO, Pajic M, van Leeuwen FW, van der Heijden I, van de Wetering K, Liu X, de Visser KE, Gilhuijs KG, van Tellingen O, Schouten JP, Jonkers J, Borst P. Selective induction of chemotherapy resistance of mammary tumors in a conditional mouse model for hereditary breast cancer. *Proceedings of the National Academy of Sciences of the United States of America* 2007; **104**(29): 12117-12122 [PMID: 17626183 PMCID: Pmc1914039 DOI: 10.1073/pnas.0702955104]

106 Bass AJ, Watanabe H, Mermel CH, Yu S, Perner S, Verhaak RG, Kim SY, Wardwell L, Tamayo P, Gat-Viks I, Ramos AH, Woo MS, Weir BA, Getz G, Beroukhim R, O'Kelly M, Dutt A, Rozenblatt-Rosen O, Dziunycz P, Komisarof J, Chirieac LR, Lafargue CJ, Scheble V, Wilbertz T, Ma C, Rao S, Nakagawa H, Stairs DB, Lin L, Giordano TJ, Wagner P, Minna JD, Gazdar AF, Zhu CQ, Brose MS, Cecconello I, Jr UR, Marie SK, Dahl O, Shivdasani RA, Tsao MS, Rubin MA, Wong KK, Regev A, Hahn WC, Beer DG, Rustgi AK, Meyerson M. SOX2 is an amplified lineage-survival oncogene in lung and esophageal squamous cell carcinomas. *Nature genetics* 2009; **41**(11): 1238-1242 [PMID: 19801978 PMCID: 2783775 DOI: 10.1038/ng.465

107 Liu K, Jiang M, Lu Y, Chen H, Sun J, Wu S, Ku WY, Nakagawa H, Kita Y, Natsugoe S, Peters JH, Rustgi A, Onaitis MW, Kiernan A, Chen X, Que J. Sox2 cooperates with inflammation-mediated Stat3 activation in the malignant transformation of foregut basal progenitor cells. *Cell stem cell* 2013; **12**(3): 304-315 [PMID: 23472872 PMCID: Pmc3594795 DOI: 10.1016/j.stem.2013.01.007]

108 Sanchez-Rivera FJ, Papagiannakopoulos T, Romero R, Tammela T, Bauer MR, Bhutkar A, Joshi NS, Subbaraj L, Bronson RT, Xue W, Jacks T. Rapid modelling of cooperating genetic events in cancer through somatic genome editing. *Nature* 2014; **516**(7531): 428-431 [PMID: 25337879 PMCID: 4292871 DOI: 10.1038/nature13906]

109 Doudna JA, Charpentier E. Genome editing. The new frontier of genome engineering with CRISPR-Cas9. *Science* 2014; **346**(6213): 1258096 [PMID: 25430774 DOI: 10.1126/science.1258096]

110 Wheeler DA, Wang L. From human genome to cancer genome: the first decade. *Genome research* 2013; **23**(7): 1054-1062 [PMID: 23817046 PMCID: Pmc3698498 DOI: 10.1101/gr.157602.113]

111 Roychowdhury S, Chinnaiyan AM. Translating genomics for precision cancer medicine. *Annu Rev Genomics Hum Genet* 2014; **15**: 395-415 [PMID: 25184532 DOI: 10.1146/annurev-genom-090413-025552]

112 Simon R, Roychowdhury S. Implementing personalized cancer genomics in clinical trials. *Nature reviews Drug discovery* 2013; **12**(5): 358-369 [PMID: 23629504 DOI: 10.1038/nrd3979]

113 Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011; **144**(5): 646-674 [PMID: 21376230 DOI: 10.1016/j.cell.2011.02.013]

114 Hanahan D. Rethinking the war on cancer. *Lancet* 2014; **383**(9916): 558-563 [PMID: 24351321 DOI: 10.1016/S0140-6736(13)62226-6]

115 Ralph C, Elkord E, Burt DJ, O'Dwyer JF, Austin EB, Stern PL, Hawkins RE, Thistlethwaite FC. Modulation of lymphocyte regulation for cancer therapy: a phase II trial of tremelimumab in advanced gastric and esophageal adenocarcinoma. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2010; **16**(5): 1662-1672 [PMID: 20179239 DOI: 10.1158/1078-0432.CCR-09-2870

116 Tran E, Turcotte S, Gros A, Robbins PF, Lu YC, Dudley ME, Wunderlich JR, Somerville RP, Hogan K, Hinrichs CS, Parkhurst MR, Yang JC, Rosenberg SA. Cancer immunotherapy based on mutation-specific CD4+ T cells in a patient with epithelial cancer. *Science* 2014; **344**(6184): 641-645 [PMID: 24812403 DOI: 10.1126/science.1251102

117 Herbst RS, Soria JC, Kowanetz M, Fine GD, Hamid O, Gordon MS, Sosman JA, McDermott DF, Powderly JD, Gettinger SN, Kohrt HE, Horn L, Lawrence DP, Rost S, Leabman M, Xiao Y, Mokatrin A, Koeppen H, Hegde PS, Mellman I, Chen DS, Hodi FS. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature* 2014; **515**(7528): 563-567 [PMID: 25428504 DOI: 10.1038/nature14011

118 Dewey FE, Grove ME, Pan C, Goldstein BA, Bernstein JA, Chaib H, Merker JD, Goldfeder RL, Enns GM, David SP, Pakdaman N, Ormond KE, Caleshu C, Kingham K, Klein TE, Whirl-Carrillo M, Sakamoto K, Wheeler MT, Butte AJ, Ford JM, Boxer L, Ioannidis JP, Yeung AC, Altman RB, Assimes TL, Snyder M, Ashley EA, Quertermous T. Clinical interpretation and implications of whole-genome sequencing. *Jama* 2014; **311**(10): 1035-1045 [PMID: 24618965 PMCID: Pmc4119063 DOI: 10.1001/jama.2014.1717]

119 Hudson AM, Yates T, Li Y, Trotter EW, Fawdar S, Chapman P, Lorigan P, Biankin A, Miller CJ, Brognard J. Discrepancies in cancer genomic sequencing highlight opportunities for driver mutation discovery. *Cancer Res* 2014; **74**(22): 6390-6396 [PMID: 25256751 PMCID: 4247168 DOI: 10.1158/0008-5472.CAN-14-1020

0008-5472.CAN-14-1020 [pii]]

120 Zhao Y, Gao Y, Chen Z, Hu X, Zhou F, He J. Low frequency of TERT promoter somatic mutation in 313 sporadic esophageal squamous cell carcinomas. *International journal of cancer Journal international du cancer* 2014; **134**(2): 493-494 [PMID: 23818232 DOI: 10.1002/ijc.28360]

121 Killela PJ, Reitman ZJ, Jiao Y, Bettegowda C, Agrawal N, Diaz LA, Jr., Friedman AH, Friedman H, Gallia GL, Giovanella BC, Grollman AP, He TC, He Y, Hruban RH, Jallo GI, Mandahl N, Meeker AK, Mertens F, Netto GJ, Rasheed BA, Riggins GJ, Rosenquist TA, Schiffman M, Shih Ie M, Theodorescu D, Torbenson MS, Velculescu VE, Wang TL, Wentzensen N, Wood LD, Zhang M, McLendon RE, Bigner DD, Kinzler KW, Vogelstein B, Papadopoulos N, Yan H. TERT promoter mutations occur frequently in gliomas and a subset of tumors derived from cells with low rates of self-renewal. *Proceedings of the National Academy of Sciences of the United States of America* 2013; **110**(15): 6021-6026 [PMID: 23530248 PMCID: 3625331 DOI: 10.1073/pnas.1303607110

122 Ding L, Wendl MC, McMichael JF, Raphael BJ. Expanding the computational toolbox for mining cancer genomes. *Nat Rev Genet* 2014; **15**(8): 556-570 [PMID: 25001846 PMCID: 4168012 DOI: 10.1038/nrg3767]

123 O'Rawe J, Jiang T, Sun G, Wu Y, Wang W, Hu J, Bodily P, Tian L, Hakonarson H, Johnson WE, Wei Z, Wang K, Lyon GJ. Low concordance of multiple variant-calling pipelines: practical implications for exome and genome sequencing. *Genome Med* 2013; **5**(3): 28 [PMID: 23537139 PMCID: 3706896 DOI: 10.1186/gm432

124 Moncunill V, Gonzalez S, Bea S, Andrieux LO, Salaverria I, Royo C, Martinez L, Puiggros M, Segura-Wang M, Stutz AM, Navarro A, Royo R, Gelpi JL, Gut IG, Lopez-Otin C, Orozco M, Korbel JO, Campo E, Puente XS, Torrents D. Comprehensive characterization of complex structural variations in cancer by directly comparing genome sequence reads. *Nat Biotechnol* 2014; **32**(11): 1106-1112 [PMID: 25344728 DOI: 10.1038/nbt.3027]

125 Cherny NI, de Vries EG, Emanuel L, Fallowfield L, Francis PA, Gabizon A, Piccart MJ, Sidransky D, Soussan-Gutman L, Tziraki C. Words matter: distinguishing "personalized medicine" and "biologically personalized therapeutics". *Journal of the National Cancer Institute* 2014; **106**(12) [PMID: 25293984 DOI: 10.1093/jnci/dju321]