RESEARCH REPORT

Stage 4 Lung Cancer

Zolman, Oliver*[1]

[1]Partner, Zolman Medical Research LLP

*oliver@zolmanmedical.com

CONFIDENTIAL

Draft Quality Reviewer: Dr Kris Verburgh, MD

Received: April 11, 2016

Accepted: April 15, 2016

Legal

Zolman Medical Research does not provide medical advice. Zolman Medical Research's reports are not to be used for treatment purposes, but rather for discussion with your treating physician. The contents of the report, such as text, graphics, images, information obtained from our licensors, and other material contained in the report ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. The primary responsibility for your medical treatment is with your treating physician and you should only follow your treating physician's advice. DO NOT change or modify your treatment plan on your own without consulting your treating physician. Always seek the advice of your physician or other qualified health provider with any questions you may have regarding a medical condition or course of treatment.

Zolman Medical Research does not recommend or endorse any specific tests, physicians, products, procedures, or other treatments that may be mentioned in the report. Reliance on any information provided by Zolman Medical Research, employees of Zolman Medical Research, or others quoted in the report by Zolman Medical Research is solely at your own risk.

Contents

Executive Summary

Purpose of this document: This document was developed for the client who is suffering from lung cancer, in order to review the therapeutic and diagnostic options available globally as of April 2016. This document should only be used by the client's qualified healthcare professionals and is not intended as medical advice. Where relevant, the client may use this document for educational purposes.

How to use this report: The report should be read from beginning to end. Summary sections of key information are provided in the opening sections. The majority of the report is located in the 'Interventions findings' section, where potentially useful interventions are listed with relevant clinical information, grouped by intervention type. At the end of each of the sub-sections of the interventions is a reference box containing full reference and hyperlinks providing immediate access to the reference material. The 'Further resources' section may be used by both the treating physician and the client to assist in their clinical practice, further their education or guide further research. The further resources section includes a list of expert persons and organisations to contact.

Client History Summary: [redacted]

Methods: Interventions that would likely have a positive benefit to risk ratio for the disease were researched using a mutually exclusive, fully comprehensive search strategy; the search framework used covers all possible types of therapeutic interventions and diagnostics, from dietary interventions to cell therapy. All of approved, off-label and pre-marketing authorisation interventions were included. NICE guidance, PubMed, Scopus, Google and Zolman Medical Research's evidence database were searched for relevant material.

Findings: Further genotyping, or full genome sequencing (costing $1,000 – $5,000) or exome sequencing ($500 - $1,000) of tumour samples, could potentially enable a targeted pharmaceutical, biologic or cell therapy. Several experimental cell therapies were found to have potential disease modifying ability, including CAR-T (Chimeric Antigen Receptor T Cell) therapy and other interventions in which patients' immune cells are enabled to better target tumour cells. Several biologics and pharmaceuticals were found to be effective including novel checkpoint inhibitors such as nivolumab and pembrolizumab, as well as pharmaceuticals targeted at specific expressed receptors on tumour cells. Several other supplement and dietary therapies were found to have an effect on slowing disease progression, secondary prevention and in quality of life. Lifestyle choices including diet and exercise were found to be potentially important factors for disease progression. Emergency interventions including medical cryopreservation were found to be indicated given the advanced disease stage.

Client History

AGE	[redacted]
SEX	[redacted]
ETHNICITY	[redacted]
PRIMARY CARE PHYSICIAN	[redacted]
DIAGNOSIS, IF ANY	**Non-small cell lung cancer, adenocarcinoma, Stage 4, T3N2M1b**
HISTORY OF DIAGNOSIS	[redacted]
MEDICATIONS	[redacted]
PREVIOUS MEDICAL HISTORY	[redacted]
FAMILY MEDICAL HISTORY	[redacted]
OCCUPATION	[redacted]
HOBBIES	[redacted]
SLEEP HABITS	[redacted]
DIET	[redacted]

EXERCISE & PHYSICAL ACTIVITY	[redacted]
SMOKING	[redacted]
ALCOHOL INTAKE	[redacted]
REPORT TYPE	**Medical Condition focused**
OTHER INFORMATION	[redacted]
THIS REPORT IS WRITTEN FOR	**The Client's primary care physician**

Summary of Priority Actions*

*DO NOT change or modify your treatment plan on your own without consulting your treating physician

Cell therapy

Acquire CAR-T therapy targeted at expressed cancer cell markers

Sequence cancer cell genotype/exome/genome to determine markers to target

Pharmaceuticals

Acquire checkpoint inhibitors nivolumab/pembrolizumab

Acquire anti-cancer pharmaceuticals (Metformin, Aspirin)

Acquire pharmaceuticals targeted at expressed cancer cell markers

Sequence cancer cell genotype/exome/genome to determine markers to target

Test for all viral infections and STDs and treat with indicated anti-virals/anti-bacterials

Consider routine viral vaccination to boost the immune response against the cancer

Consider HPV 16 and 18 serotype vaccination given

Supplements

Initiate anti-cancer / chemotherapy-protective supplement regimen

Use sample prescription chart to monitor and improve adherence

Emergency contingency; **cryopreservation arrangements**

Assess option of cryopreservation

Choose provider and source funds to cover services ($200k at Alcor, $28k at Cryonics Institute)

Obtain membership of Cryonics UK (£25 / month or £5,000 one off payment)

Dietary

Initiate Food Hourglass Diet (anti-cancer / chemotherapy-protective diet) (see Appendix)

Track diet and adjust family and friends' diets similarly to ease the transition

Non-invasive interventions

Download Moves / Pedometer app on phone to track steps - https://www.moves-app.com/

Plan exercise regime and set exercise and physical activity goals

Consider meditation, yoga, tai chi and CBT for stress, anxiety, cancer pain, sleep disturbances if indicated

Take preventive actions such as Radon and Asbestos checks and avoidance of smoke and chemicals

Ongoingly discuss and consider surgery and radiotherapy

Consider high-intensity focused ultrasound therapy

Consider combination radiotherapy-immunotherapy (E.g. ipilimumab) (Contact relevant people)

Monitor biomarkers

Weight

Vitamin D (aim for 75 – 125 nmol/l); Serum ferritin; HbA1c; fasting plasma glucose

MRI imaging (rather than CT/PET imaging where possible)

Sample Prescription Chart* – Week Beginning XXX

*Sample only DO NOT change or modify your treatment plan on your own without consulting your treating physician

Supplement (daily dose)	Mechanism	Mon	Tue	Wed	Thu	Fri	Sat	Sun
Vitamin D (2000 - 5000 IU (only once blood level measured)) ***AM***	*Anti-cancer gene expression; Target blood level of 75 - 125 nmol/L*							
Magnesium citrate (225 mg of elemental magnesium)	*Cardio-protective, chemo-protectant, anti-calcification*							
Vitamin K2 (20 – 45 mg)	*Anti-calcification, anti-osteoporosis, anti-cancer*							
Fish oil (4 g *EPA and DHA* total)	*Anti-inflammatory, anti-triglycerides, heart health*							
Metformin (850 mg slow release form / patch / with meal / with probiotics to prevent gastrointestinal upset)	*Anti-ageing, anti-diabetes, anti-cancer*							
Pterostilbene (100 – 400 mg)	*Anti-ageing, anti-oxidative damage, anti-beta-amyloid*							
Quercetin (500 mg and Bromelain 150 mg)	*Anti-senescent (ageing) cells, anti-inflammatory*							
Green tea extract (600 – 2000 mg catechins, standardised extract)	*Anti-cancer, anti-inflammatory, anti-angiogenesis*							
Glucosamine (with or without chondroitin) (1500 mg)	*Anti-arthritis, anti-ageing*							
Turmeric (3g *with black pepper)*	*Anti-oxidative damage, anti-inflammation, anti-pain*							
CoQ10 (100 mg)	*Anti-oxidative damage*							
Creatine (1.5 - 5g powder dispersed in drink); 20g 1st day loading dose	*Pro-muscle growth, anti-fatigue, anti-diabetes*							
HALF of 1 tablet multivitamin multimineral ***AM and PM*** *Slow release Vitamin C 500 mg with 25 – 100 mg bioflavonoids is optimal*	*Optimal Vit A,B,C,D E, Choline, Inositol, Biotin, Pantothenic acid, Iodine, Copper, Boron, Manganese, Selenium, Zinc, Chromium, Molybdenum*							
Aspirin (40 mg per day or 80 mg every other day), ***before bed***	*Anti-cancer, anti-cardiovascular illnesses*							
Melatonin timed release 300 micrograms to 40 mg ***before bed***	*Pro-sleep, anti-hypertensive, anti-oxidative damage*							
Lifestyle: 10k steps/day (track with phone app), 80% + of foods from the healthy part of the Food Hourglass, brush teeth ***AM and PM***, floss ***PM***, blue light filter on screens to aid sleep								
Check each box to confirm the item has been taken. If only half an item was taken write "half". If both items taken, tick twice. Please detail any problems or reasons for not taking.								

Answers to questions

1 . Are there any other targeted treatment options that could be suggested?

- Yes, depending on the cancers mutations, which can only be fully identified through full genome sequencing (now costs between $1,000 and $5,000 in America) or exome sequencing and subsequent analysis. The exome is the 2% of the genome that is most important, and hence cheaper to sequence than the full genome. Please see the Diagnostics and Monitoring section.

- Targeted treatments include cell therapy and drugs (pharmaceuticals or biologics)

2. Are there any trials/options for non-small cell lung cancer type adenocarcinoma currently that [redacted] may qualify? (UCL/King's etc)

- Yes likely, there are 857 lung cancer related clinical trials currently registered in the EU at this link of which a proportion are running and of which [redacted] could be eligible for https://www.clinicaltrialsregister.eu/ctr-search/search?query=lung+cancer . Please see the interventions section for some specific clinical trials.

- If the best clinical trial is not available, or it is not possible to access the experimental therapies you need, it is possible to work with doctors and scientists to create your own clinical trial with a group of similar patients, or your own experimental trial, in which you are the only patient subject.

3. Are there any options of stem cell treatment for this type of cancer?

- Yes, please see the interventions findings section.

4. Should we be looking drugs such as Nivolumab?

- Yes, clinical trials show it improves the immune system's ability to attack the cancer and improves quality of life and outcomes. Please see the interventions findings section for further information.

Interventions findings

Interventions were searched and assessed for benefit to risk ratio. A benefit to risk ratio is the weighing up of the potential benefits versus the potential harms of an intervention. A "positive" benefit to risk ratio is one where the benefits of undertaking an intervention likely outweigh the harms, based on scientific evidence and the profile of the patient in question.

Non-invasive interventions

- Walking
  - > 10,000 steps per day is optimal, 1 mile per day (around 4000 steps) is good initial target
  - Use phone apps such as 'Moves' or 'Pedometer' to track your daily steps
- General exercising
  - Such as sport, or pilates
  - 30 minutes a day 5 times a week vigorous exercise is optimal
- Strength exercise
  - 2 - 4x per week is optimal
- Yoga, tai chi or qigong (known as meditative movement therapies)
- Meditation (various types)
  - For anxiety, stress, fatigue, sleep disturbances, general mood disorders and cancer pain
- Cognitive behavioural therapy (CBT)
  - For stress, anxiety or depression
- Radon gas check
  - Radon gas is an odourless gas, responsible for thousands of lung cancer deaths per year in the USA, it is a leading cause of lung cancer in non-smokers
  - Radon gas can be measured in homes through the UK Radon organisation, a branch of Public Health England http://www.ukradon.org/
- Avoid lung cancer carcinogens through identifying potential sources
  - Second hand smoke
  - Asbestos
  - Silica
  - Wood dust
  - Wood smoke from wood burning stoves

  - Wood smoke from fires
  - Diesel / petrol / exhaust fumes
  - Vinyl chloride
  - Benzene / toluene
  - Metals: Aluminium, arsenic, beryllium, cadmium, chromium, nickel
  - Noxious household cleaning products
  - Aerosols (e.g. spray deodorants)
  - Polluted atmospheric regions (e.g. Main roads in cities, international cities including China)

- Avoid alcohol (maximum 1 – 2 units per week; high polyphenol red wine is the preferable beverage)

References

NHS: People with cancer need more exercise. 2012.
http://www.nhs.uk/news/2012/07July/Pages/People-with-cancer-need-more-exercise.aspx

Matthews CE, George SM, Moore SC, et al. Amount of time spent in sedentary behaviors and cause-specific mortality in US adults. Am J Clin Nutr. 2012;95(2):437-45.
http://www.ncbi.nlm.nih.gov/pubmed/22218159

Sisk A, Fonteyn M. Evidence-Based Yoga Interventions for Patients With Cancer. Clin J Oncol Nurs. 2016;20(2):181-6.
http://www.ncbi.nlm.nih.gov/pubmed/26991712

Kelley GA, Kelley KS. Meditative Movement Therapies and Health-Related Quality-of-Life in Adults: A Systematic Review of Meta-Analyses. PLoS ONE. 2015;10(6):e0129181.
http://www.ncbi.nlm.nih.gov/pubmed/26053053

Black, D., Wilson, L. and Manocha, R., 2011. Disentangling the Evidence: The Efficacy of Meditation in People with Cancer. *Perspectives on Complementary and Alternative Medicines*, p.121.

Moorey, S. and Greer, S., 2011. *Oxford guide to CBT for people with cancer*. OUP Oxford. Freely accessible at:
https://books.google.co.uk/books?hl=en&lr=&id=ckIx80o5QpEC&oi=fnd&pg=PP2&dq=+%22CBT+cancer%22&ots=WNDiYfUgnZ&sig=0y5ERj7mmLoe_JB4Xx0KITGNsJI#v=onepage&q=%22CBT%20cancer%22&f=false

Radon Gas Warning, NHS Choices.
http://www.nhs.uk/news/2009/01January/Pages/Radongaswarning.aspx

UK Radon Gas association.
http://www.ukradon.org/

Tie, X., Wu, D. and Brasseur, G., 2009. Lung cancer mortality and exposure to atmospheric aerosol particles in Guangzhou, China. *Atmospheric Environment*, *43*(14), pp.2375-2377.
http://www.sciencedirect.com/science/article/pii/S1352231009000661

Dietary interventions

- Food Hourglass Diet from "the food hourglass" book (an evidence based anti-cancer and pro-longevity diet, by Dr Kris Verburgh, MD), see Appendix
    - Likely most effective if 80 - 100% of foods and drinks that are eaten are "food hourglass compliant"

- Ketogenic Diet (may starve the cancer of sugar, of which the cancer needs to grow)
    - This is a diet of 4 parts fat to 1 part protein or carbohydrates
    - The ketogenic diet should be administered under the guidance of a qualified nutritionist with past experience

- Avoidance of high temperature cooking methods (e.g. grilling, frying), as these create cancer causing compounds (e.g. burnt parts of food) and Advanced Glycation End Products (AGEs). AGEs also contribute to cancer, heart disease and ageing through accumulating in the body
    - Use low temperature, slow cooking methods with lots of water (e.g. boiling, steaming, poaching)
    - Avoid eating burnt or browned parts of food

- Protein and calorie fasting (Lowers Serum IGF-1)
    - Eating 600 calories total with no protein for 1 - 2 days per week, this is called "calorie and protein restriction" and has been shown to have benefits on the immune system, to reduce cancer incidence and progression and on the ageing processes
    - ProLon diet: 5 day fasting once per month; 1000 calories first day, 700 calories following 4 days to a set dietary plan

- Fasting prior or after delivery of chemotherapy
    - Administration of chemotherapy immediately after or during fasting may cause the chemotherapeutic drugs to preferentially target cancer cells, whilst minimising harm to non-cancerous normal healthy cells

- Read the label on everything you eat to check for 'unhealthy ingredients' (i.e. those that are not Food Hourglass compliant, see Appendix for the Food Hourglass infographic)

- Broccoli

- 'Anti-angiogenesis' teas
    - Angiogenesis, literally meaning "blood vessel (*angio-*) creation (*-genesis*)", is the process in which new blood vessels sprout from current blood vessels to provide areas of the body that require further oxygen and nutrients. Solid cancer tumours cannot grow larger than 1 – 2 mm without harnessing the process of angiogenesis. These tumours release chemicals that cause angiogenesis to occur, causing blood vessels from nearby to grow towards the tumour to provide it with nutrients.
    - The process can be inhibited through various beverages including:
        - Green tea
        - Ginger tea

- White tea
- Chai tea

References

ProLon (Promoting Health and Longevity) Diet. Based upon study of those with Laron Syndrome (GH receptor deficiency). http://www.aboutprolon.com/faqs.aspx

The Food Hourglass, by Dr Kris Verburgh. http://www.foodhourglass.com/

Verburgh K. Nutrigerontology: why we need a new scientific discipline to develop diets and guidelines to reduce the risk of aging-related diseases. Aging Cell. 2015;14(1):17-24. http://onlinelibrary.wiley.com/doi/10.1111/acel.12284/abstract

Uribarri, J., Cai, W., Sandu, O., Peppa, M., Goldberg, T. and Vlassara, H., 2005. Diet-Derived Advanced Glycation End Products Are Major Contributors to the Body's AGE Pool and Induce Inflammation in Healthy Subjects.*Annals of the New York Academy of Sciences*, *1043*(1), pp.461-466. http://onlinelibrary.wiley.com/doi/10.1196/annals.1333.052/abstract?userIsAuthenticated=false&deniedAccessCustomisedMessage

Uribarri, J., Woodruff, S., Goodman, S., Cai, W., Chen, X., Pyzik, R., Yong, A., Striker, G.E. and Vlassara, H., 2010. Advanced glycation end products in foods and a practical guide to their reduction in the diet. *Journal of the American Dietetic Association*, *110*(6), pp.911-916. http://www.sciencedirect.com/science/article/pii/S0002822310002385

Allen BG, Bhatia SK, Anderson CM, et al. Ketogenic diets as an adjuvant cancer therapy: History and potential mechanism. Redox Biol. 2014;2C:963-970. http://www.ncbi.nlm.nih.gov/pubmed/25460731

Schmidt, M., Pfetzer, N., Schwab, M., Strauss, I. and Kämmerer, U., 2011. Effects of a ketogenic diet on the quality of life in 16 patients with advanced cancer: A pilot trial. *Nutrition & metabolism*, *8*(1), p.1. http://nutritionandmetabolism.biomedcentral.com/articles/10.1186/1743-7075-8-54

Branco AF, Ferreira A, Simões RF, et al. Ketogenic diets: from cancer to mitochondrial diseases and beyond. Eur J Clin Invest. 2016;46(3):285-98. http://www.ncbi.nlm.nih.gov/pubmed/26782788

Allen BG, Bhatia SK, Buatti JM, et al. Ketogenic diets enhance oxidative stress and radio-chemo-therapy responses in lung cancer xenografts. Clin Cancer Res. 2013;19(14):3905-13. http://www.ncbi.nlm.nih.gov/pubmed/23743570

Naveed S, Aslam M, Ahmad A. Starvation based differential chemotherapy: a novel approach for cancer treatment. Oman Med J. 2014;29(6):391-8. http://www.ncbi.nlm.nih.gov/pubmed/25584154

Cangemi A - Tumour Biol (2016) Dietary restriction could it be considered as speed bump on tumor progression road.pdf

http://www.ncbi.nlm.nih.gov/pubmed/27043958

Herr, I. and Büchler, M.W., 2010. Dietary constituents of broccoli and other cruciferous vegetables: implications for prevention and therapy of cancer. *Cancer treatment reviews*, *36*(5), pp.377-383.
http://www.sciencedirect.com/science/article/pii/S0305737210000174

Sagar SM, Yance D, Wong RK. Natural health products that inhibit angiogenesis: a potential source for investigational new agents to treat cancer-Part 1. Curr Oncol. 2006;13(1):14-26.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1891166/

Supplement and nutraceutical interventions

All supplements can be purchased from Amazon or other online suppliers from sellers that utilise GMP (Good Manufacturing Practice) certified standards.

- Multivitamin/multimineral if diet alone is not meeting vitamin requirements, or if blood vitamin and mineral levels are not in optimal range.

  This should not be undertaken until vitamin or mineral deficiencies have been identified: the CRON-o-meter software https://cronometer.com/, also available as an Android or iOS app, can be used to track vitamin and mineral intake to see if you are meeting the RDA each day

  - Beta-carotene supplementation may be harmful for smoking caused lung cancer, it is not clear if this association occurs in non-smoking induced lung cancer

  - Iron supplementation may potentiate cancer and other ageing pathways
    - 40 – 60 ng/ml ferritin serum level is likely the optimal range for longevity (normal range 11 – 300 ng/ml)
    - For example, excess iron levels can cause haemosiderin deposits that accumulate throughout the body with age

  - 100% RDA (Recommended Daily Allowance), or dose to reach the optimal blood level of
    - Vitamin A
      - Mixed carotenoids
    - Vitamin B1, B2, B3, B4, B5, B6, B7, B9, B12
    - Vitamin C
    - Vitamin D3
    - Vitamin E
      - Mixed tocopherols (4 types) and mixed tocotrienols (4 types)
    - Vitamin K1/K2
    - Pseudovitamins: Choline, Inositol, Biotin, Pantothenic Acid
    - Microminerals
      - Iodine, Copper, Boron, Manganese, Selenium, Zinc, Chromium, Molybdenum
    - Macrominerals
      - Magnesium, Potassium, Sodium, Chlorine, Calcium, Phosphorous

- Coenzyme Q10, high bioavailable form
  - 100 - 300 mg a day

- Vitamin D3 to reach 25-OH-D blood level of 100 - 150 nmol/l (*note units)*
  - Likely 5000 IU (125 micrograms) for 1 – 3 months, followed ongoingly by 2000 IU per day
  - Measure once every month for first 3 months, followed by every 3 months

- Magnesium Citrate 200 - 250 mg / day (of elemental magnesium)
    - For protection of organs such as the kidneys from chemotherapeutic drugs
    - For prevention of calcification of organs and blood vessels

- Omega 3 fish oil
    - 2 g – 5 g of EPA and DHA per day (anti-inflammatory)

- Green tea standardised extract
    - 1 - 2g polyphenols per day

- Turmeric
    - 3 g / day in a highly bioavailable form (with black pepper or as nanoturmeric)

- Vitamin K2
    - 100 micrograms to 45 miligrams per day

- Pterostilbene
    - 100 – 400 mg per day

- Quercetin
    - 500 mg per day

- Glucosamine and chondroitin
    - 1.5g per day

- Melatonin
    - For general health: 300 micrograms, 6 hour timed release version
    - Melatonin can be useful in cancer, but normally in much greater doses than 300 micrograms. Some doses used in clinical trials include 10-50 mg daily, however there has been no significant evidence of improvement of disease outcomes in trials searched. An experienced physician should tailor and follow-up the right dose together with the patient, however given the side effects at higher doses (feeling very drowsy or sad/depressed with such high doses), the benefit to risk ratio is not fully clear for high dose melatonin (> 1 mg)
    - Only available on prescription in the UK, or can purchase from Amazon.com and import via a re-routing US address, e.g. www.viabox.com

- Creatine
    - *Microcrystalline creatine monohydrate powder* is the optimal form
    - 1.5 - 5g per day, may require loading dose of 3g six times per day (18 – 20g total), followed by 2 – 5 g maintenance dose

- Anti-angiogenesis or anti-inflammatory supplements

- 100+ supplement compounds have been identified to have significant anti-angiogenesis and anti-inflammatory (e.g. anti-cox 2) properties in preclinical models and clinical trials (Sagar SM, Yance D, Wong RK, 2006)

References

Bell GA, Kantor ED, Lampe JW, Shen DD, White E. Use of glucosamine and chondroitin in relation to mortality. Eur J Epidemiol. 2012;27(8):593-603.
http://www.ncbi.nlm.nih.gov/pubmed/22828954

Mushroom extract cures HPV infections. http://www.healthline.com/health-news/mushroom-extract-cures-hpv-infections-110614#1 . Accessed April 20, 2016.

AHCC Mushroom extract for HPV treatment. https://med.uth.edu/obgyn/research/womens-health-integrative-medicine-research-program/ . Accessed April 20, 2016.

Apparent partial remission of breast cancer in 'High Risk' patients supplemented with nutritional antioxidants, essential fatty acids and Coenzyme Q10. Molecular Aspects of Medicine. 15:s231.
http://www.sciencedirect.com/science/article/pii/0098299794900337

Sagar SM, Yance D, Wong RK. Natural health products that inhibit angiogenesis: a potential source for investigational new agents to treat cancer-Part 1. Curr Oncol. 2006;13(1):14-26.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1891166/

Toyokuni S. Role of iron in carcinogenesis: cancer as a ferrotoxic disease. Cancer Sci. 2009;100(1):9-16.
http://www.ncbi.nlm.nih.gov/pubmed/19018762

Toyokuni S. Iron as a target of chemoprevention for longevity in humans. Free Radic Res. 2011;45(8):906-17.
http://www.ncbi.nlm.nih.gov/pubmed/21615276

Yamamoto Y, Watanabe K, Tsukiyama I, Yabushita H, Matsuura K, Wakatsuki A. Hydration with 15 mEq Magnesium Is Effective at Reducingthe Risk for Cisplatin-induced Nephrotoxicity in Patients Receiving Cisplatin (≥50 mg/m2) Combination Chemotherapy. Anticancer Res. 2016;36(4):1873-7.
http://www.ncbi.nlm.nih.gov/pubmed/27069173

Posadas-sánchez R, Posadas-romero C, Cardoso-saldaña G, et al. Serum magnesium is inversely associated with coronary artery calcification in the Genetics of Atherosclerotic Disease (GEA) study. Nutr J. 2016;15(1):22.
http://www.ncbi.nlm.nih.gov/pubmed/26931571

D'eliseo D, Velotti F. Omega-3 Fatty Acids and Cancer Cell Cytotoxicity: Implications for Multi-Targeted Cancer Therapy. J Clin Med. 2016;5(2)
http://www.ncbi.nlm.nih.gov/pubmed/26821053

Khankari NK, Bradshaw PT, Steck SE, et al. Dietary intake of fish, polyunsaturated fatty acids, and survival after breast cancer: A population-based follow-up study on Long Island, New York. Cancer. 2015;121(13):2244-52.
http://www.ncbi.nlm.nih.gov/pubmed/25809414

Shi J, Liu F, Zhang W, Liu X, Lin B, Tang X. Epigallocatechin-3-gallate inhibits nicotine-induced migration and invasion by the suppression of angiogenesis and epithelial-mesenchymal transition in non-small cell lung cancer cells. Oncol Rep. 2015;33(6):2972-80.
http://www.ncbi.nlm.nih.gov/pubmed/25845434

Bettuzzi S, Brausi M, Rizzi F, Castagnetti G, Peracchia G, Corti A. Chemoprevention of human prostate cancer by oral administration of green tea catechins in volunteers with high-grade prostate intraepithelial neoplasia: a preliminary report from a one-year proof-of-principle study. Cancer Res. 2006;66(2):1234-40.
http://cancerres.aacrjournals.org/content/66/2/1234.full

Zhong JH, Mo XS, Xiang BD, et al. Postoperative use of the chemopreventive vitamin K2 analog in patients with hepatocellular carcinoma. PLoS ONE. 2013;8(3):e58082.
http://www.ncbi.nlm.nih.gov/pubmed/23505456

Yoshida, T., Miyazawa, K., Kasuga, I., Yokoyama, T., Minemura, K., Ustumi, K., Aoshima, M. and Ohyashiki, K., 2003. Apoptosis induction of vitamin K2 in lung carcinoma cell lines: the possibility of vitamin K2 therapy for lung cancer. International journal of oncology, 23(3), pp.627-632.

McCormack, D. and McFadden, D., 2012. Pterostilbene and cancer: current review. Journal of Surgical Research, 173(2), pp.e53-e61.

Murakami, A., Ashida, H. and Terao, J., 2008. Multitargeted cancer prevention by quercetin. Cancer letters, 269(2), pp.315-325.

Cruz-correa M, Shoskes DA, Sanchez P, et al. Combination treatment with curcumin and quercetin of adenomas in familial adenomatous polyposis. Clin Gastroenterol Hepatol. 2006;4(8):1035-8.
http://www.ncbi.nlm.nih.gov/pubmed/16757216

Blask, D.E., Sauer, L.A. and Dauchy, R.T., 2002. Melatonin as a chronobiotic/anticancer agent: cellular, biochemical, and molecular mechanisms of action and their implications for circadian-based cancer therapy. Current topics in medicinal chemistry, 2(2), pp.113-132.

Smith RN, Agharkar AS, Gonzales EB. A review of creatine supplementation in age-related diseases: more than a supplement for athletes. F1000Res. 2014;3:222.
http://www.ncbi.nlm.nih.gov/pubmed/25664170

Kreider, R.B., Ferreira, M., Wilson, M., Grindstaff, P., Plisk, S., Reinardy, J., Cantler, E. and Almada, A.L., 1998. Effects of creatine supplementation on body composition, strength, and sprint performance. Medicine and science in sports and exercise, 30, pp.73-82.

Mcdonnell SL, Baggerly C, French CB, et al. Serum 25-Hydroxyvitamin D Concentrations ≥40 ng/ml Are Associated with >65% Lower Cancer Risk: Pooled Analysis of Randomized Trial and Prospective Cohort Study. PLoS ONE. 2016;11(4):e0152441.
http://www.ncbi.nlm.nih.gov/pubmed/27049526

Pharmaceutical and biologic interventions

- Metformin
  - 850 mg per day
  - Has anti-cancer properties for adenocarcinoma in non-smokers and very low risk profile

- Aspirin
  - 80 mg every other day, taken at night (stomach is more resistant to aspirin damage at night)
  - Or 40 mg per day, taken at night
  - Has anti-cancer properties for adenocarcinoma and low risk profile

- Targeted therapies
  - Identify gene mutations in tumour cells
  - Select a drug that targets this / these mutations
  - Over 50% of adenocarcinoma mutations have drugs that are currently approved to target them, or of which are in development (phase 2 or 3 clinical trials)
  - See Appendix Figure 1 for examples of drugs that work against specific lung cancer mutations.

- Nivolumab
  - Checkpoint inhibitor that has caused long-term remission of some non-small cell lung cancers

- Pembrolizumab
  - Novel checkpoint inhibitor; only for those with non-small cell lung cancer who express PD-L1

- Ipilimumab
  - Anti-CTLA-4 antibody, case reports of full clearance of non-small cell lung cancer when given in combination with radiotherapy (See therapeutic medical devices section)

- Biologic cancer vaccines
  - CimaVax (versus EGF receptor – all good responders with high level doses of ClimaVax had a large tendency towards improved survival)
  - Lucanix (allogenic whole tumour cells with TGF-B expression turned off, allowing immune cells to attack the tumour cells and increase the immune response; improves median survival, Phase 3 trial completed)
  - MAGRIT
  - TIME
  - INSPIRE

- HPV vaccine
  - Vaccine HPV virus select subtypes (e.g. 16 and 18), a possible cause of non-smoking induced lung cancer
  - Active Hexose Correlated Compound

- Works as an immunotherapy that has been shown to cure HPV in some patients in ongoing Phase 1 / 2
- HPV may cause or propagate lung cancer

- Other viral vaccine
  - Viral vaccines could curb tumor growth, not only HPV vaccines, but perhaps every vaccine that spurs on the immune system. In theory, one could try to regularly vaccinate against pneumococcus, influenza, TBC etc to induce immune system boosts which can push back the cancer growth (for example, a TBC vaccine is given to help to treat bladder cancer).

- Treatment of underlying lung pathology that has been missed (e.g. TB infection)

- HTERT cancer vaccine
  - "VAPER" clinical trial ongoing at Guy's Hospital, London www.kcl.ac.uk/newsevents/news/newsrecords/2016/03%20March/New-trial-launched-to-test-cancer-vaccine.aspx

---

References

News article case study of a patient with non-small cell lung cancer and achieving remission with nivolumab pharmaceutical therapy http://www.curetoday.com/publications/cure/2016/lung-2016/a-new-era-of-hope-in-lung-cancer

Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP, Meade TW. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet. 2011;377(9759):31-41. http://www.ncbi.nlm.nih.gov/pubmed/21144578

Low-dose aspirin use and cancer characteristics: a population-based cohort study. British Journal of Cancer. 2013;109(7):1921. http://www.nature.com/bjc/journal/v109/n7/full/bjc2013411a.html

Moore JG, Goo RH. Day and night aspirin-induced gastric mucosal damage and protection by ranitidine in man. Chronobiol Int. 1987;4(1):111-6. https://www.ncbi.nlm.nih.gov/pubmed/3677213

"CheckMate -057, a Pivotal Phase III Opdivo (nivolumab) Lung Cancer Trial, Stopped Early". April 17, 2015.

Sundar R, Cho BC, Brahmer JR, Soo RA (2015). "Nivolumab in NSCLC: latest evidence and clinical potential".Ther Adv Med Oncol **7** (2): 85 6.doi:10.1177/1758834014567470. PMC: 4346216.PMID 25755681.

HTERT cancer vaccine clinical trial details: http://www.kcl.ac.uk/newsevents/news/newsrecords/2016/03%20March/New-trial-launched-to-test-cancer-vaccine.aspx

Medscape, "Consistent with this variation in risk by smoking history, we found that longer use of metformin was associated with a lower risk of adenocarcinoma [31% decrease in risk]"

http://www.medscape.com/viewarticle/839691#vp_2

Vallianou NG, Evangelopoulos A, Kazazis C. Metformin and cancer. Rev Diabet Stud. 2013;10(4):228-35.
http://www.ncbi.nlm.nih.gov/pubmed/24841876

Gandini S, Puntoni M, Heckman-stoddard BM, et al. Metformin and cancer risk and mortality: a systematic review and meta-analysis taking into account biases and confounders. Cancer Prev Res (Phila). 2014;7(9):867-85.
http://www.ncbi.nlm.nih.gov/pubmed/24985407

Hatoum D, Mcgowan EM. Recent advances in the use of metformin: can treating diabetes prevent breast cancer?. Biomed Res Int. 2015;2015:548436.
http://www.ncbi.nlm.nih.gov/pubmed/25866793

World Cancer Report 2014. World Health Organization. 2014. pp. Chapter 5.1. ISBN 9283204298.
http://www.scribd.com/doc/249125578/World-Cancer-Report-2014#scribd

Wang M, Cao JX, Liu YS, et al. Evaluation of tumour vaccine immunotherapy for the treatment of advanced non-small cell lung cancer: a systematic meta-analysis. BMJ Open. 2015;5(4):e006321.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4401843/

Rodriguez PC, Neninger E, García B, et al. Safety, immunogenicity and preliminary efficacy of multiple-site vaccination with an Epidermal Growth Factor (EGF) based cancer vaccine in advanced non small cell lung cancer (NSCLC) patients. J Immune Based Ther Vaccines. 2011;9:7.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3215653/

Gene therapy interventions

- No gene therapies were identified; gene therapies that modify stem cells are included in the cell therapy section

Cell therapy interventions

- CAR-T therapy (Chimeric antigen receptor T cell therapy), *intra-pleural injection likely better than intra-venous injection*
    - These are genetically engineered immune cells that are engineered to specifically attack targets that are expressed on your cancer cells, and not on normal healthy body cells
    - Only given to those that have tried and failed chemotherapy once or twice already
    - Available in London and the USA
    - In cases, has been shown to effectively cure blood cancers and solid tumours
    - May need a special variant of the therapy, or multiple rounds
    - Injection to the tumour in situ (intra-pleural) is likely better than intravenous
    - Preclinical studies have shown intrapleurally administered mesothilin-targeted CAR-T cells were able to effectively eradicate mesothelioma and lung cancer with 30-fold greater efficiency than intravenously administered CAR-T cells; clinical trials currently underway
    - Risk of tumour lysis-syndrome, requires careful monitoring
    - Currently very expensive; potentially ranging from $20,000 - $500,000 if done privately
    - CAR-T clinical trial for non-small cell lung cancers that express WT-1 is available at - https://clinicaltrials.gov/show/NCT02408016

- Anti-cancer mesenchymal stem cell (MSC) therapy
    - These cells can be shared between people without rejection
    - It is best to use cells from someone who is of the same sex, is healthy and is age 22 or under as the cells age and become less effective
    - The cells can be modified to produce or contain anti-cancer compounds; the cells home to the cancerous cells and attach them upon injection

- T Cell cancer vaccine
    - Your T cells are trained on samples of the tumour, the ones that attack the tumour are isolated, cultured up and reinjected
    - However these have been shown to be less effective in some cancers than CAR-T therapy

- Dendritic cell cancer vaccine
    - Similarly as the T cell vaccine, but with dendritic cells, a different type of immune cell

References

Lay introduction to CAR-T therapy
https://www.technologyreview.com/s/538441/biotechs-coming-cancer-cure/

Intra-pleural injection of CAR-T therapy

http://www.cancerresearch.org/cancer-immunotherapy/impacting-all-cancers/lung-cancer

Review of third generation CAR-T therapy for solid tumours.
http://blog.aacr.org/advances-in-immunotherapy-fine-tuning-car-t-cells/.

Guo Y, Wang Y, Han W. Chimeric Antigen Receptor-Modified T Cells for Solid Tumors: Challenges and Prospects. J Immunol Res. 2016;2016:3850839.
http://www.ncbi.nlm.nih.gov/pubmed/26998495

Palucka K, Banchereau J. Cancer immunotherapy via dendritic cells. Nat Rev Cancer. 2012;12(4):265-77.
http://www.ncbi.nlm.nih.gov/pubmed/22437871

Clinical trial: Genetically Modified T Cells in Treating Patients With Stage III-IV Non-small Cell Lung Cancer or Mesothelioma:
https://clinicaltrials.gov/show/NCT02408016

Surgical interventions

- Surgery should still be considered even in advanced lung cancer with metastases, following risk benefit analysis

References

Varela, G., & Thomas, P. A. (n.d.). Surgical management of advanced non-small cell lung cancer. ,*6* (Suppl 2). Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4032956/

Therapeutic medical device interventions

- Ultrasound therapy (high intensity focused ultrasound)
- Radiotherapy (photons or protons)
    - X ray/gamma ray radiotherapy in combination with immunotherapy may be synergistic
        - Radiotherapy with Ipilimumab
            - Ipilimumab is an anti-CTLA-4 antibody; there are case reports of full clearance of non-small cell lung cancer when given in combination with radiotherapy
    - Proton beam therapy (available by NHS Proton Overseas Programme)
        - Radiotherapy with protons rather than X-rays of which hit healthy areas around the tissue as well as the tumour; it has less side effects as it only targets the cancerous tissue
    - Radiofrequency thermal ablation radiotherapy
    - Microwave thermal ablation radiotherapy
    - Stereotactic radiotherapy, also known as radiosurgery (CyberKnife)
        - Targets the tumour from multiple angles, with the tumour receiving a high dose of radiation whilst the tissues around it only receive a low dose.

References

Wolfram F, Boltze C, Schubert H, Bischoff S, Lesser TG. Effect of lung flooding and high-intensity focused ultrasound on lung tumours: an experimental study in an ex vivo human cancer model and simulated in vivo tumours in pigs. Eur J Med Res. 2014;19:1. http://www.ncbi.nlm.nih.gov/pubmed/24393333

Silvia Formenti on the Promise of Combining Radiotherapy and Immunotherapy to Treat Cancer. http://www.cancernetwork.com/oncology-journal/silvia-formenti-promise-combining-radiotherapy-and-immunotherapy-treat-cancer

Golden EB, Demaria S, Schiff PB, et al. An abscopal response to radiation and ipilimumab in a patient with metastatic non-small cell lung cancer. Cancer Immunol Res. 2013;1:365-72. http://www.ncbi.nlm.nih.gov/pubmed/24563870

Golden EB, Chachoua A, Fenton-Kerimian MB, et al. Abscopal responses in metastatic non-small cell lung cancer (NSCLC) patients treated on a phase 2 study of combined radiation therapy and ipilimumab: evidence for the in situ vaccination hypothesis of radiation. Int J Radiat Oncol Biol Phys. 2015;93:S66-S67.

Proton beam therapy – how it works. http://eandt.theiet.org/magazine/2016/04/proton-therapy.cfm

The case of Ashy King, British childhood brain cancer sufferer and proton beam therapy. http://www.telegraph.co.uk/news/health/news/12131272/Ashya-King-proton-beam-cancer-therapy-causes-fewer-side-effects.html

Smith SL, Jennings PE. Lung radiofrequency and microwave ablation: a review of indications, techniques and post-procedural imaging appearances. Br J Radiol. 2015;88(1046):20140598.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4614249/

Wang Z, Kong QT, Li J, et al. Clinical outcomes of cyberknife stereotactic radiosurgery for lung metastases. J Thorac Dis. 2015;7(3):407-12.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4387394/

Diagnostics and monitoring interventions

- A full genome OR exome (the 2% of the genome that is protein coding) sequencing of biopsy (make sure to genome sequence multiple cells, as different cells within the tumour will likely have evolved different mutations) to potentially identify mutations that can be targeted
    - Test cancer cells for WT-1, L1-CAM, ROR-1 expression, of which can be targeted with CAR-T therapy: See Juno Therapeutics' list of CAR-T biomarker targets https://www.junotherapeutics.com/pipeline/clinical/
    - Test cancer cells for ALK translocation, ROS 1 translocation, RET translocation (see Appendix Figure 2), ask your doctor how to best test for these
    - Test cancer cells for KRAS mutation, EGFR mutation, PIK3CA mutation, CTNNB1 mutation, BRAF mutation, NRAS mutation, HER2 mutation (see Appendix Figure 2 for the potential drugs that can target these if these mutations are discovered); this can be done via genome, exome sequencing or genotyping
    - Other mutations may be found of which can be targeted with other drugs, or personalised CAR-T therapies
    - Liquid biopsy (circulating single or double stranded DNA in the blood stream, shed from cancer cells) may be used too, however this technique is still being validated as a biomarker and will not cover as many mutations

- Reconfirm the diagnosis of adenocarcinoma; if the benefits of re-diagnosis outweigh the risks and there is potential uncertainty in the diagnosis

- Test for HPV and other viruses and STDs including:
    - HPV types 16 and 18
    - EBV
    - CMV
    - HSV 1 and 2
    - HIV
    - Chlamydia
    - Syphilis
    - Gonorrhoea

- Test for fasting blood glucose and HbA1c
    - Untreated diabetes increases cancer risk and viral/bacterial infection risk of which can in turn lead to cancer
    - Type 2 diabetes should be treated with metformin, diet, exercise, supplements (e.g. chromium), sleep optimisation and stress reduction alone, with other drugs only used if absolutely necessary due to their side effects

- Test Vitamin D every 3 months
    - Optimal range 75 – 125 nmol/ml

- Test serum ferritin
    - Optimal range for longevity 40 – 60 ng/ml, however this may not be the optimal range for lung cancer; however the test is important to diagnose occult hemochromatosis

- Monitor body weight for weight loss or gain. Aim for optimal body weight.

- Increasing the safety of medical imaging
    - Avoid single or multiple CT, PET, SPECT scans, other types of radionucleotide scans or X-Rays; these all use radiation that can increase the risk of cancer. Use MRI scans instead whenever possible.
    - In all cases if possible use MRI scans (these use magnets and non-harmful radiation). MRI scans can be obtained privately at a cost of £200 per body region, if the NHS cannot provide them
    - Where possible 1.5T (Tesla, a measure of the MRI's magnetic field strength) should be used rather than 3T unless indicated; MRI scans still cause DNA damage, with 3T scans causing more DNA damage than 1.5T scans, however this DNA damage has not been shown to increase the risk of cancer or any other diseases, as has been with CT, PET and SPECT scans.
    - Ensure to drink enough water to be optimally hydrated prior to your scan to improve image quality
    - Ensure to stay very still during the scan to improve image quality
    - If it is not possible to avoid a CT, PET, SPECT or X-ray scan ensure to take radioprotective actions
        - Request imaging protocols that use the minimum amount of radiation, for example CT scans can now use 10x less radiation and obtain the same diagnostic or prognostic quality, however only certain hospitals implement these protocols; speak to your radiologist to organise this
        - Ask the radiologist what your total dose of radiation is in mSv (milisiverts) and Gy (grey) before the procedure and if this can be reduced
        - Take radioprotective supplements several hours prior to radiation exposure such as 100% RDA of vitamin C, E, Selenium, Chromium, Iodine, green tea extract, Coenzyme Q10, Pterostilbene and Quercetin
        - Radioprotective supplements may also be taken before MRI scans

References

Human Longevity Inc.

- Their $25,000 health nucleus service, of which include full genome sequencing for cancer biopsies, normal healthy cell full genome sequencing, full bloods, full body imaging with MRI, full microbiome sequencing etc. https://www.healthnucleus.com/
- HLI also are developing personalised cell therapies and cancer vaccines of which could hold some worth enquiring about http://www.humanlongevity.com/science-technology/products/

Illumina personal genome/exome sequencing

- This service provides high quality full genome or exome sequencing services (exome = 2% of total genome, sequencing the protein coding regions only, and hence cheaper than full genome sequencing), it is best to contact them via the phone and discuss
  http://www.illumina.com/clinical/illumina_clinical_laboratory.html ;

Veritas Genetics (Professor George Church, Harvard)

- Genome sequencing services
  https://www.veritasgenetics.com/

Sacher, A., et al. (2016). Prospective Validation of Rapid Plasma Genotyping for the Detection of and Mutations in Advanced Lung Cancer. JAMA Oncology. DOI: 10.1001/jamaoncol.2016.0173.
http://oncology.jamanetwork.com/article.aspx?articleid=2511037

Emergency medicine interventions

- Medical cryopreservation (the storage of the body in liquid Nitrogen at very cold temperatures, with the blood replaced with cryoprotectant, with the goal to be resuscitated in the near future once medical technology has advanced)
    - This involves an advanced medical protocol, performed by paramedics and doctors to protect the body and brain from damage after legal death, for later revival; storage time is estimated at 30 - 100 years (year 2046 - 2116) before safe resuscitation is possible
    - There is evidence that: 1) the cryopreservation procedure maintains the microstructure of the patient's brain and other organs ; 2) it is now possible to freeze and thaw a rabbit brain using similar techniques and maintain the microstructure of the brain (the 'connectome'), with a small animal brain being preserved and restored for the first time in early 2016
    - The two main organisations currently are Alcor and Cryonics Institute (CI), both based in the US
    - The UK based medical charity Cryonics UK have their own cryonics ambulance and team of qualified paramedics that can administer cryopreservation services in the UK
    - Whole body cryopreservation costs at Alcor are $200,000 USD and at Cryonics Institute they are $28,000
    - Cryopreservation costs are normally paid for through life insurance, cash savings, Property Trusts or other Trusts, or through the sale of assets to pay fees upfront

- Health monitoring device that is worn 24/7, even at home, and alerts medical emergency services in case of emergency (e.g. cardiac arrest, heart arrhythmia, low oxygen saturation of the blood)

References

Alcor, the globally leading cryonics company - the FAQ section is particularly informative
www.alcor.org

Alcor costs for cryopreservation services
http://www.alcor.org/BecomeMember/scheduleA.html

Cryonics UK: These are the UK based paramedic team that perform the cryopreservation procedure on UK patients, contact Tim and Victoria
www.cryonics-uk.org/

Cryogenically frozen rabbit brain hailed as scientific first. Feb 11 2016.
http://www.huffingtonpost.com/entry/fully-intact-brain-frozen_us_56bb942ae4b0b40245c51654

Social interventions

- Friends and family
    - Encourage strong support from friends and family

- Socialising with similar patients
    - Ask your GP for local community support groups
    - Contact charitable organisations including Cancer Research UK
    - Online organisations including:
        - www.patientslikeme.com
        - www.whatnext.com (online cancer support network that connects people to peers and resources based on a specific diagnosis)
        - www.pulseofthepatient.com (cancer focused)
        - www.curetogether.com
        - www.bensfriends.com
        - www.talk.nhs.co.uk (NHS Choices Communities)
        - www.raregenomics.org (connects patients with rare genetic with genetic researchers and crowdfunds their genetic sequencing)
        - www.careacross.com (cancer focused)

- Crowdsourcing a solution has proven effective for some patients with complex diseases. This involves using social media, including Facebook, Twitter and LinkedIn as well as expert scientist group forums such as Research Gate, and expert clinician forums such as Doctors.org.uk, to share your story and encourage people to contribute their expert knowledge on potential therapies or diagnostics. Working with medical journals such as the BMJ (British Medical Journal), or other media outlets, may also be of benefit. Furthermore platforms such as GoFundMe have been used to raise tens of thousands of pounds for people with terminal illnesses.

    - Facebook
    - Twitter
    - LinkedIn
    - Research Gate
    - Doctors.org.uk
    - Patent's like me
    - Medical journals e.g. the BMJ
    - Other media
    - GoFundMe

Further Resources

Further resources were searched and assessed for benefit to risk ratio. A benefit to risk ratio is the weighing up of the potential benefits versus the potential harms of a resource. A "positive" benefit to risk ratio is one where the benefits of utilising a resource in some way likely outweigh the harms, based on prior evidence and the profile of the patient in question.

Persons and organisations to contact

Contacting expert persons or organisations in the field related to your condition may be necessary to access or decide upon certain diagnostics or therapies, or their combinations.

General tips include:

- Generally, the more people contacted regards finding a solution the better
- People are best contacted through email, Skype call or through meeting in person at group events
- It is useful to ask if there is anyone the person knows that would also be useful to talk to
- Private doctors generally have more time than NHS doctors
- Always get second opinions from doctors or scientists if possible

The following persons and organisations were found to be beneficial to contact regards their relevant expertise:

Michel Sadelain, M.D., Ph.D., and colleagues at MSKCC

- Running CAR-T intrapleural lung cancer immunotherapy clinical trial

Dr Silvia Formentia, MD

- Regards combination radiation-immunotherapy (e.g. ipilimumab and radiation therapy)

Dr Hyman, the Ultrawellness Centre - http://www.ultrawellnesscenter.com/home/

- Regards lifestyle optimisation (diet and exercise) and specific anti-cancer supplements

Professor Sam Janes at UCL/UCLH

- Currently running a genetically engineered stem cell therapy clinical trial for lung cancer - https://www.mrc.ac.uk/news/browse/combination-cell-gene-therapy-for-lung-cancer-to-be-tested-in-uk-patients/

Dr Chris Watkins, Director of Translational Research Biomedical Catalyst, MRC

- Likely will have knowledge of many relevant clinical trials or experts

Professor Dr Robert Hawkins, Christie Clinic, Manchester

- Expert in cancer cell therapy
  http://www.thechristieclinic.co.uk/find-a-specialist/professor-robert-hawkins-2

Dr Stanley Riddel, Fred Hutch, Washington, USA

- CAR-T immunotherapy expert
  https://www.fredhutch.org/en/labs/profiles/riddell-stanley.html

MD Anderson Cancer Centre

- One of the leading cancer clinics, located in Texas, USA. Their website can be searched for clinical trials
  https://www.mdanderson.org/

The MD Anderson Cancer Center Sheikh Khalifa Bin Zayed Al Nahyan Institute for Personalized Cancer Therapy

- Offer cancer genome sequencing
  https://www.mdanderson.org/education-and-research/research-at-md-anderson/personalized-advanced-therapy/sheikh-khalifa-bin-zayed-al-nahyan-institute-for-personalized-cancer-therapy/index.html

Memorial Sloan Kettering Cancer Centre

- One of the leading cancer clinics, located in New York, USA. Their website can be searched for clinical
  https://www.mskcc.org/

Cancer Research UK UCL Clinical Trials Centre

- Potentially useful to identify further UK based researchers and doctors
  http://www.ctc.ucl.ac.uk/

Cancer Research UK Imperial Centre

- Potentially useful to identify further UK based researchers and doctors
  http://www.imperial.ac.uk/cancer-research-uk-imperial-centre/

Juno Therapeutics

- US company that creates CAR-T and cancer immunotherapy cell therapies, valued at $6bn, founded in 2012 and performing many clinical trials in the US
  https://www.junotherapeutics.com/pipeline/clinical/

Clinical trials and trial databases

- EU clinical trials https://www.clinicaltrialsregister.eu/ctr-search/search?query=lung+cancer&page=1
- US clinical trials (and global) https://clinicaltrials.gov/

    - If the best clinical trial is not available, or it is not possible to access the experimental therapies you need, it is possible to design and develop your own clinical trial with a group of similar patients

Recommended reading for the client

The following articles are open access. The Client may be assisted to access pay-walled or subscription based articles upon request, by contacting Zolman Medical for further information.

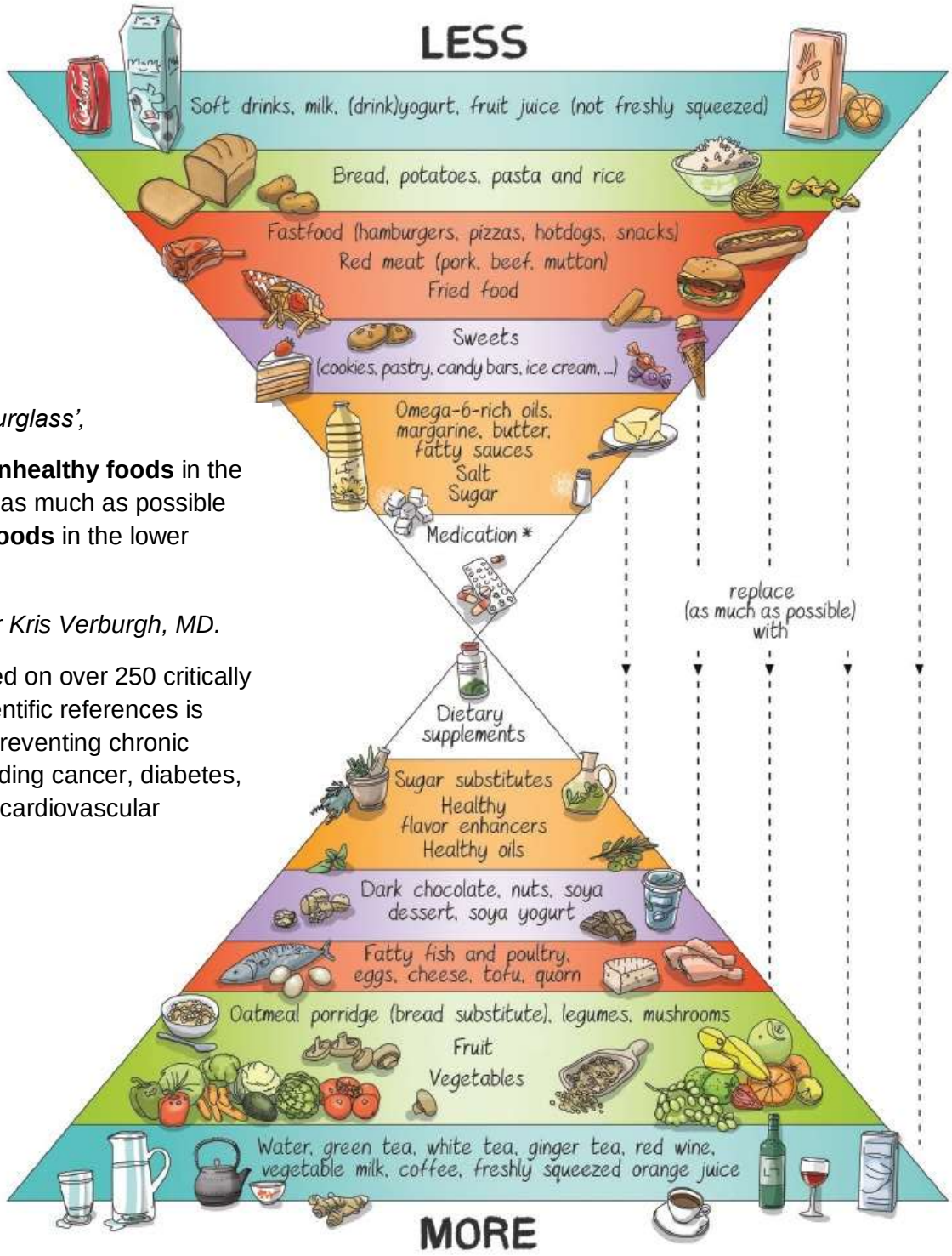
- Critical appraisal - how to assess the quality of a medical publication http://www.medscape.com/viewarticle/706399
- Hanna, Nasser (2007). "Lung Cancer in the Never Smoker Population". *Hematology-Oncology*. Medscape. http://www.medscape.org/viewarticle/566978
- https://en.wikipedia.org/wiki/Non-small-cell_lung_carcinoma
- https://en.wikipedia.org/wiki/Adenocarcinoma_of_the_lung
- http://patient.info/health/staging-and-grading-cancer
- http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-treating-by-stage
- Lung cancer NHS NICE guidance https://www.nice.org.uk/guidance/cg121
- The Food Hourglass, Dr Kris Verburgh. 2014. http://www.amazon.co.uk/The-Food-Hourglass-Kris-Verburgh/dp/0007556160

Google search terms for the client

The following terms may be searched to identify articles of interest on Google, or other search engine, that may help the client to gain a further "all round" understanding of the condition and therapeutic options, or to themselves identify new information after the research period of this report.

- Lung cancer explained
- Immunotherapy explained
- CAR-T therapy explained
- Lung cancer immunotherapy
- Lung cancer cell therapy
- Adenocarcinoma immunotherapy
- Lung cancer genome sequencing
- Adenocarcinoma cure
- Lung cancer cure
- Non-small cell lung cancer cure
- Lung cancer consultant
- Lung cancer scientist
- Lung cancer professor
- MRI explained

Appendix



'The Food Hourglass',

Replace the **unhealthy foods** in the upper triangle as much as possible with **healthy foods** in the lower triangle

Courtesy of Dr Kris Verburgh, MD.

This diet, based on over 250 critically appraised scientific references is designed for preventing chronic diseases including cancer, diabetes, dementia and cardiovascular diseases.

Smart food supplements: vitamin D, iodine, magnesium, selenium, B vitamins

Healthy sugar substitutes: stevia, tagatose, sugar alcohols, (mashed) fruits
Healthy oils: olive oil, flax seed oil, walnut oil, canola oil, soy oil, perilla-oil
Healthy flavor enhancers: spices (turmeric, parsley, thyme, rosemary, basil, oregano, mint), garlic, onion, lemon juice, vinegar (balsamico, raspberry vinegar, tomato vinegar), potassium salt
Omega-6 rich oils (use less of): corn oil, sunflower oil, palm oil, sesame seed oil

Fatty fish: salmon, mackerel, herring, anchovy, sardine
Meat substitutes: tofu (made of soy) and quorn (made of a fungus)

Legumes: beans, peas, lentils, soy

Water: can be flavoured with lemon, sage, thyme or mint
Plant milk: soy milk, almond milk, rice milk
Alcohol: maximum 2 consumptions a day for men and 1 consumption a day for women
Coffee: limited to 3 consumptions a day

* Always consult a medical doctor before changing or reducing medication

The majority of lung adenocarcinomas from never-smokers harbour a mutation in either *EGFR* or *HER2 (ERBB2)* or a fusion involving *ALK* or *ROS1* [18]. Driver mutations in adenocarcinoma occur in the *EGFR, HER2 (ERBB2), KRAS, ALK, BRAF, PIK3CA,* and *ROS1* genes (Fig. 5.1.4A). Mutations in *KRAS* and *EGFR* are mutually exclusive, as are most of the kinase domain mutations listed above, except for *PIK3CA* [19,20]. Several of these genes may have increased gene copy number or amplification, mostly of the mutant allele. *EGFR* (20%), *HER2* (2%), and *MET* (1%) may be amplified preferentially on the mutant allele. *MET* amplification occurs more frequently in resistant disease and is associated with EGFR tyrosine kinase inhibition. All of these mutations offer the possibility of targeted therapy, although only three *(EGFR* mutation, *ALK* and *ROS1* fusion) are subject to targeted treatment with currently approved drugs: gefitinib or erlotinib for *EGFR* mutation and crizotinib for *ALK* and *ROS1* fusion. Agents targeting the others are in development in phase 2 or phase 3 (Table 5.1.1).

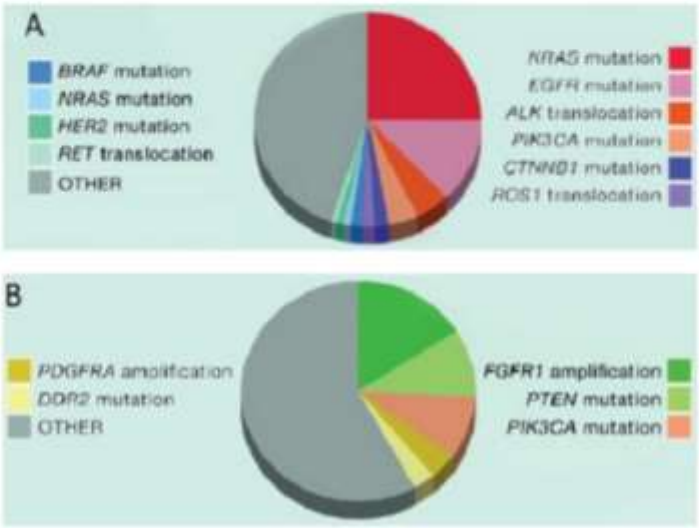


Figure 2 - (A) Mutation spectrum in adenocarcinoma. (B) Mutations in squamous cell carcinoma. Worldwide cancer Report 2014.

Gene or genetic alteration	Histological type	Therapy
Targeted therapies[a]		
EGFR mutation	Advanced adenocarcinoma	EGFR tyrosine kinase inhibitor Erlotinib, gefitinib
ALK fusion	Adenocarcinoma	Crizotinib
ROS1 fusion	Advanced adenocarcinoma	Crizotinib
Drugs in development		
HER2	Adenocarcinoma	Afatinib (BIBW 2992)
PI3KCA	NSCLC	Trastuzumab, PI3K inhibitor
BRAF	NSCLC	Sorafenib?
MET	NSCLC	Phase 2: rilotumumab (AMG 102), MetMAb
RAS	Adenocarcinoma	PI3K + MEK inhibitors

Figure 1 – Drugs approved or undergoing clinical trials that target lung cancers with specific genetic mutations. Worldwide cancer Report 2014.